# ABSTRACTS

# Abstracts of Papers to be Presented at the 38th Annual Scientific Session of the American College of Cardiology, Anaheim, California, March 19–23, 1989

**This year 4,008 abstracts (original contributions) were submitted for evaluation. Each was graded by eight recognized authorities in a special area of interest. Acceptance for presentation was based on the relative grade ranking in each of the 29 categories.**

**Ample meeting space combined with the inclusion of poster sessions again this year permitted the 1989 Annual Scientific Session Program Committee to accept 1,007 abstracts, approximately 25% of the number submitted. Many excellent contributions were received for this year's competition, and we appreciate your support and interest.**

**Arthur E. Weyman, MD, FACC**
*Chairman, 1989 Annual Scientific Session Program Committee*

**Steven E. Nissen, MD, FACC**
*Co-Chairman, 1989 Annual Scientific Session Program Committee*

## Monday, March 20, 1989
## 10:30AM–12:00NOON, California Room A
## Anaheim Convention Center
## Young Investigators' Awards Competition
## The following five abstracts are from the winning entries in the Young Investigators' Awards Competition, 38th Annual Scientific Session.

MYOCARDIAL STIFFNESS AND REPARATIVE FIBROSIS FOLLOWING CORONARY EMBOLIZATION IN THE RAT.
Eugenia Carroll M.D., Joseph S. Janicki, Ph.D., Ruth Pick, M.D., Karl T. Weber, M.D., F.A.C.C., Cardiovascular Institute, Michael Reese Hospital, University of Chicago Pritzker School of Medicine, Chicago, Illinois

The structural nature of fibrillar collagen involved in the replacement fibrosis that accompanies myocyte necrosis remains uncertain, as does its influence on the passive diastolic (DS) and active systolic (AS) stiffness ($g/cm^2$) of the myocardium. This study utilized 15 micron diameter microsphere embolization of Wistar rat hearts to address these issues. Collagen volume fraction (CVF), fibrillar collagens (picrosirius-polarization technique) and systolic and diastolic stress-strain relations of the myocardium (isolated heart technique) were determined in control rats (C, n=9) and 30 days after embolization (S, n=14). Differences included:

| | (C) | (S) | (p) |
|---|---|---|---|
| Systolic BP (mm Hg) | 126 ± 15 | 153 ± 26 | <.02 |
| LV/RV weight | 3.9 ± 0.2 | 4.0 ± 0.4 | NS |
| CVF | 6.4 ± 1.7 | 15.9 ± 5.5 | <.001 |
| AS ($g/cm^2$) | 268.0 ± 8.6 | 449.4 ± 10.4 | <.001 |
| DS (strain 5%) | 63.2 ± 12.3 | 96.7 ± 43.8 | <.05 |

No correlation was found between CVF and AS or DS. The reparative fibrosis consisted of a meshwork of short, taut, thick and thin collagen fibers that was situated in-series with muscle. Thus, not because of its concentration, but rather its fibrillar structure, alignment, and location, a reparative fibrosis will have a marked influence on myocardial stiffness.

PLATELET PLASMINOGEN ACTIVATOR INHIBITOR: PURIFICATION AND CHARACTERIZATION OF INTERACTION WITH PLASMINOGEN ACTIVATORS AND ACTIVATED PROTEIN C. William P. Fay, M.D., and Whyte G. Owen, Ph.D. Mayo Clinic/Foundation, Section of Hematology Research, Rochester, MN 55905

The interaction of Plasminogen Activator Inhibitor (PAI) and activated Protein C (APC) has been implicated to play a role in the regulation of fibrinolysis by altering the ratio of plasminogen activators to their rapid inhibitor. We have isolated PAI from platelets and quantitatively studied its interaction with APC, tissue-type plasminogen activator (t-PA), and urokinase (UK) in a purified porcine system. Incubation of PAI with APC, UK, and t-PA yielded not only SDS-stable complex formation, but also a modified inhibitor of slightly reduced molecular weight. The second order rate constants for the inhibition of t-PA, UK, and APC by PAI were $3.5 \times 10^7$, $3.4 \times 10^7$, and $1.1 \times 10^4$ $M^{-1}sec^1$, respectively. Activated Protein C inhibited PAI with a second order rate constant of $1.1 \times 10^4$ $M^{-1}sec^{-1}$. This rate was not accelerated by the addition of Protein S, phospholipid, and calcium. Platelet PAI inhibited the functional activity of APC in plasma in a heparin-independent fashion. These results indicate that: 1) PAI can function as both inhibitor and substrate of its target proteases, 2) if APC promotes fibrinolysis via inactivation of PAI, then APC must be present in concentrations several orders of magnitude greater than t-PA, or the interaction of APC and PAI must be accelerated by presently unknown mechanisms, and 3) Platelet PAI is the most rapid heparin-independent inhibitor of APC yet described. Hence, it may promote clot stability not only via inhibition of fibrinolysis, but also by inhibiting the inactivation of Factors $V_a$ and $VIII_a$ by APC.

VASCULAR RESPONSES TO LEUKOCYTE PRODUCTS IN ATHEROSCLEROTIC PRIMATES.
J. Antonio G. Lopez, M.D., Donald D. Heistad, M.D., VA Medical Center and University of Iowa, Iowa City, Iowa.

Little is known about the possible role of leukocytes in the pathogenesis of vasospasm. We hypothesized that vasoactive products released by leukocytes might produce constriction of atherosclerotic arteries. To test this hypothesis, we infused f-met-leu-phe (fMLP), a peptide which activates leukocytes to release their vasoactive products, into the perfused hind limb of normal and atherosclerotic cynomolgus monkeys. Infusion of fMLP did not change resistance of large arteries in normal monkeys. In contrast, fMLP produced pronounced constriction of large arteries in atherosclerotic monkeys. To determine whether leukotrienes, platelet activating factor (PAF) or prostaglandin $E_2$ ($PGE_2$), which are released by leukocytes, may contribute to leukocyte-induced vasoconstriction in atherosclerotic monkeys, we injected leukotriene $D_4$ ($LTD_4$), PAF, and $PGE_2$ intra-arterially into the perfused hind limb. $LTD_4$ and PAF had minimal effects on large arteries in both normal and atherosclerotic monkeys. In contrast, $PGE_2$ produced greater than ten-fold more constriction of large arteries in atherosclerotic than normal monkeys. Thus 1) pronounced constriction in atherosclerotic, but not normal, arteries during infusion of fMLP suggests that products released by leukocytes may mediate vasoconstriction in atherosclerotic vessels and 2) vasoconstrictor responses to $PGE_2$ are profoundly potentiated by atherosclerosis, which suggests that $PGE_2$ may contribute to leukocyte-induced vasoconstriction.

SELECTIVE INHIBITION OF α2-ANTIPLASMIN AUGMENTS THE POTENCY AND SPECIFICITY OF PLASMINOGEN ACTIVATORS.
Guy L. Reed MD, Gary R. Matsueda PhD, Edgar Haber MD. Cardiac Unit, Massachusetts General Hospital, Boston, MA.

Clinical trials have shown that plasminogen activator therapy significantly reduces the mortality from myocardial infarction. Yet, for a number of patients this therapy fails to lyse the coronary thrombus, or is associated with bleeding or rethrombosis. In part these failures are due to the effects of α2-antiplasmin, the protein that protects the clot from lysis by plasmin. To investigate the hypothesis that selective inhibition of α2-antiplasmin would improve the potency and specificity of plasminogen activators, we used a monoclonal antibody which specifically inhibits human α2-antiplasmin. This inhibitory antibody RWR, functions as a reversible inhibitor causing 50% inhibition of α2-antiplasmin at a molar ratio of 0.7:1 (RWR:α2-antiplasmin). In a quantitative assay of clot lysis in plasma, RWR dramatically increases the potency of tissue plasminogen activator (27-fold) and urokinase (80-fold). At the same time RWR preserves the fibrinolytic specificity of these activators and does not increase the nonspecific consumption of fibrinogen.

From these results we conclude that the combined use of a plasminogen activator and an α2-antiplasmin inhibitor will increase the potency and specificity of thrombolytic therapy.

CARDIOTOXIC EFFECTS OF ANGIOTENSIN II
Lip-Bun Tan, M.B.B.Chir., D.Phil., Jorge E. Jalil, M.D., Joseph S. Janicki, Ph.D., Karl T. Weber, M.D., F.A.C.C., William A. Clark, Ph.D., Cardiovascular Institute, Michael Reese Hospital, Univ. of Chicago, Chicago, Illinois.

The role of angiotensin II (AII) in the pathogenesis and progression of heart failure is unknown. However, we have shown that AII infusion into rats (190-300g) produces substantial cardiac myocytolysis. AII was administered via Alzet minipumps at a dose (200 ng/min, i.p.) which did not cause acute hypertension. We induced elevated endogenous AII by abdominal aortic banding with renal artery constriction. Necrotic cardiac myocytes were identified by *in vivo* administration of monoclonal antibodies against cardiac myosin and by immunofluorescence labelling. The healing process following injury was monitored by determining reparative [$^3$H]thymidine incorporation into fibroblast DNA. Exogenous AII produced scattered labelling of cardiac myocytes, indicative of necrosis, which was maximal on day 1 of infusion. Subsequently, DNA synthesis rates were increased, and reached peak level on day 2 (DNA specific activity: AII 90.0±18.6, Controls 11.4±2.3 cpm/μg, $p<0.05$). Prior to day 3 of infusion, systemic blood pressure was not significantly elevated from control. Concurrent treatment with propranolol (30 mg/kg/day s.c.) and phenoxybenzamine (5 mg/kg/day s.c.) did not attenuate the necrotic effect of AII. Increased endo-genous AII produced similar myocyte necrosis and increased DNA synthesis rate, each of which were prevented by captopril (50-80 mg/day p.o.). Aortic banding without renal artery involve-ment produced hypertension but no myocardial necrosis. We con-clude that pathophysiological levels of endogenous and exoge-nous AII was capable of inducing myocardial necrosis, which was unrelated to the hypertensive effect of AII and not secondary to adrenergic activation. Captopril was effective in preventing myocyte necrosis in our model of renovascular hypertension.

## Monday, March 20, 1989
## 10:30AM–12:00NOON, California Room D
## Anaheim Convention Center
## Detection and Treatment of Silent Myocardial Ischemia

DISCORDANCE BETWEEN RADIONUCLIDE, DOPPLER ECHO, ANGIOGRAPHIC AND AMBULATORY ECG MARKERS OF ISCHEMIA.
David C. Reed, M.D., Peter H. Stone, M.D.,FACC, Thomas L. Shook, M.D.,FACC, Lorene A. Shav, BSN, Phillip Young, Pharm.D., Robert S. Gibson, M.D., FACC and the ASIS Group. Univ of Virginia, Charlottesville, Virginia.

To determine the relationship between the mass of ischemic myocardium and silent ischemia, we prospectively evaluated 20 consecutive pts (mean age 60±5 yrs) with chronic stable angina withdrawn from anti-anginal medication and placed on placebo. After one week of placebo therapy, each pt underwent graded treadmill exercise (GTX) testing, quantitative TL-201 scintigraphy, suprasternal doppler echo of ascending aortic blood flow velocity (v) and acceleration (dv/dt) during GTX, and 48 hrs of post GTX ambulatory ECG (AECG). All 20 pts had angina and ≥1 mm ST seg ↓ during GTX; 12 pts (60%) had silent ischemia (SI) by AECG criteria (≥1 mm ST ↓ for ≥1 min) and 8 pts (40%) did not. Comparison of the two AECG defined groups showed similar GTX duration and rate-pressure products, treadmill ΣST↓ scores, prior MI and LVEF. Pts with SI were younger ($p=.05$), had less LV asynergy ($p=.07$), fewer persistent TL-201 defects ($p=.07$) and a lower prevalence of abnormal lung TL-201 uptake ($p=.04$) during GTX imaging. Importantly, there were no between group differences in doppler-derived LV ejection phase indices during GTX or the number of scintiscan segs or vascular regions showing TL-201 ischemia, despite higher angio jeopardy scores among pts with SI ($p=.05$). Pts with SI vs those without SI were more likely to have an RCA stenosis (90vs12%, $p=.01$) and inferoposterior ischemia by TL-201 (83vs12%, $p=.02$). Thus, the presence of SI on AECG does not correlate with exercise TL-201 measured ischemic burden or doppler echo indices of LV contractile reserve but in some pts is related to the site of ischemia, namely the RCA.

## EXERCISE TEST RESULTS PREDICT SILENT ISCHEMIA ON AMBULATORY MONITORING

Alan Hinderliter, M.D., Margaret Herbst, M.S.N., Edith Bragdon, M.A., Martha Ballenger, David Sheps, M.D., F.A.C.C.
University of North Carolina, Chapel Hill, N.C.

The relationships between exercise testing results and occurrence of silent ischemia (SI) during ambulatory monitoring were evaluated in 21 pts with coronary disease and ST depression (ST↓) during exercise. Symptom-limited exercise was performed on a supine bicycle ergometer, with gated blood pool scans at rest and during peak exercise. Each pt was monitored for a mean of 41 ± 8 hours during daily activities.

Nine pts had a total of 47 episodes of SI during the ambulatory monitoring period, and 12 pts had no SI. Pts in both groups were similar in their use of anti-anginal medications (4 of 9 with SI, 6 of 12 with no SI), in the frequency with which they reported angina during the exercise test (2 of 9 with SI, 4 of 12 with no SI), and in maximal HR and HRxBP product achieved during exercise. Pts with SI developed ST↓ significantly earlier in exercise (412 ± 160 vs 902 ± 314 sec, p<.01) than those with no SI. There was no significant difference between the 2 groups, however, in change in ejection fraction (ΔEF) with exercise (+5.0 ± 7.7% vs +6.3 ± 9.9%).

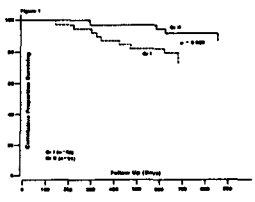
Duration of exercise at onset of ST↓ was an accurate predictor of SI; development of ST↓ in the first 2 stages of exercise was 89% sensitive and 92% specific in identifying pts with ischemia during daily activities. The 8 pts with ST↓ in Stages 1 or 2 accounted for 89% of the episodes and 73% of the total duration of SI for the entire group. In contrast, there was no value for ΔEF which helped distinguish pts with SI from those without SI.

In summary, pts with a high probability of having SI during ambulatory monitoring can be identified by the time at which significant ST↓ occurs during exercise, but not by symptoms or by ΔEF. These results suggest that SI is more closely related to the early onset of ischemia with exercise than to the magnitude of ischemia at peak exercise.

## SILENT ISCHEMIA DURING DAILY LIFE IS AN INDEPENDENT PREDICTOR OF SURVIVAL IN STABLE ANGINA

Prakash Deedwania, M.D., F.A.C.C., Enrique Carbajal, M.D., John Nelson, M.D., Lawrence Linn, VAMC/UCSF School of Medicine, Fresno, CA

Silent ischemia (SI) on ambulatory ECG monitoring (AEM) predicts poor prognosis in pts with MI and unstable angina. However the significance of SI in stable angina (SA) is not established. In this prospective blinded study, we evaluated 118 pts (mean age 63) with proved CAD and SA undergoing 24 hr AEM with validated FM system. All pts continued prescribed antianginal drugs and were followed at 3-4 month intervals. Silent ischemic events (SIEs) were defined as ST + ≥ 1 mm, 80 msec from J, lasting ≥ 60 sec, and without symptoms. Of the 118 pts, 107 had analyzable AEM data and were divided into two groups (gr): gr-1, 46 pts with SI, and gr-II, 61 pts without SI. During a mean follow-up period of 23±8 mos, Kaplan-Meier actuarial methods for the time-dependent probability of survival revealed significantly worse prognosis for gr I (p=0.023). The stepwise Cox hazard analysis of 11 variables including age, risk factors, prior MI, exercise parameters, ECG and angiographic findings revealed the presence of SI as an independent and most powerful predictor of mortality (p=0.0025) in these patients.
**Conclusion:** The presence of silent ischemia during daily life is a marker of unfavorable outcome and poor survival in patients with stable angina.



## RELATION BETWEEN ISCHEMIA DURING EXERCISE AND AMBULATORY ISCHEMIC ACTIVITY IN CORONARY ARTERY DISEASE

Arshed A. Quyyumi, M.D., Julio A. Panza, M.D., Timothy S. Callahan, Kevin E. McCarthy, M.D., Robert O. Bonow, M.D., F.A.C.C., Stephen E. Epstein, M.D., F.A.C.C, NHLBI, Bethesda, MD

Exercise (ex) induced LV dysfunction and ST depression are important indices of prognosis in pts with coronary disease (CAD). Ambulatory ischemic episodes (AIE) have been proposed as additional indices of prognosis: however, their relation to ex induced ischemia is unknown. We performed ex radionuclide angiography, treadmill ex, and 48 hr ambulatory ST monitoring free of antianginal drugs in 80 pts with CAD. AIE prevalence and duration (min/48 hrs) was evaluated in 1) pts with abnormal ejection fraction (EF) response to ex (≤2% increase) (EF↓) and normal ex EF response (≥3% increase) (EF↑) and 2) pts with and without ST↓ during treadmill ex.

| | | ExEF↑ | ExEF↓ | ExST↓ | NoExST↓ |
|---|---|---|---|---|---|
| All pts | Number of pts | 57 | 23 | 56 | 24 |
| | AIE prevalence | 67%* | 39% | 80%** | 13% |
| | AIE duration (m) | 111±20* | 45±23 | 129±20** | 2.5±1 |
| 3 VD | Number of pts | 21 | 5 | 10 | 16 |
| (n=26) | AIE prevalence | 62% | 20% | 88%** | 0% |
| | AIE duration (m) | 109±32 | 13±12 | 148±38 | 0 |

*=p<.05 **=p<.001 mean ±SE VD = vessel disease

Although the prevalence and duration of AIE were greater in pts with ↓EF with ex, there was no relation between the magnitude of EF change and the duration of AIE. In contrast, AIE duration correlated with duration of treadmill ex to ST↓ (r=-.4, p<.004). AIE were absent in 38% of pts with 3 VD and ex LV dysfunction. Thus, AIE prevalence does not identify many pts with severe disease and ex LV dysfunction; therefore, silent ischemia detection may not provide as precise prognostic information as that obtained from coronary arteriography and ex tests.

## THERAPY OF PAINFUL AND PAINLESS MYOCARDIAL ISCHEMIA IN 348 PATIENTS: RESULTS OF THE NIFEDIPINE TOTAL ISCHEMIA AWARENESS PROGRAM.

Peter F. Cohn, M.D., F.A.C.C., George W. Vetrovec, M.D., F.A.C.C., Richard Nesto, M.D., F.A.C.C. and Total Ischemia Awareness Program Investigators, SUNY Health Sciences Center, Stony Brook, New York.

The Total Ischemia Awareness Program (TIAP), a national multicenter study, assessed clinical and Holter monitoring (HM) data in 2 groups of pts, a study group (312 pts) and a control group (36 pts). All pts completed 96 hrs of HM. Of the 312 pts in the study group, 136 (44%) had at least 1 episode of myocardial ischemia. The total number of episodes was 372; 84% were painless. During Phase 1 (baseline therapy) most pts were either on long acting nitrates (LAN) or on beta blockers (BB) with or without LAN. In Phase 2, nifedipine (N) was added to study group patients only. Number of episodes of ST segment depression per pt per 48 hrs HM in Phase 1 was 2.7± 0.3 (mean±SEM) and fell to 2.1±0.2 during Phase 2 (p<.005); total duration per pt fell from 49.0 min±6 to 40.7±5 (p<.01). Effect on number of ischemic episodes of adding N to LAN and/or BB as follows:

| | LAN | | BB(+LAN) | |
|---|---|---|---|---|
| Phase 1 | 4.0±1.3 | p<.01 | 2.6±0.3 | p<.05 |
| Phase 2 | 2.2±1.2 | | 2.3±0.3 | |

Treatment with N was most beneficial in the 38 pts with >60min of ischemia per 48 hrs: mean duration fell from 127±8min to 68±15 (p<.001) and the mean number of episodes fell from 5.8±0.7 to 3.8±0.5 (p<.001). In contrast to the study group, the control group showed no differences between Phase 1 and 2. Thus, addition of N to baseline therapy was very effective in reducing total ischemic activity, especially in pts with more severe ischemia.

PAINLESS MYOCARDIAL ISCHEMIA IN DIABETIC PATIENTS WITH CORONARY ARTERY DISEASE

Hideo Mitamura M.D., Susumu Nakagawa M.D., Hisashi Katayama M.D., Susumu Ui M.D., Mitsuru Kimura M.D., Saiseikai Central Hospital, Tokyo, Japan.

Painless myocardial ischemia (PMI) has been said to develop often in diabetic Pts (DP) whereas its exact incidence and characteristics have not been systematically evaluated. We therefore studied occurrence of chest pain with regard to electrocardiographic ST segment depression during exercise in 44 consecutive Pts with angiographically proven coronary artery disease and a positive treadmill test. There were 26 DP and 18 nondiabetic Pts (NP). The two groups were comparable in age, sex, history of MI, indices of LV function, number of coronary vessels diseased. Chest pain was absent during a positive exercise test in 18/26 (69%) DP vs 3/18 (17%) NP ($p<0.005$) despite both showing similar exercise time, peak heart rate, peak blood pressure, and the degree of maximum ST depression. At 1mm ST depression, 25/26 (96%) DP and 10/18 (56%) NP were pain-free ($p<0.005$). At 2.5mm, 11/12 (92%) DP remained pain-free as compared to 2/8 (25%) NP ($p<0.01$). When the incidence of treadmill-induced chest pain was compared with that of clinically occurring chest pain, NP exhibited 12/18 (67%) concordance whereas DP showed discordance ($p<0.005$) such that 13/18 (72%) DP with PMI during a treadmill test had a history of angina. Although statistically not significant, DP with PMI tended to have a higher fasting plasma glucose level (170 vs 133 mg/dl), a higher HbAlc (9.3 vs 7.7%), and a longer diabetic history (12 vs 9 years) than DP with painful ischemia. Notably, DP with PMI had either neuropathy, nephropathy, or retinopathy more frequently (15/18 or 83%) than DP with painful ischemia (2/8 or 25%, $p<0.025$). We conclude that in Pts with diabetes, particularly in the advanced stage, PMI during exercise is common and can be seen even at severe ischemia or in Pts with a history of clinical angina.

INTRAVASCULAR REAL-TIME, HIGH RESOLUTION TWO-DIMENSIONAL ECHOCARDIOGRAPHY.

Jos R. Roelandt, Patrick W. Serruys, Nicolaas Bom, Elma J. Gussenhoven, Frans C. van Egmond, Charles T. Lancee, Harm ten Hoff, Willem J. van Alphen. Thoraxcenter, Rotterdam and Interuniversity Cardiology Institute of the Netherlands.

Direct assessment of atherosclerotic involvement of the arterial wall is a major research goal. To assess lumen morphology and the details of arterial wall disease under the endothelial surface we developed a 2 mm catheter with a 40MHz single element transducer mounted at its tip providing a 360-degree display of the vessel interrogated at 25 images/second. In vitro studies of normal and diseased arteries accurately demonstrated lumen geometry and wall tissue characteristics including atheroma. These images show extremely good correlation with the histopathologic findings. Subsequent in vivo studies both in pigs and humans showed excellent clinico-pathologic correlation of arterial atherosclerotic disease and wall dynamics. This imaging system has great potential for the accurate localisation, characterisation and quantification of atherosclerotic disease as well as the evaluation of the acute and long-term effects of pharmacological and catheter based intravascular interventions.

## Monday, March 20, 1989
## 10:30AM–12:00NOON, California Room D
## Anaheim Convention Center
## Catheter Atherosclerotic

ULTRASONIC ANGIOPLASTY USING A NEW FLEXIBLE WIRE SYSTEM.

Israel Freeman, M.D., Jeffrey M. Isner, M.D., F.A.C.C., Dov Gal, D.V.M., Gary H. Friedman, M.D., Howard Alliger, B.A., Andrew M. Grunwald, M.D., F.A.C.C., Long Island Jewish Medical Center, New Hyde Park, NY and St. Elizabeth's Hospital, Tufts University School of Medicine, Boston, MA

We investigated the use of transarterial ultrasonic angioplasty to recanalize totally occluded atherosclerotic arteries in vivo. Vascular obstructions were created experimentally in Yucatan microswine fed an atherogenic diet for 2 weeks before and 8-10 weeks following balloon endothelial denudation of the iliac arteries. A total of 5 arteries in these 4 animals were then selected for transarterial recanalization, performed via the surgically exposed internal carotid artery. An angiographic catheter was used to deliver a flexible 0.2-0.3 in.-diameter ultrasonic wire (Sonic Needle Corpl, Farmingdale, NY) to the site of the iliac occlusion. Sonication was performed at a frequency of 22 KHz, using 20-sec exposures for a total of k2-6 min. In one artery, subtotally (99%) occluded for 2.7 cm in length, the wire could not be advanced without ultrasound .With sonication, the entire length of the total occlusion was recanalized producing a residual stenosis of only 20%. In the remaining 4 arteries, ultrasonic angioplasty was used to partially recanalize total occlusions of 0.5-2.3 cm in length, producing ≥30% luminal patency. None of the arteries were perforated during the sonication process, although 3 of 5 arteries were perforated while maneuvering the guiding catheter or the wire-catheter delivery system. These preliminary findings indicate the feasibility of employing transarterial ultrasound angioplasty to recanalize atherosclerotic vascular occlusions.

INTRAVASCULAR ULTRASOUND IMAGING OF ATHEROSCLEROTIC CORONARY ARTERIES: AN IN VITRO VALIDATION STUDY

Antonio L. Bartorelli M.D., Benjamin N. Potkin M.D., Yaron Almagor M.D., James C. Gessert B.S., William C. Roberts M.D., F.A.C.C., Martin B. Leon M.D., F.A.C.C. NHLBI, Bethesda, MD

Safe and effective clinical application of new interventional therapies may require more precise imaging of atherosclerotic coronary arteries (CA). To determine the reliability of catheter-based intravascular ultrasound (US) as an imaging modality, a miniature prototype US system (1 mm transducer, 25 MHz frequency, 0.1 mm axial resolution, and 0.4 mm lateral resolution) was used to acquire real-time 2D vessel wall images in 32 necropsy CA segments (54 sites) with moderate or severe atherosclerosis from 13 patients. Comparable 360° US images and transverse histology (H) sections were analyzed using a computer video planimetry system. US and H measurements correlated significantly (all $p<.0001$) for total cross-sectional area ($r=.94$), lumen area ($r=.85$), % cross-sectional narrowing ($r=.84$), and linear plaque thickness dimensions measured at 0°, 90°, 180°, and 270° ($r=.92$). Moreover, predominant H plaque composition was accurately predicted by US images in 98% of examined sites. CA anatomic features easily discernable were the media-adventitia interface, the plaque-lumen interface, and plaque composition subtypes including 1) calcified lesions-bright echoes casting an acoustic shadow, 2) fibrous lesions-dense, homogeneous echoes, and 3) lipid-filled lesions-zones of relative echo lucency. From these data, we conclude that intravascular US imaging of atherosclerotic CA 1) precisely defines cross-sectional and linear vessel dimensions and 2) accurately determines plaque distribution and composition. Thus, catheter-based intravascular US of atherosclerotic CA has great potential both as a diagnostic modality and for real-time guidance of interventional procedures.

**INTRALUMINAL TWO-DIMENSIONAL ULTRASOUND ANGIOSCOPIC QUANTITATION OF ARTERIAL STENOSIS: COMPARISON WITH EXTERNAL HIGH-FREQUENCY ULTRASOUND IMAGING AND ANATOMY**

Natesa Pandian MD, FACC, Andreas Kreis MD, Thomas O'Donnell MD, Alex Sacharoff PhD, Edward Boleza PhD, Richard Caro PhD. Tufts-New England Medical Center, Boston, Massachusetts.

External high frequency ultrasound imaging (ExHFU) has been shown to be capable of defining peripheral and coronary arterial stenosis (St). Recently a new, catheter-based, intraluminal ultrasound angioscopic imaging method has been developed. We evaluated, in this study, the accuracy of ultrasound angioscopy (UA) in quantifying in arterial St. The prototype device (Summit Technology) we used has a 20 MHz transducer rotating at 1800 rpm within the tip of a 6 Fr catheter. Arterial segments (n=20) of various size (5-59 $mm^2$ lumen area by anatomy) were imaged in control and after experimental St both by ExHFU and by UA. Lumen areas were measured from calibrated ultrasound images in control and after St, and % cross-sectional area St calculated. These data were compared to % area St derived from calibrated anatomic photographs of the arteries taken in control and after St. Both UA and ExHFU yielded high-resolution, two-dimensional, circumferential images of the arteries. Alterations in vessel area and shape were apparent after creation of St. The correlations for quantifying arterial % area ST were:

ExHFU (y) vs Anatomy (x) y=0.69x+22 r=0.82 p<0.001
UA (y) vs Anatomy (x): y=0.65x+21 r=0.92 p<0.001
UA (y) vs ExHFU (x) y=0.72x+14 r=0.86 p<0.001

Thus, intraluminal UA provides a reliable new imaging approach to quantify arterial stenosis. Catheter-based ultrasound angioscopy, with its ability ot image arteries inaccessible to ExHFU, has a significant potential in guiding and gauging interventional therapy for coronary and other arterial stenosis.

**DETECTION OF INTRAVASCULAR THROMBUS BY HIGH FREQUENCY INTRALUMINAL ULTRASOUND ANGIOSCOPY: IN VITRO AND IN VIVO STUDIES**

Natesa Pandian MD, FACC, Andreas Kreis MD, Barbara Brockway BS, Alex Sacharoff PhD, Edward Boleza PhD, Richard Caro PhD. New England Medical Center Hospitals, Tufts University School of Medicine, Boston, Massachusetts.

Detection of intravascular thrombus currently requires angiography. To assess whether ultrasound angioscopy, a new technique which can provide intraluminal two-dimensional ultrasound images, would be of value in the detection of intravascular thrombi, we used a catheter-based 20 MHz ultrasound probe (Summit Technology) *in vitro* in 10 arterial segments with experimental thrombi of various size. Ultrasound angioscopy provided circumferential, high resolution images of all vessls and detected the intraluminal thrombi in all. In the ultrasound angioscopic images, thrombi appeared as granular echo-dense masses with various greylevel shades. We measured the maximum thrombus width and area from calibrated ultrasound angioscopic images and compared them to similar measurements made from calibrated anatomic photographs of the thrombus in the vessel. The correlations between anatomic (x) and ultrasound angioscopic measurements (y) were excellent both in assessing the luminal area occupied by the thrombus (y=0.9x+0.53, r=0.98, p<0.001) and for maximum thrombus width (y=0.69x+0.95, r=0.87, p<0.01). When intraluminal thrombi was produced in carotid arteries *in vivo* in 11 dogs and the vessels imaged, ultrasound angioscopy displayed real-time, two-dimensional images of the blood vesssls, detected the thrombi in all, and also allowed visualization of the dynamics and evolution of thrombus formation. This new technique thus offers a valuable approach in the evaluation and study of vascular diseases with associated intraluminal thrombosis.

EVALUATION OF MIXED ATHEROSCLEROTIC PLAQUES BY QUANTITATIVE ULTRASONIC METHODS.

P.A.N. Chandraratna, M.D., F.A.C.C., Joie P. Jones, Ph.D., Shahbudin H. Rahimtoola, M.D., F.A.C.C., Steve Kaiser, LAC-USC Medical Center, Los Angeles, CA.

We have previously shown that quantitative ultrasonic methods (QUS) can differentiate between fatty (FAP), fibrous (FIP) and calcific plaques (CP). To assess the role of QUS in evaluating mixed atherosclerotic plaques, 2000 freshly excised specimens of human abdominal aorta were suspended in a water tank and scanned using a rectilinear ultrasound scanner. A data acquisition system based on the TRW 8-bit 20 mHz A/D board and IBM AT computer was used. A matrix of A-lines was taken over a specified region of interest and the RF waveforms associated with each A-line recorded. The acoustic impedance (Ac Imp, CGS Rayl $10^{-5}$) and attenuation coefficient (At Coef, db/cm/mHz)of 2000 areas of normal aorta (NL), 550 FIP, 480 FAP, 610 CP, 320 partly fibrous and partly fatty, 230 partly fatty and partly CP and 124 partly fibrous and partly CP were determined.

| | NL | FIP | FAP | CP |
|---|---|---|---|---|
| Ac Imp | 1.5±0.04 | 1.6±0.02 | 1.7±0.03 | 1.8±0.02 |
| At Coef | 0.6±0.05 | 0.7±0.06 | 1.8±0.2 | 5.3±0.4 |

The Ac Imp and At Coef of partly fibrous and partly fatty plaques were between FIP and FAP, in proportion to the amount of fibrous and fatty tissue determined histologically. The Ac Imp and At Coef of partly fatty and partly CP, were between FAP and CP, in proportion to the amount of fat and calcium. In partly fibrous and partly CP the Ac Imp was between fibrous and CP (i.e. in the range of FAP); however, the At Coef was much higher than FAP. CONCLUSION: QUS is useful in evaluating mixed plaques, and the AC Imp and At Coef values depend on their histological compositon.

## Monday, March 20, 1989
## 10:30AM–12:00NOON, Garden Grove Room
## Anaheim Convention Center
## Non-Q Wave Myocardial Infarction

THE PROGNOSTIC SIGNIFICANCE OF FIRST MYOCARDIAL INFARCTION TYPE (Q-WAVE VS NON-Q-WAVE)

Jesaia Benhorin M.D., Arthur J. Moss M.D., F.A.C.C., David Oakes Ph.D., Frank Marcus M.D., F.A.C.C., Elizabeth Hahn M.A., Stephen Algeo M.D., and the Multicenter Diltiazem Post-infarction Research Group, University of Rochester, Rochester, NY.

The prognostic significance of first myocardial infarction (MI) type (Q-wave [QMI] vs non Q-wave [NQMI] MI) was determined from our multicenter data-base of 777 placebo treated pts, followed for 1-4 years after their first acute MI. Two hundred twenty four pts had NQMI and 553 pts had QMI. Pts with NQMI were more likely to be females (p=0.05), to be treated with beta blockers at randomization (p<0.001), and to have significantly higher post-MI LVEF than pts with QMI (53±12% vs 46±13%, respectively, p=0.0001). Cardiac mortality and non-fatal reinfarction rates were similar in both groups at one year (4% vs 5.2%, and 7.6% vs 5%, respectively, p=ns), and at total follow-up (6.3% vs 7.6%, and 10.3% vs 7.8%, respectively, p=ns). Cox survivorship analyses, using stepwise selection from 8 pertinent baseline clinical variables other than MI type revealed that frequent VPCs, lack of beta blocker therapy, advanced NYHA class, and pulmonary congestion were those that carried significant and independent risk for subsequent cardiac mortality (hazard ratio (HR): 2.5, 2.3, 2.2, 1.6, respectively). Adding MI type to this optimal model did not demonstrate that it carries an independent risk for subsequent cardiac mortality (HR 1.3, p=ns).

Conclusion: MI type (QMI vs NQMI) does not significantly change the risk of post-MI cardiac mortality after adjustment for pertinent baseline clinical variables in pts with first MI.

FAVORABLE EFFECT OF DILTIAZEM ON LATE MORTALITY AND REINFARCTION AFTER NON-Q-WAVE MYOCARDIAL INFARCTION: MULTICENTER DILTIAZEM POST-INFARCTION TRIAL (MDPIT).

William E. Boden MD, FACC; Robert E. Kleiger MD, FACC; J. Philip Miller, Henry Greenberg MD, FACC; Ronald J. Krone, MD, FACC; W. David Hager MD, FACC; Jonathan Abrams MD, FACC; Arthur J. Moss MD, FACC; MDPIT Research Group, Harper Hospital, Wayne State University, Detroit, MI.

One of the principal prespecified findings from MDPIT, a large prospective study of prophylactic diltiazem (DTZ) 240 mg/day vs. placebo (PLC) in post-MI pts followed for up to 4 1/2 years (mean = 25 mo; range = 12-52 mo), was a significant 34% reduction in cumulative first recurrent cardiac events (cardiac death [CD] or non-fatal reinfarction [MI]) in 634 non-Q wave (NQ) MI pts who received DTZ; Cox hazard ratio =*0.66 (0.44-0.98). Because a prior short-term multicenter trial of DTZ in NQMI showed a cumulative 51% reduction in early (≤14 day) reinfarction, but not mortality, we sought to determine within the MDPIT NQMI cohort whether: a) late MI and CD were concordantly reduced by DTZ during followup, and; b) there was evidence that the significant post-MI treatment effect attenuated over time. Within the NQMI cohort, there was a total of 46 cardiac deaths (CD) and 62 non-fatal MI during the 52 mo followup, of which 67 occurred on PLC and 41 on DTZ. Comparative cumulative cardiac events (CD and MI) for PLC vs DTZ subgroups, using the Cox proportional hazards model, revealed:

| | 6moCD;MI | 1yrCD;MI | 2yrCD;MI | ≥ 3yrCD;MI | TOTAL |
|---|---|---|---|---|---|
| PLC(n=338) | 13;23 | 21;29 | 24;34 | 30;37 | 67 |
| DTZ(n=296) | 8; 6 | 12;13 | 13;20 | 16;25 | *41 |

CONCLUSION: 1) Diltiazem was associated with a parallel reduction in both mortality and reinfarction after NQMI; 2) This significant overall beneficial effect was evident early in the post-infarction period and was sustained throughout the duration of followup.

ROLE OF ELECTROCARDIOGRAPHIC LOCATION ON DILTIAZEM TREATMENT EFFECT IN NON-Q WAVE MYOCARDIAL INFARCTION: MULTICENTER DILTIAZEM POST-INFARCTION TRIAL (MDPIT).

William E. Boden MD, FACC; Henry Greenberg MD, FACC; Robert E. Kleiger MD, FACC; John Gillespie MD, FACC; Edward M. Dwyer, Jr. MD, FACC; Ronald J. Krone MD, FACC; MDPIT Research Group; Harper Hospital, Detroit, MI.

A prespecified subgroup analysis of MDPIT showed that diltiazem (DTZ) therapy reduced first recurrent cardiac events (RCE) (cardiac death or non fatal reinfarction), the primary MDPIT endpoint, in 634 non-Q wave (NQ) MI pts during a 25 ± 8 mo followup. To assess whether DTZ benefit was related to electrocardiographic (ECG) site (anterior [ANT], inferior [INF], combined [ANT+INF+LAT]) or type of (first [1st] acute vs. prior [P] MI + acute) NQMI, we compared RCE at 1 yr of followup, using the Cox model, among various subgroups of NQMI patients randomly assigned to DTZ or placebo (PLC). Event rates (1 yr) and p values ($\chi^2$:2-tail, Fisher Exact Test) based on type of NQMI, of which 511/634 (81%) were 1st NQMI, revealed:

| | RCE/All NQMI | | RCE/1st NQMI | | RCE/PMI+NQMI | |
|---|---|---|---|---|---|---|
| PLC | 51/338 (15%) | P=.055 | 37/278 (13%) | P=.066 | 14/60 (23%) | N.S. |
| DTZ | 29/296 (10%) | | 19/233 (8%) | | 10/63 (16%) | |

For site of MI, 409/634 (65%) NQMI were localizable (LOC) by ECG (ANT = 33%; INF = 41%; combined = 26%), while 225/634 (35%) NQMI were non-localizable (NL) by ECG ST/T waves. Among specific ECG subgroups of LOC-NQMI, there were no treatment differences by $\chi^2$, but overall:

| | RCE/LOC-NQMI | | RCE/NL-NQMI | | RCE/NL-1stNQMI | |
|---|---|---|---|---|---|---|
| PLC | 32/219 (15%) | N.S. | 22/119 (18%) | P=.009 | 17/92 (18%) | P=.010 |
| DTZ | 22/190 (12%) | | 7/106 (7%) | | 4/76 (5%) | |

CONCLUSION: 1) Among all NQMI, DTZ was more beneficial in 1st NQMI pts; 2) the overall prevalence of non-localizable NQMI was 35%; 3) in this subgroup, DTZ resulted in a significant 3-fold decrease in 1 yr RCE, irrespective of prior ECG evidence for MI.

CORONARY ANATOMY PRECEDING NON-Q WAVE MYOCARDIAL INFARCTION.

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A recent report suggests that the pre-existing stenosis in the infarct related artery is frequently more severe in patients with non-Q wave myocardial infarction (MI) than with Q wave MI. To study this possibility, we evaluated 58 patients (21 with non-Q wave MI, 37 with Q wave MI) who had undergone coronary angiography 819±813 days (mean±SD) prior to suffering MI. Coronary angiography 12±10 days after MI was used to identify the infarct related vessel. The most severe lesion in the infarct related vessel at the initial angiogram (prior to infarct) was measured using a computerized quantitative coronary angiographic system. The infarct related artery frequently did not contain a high grade stenosis at the first angiogram. The most severe diameter stenosis of the infarct-related artery prior to MI was 44±19% in the non-Q MI and 47±20% in the Q wave MI (p=NS). Furthermore, only 7 of 21 (33%) patients with non-Q wave and 15 of 58 (29%) patients with Q wave MI initially had greater than 50% stenosis in the infarct related vessel. The artery initially containing the most severe stenosis was subsequently responsible for the MI in only 9 of 21 patients (43%) with non-Q wave and 13 of 37 patients (35%) with Q wave MIs (p=NS). No relation existed between the initial severity of the lesion in the infarct vessel and the time to develop MI in either group ($r^2$<0.01, p=NS).

Conclusion: There is no difference in the coronary stenosis in the infarct related artery that precedes Q and non-Q wave MI. Both frequently develop from nonobstructive (≤50% stenosis) coronary artery lesions. It is difficult to predict the time or location of a subsequent Q or non-Q MI from analysis of the first coronary angiogram.

LACK OF ASSOCIATION BETWEEN EARLY ADMINISTRATION OF THROMBOLYTIC THERAPY AND THE DEVELOPMENT OF NON-Q WAVE MYOCARDIAL INFARCTION.

Michael McKinney MD, David C Booth MD FACC, John Gurley MD, Cindy Grines MD, Marcelo Branco MD, Anthony DeMaria MD FACC. The University of Kentucky, Lexington, Ky.

Recent reports have suggested an association between early reperfusion and development of non-Q wave myocardial infarction (MI). To test this hypothesis, we evaluated data from 108 patients enrolled in three thrombolysis protocols employing tissue plasminogen activator. Entry criteria included ST segment elevation of ≥1 mm in two or more contiguous limb leads or ≥ 2 mm in precordial leads on ECG, ≥ 30 minutes chest pain unrelieved by nitroglycerin, and no contraindications to lytic therapy. Thirty patients (28%) were excluded due to failure to achieve reperfusion (TIMI Flow 0-1) at the 90-minute catheterization, 5 of whom (16%) had non-Q wave MI. Twenty two of 78 recanalized patients (39%) sustained non Q-wave MI, while 56 (61%) evolved Q-wave MI. Patients with non-Q wave MI were significantly more likely to have a patent infarct vessel than patients with Q-wave MI ($p < .0001$ by Chi square). Time from pain onset to lytic drug administration did not differ between non-Q and Q wave MI, 202±78 min vs 201 ± 64 min. Peak creatine kinase was significantly less for non-Q compared to Q wave MI, 1936 IU ± 2903 vs 3010 ± 2268, $p < .05$, as was maximal ST elevation on the presenting electrocardiogram, 2.4 ± 1.3 mm vs 4.3 ± 2.6, $p < .0016$. Conclusions: Compared to Q wave MI, non-Q wave MI is associated with less ST elevation and myocardial necrosis. A patent vessel is more likely to be associated with non-Q wave MI. Evolution of non-Q wave MI is largely independent of time of institution of thrombolytic therapy, suggesting that a degree of spontaneous reperfusion may be necessary to preclude evolution to Q wave MI.

RECOVERY OF REGIONAL MYOCARDIAL FUNCTION AFTER SUCCESSFUL CORONARY ANGIOPLASTY EARLY AFTER A NON-Q-WAVE MYOCARDIAL INFARCTION

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Repeated ischemic attacks early after a non-Q-wave myocardial infarction (MI) may lead to prolonged regional myocardial dysfunction. The aim of this study was to determine whether in patients with angina early after a non-Q-wave MI, the regional myocardial dysfunction due to stunning of the myocardium might be improved by coronary angioplasty (PTCA). The study population consisted of 36 patients undergoing successful PTCA within 30 days after a non-Q-Wave MI, in whom sequential left ventricular angiography of adequate quality was performed before the initial procedure and at a follow-up at 6 months.
Global and regional left ventricular function was studied from the 30° right anterior oblique projection using an automated hardwired endocardial contour detector. Regional contribution to the global ejection fraction (CREF) was determined along a system of 20 coordinates on the pattern of actual endocardial wall motion. The systolic segmental volume change was considered as a parameter of regional pump function.

| | Before PTCA | at 6-month F/U |
|---|---|---|
| global EF (%) | 60 ± 9 | 67 ± 6* |
| Sum of abnormal CREF (%) | 12.6 ± 4.8 | 20.1 ± 7.7* |
| Sum of normal CREF (%) | 46.4 ± 11.9 | 44.5 ± 11.9* |

* $p < 0.005$

Conclusion: The significant increase in global ejection fraction was primarily due to a significant improvement in the regional myocardial function of the infarct zone. The results suggest that regional myocardial dysfunction, due to stunning of the myocardium in patients with angina early after a non-Q-wave MI, may be improved after successful PTCA.

**A New Approach to In Vivo Measurement of Conorary Blood Flow Utilizing High-Speed Coronary Angiography:**

Steven E. Nissen MD FACC, John C. Gurley MD, David Haynie MD Kevin Sublett MD, Joyce Evans, and Anthony N. DeMaria MD FACC
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Although previous efforts have attempted to measure coronary blood flow (CBF) from cineangiographic (cine) transit-time, this approach has been hindered by limitations in framing rate and inability to precisely calculate distance. Therefore, we devised a technique which employed high-speed cine and a calibrated coronary guidewire to measure distance in order to calculate CBF and coronary flow reserve (CFR) from transit-time. Anesthesized open-chest dogs were instrumented with an ultrasonic flow probe and a pneumatic occluder on the Circumflex (LCx). A 0.018 inch guide wire with radiopaque markings at 1 cm intervals was placed in the LCx through a 5 Fr catheter. Boluses of 1-3 ml contrast were injected and cine performed at 60 or 120 FPS under basal conditions and after induction of reactive hyperemia by brief coronary occlusion. Twenty-five injections were performed at varying levels of CBF. Transit-time from a proximal to distal marker was determined by counting the number of cine frames during passage of the contrast wavefront. The distance between markers was divided by the transit-time to yield flow velocity in cms/sec. Cross-sectional area (CSA) was calculated from the coronary diameter. CBF was computed as CSA x flow velocity. CFR was calculated as the ratio of flow during hyperemia divided by basal flow. LCx flow by ultrasonic probe varied from 13.4 to 100.6 ml/min. Flow velocity from 120 FPS cine ranged from 7.4 to 22.2 cms/sec and calculated CBF varied from 21.8 to 84.2 ml/min. There was a close correlation for measures of CBF by cine and ultrasonic probe, r=0.85. CFR by ultrasonic probe ranged from 1.7 to 7.5:1 and was somewhat lower by cine, 1.2 to 3.86. The correlation for CFR by flow probe and high-speed cine was close, r=0.82. Framing rates <120 FPS lacked sufficient temporal resolution to accurately measure CBF, r=0.47. Thus, these data demonstrate that high-speed cine combined with a calibrated guidewire can accurately measure CBF and CFR from coronary transit-time in an animal model. Framing rates below 120 FPS were inadequte to perform these calculations.

## Monday, March 20, 1989
## 10:30AM–12:00NOON, California Room C
## Anaheim Convention Center
## Digital Cardiovascular Imaging and Ultrafast CT

EFFECT OF X-RAY DOSE ON ACCURACY AND PRECISION OF QUANTITATIVE DIGITAL CORONARY ANGIOGRAPHY

Kenneth G. Morris, MD, Jack T. Cusma, Ph.D., Thomas M. Bashore, MD, Duke and VA Medical Centers, Durham, NC

The x-ray dose required for optimum quantitative digital coronary angiography (QDCA) has significant importance to digital imaging equipment design and selection. To assess the effect of x-ray dose on the accuracy and precision of QDCA, 12 coronary stenoses were created in 7 dogs using plastic clips of varying diameters. ECG gated QDCA were acquired in a $512^2$ x 10 bit matrix and a 5" image intensifier mode. Each QDCA was acquired at x-ray doses of 25, 50, 250 and 750 μR. The hearts were fixed in situ by perfusion with iced 10% formalin and the coronary arteries were then casted by perfusion with RTV silicone gel at 100 mm Hg. Each stenosis was then analyzed by projection microscopy of cast cross-sections from stenotic and reference segments. Regression coefficients (r) and standard errors (SEE) for reference and stenosis diameters (RefD and StD) and % area stenosis for both geometric (%GEO) and videodensitometric (%VID) techniques at each of the x-ray doses are summarized below, r (SEE).

| | 750 μR | 250 μR | 50 μR | 25 μR |
|---|---|---|---|---|
| RefD | .84(.17) | .85(.17) | .88(.15) | .95(.10) |
| StD | .75(.23) | .75(.23) | .79(.21) | .82(.20) |
| %GEO | .77(6.2) | .66(12.6) | .88(8.0) | .86(8.6) |
| %VID | .75(11.0) | .73(11.5) | .76(10.9) | .80(10.1) |

Precision was assessed by comparison of regression analysis of paired data from the 2 lower doses with those of the 2 higher doses (r=.93, SEE 5.4 and r=.92, SEE 4.7 respectively). Despite obvious differences in subtracted image quality, the accuracy and precision of QDCA with higher x-ray doses was not superior to that with standard cine doses. This suggests that a 10 bit pixel depth is not needed in the design of equipment for QDCA. Adequate QDCA can be obtained at a lower x-ray dose.

EFFECT OF SUBCRITICAL STENOSIS ON CORONARY AND MYOCARDIAL FLOW RESERVE IN TERRITORY SUPPLIED BY OTHER NON-STENOTIC ARTERIES

Helmut Schühlen M.D., Neal Eigler M.D., J Martin Pfaff Ph.D., James Whiting Ph.D. Cedars-Sinai Medical Center, Los Angeles, California

Coronary artery flow reserve (CFR) and regional myocardial flow reserve (MFR) may be different if stenosis enlarges the territory supplied by non-stenotic arteries. An index of MFR may be the contrast media mean transit time (distribution volume/flow) assuming that the resting volume inversely reflects the vasodilatory capacity of the microcirculation. MFR was calculated by digital angiographic impulse response analysis of 73 left coronary injections in 11 open-chest dogs with flowmeters on the left anterior descending and circumflex arteries. Under resting conditions in the absence of contralateral stenosis, regional MFR correlated with CFR (MFR = 2.2 CFR + 2.4; r=0.75). Although subcritical contralateral stenosis (contralateral CFR = 1.8±0.5) did not affect ipsilateral resting flow (24±4 to 24±3 ml/min; p=NS) or CFR (3.3±0.6 to 3.5±0.7; p=NS), MFR was reduced (11.3±2.3 to 9.4±3.0 $min^{-1}$; $p<0.02$). Conclusions: (1) Myocardial perfusion reserve reflects coronary flow reserve in the absence of contralateral stenosis. (2) Coronary flow reserve is not altered by contralateral stenosis. (3) Myocardial perfusion reserve is reduced by contralateral stenosis because the distribution volume of the ipsilateral artery increases.

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**DIGITAL FLASHING TOMOSYNTHESIS (DFTS) - AN ALTERNATIVE TO CINE TECHNIQUE IN CORONARY ANGIOGRAPHY**

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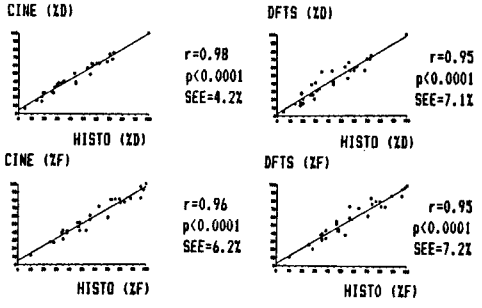
DFTS is a digital radiographic technique for coronary angiography. Four simultaneously flashed X-ray tubes generate images for 3-D reconstruction. DFTS images can be used directly for visual interpretation and computerized analysis. Coronary arteries of 24 human hearts were filled at a pressure of 100 mm Hg with a fixative consisting of contrast medium and methylmetacrylate. Postmortem angiograms were examined with CINE technique and with DFTS. 40 arterial segments were prepared by a sawing and grinding technique. The angiographic degree of stenosis by lumen diameter (%D) and lumen area (%F) methods was determined using the histologic degree of stenosis as a reference (HISTO):




Conclusion: DFTS technique seems to be a good alternative to standard CINE technique for the coronary angiography.

NONINVASIVE LOCALIZATION OF ACCESSORY PATHWAYS

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We attempted to localize accessory pathways (AP's), by obtaining dynamic computerized tomograms (CT's) in 19 pts. with pre-excitation and in 10 normals. Contrast enhanced dynamic CT's were acquired when pts. were minimally (sinus rhythm) and maximally pre-excitated (atrial pacing). CT images were mathematically transformed using a first harmonic Fourier phase analysis technique. Phase images were color encoded allowing objective analysis of ventricular contraction patterns. CT phase images were interpreted blindly by 2 experienced readers. All 19 pts. also had AP's located during electrophysiologic study by endocardial mapping (EM), and AP's were verified in 16/19 at surgery (8) or by successful transvenous ablation (8). AP's were left free wall in 9, left paraseptal in 1, septal in 7, right free wall in 1, and both septal and left fee wall in 1. In all 7 with septal AP's, initial contraction of the septum was followed by near simultaneous contraction of both ventricles and lastly by late rightward septal motion. In 7/9 with left lateral AP's, maximal pre-excitation consistently induced a uniform CT pattern which originated in the lateral LV wall and moved to the septum and finally to right ventricle. Two pts. with left lateral AP's were not correctly diagnosed. One was misdiagnosed a dual pathway (left free wall and septal) while the other had a major wall motion abnormality (due to infarction) in the region of the AP. Discrepant findings also occurred in the left paraseptal AP. AP location correlated with EM, in 16/19 (84%), and could be corroborated at surgery (8) or catheter ablation (8) in 14/16 (88%). Conclusions: We found excellent agreement between CT and EM (or surgery-ablative techniques) for AP localization. This study documents a unique non-invasive method of AP localization. Inaccurate findings occurred in 3 pts. with left sided pathways and 1/3 had an associated with wall motion abnormality. A unique pattern of late septal motion seen only in septal AP's is described.

RIGHT VENTRICULAR MASS CAN BE ACCURATELY ASSESSED BY ULTRAFAST COMPUTED TOMOGRAPHY.

Zina D. Hajduczok, M.D., Robert M. Weiss, M.D. and Melvin L. Marcus, M.D., FACC; Dept. of Med., CV CTR, U of Iowa, Iowa City, Iowa

There is currently no clinical approach to precisely measure RV mass. We postulated that the radiologic mode of ultrafast computed tomography (Cine CT) [3 mm thick slices, 0.7 mm resolution] would allow sufficient resolution to accurately estimate RV mass. Using this radiologic mode we serially imaged the entire RV from apex-to-base gated to end-diastole, and applied Simpson's rule to calculate mass of the RV free wall. Thirteen mongrel dogs (weight 6-30 kg) were studied. The free wall mass of the RV ranged from 12.0 to 47.5 g and averaged 35.4 ± 3.7 g (x̄±SE). The correlation between RV mass estimated by Cine CT and actual RV mass was r=0.85, SEE=5.5g, slope=0.99, intercept=-1.8, accuracy =±6%. Intra- and interobserver variability (r=0.99 and r=0.98 respectively) was excellent. Seven normal young healthy males were also studied. The free wall mass of the RV ranged from 48.3 to 67.4 g and averaged 54.6 ± 2.8 g (x±SE). The LV/RV ratio averaged 3.2 ± 0.2/1. These results are in agreement with human autopsy data in healthy males reporting mean RV mass = 46 g and LV/RV ratio = 3.4/1. Because imaging every 3 mm slice from apex-to-base requires two contrast injections, we determined the accuracy of RV mass measurements if only every fourth 3 mm slice with interpolation was employed. RV mass measurements using every slice or every fourth slice with interpolation were nearly identical (dogs r=0.99, humans r=0.98). Conclusions: High resolution CT imaging of every fourth 3 mm tomogram allows accurate measurements of RV mass using only one contrast injection (40-60 cc), thus permitting the study of progression and regression of RV mass in patients with various diseases.

## Monday, March 20, 1989
## 10:30AM–12:00NOON, Santa Ana Room 1
## Anaheim Convention Center
## Atrial Naturetic Factor in Congestive Heart Failure

ATRIAL NATRIURETIC FACTOR INHIBITION OF RENIN DURING RENAL HYPOPERFUSION: ROLE FOR THE MACULA DENSA.

Patricia G. Cavero, M.D., Lawrence L. Aarhus, Wayne L. Miller, M.D., Margaret M. Redfield, M.D., John C. Burnett, Jr., M.D., Mayo Clinic, Rochester, Minnesota

We have reported that elevated endogenous atrial natriuretic factor (ANF) inhibits increases in plasma renin activity (PRA) in acute congestive heart failure (CHF) despite decreases in renal perfusion pressure (RPP). We tested the hypothesis that the mechanism of ANF inhibition of PRA during decreased RPP is linked to ANF maintenance of sodium delivery from the proximal tubule (PT) to the macula densa. Therefore, RPP was decreased 15% by supra-renal aortic clamping in anesthetized dogs with (n=4) and without (n=4) infusion of ANF (10 ng/kg/min, i.v.) to mimic plasma concentrations in acute CHF. Without ANF, decreased RPP increased PRA from 2.04±0.60 to 4.07±0.69 ngAI/ml/hr (p<.05). PRA activation was associated with a decrease in sodium delivery from the PT as determined by the fractional excretion of lithium ($FE_{Li}$), a marker for PT sodium reabsorption, during the initiation of decreased RPP (36.0±4.1 to 30.9±3.8%, p<.05). In contrast, physiologic increases in plasma ANF (37.8±6.0 to 170.8±36.0 pg/ml, p<.05) prevented activation of PRA (3.24±1.4 to 4.65±1.3 ngAI/ml/hr, NS) and the decrease of sodium delivery to the macula densa by maintaining sodium delivery from the PT ($FE_{Li}$ 40.7±7.2 to 42.6±18.0%, NS). These studies support the hypothesis that physiologic concentrations of ANF may inhibit increases in proximal tubule sodium reabsorption. ANF may, therefore, prevent activation of PRA during reductions in RPP in acute CHF by maintaining sodium delivery to the macula densa.

N-TERMINAL (1-25) ATRIAL NATRIURETIC FACTOR IN HUMANS WITH CONGESTIVE HEART FAILURE: A MARKER FOR ENDOGENOUS SECRETION.

Denise M. Heublein, Don W. Heser, Brooks S. Edwards, M.D., Margaret M. Redfield, M.D., Wayne L. Miller, M.D., Pai Kao, M.D., John C. Burnett, Jr., M.D., Mayo Clinic, Rochester, Minnesota

Atrial natriuretic factor (ANF) may be co-secreted as a biologically active C-terminal peptide (99-126) and a non-biologically active N-terminal peptide (1-25). While the C-terminal 99-126 peptide is established to be increased in congestive heart failure (CHF) due to increased cardiac filling pressures (CFP), it is unclear if N-terminal peptide is elevated in parallel. Employing specific RIAs with no cross-reactivity, we investigated N-terminal (1-25, C-8 Bond-elut extraction) and C-terminal (99-126, C-18 Bond-elut extration) fragments in normals (n=59) and in subjects with CHF (n=11). Secondly, in CHF, we determined the response of C- and N-terminal ANF to a non-hypotensive dose of ANF with the objective of determining if N-terminal 1-25 would parallel CFP and thus serve as a marker for endogenous ANF secretion during exogenous administration of biologically active ANF. In normals, C-terminal (99-126) was 27±1 pg/ml and N-terminal (1-25) was 556±28 pg/ml. In CHF, both forms were comparably increased: C-terminal, 341±42 pg/ml, and N-terminal, 8123±1377 pg/ml. Exogenous ANF significantly increased C-terminal (99-126) to 483±62 pg/ml. N-terminal (1-25) remained unchanged at 7737±1541 pg/ml as did atrial pressures. These studies demonstrate elevation of both C- and N-terminal ANF in CHF. Further, N-terminal ANF (1-25) parallels CFP in CHF during exogenous ANF infusion and may thus serve as an important marker for endogenous ANF secretion during administration of biologically active ANF.

DOES TOLERANCE TO ATRIAL NATRIURETIC FACTOR (ANF) DEVELOP DURING 24 HOUR-INFUSION IN PATIENTS WITH CONGESTIVE HEART FAILURE?

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ANF may improve cardiac performance in patients with congestive heart failure by reducing pre- and afterload. However, long-term effects may be limited by down-regulation of responsiveness. Therefore, we studied the effect of 20 to 24 hour-infusion of ANF in patients with chronic heart failure (n=8) on hemodynamics. ANF was titrated to produce a 30% reduction in pulmonary wedge pressure (PCW) or 20% increase in CO. The maximal titration dose fullfilling these criteria (average 0.08 µg/kg/min) was then maintained for 20 to 24 hours. Urine volume, sodium and potassium were measured every four hours and subsequently replaced. Initially, ANF significantly reduced PCW by 30±12%, total peripheral resistance (TPR) by 21±8% and increased CO by 17±6% ($p<0.05$). During 24-hour infusion PCW, CI, and TPR returned towards preinfusion values despite the fact, that pharmacological plasma ANF levels were maintained during the 24 hour ANF-infusion. Patients with high filling pressures at baseline (above 25 mm Hg) did not change hematocrit in contrast to patients with low filling pressures. After discontinuation of ANF infusion, two patients experienced dramatic increases in heart rate, mean arterial pressure and PCW along with severe angina pectoris. Conclusions: 1. The hemodynamic effects of ANF are diminished during 24 hour-infusion; 2. Extravasation of fluid due to ANF may depend on preexisting filling pressures; 3. The applicability for long-term intravenous application might be hampered by the development of partial tolerance and adverse effects during withdrawal.

VENTRICULAR LEVELS OF THE ATRIAL NATRIURETIC FACTOR AND OF ITS MESSENGER RIBONUCLEIC ACID AT THE TIME OF HEART TRANSPLANTATION

Jean-Jacques Mercadier M.D., Ph.D., Marie-Alphonse Zongazo M.D., Rémi Urbain M.S., Yves Lépine M.D., Paul Kléro de Rosbo M.D., Paul D. Allen M.D., Michel Komajda M.D., Alain Carayon M.D., Ketty Schwartz Ph.D. INSERM Unité 127, Hôpital Lariboisière, Paris, France.

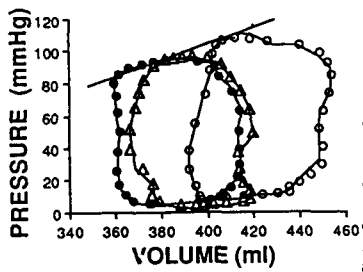
Recent data have shown in animal models of heart failure and in the failing human heart that, beside the atria, the ventricles could contribute to the increased plasma ANF levels reported during cardiac failure. In order to precisely quantify the capacity of the failing LV to contribute to this increase, the levels of Atrial Natriuretic Factor (ANF) and of its messenger ribonucleic acid (mRNA) were measured in LV samples from 7 patients free of heart disease maintained under life support whose hearts had been ultimately rejected for transplantation (CI), and from 21 transplanted hearts (8 coronary artery disease, CAD; 8 dilated cardiomyopathy, DC; 5 miscellanous). Ventricular levels of ANF mRNA and of immunoreactive ANF (IR-ANF) were assayed by dot blot hybridization with a synthetic oligonucleotide probe and by radioimmunoassay, respectively. ANF mRNA level in control ventricles was 1.5±1.4% (mean±SD) that in the right atrium of one of the control hearts used as a standard. It increased to 16.2±23.8% in the transplanted hearts (range: 1-103%, $p<0.01$ vs. CI). IR-ANF in control ventricles was 12.5±4.6 pg/mg of wet tissue and increased to 23.3±19.2 pg/mg in the transplanted hearts (range: 4-98 pg/mg, $p<0.025$ vs. CI). ANF mRNA and IR-ANF levels did not differ between DC and CAD.

We conclude: 1. that at the time of transplantation some ventricles contain increased levels of ANF and ANF mRNA and thus might contribute to increased plasma ANF levels; 2. that the ventricular levels of ANF and ANF mRNA are highly variable from one heart to another, ranging from normal to markedly elevated values indicating various levels of ventricular ANF gene recruitement at the stage of heart transplantation.

LACK OF INOTROPIC EFFECT OF ATRIAL NATRIURETIC FACTOR IN HUMANS WITH HEART FAILURE: DEMONSTRATION BY LEFT VENTRICULAR END-SYSTOLIC PRESSURE-VOLUME ANALYSIS

Marc J. Semigran MD, Constantine N. Aroney MBBS, G. William Dec MD FACC, Howard C. Herrmann MD, Charles A. Boucher MD FACC, Michael A. Fifer MD FACC. Massachusetts General Hospital and Harvard Medical School, Boston, MA

To assess the inotropic effect of atrial natriuretic factor (ANF) independent of its effect on ventricular loading conditions, we employed LV end-systolic pressure-volume (ESPV) analysis in 9 pts with heart failure (NYHA class II-IV, LV ejection fraction 14±1% mean±SEM) undergoing cardiac catheterization. The baseline LV ESPV relation (solid line in figure) was constructed from micromanometer LV pressure and simultaneous LV volume (gated scan), before (O-O) and during (●-●) nitroprusside infusion. During ANF infusion (Δ-Δ, dose 0.43±0.05 µg/kg/min), mean arterial pressure (89±3 to 80±2 mmHg, $p<.01$) and LVEDP (24±2 to 16±3 mmHg, $p<.01$) decreased. Peak LV +dP/dt (1054±104 to 945±83 mmHg/s) was unchanged. CI increased during ANF infusion (2.0±0.2 to 2.4±0.2, L/min/m$^2$ $p<.01$). Seven of nine pts had no shift in the ESPV relation, one had a slight rightward shift, one had a slight leftward shift.




Conclusions: (1) ANF has no inotropic effect in humans with heart failure. (2) ANF increases cardiac index by afterload reduction.

IN THE HUMAN, EXPRESSION OF VENTRICULAR ANF IS INDEPENDENT OF VENTRICULAR DILATATION.
Brooks Edwards, M.D., Peggy Puetz, Lester Wold, M.D., Guy Reeder, M.D., Richard Rodeheffer, M.D., John C. Burnett Jr, M.D., Mayo Clinic, Rochester, Minnesota.

Under physiologic conditions, atrial natriuretic factor (ANF) is localized only to atrial cardiocytes and released by atrial stretch. We have reported the presence of ventricular ANF (V-ANF) in states of congestive heart failure with cardiac dilatation. Therefore, we hypothesize that ventricular dilatation is required for the expression of V-ANF. The presence of V-ANF was assessed by immunohistochemical analysis of ventricular tissue obtained by endomyocardial biopsy. Studies were performed in 17 humans with dilated (DCM) and 8 with restrictive (RCM) physiology. Additionally, we determined plasma ANF, ejection fraction (EF), left ventricular end diastolic volume index (LVEDVI, normal <100 ml/$m^2$) and pressure (LVEDP normal <14 mmHg). Plasma ANF was elevated but not different between the two groups (151±39 vs 169±35 pg/ml ns, Normal range 20-77 pg/ml) (*p<.05)

| | EF% | LVEDVIml/$m^2$ | LVEDP mmHg |
|---|---|---|---|
| DCM | 41±3 | 134±13 | 20±2 |
| RCM | 61±2* | 78±5* | 25±4 |

V-ANF was observed in 88% of DCM and 75% of RCM subjects. V-ANF was associated with elevated LVEDP but not LVEDVI. The data demonstrate the high prevalence of V-ANF expression in humans with systolic or diastolic dysfunction and indicate that ventricular induction of ANF occurs independent of dilatation.

Q WAVES IN HYPERTROPHIC CARDIOMYOPATHY: PRESENCE AND LOCALIZATION ACCORDING TO THE SITE AND EXTENT OF RIGHT AND LEFT VENTRICULAR HYPERTROPHY.
Robert Lemery, MD, Shaughan Dickie, Vic Aber, MSc, Angelika Kleinebenne, MD, Petros NihoYannopulos, MD, William J. McKenna, MD, St-Georges, London, UK, and Montreal Heart Institute, Montreal, Canada.

The determinants for the presence of Q waves in hypertrophic cardiomyopathy (HCM) are unclear. We correlated localization of Q waves in HCM with the site of right and left ventricular hypertrophy (RVH, LVH) as determined by echocardiography. The study group consists of 73 consecutive patients (pts) with HCM, 39 males and 34 females, aged 17-67 years (mean 40). RVH was seen in 44%; LVH was asymmetrical in 56%, symmetrical in 35%, and distal in 9%. Localization of LVH did not differ significantly according to the presence of RVH. Q waves were present in 19 pts, overlapped between sites, and were located either inferiorly (13 pts), anteriorly (9 pts), or laterally (4 pts). In these pts, Q wave localization was correlated with the ratios of the thickness of: upper and lower segments of the septum, posterior and free wall of the LV and of RV.

Analyzing 40 combinations of LV and RV wall thickness, by stepwise discriminant analysis, Q waves were significantly related to the ratio of the thickness of the upper anterior septum (UAS) to the mean RV (p<.001). The sensitivity and specificity of UAS/RV for localizing Q waves were respectively 79% and 95%.

We conclude that in HCM, Q waves are 1- determined by the ratio of the UAS to RV thickness, and 2- are absent in the presence of RVH.

## Monday, March 20, 1989
## 10:30AM–12:00NOON, Santa Ana Room 2
## Anaheim Convention Center
## The Electrocardiograph as a Diagnostic Predictive Technology

R AND S WAVE AMPLITUDE CHANGES WITH ACUTE TRANSMURAL ISCHEMIA.
Shlomo Charlap, M.D., F.A.C.C., Jacob Shani, M.D., F.A.C.C., Nancy Schulhoff, B.S.N., Alvin Greengart, M.D., F.A.C.C., Subbarao Mylavarapu, M.D.,Gerald Hollander, M.D., F.A.C.C., Brad Herman, M.D., Edgar Lichstein, M.D., F.A.C.C. Maimonides Medical Center, SUNY, Health Science Center at Brooklyn, Brooklyn, N.Y.

Increases in R and S wave amplitudes (amp) have been proposed as additional ECG markers of myocardial ischemia, but these changes have been primarily described during exercise testing associated with ST segment depression. PTCA serves as a model of acute transmural ischemia with corresponding ST segment elevation (STe). To investigate the pattern of R and S wave amp changes with transmural ischemia, hemodynamic data and precordial ECG leads V1-V4 were recorded at baseline and during inflation in 31 pts with LAD PTCA and STe of ≥1 mm in at least one precordial lead. Results: The sum of R wave amp increased in 18 pts, was unchanged in 8, and decreased in 4. The sum of S wave amp decreased in 27 pts (including 2 with complete loss of S wave), was unchanged in 3, and increased in 1. Mean R wave amp change was + 4.65 ±8.1 mm (range -6 to +28 mm), mean S wave amp change was - 12.5 ± 9.2 (-35 to +3) and mean precordial STe was + 13.8 ± 11.2 (+2 to +35 ). Absolute R wave amp change correlated directly with STe ( p<.007), while S wave amp change correlated inversely ( p<.001). Only changes in STe correlated with changes in pulmonary wedge pressure(PW)( p<.006). Fifteen pts who demonstrated both increases in R wave and decreases in S wave amp did not differ from the rest in extent of LV dysfunction with inflation (PW:24.6 vs 22.9 mm Hg, p=ns).
Conclusions: Decreases in S wave amplitude and less commonly, increases in R wave amplitude are seen with diagnostic STe. However, the independent value of these amplitude changes as markers of myocardial ischemia appears to be limited.

100% SPECIFICITY IN LOCALIZING VENTRICULAR PREEXCITATION SITE IN WPW SYNDROME WITH THE ECG.
Robert Frank M.D., Eric Chandon M.D., Guy Fontaine M.D., FACC. Hôpital Jean Rostand - Ivry - France.

The low specificity of the usual criteria to localize the preexcitation site has been reevaluated on 62 pts with a single accessory pathway (AP), submitted to epicardial mapping: 28 left free wall (LL), 11 left (LPS) and 11 right (RPS) posteroseptal, 8 right lateral (RL) and 4 right anteroseptal AP (RAS). An algorythm was built giving 100% specificity in this series using delta wave and QRS orientations in right precordial leads (DV1,DV2,QV1,QV2,+,=,-) and in the frontal plane (AD, AQ), combined with the presence of right or left ventricular hypertrophy (RVH,LVH) or not (N). Each criteria is applied to the remaining population:

1- QV1+ or QV1= and N: LL (19/28)
2- QV1+,QV1= and AD>=30° and AQ>=15°: LL (3/28) (LVH)
3- AD>=75°: LL (5/28)
4- AD>=60° and QV2= and LVH: LL (1/28) (LVH)
5- AD>=60° and AQ>=75° and N: RAS (1/4)
6- DV2-: RAS (2/4)
7- QV2+ and AD<=-45°: LPS (8/11)
8- and DV1+: LPS (2/11)
9- and AQ<=-45° and RVH: LPS (1/11)
10- and AQ>-45°: RPS (3/11)
11- Heart N and AQ<=0°: RPS (3/11)
12- and AQ>0°: RL (4/8)
13- AD>=30° and AQ>=30°: RAS (1/4) (LVH)
14- AD<=-60°: RPS (2/11) (LVH)
15- AQ<=-15° and LVH: RPS (3/11)
16- and RVH: RL (3/8)
17- AQ<=0° and AD<=0°: RL (1/8) (LVH)

The high degree of specificity was demonstrated on another series of 55 LL, 9 LPS, 17 RPS, 10 RL and 5 RAS AP. Only 2 LPS were identified as LL, and 1 RPS as RL.

RIGHT VENTRICULAR ELECTROCARDIOGRAPHIC ABNORMALITY IN ORTHOTOPIC HEART TRANSPLANT PATIENTS

Jasvinder Sandhu MD, Edward Curtiss MD, FACC, William Follansbee, MD, FACC, Tony Zerbe, MD, Robert Kormos, MD
University of Pittsburgh, Pittsburgh, Pennsylvania

The pre-discharge 12 lead ECG of 191 recent heart transplant pts were reviewed. The prevalence of right bundle branch block QRS morphology, either right bundle branch block (RBBB, QRS≥120 ms, n=20) or incomplete right bundle branch block (IRBBB, QRS<120 ms, n=67), collectively termed RV ECG abnormality (RVECGA), was 46%. The QRS duration in IRBBB pts was longer than in pts without RVECGA (95±11 vs 86±8 ms; p=0.000). Of the 64 RVECGA pts who had an ECG on the first post-transplant day, 77% had already developed RVECGA. RVECGA prevalence was similar in pts with a prior definite episode of rejection (29/63) compared to pts who definitely did not have rejection (31/70). For pts with and without RVECGA, donor ischemic time (172±43 vs 181±42 min, respectively) and pre-operative pulmonary vascular resistance (2.1±1.7 vs 2.4±1.9 Wood units, respectively) were similar.

A subgroup of 46 consecutive pts were studied with right heart catheterization and radionuclide angiography pre-discharge. RVECGA (n=21) was only related to a greater left anterior oblique angle required to best separate the ventricles (69±11 vs 59±9 degrees; p=0.019), and to the presence of RV dysfunction (13/21 vs 6/25 pts; p=0.009), both from the radionuclide study. Excluding the 7 RBBB pts in this subgroup, QRS duration was longer in those with RV dysfunction (97±12 vs 84±10 ms; p=0.008).

The high prevalence of RVECGA appears to be related to the posterior rotation of the transplanted heart in the thorax resulting from surgical technique, and to RV dysfunction, the latter probably accounting for the longer QRS duration seen with IRBBB.

ABNORMAL QT/$QS_2$ RATIO AT REST AND EXERCISE IN ROMANO-WARD LONG QT PATIENTS, NORMALIZED BY BETA-BLOCKER THERAPY.

G. Michael Vincent M.D., Deepak Jaiswal M.D., Katherine Timothy B.S., LDS Hospital, University of Utah, Salt Lake City, UT

The QT/$QS_2$ ratio has been reported to reflect sympathetic cardiac tone in normals (Nls). Romano-Ward Long QT syndrome (LQTS) patients are thought to have an abnormality of right cardiac sympathetic effect. Exercise (Ex) modifies sympathetic tone. We, therefore, proposed that the QT/$QS_2$, as a marker for sympathetic tone, would be different during Ex in LQTS than in Nls. We compared QT/$QS_2$ at rest and during bicycle exercise in 5 familial LQTS, mean QTc 0.48±.04 sec., and 8 age matched Nls, mean QTc 0.40±.03. The subjects were on no medications. A phonocardiogram and ECG were simultaneously recorded at a paper speed of 100 mm/s. Records were obtained while unmedicated, after IV Esmolol (Es) and after Es plus Atropine (At). At rest, LQTS QT/$QS_2$ was longer than Nls, 1.16±0.14 vs 0.95±.04, P<.005. With Ex, LQTS QT/$QS_2$ increased from rest 1.16±.14 to Ex 1.58±.01, a significantly greater increase than in Nls, 0.95±.04 to 1.16±.13, P<.001. Nls QT shortened from 0.39±.03 to 0.31±.02, and $QS_2$ even more, 0.41±.03 to 0.26±.04, and thus QT/$QS_2$ ratio increased (rest 0.95 to Ex 1.16±.13). In LQTS, $QS_2$ decreased, 0.41±.01 to 0.26±.01, similar to Nls, but QT shortened less, 0.46±.06 to 0.42±.05, than in Nls, and thus QT/$QS_2$ increased more than Nls. IV Es abolished the exaggerated response of LQTS, so QT/$QS_2$ before and after Ex were similar to Nls, 1.10±.10 to 1.06±.07 vs 0.99±.05 to 1.03±.09, respectively, P=NS. Es and At produced results similar to Es alone. These results support the concept of abnormal sympathetic tone in LQTS, manifested by abnormal QT/$QS_2$ at rest and Ex, and blocked by Es. The QT/$QS_2$ ratio may serve as a diagnostic marker for LQTS and also as an indicator of therapeutic efficacy.

IMPROVED ELECTROCARDIOGRAPHIC IDENTIFICATION OF PATIENTS WITH THE LONG QT SYNDROME (LQTS)

Jesaia Benhorin M.D., Mario Merri M.S., Michela Alberti M.S., Emanuela Locati M.D., W Jackson Hall Ph.D., Arthur J Moss M.D., F.A.C.C., Peter J Schwartz M.D., F.A.C.C., University of Rochester, Rochester, NY, and University of Milan, Milan, Italy

The conventional ECG criterion for LQTS diagnosis is a prolonged heart-rate corrected QT interval (QTc). In order to improve the ECG diagnostic accuracy of LQTS, logistic regression models were applied to a database of 7 independent ECG repolarization variables (REPV) measured on digitized 12-lead ECG recordings of 315 normals and 37 LQTS pts (QTc>0.44 sec), age 17-60 years. REPV which independently identified LQTS (p<0.001) included the heart-rate corrected S offset to T max (SoTm) interval (T1), which is highly correlated to the QTc, as well as the time to accumulate 25-75% of total repolarization area [TRA] (T2), %TRA accumulated at T offset (T3), T wave area symmetry ratio (T4), and the standard deviation of SoTm in leads V1-V6 (T5). The performances of selected models in identifying pts with LQTS in the combined study population were:

| Variables in Model* | Misclassification Rate (%) LQTS | Normal | All | Sens. | Spec. |
|---|---|---|---|---|---|
| T1 | 18.9 | 5.1 | 6.5 | 81 | 95 |
| T2 - T5 | 18.9 | 4.8 | 6.3 | 81 | 95 |
| T1 - T5 | 5.4 | 3.8 | 4.0 | 95 | 96 |

* Measured in lead V5 except T5; cutoff probability = 0.2

Conclusion: The quantitation of five independent repolarization variables significantly enhances the identification of pts with LQTS.

## Monday, March 20, 1989
## 10:30AM–12:00NOON, California Room B
## Anaheim Convention Center
## Coronary Risk Interventions

RISK FACTORS AND MORTALITY IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL AFTER 10.5 YEARS OF FOLLOW-UP.

The MRFIT Research Group

The MRFIT clinical trial provides one of the largest prospective analyses of lipoproteins, other risk factors and mortality. The baseline LDL cholesterol was strongly related to CHD death at 10.5 years, relative risk (RR) = 2.2 (highest quintile/lowest quintile) but only weakly associated with total mortality (RR = 1.3). Regression coefficients corresponding to LDL cholesterol indicated that a 10 mg/dl lowering was associated with a 7.4% reduction in CHD and a 2.3% reduction in all cause mortality. The HDL cholesterol was inversely associated with CHD death (RR for highest vs. lowest quintile = 0.45) and weakly associated with all cause mortality (RR = 0.89). Regression coefficients corresponding to HDL cholesterol indicated that a 5 mg/dl increase was associated with an 11.2% reduction in CHD and a 2.1% reduction in all cause mortality. Neither LDL or HDL cholesterol was associated with death from stroke. The body mass index (BMI) was inversely associated with CHD death in both univariate and multivariate analyses (P < 0.01). This inverse association was evident in both normotensive and hypertensive men. Only cigarette smoking was a significant risk factor for all major causes of death (CHD, stroke and cancer) and total mortality.

## EFFECT OF ESTROGEN REPLACEMENT AND CORONARY ARTERY DISEASE ON SURVIVAL IN POSTMENOPAUSAL WOMEN.

Jay M. Sullivan M.D. F.A.C.C., Roger Vander Zwaag, Ph.D., Jeff P. Hughes M.A., Frank W. Kroetz M.D., Kodangudi B. Ramanathan M.D. F.A.C.C., Edgar C. Schick M.D. F.A.C.C., David M. Mirvis M.D., University of Tennessee, Memphis, TN.

The relationship between postmenopausal estrogen use, coronary stenosis and survival was examined in 2268 women undergoing coronary angiography. The patients were selected for study if their age was 55 years or older at the time of angiography or if they had previously undergone bilateral oophorectory. Postmenopausal estrogen use for 1178 cases of coronary artery disease (>70% stenosis) and 644 cases of mild to moderate coronary artery disease (35 to 69% stenosis) was compared with 446 control subjects (0% stenosis) using life-table analysis. Over 10 years of follow-up, there was no significant difference in survival among patients initially free of coronary lesions on arteriography who had either never used (377) or ever used (69) estrogens. Among patients with mild to moderate coronary stenosis, 10 year survival of those who never used estrogens was 85.0% and was 95.6% among 99 ever users ($p<0.03$). Survival was 60.0% among those with >70% coronary stenosis who never used estrogen and 97.0% among 70 ever users. Never users were older (65 vs 59 yrs), had a lower proportion of cigarette smokers (40% vs. 57.1%), a higher proportion of diabetics (21.7% vs. 12.9%) and hyperlipidemics (58% vs 44%) and approximately equal numbers of hypertensives (56.0% vs 54.3%). We conclude that estrogen replacement after menopause prolongs survival when coronary artery disease is present but has less effect in the absence of coronary artery disease.

## DIETARY INTAKE OF SATURATED FAT AND CHOLESTEROL IN EARLY CHILDHOOD: IMPLICATIONS FOR PREVENTION OF ATHEROSCLEROSIS

Katrina Holt, MS RD, Audrey Hay, PhD RD, Constance Kies, PhD, Janet Wilson MT (ASCP), Bruce McManus, MD, PhD, FACC, University of Nebraska Medical Center, Omaha, NE.

Primary prevention, begun in early childhood, may be the best approach to further reduce or delay morbidity and mortality from coronary heart disease (CHD). As participants in the statewide Nebraska Diet-Heart Study, 363 1-to-5 year-olds underwent comprehensive historical, physical, and laboratory study. Macronutrients in the diet, as judged by a 24-hour dietary recall and food frequency questionnaire, were analyzed with respect to the blood lipid cholesterol, triglycerides, HDL-C, LDL-C, and apolipoproteins A-1 and B. Correlations of variable magnitude occurred between dietary content and blood parameters. Notably, eating patterns were clearly established by 1 year of age and intakes continued constant through age 5 for both boys and girls. In comparison with AHA dietary recommendations, a majority of the preschool children were consuming excesses. Mean dietary intakes were higher in total fat (32-37%) than prudent guidelines, lower in carbohydrate (49-54%), similar in protein (14-16%), and were characterized by a very low P/S ratio (0.22-0.35). Mean cholesterol intake was 127-212 mg/day, and 105-153 mg/day/1,000 kcal. By current guidelines of the National Cholesterol Education Program, preschool Nebraskan girls by age two and boys by age five have a mean total plasma cholesterol of 170 mg/dl which is considered "high-risk". Early childhood dietary intakes of Nebraskan children suggest unhealthy intakes of fat, saturated fat, and cholesterol, and these are reflected in "high-risk" lipid profiles. Modification of undesirable natural histories of atherosclerotic disease must be addressed beginning in preschool.

## PRIOR BETA BLOCKER THERAPY IMPROVES 28 DAY POST INFARCTION SURVIVAL.

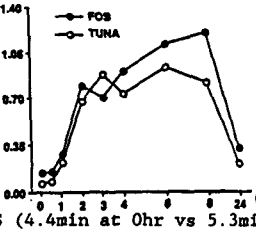
SM Nidorf, R Parsons, PL Thompson, K Jamrozik, MST Hobbs. Departments of Cardiovascular Medicine and Clinical Epidemiology, Queen Elizabeth II Medical Centre, Perth, Western Australia.

We evaluated the influence of the prior use of a Beta Blocker (BB) on 28 day survival following acute myocardial infarction (AMI). All patients hospitalized with a diagnosis of AMI in Perth between 1984-86 had clinical data recorded prospectively in the MONICA project. Of 1,824 patients, 23% were on a BB at the time of AMI. Although this group was older ($p<0.001$) and more likely to have a past history of AMI, angina and/or hypertension ($p<0.001$) than patients not on a BB, 28 day mortality was similar in both groups (13.0% vs 13.5%). A logistic regression model used to adjust for factors predictive of cardiac death at 28 days, including age, past AMI and the development of pulmonary oedema or cardiac arrhythmias, showed that patients on BBs had an independent benefit (Relative Risk 0.45 $p<0.001$). This beneficial effect was most evident in patients surviving >24 hours (RR 0.33 $p<.0.003$) and in patients with a past AMI (RR 0.50 $p<0.001$). Whilst the incidence of heart block and ventricular fibrillation was similar in both groups, the mean peak creatine kinase was lower in the BB group ($p<0.03$). These data suggest that patients taking a BB prior to the onset of AMI had a significant early survival advantage.

## ABSORPTION AND EFFECT ON PLATELET FUNCTION FROM SINGLE DOSE CONCENTRATED FISH OIL COMPARED WITH TUNAFISH

DI Silverman, JA Ware, FM Sacks and RC Pasternak, FACC Harvard-Thorndike Lab and Beth Israel Hospital, Boston MA.

Fish oil supplements(FOS) have recently been employed as an alternative to fish for various indications. To compare the absorption and effect on platelet aggregation (PL-AGG) of n-3 fatty acids(n-3FA) in FOS vs. fish, we gave a fatty meal containing n-3FA either as 12 gms FOS(35% total n3-FA) or 182 gm tuna (10.9 gm total fat, 22% total n3-FA) to 8 subjects in a crossover trial and measured plasma triglyceride(TR), eicosapentaenoic acid (EPA) and docosahexaenoic acid(DHA) content in TR over 24hr. We also measured bleeding time (BT) and PL-AGG at 0 and 4 hours. The graph shows absorption data for mean EPA levels over 24 hr during both phases of the trial. Results are similar for DHA and TR. There was no significant difference between FOS and tuna in peak absorption or time to peak for EPA or DHA. PL-AGG to the thromboxane A2 mimetic U466619 was inhibited at 4 hours after FOS (69 vs 25mm/min, $p<0.05$) and tuna (69 vs 45 mm/min, $p<0.05$).




BT was mildly prolonged after FOS (4.4min at 0hr vs 5.3min at 4hr, $p=0.1$). PL-AGG induced by epinephrine, ADP, or collagen was mildly reduced after both FOS or TUNA. We conclude 1)EPA appears rapidly in plasma after a single dose of n-3FA as either FO or TUNA, in equivalent amounts at similar times. 2)This is associated with reduced PL-AGG soon after ingestion. The decrease in PL-AGG from n3-FA suggests that the anti-aggregatory effect of n3-FA on platelets cannot be due solely to its incorporation into megakaryocytes.

**THE MAJORITY OF PHYSICIANS USE DRUG THERAPY FOR ISOLATED SYSTOLIC HYPERTENSION.**

John B. Kostis, M.D., F.A.C.C., Mary B. Breckenridge, Ph.D., UMDNJ-Robert Wood Johnson Medical School, New Brunswick, New Jersey.

The advisability of treating isolated systolic hypertension (ISH) in the elderly is a matter of debate.

We surveyed current clinical practices for ISH among members of the American College of Physicians - New Jersey Chapter and the New Jersey Academy of Family Physicians (N=1514). The response rate was 87%.

For ISH in patients aged 60 and older, 88% of the 1317 respondents use drug therapy, with small variations by specialty, type of practice, and physician's age. The first line drug is a diuretic for 65%, and a beta blocker for 11%. The most common second line drug choices are a beta blocker (28%), a central alpha agonist (19%), and a diuretic (18%). The lowest systolic pressure considered for drug use varied more within specialties than between specialties.

The patient's age appears to enter strongly into decisions on drug use. While 84% of those who use drug therapy for ISH consider doing so at systolic pressures of 170 or less for persons aged 60-69, only 76% would do so for persons aged 70-79, and 55% for those aged 80+.

Although proof of a beneficial effect on morbidity and mortality is not available, a majority of physicians surveyed use pharmacologic therapy, usually diuretics, for ISH.

## Monday, March 20, 1989
## 2:00PM–3:30PM, Anaheim Room
## Anaheim Convention Center
## Peripheral Vascular Disease: Technics for Revascularization

GUIDED PERCUTANEOUS PULSED LASER ANGIOPLASTY : RESULTS AND FOLLOW-UP.

Herbert J. Geschwind, M.D., F.A.C.C., Jean-Luc Dubois-Randé, M.D., Gérard Poirot, M.D., Georges Boussignac, M.D., University Hospital Henri Mondor, Créteil, France.

From July 1987 to July 1988, laser angioplasty (LA) was performed in 31 patients (pts) with total occlusions of the superficial femoral artery or the iliac artery (4 to 25cm length). The system (MCM Smart Laser™) included: 1/ a treatment pulsed dye laser operating at 480 nm, 15-49 mJ/pulse, 2 sec ; 2/ a diagnostic HeCd laser operating at 325 nm, 5 mW, 50 msec ; 3/ a single 500 µm or 200 µm optical fiber that transmitted excitation light, fluorescence emission from the tissue in contact with the distal fibertip and the tissue ablation dye laser. The treatment laser was continuously guided by a computerized logic system which allowed the treatment laser light to be emitted only on atheroma targets. The procedure was completed by balloon angioplasty. Laser recanalization was obtained in 28 patients. The three failures were due to inability to mechanically direct the laser beam toward the occlusion. In 1 patient subsequent balloon angioplasty could not be performed. There were perforations and dissections due to mechanical manipulations of the guidewire or the fiber with no apparent clinical sequelae. Follow-up was assessed by Doppler (28 pts) and angiograms (11 pts). Five pts had short-term reocclusions which were successfully treated by thrombolysis. At 1 to 12 months (mean 5.8) follow-up, patency was demonstrated in 23 patients. Conclusions: 1/ pulsed dye laser is effective in recanalizing long occlusions, 2/ under spectroscopic guidance, laser angioplasty is safe, 3/ technical failures may be avoided by improved deflectable catheters, 4/ the rate of patency (82 %) is acceptable, considering the severity of lesions.

FACTORS ASSOCIATED WITH RESTENOSIS FOLLOWING SUCCESSFUL PERIPHERAL ATHERECTOMY.

Matthew Selmon, MD; Gregory Robertson, MD; Tomoaki Hinohara, MD, FACC; Neil White, MD; Michael Rowe, MD; John Simpson, MD, FACC; Sequoia Hospital, Redwood City, CA.

Peripheral atherectomy (PA) has been shown to be an effective procedure for the treatment of occlusive peripheral vascular disease. However, restenosis (RS) in the convalescent phase has been observed. The purpose of this study is to evaluate RS following successful PA and identify the factors associated with RS. One hundred and seven patients (pts) underwent successful PA. Six month follow up was available for 90 pts (angiographic in 51, Doppler in 32, and clinical symptoms in 7). Clinical RS was observed in 28 (angiographic evidence of RS in 25, Doppler evidence of RS in 3). Univariate analyses were performed on the following variables: lesion location, pre PA stenosis (total or subtotal stenosis), post PA stenosis (residual stenosis $<$ or $\geq$ 30%), lesion length ( $<$ or $\geq$4.0cm), diabetes, smoking, hypertension, hyperlipidemia, sex, age. Factors associated with RS were residual stenosis $\geq$30% ($p=0.005$) and lesion length $\geq$4.0cm ($p= 0.05$). RS was observed in 47% of PR with $\geq$30% residual stenosis but 23% of PR with $<$30% residual stenosis. RS was 73% in lesions $\geq$4.0 cm and 24% in lesions $<$ 4 cm. RS was 16% in lesions $<$ 4 cm which had $<$ 30% residual stenosis. In conclusion, RS occurs following successful PA, however, the incidence of RS was significantly lower when less than 30% residual angiographic stenosis was achieved. This preliminary report suggests that the goal of the PA procedure should be aimed at achieving the least residual stenosis to prevent RS.

**COMBINED LASER/THERMAL RECANALIZATION OF PERIPHERAL ARTERY OCCLUSIONS.**

David C. Cumberland M.D., Anna M. Belli M.D., Richard K. Myler M.D., F.A.C.C., Simon H. Stertzer M.D., F.A.C.C., John C. Crew M.D., Northern General Hospital, Sheffield, England and San Francisco Heart Institute, Seton Medical Center, Daly City, CA

The "hot tip" probe, a purely thermal device powered by laser energy, has been found to be a useful adjunct to balloon angioplasty (BA) by recanalizing peripheral arterial occlusions not passable with a conventional guidewire (and therefore, impossible to treat with BA alone). Success has been achieved in 56% of such cases and there is a patency rate of 73% at one year.

A new device, the Spectraprobe PLR, has a distal portal that allows 20% of the laser light to escape; thus, this device combines both thermal and direct laser energy. A 2.5 mm diameter tip Spectraprobe was used to traverse 32 peripheral artery occlusions: 9 iliac occlusions of 5-7 (mean 5.8) cm long and 23 femoral/popliteal occlusions 5-32 (mean 14) cm long. 25 of these 32 (78%) were successful. There were two minor perforations, both without sequelae. The mean luminal diameter channel produced by this device was 2.45 mm $\pm$ 0.75 (SD), which is 50% larger than that achieved with the thermal probe alone.

The combination of direct laser and thermal energy appears to be more effective and provides a larger channel than by thermal means alone. Greater tissue ablation may explain these results. The Spectraprobe may be an important device for improving long-term patency of occlusions following peripheral balloon angioplasty.

**RADIOFREQUENCY THERMAL ANGIOPLASTY FOR THE TREATMENT OF PERIPHERAL VASCULAR OCCLUSIVE DISEASE: PRELIMINARY RESULTS OF A CLINICAL TRIAL**

Warren Grundfest, M.D., Frank Litvack, M.D., F.A.C.C., Ann Hickey, M.D., Louis Adler, M.D., Robert Foran, M.D., Phillip Levin, M.D., Jacob Segalowitz, M.D., Lisa Hestrin, M.P.H., James Forrester, M.D., F.A.C.C., Cedars-Sinai Medical Center, Los Angeles, California.

We report the first results of radio frequency (RF) thermal angioplasty for the treatment of peripheral vascular occlusive disease in 12 patients, mean age 70.3 yrs., (range 53-79). All were candidates for peripheral bypass surgery. There were 13 lesions in the SFA and proximal popliteal distribution: 8 occlusions with mean length of 12 cm (range 4-17 cm), ankle brachial index (ABI) mean 0.47 (range 0.38-0.91) and 5 stenoses, 87% mean diameter, mean ABI 0.70 (range 0.35-0.94). We used a 2.3 mm gold tipped RF thermal angioplasty catheter at 20 watts. Primary recanalization followed by balloon angioplasty was achieved in 9 of 12 (75%) with residual stenosis less than 20% in successful cases. The 3 failures occurred in heavily calcified vessels; in two the diameter was less than 4 mm. There were no complications secondary to the RF thermal angioplasty. Post-procedure mean ABI for occlusions was 1.05 (range 0.81-1.40): a mean improvement of 0.47. For stenoses ABI was 0.96 (range 0.87-1.05): mean improvement of 0.24. All successful patients became asymptomatic and remained so at mean of 1 month follow up. In unsuccessful cases 1 of the 3 patients went on to elective bypass surgery. **Conclusion:** In selected cases, radiofrequency thermal angioplasty is effective in recanalizing occluded peripheral vessels, providing a practical, low cost alternative to laser thermal angioplasty or bypass surgery.

CONTRASTING EFFECTS OF CONTINUOUS WAVE AND PULSED LASER IRRADIATION ON VASOREACTIVITY OF ATHEROSCLEROTIC VESSELS IN VITRO

Anthony J. Rongione, B.A., Dov Gal, D.V.M., Stephen T. DeJesus, B.A., Saurabh K. Chokshi, M.D., Richard H. Clarke, Ph.D., Jeffrey M. Isner, M.D., Tufts University School of Medicine, Boston, MA

Previous studies from our laboratory have demonstrated that continuous wave (CW) and pulsed (P) laser (L) irradiation (I) have qualitatively different effects on the vasomotor reactivity of non-atherosclerotic vascular segments: heating associated with CW LI produces contraction (CON); lack of similar heating with P LI produces relaxation (RELAX). Because response of atherosclerotic (Ath) segments is more relevant to use of LI for revascularization, we studied effects of CW vs. P LI on rings of Ath aorta from rabbits fed an Ath diet pre- and post-balloon endothelial (Endo) denudation. Rings were mounted in Krebs bicarbonate buffer (95% $O_2$-5% $CO_2$, pH=7.4, 37°C); ring tension and temperature (temp) were simultaneously recorded during fiber-mediated CW or P LI. CW LI (argon {488, 514 nm} 20-sec exposures, n=57) at all powers >1.0 watt consistently produced Endo-independent contraction (807±140mg {m±SEM}) associated with increased ring temp up to 60°C. In contrast, P LI (excimer {351nm}, 10-100 Hz, 20-60-sec exposures, n=133) in no case caused contraction, but instead produced Endo-independent relaxation (360mg±23) at all fluences (up to 5 J/cm$^2$); ring temp never exceeded 10°C. These results are neither qualitatively nor quantitatively different from responses to CW and P LI reported previously using non-Ath vessels. Conclusions: CW and P LI produce directionally opposite changes in vascular tone in Ath, as well as normal, vessels. Lack of increased vascular tone in Ath segments treated with P LI suggests that clinical applications of P LI may be less likely to provoke spasm.

PERCUTANEOUS LASER ANGIOPLASTY OF PERIPHERAL ATHEROSCLEROTIC OBSTRUCTIONS BY THE UNICORN-CAP (Tm) PROBE SYSTEM: A MULTICENTER STUDY.

Garrett Lee, M.D., F.A.C.C., Ronald R. Masden, M.D., F.A.C.C., Daniel Scharf, M.D., F.A.C.C., Jeffrey A. Weiss, M.D., Robert L. Falk, M.D., Gerald D. Temes, M.D., George E. Pool, Hal Coons, M.D, Agustin J. Argenal, M.D., F.A.C.C., David Wixson, M.D., Dean T. Mason, M.D., F.A.C.C., Northern California Heart and Lung Institute, Concord, California.

Since arterial perforation is the major limitation of current laser delivery systems, we studied a new laser probe (Unicorn-Cap, Xintec Corporation, Oakland, CA) to percutaneously recanalize peripheral arteries in 26 patients (13 males, 13 females, age range 55-85 years). The catheter comprises a leading steerable 0.035" coaxial guidewire attached to the metal cap which is connected to a portable Nd:YAG laser system (Model XT-10, Xintec Corporation). Thirty-three atherosclerotic lesions (16 stenoses and 17 occlusions ≤10 cm) in iliac, femoral or popliteal vessels were successfully recanalized without complications (no perforations, spasm or significant adhesiveness). Laser therapy was the sole intervention in three; the remainder were followed by balloon angioplasty. Symptom relief and/or leg salvage was achieved with improved ankle/arm index. Thus this novel coaxial-guided laser probe system provides effective and safe revascularization of peripheral disease in appropriately selected patients.

## Monday, March 20, 1989
## 4:00PM–5:30PM, Anaheim Room
## Anaheim Convention Center
## Thrombolytic Therapy in Acute Coronary Syndromes

ANGIOSCOPIC ENDOTHELIAL MACROPATHOLOGY IN PATIENTS WITH ACUTE CORONARY SYNDROMES.

Kyoichi Mizuno M.D., Akira Miyamoto M.D., Kimio Satomura M.D., Toshio Shibuya M.D., Yasuhiro Okamoto M.D., Hidetaka Seguchi M.D., Kazushige Isojima M.D., Akira Kurita M.D., Tsunenori Arai Ph.D., Haruo Nakamura M.D. National Defense Medical College, Saitama, Japan.

To investigate the pathophysiology of acute coronary syndromes including unstable angina and acute myocardial infarction, we performed percutaneous transluminal coronary angioscopy in 63 patients [acute (<6h) myocardial infarction (AMI) 9, unstable angina 7, recent (3 days to 4 weeks) myocardial infarction (RMI) 13, stable angina 13, old (>4 weeks) myocardial infarction (OMI) 21] using a new angioscope which has an inflatable balloon and angulation mechanism. Good visualization was obtained in 50 patients. The main observations were as follows.

| | Thrombi | Ragged surface | Yellow plaque |
|---|---|---|---|
| AMI | 100% | (33%) | (17%) |
| Unstable angina | 50% | (50%) | (25%) |
| RMI | 13% | 88% | 75% |
| Stable angina | 0% | 17% | 25% |
| OMI | 0% | 0% | 10% |

( ): exact number might be masked by overlying thrombi

White or mixed white and red thrombi were observed in cases of acute coronary syndromes. Necrosis-ridden matured xanthomatous ulcerated plaque with or without tipped thrombi, ragged, irregular surface were observed in patients with acute coronary syndromes and those within one month after AMI attack. Conclusions: (1) Thrombi overlying a rupture in the lining of the plaque may play a major role in acute coronary syndromes. (2) Lipid-rich gruel atheroma and thinning fibrous caps may precede its rupture. (3) Angioscopy may provide a new understanding of endothelial pathology in living man.

## PATIENTS WITH ST SEGMENT DEVIATION AND UNSTABLE ANGINA HAVE CONSISTENT INCREASES IN THROMBIN ACTIVITY.

Paul R. Eisenberg M.D. F.A.C.C., Joseph L. Kenzora M.D. F.A.C.C., Colleen Schaab, R.N. and Allan S. Jaffe M.D. F.A.C.C., Washington University, St. Louis MO.

Reversible ST segment and/or T wave changes in patients with unstable angina are associated with increased cardiovascular morbidity. Because it is felt that many of these patients harbor nonocclusive coronary thrombi, administration of antithrombotic and/or fibrinolytic agents has been advocated. However, prospective noninvasive criteria for identifying patients with thrombi are not available. To define the incidence of thrombosis and the sensitivity and specificity of specific electrocardiographic (ECG) patterns for its detection in patients with unstable angina, we measured plasma levels of fibrinopeptide A (FPA), a sensitive marker of thrombin activity in 26 patients with unstable ischemic symptoms and ECG changes. FPA was measured by radioimmunoassay from samples obtained a mean of 9.1±1.4 (SE) hrs after chest pain. Elevated FPA (≥ 2.0 ng/ml) occurred in 65% (17/26) of patients. FPA was normal in 9 patients and moderately elevated in 5 others (≤5 ng/ml) with T wave changes alone (mean = 2.3±0.3 ng/ml, range = 2.0-4.6 ng/ml). In contrast, all 12 patients with reversible ST segment shifts had elevations of FPA (mean = 19.0±10.0 ng/ml, $p< 0.01$ compared to those with T wave changes only). In 9 of 12, elevations were greater than the maximal elevation observed in patients with T wave changes alone. Four of the five patients (including the 2 with ST segment elevation) with marked elevations of FPA (≥ 8.0 ng/ml) had findings consistent with thrombus by angiography. Thus, evidence of active thrombosis is common in patients with unstable angina. In contrast to patients with T wave changes and unstable angina in whom increased thrombin activity is infrequent, and if present is at most modest, patients with unstable angina and ST segment deviation manifest consistent and frequently marked increases in thrombin activity. Accordingly, they are more suitable for treatment with anticoagulants and/or fibrinolytic agents.

## EFFECTS OF UROKINASE AND HEPARIN ON LESION GEOMETRY IN UNSTABLE ANGINA.

Mara Sansa M.D., Carmelo Cernigliaro M.D.,Ignazio Simonetti M.D., Ospedale Maggiore, Novara, Italy, and University of Pisa, Italy.

The effects of urokinase (UK) and heparin (H) on the geometry of a <100% ischemia-producing lesion were investigated in 43 Pts with unstable angina (UA) on maximal medical therapy with Ca-blockers, ß-blockers and nitrates. After baseline coronary angiography, Pts were randomized to UK ($10^6$ U bolus followed by H infusion at 800 to 1200 U/hr), H alone ($10^3$ U bolus + 800 to 1200 U/hr infusion, or placebo (P). Angiography was repeated at 1 hr and 8 days of treatment. Eight Pts were excluded after the first study (1 in the H group and 7 in the P group) because of non Q-wave MI and/or need for emergency revascularization. In the remaining 35 Pts, lesion minimum cross-sectional area (MCSA; Brown/Dodge method) was blindly measured on orthogonal pairs of angiograms taken in the same view at baseline, 1 hr and 8 days of treatment. Changes in MCSA ($mm^2$) were (mean±SEM; *=$p<0.05$ vs Control):

| | Control | 1 hr - (%) | 8 days - (%) |
|---|---|---|---|
| UK(n=12) | .84±.16 | .94±.17(16±6)* | 1.0±.18(25±12)* |
| H (n=12) | .64±.14 | .66±.13 ( 6±6) | .79±.17 (27±8)* |
| P (n=11) | .65±.15 | .69±.16 ( 6±6) | .71±.20 (7±15) |

Lesion MCSA in the excluded Pts (.70±.15) was not different from that measured in the included ones . In conclusion: 1) either UK or H can improve the geometry of the ischemia-producing lesion in UA; 2) UK is provided by a faster effect than H; 3) both drugs provide a better prognosis for UA than standard medical therapy.

## INABILITY OF THROMBOSIS RELATED MARKERS TO DISTINGUISH BETWEEN UNSTABLE AND STABLE ANGINA PECTORIS.

Dimitrios Alexopoulos MD, David Stump MD, Pramod Deshmukh MD, Susan Borrico BS, Richard Gorlin MD, FACC, Valentin Fuster MD, FACC, John A. Ambrose MD, FACC. The Mount Sinai Medical Center, New York, NY

Angiographic and pathologic data indicate a role for thrombus formation in the pathogenesis of unstable angina (USAP). The value of thrombosis related markers in peripheral blood like fibrin D-dimer and plasminogen activator inhibitor (PAI) -an index of endogenous fibrinolytic activity- in distinguishing between USAP and stable angina pectoris (SAP) is unclear. We prospectively analyzed D-dimer (ELISA, µg/ml) and PAI (enzymatic assay using chromogenic substrate, IU/ml) in the peripheral blood of 53 pts (34 with USAP and 19 with SAP). For each patient with USAP a baseline sample prior to any heparin treatment was drawn 0 to 6 hrs after rest pain (median 2.5) and 24-48 hrs later. Samples were analyzed blindly to the clinical data (SAP vs USAP, recurrent chest pain within 72 hrs) or coronary angiographic findings.

RESULTS:(median,range)

| | SAP | USAP(baseline) | USAP(24-48hrs) |
|---|---|---|---|
| D-dimer | .05(.03-.39) | .07(.03-.30) | .05(.02-.33) |
| PAI | 5(3.9-11) | 5.9(3.9-40) | 5.4(3.9-11) |

There were no significant differences between groups. Baseline samples in pts with USAP drawn 0 to 1 hour after rest pain were similar to samples 4 to 6 hours after rest pain. Coronary anatomy (acute lesions or presence of thrombus) and recurrent chest pain (n=18 of 34) could not be differentiated by the studied markers or their change over 24-48 hrs. Thus, peripheral markers of thrombosis appear unable to distinguish USAP from SAP. Although coronary thrombus formation is important in USAP, the amount may be too small for detection in the periphery.

## THROMBOLYTIC THERAPY IN UNSTABLE ANGINA AND NON Q-WAVE MYOCARDIAL INFARCTION: A RANDOMIZED TRIAL OF UROKINASE VERSUS ASPIRIN.

Theodore L. Schreiber M.D., F.A.C.C.; Gregory Macina M.D., F.A.C.C.; Paul Bunnell, B.S.; Ann McNulty, R.N.; David H. Miller M.D., F.A.C.C.; Richard B. Devereux M.D., F.A.C.C.; Barbara Gerling, M.D.; Richard Tenney, M.D., F.A.C.C.; Benjamin Zola M.D., Cornell Medical College, New York, NY

The pivotal role of thrombosis in unstable angina (UA) and non Q-wave myocardial infarction has recently been established. To assess whether thrombolytic therapy is superior to conventional aspirin therapy (ASA) in arresting progression to recurrent ischemic endpoints -- intractable ischemia (II) or transmural infarction (MI) -- 25 patients presenting with a typical clinical history of UA, and abnormal ECGs with subendocardial ischemia, were randomized to receive either urokinase (UK) 3.0 mill U/30 min intravenously followed by heparin (12 pts), or ASA 325 mg. daily (13 pts). Morphologic severity of the culprit lesion was graded by coronary arteriography at 24-48 hrs: 4+, definite thrombus; 3+, ulceration/probable thrombus; 2+, ulceration/possible thrombus; 1+, ulceration alone; and 0, chronic lesion. At 7 days, 8/13 ASA pts vs 3/12 UK pts (62% vs 25%, p = .07) had progressed to a primary ischemic endpoint (ASA, 5 MIs, 3 II vs UK, one death, 2 II). Mean morphologic severity score was equal in both groups (3+). We conclude that UK appears superior to ASA in arresting progression of UA to major ischemic endpoints without major amelioration of culprit lesion morphology. Large scale randomized trials to assess this therapy are warranted.

INTERMITTENT UROKINASE THERAPY AS A NEW STRATEGY CONCEPT IN UNTRACTABLE ANGINA PECTORIS

Matthias Leschke M.D., Helmut Höffken M.D., Martin Vogt M.D., Wolfgang Motz M.D., Bodo E. Strauer M.D. F.A.C.C.
Dept. of Medicine, University of Düsseldorf, W. Germany

Patients with severe diffuse coronary artery disease can benefit from an optimized blood fluidity. Accordingly, 16 patients with end-stage coronary artery disease and angina pectoris (AP) refractory to conventional medical treatment (nitrates, calciumchannel-blockers, betablockers) were treated with 250 000-500 000 Urokinase (UK)/day for 4 months. UK-therapy aimed at an improvement in blood fluidity and myocardial microcirculation due to fibrinogenolysis. Under UK the fibrinogen level (345±98 mg/dl) decreased to 201± 59mg/dl ($p<0.001$). Plasma viscosity and erythrocyte aggregation decreased from 1.42±0.08 to 1.31±0.06 m Pas ($p<0.001$) and from 14.6±4.4 to 12.3±3.6 ($p<0.01$) ,respectively. As early as after 3 weeks of therapy the daily episodes of AP were reduced (1.9±0.6 vs. 1.3±1.4, $p<0.02$) with a consecutively reduced nitrate consumption. The maximum working capacity (bicycle) increased significantly from 15104±6648 Joule to 24010±13790 Joule by 59%. In 10 of 12 patients exercise thallium perfusion scan improved. Cardiac index sligthly rose from 2.6±0.4 to 2.9 ±0.5 l/min/$m^2$and ejection fraction from 45.8±19.2% to 50.8±16.8%.

Conclusions: (i) Patients with end-stage coronary artery disease can show symptomatic improvement under a chronic urokinase therapy. (ii) The increased exercise tolerance is induced by fibrinogenolysis and improved blood fluidity as indicated by decreased plasma viscosity and erythrocyte aggregation. (iii) Due to therapeutical increase of myocardial perfusion left ventricular pump function is slightly improved.

ONE - TWO YEAR FOLLOW-UP AFTER PRIMARILY SUCCESSFUL VALVULOPLASTY FOR CALCIFIED AORTIC STENOSIS.

Christoph Spielberg M.D., Irmtraud Kruck M.D., Thomas Linderer M.D., Rolf Schröder M.D., F.A.C.C.
Klinikum Steglitz, Free University Berlin, FRG

From June 1986 to September 1987, balloon valvuloplasty (VP) of aortic stenosis was performed in 33 patients(mean age 74 years)with repeat-VP in 6 cases. Overall reduction of peak gradient was -53% and increase in valve area was +90%.

Immediately after VP, 76% of the patients were asymptomatic or significantly improved. 4 patients remained symptomatic. There was 1 early valve replacement because of VP-induced aortic insufficiency and 3 early deaths occurred within 4 weeks after VP. Follow-up included 23 invasive controls and repeat Doppler-echocardiography (DE) every 2-3 months in all patients. Restenosis (loss of initial gain in valve area and/or loss of gradient reduction >50%) was seen in over 80% of the patients. DE showed progressive loss of achieved gradient reduction at each control: 1-3 days after VP -28%, after 3 months -48%, after 4-6 months -60%, >7 months -74%.

After a mean follow-up of 17 months (11-26 mo.), 10 patients were deceased, 12 had valve replacement, and to 4 surgery had been strongly suggested. Only 7 patients (21%) were still clinically improved. Conclusions: VP of calcified aortic stenosis is a solely palliative procedure with an unacceptably high restenosis-rate and a poor clinical outcome after >12 months. It seems no realistic alternative to valve replacement.

## Monday, March 20, 1989
## 2:00PM–3:30PM, California Pavilion D
## Anaheim Hilton Hotel
## Balloon Valvuloplasty in Aortic Stenosis

FOLLOW-UP OF BALLOON AORTIC VALVULOPLASTY: RESULTS IN 192 CASES.

Richard E. Kuntz, MD. Bradley M. Leonard, MD, Raymond E. Erny, MD, Marc J. Levine, MD, Patricia C. Come, MD, FACC, Daniel J. Diver, MD, Robert D. Safian, MD, William Grossman, MD, FACC, Raymond G. McKay, MD. Harvard-Thorndike Laboratory, Beth Israel Hospital, Boston, MA.

Percutaneous balloon aortic valvuloplasty (BAV) for the treatment of calcific aortic stenosis (AS) was performed in 192 patients (pts) with a mean age of 77 years (range 35-93), resulting in the reduction of the peak aortic valve gradient from 71±28 to 36±14 (mm Hg*), improvement of the aortic valve area (AVA) from .6±.2 to .9±.3 ($cm^2$*), and improvement of the cardiac output from 4.5±1.4 to 4.9±1.5 (L/min*). Post-BAV, but prior to hospital discharge, there were 7 early deaths and an additional 5 pts who required aortic valve replacement. Of the 180 pts successfully dischaged (mean follow-up 14±4 months, range 3-29), 49 (27%) have developed recurrent symptoms and 30 (17%) have died. The remaining 101 pts (56%) are asymptomatic or improved. Improvement in left ventricular ejection fraction (EF) was seen in pts with an initial low EF, from 37% pre-BAV to 44% post-BAV, to 55% at 5 months mean follow-up. Repeat catheterization has been performed in 36 pts (6 months mean follow-up time) including 22 symptomatic and 14 asymptomatic pts. Late restenosis (defined as a loss of >50% of the initial improved increase in AVA post-BAV) was demonstrated in 20/22 (91%) of the asymptomatic and 8/14 of the symptomatic pts.

Conclusion: BAV can provide effective short-term palliation of symptoms in the majority of pts referred with calcific AS, however late restenosis and mortaltiy rates remain high. *p<.01

CATHETER BALLOON VALVULOPLASTY OF NECROPSY STENOTIC AORTIC VALVES: ETIOLOGY OF AORTIC STENOSIS IS A MAJOR FACTOR IN EARLY "RESTENOSIS"

Bruce F. Waller, MD, FACC, Charles R. McKay, MD, FACC, Ray Erny, MD, Randy Morgan, Emile Mohler, MD. Indiana University, Indpls, IN

Three major causes for adult aortic valve (AV) stenosis (AS) are: congenital bicuspid (usually absent commissural ([C] fusion), rheumatic (fused C) and degenerative (old age) (absent C fusion with mounds of calcium in sinus of Valsalva). Present concepts of catheter balloon valvuloplasty (CBV) invoke C splitting and/or cuspal cracking. To test the theory that stenotic AV without C fusion (i.e. nonrheumatic) result in minimal cuspal injury but stretching of aortic walls at C sites and potentially result in early "restenosis", we dilated 30 stenotic necropsy AV: 8 congenitally bicuspid, 8 old age 3-cuspid and 4 rheumatic 3-cuspid. All 16 nonrheumatic AS valves had superficial and minor cuspal cracks which did little to improve cuspal mobility but all 16 had aortic wall stretching at nonfused C sites during balloon inflation. In contrast, 4 rheumatic AS valves had commissural splitting with or without cuspal cracks which resulted in improved AV mobility. Minimal C aortic wall stretching occurred in the rheumatic valves. These results suggest that initially clinically successful CBV procedures on nonrheumatic causes of AS may be related to aortic wall stretching with minimal cuspal injury. The overstretched aortic walls are likely to have recoil and patients clinically return with early "restenosis". Maximal C injury and minimal aortic wall stretching in rheumatic AS should result in a low incidence of "early restenosis". Thus, efforts should be directed at clinically recognizing AS etiologies before CBV in order predict the likelihood of limited therapeutic success and/or the likelihood of early "restenosis."

SECOND DILATATION FOR RESTENOSIS FOLLOWING SUCCESSFUL BALLOON AORTIC VALVULOPLASTY: RESULTS, PATHOLOGY AND MECHANISM.

Ted Feldman MD FACC, Seymour Glagov MD, Y. Christopher Chiu MD, John D. Carroll MD. The University of Chicago, Chicago, Illinois.

Restenosis after balloon aortic valvuloplasty (BAV) is common, occurring in as many as half of pts in the first year. For many pts, redilation is the preferred therapy for restenosis. We examined results of second dilations and the histology of restenosed valves excised during valve replacement for restenosis.

Six of an initial 50 patients with calcific aortic stenosis underwent second BAV for restenosis. The mean age was 81±7 years. The interval between 1st and 2nd dilatations was 9.7±2.5 months (range 6-12 mos).

| | AREA PRE | AREA POST | CHANGE |
|---|---|---|---|
| 1st BAV | .53±.14 | .95±.18 | .42±.12 |
| 2nd BAV | .59±.15 | .79±.22 | .20±.11* |

The change in valve area after second BAV was only half as great as first BAV ($p<0.01$). Second BAV was done at a time when our overall results were greatly improved (post BAV area 1.08 vs .86 $cm^2$, $p<0.01$).

Multiple histologic sections from excised, restenosed valves from 5 pts showed zones of active capillary and cellular proliferation in crevices between calcific nodules in 3 cases. Associated foci of ossification were seen in 2 of these. Stenotic (non BAV) control valves (n=9) showed no ossifications.

CONCLUSIONS: 1) Histologic changes in restenosed valves differ from those seen initially in calcific aortic stenosis, with granulation, fibrosis and ossification being present. 2) These findings may help to explain the limited results of second dilations for restenosis.

FAILURE OF BALLOON AORTIC VALVULOPLASTY TO RESULT IN SUSTAINED CLINICAL IMPROVEMENT IN PATIENTS WITH DEPRESSED LEFT VENTRICULAR FUNCTION.

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Return of symptoms (sx) after balloon aortic valvuloplasty (BAV) occurs variably within 3 to 6 months. To determine whether invasive hemodynamic parameters are predictive of early return of symptoms, 50 consecutive pts were evaluated pre and post BAV using high-fidelity pressure and digital imaging methods. Stroke work was defined from pressure-volume loops. The acute hemodynamic changes observed in pts with improved symptoms at 3 months were compared to those in whom recurrent sx occurred.

| Acute Changes: | | Improved Symptoms n = 38 | Recurrent Symptoms n = 12 |
|---|---|---|---|
| AVA | Pre-BAV | 0.5 ± 0.2 | 0.5 ± 0.1 |
| ($cm^2$) | Post BAV | 0.7 ± 0.2 | 0.8 ± 0.2 |
| LVEF | Pre-BAV | 51 ± 17 | 31 ± 18* |
| (%) | Post BAV | 53 ± 16 | 34 ± 18* |
| Stroke Work | Pre-BAV | 14.6 ± 6.1 | 8.8 ± 4.3* |
| (erg x $10^6$) | Post BAV | 12.4 ± 5.5 | 8.4 ± 4.2 |
| Peak + dp/dt | Pre-BAV | 1778 ± 423 | 1325 ± 469* |
| (mmHg/sec) | Post BAV | 1584 ± 380 | 1241 ± 450* |

*$p < 0.005$ recurrent symptoms vs. improved symptoms

The final aortic valve area (AVA) did not predict which pts developed recurrent sx. Early return of sx occurred in pts with baseline depressed LV function (as evidenced by a low EF, SW and peak + dP/dt).

Thus, aortic valvuloplasty in pts with intrinsically depressed LV performance does not appear to result in sustained clinical improvement at 3 months compared to pts with preserved LV function.

NEW DEVELOPMENTS IN AORTIC BALLOON VALVULOPLASTY

Alain Cribier M.D., F.A.C.C., Fernando Grigera M.D., Hélène Eltchaninoff M.D., Eric Lefebvre M.D., Jacques Berland, M.D. and Brice Letac M.D, F.A.C.C.
University of Rouen, France.

In our initial experience (Group A) of 182 patients (Pts) aortic balloon valvuloplaty (BV) was performed with non - specific catheters (NSC) designed for dilatation of pulmonic valves and peripheral arteries; maximal balloon size used was > 20 mm in only 9 % of the cases; no arterial sheath (ASh) were used for NSC femoral insertion. In the 146 following Pts (Group B), advances in BV consisted in the use of: 1) a double size balloon catheter specifically designed for BV of the aortic valve in all Pts, 2) larger balloon sizes : > 20 mm in 52 % of the cases (23 mm or 25 mm), 3) a 14 F ASh in the last 69 Pts. Pre-BV clinical and hemodynamic data were similar in the two groups. Results and complications were compared in Group A and B : mean duration of BV : 120 ± 32 mn vs 35 ± 16 mn ($p<.05$), post-BV mean gradient (mm Hg) and valve area ($cm^2$) : 29 ± 14 vs 26 ± 12 ($p<.05$) and .92 ± .3 vs 1.05 ± .3 ($p<.001$), increased valve area to >= 1 $cm^2$ : 36 % vs 52 % ($p<.01$); in-hospital mortality : 5 % vs 3 %, stroke: 2 % vs .7 %, pericardial tamponade : 2 % vs .7 %, severe aortic regurgitation : .6 % vs .7 %. Vascular complications and need for surgical repair were unchanged in the two groups when ASh was not used: 14.8 % and 5.5 % vs 14.2 % and 5 % but decreased to 4.9 % and 0 % with the use of ASh in Group B.

Conclusions : with these new developments, aortic balloon valvuloplasty has become a simpler, faster and more effective procedure. The rate of major complications tends to decrease. The use of a 14 F arterial sheath has markedly reduced the number of vascular complications and the need for femoral artery surgical repair.

## Monday, March 20, 1989
## 4:00PM–5:30PM, California Pavilion D
## Anaheim Hilton Hotel
## Long-Term Follow-Up of Mitral Balloon Valvuloplasty

SIX MONTH FOLLOW-UP OF MITRAL BALLOON VALVULOPLASTY

Raoul Bonan, M.D., F.A.C.C. for the NHLBI Balloon Valvuloplasty Registry, Coordinating Center, University of Washington, Seattle, WA.

Twenty-three centers entered 223 pts undergoing mitral balloon valvuloplasty (MBV) into the Balloon Valvuloplasty Registry (BVR) between 11/87 and 9/88. Of the first 47 pts having MBV >6 mo. ago there were 4 early (3 cardiac, 1 noncardiac) deaths (9%). To determine the early clinical course of pts following MBV we have compared the functional status of the 30 surviving pts at baseline, 5 wks and 6 mo. There were 7 men 60+21 yrs of age and 23 women age 54±21 yrs. Mitral stenosis was severe in 43% and moderate in 43%. Mild mitral regurgitation was present in 27% and moderate in 7%. At baseline congestive heart failure (CHF) was present in all pts but was severe (class III or IV) in 73%. At 5 wks CHF was still present in 53% but was severe in only 23%. By 6 mo. CHF was present in 57% but was severe in only 17%. A history of syncope was present in 17% at baseline, 7% at 5 wks and in 10% between 5 wks and 6 mo. Angina was infrequent both before and following MBV. At 5 wk follow-up, 73% of pts were improved, 20% were unchanged and 7% were worse. At 6 mo., 80% were reported improved, 13% unchanged and 7% were worse. Rehospitalization had been required in 17% by 5 wks and in 33% between 5 wks and 6 mo.

Thus MBV results in substantial clinical improvement by 5 wks with further clinical improvement over the next 5 mo. Early mortality was high (9%) and late mortality occurred in 1/43 pts (2%) MBV may be a suitable alternative to mitral valve surgery in selected pts who are at increased risk for surgery.

LONG-TERM FOLLOW-UP OF PATIENTS UNDERGOING CLOSED TRANSVENTRICULAR MITRAL VALVE COMMISSUROTOMY

David R. Holmes Jr. M.D., F.A.C.C., Robert L. Frye M.D., F.A.C.C., Rick A. Nishimura M.D., F.A.C.C., Duane M. Ilstrup, LaVon N. Hammes, Hartzell V. Schaff M.D., F.A.C.C., John W. Kirklin M.D., F.A.C.C., Mayo Clinic, Rochester, Minnesota.

Surgical transventricular mitral valve dilatation (TVMVD) as performed in the 1960's and percutaneous mitral balloon valvuloplasty of the 1980's both involve nonvisually-directed dilatation of the mitral valve. Long-term follow-up of the former may allow a comparison cohort for the latter. Two hundred sixty seven pts underwent TVMVD for significant mitral stenosis at Mayo Clinic from 1960-1964; 207 females, 60 males, mean age 43.6 years (yrs). Sixty-one percent were NYHA functional class III or IV. In these pts, 24.1% had LA thrombus at surgery. Thirty-day perioperative complications included death, 2.6%; cerebrovascular accident (CVA), 1.9%; non-central nervous system embolus, 1.1%; and new or worsened mitral insufficiency in 22.5%. Following surgery, 92% were symptomatically improved; improvement lasted 1 - 2 years in 12.4%, 3 - 4 yrs in 24.4%, 5 - 10 yrs in 28.8%, and 10 - 20 yrs in 24.4%. During a mean follow-up of 15.5 yrs, actuarial survival free of death, mitral valve replacement (MVR) and CVA were:

| | 1 Yr | 5 Yrs | 10 Yrs | 15 Yrs | 20 Yrs | 25 Yrs |
|---|---|---|---|---|---|---|
| Death | 94.3% | 89.9% | 79.7% | 70.3% | 60.4% | 46.0% |
| MVR | 98.3% | 91.0% | 74.7% | 53.7% | 41.4% | --- |
| CVA | 98.4% | 97.5% | 93.1% | 88.1% | 85.5% | 82.4% |

Conclusion: Symptomatic improvement from TVMVD (and possibly mitral balloon valvuloplasty) is maintained at least 3 - 4 yrs in approximately 75% of pts. At the end of 10 yrs, approximately 75% remain free of mitral valve replacement.

ADVANTAGES OF INOUE-BALLOON(SELF-POSITIONING BALLOON) IN PERCUTANEOUS TRANSVENOUS MITRAL COMMISSUROTOMY(PTMC) AND AORTIC VALVULOPLASTY(PTAV).

Kanji Inoue, M.D., Masakiyo Nobuyoshi, M.D., F.A.C.C., Chanrong Chen, M.D., Jui Song Hung, M.D., Kochi Municipal Hospital, Kochi, Japan and 60 Collaborating Institutions in Japan, China and Taiwan

Clinical application of non-surgical mitral commissurotomy was firstly success in 1982 by using the Inoue-Balloon, and recently its clinical use has been rapidly increased, 713 patients (pts). The technical success rate was 97%. PTMC resulted in a decrease in mitral valve gradient from 12.0 ± 5.9 to 5.4 ± 3.0 mmHg and in an increase of mitral valve area from 1.22 ± 0.44 to 2.13 ± 0.76 cm2. No patients died due to PTMC. Complication included 2 (0.3%) cerebral embolisms, and 10 (1.4%) severe mitral regurgitations. The Inoue-Balloon has also been used in the antegrade aortic valvuloplasty in 58 pts. The technical success rate was 96%. PTAV resulted in a decrease in aortic valve gradient from 87 ± 29 mmHg to 44 ± 16 mmHg, and in an increase of aortic valve area from 0.50 ± 0.20 to 0.87 ± 0.39 cm2. One patient died due to a severe aortic regurgitation. Three patients underwent a subsequent aortic valve replacement for an increase of regurgitation. The advantages of the Inoue-Balloon are as follows. It has a large diameter (25 - 31 mm in mitral, 18 - 25 mm in aortic) with a low profile (4.5 mm in mitral, 4.0 mm in aortic). The balloon is easily placed at the right position. The balloon does not slip out of the valve during dilatation. Inflation and deflation can be totally completed within 5 seconds. These advantages allow a high success rate, good efficacy and low risk in PTMC and PTAV.

**LONG-TERM FOLLOW-UP IN 105 PATIENTS UNDERGOING PERCUTANEOUS BALLOON MITRAL VALVULOPLASTY.**

Marc J. Levine, M.D., Raymond E. Erny, M.D., Bradley M. Leonard, M.D., Ronald D. Jenkins, M.D., Gregg J. Reis, M.D., Daniel J. Diver, M.D., Robert D. Safian, M.D., Patricia C. Come, M.D., F.A.C.C., Raymond G. McKay, M.D. Harvard-Thorndike Laboratory, Beth Israel Hospital, Boston, MA

Single or double balloon mitral valvuloplasty (BMV) was successfully performed in 97 of 105 pts with critical mitral stenosis (MS) (age 27 to 83 years), including 51% with significant valvular calcification. 54% were considered high surgical risk due to advanced age, severe pulmonary hypertension or heart failure, or need for coronary artery bypass grafting or aortic valve replacement. Post BMV, there was improvement in mitral valve area (MVA; 1.0±0.4 to 1.9±0.7cm$^2$*), mean mitral gradient (14±5 to 7±3 mmHg*), CO (4.2±1.2 to 5.0±1.6 L/min*), pulmonary capillary wedge pressure (24±7 to 16±6 mmHg*), mean PA pressure (39±15 to 31±12 mmHg), and pulmonary vascular resistance (335±351 to 277±232 dynes-sec-cm$^{-5}$*). Complications included 1 death, 2 left atrial perforations, 1 stroke, one TIA, one myocardial infarction, and 21 small atrial septal defects (mean Qp/Qs=1.4±0.4). There have been 8 late deaths unrelated to the procedure. Two pts underwent valve replacement due to suboptimal symptom relief and 4 other pts developed recurrent symptoms 16 months after BMV; 2 of these responded to repeat BMV (9 and 13 months after initial BMV, respectively), one underwent valve replacement, and one is being mangaged medically. All other pts (88%) remain symptomatically improved 14±8 (range 1 to 30) months post BMV. Serial echo/doppler studies at 3, 6, and 12 months after BMV demonstrate persistent improvement in MVA. Follow-up (F/U) catheterization was performed in 20 pts 11±6 months after BMV, only 4 of whom were symptomatic:

| | Pre-BMV | Post-BMV | F/U |
|---|---|---|---|
| MVA | 0.8±0.3 cm$^2$ | 1.8±0.8 cm$^{2*}$ | 1.5±0.6 cm$^{2*}$ |

**Conclusion:** BMV in adult pts with MS results in longterm improvement in valve function and symptoms. (* $p < .01$)

EARLY AND LONGTERM RESULTS AFTER MITRAL VALVULOPLASTY AS COMPARED WITH VALVE REPLACEMENT

Felicitas Kraus MD, Serban Dacian MD, Caroline Rudolph MD, Donald Hall MD, FACC, Werner Rudolph MD, FACC.
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To compare the results of successful valvuloplasty (VP) with those of valve replacement (VR) for severe mitral stenosis, studies were performed in 63 pats with pre-existing valve orifice area <1.0 qcm/qm (1.1±0.4 qcm prior to VP and 1.1±0.4 qcm prior to VR). Before, 1 week(w) and 1/2 year(y) after VP as well as before, 2-3 w and 1/2 y after VR resting (R) and exercise (EX) hemodynamics as well as $O_2$-saturation in the pulmonary artery (PA) were determined.

| | PAPm (mmHg) | | SV (ml) | | PA-$O_2$ (sat%) | | HR (b/min) | |
|---|---|---|---|---|---|---|---|---|
| | R | Ex | R | Ex | R | Ex | R | Ex |
| pre VP | 30 | 63 | 57 | 54 | 61 | 37 | 72 | 128 |
| post VP (1w) | 23 | 51 | 67 | 67 | 64 | 41 | 69 | 126 |
| post VP(1/2y) | 22 | 51 | 64 | 64 | 66 | 40 | 65 | 126 |
| pre VR | 27 | 61 | 70 | 67 | 65 | 40 | 70 | 123 |
| post VR(2-3w) | 19 | 43 | 66 | 79 | 64 | 39 | 81 | 118 |
| post VR(1/2y) | 17 | 42 | 65 | 75 | 67 | 41 | 74 | 115 |
| p values | | | | | | | | |
| pre VP vs VR | ns | ns | .01 | .005 | .025 | .01 | ns | ns |
| postVPvsVR(1/2-3w) | .05 | .005 | ns | .05 | ns | ns | .005 | ns |
| postVPvsVR(1/2y) | .005 | .005 | ns | .05 | ns | ns | .025 | ns |

Both early and during longterm follow-up after VP, at R and during EX, PA-pressure was higher than after VR. As it had been prior to the procedure, during EX after VP, stroke volume was also lower.
Thus, VP leads to improvement in hemodynamics at R and during EX which are not, however, comparable to those obtained by VR.

COMPARISON OF LONG-TERM HEMODYNAMIC EVALUATION BETWEEN PERCUTANEOUS MITRAL VALVULOPLASTY AND MITRAL VALVULAR REPLACEMENT FOR SEVERE MITRAL STENOSIS.

Christian Spaulding, M.D., Raoul Bonan, M.D., F.A.C.C., Antonio Serra, M.D., Jacques Crépeau, M.D., Ihor Dyrda, M.D., F.A.C.C., Conrad Pelletier, M.D., Montreal Heart Institute, Montreal, Canada.

We compared long-term hemodynamic evolution after percutaneous mitral valvuloplasty (PMV) and mitral valve replacement (MVR) for severe mitral stenosis. PMV was performed in 33 pts (group 1) and MVR in 21 (group 2) using porcine in 13 and mechanical valves in 8. Cardiac catheterization was done before the procedures and 6.28±1.34 mo. after PMV and 17.3±19.4 mo. after MVR. Initial clinical status and hemodynamic measurements at rest were similar in both groups. The following variations in mean mitral valve area (MVA) and cardiac index (CI) were noted:

| | Group 1 (PMV) | Group 2 (MVR) | p |
|---|---|---|---|
| Initial MVA (cm2) | 1.16±0.416 | 1.2±0.11 | NS |
| Post procedure MVA at rest | 1.799±0.775 | 2.553±0.786 | <0.05 |
| Post procedure MVA during exercise | 2.88±1.24 | 3.22±0.911 | NS |
| Initial CI (l/min/m2) | 2.695±0.913 | 2.504±0.52 | NS |
| Post procedure CI at rest | 2.49±0.710 | 2.956±0.67 | <0.05 |
| Post procedure CI during exercise | 5.00±1.46 | 5.25±1.45 | NS |

In conclusion, PMV may not be as efficient as MVR in increasing MVA and CI, but during exercise this difference disappears, suggesting that similar valve performance is obtained after PMV.

## Monday, March 20, 1989
## 2:00PM–3:30PM, Marriott Hall North
## Anaheim Marriott Hotel
## Electrophysiologic Testing of Ventricular Tachycardia

RELATION OF INDUCIBILITY OF VENTRICULAR ARRHYTHMIAS TO SYMPTOMS IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY - RELEVANCE OF INDUCED POLYMORPHIC VENTRICULAR TACHYCARDIA.

Lameh Fananapazir, M.D., Cynthia Tracy, M.D., Judith B. Winkler, B.S., Martin Leon, M.D., Richard Cannon, M.D., Stephen E. Epstein, M.D., F.A.C.C., NHLBI, Bethesda, MD

Programmed ventricular stimulation (PVS) using >2 premature stimuli (PS) in pts with hypertrophic cardiomyopathy allegedly induces non-specific polymorphic ventricular tachycardia (VT). We studied the relation of inducibility of polymorphic and monomorphic VT to symptoms, >3 beat VT on 48-hour Holter monitor and aggressiveness of PVS (number and prematurity of PS and number of ventricular sites tested), in 106 pts. PVS of up to 3 PS, 3 drive pacing rates (600, 500 and 400 bpm), and 2 RV and an LV site, induced sustained (>30 beat or requiring cardioversion) ventricular arrhythmia in 44 (42%) pts. The arrhythmia was polymorphic VT in 32 (73%) pts, monomorphic VT in 10 (23%) pts and ventricular fibrillation in 2 (5%) pts. The relation between presenting symptoms and inducibility of ventricular arrhythmias, including polymorphic VT was significant (p<0.02):

| Presentation | No. Pts | All arrhythmias ≤2 PS | All arrhythmias >2 PS | Polymorphic VT |
|---|---|---|---|---|
| Cardiac Arrest | 13 | 1 (8%) | 10 (80%) | 8 (62%) |
| Syncope | 41 | 8 (20%) | 20 (50%) | 12 (30%) |
| Presyncope | 29 | 3 (10%) | 9 (30%) | 6 (21%) |
| No symptoms | 23 | 1 (4%) | 5 (23%) | 5 (23%) |

Incidence of induced polymorphic (compared with monomorphic VT) was unaffected by aggressiveness of PVS. The incidence of non-sustained VT on Holter was unrelated to symptoms or inducibility of VT. We conclude, 1) sensitivity of PVS using 2 PS is low for identifying symptomatic pts with inducible VT, 2) inducibility of monomorphic as well as polymorphic VT may indicate cardiac electrical instability and provide a guide to therapy.

ROLE OF ELECTROPHYSIOLOGIC TESTING IN PATIENTS WITH ASYMPTOMATIC NONSUSTAINED VENTRICULAR TACHYCARDIA: RELATIONSHIP TO VENTRICULAR FUNCTION AND THE PRESENCE OR ABSENCE OF CORONARY ARTERY DISEASE.

Stephen Hammill M.D., Jane Trusty R.N., Bernard Gersh M.D., Michael Osborn M.D., Douglas Wood M.D., David Holmes M.D., Mayo Clinic, Rochester, MN

105 pts with asymptomatic nonsustained ventricular tachycardia (VT) were evaluated prospectively to assess the value of electrophysiologic testing (EP) in pt subgroups which included normal or abnormal ejection fraction and the presence or absence of coronary artery disease. EP consisted of 3 extrastimuli delivered during sinus rhythm and right ventricular pacing at 100 and 150 bpm from 2 sites. A positive test (EP+) was defined as monomorphic VT lasting ≥30 sec or requiring cardioversion. EP+ pts were treated using serial drug testing including amiodarone. An event during follow-up was defined as sustained VT requiring physician intervention for termination or out-of-hospital cardiac arrest.

Results. (Mean follow-up 15 months). **Group 1:** In 55 pts with an ejection fraction(EF) ≥40% there were no events and 4 were EP+. **Group 2:** In 50 pts with EF <40%, **Group 2A** had 26 with coronary artery disease (CAD) (mean EF 28%) of whom 12 were EP+ with 1 event and 14 EP- with 3 events; and **Group 2B** had 24 with nonCAD (dilated cardiomyopathy in 23) (mean EF 24%), of whom 2 were EP+ with no events and 22 EP- with 8 events.

Conclusions: 1) Pts with EF ≥40% had low inducibility (7%), no events and do not require EP; 2) Pts with EF <40% and nonCAD had low inducibility (8%), a 33% event rate and did not benefit from EP; and 3) Pts with EF <40% and CAD had high inducibility (46%), a negative study was of no value, and EP guided therapy appeared helpful.

ELECTROPHYSIOLOGIC TESTING IN PATIENTS WITH ASYMPTOMATIC NONSUSTAINED VENTRICULAR TACHYCARDIA PREDICTS RISK OF SUDDEN DEATH OR SUSTAINED VENTRICULAR TACHYCARDIA WITHIN THE FIRST YEAR BUT NOT THEREAFTER.

Edward J. Loughery, M.D., William M. Miles, M.D., FACC, Naomi S. Fineberg, Ph.D., James J. Heger, M.D., FACC, Lawrence S. Klein, M.D.,FACC, Douglas P. Zipes, M.D., FACC, Eric N. Prystowsky M.D., FACC, Indiana Univ School of Med, Krannert Inst of Cardiol, VAMC, Indpls, IN

We prospectively performed drug-free electrophysiologic studies (EPS) on 79 patients (pts) (age 57.1 ± 13.3 yrs) with asymptomatic nonsustained ventricular tachycardia (VTNS). Pts had coronary artery disease (CAD)(n=55), cardiomyopathy or valvular heart disease (HD)(n=16) or no structural HD (n=8). Using up to 3 extrastimuli (S4), group (gp) I (54/79, 68%) had either no VT (n=21), VTNS (n=25) or ventricular fibrillation (VF) with S4 (n=8) induced at EPS. Gp II (25/79, 32%) had either sustained monomorphic VT (VTS)(n=20) or VF with < S4 (n=5) induced at EPS. No gp I pt was treated, and only 16/25 gp II pts received therapy (guided by serial EPS in 11/16 pts). Survival curve analysis showed that survival without VTS or sudden death (SD) in gp I pts was almost twice as long as in gp II pts (41.6 ± 2.5 vs 23.9 ± 3.5 mo; p=0.013). Of note, the greatest difference in VTS/SD-free survival occurred in the first 13 mo of followup (47/54 gp I vs 17/25 gp II pts, p <0.05). In contrast, at the end of the followup period (mean 22.5 mo, range 0.4 to 50.5) there was no difference in VTS/SD-free survival (42/54 gp I vs 16/25 gp II). We conclude: 1) in pts with asymptomatic VTNS, induction of VF with < S4 or VTS at EPS predicts a shorter VTS/SD-free survival time than induction of no VT, VTNS, or VF requiring S4; 2) reevaluation of risk may be appropriate at 1 yr, possibly because of disease progression.

SHOULD THE INDUCTION OF NONSUSTAINED VENTRICULAR TACHYCARDIA DURING BASELINE ELECTROPHYSIOLOGIC TESTING CONSTITUTE A POSITIVE STUDY?

Christopher A. Bonnet, M.D., James J. Elson, M.D., Ph.D., Susan B. Fiedler, R.N., Richard N. Fogoros, M.D., F.A.C.C., Allegheny General Hospital, Pittsburgh, Pennsylvania.

The induction of nonsustained ventricular tachycardia (NSVT) during baseline electrophysiologic study (EPS) is often considered a nonspecific finding, and such patients are often regarded as being non-inducible. Of 148 consecutive patients presenting with sustained ventricular tachycardia or cardiac arrest, 33 (Group A) had > 10 beats of NSVT (17±8 beats) as the only inducible arrhythmia at baseline EPS. Twenty-four (Group B) were considered noninducible (< 10 beats of ventricular tachycardia). Between groups there were no significant differences in age or sex distribution, or in severity of underlying cardiac disease. Patients in Group A received aggressive therapy guided by serial EPS, which included implantation of the automatic implantable cardioverter-defibrillator in 10. Patients in Group B received no antiarrhythmic therapy. The mean follow-up was 35±16 (±SD) months for Group A and 25±17 months for Group B. The actuarial incidence of recurrent sustained ventricular tachycardia or cardiac arrest (±SE) was:

| Months | Group A (n=33) | Group B (n=24) | P |
|---|---|---|---|
| 6 | 6±4% | 0% | < .01 |
| 12 | 15±6% | 0% | < .01 |
| 24 | 24±8% | 6±6% | < .05 |

Conclusions: Patients in whom NSVT of at least 10 beats in duration is the only arrhythmia inducible at baseline are at a significantly higher risk of arrhythmia recurrence (despite aggressive therapy) than patients who are noninducible. Our data suggests that the induction of NSVT at baseline EPS should be considered a positive study.

FAVORABLE OUTCOME OF PATIENTS WITH VENTRICULAR TACHYCARDIA OR FIBRILLATION AND A NORMAL ELECTROPHYSIOLOGIC STUDY

Soo G. Kim M.D., F.A.C.C., Alan P. Aboaf B.S., Anthony D. Mercando M.D., John D. Fisher M.D., F.A.C.C., Montefiore Medical Center, Bronx, NY

A subset of patients with ventricular tachycardia (VT) or ventricular fibrillation (VF) is not inducible at baseline by programmed stimulation (PES) and thus does not qualify for PES guided antiarrhythmic drug therapy (Rx). The prognosis of these pts is unclear. We studied 25 pts (coronary artery disease in 11, cardiomyopathy in 9, others in 5) who had sustained (≥30 seconds or required cardioversion) VT (n=16) or VF (n=9) not associated with remediable causes or an acute myocardial infarction. Mean ejection fraction was 54 ±15%. PES protocol included 3 extrastimuli and rapid pacing at 2 sites. All pts were noninducible (≤10 beats) by PES at baseline before Rx. All had Holter monitors before and after drug Rx. In 18 pts frequent (≥10/hour) ventricular ectopy was noted. Infrequent ventricular ectopy was noted in 7 pts. Antiarrhythmia Rx was guided by Holter monitoring or chosen empirically (beta-blockers in 4). One pt received an implantable defibrillator while none had coronary bypass or angioplasty. No pts had exercise induced arrhythmias at discharge. During follow up (28±18 months), 2 pts had nonfatal VT, 2 had sudden death (6 and 20 months), and 2 died of congestive heart failure. Actuarial survival rates at 1, 2, 3 and 4 years were 95%, 90%, 90% and 90% for sudden death, 95%, 85%, 79% and 79% for total cardiac death and 90%, 85%, 76% and 76% for arrhythmia free survival, respectively. Conclusion: Pts with sudden death and a normal PES study have a very good prognosis at 4 years - 90% had no sudden death. This favorable outcome may be due to the relatively good ventricular function or the antiarrhythmic Rx in this study.

MULTIPLE MORPHOLOGIES OF INDUCED VENTRICULAR TACHYCARDIA: ROLE OF ANTIARRHYTHMIC DRUGS AND CLINICAL IMPLICATIONS.

Marc Dubuc, M.D., Teresa Kus, M.D., Ph.D., Wilhelm Kaltenbrunner, M.D., Dominique Lacroix, M.D., Mohammad Shenasa, M.D., Ph.D., F.A.C.C., Sacré-Coeur Hospital, University of Montreal, Montreal, Canada.

Different morphologies of ventricular tachycardia (VT) are believed to represent different sites of origin and/or different epicardial breakthroughs of cardiac activation. It implies also a different sequence of activation that may interfere with recognition of VT by devices using morphology criteria for termination. We studied the effect of antiarrhythmic drugs (AAD) on VT morphology as defined by frontal and horizontal axis criteria. Twenty-three coronary artery disease Pts with a mean age of 63 ± 6 yrs had serial programmed electrical stimulation (PES) using right ventricular (RV) drive at 2 basic cycle lengths and 1 to 3 extrastimuli at 2 RV sites were done without and on drug. All Pts had several inductions of VT at every study. In the drug-free state, all 23 Pts manifested only one induced VT morphology that was identical to the spontaneous "clinical VT" morphology. Subsequently, all Pts had 1-4 PES on AAD. In 8 Pts (35%), at least one new morphology appeared on AAD and, in 6 of these, the morphology induced at the drug-free study was no longer inducible. In the remaining 15 Pts, VT morphologies on AAD were unchanged. Therefore, in 35% of Pts on AAD, new VT morphologies appeared and in 75% of these, the original "clinical VT" was no longer inducible. We conclude that new VT morphologies may be caused by the use of AAD and this will have major clinical impact in the use of AAD in Pts with implantable devices that use morphology criteria for recognition and termination of VT.

## Monday, March 20, 1989
## 4:00PM–5:30PM, Marriott Hall North
## Anaheim Marriott Hotel
## Clinical Electrophysiology: Ventricular Tachycardia

THE LONG QT SYNDROME INTERNATIONAL PROSPECTIVE REGISTRY

Peter J. Schwartz, MD,FACC*, Arthur J. Moss, MD,FACC**, Emanuela Locati,MD*, Richard S. Crampton,MD,FACC***, Daniel Tzivoni,MD,°, Arthur Garson,MD,FACC°°, G.Michael Vincent,MD,FACC°°°, *Univ. of Milan, **Univ. of Rochester, ***Univ. of Virginia, °Univ. of Jerusalem, °°Texas Children's Hospital, °°°Univ. of Utah

The international prospective registry for the idiopathic long QT syndrome (LQTS), established in 1979, has enrolled 1766 subjects as of July 1988. Besides specific projects, the main objectives of this study include definition of the natural history of LQTS, risk stratification particularly for the asymptomatic family members with a prolonged QT interval, and long term assessment of therapy. The population includes 250 probands (first patient diagnosed as affected by LQTS in a family) and 1516 first and second degree family members. For 617 family members the ECG analysis and clinical history is not yet complete. Among the probands 67% are females, 7% have congenital deafness, 84% have history of syncope and/or cardiac arrest, 63% had their first episode below age 15, 92% are treated, and 20% had left stellectomy. Pharmacologic and surgical antiadrenergic interventions confirm high long term therapeutic efficacy. Among the 646 patients with prolonged QT interval (QTc>440 msec), 46% were symptomatic. A significant finding is the fact that among the 503 family members with normal QT interval, 30 (6%) had syncope. This confirms the concept that LQTS has a wide spectrum and that, among affected families, the disease may become fully manifest even in the absence of a prolonged QT interval of the surface ECG.

ETIOLOGY OF POLYMORPHIC VENTRICULAR TACHYCARDIA IN THE ABSENCE OF PROLONGED QT

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Polymorphic ventriclar tachycardia (Poly-VT) is known to be associated with QT prolongation, either congenital or secondary to drug therapy or electrolyte imbalances. The clinical correlates of Poly-VT with normal QT interval are unclear. Data from 18 patients presenting with Poly-VT unassociated with QT prolongation are reported here. There were 14 males and 4 females. QT interval averaged 390 ± 40 msec. Mean age was 63 ± 11 years. Mean left ventricular ejection fraction was 36 ± 9%. Sixteen of the 18 patients had severe coronary disease while 14 had prior myocardial infarctions. In 13 patients, a high grade stenosis (>90%) could be identified in at least one artery which supplied viable myocardium. Poly-VT was abolished in all patients who underwent successful revascularization surgery. One patient, who had 99% stenosis of the right coronary artery supplying an infarcted inferior wall, had exercise induced Poly-VT which persisted even after Amiodarone therapy. Poly-VT was abolished after successful agioplasty (PTCA) of the stenotic vessel. Two patients also responded to Amiodarone treatment. Three patients died from medically refractory arrhythmias prior to surigical intervention.

Conclusions: Clinical Poly-VT without QT prolongation is most likely assocciated with high grade coronary artery stenoses. Revascularization surgery (or PTCA) appears to be an effective therapy to abolish Poly-VT and should be considered urgently in patients who present with this entity.

NEW CRITERION FOR DIAGNOSIS OF SUSTAINED BUNDLE BRANCH REENTRY TACHYCARDIA.

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The distinction of sustained bundle branch reentry tachycardia (SBBRT) from ventricular (V) tachycardia originating from V muscle with secondary His bundle (H) activation can pose a problem. We postulated that in SBBRT, variations in H-H intervals (delta HH) should precede similar V-V intervals changes (delta VV). Whereas, in tachycardia of V origin with incidental activation of the H, delta HH will be expected to follow delta VV.

Electrophysiologic data was analyzed in 20 consecutive patients in whom 23 SBBRT's were induced in the laboratory. When delta HH during the second, third, and fourth tachycardia beats were plotted against succeeding delta VV, the correlation coefficients were 0.98 and 1.00. In contrast, when delta HH of the same beats were compared to delta VV of the preceding beats, the correlation coefficients were -0.29 and -0.46.

Conclusions: (1) Spontaneous H-H cycle length (CL) variations producing corresponding V-V CL changes in subsequent complexes with no relation to the preceding V-V CL's may be the most reliable diagnostic criterion of SBBRT as the mechanism. (2) Such data would strongly argue against ventricular myocardial origin of these tachycardias.

HIS-PURKINJE ACTIVATION DURING VENTRICULAR TACHYCARDIA: A DETERMINANT OF QRS DURATION.

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Patients with ventricular tachycardia (VT) may have several VT morphologies with differing QRS durations. To test if the timing of His-purkinje activation may determine QRS duration, we recorded His bundle potentials (quadripolar catheters) and measured VH intervals (onset QRS-His potential) during 59 VTs in 24 patients (1-7 VTs/patient). His potentials were visible in 55 VTs (93%) and in each patient during at least 1 VT. VH intervals ranged from -38 to 246 ms (mean 67±55 ms). The mean cycle length of 45 (76%) VT showing a 1:1 QRS:H relationship was longer than the 14 (24%) VT without a 1:1 QRS:H ratio (349±70 ms vs 310±55 ms, $p<0.05$). In 8 patients having ≥3 VTs with measurable VH intervals, regression analysis showed a close correlation between QRS duration and VH (mean r=0.878), but not between QRS duration and VT rate (mean r=0.455). Catheter mapping during 23 VTs showed 14 VTs from the basal 1/2 of the heart had shorter VH intervals than 9 VTs from the apical 1/2 (22±32 ms vs 87±67 ms, $p<.02$) but there was no difference in VH during VT of septal origin (63±65 ms) vs free wall origin (63±73 ms). In sum: 1) His potentials are visible during VT in >90% of VTs and associated with the QRS, rather than dissociated, in the majority of these; (2) the close correlation between VH and QRS duration in VT suggests that the His-purkinje system is important in ventricular activation during VT but (3) more work is needed to determine if there is His-purkinje participation in the VT circuit.

USE-DEPENDENT PROLONGATION OF VENTRICULAR TACHYCARDIA CYCLE LENGTH BY TYPE IA AND IC DRUGS.

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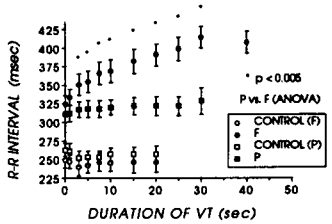
The *in vitro* time course of use-dependent sodium channel blockade by Type IA and IC antiarrhythmic drugs differs markedly. We studied 29 sustained monomorphic ventricular tachycardias (VT) in 27 patients. Identical control (C) and drug VT morphologies (Leads I, aVF, V1) were induced before and after either procainamide (P) or flecainide (F) therapy. VT cycle length (CL) at onset was not significantly different for P and F controls (263±9 vs. 249±10 ms) and did not change over 20 sec of observation (see inset). Following P (n=15), VT CL at onset increased to 311±11 ms ($p<0.001$, vs. C) and did not change thereafter (VT CL = 320±10 ms after 30 sec). Although F (n=14) also produced a prolongation of VT CL at onset (324±12 ms; $p<0.001$, vs. C), VT CL continued to increase over time to a steady state value of 408±14 ms. The mean change between onset and steady state VT CL following F (83±9 ms) was significantly greater than that following P (9±4 ms) ($p<0.005$). The time constant for this "use-dependent" prolongation of VT CL by F was 13.2±1.3 sec. Beat-to-beat mean arterial pressure, measured in 5 VT's during therapy with F, increased from an onset value of 62±2 to 97±7 mm Hg. The time course of the observed hemodynamic response was similar to the use-dependent VT CL prolongation.

In conclusion: P and F produce similar changes in VT CL at onset, but only F was associated with additional use-dependent changes in VT CL. Use-dependent prolongation of VT CL by F may be an important determinant of clinical hemodynamic tolerance of VT during therapy with Type IC drugs.



TIME-DEPENDENT ELECTROPHYSIOLOGIC CHANGES AFTER EXPERIMENTAL MYOCARDIAL INFARCTION: PARALLEL CHANGES IN INDUCIBILITY OF VENTRICULAR ARRHYTHMIAS AND THE SIGNAL-AVERAGED ELECTROCARDIOGRAM.

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This study sought to identify the relationship between late potentials (LPs) detected on the body surface in a canine model of post-infarction ventricular tachycardia (VT) with the results of programmed cardiac stimulation (PCS) at different stages after anteroapical myocardial infarction (MI). Signal-averaged ECG was performed in 11 dogs immediately prior to PCS at 5 day intervals during the first 3 weeks after MI. PCS was performed from 3 ventricular sites with ≤3 extrastimuli. VT was defined as >10 nonstimulated monomorphic ventricular beats. LPs were defined as QRS duration >58ms, voltage in the last 20 ms of the QRS <20uV and late potential duration >18ms, using a bidirectional 4 pole Butterworth filter (40-250 Hz).

**Results:** During stage I (0-3 days), 5 dogs were studied: none had LPs and no VT was induced. During stage II (4-10 days), 18 studies were performed. In 5, LPs were present: 4 had VT and 1 had VF induced. Two additional dogs without LP had VF induced. During stage III (>10 days), 10 studies were performed. Two dogs had LPs and each had VT; an additional 3 dogs without LP had VF and no arrhythmia was induced in the remainder. In all cases where a LP appeared, VT or VF was induced at that day's study. In 2 dogs, disappearance of LPs coincided with failure to induce VT.

**Conclusion:** There is a close relationship between temporal changes in signal-averaged ECG and response to PCS after canine MI, suggesting that inducibility of VT is dependent on changes in cardiac conduction.

## Monday, March 20, 1989
## 2:00PM–3:30PM, California Room D
## Anaheim Convention Center
## Color-Flow Doppler: Relationship of Flow Maps to Jet Dynamics

LIMITATIONS OF COLOR DOPPLER IN ANALYSIS OF VALVULAR REGURGITATION.

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Attempts have been made to quantify regurgitation based on color Doppler(CD) imaging. To test the ability of (CD) to distinguish volume(VOL) from velocity(VEL), we constructed an apparatus that allowed us to observe the CD pattern of different VOLs flowing at different VELs. A bath of Hespan$^{R}$ was fitted with a CD transducer and the tube of a power injector so that flow was directed at the transducer. The injector was used to deliver a precise VOL(ml) at identical rates(ml/sec). The actual VEL of flow was altered independently, according to the Bernoulli theorem, by changing the orifice diameter(OD)(1 vs. 2mm). Thus the relative effects of changes in VOL vs. VEL on the CD flow pattern could be compared. The CD pattern was graded, in a blinded fashion, on a scale from 1+ to 4+, and the area encompassed in the color flow pattern was planimetered. Each measurement was repeated eight times.

| | VOL(ml) | OD(mm) | VEL | CD GRADE | AREA ($cm^2$ mean ± SEM) | |
|---|---|---|---|---|---|---|
| A) | 3 | 2 | lo | 1+ | 22.0 ± 1.3 | p<.0001 |
| B) | 3 | 1 | hi | 3+ | 44.9 ± 1.6 | p<.0001 |
| C) | 6 | 2 | lo | 2+ | 32.4 ± 1.3 | p<.0001 |
| D) | 6 | 1 | hi | 4+ | 66.7 ± 3.2 | |

Equal VOLs injected at higher VELs received a higher CD grade(A vs B, C vs D)=(3+ vs 1+, 4+ vs 2+) and resulted in a larger CD area(44.9 vs 22 $cm^2$, p<.0001; 66.7 vs 32.4 $cm^2$, p<.0001). Furthermore, a lesser VOL(3 vs 6ml)(B vs C) appeared greater(3+ vs 2+, 44.9 vs 32.4 $cm^2$, p<.0001) when flowing at higher VEL(i.e through the smaller OD). These data indicate that CD flow pattern is principally a function of VEL rather than VOL. CD analysis may under or overestimate regurgitant VOL depending upon VEL of regurgitant jet.

CONSISTENCY OF COLOR FLOW DOPPLER ESTIMATION OF REGURGITANT FLOW RATE ACROSS VARYING SIZE ORIFICES AND MULTIPLE ORIFICE COMMUNICATIONS USING FLOW CONVERGENCE CONCEPTS: STUDIES IN AN "IN-VITRO" MODEL.

Valdir Moises, M.D., Robin Shandas, B.S., Benedito Maciel, Miguel Beltran, M.D., Franco Recusani, M.D., David J. Sahn, M.D., FACC. Univ Calif, San Diego, CA.

We previously showed that regurgitant flow rate (FR) can be estimated using color flow Doppler (CFD) measurements of the flow convergence (FC) region proximal to a regurgitant (REG) orifice (ie., on the LV side of the MV for MV REG). FC is imaged as concentric aliasing towards the orifice. If the first alias is a hemispheric isovelocity boundary of flow going into the orifice, FR can be estimated using the radius (R) from the alias to the orifice and the known Nyquist limit (NL). In a constant flow model, we imaged the FC region for flow through 7, 16, 19.6, and 28.2$mm^2$ orifices and for flow simultaneously through 2 adjacent orifices (9.6 and 19.6 $mm^2$) for FR from 1.04 to 5.8 L/min using a Toshiba SSH65A, 3.75 MHz and 4kHz pulse repetition frequency (NL=54 cm/sec). FR by CFD was calculated from the hemisphere surface area $2\pi R^2$ X NL. R was independent of gain and of the angle from which the FC was imaged. CFD FR calculated across the individual orifices correlated well to the measured FR (r=0.80, r=0.92, r=0.93, and r=0.91, respectively for each orifice) and the regression relationships had similar slopes and intercepts. For the flow crossing 2 orifices, FR calculated from the FC for each, separately, and summed, also correlated well with measured FR (r=0.91). Identification of flow velocity isopleths from the laminar FC region imaged by CFD can be used to estimate FR across a wide range of REG orifices, as well as across multiple orifice regurgitant lesions.

HOW TURBULENT IS A TURBULENT JET? AN IN VITRO COLOR FLOW DOPPLER STUDY

James D. Thomas, MD, Chun-ming Liu, MD, John P. O'Shea, MB BS, Ravin Davidoff, MB BS, Shawn McGlew, Arthur E. Weyman, MD, FACC. Noninvasive Cardiac Laboratory, Massachusetts General Hospital, Boston, MA.

Accurate quantification of valvular regurgitation by color flow Doppler echocardiography demands an understanding of the the natural velocity variation inherent in turbulent jet flow. In order to define the statistical characteristics of turbulent jets, we examined pulsed Doppler and color Doppler M-mode recordings from an *in vitro* model of valvular regurgitation. Jets resulting from blood flow through circular orifices of 0.1 to 0.5 $cm^2$ with flow rates from 10 to 100 $cm^3$/sec were digitized at 1 mm spatial by 4 msec temporal resolution. **RESULTS:** Mean axial velocity was observed to decay inversely with distance from the orifice, and to have an approximately Gaussian profile at any given depth. With flow held constant, however, instantaneous velocity throughout the jet fluctuated 28 to 35% about the local mean velocity, with distinct 'rippling' apparent in the M-mode display, consistent with propagation of turbulent eddies. Fourier analysis revealed power spectrum peaks between 12 and 30 Hertz, with higher frequencies occurring closer to the orifice. The random variation in velocity caused the jet axis to swing chaotically ±.2 cm from its mean. Conversion to laminar flow in this model occurred at jet Reynolds numbers between 200 and 300 at which time variations in both velocity and axis position abruptly decreased (p<.001). **CONCLUSION:** Turbulent jets have predictable average velocity profiles but significant instantaneous variance both in velocity and shape. Quantitative color flow analysis must use careful data averaging techniques to overcome this random variability.

EFFECT OF RECEIVING CHAMBER COMPLIANCE ON THE SPATIAL DISTRIBUTION OF REGURGITANT JETS AS IMAGED BY COLOR DOPPLER FLOW MAPPING: AN IN-VITRO STUDY. Benedito Maciel, M.D., Valdir Moises, M.D., Robin Shandas, B.S., Iain Simpson, M.D., Miguel Beltran, M.D., Lilliam Valdes-Cruz, M.D., FACC, David J. Sahn, M.D., FACC, Univ Calif, San Diego, CA.

In order to study the effect of atrial compliance on color Doppler (CD) imaging of regurgitant jet areas (RJA), we varied regurgitant flow rate (RFR) from 80 to 400 ml/min through a 1.5mm² orifice into receiving chambers (RC) of different compliances (C=1,2,4.5 and 9 ml/mmHg) using a closed, constant flow system. Color RJA obtained using a Toshiba SSH65A, at constant gain, 3.75MHz and 4kHz pulse repetition frequency and continuous wave maximal jet velocities for calculation of RFR (Irex IIIB) were recorded from an atrial-viewing window. For each chamber at a constant residual volume (150ml), RJA correlated linearly with RFR (r=0.97, 0.98,0.98, 0.99) and with pressure gradient across the orifice (r=0.98,0.97,0.98, 0.99) for the 4 differing compliance RCs respectively. At the same RFR, color RJA increased with increasing chamber compliance up to C-4.5 ml/mmHg, but at very high compliance no further increase in RJA was observed. When residual RC volumes were increased stepwise (110,130, & 150ml) at constant RC compliance (2 ml/mmHg) with constant RFR, the RJA decreased with increasing volume and pressure in the RC. Our results showed that RJA has a nonlinear relationship with compliance at constant RFR and suggest that in a pulsatile system the pressure/volume relationship inside the RC should be a major determinant of RJA as imaged by CD. Even at constant compliance, changes in volume and ambient pressure of the RC can result in significant changes in RJA, independent of modifications in regurgitant volume.

VALIDATION OF A METHOD TO ESTIMATE REGURGITANT FRACTIONS USING THE POWER MODE IN A DOG MODEL
David D. Kandath, M.D., Frederick Helmcke, M.D., Elizabeth F. Philpot, M.S., Adelino Parro, Jr., M.D., William G. Tracy, Swav Lobodzinski, Ph.D., Ajit P. Yoganathan, Ph.D., Navin C. Nanda, M.D., F.A.C.C., University of Alabama at Birmingham, Alabama

Power mode in color Doppler, which emphasizes display of signal intensity, was used to estimate regurgitant fractions (RF) resulting from induced pulmonic and aortic regurgitations in open chest dogs. The degrees of regurgitation were varied by banding the distal artery, punching multiple holes in the valves or volume loading. Using a computer algorithm, the strength of the color intensities (I) were scaled from 0 to 8. The numbers of pixels with the specific I grades were counted in delineated regurgitant and forward flow areas recorded using power mode. Each grade was scaled assuming that maximum intensity corresponded to maximum number of moving red blood cells (RBC) in a pixel. The relative number of RBC/mm was then estimated for each area by multiplying number of pixels with specific I by number of RBC represented by that I. Readings were taken at early, mid, and late systole and diastole for forward and regurgitant flows respectively and averaged to determine the number of RBC/mm. Because they represented only one instance in time, the numbers were multiplied by the cycle time to obtain the final relative number of RBC/mm. The ratio of numbers obtained for regurgitant and forward flows were calculated to determine RF. The pulmonic RF (n=9) ranged from 4-92% (mean 42%) and correlated very well with RF calculated by comparing forward and reverse flows measured in the PA using an electromagnetic flowmeter (r=0.94). The aortic RF (n=8) ranged from 42-100% (mean 74%) and also correlated well (r=0.86).

**THE PROFILE OF A REGURGITANT COLOR JET IS INDEPENDENT OF ORIFICE SHAPE.**
John P. O'Shea, M.B.B.S., F.R.A.C.P., James D.Thomas, M.D., Aleksandar D. Popovic, M.D., Tracy Svizzero, Arthur E. Weyman, M.D., F.A.C.C. Massachusetts General Hospital, Boston, MA.

The quantitative evaluation of color flow jets using two-dimensional Doppler echocardiography (2DDE) frequently assumes that such jets are circularly symmetrical or conical in shape. However, valvular orifices are frequently irregular in shape and it remains uncertain whether such an assumption of circular symmetry applies with validity to orifices of varying eccentricity. To explore this assumption, we analyzed the size and shape of color flow jets in an in-vitro model of valvular regurgitation, using a constant driving pressure. Color jet profiles were digitized for each of the following combinations: 3 orifice sizes (0.1, 0.3 and 0.5 cm2); 4 degrees of eccentricity, for each orifice size, with the major/minor axis ratio of each orifice varying from 1:1 (circular) to 5:1 (elliptical) and laminar vs turbulent jets, for each combination. The width of each jet was measured in two orthogonal planes at 1 cm intervals from the orifice to a distance of 5 cm downstream and their ratio of eccentricity (ER) calculated. **RESULTS:** Taking all elliptical orifices together, jet profile was distinctly elliptical from the orifice (ER = 1.75, $p < 0.01$ vs circularity) to 2 cm downstream (ER = 1.3, $p < 0.05$), but thereafter became more circular until by 5 cm downstream, all jets were circular (ER = 1.0, p = ns). Multilinear analysis revealed that larger and more eccentric orifices preserved their elliptical profile longer ($p < 0.02$). While laminar flow tended to preserve shape longer than turbulent flow, this did not reach statistical significance. **CONCLUSION:** In this in-vitro model of valvular regurgitation, color jet profile rapidly becomes independent of orifice shape. Quantitative color flow Doppler analysis, which assumes axial jet symmetry, therefore appears valid.

## Monday, March 20, 1989
## 4:00PM–5:30PM, California Room D
## Anaheim Convention Center
## Color Flow Doppler: Clinical and Experimental Studies

IMPACT OF INTRAOPERATIVE ECHOCARDIOGRAPHY: THE FIRST 1,000 PATIENTS.
Martin E. Goldman, M.D.,F.A.C.C., Theresa Guarino RN, Scott Lazar, John Fotiades, Andrew Rothschild, Laura Andreae, M. Hasan Jethabhai, Bruce P. Mindich, M.D., F.A.C.C., Mount Sinai Hospital, New York, New York.

Intraoperative Echocardiography (IOE) is a new method to evaluate ventricular and valvular function, which requires technical expertise and may prolong the procedure. Therefore, to determine the potential benefits of IOE, we reviewed 1,000 consecutive operations performed with IOE between 1982 and 1988 by a single surgeon, for "new" information provided, alteration (alt) of operation (i.e. valve procedure performed or not) and therapeutic interventions (therap) dictated by IOE. There were 570 men, 430 women, mean age 63 years, who had: 409 valve operations; 230 coronary bypasses (CAD); 286 CAD and valve; 77 other procedures.

| | 1982-83 | '84 | '85 | '86 | '87 | '88 |
|---|---|---|---|---|---|---|
| #IOE | 68 | 211 | 178 | 182 | 228 | 133 |
| valve | 29 | 60 | 73 | 72 | 93 | 76 |
| CAD + valve | 5 | 23 | 39 | 54 | 83 | 31 |
| CAD | 30 | 116 | 56 | 44 | 39 | 16 |
| % new | 1 | 6 | 12 | 26 | 29 | 19 |
| % alt | 6 | 9 | 17 | 31 | 30 | 21 |
| % therap | 0 | 2.4 | 5.1 | 6 | 12.3 | 10 |

Of the 1,000 pts studied with IOE monitoring, the operation was altered in 206 pts, new information obtained in 174, and a therapeutic intervention was instituted in 61 based on the IOE. IOE had significantly greater impact on valvular than CAD cases (22.6% vs. 2.3%). Importantly, 35 pts needed re-institution of bypass due to problems detected by IOE. Therefore, IOE has a major impact on open heart surgery and can significantly alter surgical and therapeutic approaches.

CAN COLOR DOPPLER/TWO DIMENSIONAL ECHOCARDIOGRAPHY IDENTIFY THE NEED FOR TRICUSPID VALVE REPAIR?
Hirday K. Chopra, M.D., PoHoey Fan, M.D., Dinyar Daruwala, M.D., Kanwal K. Kapur, M.D., Raj Ballal, M.D., Sally Moos, Navin C. Nanda, M.D., F.A.C.C., Albert D. Pacifico, M.D., F.A.C.C. University of Alabama at Birmingham, Alabama

Tricuspid regurgitation (TR) severity was assessed preoperatively by color Doppler in 94 Pts who subsequently underwent mitral and/or aortic valve replacement. Of these, 56 Pts (Group A) also required tricuspid valve (TV) annuloplasty because TR was judged to be severe intraoperatively. In the remaining 38 Pts (Group B) TV annuloplasty was not done because TR was judged not severe during surgery. Using apical 4 chamber and parasternal short axis views, the severity of TR was assessed by color Doppler by taking a ratio of maximum area of TR signals to right atrial area. This ratio was found to be >34% (mean 50.55±11.65%) in 54/56 Pts (94%) in Group A, and <34% (mean 27.53±6.96%, p<.001) in 36/38 Pts (95%) in Group B. Maximum diastolic tricuspid annulus diameter (using same 2D echo planes) was >38mm (mean 44.79±7.03 mm) in 50/56 (89%) in Group A and <38mm (mean 28±5.67 mm) in 37/38 (97%) in Group B (p<.001). Percentage shortening of tricuspid annulus diameter (maximum minus minimum/maximum diameter x 100) was <25% (mean 17.78±6.62%) in 51/56 (97%) in Group A, and >25% (mean 32.47±6.6%) in 35/38 (92%) in Group B (p<.001). Doppler derived pulmonary artery systolic pressure and 2D echo RV ejection fraction did not distinguish the two groups. Both color Doppler and 2D echo are useful in identifying Pts who would require TV repair for severe TR during mitral and/or aortic valve replacement.

QUANTITATIVE EVALUATION OF VENTRICULAR SEPTAL DEFECTS BY COLOR DOPPLER FLOW IMAGING
Edward Harlamert, M.D.; Michael Harrison, M.D., FACC; Mikel Smith, M.D., FACC; David Booth, M.D., FACC; Claudine Moffett; Oi Ling Kwan, B.S.; Anthony DeMaria, M.D., FACC; University of Kentucky, Lexington, Kentucky
Preliminary data have suggested that the severity of congenital ventricular septal defect(VSD) may be estimated by color Doppler flow imaging(CDFI). However, no data regarding the usefulness of CDFI to predict the severity of acquired VSD accompanying acute myocardial infarction (AMI) has been reported. Accordingly, we performed CDFI and cardiac catheterization in 13 VSD pts (7 with AMI and 6 children with congenital VSD). The interventricular septum was interrogated in the standard parasternal, apical and subcostal views to depict the largest flow disturbance(jet) from the LV to RV through the VSD. Maximal jet area(MJA) was measured as the outer border of the largest clearly defineable jet during frame-by-frame analysis. MJA was corrected for body surface area, as MJA/BSA=maximal jet area index(MJAI), to standardize the pediatric and adult populations. Cardiac catheterization was performed to obtain hemodynamic and $O_2$ saturation information. MJA and MJAI were compared to shunt flow ratio (QP/QS), RV to LV systolic pressure ratio (RVP/LVP), and mean pulmonary artery pressure(MPAP). Results: MJA and MJAI correlates with QP/QS (r= 0.76 and 0.72 respectively) in adults with VSD secondary to AMI. MJAI also correlates with QP/QS in congenital VSD and in the combined population (r=0.71 and 0.70 respectively). MJAI exhibits no correlation with MPAP (r=0.50) nor with RVP/LVP (r=.55). Finally, we observed that significant (>2:1) shunting through the VSD occurred only when MJAI was >4$cm^2/m^2$ and in adults when MJA was >6 $cm^2$. Thus, these data indicate that the area of flow disturbance by CDFI may be used to estimate the severity of VSD in pts with AMI, as well as, pts with congenital lesions.

DIAGNOSIS OF LEFT VENTRICULAR PSEUDOANEURYSM BY COLOUR DOPPLER FLOW MAPPING.
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Left ventricular pseudoaneurysm (LVPA) is defined as a cardiac rupture contained by adherent pericardium. It is an unusual complication of myocardial infarction, cardiac surgery and chest trauma. Due to the tendency for LVPAs to rupture, early recognition is of paramount importance, as surgical repair may be curative. Eleven consecutive patients with cardiac rupture forming LVPAs have been studied using colour flow mapping (CFM), 5 with acute rupture following myocardial infarction, 2 following stab wounds, 1 late rupture of a calcified "true LV aneurysm", 1 post surgical resection of an LV aneurysm and 2 resulting from LV venting. Recurrent rupture following repair of LVPA occurred in 2 pts. The study group therefore consisted of 13 cases. In all 13 cases the diagnosis was confirmed by angiographic and surgical information. The diagnosis was suspected clinically in only 6/13. 2-D echo alone confirmed the diagnosis in 7/13. In all 13 CFM demonstrated turbulent trans-myocardial flow in and out of the LVPA cavity at the rupture site as well as the abnormal flow pattern within the pseudoaneurysm. Pulsed Doppler at the defect site revealed a characteristic multiphasic "to and fro" flow pattern whose peak velocity demonstrated a consistent respiratory variation. This intracardiac flow pattern is diagnostic of a LVPA. We conclude that in view of the above findings CFM is a valuable addition to 2-D echo with integrated Doppler in the diagnosis of cardiac rupture with LVPA.

TWO DIMENSIONAL/COLOR DOPPLER ASSESSMENT OF VENTRICULAR SEPTAL DEFECTS.
Albino de Souza M.D., Frederick Helmcke M.D., Edward V. Colvin, M.D., F.A.C.C., Benigno Soto M.D., F.A.C.C., Navin C. Nanda M.D., F.A.C.C., Robert P. Gatewood, Jr., M.D. University of Alabama at Birmingham, AL.

Color Doppler (CD) examinations were performed in 54 Pts with 58 ventricular septal defects (VSD) proven surgically/anatomically. All Pts also had angiocardiograms. CD examination detected all VSDs and correctly categorized the site and extension of VSDs in 49/58 (84%). All perimembranous (PM) VSDs were diagnosed in the LVO short axis plane as an area of discontinuity adjacent to septal tricuspid valve leaflet attachment. Of 15 Pts with inlet extension, 13 showed color flow signals only along the septal tricuspid leaflet. Of 23 PM VSD with outlet extension, 19 had flow signals moving directly towards the RV outflow tract. One PM VSD with trabecular extension showed flow signals directed toward RV anterior wall. Muscular VSDs were similarly categorized correctly by CD as inlet, outlet and trabecular in 12/15 Pts. All 4 doubly committed VSDs were correctly diagnosed as an area of discontinuity adjacent to the pulmonary valve in the short axis view with flow signals directly moving through VSD into RV outflow and PA. CD misclassified 2/15 PM inlet VSD, and 4/23 PM outlet VSDs probably because the VSD jet was deflected by a fibrous tag (PM inlet) and aneurysm/prolapse of aortic valve into VSD (4 PM outlet). Angiography correctly detected all VSDs and correctly classified their site and extension in 46/58 (79%). It misclassified 3/15 PM inlet and 4/23 PM outlet VSD. It also missed 3/15 muscular VSD and 1/4 doubly committed VSD. The accuracy of CD approaches that of angiocardiography in detection, location and extension of VSD.

DEMONSTRATION OF JET ENTRAINMENT - AN INTERACTION WHICH CAUSES PARALLEL JETS TO MERGE AND CROSS: IN-VITRO EXPERIMENTS USING COLOR DOPPLER FLOW MAPPING AND OPTICAL VISUALIZATION. Robin Shandas, B.S., Valdir Moises, M.D., Benedito Maciel, M.D., David J. Sahn, M.D., Dorian Liepmann, M.S. Univ Calif, San Diego, CA.

The imaging of multiple jets within a single cavity, such as in combined AO insuffiency (AI) and mitral stenosis (MS), has at times been confusing as the jets often appear to merge and their velocities (VELs) are sometimes difficult to interrogate separately on continuous wave (CW) Doppler studies. We studied the behavior of dual parallel jets into a modeled LV chamber, by both color Doppler flow mapping (CDFM) (Toshiba SSH65A, 3.75 MHz, 4kHz), and by optical visualization using india ink and a high resolution video camera. When a medium to low VEL (1-2.5 m/sec) jet entered the chamber through a 19mm² orifice parallel to a high VEL (4-7m/sec) laminar jet flowing through orifices 0.05 to 1.5 mm² in the same direction, the CDFM studies showed consistently that the larger jet deviated toward the smaller jet, and rather than repel each other away, the flow streams appeared to meet and cross each other, resulting in a turbulent, swirling flow towards the apex. With optical visualization it was clear that VEL recruitment in the region between the 2 jets draws the larger jet towards and across the smaller jet, resulting in their merging into a turbulent decelerating flow. The resulting angular deviation for the larger jet towards the smaller jet was as much as 45°, sometimes resulting in their crossing within 2cm of their origin. Our studies lend insight into the behavior of multiple parallel jets, such as the co-mingling of AI and MS jets which often merge, regardless of the valve morphology, provided they enter the ventricle in close proximity.

## Monday, March 20, 1989
## 2:00PM–3:30PM, Garden Grove Room
## Anaheim Convention Center
## Left Ventricular Function After Myocardial Infarction

**NATURAL HISTORY OF LEFT VENTRICULAR FUNCTION CHANGES AFTER MYOCARDIAL INFARCTION.** Sidney O. Gottlieb, M.D.,FACC, Lewis C. Becker, M.D., FACC, Alan D. Guerci, M.D., E. David Mellits, Sc.D., Gary Gerstenblith, M.D., FACC. Johns Hopkins Med. Inst., Baltimore, Maryland.

The impact of strategies designed to decrease infarct (MI) size is often assessed by serial non-invasive measures of LV function. The natural history of global and regional LV ejection fraction (EF) changes was therefore studied in 83 pts with acute MI (62 Q wave, 21 non-Q) who had not received thrombolytic therapy by serial gated blood pool studies performed on days 1, 10, and 42. (Data are presented as mean ± SD):

| Global EF(%) | Q wave(62) | Non-Q (21) |
|---|---|---|
| Day 1 | 52 ± 12 | 61 ± 12 |
| Day 10 | 51 ± 12 | 61 ± 10 |
| Day 42 | 49 ± 11 | 60 ± 9 |
| REMOTE ZONE EF(%) | | |
| Day 1 | 62 ± 11 | 65 ± 10 |
| Day 10 | 58 ± 13 | 64 ± 12 |
| Day 42 | 54 ± 13 | 62 ± 12 |
| INFARCT ZONE EF(%) | | |
| Day 1 | 34 ± 12 | 44 ± 13 |
| Day 10 | 41 ± 16 | 51 ± 11 |
| Day 42 | 38 ± 15 | 51 ± 11 |

Thus, during the first 6 weeks post MI, global EF remained constant while infarct zone EF increased and remote zone EF decreased in both Q and non-Q wave MI ($p<.01$ for regional EF changes ANOVA over time for both Q and non-Q groups). The spontaneous improvement in infarct zone EF appeared to be complete by 10 days, suggesting that resolution of myocardial stunning occurs within this time frame. This natural history data must be considered when evaluating the impact of interventions designed to preserve regional LV function.

**CHRONIC REDUCTION OF LEFT VENTRICULAR VOLUMES AT REST AND EXERCISE IN PATIENTS TREATED WITH NITROGLYCERIN FOLLOWING ANTERIOR MI**

Dennis P. Humen M.D., Lillian McCormick RTNM, and Bodh I. Jugdutt M.D. University of Alberta, Edmonton, Canada.

Treatment with nitrogylcerin (NTG) has been shown to modify left ventricular shape distortion following anterior wall MI (AMI). In order to determine whether these anatomic changes affect function at rest and exercise, a series of patients (pts) were studied in the post-infarct period. All pts were treated with IV NTG for the first 48 hrs. of hospitalization and then randomized to double-blind treatment groups consisting of buccal NTG (1 to 3 mg) TID (19pts), or placebo (14 pts). Patients were studied a mean of 10 months following myocardial infarction. Study medication had been discontinued 6 weeks following admission for AMI.

Gated radionuclide ventriculograms were obtained at rest and at each stage of a symptom-limited semi-recumbent exercise cycle protocol consisting of 3 min stages and 25 W increments. Images were analysed to obtain ejection fraction and left ventricular volumes using a calibrated non-geometric method.

At rest there was no significant difference between groups in age, heart rate, blood pressure, or ejection fraction. The NTG treated group however, had significantly smaller hearts in systole and diastole at rest which was maintained at submaximal exercise and at maximal stress.

| | EDV rest | EDV ex | ESV rest | ESV ex |
|---|---|---|---|---|
| NTG | 121±9* | 139±11*‡ | 74±9* | 80±11 |
| PLACEBO | 146±10 | 165±11‡ | 93±9 | 99±11 |

*p<.05 vs PLACEBO, ‡p<.05 vs rest values= mean±SD (mls)

We conclude that treatment with NTG for 6 weeks following AMI modifies healing to provide smaller cardiac volumes at rest and exercise. This beneficial effect is present long after withdrawal of the interventional agent (NTG) and is considered to be secondary to altered left ventricular topography caused by reduced infarct expansion and shape distortion.

**TIME COURSE OF IMPROVED FUNCTION FOLLOWING POST-INFARCTION ANGIOPLASTY: EVIDENCE FOR "HIBERNATION" EVEN IN "INFARCTED" MYOCARDIUM.**

Michael Drossner, M.D., James L. Weiss, M.D., F.A.C.C., Gary Gerstenblith, M.D., F.A.C.C., Jean Cadden, Harlan F. Weisman, M.D., F.A.C.C., Jeffrey A. Brinker, M.D., F.A.C.C., Johns Hopkins Hospital, Baltimore, Maryland.

There has been considerable interest in the role of "hibernation" in dysfunctional regions early post-infarction. We examined the effect of coronary angioplasty (PTCA) of flow-limiting lesions serving infarct zones. The time course of the change in regional myocardial function following PTCA of the infarct related artery performed a mean of 8 days post-infarction in 15 stable patients was studied by two dimensional echoes (2DE) obtained before, and then one day and four weeks following PTCA. 2DEs were read in a blinded randomized fashion by 2 observers. Wall motion was scored for 7 segments: -1=dyskinetic, 0=akinetic, 1=hypokinetic, 2=normal. Results over time were analyzed by ANOVA. Average infarct score increased from 0.96±.16 before PTCA to 1.26±.14 one day following PTCA and to 1.32±.16 at four weeks ($p=.001$). Global EF, by the bullet formula, increased from 40±2% before PTCA to 51±4% at one day and to 54±3% at a mean of four weeks ($p=.01$). Thus, most of the improvement in infarct zone function after PTCA was immediate as evidenced by a 31% improvement in infarct score at one day and only an additional 5% improvement at four weeks. Patients with the most severe wall motion abnormalities before PTCA evidenced the most improvement in infarct zone function. The early benefit in hypokinetic, akinetic and dyskinetic areas indicates that viable, reversibly depressed (i.e. "hibernating") regions are present even in presumably "infarcted" myocardium and that revascularization results in functional improvement.

LONG-TERM IMPROVEMENT OF LEFT VENTRICULAR FUNCTION AFTER MYOCARDIAL INFARCTION WITH AND WITHOUT THROMBOLYTIC THERAPY BY LATE PTCA OF THE INFARCT-RELATED ARTERY.

Thomas Linderer M.D., Bettina Guhl, Jutta Nöring, Thomas Brüggemann, Luise Schnitzer M.D., Christoph Spielberg M.D.,Rolf Schröder M.D.,F.A.C.C., Dpt. of Cardiology, Klinikum Steglitz, Free University Berlin, FRG

Low grade residual stenosis of the infarct-related artery after thrombolytic (LYS) treatment of myocardial infarction (MI) results in long-term improvement of LV function, as we showed in a previous study. The aim of this study was to evaluate the effect of treatment of a high-grade residual stenosis by elective PTCA on LV function after MI. We compared ejection fraction (EF) and regional wall motion abnormalities (asynergy index) from LV angiograms before and 7 months after successful PTCA in 145 Pts with previous MI. Data were analyzed with regard to time between MI and PTCA (≤30 days, mean 14 days or >30 days, mean 9 months), thrombolytic therapy (LYS or no LYS) and baseline EF (≤55% or >55%).

Results:

| | | Ejection fraction | | | Asynergy Index | | |
|---|---|---|---|---|---|---|---|
| | N | before | 7 mo | p | before | 7 mo | p |
| ≤30 days | 75 | 63 | 66 | 0.013 | 113 | 69 | 0.005 |
| >30 days | 70 | 57 | 61 | 0.002 | 193 | 117 | 0.000 |
| LYS | 72 | 62 | 65 | n. s. | 118 | 75 | 0.012 |
| no LYS | 73 | 58 | 63 | 0.000 | 185 | 109 | 0.000 |
| EF > 55% | 101 | 67 | 68 | n. s. | 64 | 47 | n. s. |
| EF ≤ 55% | 44 | 44 | 54 | 0.000 | 352 | 197 | 0.000 |

Conclusions:

Restoration of sufficient flow through an infarct-related coronary artery improves LV global and regional function independent of former thrombolytic therapy, even when PTCA is performed late after MI. Patients with severely depressed LV function seem to benefit most.

IMPROVEMENT OF GLOBAL AND REGIONAL LEFT VENTRICULAR FUNCTION WITH INTRAVENOUS APSAC IN ACUTE MYOCARDIAL INFARCTION. RESULTS OF A MULTICENTER DOUBLE BLIND TRIAL.

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University Hospital 38000 GRENOBLE FRANCE

231 pts were randomly allocated within 5 hours after the onset of a first myocardial infarction (MI) either to anisolated streptokinase plasminogen activator complex (APSAC) 30 mg over 5 minutes or to heparin (5000 IU bolus). A RAO left ventricular (LV) angio was performed under nitroglycerin infusion (1 mg/hour), 4±1.1 days later and blindly analyzed : LVEF were measured by the Simpson method ; regional wall motion by the Leighton method : according to the shortening of each LV hemiaxis, a dysynergic score was calculated for each pt. The coronary patency rate was 77% in APSAC and 37% in Heparin** :

| | LVEF | | DYSINERGIC SCORE | |
|---|---|---|---|---|
| | APSAC | HEPARIN | APSAC | HEPARIN |
| Overall | .52±.13 | .47±.13** | 9.8±6 | 13.3±9** |
| Ant. MI | .47±.13 | .40±.16* | 13.3±8 | 18.8±8** |
| Inf. MI | .56±.11 | .51±.09* | 7.7±4 | 9.3±4* |

** p < .002 *P < .05

Early infusion of APSAC in AMI is safe, produces a high short-term patency rate and a significant preservation of LV function especially in ant. MI.

Sustained left ventricular function benefit one year after thrombolytic therapy.

Harvey White M.B., F.A.C.C., John Rivers M.B., Morimasa Takayama M.D., Michael Brown M.B., Robin Norris M.D., John Ormiston M.B.,
Green Lane Hospital, Auckland, New Zealand.

Early Preservation of left ventricular function has been well shown following thrombolytic therapy. However, it is not known whether this benefit is maintained long-term. In a randomised double-blind trial of Streptokinase (sk) 1.5 X $10^6$ u infused over 30 min vs placebo 155 patients had biplane cineangiograms at 3 weeks after a first myocardial infarction. At 12 months 119 patients (77%) had repeat cineangiograms. Analysis of cineangiograms was blinded and ejection fractions (EF) and end-systolic volumes (ESV) were measured.

| | Placebo (n = 61) | Streptokinase (n = 58) | p |
|---|---|---|---|
| 3 weeks | | | |
| EF(%) | 52 ± 12 | 59 ± 10 | < 0.05 |
| ESV(ML) | 72 ± 40 | 51 ± 22 | < 0.05 |
| 12 months | | | |
| EF (%) | 53 ± 13 | 60 ± 12 | <0.05 |
| ESV (ML) | 72 ± 42 | 59 ± 35 * | <0.05 |

* Δ ESV in sk group from 3 weeks to 12 months, p = 0.01

CONCLUSION After thrombolysis the left ventricular ejection fraction benefit is maintained at one year. In addition end-systolic volumes are smaller than in placebo-treated patients but left ventricular dilatation occurs in the Streptokinase-treated patients.

## Monday, March 20, 1989
## 4:00PM–5:30PM, Garden Grove Room
## Anaheim Convention Center
## Prognosis After Myocardial Infarction

IS COMPLETE HEART BLOCK IN INFERIOR MYOCARDIAL INFARCTION A BENIGN PHENOMENON FOLLOWING REPERFUSION THERAPY?

P Clemmensen M.D., ER Bates M.D. F.A.C.C., RM Califf M.D. F.A.C.C., M Hlatky M.D. F.A.C.C., BS George M.D., DJ Kereiakes M.D. F.A.C.C., L Aronson B.S., E Berrios R.N., EJ Topol M.D. F.A.C.C. Duke University Medical Center, Division of Cardiology, Durham, North Carolina and the TAMI Study Group.

In the pre-thrombolytic era it was established that complete heart block (CHB) in Pts with inferior myocardial infarction (IMI) was associated with increased mortality. To assess the outcome of Pts with CHB after reperfusion therapy, 372 consecutive Pts entered into the TAMI Trials with IMI and the infarct related artery (IA) angiographically identified as the right coronary artery were studied. In the 54 (15%) Pts who developed CHB the majority of the episodes originated on the first day (87%). The table displays acute and follow up findings in the 2 groups. (Mean ± 1 standard deviation (SD)).

| | NO CHB | CHB | |
|---|---|---|---|
| N | 318 | 54 | |
| Age | 56 ± 10 | 59 ± 10 | |
| LV Ejection Fraction (%) | 55 ± 10 | 54 ± 9 | |
| Delta EF day 7 (%) | 0 ± 8 | -4 ± 6 | * |
| Infarct zone (SD/chord) | -2.37 ± 1.1 | -2.88 ± 1.0 | |
| Multivessel disease | 66% | 57% | |
| Reocclusion | 16% | 27% | |
| IA patency | 91% | 89% | |
| Mortality | 4% | 19% | ** |

* p = 0.025, ** p < 0.001.

Conclusion:

The occurrence of CHB during IMI treated with reperfusion therapy is an ominous sign and should not be ignored dispite successful reperfusion.

## EARLY INTERVENTION WITH LOW DOSE ASPIRIN IN FIRST ACUTE TRANSMURAL ANTERIOR MYOCARDIAL INFARCTION : INFARCT SIZE, CLINICAL OUTCOME AND FOLLOW-UP

Freek W.A. Verheugt, M.D., F.A.C.C., Arnoud van der Laarse, M.D., Albert J. Funke Kupper, M.D., Luc G.W. Sterkman, M.D., Jan P. Roos, M.D.. Department of Cardiology, Free University Hospital, Amsterdam, The Netherlands

Recent reports indicate, that low dose aspirin (ASA) given early to patients (pts) with acute myocardial infarction (AMI) improves short-term survival. However, the mechanism of mortality reduction with early ASA is unclear.
In a prospective double-blind trial we randomised 100 consecutive pts with first transmural anterior AMI within 12 hours after first symptoms to 100 mg ASA qd (n=50) or placebo (PLBO, n=50). Intravenous thrombolytic therapy (< 4 hours after symptom onset) was given to 50 pts (24 ASA, 26 PLBO), as was 50 mg subcutaneous heparin to all pts bid till mobilisation. Infarct size was measured as cumulative plasma release of lactate dehydrogenase within the first 72 hours after admission ($LDH_{72}$). Study medication was continued during the first 3 months and follow-up is complete in all pts.

| 3 MONTHS FOLLOW-UP | | ASA (n=50) | PLBO (n=50) | |
|---|---|---|---|---|
| cumulative $LDH_{72}$ (U/L ± SD) | | 1431 ± 782 | 1592 ± 1082 | ns |
| postinfarct angina | (pts) | 13 | 10 | ns |
| recurrent infarction | (pts) | 2 | 9 | <0.05 |
| mortality | (pts) | 10 | 12 | ns |

Thus, early intervention with low dose ASA in first transmural anterior AMI does not seem to influence infarct size. However, early ASA reduces the incidence of reinfarction. Prevention of reinfarction rather than reduction of infarct size might be the basis for the excellent results of early intervention with ASA in pts with AMI.

## MYOCARDIAL INFARCTION WITH MINIMAL CORONARY ATHEROSCLEROSIS: A SYNDROME OF YOUNG WOMEN WITH GUARDED LONG TERM PROGNOSIS.

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Myocardial infarction (MI) usually follows coronary thrombosis in patients with severe coronary stenosis. We found a residual coronary stenosis (RS) of $\leq$ 50% documented angiographically at 90 min of therapy in 43 of 777 (5.5%) patients enrolled in The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Trials of intravenous thrombolytic therapy with tissue plasminogen activator (t-PA), Urokinase (UK) or combination t-PA/UK therapy for MI. Compared to patients with $>$ 50% RS at 90 min, patients with minimal RS were younger (median 49 vs 57 yrs; p=<.001), more often women (28% vs 19%; p=.026), had fewer diseased vessels (100% $\leq$ 1 vessel disease vs 50%; p=<.001) and had better resting LV function (median LVEF 57% vs 51%; p=.018). History of angina, smoking and infarct artery location were similar in both groups. Hospital mortality was 7% in RS $>$50% and 2% RS $\leq$50%. At mean follow-up $>$1.5 yrs, non-fatal reinfarction and death were similar for both groups (8% and 5% RS $\leq$ 50% vs 5% and 3% RS $>$50%.) Minimal coronary atherosclerosis after thrombolysis predominately affects young women and is likely due to thrombosis and/or spasm. Although minimal RS patients are younger, have better LV function and less extensive coronary disease, they remain at substantial risk for reinfarction or death despite empiric therapy with aspirin, calcium channel blockers and nitrates.

## AGE RELATED RISK FACTORS AND MECHANISM OF DEATH FOLLOWING MYOCARDIAL INFARCTION. EXPERIENCE FROM THE MULTICENTER DILTIAZEM POSTINFARCTION TRIAL.

Frank I. Marcus, MD, FACC, Karen Friday, MD, FACC, John Mc Cans, MD, Thomas E. Moon, Ph.D., Elizabeth Hahn, MA, Leonard Cobb, MD, FACC, Jesse Edwards, MD, FACC, and Lewis Kuller, MD, FACC. University of Arizona Health Sciences Center, Tucson, Arizona.

The basis for the excess mortality with age after acute myocardial infarction (AMI) is not clear, nor is it known whether the mode of death is altered with age. We examined age related factors predictive of mortality and age related mechanisms of the 333 deaths in 2466 patients after AMI. There were 3 age groups with increasing mortality rates, ages 25-49 (N=499), 50-64 (N=1228) and 65-75 (N=739). There was a significant age related increase in the proportion of patients with the following baseline characteristics: NYHA functional class II-IV one month before AMI, pulmonary congestion by chest xray, VPCs $\geq$ 10/hr, BUN $>$ 35 mg/dl, and a decrease in the use of beta blockers at randomization (all p=.0001) as well as an increase in the proportion of pts with prior MI and LVEF < 40% (p=.007 and .047 respectively). These baseline characteristics did not differ by treatment (placebo vs diltiazem). However, multivariate Cox proportional hazard regression still identified age as an independent risk factor for cardiac death. The proportion of arrhythmic and myocardial failure deaths did not vary by treatment or age group (p=1.0 and p=.70 respectively). Conclusion: There is an increased proportion of baseline risk factors after AMI with increasing age; however, age itself is an independent risk factor for cardiac death. The mechanism of death does not differ with age.

## ASSESSING INFARCT EXPANSION IN AN ECHOCARDIOGRAPHIC WALL MOTION INDEX IMPROVES PREDICTION OF OUTCOME AFTER MYOCARDIAL INFARCTION.

Jay H. Chappell, M.D., Louis A. Nassef, M.D., F.A.C.C., Richard J. Butcher, M.D., F.A.C.C., Francis J. Menapace, M.D., F.A.C.C., Geisinger Medical Center, Danville, Pa.

To test if measuring infarct expansion (IE) improves the echocardiographic prediction of in-hospital complications after myocardial infarction, an established 14 segment wall motion index (WMI-1) was modified to include a bias for IE (WMI-2). Echocardiograms from within 72 hours of admission were analyzed blinded to outcome in 100 pts. with a first myocardial infarction not treated by reperfusion. Criteria for IE were abnormal LV diastolic contour with regional cavity enlargement (defined if apical long axis/LV long axis length $\geq$ 0.5 or if basal abnormal/normal short axis length $\geq$ 1.2). Criteria for aneurysm were as above plus discrete demarcation of normal from abnormal segments and suitability for surgical resection. Segments were scored in WMI-1 as 1=normal, 2=moderate hypokinesis, 3=akinesis, 4=dyskinesis, 5=aneurysm, and in WMI-2 as 1=normal, 2=moderate hypokinesis, 3=akinesis, 4=dyskinesis plus 1 for IE and 2 for aneurysm. Mean scores per segment were reported.

| RESULTS IN 100 Pts. | Death(12) | | Ventricular Tachycardia(11) | | Congestive Heart Failure(29) |
|---|---|---|---|---|---|
| WMI-1 $\geq$ 2.0 | 9 | p<0.01 | 7 | N.S. | 24 p<0.001 |
| WMI-1 < 2.0 | 3 | | 4 | | 5 |
| WMI-2 $\geq$ 2.0 | 11 | p<0.001 | 9 | p<0.02 | 26 p<0.001 |
| WMI-2 < 2.0 | 1 | | 2 | | 3 |
| Sensitivity* | .75 vs .92 | | .64 vs .82 | | .83 vs .90 |
| Specificity* | .68 vs .64 | | .66 vs .62 | | .82 vs .76 |

*Results are WMS-1 vs WMS-2.

CONCLUSION: A measure of infarct expansion improves the echocardiographic prediction of in-hospital complications after first myocardial infarction.

ANTECEDENT ANGINA: A CLINICAL MARKER FOR PATIENTS AT HIGH RISK FOLLOWING THROMBOLYTIC THERAPY.
Nicholas A. Ruocco, Jr., M.D., FACC, Bruce Bergelson, M.D., David P. Faxon, M.D., FACC, Thomas J. Ryan, M.D., FACC, for the TIMI Investigators, Boston University Medical Center, Boston, MA.

To determine whether a history of angina prior to myocardial infarction (MI) identifies patients (pts) at higher risk for subsequent ischemic events following thrombolytic therapy we analyzed data available as of 6/5/88 from the TIMI II B Trial. Among the 1629 pts who received rt-PA and were randomly assigned to No-PTCA, 842 had antecedent angina (AA). Compared to those without AA, they had significantly more hypertension (42.7% vs 32.9%, p<.001), a greater incidence of prior MI (23.4% vs 3.6%, p<.001) and experienced more post infarction angina (30.3% vs 21.3%, p<.001), and recurrent infarctions while hospitalized (4.8% vs 2.5%, p<.02). The need for emergency catheterization and CABG prior to discharge was significantly higher in the group with AA (14.0% vs 8.6% and 11.4% vs 5.5%, respectively, p<.001). Exercise tests at discharge were positive more frequently in the AA group (25.5% vs 18.9%, p<.005). Angiography data from 1435 pts undergoing routine catheterization per protocol from the 1634 similar pts randomly assigned to 18-48 hr PTCA showed a more significant residual stenosis among the 752 pts from that cohort who had AA compared to those without AA (80.9% ± 0.7 vs 76.3% ± 0.9, p<.001). These data suggest AA identifies a high risk subgroup of pts following thrombolytic therapy. The influence of routine coronary arteriography followed by appropriate revascularization in this clinically identifiable group will be discussed.

## Monday, March 20, 1989
## 2:00PM–3:30PM, California Room C
## Anaheim Convention Center
## Assessment of Myocardial Viability by Nuclear Methods

EARLY POST-THROMBOLYSIS ASSESSMENT OF NECROSIS AND VIABILITY WITH REST-REDISTRIBUTION THALLIUM SCINTIGRAPHY: CORRELATION WITH POSITRON EMISSION TOMOGRAPHY (PET).
Todd S. Kotler MD, Christoph Nienaber MD, Allan S. Lew MD, FACC, Jamshid Maddahi MD, FACC, Heinrich Schelbert MD, FACC, Daniel S. Berman MD, FACC, Cedars-Sinai Medical Center and UCLA School of Medicine, Los Angeles, CA.

The ability of day-1 rest-redistribution planar thallium-201 myocardial scintigraphy (Tl) to distinguish between viable and necrotic myocardium following thrombolysis was studied in 11 pts with first anterior MI and documented reperfusion. Nine segments comprising the LAD territory on rest, 4 and 24 hr planar Tl images were scored visually (0=normal to 3=severe defect). Redistribution scores were summed to yield indices of necrosis based on 4 and 24 hr images. These results were correlated with N-13-ammonia and F-18-deoxyglucose PET images on day 33±15. Necrosis and viability by PET were based on circumferential profile analysis. The percent necrosis by both 4 and 24 hr Tl correlated with PET (r=.74, p=.009), but Tl overestimated necrosis relative to PET (slope of regression=3.4). Tl and PET images were also compared for segmental agreement in 3 composite segments in the LAD territory. PET showed criteria for viability in 5/6 normal Tl segments, 6/7 segments with reversible Tl defects and 10/20 segments with non-reversible Tl defects at 4 hrs. There were similar results at 24 hrs.
Conclusions: 1) A visual index of necrosis derived from early post-thrombolysis Tl correlates with the extent of necrosis by PET; 2) a normal or reversible pattern of Tl-201 uptake is predictive of viability; but 3) 50% of segments with nonreversible Tl defects also show viability by PET. These results suggest that Tl-201 myocardial uptake is a specific but insensitive marker of viability in the early period following thrombolysis.

RECOVERY OF MYOCARDIAL METABOLISM BY PET PRECEDES IMPROVEMENT OF ISCHEMIC WALL MOTION AFTER PTCA.
Christoph Nienaber M.D., Richard Brunken M.D., F.A.C.C., Todd Sherman M.D., Lawrence Yeatman M.D., Sanjiv S. Gambhir M.S., Janine Krivokapich M.D., F.A.C.C., Linda Demer M.D., Ph.D., John Child M.D., F.A.C.C., Heinrich Schelbert M.D., F.A.C.C., UCLA School of Medicine, Los Angeles, California

To evaluate the temporal relationship between recovery of regional function, blood flow and glucose metabolism in post-ischemic myocardium, we studied 11 pts with 2-D echo and PET using N-13 ammonia and F-18 deoxyglucose before and within 48 hours of PTCA (Group I). Five pts (Group II) were re-studied at 63±17 days. Wall motion abnormalities (WMA) as independently graded on a scale from -1 (dyskinetic) to 3 (normal), were present in all areas supplied by the target vessel (9 LAD, 2 CFX) and displayed metabolism-perfusion mismatch (MM) prior to PTCA. Pre- and post-PTCA area stenosis was evaluated by quantitative coronary angiography. Circumferential profile analysis was used to quantify MM extent as % myocardium affected and MM score as the product of MM extent and deviation from normal.

| Results: | | Pre-PTCA | Post-PTCA | F/U-PTCA |
|---|---|---|---|---|
| % area stenosis | | 90 ± 9.6 | 53 ± 24*** | |
| MM Extent | I: | 24.7 ± 13 | 9.8 ± 9.1** | |
| | II: | 26.1 ± 16 | 5.3 ± 5.5** | 3.35 ± 3.3** |
| MM Score | I | 202 ± 291 | 53.7 ± 121** | |
| | II: | 256 ± 368 | 15.4 ± 25** | 8.2 ± 7.7*** |
| WM Score | I: | 0.84 ± .82 | 1.22 ± 1.14 | |
| | II: | 0.61 ± .87 | 0.94 ± 1.04 | 1.1 ± 1.0* |
| Segments w WMA: | | 5.5 ±4.3 | 4.7 ±3.3 | 2.6 ± 2.1* |

(*p<.05; **p<.02; ***p<.001 vs pre-PTCA)

Conclusions: 1, PET documents successful PTCA by improvement of myocardial blood flow/metabolism mismatch and predicts delayed recovery of wall motion. 2, Improvement in blood flow and metabolism precedes recovery of function in post-ischemic myocardium.

FREQUENCY OF LATE DEFECT REVERSIBILITY IN SPECT TL-201 STRESS REDISTRIBUTION STUDIES.
L. de Yang, M.D., D. Berman, M.D., FACC, H. Kiat, M.D., K. Resser, J. Friedman, M.D., L. Roy, A. Rozanski, M.D., FACC., J.Maddahi, M.D., FACC. Cedars-Sinai Medical Center, Los Angeles, CA

To determine the frequency of late (18-72 hr) reversibility (LR), we assessed 118 consecutive pts who had multiple non-reversible (NR) defects at 4 hr on Tl-201 stress-redistribution SPECT and underwent 24 hr imaging. On SPECT, 20 segments were scored visually. Fifty-three % (62/118) of pts and 22% (164/762) of 4 hr NR segments demonstrated LR. Of 1047 segments demonstrating stress defects, 27% (285) demonstrated R by 4 hrs, significantly less than the 43% (449) demonstrating R by combined 4 hr and late imaging (p<.0001). More pts with LR had ECG ST depression (57% vs 25%, p<.0005), chest pain (23% vs 14% p=NS), and fewer had prior MI (53% vs 66% p=NS) than pts with only late NR defects. To evaluate if selection bias for late imaging influenced our results, pts having late studies were compared to 98 randomly selected pts with 4 hr NR defects but without late imaging. Clinical and ECG indices of ischemia and frequency of prior MI were comparable, and Tl-201 defects were only slightly more extensive and severe in the late imaging group vs the group imaged at 4 hr only.

Conclusion: LR is common, occurring in approximately 1/2 of pts and 1/5 of regions with 4 hr NR stress defects. Late imaging significantly increases the detection of reversible defects by Tl-201 SPECT. The much higher association of ECG evidence of ischemia in pts with LR compared to pts with only late NR defects suggests that LR reflects myocardium that is still viable but highly jeopardized. Thus, our results suggest that pts with NR defects at 4 hr should undergo late imaging.

RIBOSE INFUSION POST-ISCHEMIA ALTERS THALLIUM-201 MYOCARDIAL CLEARANCE IN PATIENTS WITH CORONARY DISEASE.
Neal Perlmutter M.D., Richard Wilson M.D., F.A.C.C., Debra Angello M.D., Robert Palac M.D., F.A.C.C. Oregon Health Sciences University, Portland, Oregon.

We have previously shown that ribose infusion post-ischemia accelerates thallium-201 (Tl-201) redistribution in pts with coronary artery disease (CAD). In order to investigate the mechanism of this effect, 17 pts underwent two exercise Tl-201 stress tests, performed 1-2 weeks apart. After immediate post-exercise planar imaging, pts received either intravenous ribose (3.3 mg/kg/min x 30 min) or saline. Imaging was then performed one and four hours post-exercise. Pts exercised to the same double product on the second test and received the opposite infusion. Blood thallium levels were drawn before, during, and at the end of infusion, as well as at 30, 60, 120, and 180 minutes post infusion. Reversible defects (by count profile analysis) identified 55 ischemic regions; corresponding non-ischemic regions contained the maximum Tl-201 activity in that projection. Tl-201 clearance rates for both regions were calculated as % washout. At one hour post-exercise, Tl-201 clearance in nonischemic regions was higher after ribose infusion, as compared to saline (24.3±3.9 vs. 19.8±3.4%, p=0.001). Simultaneously, in ischemic regions, Tl-201 clearance was lower after ribose infusion (11.0+3.2 vs. 13.5±3.1%, p=0.02). At four hours post-exercise, nonischemic regional Tl-201 clearance remained higher after ribose infusion (48.6±3.1 vs. 40.2±4.2%, p=0.00004), although no differences were seen in ischemic regional clearance. Tl-201 blood levels were not significantly different between the two tests. Ribose appears to accelerate Tl-201 redistribution in pts with CAD by altering Tl-201 myocardial clearance, mostly by accelerating nonischemic Tl-201 washout.

RELATION OF MODIFIED FATTY ACID UPTAKE TO WALL MOTION AND CORONARY ANATOMY.
Vasken Dilsizian, M.D., Thomas P. Rocco, M.D., Alan J. Fischman, M.D., Charles A. Boucher, M.D., F.A.C.C., H. William Strauss, M.D., F.A.C.C. Massachusetts General Hospital, Boston, Massachusetts.

To assess modified fatty acids (MFA) as an imaging approach for coronary artery disease (CAD), we studied 10 such pts who underwent symptom-limited maximal exercise and cardiac catheterization (CATH). The regional distribution of I-123 labeled 9-methyl-pentadecanoic acid (MFA) at peak exercise (initial) was compared to segmental wall motion (WM) and percent coronary stenosis by CATH. No pts with unstable angina or acute-phase myocardial infarction were included. Images were acquired in the 3 standard projections and segmental MFA uptake score was assigned as either abnormal (reduced/ absent) or normal. CATH WM was scored as normal (NL), hypokinetic (HK) or akinetic (AK). WM data were available in 77 segments. The MFA correlation data follow:

| MFA Uptake | Segmental Wall Motion | | |
|---|---|---|---|
| Initial | NL | HK | AK |
| Normal | 35 | 12 | 1 |
| Abnormal | 8 | 12 | 9 |

p<.001 by Chi-square analysis

Thus, in viable segments, as evidenced by preserved wall motion (NL or HK), initial MFA uptake is normal in 47/67 (70%), in contrast to only 1/10 (10%) segments with akinesis. Of the 9 AK segments with abnormal MFA, 5 had total coronary occlusion, and 4 had critical but subtotal stenosis.
In conclusion, MFA uptake correlates with regional wall motion and coronary anatomy in CAD pts.

NON-INVASIVE IDENTIFICATION OF VIABLE VERSUS INFARCTED MYOCARDIUM BY AUTOMATED THREE-DIMENSIONAL CARDIAC POSITRON EMISSION TOMOGRAPHY WITH GENERATOR PRODUCED RUBIDIUM -82.
Dahlia Garza,M.D., David R. Sease,M.D., Michael E.Merhige, M.D.,FACC, Keri Hicks,M.S., Nizar Mullani,B.S., K. Lance Gould,M.D.,FACC. The University of Texas Medical School, Houston, Texas.

In order to determine whether transmural myocardial infarction vs viable myocardium can be determined by positron emission tomography (PET) perfusion imaging of generator produced rubidium-82 (Rb-82), seven acutely instrumented dogs had cardiac PET using intravenous Rb-82 and intra-atrial radiolabelled microspheres before, during, and after snare occlusion of the left anterior descending artery. Animals were sacrificed, heart slices soaked in triphenyltetrazolium chloride (TTC), and, at the center of the infarction, percent of transmural wall thickness that was TTC - was measured visually by ruler. Heart slices were then cut into one gram samples, labelled as TTC +, -, or +/- and microsphere perfusion in cc/g/min determined. PET images were automatically processed to provide short axis tomograph. Relative perfusion as percent of normal in tissue samples by microspheres closely paralelled absolute perfusion in cc/min/g and predicted normal, critically ischemic, mixed infarcted/viable, and infarcted myocardium from relative perfusion distribution rather than absolute flow. Minimum activity of Rb-82 at the center of image defects, expressed as percent of normal by PET, correlated linearly (r=.95) with percent wall thickness that was infarcted (TTC -) at the center of the infarct.
CONCLUSION: The presence of transmural myocardial infarction vs ischemic viable myocardium can be non-invasively determined by automated three-dimensional cardiac PET with generator produced Rb-82.

## Monday, March 20, 1989
## 4:00PM–5:30PM, California Room C
## Anaheim Convention Center
## TC-99m Isonitriles in the Evaluation of Perfusion

THE ASSESSMENT OF ISCHEMIA DURING OCCLUSION AND REPERFUSION USING METHOXY-ISOBUTYL ISONITRILE.
Albert Sinusas M.D., Kimberly Weber B.S., Denny Watson Ph.D., Todd Greenwald M.D., Mirta Ruiz M.D., William Smith M.S., George Beller M.D. F.A.C.C., University of Virginia, Charlottesville, Virginia.

Methoxy-Isobutyl Isonitrile (MIBI) lends itself to the evaluation of myocardial salvage following reperfusion (RP), since it does not redistribute. To define MIBI uptake before and after RP, 11 open chest dogs underwent 3 hrs of LAD occlusion (OCC) and 3 hrs of RP. MIBI was injected either during OCC (5 dogs; Group I), or after 90 min of RP (6 dogs; Group II). An in vivo risk area (IRA) was planimetered from MIBI autoradiographs of myocardial slices. Anatomic Risk Area (ARA) and infarct areas were defined by dual injection of monastral blue and TTC post-mortem. ARA (34 ± 7% LV; n=11) and infarct areas (15 ± 5% LV) were comparable in both groups. Flow was assessed by microspheres. The LV was divided into 96 segments for gamma well counting, and resulting flows and MIBI activity were normalized to non-ischemic values. In Group I, MIBI endocardial uptake following injection during OCC correlated linearly with OCC flow (r=0.79). In Group I, IRA by MIBI was consistently smaller (IRA = 0.68 x ARA + 0.9; r=0.89), than the ARA reflecting the contribution of collateral flow. In Group II, MIBI uptake in the central ischemic zone 90 min after RP, was 25 ± 21% of nonischemic uptake, whereas flow was restored to 86 ± 61% of nonischemic flow. Endocardial MIBI uptake during RP correlated better with the OCC flow (r=0.88) in these dogs.

Thus, 1) MIBI uptake during OCC defines an in vivo risk area which is smaller than the anatomic risk area, and 2) MIBI uptake at 90 min of RP following 3 hrs of OCC appears to be reflective of ischemic conditions, and not just flow restoration.

SERIAL CHANGES IN MYOCARDIAL PERFUSION USING TOMOGRAPHIC TECHNETIUM-99M METHOXY ISOBUTYL ISONITRILE (Tc-MIBI) FOLLOWING REPERFUSION THERAPY OF MYOCARDIAL INFARCTION

Patricia A. Pellikka, M.D., Thomas Behrenbeck, M.D., Mario S. Verani, M.D., FACC, John J. Mahmarian, M.D., Frans J. Wackers, M.D., FACC, Raymond J. Gibbons, M.D., FACC, Mayo Clinic, Rochester, Minnesota.

Resting myocardial perfusion images using Tc-MIBI were obtained in 19 patients during their first acute myocardial infarction. Tc-MIBI was injected intravenously BEFORE acute treatment with thrombolytic therapy or coronary angioplasty at 18 to 48 hours (EARLY), and at 7 to 14 days (LATE). The absence of redistribution of Tc-MIBI permitted tomographic imaging up to 8 hours after administration to determine the extent of hypoperfused myocardium (% LVHYPO) at the time of administration. % LVHYPO was quantitated by a technique validated in phantoms (r=0.99 vs true defect). Reperfusion was successful in 14 patients; 5 patients had persistent occlusion of the infarct-related artery. In the patients with reperfusion, there was a significant ($p<.03$) decrease in % LVHYPO between the BEFORE and EARLY studies (-8%±13%) consistent with myocardial salvage, and a further decrease ($p<.0003$) between the BEFORE and LATE studies (-16%±12%). In the 5 patients with persistent occlusion, there was an insignificant increase in % LVHYPO in the control patients EARLY (2%±6%) and LATE (1%±7%). % LVHYPO measured LATE correlated significantly (r=-0.82) with resting ejection fraction and with regional wall motion score in the infarct segment (r=-0.80 for anterior, r=-0.78 for inferior). Conclusions: 1) Tomographic Tc-MIBI is an excellent quantitative tool for assessing the efficacy of reperfusion therapy in acute myocardial infarction. 2) Improvement in myocardial perfusion is detectable by 18-48 hours, and substantial additional improvement occurs LATE.

**TOMOGRAPHIC MYOCARDIAL PERFUSION IMAGING WITH TECHNETIUM-99m 2-METHOXY ISOBUTYL ISONITRILE (MIBI) AND THALLIUM-201: THE SENSITIVITY AND REPRODUCIBILITY OF SEMI-QUANTITATIVE ASSESSMENTS OF MYOCARDIAL PERFUSION AND REGIONAL SYSTOLIC FUNCTION**

A. Iain McGhie, MD, Joel K. Kahn, MD, Marvin S. Akers, BS, Tracy L. Faber, PhD, James R. Corbett, MD, FACC. U.T. Southwestern Medical Center, Dallas, TX.

Simultaneous assessments of segmental myocardial perfusion and systolic function are possible with gated tomography and technetium-99m 2-methoxy isobutyl isonitrile (Tc-99m MIBI). Thirty one patients were studied following symptom limited exercise stress. Two blinded observers assessed semi-quantitatively segmental perfusion (0-3) and systolic thickening (0-2); maximal scores indicating normal perfusion or thickening, and scores of 0 indicating absence of perfusion or thickening. Twenty-eight segments from four representative sectional images were scored for each study. Gated MIBI tomography identified abnormalities of perfusion in 84% of the 62 stenosed distribution whereas ungated MIBI tomography identified 66% and thallium-201 (Tl-201) tomography identified 52% ($p<0.05$). Abnormalities of thickening were present in 60% of stenosed coronary distributions, and retained thickening was present in 90% of the coronary distributions with reversible defects. The mean kappa statistic for the interrater agreement of segmental assessments of myocardial perfusion were: gated MIBI .67±.11 (SD)(range 0.48-0.87), ungated MIBI .72±.14 (range 0.46-1.0), and Tl-201 .61±.11 (range 0.31-0.74). The mean kappa statistic for assessment of systolic thickening was .70±.15 (range 0.35-0.93). Thus, in comparison to Tl-201 tomography, Tc-99m MIBI tomography (gated and ungated) provides improved sensitivity and reproducibility.

**ASSESSMENT OF "NO REFLOW" PHENOMENON DURING REPERFUSION WITH $^{99m}$Tc-MIBI AND $^{14}$C-DEOXYGLUCOSE.**

Jose R. Azpiri, M.D., Fayez Dawood, B.Sc., Charles Lefkowitz, M.D., Ray Riley, B.Pharm., Peter Liu, M.D. F.A.C.C. Toronto General Hospital, Toronto, Canada.

Coronary reperfusion (REP) can be associated with the "no reflow" phenomenon, limiting the efficacy of reperfusion. To define "no reflow", particulate tracers such as microspheres (MS) have been used, which are of considerable size. Therefore it is not clear whether diffusion of micromolecules to the "no reflow" area is also impaired during reperfusion, and whether metabolic substrates such as glucose can continue to reach these cells.

We studied 9 dogs using a 2 hr occlusion (OC)/1 hr reperfusion model with MS injected during OC, immediately after (IM) and again at 45 min post-reperfusion. $^{14}$C-deoxyglucose (DG) was infused during REP to assess metabolic activity; and Tc-MIBI, a soluble small perfusion tracer was given at 55 min post-REP to assess molecular diffusion. The heart was sliced and counted for Tc-MIBI, DG and MS from infarcted (INF), border (BORD) and normal (NML) zones as defined by TTC staining. Results are as follows (mean ± SD):

| | Microsphere Blood Flows | | | | |
|---|---|---|---|---|---|
| | OC[a] | IMREP[a] | 45mREP[a] | TcMIBI[b] | DG[c] |
| INF | .14±.1 | 1.5±1.9 | 1.05±1.0* | 2.58±2.3** | 9.2±6.6 |
| BORD | .86±.4 | 1.4±.6 | 1.5±.76 | 4.51±2.0 | 15.1±6.7 |
| NML | 1.2±.5 | 1.5±.58 | 1.7±.91 | 5.35±1.6 | 15.4±8.2 |

a = flow in ml/min/gm; b = cpm/gm x $10^{-5}$; c = cpm/gm x $10^{-3}$; * $p<.03$ INF vs NML; ** $p<.01$ INF vs NML.

The correlation between Tc-MIBI activity and 45 min REP microsphere flow was excellent at $r=0.92$ ($p<0.001$).

*Conclusions*: (1) Tc-MIBI and microspheres show similar patterns of "no reflow", suggesting impairment of micromolecular diffusion. (2) Deoxyglucose uptake suggests persisting metabolic activity in the infarct zone at 3 hours. (3) Combined use of Tc-MIBI and DG has the potential to monitor "no reflow" in man.

CLINICAL COMPARISON BETWEEN THALLIUM-201 AND Tc-99m METHOXY ISOBUTYL ISONITRILE (MIBI) MYOCARDIAL PERFUSION IMAGING FOR DETECTION OF CORONARY ARTERY DISEASE.

Raymond Taillefer M.D., Denis-C. Phaneuf M.D., F.A.C.C., Raymond Lambert M.D., Georges Dupras M.D., Jean Grégoire M.D., Jean Léveillé M.D. Hôtel-Dieu de Montréal Hospital, Montréal, Québec, Canada.

Tc-99m-MIBI (methoxy isobutyl isonitrile) is a new Tc-99m-hexakis analog that can be used as a myocardial perfusion imaging agent. The purposes of this study were to compare MIBI to Tl-201 thallous chloride myocardial stress scintigraphy in patients referred for investigation of chest pain and to evaluate the sensitivity of MIBI in detection of coronary artery disease. One hundred patients were prospectively studied with both Tl-201 and MIBI planar imaging. Sixty-five patients had a current coronary angiography. There was a total of 97 significantly (≥70%) stenosed major coronary arteries. MIBI (25mCi) study was done within a week of the Tl-201 scan with reach of identical double products upon standard treadmill stress testing. Rest studies with MIBI were obtained 24-48 hours after the stress test using the same acquisition parameters and same dose. Analysis was performed by 3 blinded observers. The left ventricle was divided into five segments in each image. Analysis of Tl-201 and MIBI results in 1500 left ventricle segments showed an overall agreement in 1326/1500 (88.4%) segments. Correlation between the patient diagnosis on the Tl-201 and MIBI studies showed an agreement in 89 patients (89%). Tl-201 revealed myocardial uptake defects in 526 segments detecting 72 out of 97 (74.2%) significantly stenosed coronary arteries and MIBI detected 513 segments corresponding to 68 (70.1%) stenosed arteries (no significant statistical difference). In conclusion, these results show a good correlation between Tl-201 and MIBI myocardial imaging in detection of significant coronary artery disease.

**ASSESSMENT OF MYOCARDIAL VIABILITY WITH TECHNETIUM-99m 2-METHOXY ISOBUTYL ISONITRILE (MIBI) AND GATED TOMOGRAPHY IN PATIENTS WITH CORONARY ARTERY DISEASE.**

Joel K. Kahn, MD, Iain McGhie, MD, Tracy L. Faber, PhD, Michael N. Sills, MD, Marvin S. Akers, BS, James T. Willerson, MD, FACC, James R. Corbett, MD, FACC.
U. of Texas Southwestern Medical Center, Dallas, TX.

Gated tomography with the technetium-99m labeled cardiac perfusion agent 2-methoxy isobutyl isonitrile ($^{99m}$Tc MIBI), allowing simultaneous assessments of LV perfusion and segmental function following exercise and rest, may allow enhanced differentiation of ischemic (ISC) and infarcted myocardium. Twenty-nine patients with documented coronary disease were studied. Perfusion defect (PD) severity and reversibility determined quantitatively with computer generated circumferential profiles were compared to regional systolic thickening scored semi-quantitatively: 2 normal, 1 hypokinetic, 0 akinetic. There were 48 PDs. By ECG and contrast left ventriculography 18 PDs were in regions of prior MI (11 Q-wave,7 non-Q). Defect severity was greater in infarcted than ISC regions (45±3% uptake vs. 58±3%, p<.05), and in Q than non-Q wave MI (37±4% uptake vs. 58±3%, p<.01). Systolic thickening was less in infarcted (Q-wave 0.4±.1, non-Q 0.8±.3) than in ISC regions (1.8±.1,p<.01). Infarcted and ischemic regions were better separated by abnormal systolic thickening (16/18 MI, 6/30 ISC) than by severely reduced uptake (<50% uptake) (9/18 MI, 7/30 ISC,p<.05) or PD irreversibility (9/18 MI, 5/30 ISC,p<.05). Thus, gated tomography with $^{99m}$Tc MIBI, permitting simultaneous assessments of LV segmental perfusion and systolic thickening, enhances the differentiation of ischemic and infarcted myocardium.

## Monday, March 20, 1989
## 4:00PM–5:30PM, Santa Ana Room 1
## Anaheim Convention Center
## Cellular and Subcellular Aspects of Coronary Pathophysiology

IMMUNOHISTOCHEMICAL DETECTION AND LOCALIZATION OF TUMOR NECROSIS FACTOR IN HUMAN VASCULATURE

Peter Barath, M.D., Ph.D, Michael C. Fishbein, M.D., FACC, Jin Cao, M.D., James Fagin, M.D., James Forrester, M.D., FACC, Cedars-Sinai Medical Center, Los Angeles, CA

Since several aspects of the histologic sequence of atheroma evolution (neovascularization, central hemorrhagic necrosis, endothelial erosion/disruption) parallel tumor evolution, we hypothesized that similar cytokines might drive both processes. As tumor necrosis factor (TNF), a product of activated macrophages, has the capability of producing all these histologic changes, we developed an immunohistochemical staining using monoclonal TNF antibody against rTNF. We used formalin fixed, paraffin embedded sections from 8 normal human coronary arteries, 6 normal femoral arteries, 14 coronary arteries with different stages of atherosclerotic disease, 6 tibial arteries from amputation, and 4 specimens from carotid endarterectomy. We also stained 5 necrotizing colon cancer as positive controls. TNF was positive in 10 of 14 atherosclerotic coronary arteries, and all tibial arteries and endarterectomy specimens. TNF is localized in smooth muscle cells (SMC), endothelial cells and macrophages within the human arteries. The most intensive staining was found in the SMC (media, vasa vasora and newly formed vessel). Macrophages revealed intracellular staining, while the staining of SMC's and endothelial cells was localized to the cell surface. In the colon tumors the TNF was localized in both tumor and inflammatory cells.

**CONCLUSION:** We reported the first detection of tumor necrosis factor in human arteries. The difference in frequency distribution between normal and atherosclerotic arteries suggest its possible role in the evolution of atheroma, particularly since the known effects of this cytokine paralell that of atheroma evolution.

ANGIOGRAPHIC DEMONSTRATION OF HYPERCONSTRICTION INDUCED BY SEROTONIN AND AGGREGATING PLATELETS IN PORCINE CORONARY ARTERIES WITH REGENERATED ENDOTHELIUM.

Hiroaki Shimokawa M.D., Paul M. Vanhoutte M.D., Mayo Clinic and Mayo Foundation, Rochester, Minnesota

In isolated coronary arteries, the endothelium inhibits the contractions induced by serotonin and aggregating platelets. This effect is reduced after regeneration. The present study was designed to examine whether those in vitro observations could be reproduced in vivo. Sixteen male Yorkshire pigs underwent balloon endothelium-removal for either left anterior descending (n=9) or left circumflex (n=7) coronary arteries. After 4 weeks an angiographic study was performed; at this time the presence of a full endothelial lining was confirmed histologically. The control coronary angiogram showed no stenotic lesions in the previously denuded artery. Intracoronary injection of serotonin (10 μg/kg) caused hyperconstriction in the previously denuded artery (55 ± 4%) compared with control coronary artery (13 ± 2%). This hyperconstriction was associated with ischemic ECG changes (7/16 cases) and could be repeatedly induced. Intracoronary injection of aggregating platelets (obtained from 300 ml autologous blood with recovery rate 30-40% and stimulated by 5 mg collagen) caused constriction in the previously denuded (32 ± 5%) but not in the control artery (4 ± 2%) (n=6). The hyperconstrictions induced by serotonin and aggregating platelets were inhibited by intravenous treatment with ketanserin (a $5HT_2$ -serotonergic blocker; 1 mg/kg). Conclusions: 1, The normal endothelium reduces the vasoconstriction induced by serotonin and aggregating platelets in vivo: 2, The inhibitory effect of the endothelium is reduced after regeneration, allowing hyperconstriction and/or vasospasm.

ENDOTHELIUM-DEPENDENT INHIBITION OR ERGONOVINE-INDUCED CONTRACTION IS IMPAIRED IN PORCINE CORONARY ARTERIES WITH REGENERATED ENDOTHELIUM

Hiroaki Shimokawa M.D., Nicholas A. Flavahan Ph.D., John T. Shepherd M.D., F.A.C.C., Paul M. Vanhoutte M.D., Ph.D., Mayo Clinic and Mayo Foundation, Rochester, Minnesota

The inhibitory effects of the endothelium on ergonovine-induced contraction was examined in porcine coronary arteries under normal conditions and after endothelial regeneration. Endothelium-dependent responses were examined in vitro in normal Yorkshire pigs (n=16) and in pigs which had undergone coronary balloon endothelium-removal 4 weeks before the study (n=10). The presence of a complete endothelial lining was confirmed histologically. In rings from normal coronary arteries contracted with prostaglandin $F_{2\alpha}$, ergonovine caused endothelium-dependent relaxations, which were inhibited by pertussis toxin (inhibitor of the Gi protein linked to adenylate cyclase), and abolished by hemoglobin (inactivator of endothelium-derived relaxing factor). In quiescent rings, ergonovine caused contractions, which were inhibited by the endothelium or ketanserin ($5HT_2$-serotonergic blocker); this endothelium-dependent inhibition was abolished by hemoglobin. In rings from arteries with regenerated endothelium, relaxations to ergonovine were reduced significantly and the inhibition by pertussis toxin was virtually absent. The endothelium-dependent inhibition of the ergonovine-induced contractions and the endothelium-dependent contraction to hemoglobin were reduced. Conclusions: 1, The endothelium inhibits the contractions evoked by ergonovine; 2, The inhibitory effects of the endothelium is impaired after regeneration, in part because of dysfunction of endothelial Gi protein.

ANTIPLATELET ANTIBODY [7E3 F(ab')$_2$] PREVENTS RETHROMBOSIS ATER TISSUE-TYPE PLASMINOGEN ACTIVATOR INDUCED CORONARY ARTERY THROMBOLYSIS IN A CANINE MODEL.

Judith K. Mickelson M.D., FACC, Paul J. Simpson Ph.D., Megan Cronin, Eric D. Laywell B.S., Jon W. Homeister B.S., Jan M. Kitzen Ph.D., Benedict R. Lucchesi M.D., Ph.D., The University of Michigan, Ann Arbor, MI

Rethrombosis (RT) may complicate initially effective thrombolytic therapy. Platelets interacting with injured vascular endothelium in a region along the coronary artery with reduced luminal cross sectional area contribute to RT. Antibody (**AB**) that inhibits platelet aggregation was tested in animals with a critical stenosis, electrically induced thrombosis and rt-PA (25 mg) induced reperfusion of the left circumflex coronary artery (LCCA) to determine if **AB** (0.8 mg/kg bolus at the time of lysis) could prevent RT. Time required for thrombosis, thrombolysis and rethrombosis (if it occurred) was similar with **AB** (n=9) or saline (**CT**, n=10). Baseline LCCA blood flow (CBF) was similar in both groups but fell in the **CT** group (25±3 to 0±0 ml/min) as RT occurred in each case (50±9 min after lysis). With **AB** only 2/9 had RT and CBF stabilized (24±4 to10±2ml/min, n=9). Oscillations in CBF preceded RT in **CT** animals but seldom occurred in **AB** treated animals (5.2±0.9 vs 0.7±0.4 oscillations, p<0.05). Thrombus mass in the LCCA after 3 h was greater in **CT** than **AB** group (7.0±2.3 vs 1.5±0.7mg, p<0.05). Area of LV at risk (AR) for infarction (IN) was similar (**CT**:35±3%, **AB**:34±4%) but IN/AR was larger in **CT** animals (35±9% vs 6±4%, p<0.05). Platelets aggregated (AG) similarly at baseline. ADP, but not arachidonic acid (AA) induced AG diminished 50% after rt-PA. The limited AG with ADP correlated with decreased fibrinogen in both groups (p<0.05). ADP and AA induced AG was further inhibited after **AB** administration (p<0.001). In this canine model, antibody to platelet GPIIb/IIIa receptors prevented rethrombosis and stabilized reperfusion CBF, thus reducing infarct size. Since rethrombosis was not entirely eliminated, components in addition to platelets and non-occlusive thrombi must effect coronary vasomotor tone in the damaged artery after rt-PA induced thrombolysis.

MEMBRANE INCORPORATION OF UNSATURATED FATTY ACIDS INCREASES LDL METABOLISM BY U937 MONOCYTES.

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While the link between dietary unsaturated fatty acids (UFA) and reduction in LDL cholesterol is firmly established, the molecular mechanism by which this occurs remains unknown. Since the degree of membrane fatty acid saturation can affect membrane dependent cell functions and fluidity, we measured LDL binding at 4°C, uptake at 37°C and degradation at 37°C in U937 monocytes that were unmodified (C) or modified by plasma membrane enrichment with oleate (O)- a mono-UFA, linoleate (L)- a poly-UFA, and stearate (S)- a saturated fatty acid.

| | Binding (ug/10$^6$cells/4°) | Uptake (ug/10$^6$cells/4°) | Degradation (ug/10$^6$cells/4°) |
|---|---|---|---|
| C | 0.17±0.04 | 1.21±0.18 | 1.32±0.18 |
| S | 0.15±0.04* | 0.92±0.14** | 1.53±0.21* |
| O | 0.25±0.06** | 2.43±0.27*** | 2.94±0.21*** |
| L | 0.36±0.04*** | 2.63±0.18*** | 3.90±1.0*** |

[*, p=NS; **, p<0.05; ***, p<0.001]

Compared to C, O-enriched cells had an 11.8 ± 2.7 mole % increase in membrane O while L-enriched cells had a 9.7 ± 1.8 mole % increase in membrane L. S-enriched cells had a 4.0 ± 0.4 mole % increase in membrane S. Plasma membrane fluidity measurements showed the following order of fluidity: L > O > C = S enriched cells. UFA incorporation into cell membranes increases LDL binding, uptake, and degradation. Poly-UFA incorporation results in augmented LDL binding (p<0.02) in comparison to mono-UFA incorporation, while uptake and degradation were not statistically different. These data suggest a possible mechanism for the role of dietary UFA, in general, and the equivalency of mono-UFA and poly-UFA, in particular, in lowering LDL cholesterol.

GENETICALLY-INDUCED ATHEROSCLEROSIS ATTENUATES ENDOTHELIALLY MEDIATED RELAXATION

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We studied endothelial function in Watanabe Heritable Hyperlipidemic (WHHL) rabbits, which at 20 weeks on a normal diet develop spontaneous aortic atherosclerosis (ATH) morphologically similar to human ATH. Aortic segments (n=100) with and without endothelium (+/-EN) from 8 age-matched (27-30 wk) WHHL and 8 New Zealand White (NZW) rabbits were studied using standard tissue bath techniques (Krebs-Ringer-bicarbonate buffer gassed with 95%02-5%C02; 37oC). Concentration response curves [10-9-10-4M] were performed to histamine(H), to noradrenaline (NA), and (after precontraction) to acetylcholine (ACh), both with and without 150u/ml superoxide dismutase (SOD). Responses were normalized to and expressed as a percentage of the response to supramaximal KCl for contraction (%K+), or to 10-4M 3-isobutyl-1-methylxanthine for relaxation (%R).

| | ACHmax(%R) | ACh EC50 | Hmax(%K+) | H EC50 |
|---|---|---|---|---|
| NZW-EN | - | - | 90±9 | 1.2E-5M |
| NZW+EN | 54±2 | 3.7E-7 | 89±8++ | 1.2E-5M++ |
| WHHL+EN | 29±1* | 3.6E-7+ | 141±11++,* | 6.2E-6M++,* |
| WHHL-EN | - | - | 150±12* | 5.5E-6M* |

*=p<0.005 vs. NZW; +=NS vs. NZW; ++=NS vs. same-EN

The contractile response to NA was similar in all groups. Neither NA- nor H-induced contraction was significantly altered by EN removal in NZW or WHHL. These data suggest that endothelium-dependent relaxation does not importantly modify either H- or NA-induced contraction in this model. SOD did not enhance relaxation to ACh. We conclude that the spontaneous ATH in WHHL attenuates receptor-mediated, endothelium-dependent relaxation in a manner not oxidation-rate limited.

## Monday, March 20, 1989
## 2:00PM–3:30PM, Santa Ana Room 2
## Anaheim Convention Center
## Arrhythmia Induction and Remission

CAFFEINE IS PROARRHYTHMIC IN PATIENTS WITH ORGANIC HEART DISEASE.

Scott L. Harris M.D., Rita D. Hill R.N., Abraham Varaghese Ph.D, Addison A. Taylor M.D., Cathy Rosene R.N., Marilyn J. Francis R.N, Craig M. Pratt M.D. FACC, Baylor College of Medicine, Houston, Texas.

Caffeine (CAF) has been implicated as a cause of excessive cardiovascular mortality. One mechanism might be the provocation of ventricular tachycardia (VT). In two recent studies CAF has failed to provoke ventricular arrhythmia (VA) in normal subjects. By studying a higher risk population, we conclude that CAF is frequently proarrhythmic. We report on 24 patients (pts) with VA enrolled in a double blind placebo controlled 8 week study with ambulatory electrocardiographic (48 hour baseline) recording, using a specialized kitchen serving a CAF free diet; comparing placebo to CAF dose 1 (450 mg/day), or CAF dose 2 (900 mg/day); with peak/trough CAF levels. Study group: 24 pts, 16 ♂, 8 ♀, mean age 58 yrs, mean left ventricular ejection fraction (LVEF) 44%. 14/24 had LVEF <50%, 10 pts had coronary artery disease. Results:

| | Placebo | CAF 1 | CAF 2 |
|---|---|---|---|
| VPB/hr | 232.5±3.2 | 324.1±112.7 | 299.2±163.1 |
| Pairs/day | 6.8±3.6 | 8.3±4.7 | 11.5±6.2* |
| VT runs/day | 4.4±2.5 | 8.9±4.5 | 21.6±13.7* |

*p=0.01 vs placebo; VPB=ventricular premature beat.

10/14 pts with no VT at baseline developed VT on CAF. All pts with VT at baseline continued to have VT on CAF. Three pts (mean LVEF=33%) with no VT at baseline developed sustained VT on CAF. (Lengths 24, 23 and 52 beats; rates 181, 158 and 205 respectively). Conclusion: Patients with organic heart disease and VA should avoid caffeine because of the demonstrated proarrhythmic effect.

COMBINED AMBULATORY EEG AND ECG MONITORING FOR EVALUATION OF SYNCOPE. Lou-Anne M. Beauregard, M.D., F.A.C.C., Rosemary Rudderow, B.S.N., Caprice H. Rogers, B.A., Barbara Lightfoot, A.B., Paul L. Schraeder, M.D., Travis Toly, M.D., Harvey L. Waxman, M.D., F.A.C.C. Robert Wood Johnson Medical School, Camden, New Jersey.

Patients who have syncope frequently undergo both a cardiac and neurologic evaluation to determine the cause. Recently the 24 hr EEG has proven highly sensitive in detecting pts with epilepsy in whom the diagnosis was not made on routine EEG monitoring. The ambulatory EEG includes 8 EEG channels and 1 ECG channel. The purpose of this study was to evaluate combined EEG/ECG monitoring in pts with suspected neurologic syncope(NS) or non-neurologic syncope(NNS). A simultaneous Holter monitor was applied to provide two additional ECG leads.

A total of 25 pts underwent combined EEG/ECG monitoring using the Oxford Medilog 9000 EEG monitor and standard Holter recorders. Pts included 14 males and 11 females, aged 11-87 yrs, 13 with NS and 12 with NNS. Of 13 pts with NS, 6 had ECG abnormalities, 3 had seizure activity on EEG and 1 had both ECG and EEG abnormalities. ECG abnormalities included sinus bradycardia, ectopic atrial rhythm and atrial tachycardia. In 12 pts with NNS, 5 had ECG abnormalities, e.g. sinus bradycardia, atrial fibrillation or pauses, 1 had EEG slowing and 1 had bradycardia and abnormal EEG activity. Three pts had ECG abnormalities not detected on the ECG channel of the ambulatory EEG. Of 13 pts with NS, combined EEG/ECG revealed an abnormality in 10(77%), and in 12 pts with NNS, an abnormality was found in 7(58%). In pts with NNS, the EEG was abnormal in only 2(17%).

CONCLUSIONS: Noninvasive evaluation of syncope includes both EEG and ambulatory ECG monitoring. Combined ambulatory EEG/ECG monitoring may increase yield and detect episodic abnormalities more efficiently.

SPONTANEOUS VARIABILITY IN VENTRICULAR ARRHYTHMIAS DURING CHRONIC "EFFECTIVE" ANTIARRHYTHMIC THERAPY.

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Spontaneous variability (V) has previously been determined for recordings (R) of untreated but not treated ventricular arrhythmias (VA). Thus, we assessed how frequently clinically noteworthy increases in VA occur in treated Pts with chronic, complex VA in order to discriminate true loss of drug efficacy from V. V in percent suppression (S) of total VA (TVA) and repetitive VA (RVA) was determined in 23 consecutive cases with chronic VA and multiple R during chronic therapy with initially "effective" antiarrhythmic drugs. Effective S was defined as $\geq$70% reduction in TVA and/or $\geq$90% in RVA. V in S was substantial, the overall (group) standard deviation averaging 29$\pm$60% for TVA and 25$\pm$53% for RVA. Trends (NS) emerged which suggested greater V for those with idiopathic disease, higher ejection fraction, low initial arrhythmia frequency, and no beta-blocker therapy. Each of the 23 cases was then assigned to 1 of 5 categories according to the S of TVA and RVA during follow-up. The categories were (A) always suppressed, (B) suppressed during all except one day and then within 10% of criteria, (C) S interspersed with "loss of S," (D) never suppressed, and (E) VA rate above baseline. The number (percentage) of cases in each category was:

| | A | B | C | D | E |
|---|---|---|---|---|---|
| TVA | 10 (43%) | 2 (9%) | 7 (30%) | 2 (9%) | 2 (9%) |
| RVA | 10 (43%) | 2 (9%) | 8 (35%) | 0 (0%) | 3 (13%) |

Thus, V on a single R is high during therapy and may not indicate loss of drug efficacy; loss of S on multiple R (D) and V above baseline (E) may form a better basis for adjusting therapy.

INCREASED VENTRICULAR ECTOPIC ACTIVITY DURING ISCHEMIC EPISODES IN AMBULATORY PATIENTS

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Bikur Cholim Hospital, Jerusalem, Israel

In order to investigate an association between increased ventricular ectopic activity (VEA) and ischemic episodes during everyday activities, we studied prospectively 75 consecutive patients with proven coronary disease, ischemic episodes on Holter monitoring, positive treadmill tests, known ventricular arrhythmias and no antiarrhythmic therapy. In these 75 patients 719 ischemic episodes were recorded during 127 24-hour monitoring periods. Among 43 pts with no baseline VPB's or with <14 VPB's/24 hours, none had increased VEA during ischemia. Of 32 patients who had baseline VPB's >14/24h (average 243/VPB's/24h), in 11 pts increased VEA was observed in 47 episodes (out of a total of 174); during 40 episodes the number of single VPB's increased 30 fold on the average; during 4 episodes trigeminy appeared and during another 3 bigeminy was observed. More complex ventricular ectopy was not observed. There was no correlation between the severity of the episode (degree of ST depression and duration of ischemia) and the increased VEA. The increased VEA appeared during the recovery (reperfusion) phase of the episodes in 88%. Among the 11 pts with increased VEA, only 4 developed VPB's during treadmill testing. No correlation was found between arrhythmias during the episodes and symptoms or lack of symptoms of the patients.

HIGH INCIDENCE OF REMISSION IN PATIENTS WITH INCESSANT VENTRICULAR TACHYCARDIA DISCONTINUED FROM ANTIARRHYTHMIC DRUGS

Robert J. Hariman, M.D., F.A.C.C., Jose L. Gallastegui, M.D., F.A.C.C., Dayi Hu, M.D., Karen J. Beckman, M.D., Jerry L. Bauman, Pharm.D., University of Illinois, Chicago Illinois

Prognosis of patients (pts) with incessant (INC) ventricular tachycardia (VT) not due to acute myocardial infarction (AMI), acute myocarditis or drug toxicity is unknown. We studied and followed 17 pts with INC VT, ages 52.9$\pm$20.6 years, for 59$\pm$35 months (mos) since the diagnosis (DX) of incessant VT. INC VT was defined as episodes of sustained VT, rate > 120 bpm, symptomatic, lasting > 24 hours, and upon 24 hour ECG recording showed VT beats >50% of total beats. Nine pts had coronary artery disease (CAD), 4 cardiomyopathy (CM) and 4 no organic heart disease (OHD). The pts were divided into 2 groups (GR): GR I (4 pts) had left ventricular (LV) ejection fraction (EF) < 40% (range 17-34%) and GR II (13 pts) had LV EF > 40% (range 41-67%). Of GR I, 2/4 pts (50%) had sudden cardiac deaths (SCD) while on antiarrhythmic drugs (AAD) and 1 additional pt died of LV failure within 22 mos after DX. Of GR II pts, 1/13 (8%) had SCD while on AAD, and 1 additional pt died of AMI within 26 mos after DX. Of the surviving GR II pts, AAD were stopped in 4 pts because of drug side effects 1 week to 61 mos after DX; none of these 4 pts had VT recurrence (follow-up off AAD 67$\pm$14 mos). On the basis of the above results, attempts were made to stop AAD in 6/7 asymptomatic pts on AAD, who consented. No VT recurrence occurred in 5/6 pts during these attempts (follow-up off AAD 15$\pm$4 mos), one pt had VT recurrence within 2 weeks off AAD and was put back on AAD. Thus, of all 11 surviving GR II pts, 9/11 pts (82%) had remission off AAD. These pts had CAD (4), CM (2) and no OHD (3). Conclusions: 1) Prognosis of pts with INC VT and good LV EF is good, 2) High remission rate in these pts warrants trials of stopping AAD, when pts become totally asymptomatic on AAD.

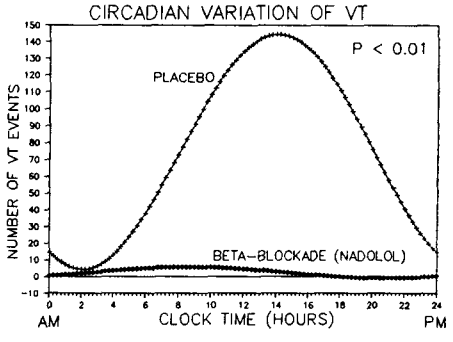
EFFECT OF BETA-BLOCADE ON THE CIRCADIAN VARIATION OF VENTRICULAR ARRHYTHMIAS.

Koonlawee Nademanee, M.D., F.A.C.C., Adeoye Y. Olukotun, M.D., Helen A. Robertson, B.S., Bryna J. Harwood, Bramah N. Singh, M.D., F.A.C.C., VA Medical Center, Los Angeles, California.

Although the mechanism responsible for the circadian variation in the incidence of sudden death is unknown, the possibility exists that it may be related to the diurnal increase in frequency of PVCs and VT. Thus, we studied the circadian variation of PVCs and VT beats and its response to beta-blockade in 33 patients with malignant ventricular arrhythmias. All patients underwent a single-blind placebo controlled protocol and were treated with nadolol (N) in an incremental dose (20-160 mg/day). Holter recordings were obtained at least twice during the placebo treatment and serially during N therapy.

Using the cosiner method to analyze the circadian rhythms of PVCs and VT, we found that during baseline 26 patients had a significant diurnal increase in PVCs. This was quite reproducible in its peak time (between 1PM-6PM, r=.67; p < 0.001) and amplitude (Amp = maximum frequency, r=.93). N suppressed the Amp of the PVC rhythm and had marked effects on VT (see Figure).

Conclusions: There are significant diurnal increases of ventricular arrhythmias (peaking in PM), which are probably due in part to increased sympathetic activity; beta blockade suppressed PVCs Amp, and VT circadian rhythm.




DOES AMBULATORY ST SEGMENT MONITORING CONFER ADDED INFORMATION TO THAT OF EXERCISE TESTING IN THE INVESTIGATION OF PATIENTS WITH CORONARY ARTERY DISEASE - A STUDY OF 277 PATIENTS

David Mulcahy MRCPI, Jennifer Keegan MSc, Jane Sparrow BEd, Amanda Park SRN, Christine Wright SRN, Kim Fox MD. National Heart Hospital, London, England.

It has been reported that ischaemia in the ambulatory setting may result from differing mechanisms to those in the formal exercise setting. Thus one might expect ambulatory ST monitoring (AM) to be a complementary investigation to that of exercise testing (Ex Test) in the detection of ischaemia in pts with coronary artery disease (CAD).

We investigated 277 pts (231 males) aged 30-77 yrs (mean 55.5 yrs) with proven CAD (78 single, 89 two, 110 three vessel disease). All pts underwent treadmill Ex Tests and 48 hrs of AM (total=11,964 hrs). 146 pts (53%) were studied off all routine therapy. Of the Ex Tests performed 187 (67%) were positive for ischaemia. During 11,964 hrs of AM 881 ischaemic episodes (>1mm ST depression persisting for >1min) were recorded (645 (73%) silent). 808 ischaemic episodes (92%) occurred in pts with a positive Ex Test, and only 73 (8%) in those with a negative test. The frequency and total duration of ischaemia were strongly related to a positive Ex Test ($p<0.001$, and $p<0.001$) both in groups off and on therapy. Only one pt with a negative Ex Test had frequent daily (>5/day) episodes of ischaemia, and had documented coronary artery spasm.

In summary, AM contributes little further to the results of Ex Test in terms of the detection of ischaemia, and is indicated only in those with a history suggestive of coronary spasm or when a meaningful Ex Test cannot be performed. The strong relationship between ischaemia in the ambulatory and formal exercise setting suggests that the underlying mechanisms of ischaemia are similar.

## Monday, March 20, 1989
## 4:00PM–5:30PM, Santa Ana Room 2
## Anaheim Convention Center
## Risk Reduction

HOLTER-MONITORING AND PROGRAMMED VENTRICULAR STIMULATION TO PREDICT CLINICAL OUTCOME IN PATIENTS WITH MALIGNANT VENTRICULAR TACHYARRHYTHMIAS

Dietrich Andresen, M.D., Gerhard Steinbeck, M.D., Ralph Haberl, M.D., Rolf Schröder, M.D., F.A.C.C., University of Berlin and Munich, FRG

Little is known about the clinical course of patients (Pts) left untreated after documented sustained ventricular tachycardia (VT) or primary ventricular fibrillation without acute MI (VF). In a prospective study, we followed 70 Pts (38 with VT, 32 with VF), who underwent programmed ventricular stimulation (PVS) and 24-h Holtermonitoring (HM) before being discharged without antiarrhythmic drug therapy. (Mean follow up was 12.6 mos). Results:

| PVS: | | + | + | − | − |
|---|---|---|---|---|---|
| HM : | | + | − | + | − |
| Pts (n): | 70 | 29 | 11 | 16 | + |
| Follow up: total: | ↓ | ↓ | ↓ | ↓ | ↓ |
| recurrences: | 23 | 14 | 4 | 3 | 2 |
| rec. VT: | 17 | 8 | 4 | 3 | 2 |
| SD: | 6 | 6 | 0 | 0 | 0 |

(Definitions: PVS + = inducibility of sustained VT or VF. HM + = detection of frequent ventricular extrasystoles/ frequent ventricular pairs/ventricular tachycardia, rec. VT = Pts with recurrences of VT, SD= Pts with sudden death). Conclusion: A discordant PVS and HM finding cannot distinguish VT/VF-patients who will have recurrences from those who will not. Concordant PVS findings are more predictive of good and poor outcome. In all Pts who died suddenly, both PVS and HM were positiv. Thus, only by combining HM and PVS it is possible to identify a subgroup of VT/VF-Pts as candidates for alternative antiarrhythmic therapy.

ENHANCING PREDICTION OF INDUCED VENTRICULAR TACHYCARDIA IN PATIENTS WITH NON-SUSTAINED RUNS BY THE SIGNAL AVERAGED ELECTROCARDIOGRAM

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A systematic analysis of the value of the signal averaged ECG (SAECG) in predicting the induction of sustained VT in pts with non-sustained VT was conducted in 75 pts. Twenty-two pts (29%) had induced VT on programmed stimulation and 53 (71%) did not. Each SAECG was analyzed at 11 high pass filter settings, 10 to 100 Hz and the low pass was fixed at 250 Hz. QRS duration, low amplitude signal <40μV (LAS), and root mean square voltage of the last 40 ms of the QRS (RMS) were grouped alone and in every possible paired combination and analyzed for sensitivity (Sens), specificity (Spec), positive (Pos), negative (Neg) and total predictive accuracy (PA) to predict inducibility. Normal values were based on data from 100 normal subjects. RESULTS: 561 combinations were analyzed. Statistical parameters and selected combinations are shown below:

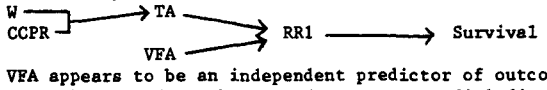
| Combination/(%) | Sens | Spec | PosPA | NegPA | TotalPA |
|---|---|---|---|---|---|
| Highest | 91 | 96 | 89 | 95 | 91 |
| Lowest | 59 | 68 | 53 | 84 | 73 |
| RMS(25Hz,40Hz) | 82 | 94 | 86 | 93 | 91 |
| LAS-RMS(25Hz) | 82 | 89 | 75 | 92 | 87 |
| LAS-RMS(40Hz) | 82 | 89 | 75 | 92 | 87 |
| LAS-RMS(80Hz) | 73 | 91 | 76 | 89 | 85 |

CONCLUSIONS: 1) The total predictive accuracy of the SAECG for inducibility of sustained VT in pts with non-sustained VT was as high as 91%. 2) combinations of parameters paired at different filter settings were superior to those at same setting, with optimal prediction observed using RMS(25Hz) paired with RMS(40Hz).

FACTORS PREDICTING SURVIVAL FROM PREHOSPITAL CARDIAC ARREST

Donald D. Brown, M.D., F.A.C.C., Kenneth R. Stults, M.S., Younghae Chung, M.S., Richard E. Kerber, M.D., F.A.C.C., University of Iowa, Iowa City, Iowa.

Improving cardiac arrest survival requires understanding the relative importance of several factors which might be amenable to modification either directly or indirectly. Using multivariate techniques we analyzed data from 444 ventricular fibrillation (VF) cases (300 witnessed) to assess the relative impact on survival of age, witnessed arrest (W), citizen CPR (CCPR), initial VF amplitude (VFA), time in arrest (TA), and rhythm resulting from the first shock (RR1). RR1 was a strong ($p<.001$) predictor of survival; the survival rate was 24% when RR1 was organized, 8% when it was VF, and 6% when it was asystole. VFA and TA were each strong ($p<.001$) determinants of RR1, but were only weakly correlated with one another ($r=-.17$). W was a strong ($p<.001$) predictor and CCPR a weak ($p<.10$) predictor of survival, but neither was significantly associated with RR1. Thus, the following model is hypothesized:




VFA appears to be an independent predictor of outcome through RR1 and may be dependent on myocardial disease and drugs. The mechanism for the associations of W and CCPR with survival probably result chiefly from their association with shorter TA's.

VARIABILITY OF NEGATIVE T WAVE IN LEFT VENTRICULAR HYPERTROPHY, THE POSSIBLE RESULT OF CONTRACTION-EXCITATION FEEDBACK.

Yasuro Sugishita, M.D., F.A.C.C., Keiji Iida, M.D., Takashi Miyauchi, M.D., Iwao Ito, M.D., Katsutoshi Goto, Ph.D., Dept. of Med., Univ. of Tsukuba, Tsukuba, Ibaraki, Japan

Studies have revealed that changes in ventricular shortening lead to changes in action potential duration via contraction-excitation feedback in man. We studied the influence of the changes in LV contraction on the variability of negative T wave (NT) in 18 Pts with hypertrophic cardiomyopathy (HCM) and 9 Pts with aortic regurgitation. ECG and echocardiograms were studied by symptom-limited ergometer exercise test, isoproterenol (0.02 μg/kg/min for 5 min) infusion and the depression of systolic blood pressure by 30 mmHg by sodium nitroprusside infusion. No Pt had coronary artery disease. By exercise, in HCM, fractional shortening (FS) obtained from echocardiography increased (40±7 → 47±7%*) and NT became less deep (-1.3±0.5 → -0.8±0.4 mV*); but in aortic regurgitation, FS and NT did not change significantly. The changes of T wave (ΔT) correlated significantly with the changes of FS (ΔFS) in all patients ($r=0.80$*). By isoproterenol in HCM, FS increased (41±5 → 54±8%*) and NT became less deep (-1.3±0.4 → -0.5±0.4 mV*), and ΔT correlated with ΔFS significantly ($\Delta T=0.055\Delta FS+0.15$, $r=0.72$*). By nitroprusside (measurements were performed before heart rate increased), FS increased (44±5 → 46±7%*) and NT became less deep (-1.0±0.5 → -0.7±0.5 mV*), and the relation between ΔFS and ΔT were on the regression line obtained by isoproterenol, as mentioned above. With nitroprusside, R amplitude/T depth became smaller. Conclusion: These data suggest that the changes in LV shortening in human LV hypertrophy produce the changes in the depth of NT via contraction-excitation feedback. *$p<0.001$

PROGNOSTIC VALUE OF LATE POTENTIALS IN HYPERTROPHIC CARDIOMYOPATHY.

Tim Cripps M.D., John Camm, F.A.C.C., William McKenna, F.A.C.C., St George's Hospital Medical School, London, England.

The value of late potentials (LP) in predicting arrhythmias was assessed in 31 patients (pts.) with hypertrophic cardiomyopathy (HCM). Maximum echocardiographic wall thickness was 15-29mm, median 22mm; 15 patients were on amiodarone (median dose, 200 mg/day); 12 of the patients were young (<25 years), and of these 3 had been resuscitated from out-of-hospital ventricular fibrillation (VF). All 31 patients had 48 hour Holter monitoring; 8 had non-sustained ventricular tachycardia (VT) and one had sustained VT. None of the 3 young patients with a history of VF had arrhythmias on Holter. LP were detected using Simson's method; patients with bundle branch block were excluded and a prolonged filtered QRS was not considered positive for LP if the surface QRS was >120ms. LP were present in 7/31 (23%). There was no difference between the incidence of LP in those with and without amiodarone therapy and there was no correlation with the degree of echocardiographic left ventricular hypertrophy. Of the 4 patients with a history of life-threatening arrhythmias 3 (the one with sustained VT and 2 of the 3 with VF) had late potentials. The sensitivity for the prediction of life-threatening arrhythmias by LP was thus 75%, the specificity 85% and the positive predictive accuracy 43%. Of the 9 patients with non-sustained VT, 4 had LP compared with 3/22 without VT ($p<0.05$). All 8 patients with non-sustained VT have had a benign course. Conclusions: the presence of LP in patients with HCM correlates both with 1) the occurrence of life-threatening arrhythmias and 2) non-sustained VT, a known prognostic marker in HCM. Signal averaged electrocardiography may be of value in the assessment of the risk of sudden death in HCM, especially in the younger age group, where currently no prognostic indicator exists.

## Monday, March 20, 1989
## 2:00PM–3:30PM, California Room B
## Anaheim Convention Center
## Risk Factors in Coronary Disease

THREE DECADE TRENDS IN INCIDENCE OF CORONARY DISEASE AND RISK FACTORS IN THE FRAMINGHAM STUDY.

W.B. Kannel M.D.; R.G. D'Agostino Ph.D.; A. Belanger M.A.

Substantial declines in U.S. Coronary Heart Disease (CHD) mortality are well documented, but secular trends in incidence and associated risk factors based on uniform assessment are unavailable. Trends in CHD prevalence, incidence and case fatality rates are examined in the Framingham study over the 1950's, 1960's and 1970's (biennial exams 3-12). Significant increases in CHD ($p<.01$) and myocardial infarction (MI) prevalence were noted in men and for MI in women. CHD prevalence increased 1.6 fold in men and 1.3 fold in women. Men also showed increases in MI and MI-by electrocardiogram (ECG) in both sexes, although this was significant only in women ($p<.05$).

Modest but significant decline in CHD mortality was noted in women ($p<.05$). Sudden death mortality showed no obvious trends, even excluding those with prior overt CHD. CHD case fatality rates declined from 26 to 20% in men; no significant trends were noted in women.

Hypertension and cholesterol values have declined over the three decades. Left ventricular hypertrophy as shown on ECG is dramatically reduced. Cigarette smoking declined substantially in men but increased slightly in women. Obesity increased in men but not women, and diabetes increased sharply in prevalence in both sexes.

The data suggest that we may be seeing milder cases of CHD lately and that medical care may be prolonging life in those with established disease.

## SURVIVAL AND QUALITY OF LIFE IN CIGARETTE SMOKERS VERSUS QUITTERS RANDOMIZED TO MEDICINE OR CABG IN THE CORONARY ARTERY SURGERY STUDY (CASS): 10 YEAR FOLLOW-UP.

J. Bradley Cavender MD, William J. Rogers MD, FACC, Lloyd D. Fisher PhD, FACC, Bernard J. Gersh MD, FACC, C. Joan Coggin MD, FACC, William O. Myers MD FACC for the CASS Investigators. UAB Medical Center, Birmingham, AL.

To determine the effects of continued cigarette smoking on patients with coronary artery disease, we examined the clinical outcome after 10 years' follow-up in patients randomized to medical therapy (N = 390) or surgery (CABG)(N = 390) in the NHLBI Coronary Artery Surgery Study (CASS). Patients smoking at entry were classified at the 6 month follow-up as Quitters (N = 97) if they had quit smoking or as Non-Quitters (N = 187) if they had continued smoking.

Among all randomized patients, survival at 10 years was 83% in patients not smoking at baseline, 84% in Quitters, and 72% in Non-Quitters (p = .004). Of smokers randomized to CABG, 10 year survival was 90% in Quitters and 73% in Non-Quitters (p = .02); whereas, among smokers randomized to medicine, 10 year survival was 76% in Quitters and 71% in Non-Quitters (pNS). Overall, patients smoking throughout the followup period had a relative risk of death of 1.99 (p = .0001) that of non-smokers after adjustment for baseline covariates (Cox).

Additionally, at 10 years Quitters had significantly less angina (Quitters--no angina: 53%, Non-Quitters--no angina: 34%, p = .003) and significantly less activity limitation (Quitters--no limitation: 36%, Non-Quitters--no limitation: 20%, p = .006). Furthermore, among patients having CABG and who smoked at any time during followup, there was a trend toward more repeat CABG's than among non-smokers (13% vs 8.5%, p = .10).

Thus, continued or incomplete cessation of cigarette smoking among randomized CASS patients resulted in decreased survival (especially among CABG patients), more angina, greater impairment of physical activity and a trend toward more repeat CABGs.

## FAMILY HISTORY PREDICTORS OF HIGH BLOOD CHOLESTEROL LEVELS IN 4TH GRADE SCHOOL CHILDREN.

Dennis M. Davidson M.D., Cynthia A. Iftner R.D., Beverly J. Bradley Ph.D., Sandra M. Landry P.N.P., Madalene Y. Rose R.N., Nathan D. Wong Ph.D., University of California, Irvine, California

To examine the predictive value of a family history (FHx) of cardiovascular risk indicactors in the determination of children with high levels of blood cholesterol, we studied 625 fourth-graders whose parents provided parental and grandparental history of: myocardial infarction (MI), coronary bypass surgery, high blood pressure, high blood cholesterol, diabetes, and smoking. Of the 625, 113 were Spanish-surnamed (SS) and 136 were Vietnamese-American (VN). Mean total blood cholesterol (TC) (by fingerstick) for all children = 171.40 mg/dl with SS= 167.5 and VN= 175.1 (p<.05). Children with a reported FHx of high blood cholesterol had TC=179.0; 37% had TC >= 190 and 25% had TC >= 200. These levels contrasted significantly (p<.001) with children with no FHx of high blood cholesterol (mean TC= 168.5). Within this group, TC levels were similar in those children with a FHx of MI at age 55 or younger (TC= 168.1) and all others (TC= 168.6). Of the 625 children tested, 123 had TC >= 200 mg/dl. However, only 42 of the 123 had reported either a) a FHx of high blood cholesterol or b) a FHx of MI at age 55 or younger. Thus, adherence to the current policy recommending TC screening of only children with a positive family history would have failed to detect nearly 2/3 of children in this study whose TC levels were above current adult guidelines of 200 mg/dl.

## CHRONIC IMPAIRMENT OF PARASYMPATHETIC CARDIAC CONTROL IN HEAVY SMOKERS.

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From Framingham study, relative risk of sudden coronary death (SCD) in men has been reported to be ten times higher in smokers than in non-smokers. Smoking seems to increase the vulnerability to ventricular fibrillation (VF) through altering autonomic functions. Therefore, in this study, we investigated the chronic effects of cigarette smoking on autonomic functions by analyzing the heart rate variability in 56 male smokers (31 moderate (1-24 per day) and 25 heavy (>=25 per day) smokers) more than 12hr after the last smoking and in 25 healthy male non-smokers. The autoregressive spectral analysis was used to determine the power spectral density (PSD) of R-R interval variability. The PSD contains two major components reflecting respiratory sinus arrhythmia (RSA) and 0.04-0.15Hz fluctuation of cardiovascular system, that provide quantitative indices of parasympathetic cardiac control and sympathetic activity with vagal modulation, respectively. The RSA component was significantly smaller in magnitude in heavy smokers than in moderate and non-smokers. The difference was especially marked in younger subjects. Whereas the other component was not different between three groups. Conclusions: 1, parasympathetic cardiac control is chronically reduced by heavy smoking especially in younger subjects; 2, since increased incidence of SCD and VF has been demonstrated in patients with decreased parasympathetic cardiac control, the finding of this study explains a mechanism of increased coronary mortality in smokers, especially, in young smokers; 3, much more attention should be paid on SCD and VF in young heavy smokers.

## COFFEE USE AND ACUTE MYOCARDIAL INFARCTION.

Arthur L. Klatsky M.D., F.A.C.C., Mary Anne Armstrong M.A., Gary D. Friedman M.D., Kaiser Permanente Medical Center, Oakland, California.

Evidence that coffee use may increase risk of coronary artery disease (CAD) has been conflicting, but reports of an association of blood cholesterol levels with coffee strengthen the plausibility of a coffee-CAD link. We did a new prospective study of these relationships among 129,672 persons. In the years 1978-1986, 740 persons were hospitalized for an acute myocardial infarction (AMI) and 1,174 persons were hospitalized for other CAD diagnoses. Analysis was controlled for age, sex, race, smoking, alcohol use, tea use, and education. Coffee use was associated with increased risk of AMI. Using non-drinkers of coffee as the reference, the relative risks (95% confidence intervals) for AMI follow: 1-3 cups per day=1.14 (0.91-1.42); 4-6 cups/day=1.36 (1.05-1.75), p= 0.02; 6+ cups/day=1.45 (1.03-2.04), p=0.03. The coffee-AMI relationship remained significant when controlled for blood cholesterol, blood glucose, Quetelet index, or baseline heart disease, singly, or combined. A significant coffee-AMI relationship was found in men, women, whites, blacks, never smokers, and current smokers, but not in exsmokers. In the earlier study years (1978-1982) the relationship was stronger (relative risk of AMI for 4+ vs. no cups/day=1.85 [1.26-2.74], p=0.002), which raises the possibility of a short-term effect. Tea use was not related to AMI; neither coffee nor tea use was related to other CAD diagnoses. We conclude that: 1. these data suggest a weak independent relationship of coffee use to AMI, not explained by the coffee-cholesterol link; 2. persons at risk of AMI who drink 4+ cups of coffee per day should consider reduction of intake.

HOUSESTAFF PRACTICE OF PREVENTIVE CARDIOLOGY: WHO'S NOT DOING WHAT? Marian Limacher, M.D., FACC, Yvonne Brinson, R.N., Nancy Norvell, Ph.D., A. Daniel Martin, Ph.D., C. Richard Conti, M.D., FACC. The University of Florida and Gainesville VAMC, Gainesville, FL.

To determine how completely house officers on different services evaluate pts at risk for coronary heart disease (CHD), 30 randomly chosen GVAMC discharge records were reviewed from each of three in-patient services: Cardiology (Card), General Medicine (Med), and General Surgery (Surg). Twenty-eight Card pts had diagnoses of existing CHD, no Med pts had CHD and 8 Surg pts had peripheral vascular disease. Documentation of historical and measurable risk factors was noted. Interns invariably documented family history, age of CHD onset, blood pressure, cigarette, cholesterol (chol), diabetes and alcohol history more frequently than residents on all services. Diet and physical activity were documented in less than 10% of all charts. Family history and onset age of family heart disease were more frequently obtained by Card (93% and 50%) than Med (63%** and 10%*) or Surg (7%*** and 0***). Chol history was documented for 50% of Card pts, but only 3%*** of Med and 7%*** of Surg pts. However, Card and Surg pts were more likely to have a chol level drawn: 57% Card and Surg vs 23%* Med. In contrast, the majority of pts on all services had cigarette and alcohol history documented: Card 100% and 87%, Med 90% and 73%, and Surg 77% and 77% (p=NS). {*p<.05, **p<.01, ***p<.001 by chi square} Conclusions: The chart survey method indicates that most preventive screening occurs in pts who already have a diagnosis of CHD. However, chol, diet, activity and onset age of family CHD are still not routinely addressed. Educational efforts for housestaff must be expanded to increase screening effectiveness for all pts at risk.

## Monday, March 20, 1989
## 4:00PM–5:30PM, California Room B
## Anaheim Convention Center
## Cardiovascular Disease in the Elderly

RISK FACTORS FOR CORONARY MORTALITY IN ELDERLY SURVIVORS OF MYOCARDIAL INFARCTION: THE FRAMINGHAM STUDY.
Nathan D. Wong Ph.D., Kara L. Kerns, William B. Kannel M.D., University of California, Irvine, California.

Recognized standard and clinical risk factors for coronary heart disease were evaluated in relation to long-term prognosis following initial myocardial infarction (MI) in elderly participants of the Framingham Heart Study. 140 men and women aged 65 to 88 years (mean age= 71.3 years) returned for a scheduled biennial examination following MI where risk factors were measured, and a resting electrocardiogram (ECG) and chest x-ray were performed. Mean follow-up was 8.2 years and 39 subjects subsequently died of coronary disease. Cox regression demonstrated age to be positively associated ($p<0.01$) with coronary mortality, and males were at more than four times the risk than females ($p<0.01$). A 50 mg/dl increment in serum cholesterol level was associated with a 67% increase in risk of coronary death ($p<0.05$). Reported smoking in the past year, or the presence of diabetes, hypertension, or obesity did not emerge as prognostic indicators. Of clinical factors, the risk of coronary mortality was 12.7 times greater in those with left ventricular hypertrophy by ECG ($p<0.001$), 2.9 times greater in those with non-specific T-wave abnormalities ($p<0.01$), and 4.3 times higher in those experiencing an interim re-infarction ($p<0.01$). These associations were adjusted for the effects of age, sex, and cholesterol. Cardiomeagaly on x-ray, diuretic usage, functional class level, and other ECG indicators did not add prognostic information. These results argue for close monitoring of older individuals with left ventricular hypertrophy and T-wave abnormalities on follow-up ECG, and suggest that efforts to control elevated serum cholesterol levels may be beneficial in this population.

SILENT CORONARY ARTERY DISEASE IN ELDERLY MEN: LOW EXERCISE TOLERANCE IS STRONGLY ASSOCIATED WITH MULTIVESSEL DISEASE.
Dalane W. Kitzman M.D., Miriam C. Morey M.A., Robert J. Sullivan M.D., Gail M. Crowley R.N., Robert C. DiPasquale M.S., Michael B. Higginbotham M.B., Duke and V.A. Medical Centers, Durham, North Carolina.

In symptomatic elderly men, exercise duration and ST segment depression during exercise treadmill testing (ETT) have additive predictive value for coronary artery disease (CAD). However, in asymptomatic elderly men, little information is available regarding the diagnostic utility of ETT. We performed fatigue limited ETT on 64 consecutive men entering a geriatric ($\geq$ age 65) fitness program who had no prior clinical manifestation of CAD. Prospectively, all entrants (n=16) with a +ETT were offered coronary angiography. Of the 12 who accepted, 10 had $\geq$ 2mm flat ST segment depression and 2 had $\geq$ 1mm ST segment depression during the ETT. At angiography, 7 patients (58%) had significant CAD ($\geq$ 75% narrowing), 2 had insignificant CAD (<75% narrowing) and 3 had normal coronary arteries. Multivessel CAD was present in 4 patients (33%). No subject developed ischemic symptoms or had complications during the ETT. Fifty-eight (91%) of the entrants exercised beyond the end of Bruce stage 1 equivalent (5 METS). Four (67%) of the 6 entrants who did not complete stage 1 had a +ETT, and all 4 had multivessel disease at angiography ($p=0.002$, Fisher's exact test). For entrants with a +ETT, the association between multivessel CAD and low exercise tolerance was confirmed by logistic analysis ($p=0.0001$). Thus, asymptomatic elderly men can safely perform fatigue limited ETT and most will complete Bruce stage 1 equivalent. The majority of those who develop ST segment changes will have significant CAD, particularly if they demonstrate low exercise tolerance.

CARDIOVASCULAR RISK OF HYPERTENSION IN THE OLD OLD: THE BRONX LONGITUDINAL AGING STUDY.
Steven Greenberg M.D., Howard Guzik M.D., William Frishman M.D., FACC, Wee Lock Ooi Ph.D., Miriam Aronson Ed.D., Albert Einstein College of Medicine, Bronx, N.Y.

In order to assess the risk of systemic hypertension in the extreme elderly and the efficacy of treatments, we studied prospectively an elderly subject cohort of 488 noninstitutionalized individuals (aged 75-85 years at entry) for eight years. Hypertension was defined by history and auscultatory blood pressure values above 140/90 mmHg, off or on therapy. Sixty-three percent of the subjects (n=312) were hypertensive at the time of initial study or were receiving antihypertensive drug treatment; 37% were normotensive off drug treatment. The hypertensive patients showed a predominant elevation of systolic blood pressure. Only 30% of the hypertensive subjects were well controlled on drug treatment. Subjects with hypertension demonstrated a higher incidence of cardiovascular morbid and mortal events compared to the non-hypertensive subjects. Subjects with hypertension had a 15.4% incidence of new stroke versus a 3.9% incidence in non-hypertensives ($p=0.004$), hypertensive subjects had a 23.5% incidence of silent and painful myocardial infarctions versus 13.9% in non-hypertensives ($p=0.04$). Poorly-controlled hypertensives, especially those with LVH on ECG, had the highest incidence of new myocardial infarction (30%), a significant difference from the well-controlled patients ($p=0.006$). Hypertension, especially systolic hypertension, is an extremely common finding in the old old. It is associated with an increased risk of stroke and myocardial infarction which may be modified by antihypertensive drug treatment.

DECREASED REJECTION IN OLDER CARDIAC TRANSPLANT PATIENTS
Steven K. Rowe, M.D., James B. Young, M.D., F.A.C.C., George P. Noon, M.D., F.A.C.C., Michael E. DeBakey, M.D., F.A.C.C., Baylor College of Medicine, Houston, Texas

There may be a survival advantage in older heart transplant (HT) patients (Pt) (55-68 years). These Pts may experience less rejection compared to younger Pts, but this is controversial. To study the effect of age on rejection in heart transplantation, we analyzed 90 consecutive orthotopic HT in 89 Pts. 30 Pts >55 years (range 13-68), 13>60 years (including the oldest Pt in the International Registry, 68 years). Follow-up was 13.5±13 (mean±SD) months. Overall mean age=46.5±14 years. Men/women=76/13; mean EF=20%±4; previous heart surgery=38; inotropic support=32; intraaortic balloon pump=10; etiology: coronary artery disease=50; dilated cardiomyopathy=26; other=13. Results: Initial hospital stay = 31±49 days; readmissions/ Pt*year=1.35±2; total days readmissions/Pt*year=13±28; rejection/Pt*year=1.8±4.5; infection/Pt*year=3,6±10. Rejection was diagnosed by McAllister grade (0-10). Moderate (5) or above was defined as significant rejection requiring treatment. Linear covariant analysis demonstrated decrease in rejection episodes/Pt with advancing age (p=0.02, r=-0.27). Older Pts tended to experience rejection later. This occurred without any difference in infection (p>.05, r=-0.03), length of hospital stay (p>.05, r=-0 .01), or readmission days (p>.05, r=-0.023). Overall actuarial one year survival was 72% with age not adversely affecting outcome (p=0.86). Conclusions: Older Pts can undergo cardiac transplantation successfully and expect no survival penalty, increased infection or requirement for readmission. The incidence of rejection appears to decrease with advancing age. This may allow modulation of immunosuppressive regimens resulting in reduced incidence of related morbidity and mortality.

THE POTENTIAL ROLE OF TRANSESOPHAGEAL ECHO IN THE DEFINITION OF INTRACARDIAC SOURCES OF EMBOLI IN TRANSIENT ISCHEMIC ATTACKS.
Gheorge Pop M.D., George Sutherland M.D., Jos Roelandt F.A.C.C., Thoraxcenter, Erasmus University, Rotterdam, the Netherlands.

To compare and contrast the role of precordial (PE) and transesophageal echo (TEE) in the definition of potential intracardiac sources of emboli, 70 patients with a recent unequivocal transient ischemic attack (TIA) were studied. The patients studied were subdivided into 2 Groups. Group 1 (52 pts) with no clinical cardiac abnormality and Group 2 (18 pts) with one or more abnormal cardiac findings on clinical examination. In Group 1, PE appeared normal in all 52 pts but TEE defined significant clinically unsuspected abnormalities in 4 pts which could predispose to a TIA (1 left atrial appendix thrombus; 1 aortic dissection; 1 thrombus on posterior mitral leaflet and 1 mitral valve prolapse in a young patient). In Group 2 13/18 had both normal PE and TEE studies while 5 had both abnormal PE and TEE studies. The latter 5 had either left atrial and/or left ventricular dilatation visualised on both PE and TEE studies but only TEE clearly defined significant left atrial appendix thrombus in 2 pts. In addition, in 29 of the 70 pts TEE identified widespread ascending and descending aortic atherosclerotic placques not visualised from the precordial approach. We conclude that TEE does significantly increase the yield of potential intracardiac sources for emboli in patients with transient ischemic attacks.

AORTIC STENOSIS IN THE ELDERLY: AORTIC BALLOON VALVULOPLASTY VS. AORTIC VALVE REPLACEMENT
James Srebro MD, Sergio Manubens MD, Paul Yock, MD, FACC, Thomas Ports, MD, FACC, University of California, San Francisco

Critical aortic stenosis is a therapeutic dilemma in the elderly (>80). In order to study the risks and benefits of aortic balloon valvuloplasty (ABV) as compared to aortic valve replacement (AVR), we reviewed the clinical course of patients who underwent these procedures in our institution since 1980 In demographically similar groups of patients (age, sex, symptoms and hemodynamics at presentation), the in-hospital mortality was significantly lower in 29 patients who underwent ABV (4%) compared to 29 who had AVR (17%). Morbidity, including myocardial infarction, cerebrovascular accident and transient ischemia attacks was also substantially lower for ABV (7% vs. 30%). Only 20% of patients undergoing ABV required blood transfusion whereas all who underwent AVR required blood products (mean 10 units). The duration of hospitalization for ABV was much shorter than AVR (3 vs. 17 days) at an average cost of $9,500 compared to $32,000 for AVR. Long-term follow-up suggests that patients who undergo ABV more frequently (33% vs. 0%) experience deterioration of functional class over a mean follow-up period of 9 months. We conclude that ABV can be performed with low morbidity in the very elderly, but with less sustained benefit than AVR which has substantially higher morbidity and mortality in this population

## Monday, March 20, 1989
## 2:00PM–3:30PM, California Room A
## Anaheim Convention Center
## Peripheral Changes in Congestive Heart Failure

CAPILLARY DENSITY, FIBER TYPE AND ENZYME COMPOSITION OF SKELETAL MUSCLE IN CONGESTIVE HEART FAILURE.
Clyde W. Yancy, Jr. M.D., Dorabeth Parsons, Ph.D., Lynda Lane M.S., R.N., Melissa Carry, M.D., Brian G. Firth, M.D., F.A.C.C., C. Gunnar Blomqvist, M.D., F.A.C.C. UT Southwestern Medical Center, Dallas, Texas.

Patients with congestive heart failure (CHF) may have impaired maximal oxygen uptake partly because of peripheral maladaptations to skeletal muscle hypoperfusion. To evaluate structural and functional changes in skeletal muscle in CHF, we performed needle biopsies of the vastus lateralis muscle in six patients (5 men, 1 woman; age 50.3) with CHF (LVEF 0.26; $VO_2$max 13.5 ml/kg/min) and compared these data with reference data from sedentary controls (CON) and highly fit subjects (HF). Immunocytochemistry using biotinylated lectin and computerized image analysis was used to identify and quantitate capillaries and skeletal muscle fibers. Skeletal muscle capillary (cap) density was markedly reduced (251.5 cap/mm$^2$ ± 37.7 [$\bar{x}$ ± S.E.], CON 334.96 ± 87.86; HF 414.4 ± 40.3). Capillary to muscle fiber ratio was decreased (1.15 cap/fiber ± 0.28, CON 1.39 ± 0.3; HF 4.15 ± 0.6). Fiber type analysis revealed high per cent type II fiber (71.3% ± 7.4, normal 55%), but reduced type II fiber cross-sectional area (3510.5 u$^2$ ± 496.5; HF > 6000). Enzyme assays yielded normal phosphofructokinase activity but markedly impaired succinate dehydrogenase activity (1.18 umol/gm/min ± 0.19, CON 5.6-8.0). In summary, skeletal muscle in CHF demonstrates: 1) impaired vascularity that may limit perfusion; and 2) important alterations in muscle fiber type and function that may limit oxidative and favor anerobic metabolism. These data suggest that peripheral maladaptations may contribute significantly to impaired exercise capacity and reduced maximal oxygen uptake in congestive heart failure.

SKELETAL MUSCLE METABOLIC ABNORMALITIES IN HEART FAILURE ARE IN PART DUE TO INTRINSIC SKELETAL MUSCLE CHANGES.

Donna Mancini M.D., E. Coyle Ph.D., N. Ferraro R.N., R. Seestedt B.S., Britton Chance Ph.D., John R. Wilson M.D., University of Pennsylvania, Philadelphia, Pennsylvania.

Patients with heart failure exhibit abnormal skeletal muscle P-31 NMR metabolic responses to exercise. To investigate whether these abnormalities are related to intrinsic skeletal muscle changes, we performed gastrocnemius biopsies and obtained P-31 NMR spectra during submaximal calf exercise in 21 patients with heart failure (Peak $\dot{V}O_2$=15.6±5.1 ml/kg/min; EF=19.7±7%). Biopsies were analyzed for fiber type and area, capillarity, citrate synthase (CS), phosphofructokinase, lactate dehydrogenase, and β-dehydroxyacyl Co dehydrogenase (BOAC). P-31 NMR spectra and systemic $\dot{V}O_2$ were obtained during plantarflexion performed at 3 workloads. The slope of the relationship between $\dot{V}O_2$ and the inorganic phosphorus/phosphocreatine ratio was used to assess muscle metabolism. Patients were divided into those with 31-P NMR slopes below (Group I) vs. above (Group II) the mean slope for the entire group. Patients with the least abnormal spectra (Group I) exhibited higher peak $\dot{V}O_2$ (I: 19.4±5.8; II: 13.3±2.5 ml/kg/min; p<0.05), larger calf circumferences (I: 35.3±2.2; II: 32.1±1.3 cm; p<0.01), significantly greater BOAC (I: 5.10±1.69; II: 2.97±0.66 mol/kg-protein/hr; p<0.005) and CS (I: 5.8±2.0; II: 3.59±1.06 mol/kg-protein/hr) concentrations and tended to have more type I fibers (I: 57.5±16.5; II: 45.1±18.7%; NS). No difference was found in capillarity or fiber area. These data suggest that abnormal skeletal muscle metabolic responses in heart failure are in part due to intrinsic muscle changes. These intrinsic changes may be due to deconditioning as the state of conditioning influences oxidative and lipolytic enzymatic activity, fiber type, and muscle mass.

TEMPORAL DISSOCIATION BETWEEN INVASIVE AND NON-INVASIVE DETERMINATION OF ANAEROBIC THRESHOLD IN CHRONIC HEART FAILURE.

Stuart D. Katz M.D., Robert Berkowitz M.D., Peter Keller M.D., Thierry H. LeJemtel M.D., Edmund H. Sonnenblick, M.D., FACC, Albert Einstein College of Medicine, Bronx, N.Y.

Twelve patients with chronic heart failure ($VO_2$ max 9.0-14.4 ml/kg/min) exercised on a bicycle using a 5 watt/min ramp protocol. Lactate anaerobic threshold (LAT) was derived from a log-log plot of arterial lactate obtained very minute during exercise. Ventilatory anaerobic threshold (VAT) was measured by standard (std) methods ($VO_2$, $VCO_2$, RQ, VE, Pet $O_2$, Pet $CO_2$, $VE/VCO_2$, $VE/VO_2$) and a computerized v-slope method. Results were:

| | Time to AT (sec) | % $VO_2$ Max at AT | Arterial Lactate at AT (mmol/L) |
|---|---|---|---|
| LAT | 252 | 80 | 1.6 |
| VAT std-method | 340* | 83* | 2.6* |
| VAT v-slope method | 377* | 87* | 2.7* |

* = p<0.05 vs LAT

VAT by std-method and v-slope method did not correlate (r = 0.24 for $VO_2$ at VAT; r = -.02 for time to VAT). Lactate anaerobic threshold could not be detected in patients with $VO_2$ max <11 ml/kg/min as arterial lactate rose linearly within 120 seconds of exercise, while $VO_2$ was already >70% of $VO_2$ max. In remaining patients, lactate anaerobic threshold occurred earlier during exercise, at lower $VO_2$ and arterial lactate than VAT by either method. Thus, lactate anaerobic threshold does not coincide with VAT in patients with severely impaired aerobic capacity. Such temporal dissociation questions the physiologic basis of anaerobic threshold determination in chronic heart failure.

DECREASED AEROBIC OXIDATIVE CAPACITY IN SKELETAL MUSCLE IN CHRONIC HEART FAILURE

Martin J. Sullivan, MD, Michael B. Higginbotham, MB, Howard J. Green, MD, Frederick R. Cobb, MD, Duke and VA Medical Centers, Durham, NC

In order to determine if an abnormality in skeletal muscle metabolic function exists in chronic heart failure (HF), 11 Pts with HF (ejection fraction 17±9%, peak $VO_2$ 13±6 ml/kg/min) and 8 normal subjects (NL)(peak $VO_2$ 29±9 ml/kg/min) underwent biopsy of the vastus lateralis skeletal muscle. Enzymatic analysis included: phosphofructokinase (PFK), phosphorylase (PHOS), lactate dehydrogenase (LDH), citrate synthetase (CS), succinate dehydrogenase (SDH), and 3-hydroxyacl CoA dehydrogenase (3HAD). Results are expressed as μ moles/mg protein/min:

| | NL | HF |
|---|---|---|
| PFK | 207 ± 65 | 222 ± 43 |
| PHOS | 55 ± 14 | 53 ± 6 |
| LDH | 1147 ± 543 | 1111 ± 289 |
| CS | 45 ± 20 | 26 ± 7* |
| SDH | 80 ± 16 | 51 ± 15† |
| 3HAD | 28 ± 10 | 18 ± 7* |

*p<0.05 NL vs HF; †p<0.001 NL vs HF

These data indicate that enzymatic pathways involved in glycogenolysis and glycolysis are intact in patients with HF while the metabolic capacities for aerobic oxidation and fatty acid utilization are markedly reduced. These results suggest that intrinsic abnormalities in aerobic skeletal muscle function may contribute to decreased exercise tolerance due to early lactate production in Pts with chronic heart failure.

PREDICTORS OF MORTALITY CHANGE AS THE DISEASE PROGRESSES IN PATIENTS WITH CHRONIC HEART FAILURE.

Stephen S. Gottlieb MD, Lawrence Baruch MD, Marrick L. Kukin MD, Janine L. Bernstein MS, Gerald W. Neuberg MD, Milton Packer MD, FACC. Mt. Sinai School of Medicine, New York, NY

Long-term follow-up studies in chronic heart failure (CHF) have disagreed strongly as to which pretreatment variables are the principal determinants of survival. The reasons for such differing views are unknown, but it is possible that prognostic variables may change in importance as CHF progresses. To evaluate this hypothesis, we measured plasma renin activity (PRA, ng/ml/hr) & norepinephrine (PNE, pg/ml), LV ejection fraction by nuclear ventriculography (EF, %), and the frequency of ventricular premature beats (VPB/day) and ventricular tachycardia (VT/day) on 24-hour Holter monitoring in 119 pts with class II, III and IV CHF before treatment with vasodilators; * = p<0.05.

| CHF Class | PRA | PNE | EF | VT | VPB |
|---|---|---|---|---|---|
| II (n=34) | 2.5 | 451 | 20 | 6 | 3046 |
| III-IV (n=85) | 7.1* | 815* | 19 | 109* | 4506 |

As CHF increased in severity (from class II to III-IV), EF did not ↓, but neurohormonal systems (PNE and PRA) became activated and VT events ↑ in frequency. Despite a similar EF in the 2 groups, class III-IV pts had a less favorable long-term survival than class II pts (64% vs 82% 1-year survival), p < 0.05.

The determinants of mortality were assessed in each functional group by Cox analysis. In class II pts, EF and VT were the only independent predictors of survival, and mortality was not related to the degree of neurohormonal activation. In contrast, in class III-IV pts, PNE and VT were the only independent predictors of survival, and EF provided no additional prognostic information.

In conclusion, the determinants of survival change as CHF progresses. Neurohormonal variables are important predictors of survival only in severe CHF, when neurohormones are most activated. In this advanced stage, cardiac function (as assessed by EF) is no longer the principal determinant of mortality.

RECOVERY OF SMALL AND LARGE ARTERY VASOCONSTRICTION IN SEVERE HEART FAILURE FOLLOWING HEART TRANSPLANTATION.

J. Malcolm O. Arnold MD, John R. Imrie MD, Gordon E. Marchiori PhD, F. Neil McKenzie MD, Peter W. Pflugfelder MD, William J. Kostuk MD, FACC, University of Western Ontario, London, Ontario, Canada.

Marked peripheral vasoconstriction of small and large arteries occurs in severe chronic heart failure (CHF), but it is not known if these changes improve uniformly after heart transplantation (TXP). We compared 11 patients with severe CHF before, 10 days and 30 days following TXP with 6 normal subjects of similar age. Forearm blood flow (FBF) was measured by venous plethysmography at rest and after 10 min of arterial occlusion (peak reactive hyperemia - PRH). Forearm vascular resistance (FVR) = mean BP÷FBF. Brachial artery diameter (D) was measured pre-TXP and at 30 days post-TXP with a zero-crossing pulsed Doppler system incorporating an adjustable range-gated time system and a double transducer probe. Arterial pulse wave velocity (PWV) was measured with paired transducers over the brachial and radial arteries and brachial artery compliance (BAC) was calculated as $\pi/4(D/PWV)^2$ where p is blood density. Mean ± s.e. *p<0.02 vs. normal

| | FVR (units) | PRH (ml/100ml/min) | D (mm) | BAC ($cm^4$/dyne/$10^7$) |
|---|---|---|---|---|
| NORMAL | 22.6±2.9 | 36.9±2.1 | 4.7±0.1 | 2.2±0.4 |
| CHF | 70.5±8.2* | 17.1±1.5* | 3.8±0.3* | 1.2±0.2* |
| 10 DAYS | 51.4±4.4* | 17.0±2.3* | ------- | ------- |
| 30 DAYS | 61.6±4.5* | 27.0±2.7* | 4.9±0.2 | 2.3±0.4 |

These results demonstrate that the significant constriction seen in small and large arteries in severe CHF is not uniformly improved post-TXP. This could be due to different mechanisms contributing to the constriction in small and large arteries during CHF or possible vascular effects of cyclosporin on arterioles.

EXERCISE ALTERS GUANINE NUCLEOTIDE BINDING PROTEINS

Evelyn M. Horn M.D., F.A.C.C., Gerald W. Neuberg M.D., Bruce Morrow, Won Chaekal, Rafael E. Pajaro M.D., Alex deCholnoky, Melvin B. Weiss M.D., F.A.C.C., John P. Bilezikian M.D., Columbia University, College of Physicians & Surgeons, New York, N.Y.

Exercise has been shown to be associated with an increase in lymphocyte (lymph) beta-adrenergic receptor density (BAR) and adenylate cyclase activity. Since physiological modulation of the BAR complex may also affect post-receptor elements, we studied lymph BAR, cAMP and stimulatory and inhibitory G proteins (Gs and Gi) at rest and at peak exercise in normal and athletic subjects. Seven subjects exercised 11 ± 0.8 min. Heart rate increased from 56.4 ± 4 to 184 ± 4.2 on a flexible 1 min incremental protocol and $VO_2$ achieved was 47 ± 6.9 ml/min/kg. In response to exercise, BAR increased (23.1 to 48.8 fmol/mg, p<.01), Gi increased (2 ± 0.3 to 3.5 ± 0.6 compared to a standardized membrane preparation, p<.05), Iso stim/basal cAMP increased (2.45 ± 0.5 to 5.1 ± 0.8, p<.02); Gs remained unchanged.

Thus, exercise-enhanced beta-adrenergic receptor function is not due to an increase in Gs. It remains possible that coupling between BAR and Gs is enhanced after exercise. In addition, pertussis toxin substrate is increased with exercise and this may further affect signal-transduction at the level of the BAR.

## Monday, March 20, 1989
## 4:00PM–5:30PM, California Room A
## Anaheim Convention Center
## Hormonal and Metabolic Effects of Exercise

RELATIONSHIP OF LEFT AND RIGHT ATRIAL PRESSURES TO ATRIAL NATRIURETIC FACTOR ELABORATION DURING EXERCISE IN NORMAL MAN

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From studies using volume loading maneuvers, it is known that increases in right atrial pressure (RAP) are related to atrial natriuretic factor (ANF) release. Although the left atrium also contains ANF granules, the contribution of left atrial pressure to ANF release is unclear. We examined the effect of progressive exercise on arterial plasma ANF concentration and right and left atrial pressures in 20 normal male subjects performing maximal (MAX) upright bicycle exercise during right heart and brachial arterial catheterization. Measurements included mean RAP (mmHg), balloon occluded pulmonary capillary wedge pressure (PWP,mmHG), heart rate (HR), mean arterial pressure (MAP,mmHg), and arterial lactate (LAC,mmol/l). Plasma ANF concentration (pg/dl) was measured following extraction by radioimmunoassay for alpha human ANF. Displayed below are the means for rest and MAX (*p<0.0001, rest vs. MAX) and the regression correlation coefficients for △ rest to MAX vs △ ANF rest to MAX.

| | REST | MAX | r |
|---|---|---|---|
| ANP | 37.4±14.5 | 62.4±35.6* | |
| RAP | -2.2± 2.0 | 1.8± 2.5* | 0.24 (p=0.32) |
| PWP | 1.2± 3.3 | 8.8± 4.9* | 0.63 (p=0.001) |
| HR | 77.8±18.9 | 162.7±23.7* | 0.43 (p=0.07) |
| MAP | 102.2± 13.3 | 131.8±17.1* | -0.10 (p=0.69) |
| LAC | 0.6± 0.4 | 8.8± 2.4* | -0.11 (p=0.65) |

Thus, in normal man, intense dynamic exercise is a potent stimulus for ANF release, and this correlates best with the rise in PWP. These data indicate that during exercise, left atrial pressure is an important mediator of ANF release.

ABNORMAL TISSUE GLYCOGEN DEPLETION PATTERNS DURING SUBMAXIMAL EXERCISE IN RATS WITH A CHRONIC MYOCARDIAL INFARCTION AND HEART FAILURE.

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Rats that have received sham operations (SH) will exercise for longer periods of time at a given absolute level of submaximal exercise than rats with a chronic myocardial infarction (MI) and moderate compensated heart failure. The reason for the early onset of fatigue found in the MI rat remains unclear, but may be related to abnormal rates of glycogen (glyc) utilization in the tissues since the point of fatigue coicides with depletion of these glyc stores. In the present study glyc concentrations were measured in the liver, diaphragm, and different skeletal muscles of the hindlimb (soleus, plantaris, and white gastrocnemius) of SH and MI rats at rest and following 15 and 30 min of submaximal treadmill exercise. Patterns of glyc utilization for these different tissues were compared in animals exercising at the same absolute and relative workloads. Results demonstrated that when SH and MI rats exercised at the same absolute workloads (15% grade, 28 m/min) that the glyc concentrations found in the liver, diaphragm and the different skeletal muscles were significantly reduced after 15 and 30 min of exercise when compared to those found at rest. However, the patterns of glyc depletion found in the diaphragm and white gastrocnemius muscle of the MI rat were significantly different (p<0.05, 2-way ANOVA) than those found in the SH rat as the glyc concentrations found in these tissues appeared to be lower in the MI rat after 15 and 30 min of exercise. When SH and MI rats exercised at the same relative workloads (~70% of maximal oxygen uptake) again the glyc concentrations found in the liver, diaphragm and the different skeletal muscles were significantly reduced after 15 and 30 min of exercise when compared to those found at rest. However, the patterns of glyc depletion found in all the tissues were similar in the SH and MI rat as were the magnitude of the responses. These results suggest that abnormalities in glyc utilization may be associated with the early onset of muscular fatigue found post-MI when performing at a given absolute level of submaximal work. In addition, abnormal patterns of glyc depletion in the diaphragm may be contributing to the feeling of breathlessness commonly found during submaximal work in heart failure through respiratory fatigue.

THE EFFECT OF COMBINED DYNAMIC EXERCISE AND HEAD-OUT WATER IMMERSION ON ATRIAL NATRIURETIC PEPTIDE.
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An increase in RA pressure and sympathetic neural activity are considered possible mechanisms for release of atrial natriuretic peptide (ANP) during exercise. During head-out water immersion (WI), we previously showed that RA pressure increases immediately upon rest WI but remains unchanged from rest to peak exercise. To evaluate the effect of exercise combined with WI on ANP release, 9 young men underwent 45 min rest seated WI and cycle exercise tests on land and WI at work loads (5 min) corresponding to about 40, 60, 80, and 100% maximal oxygen consumption ($\dot{V}O_2max$). Results: $\dot{V}O_2max$ did not differ in WI and land (35.7±2.6 vs 36.4±3.0 ml/kg/min). During the rest session, ANP averaged 16±4 pg/ml on land and increased to 24±4, 32±10, 37±9 and 63±26 pg/ml with 5, 15, 30 and 45 min WI, respectively (P<0.05). During the exercise sessions, ANP responses (pg/ml) on land, WI, and WI-adjusted for WI time effect (based on rest session) were:

| | Land | WI | WI-adjusted |
|---|---|---|---|
| Sit | 25±4 | 20±5 | 14±3 |
| 40% $\dot{V}O_2max$ | 23±4 | 52±17¥ | 36±10 |
| 60% $\dot{V}O_2max$ | 28±5 | 98±27¥ | 59±15 |
| 80% $\dot{V}O_2max$ | 48±38* | 173±64*¥ | 155±61¥ |
| $\dot{V}O_2max$ | 68±13* | 183±69*¥ | 166±66* |

(Means±SE; *P=<0.05 compared to sit within each environment; ¥=P<0.05 compared to land at same stage)

Plasma norepinephrine at peak exercise was significantly (P<0.05) lower in water (1885±393 pg/ml) compared to land (3532±570 pg/ml). The results indicate that ANP progressively rises with increased exercise intensity in WI as on land. In addition, both exercise and WI contribute to a rise in ANP. We conclude that 1) increases in plasma norepinephrine and ANP during exercise are not tightly coupled and 2) a rise in RA pressure from rest to exercise is not required for release of ANP with exercise.

EXERCISE TRAINING ALTERS CATECHOLAMINE METABOLISM IN HEALTHY OLDER MEN
Todd D. Miller M.D., Ray W. Squires Ph.D., Paul J. Rogers M.D., Bruce Banwart, Ann Knobbe, Alfred A. Bove M.D., Ph.D., F.A.C.C., Gertrude Tyce Ph.D., Mayo Clinic, Rochester, Minnesota

Prior studies examining the effects of exercise training on autonomic regulation have focused on changes in plasma levels of free norepinephrine (NE) and epinephrine (E) and have reported conflicting results. Catecholamine synthesis and degradation is considerably more complex and involves the NE and E precursor dopamine (DA) and numerous metabolites. Our goal was to determine if exercise training alters catecholamine metabolism in an older population by additionally measuring 24-hour urine levels of these 3 catecholamines and their major metabolites (normetanephrine, metanephrine, vanillylmandelic acid for NE and E; 3-methoxytyramine and homovanillic acid for DA), reasoning that these values might reflect daily sympathetic activity more accurately than isolated plasma values. Seventeen healthy men ages 52-75 underwent 16 weeks of exercise training. Peak oxygen uptake increased 21% from 21.3 to 25.7 ml $O_2$/kg/min (p<0.005). Urine values ([mean ± SD] ug/24 hrs) before and after training were:

| | Before | After | p Value |
|---|---|---|---|
| [DA + metabolites] | 4986 ± 1007 | 6269 ± 1916 | <0.05 |
| [NE + E + metabolites] | 7386 ± 2227 | 6712 ± 1690 | NS |

Thus exercise training increased urine metabolites of DA (a catecholamine with unique selective renal vasodilatory properties in low concentrations) without altering metabolites of NE and E in healthy older men.

BLOCKADE OF ADENOSINE RECEPTORS WITH AMINOPHYLLINE. EFFECTS ON EXERCISE CAPACITY IN STABLE ANGINA
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It is well recognised that the adenosine (A) released in the coronary circulation during exercise is responsible for the metabolic vasodilation of small vessels. In atherosclerotic epicardial arteries the decrease in post-stenotic pressure consequent to A-induced vasodilation might result in subendocardial underperfusion and increase the severity of ischemia. To test this hypothesis, we performed a single-blind, placebo-controlled randomized study in 10 patients (pts) with stable angina pectoris and documented coronary artery disease using the A antagonist aminophylline (Am). Immediately following intravenous administration of Am (7 mg/kg over 10 min) or placebo, pts underwent treadmill exercise testing (modified Bruce) on 2 consecutive days. Am increased exercise duration from 8.5±2.9 min to 11.2±2.2 min, p<0.002. Furthermore, with Am, compared to placebo, all pts developed 1mm ST depression at a higher heart rate (HR, bpm) (130±21 vs 108±16, p<0.001) and at a higher rate-pressure product (RPP, bpmxmmHgx$10^{-2}$) (205±41 vs 165±26, p<0.001). In 5 pts with angiographically documented collaterals the improvement in HR and in RPP at 1mm ST depression was greater than in the remaining 5 pts without collaterals (ΔHR 27±6 vs 15±10, respectively; ΔRPP 55±28 vs 25±17, respectively) Thus, blockade of A receptors with Am improves exercise capacity indicating that A-induced vasodilation can be detrimental. The more pronounced beneficial effect of Am in patients with collaterals could be explained by an increase in perfusion pressure from collateral donor arteries.

## Monday, March 20, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 2:00PM–3:00PM
## Pacific Room, Anaheim Convention Center
## Coronary Atherosclerosis and Angioplasty

EFFECTS OF CYCLOSPORINE ON SERUM LIPOPROTEINS
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Accelerated atherosclerosis is a leading cause of death in long-term survivors of heart and renal transplant (TP) and may be exacerbated by the frequent occurrence of post TP hyperlipidemia(HPL). Attempts to define the mechanism for HPL in TP patients are confounded by dramatic changes in metabolism and nutritional status post TP as well as multiple immunosuppressive and antihypertensive drugs. To avoid these pitfalls and determine if cyclosporine alone adversely affects lipids, we measured lipoprotein levels in a prospective, double-blinded, randomized, placebo-controlled trial of cyclosporine(CS) in 36 men with amyotrophic lateral sclerosis. Mean (±SD)(mg/dl) serum total cholesterol(TC), LDL cholesterol, triglycerides (TG), apolipoprotein B (ApoB) are shown below.

| | CS N=18 | | | Placebo N=18 | | |
|---|---|---|---|---|---|---|
| | Baseline | 2mo | P | Baseline | 2 mo | P |
| TC | 202±53 | 245±52 | <.01 | 205±36 | 212±38 | NS |
| LDL | 112±39 | 148±42 | <.01 | 125±36 | 128±30 | NS |
| ApoB | 74±23 | 86±22 | <.02 | 80±19 | 83±17 | NS |
| TG | 247±135 | 290±162 | NS | 223±118 | 231±131 | NS |
| HDL | 41±6 | 30±8 | NS | 38±8 | 38±7 | NS |

Significant increases in TC, LDL and ApoB occurred only in the CS group. This study conclusively shows that cyclosporine therapy alone adversely affects serum lipoproteins by increasing total cholesterol due primarily to an increase in LDL cholesterol.

**PROGRESSION OF CORONARY ATHEROSCLEROSIS AND ENHANCED THROMBIN-INDUCED PLATELET AGGREGABILITY.**

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Platelets may play a role in coronary artery disease (CAD) progression and anti-platelet therapy has been shown to prevent the sequellae of CAD progression. The relationship between platelet function and CAD progression was studied in 53 pts who underwent repeat coronary arteriography after 2 yrs in a prospective study (Contr Clin Trials 8: 216, 1987). Selection criteria included a high risk of CAD progression based upon young age and diffuseness of CAD. No pt was taking anti-platelet drugs. CAD progression was defined as a decrease ≥0.4 mm in arterial diameter measured quantitatively using the Coronary Angiographic Analysis System of Reiber et al. The platelet aggregation response (change in optical density, Δ O.D. and area under the aggregation curve) to ADP, collagen and epinephrine in platelet rich plasma was similar in pts with and without progression, as were indices of platelet function including platelet factor 4, β-thromboglobulin and $TxB_2$ levels. Clinical features of the 2 groups were also similar. However, aggregation to thrombin was greater in those who progressed:

| Group | n | Δ O.D. | Surface area(cm2) |
|---|---|---|---|
| Progression | 22 | 1.12±.22 | 1.65±.22 |
| | | p=.016 | p=.019 |
| No progression | 31 | 0.5±.11 | 1.09±.11 |

Thus, progression of CAD is associated with a selective enhancement of thrombin-induced platelet aggregation. This may be a useful marker for CAD progression. Whether inhibition of thrombin activity prevents CAD progression needs further evaluation.

**CORRELATION OF CORONARY ARTERIAL WITH SYSTEMIC ATHEROSCLEROSIS.**

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It is well established that patients with peripheral atherosclerosis (ASCL) have a high risk of also having coronary ASCL, but a possible converse relationship has not been comprehensively investigated. We studied the coronary and aortic-iliac-femoral (AIF) arteriograms of subjects enrolled in the Program on Surgical Control of the Hyperlipidemias (POSCH). POSCH is a randomized, controlled, secondary intervention clinical trial of hyperlipidemic subjects, ages 30-64 years with 1 myocardial infarction and angiographically demonstrable coronary ASCL. Of the 838 enrolled subjects, 436 had diagnostic visualization of all parts of the coronary and AIF systems. Indices were used to score the severity of the ASCL. The AIF index was the sum of stenosis in the aorta and its 6 major branches, the coronary index the weighted sum of stenosis of the left main coronary artery and the 13 segments of its branches.

| AIF | Coronary Index (% of subjects) | | | | |
|---|---|---|---|---|---|
| Index | 1-99 | 100-199 | 200-299 | > 300 | n |
| 0 | 57 | 45 | 32 | 25 | 194 |
| 1-80 | 35 | 42 | 49 | 42 | 184 |
| > 80 | 8 | 13 | 19 | 33 | 58 |
| n | 104 | 231 | 89 | 12 | 436 |

The p-value was 0.0083. Conclusions: 1) Peripheral ASCL frequently may be absent even when coronary ASCL is severe, 2) Nevertheless, the severity of peripheral ASCL, if present, strongly correlates with that of coronary ASCL.

**CORONARY ATHEROSCLEROSIS IMPAIRS CONTROL OF SHEAR STRESS**

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In experimental studies, abnormal wall shear stress (Tau) impairs endothelial function and may lead to coronary atherosclerosis (CAD). We tested the hypothesis that 1) increasing shear stress is associated with dilation of normal arteries under conditions of increased flow, and 2) in CAD, loss of this reactive dilation leads to abnormal increases in Tau. Adenosine 0.22 to 2.2 mg/min was infused via a 2.5 F Doppler flow catheter positioned in the middle segment of the left anterior descending artery (LAD) in 8 patients with mild CAD, but no flow limiting stenoses, and in 10 patients with entirely smooth coronary arteries. Quantitative angiography and coronary flow velocity corrected for cross-sectional area (CBF) were used to estimate Tau in a proximal LAD segment exposed to changes in flow but not to adenosine. Peak increase in CBF was the same in smooth (371±65%) and irregular segments (377±50%). However, at peak flow, smooth segments dilated more (16.3±2.7% from 2.77±.18 mm) than irregular segments (2.0±1.5% from 3.05±0.19 mm) ($p<.001$) and Tau increased by only 189±23% in smooth segments, but increased more in irregular segments, 365±52% ($p<.01$). In each patient, smooth segments showed linear dilation with increasing Tau (slope 7.4±0.9%), whereas irregular segments dilated less and showed greater increases in Tau (slope 0.9±0.6%) ($p<.01$). Thus, smooth coronaries tend to dilate with, and thereby limit, increases in Tau. At equal increases in CBF, lack of dilation in irregular coronaries leads to a doubling of Tau compared to smooth segments. Failure to limit Tau in CAD may perpetuate both functional disturbances of coronary endothelium and progression of atherosclerosis.

**CYTOTOXIC B CELL ANTIBODIES: INSENSITIVE PREDICTOR OF CORONARY DISEASE POST HEART TRANSPLANT**

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The development of coronary artery disease (CAD) after heart transplant (HTP) is a silent progressive process that is felt to be a form of chronic rejection. Circulating cytotoxic B cell antibodies (CytoBab) have been demonstrated during chronic renal allograft rejection and previously reported in one study to be a useful predictor for the development of CAD and myocardial infarction (MI) after HTP. Although this study has been frequently cited (Circ 68[sup 2]:94, 1983), it was done prior to the use of cyclosporine and has not been corroborated. We prospectively followed the development of CytoBab in 25 patients (pt) who underwent orthotopic HTP and had followup (F/U) catheterization (cath) or autopsy (mean F/U 20 mos). Four pts had cath evidence of CAD and 3 pts had MI at autopsy with CAD present (7/25; 28%). All pts had baseline CytoBab measured prior to HTP and 6 months post HTP or at the time of catheterization.

| New CytoBab | CAD Present | CAD Absent |
|---|---|---|
| Present | 1 | 0 |
| Absent | 6 | 19 |

New CytoBab were noted in only 1/7 (14%) of heart transplant patients with documented CAD. We conclude that cytotoxic B cell antibodies infrequently develop after heart transplant in patients treated with cyclosporine and prednisone and are an insensitive predictor for the development of coronary artery disease.

DETAILS OF CORONARY STENOSIS MORPHOLOGY INFLUENCE ITS HEMODYNAMIC SEVERITY AND DISTAL FLOW RESERVE Frank A. Fedele, MD, Barry Sharaf, MD, Albert S. Most, MD, FACC, Henry Gewirtz, MD, RI Hospital, Providence, RI

Differences in coronary flow reserve with anatomically similar coronary artery stenoses (CAS) have been attributed to 1) non-standard physiological conditions, 2) inadequacies of measurements of CAS dimension and/or coronary blood flow (CBF), 3) inadequate hyperemic stimulus. This study tested the hypothesis that details of CAS geometry also may contribute importantly to such differences. A simple (SMPL) and complex (CMPX) CAS, each of which reduced vessel cross-sectional area by 84%, was introduced in random order into the left anterior descending coronary artery of nine closed chest, sedated pigs. The SMPL CAS had a single lumen while the CMPX CAS had five small lumena whose combined area equalled that of the SMPL CAS. Measurements of hemodynamics and regional myocardial blood flow (microspheres) were made at control and after 10 min of adenosine infused at 400 μg/min and then at 800 μg/min distal to each stenosis. Both heart rate and aortic mean pressure did not change versus initial control (129 ± 4 min and 120 ± 10 mmHg, mean ± SD, respectively) during the study. Baseline trans-stenosis flow (ml/s) was similar at each control (1.05 ± 0.35 versus 0.92 ± 0.34, SMPL versus CMPX, respectively, p = ns). At maximal adenosine, total flow with SMPL was 3.44 ± 0.92 versus 2.77 ± 0.51 for CMPX CAS (P < .05). Distal zone maximal endocardial flow with the SMPL CAS (3.83 ± 1.17; ml/min/g) also was greater (P < .01) than that with the CMPX CAS (2.76 ± 0.83). Although flow with CMPX CAS was similar at baseline and lower at maximal hyperemia versus SMPL CAS, resistance was greater (P < .01) for CMPX CAS both at baseline (13.2 ± 3.9 vs 7.1 ± 2.0 mmHg/ml/s) and at maximal flow (19.7 ± 4.5 vs 13.4 ± 3.0). Thus, differences in details of CAS geometry may contribute importantly to differences in coronary flow reserve, especially in the endocardium, despite comparable reduction in vessel cross-sectional area.

CLINICAL SAFETY AND EARLY COURSE FOLLOWING PROLONGED INFLATIONS IN ELECTIVE TRANSLUMINAL CORONARY ANGIOPLASTY Mitchell W. Krucoff, M.D., James B. Reese, PhD, Mary K. Kehoe, R.N., Yvette R. Jackson, R.N., Charlene W. Wisdom, PhD, Kenneth M. Kent, M.D., F.A.C.C. Duke University Medical Center, Durham, North Carolina.

Prolonged balloon inflations during angioplasty (PTCA) were previously avoided, but more recently have been suggested as a means of mechanically stabilizing a dilatation site and even of reducing rate of restenosis. To assess the early response to prolonged inflations, 28 patients for elective PTCA were prospectively randomized to shorter (60-90 seconds) or longer (4-5 minutes) inflations. Continuous digital 12-lead ST segment monitoring (Mortara ELI-ST) was performed overnight (mean 19 hours) following successful PTCA, and serial CPK isoenzymes were drawn q8h. Oxygenated Fluosol- DA 20% was infused distal to the inflated balloon in both groups. Ischemic episodes (ST) after PTCA were defined as > 1 mm ST deviation in 2 leads or 2 mm ST deviation in 1 lead lasting > 60 seconds; infarction (MI) was defined as > 3X normal CPK-MB. A total of 7 endpoints (ST, MI) were seen in 4 patients, as:

| | PTS | ST | MI |
|---|---|---|---|
| SHORT (15) | 4 (27%) | 4 (27%) | 3 (20%) |
| LONG (13) | 0 ( 0%) | 0 ( 0%) | 0 ( 0%) |

P = 0.07

Mean final stenosis was 27% in the SHORT group and 21% in the LONG group (NS). Thus, long balloon inflations during elective PTCA do not appear to have an adverse effect on early patient outcome. In addition, there appears to be a trend toward a possible protective or stabilizing effect, reducing episodes of ischemia and infaction with prolonged balloon inflation.

IN VIVO PHOTOSENSITIZER ENHANCED LASER ANGIOPLASTY IN ATHEROSCLEROTIC YUCATAN MINISWINE

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Photosensitization of atherosclerotic (Ath) plaque with exogenous chromophores may confine laser irradiation (LI) injury to Ath plaque and allow safer and more efficacious laser angioplasty. Dihematoporphyrin ether (DHE) accumulates preferentially in plaque, and previous in vitro LI studies have shown confinement of LI injury to plaque. To further evaluate DHE enhanced laser angioplasty, 5 Ath Yucatan miniswine with 8 iliofemoral stenoses (Sten) were treated with 2.5mg/kg of DHE IV. 24 hrs later, 632nm continuous wave LI was delivered to Sten using a 200μ core optical fiber with a 582μ x 1cm diffusing tip. Angiograms were performed before, immediately after and 2 weeks following LI. 6/8 vessels showed improvement. Control mean Sten was 71%, immediate post LI was 55% and 2 weeks post LI was 19% Sten. In 4/6 responding vessels, there was 0% Sten at 2 weeks post LI and the previously stenotic segments appeared normal. 2/6 responders showed only modest improvement, from control mean Sten of 83% to 55% Sten at 2 weeks. 2/8 vessels showed no improvement. There were no perforations or dissections. The excellent results in some vessels demonstrate the potential of photosensitizer enhanced LI as very effective primary therapy of Ath. The time course of improvement indicates that both immediate thermal and delayed photochemical (photodynamic therapy) effects are operative. Further studies are required to identify reasons for failure in some vessels.

SEISMOCARDIOGRAPHY FOR DETECTION OF CORONARY ARTERY OCCLUSION DURING CORONARY ANGIOPLASTY: A PRELIMINARY REPORT

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Seismocardiography is a new noninvasive test for the detection of myocardial ischemia. Based on techniques from the field of seismology, the method analyzes compression waves transmitted from the heart during its movement. We hypothesized that obstruction of coronary artery blood flow by balloon inflation during angioplasty would produce a change in left ventricular function that would alter the compression waves recorded by the seismocardiograph. To test this hypothesis, we recorded the seismocardiogram before, during, and after coronary angioplasty of 13 arteries in 11 patients with coronary artery stenosis. The recordings were made during the first balloon inflation. The balloon was inflated for one minute in each case. During inflation of the balloon in 12 of the 13 arteries, the seismocardiographic waves developed a change in morphology. Changes were usually apparent by 30 seconds after inflation. The changes returned to baseline by 5 minutes after inflation. For the left anterior descending artery, 1 of 1 had changes; for the circumflex, 3 of 3; and for the right coronary, 8 of 9 had changes.

We conclude that reversible changes consistently occurred in the seismocardiogram in these patients during occlusion of a coronary artery by an angioplasty balloon catheter. These changes may have been due to changes in left ventricular function induced by myocardial ischemia. Seismocardiography may be useful for monitoring patients during angioplasty and during clinical syndromes associated with occlusion of a coronary artery, such as acute myocardial infarction. Because of the reversibility of the abnormalities on the seismocardiogram, it may be useful for monitoring thrombolytic therapy during infarction.

KETANSERIN PREVENTS ACUTE OCCLUSION BUT NOT RESTENOSIS AFTER PTCA.

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Restenosis remains the major problem following successful PTCA, ocurring in about 25-35% within six months. In ischemic heart disease, platelet serotonin efflux is increased triggering platelet activation. In 21 patients (pts) with coronary heart disease and PTCA the influence of the $S_2$-serotonergic receptor antagonist ketanserin (0,1mg/min for 24 hours) on early ($24^{h}$) and late (4 months) restenosis was investigated with quantitative angiography. 22 pts treated with conventional therapy served as a control group. 24 hours after PTCA 3 pts in the control group, but no pt in the ketanserin group developed restenosis or occlusion ($p<0.05$) Diameter stenosis was unchanged in the ketanserin group, but increased by 12% in the controls ($p<0.05$). After 4-6 months follow up the restenosis rate in the control group was 29%, in the ketanserin group 33% (ns).
Thus, ketanserin infused over 24 hours after PTCA prevents occlusion and early restenosis, but does not influence the incidence of restenosis after 4-6 months.

OXIDATION OF SULFHYDRYL GROUPS OF SERUM ALBUMIN IN CORONARY ARTERY DISEASES

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Oxygen free radicals have been implicated in the pathogenesis of myocardial ischemic-reperfusion injury. Sulfhydryl(SH) groups are known to be oxidized by free radicals. Albumin(Alb) is a major protein of the SH contents in serum. Alb with SH group is mercaptalbumin (MA), a reduced form, and Alb with mixed disulfide(-SS-) is nonmercaptalbumin(NA), an oxidized form. We studied the effects of myocardial ischemia on the SH groups of serum Alb in patients(pts) with effort angina pectoris (EAP) and acute myocardial infarction(AMI) and normal controls. MA and NA were determined by high performance liquid chromatography using Asahipack GS-520 column. %MA[ = MA/(MA+NA) x 100] was evaluated by elution profile of 5 µl of serum.

* $p<0.01$

| | No. of cases | %MA |
|---|---|---|
| EAP | 15 | 64.7±3.2 * |
| AMI; acute phase (2.7±0.8 hrs from the onset) | 10 | 59.4±4.7 * |
| AMI; subacute phase (70.1±8.1 hrs from the onset) | 10 | 49.8±5.9 * |
| NORMAL CONTROLS | 15 | 69.7±4.2 |

MA decreased in pts with EAP and AMI as compared with normal controls. Decrease of MA in AMI was greater than that in EAP. In AMI, further decrease of MA was observed in subacute phase as compared with acute phase.
In conclusion, myocardial ischemia seems to induce the oxidation of SH groups of serum Alb.

## Monday, March 20, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 3:00PM–4:00PM
## Pacific Room, Anaheim Convention Center
## Myocardial Ischemia: Consequences and Treatment

NEUTROPHIL FUNCTION IN ISCHEMIC HEART DISEASE.

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Neutrophils are involved in the remodeling of myocardium following ischemia and contribute to reperfusion injury and extension of ischemic damage. To further characterize neutrophil function in ischemic heart disease (IHD), neutrophil chemotaxis, leukotriene B4 (LTB4) generation, and plasma elastase levels were measured in 20 patients (pts) with stable angina pectoris (SAP), 17 pts with unstable angina pectoris (UAP) or acute myocardial infarction (AMI), and in 20 age-matched control subjects. Neutrophils from pts with SAP exhibited markedly increased chemotactic activity (48%) and LTB4 generation (103%) as compared to age-matched controls (both $P<0.01$). These cells had normal morphologic appearance by electron microscopy and did not clump spontaneously ex vivo. In contrast, neutrophils of pts with UAP or AMI appeared highly activated by electron microscopy with pseudopod formation and extrusion of granules and clumped spontaneously ex vivo in 50% of pts. Chemotactic activity and LTB4 generation by neutrophils from these pts were in the normal range suggesting prior in vivo activation. Plasma levels of peptide Bß, a product of fibrin degradation by neutrophil elastase, were 15-fold higher ($P<0.001$) in pts with UAP or AMI (588±171 pmoles/L, n=12) than in pts with SAP (37±25 pmoles/L, n=10) or control subjects (40±22 pmoles/L, n=14), confirming in vivo neutrophil activation. This study identifies enhanced neutrophil function in pts with SAP. Intense neutrophil activity and subsequent elastase release may relate to fibrin degredation, reperfusion injury, and myocardial tissue remodeling following coronary thrombotic events.

EXTENT OF JEOPARDIZED MYOCARDIUM: IMPORTANCE OF LOCATION, SEVERITY AND EXTENT OF CORONARY STENOSIS.

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Left main, multivessel, and proximal left anterior descending (LAD) coronary artery disease (CAD) identify pts at an increased risk for cardiac events, presumably because of the large extent of jeopardized myocardium (EJM). This pathophysiologic assumption, however, has not been proven. Accordingly, we evaluated the EJM in 221 consecutive pts with significant (>50% stenosis) CAD. EJM (% LV) was estimated from exercise thallium-201 tomographic images using a computer algorithm validated in our laboratory. EJM (mean ± SD) was significantly greater in pts with double (23.2±16.1%, $p<.05$) or triple (28.3±13.4%, $p<.01$) vessel CAD than in those with single (18.6±15.4%) vessel CAD. In pts with single vessel CAD (N=53), EJM was affected by stenosis severity and location as follows:

| | EXTENT OF JEOPARDIZED MYOCARDIUM (% LV) Stenosed Coronary Artery | | |
|---|---|---|---|
| % Stenosis | LAD (N=20) | Right (N=24) | Circumflex (N=9) |
| >50% | 25.5±16.3*† | 13.7±10.4 | 12.7±10.9 |
| ≥70% | 34.2±10.8*† | 18.2±8.7 | 13.0±9.8 |
| 100% | 33.7±11.6* | 19.6±8.8 | 17.5±12.0 |

*$p<.01$ vs right; †$p<.05$ vs circumflex

EJM was larger ($p<.05$) in proximal LAD (35.6±17.2%) than in mid LAD (21.7±12.5%), proximal right (18.3±12.0%) or proximal circumflex (18.8±11.4%) stenoses. In conclusion, our data demonstrate that EJM does increase with increasing extent and severity of CAD. Stenoses in the proximal LAD artery affect an LV area twofold larger than stenoses of comparable severity in the proximal right or circumflex arteries.

Identification of transient regional myocardial metabolic abnormalities in patients with chronic stable angina using positron emission tomography (PET)

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To evaluate metabolic changes associated with transient myocardial ischemia we studied 5 patients with severe single vessel CAD and chronic stable angina.All pts had no clinical or angiographic evidences of myocardial infarction. Measurements of myocardial glucose uptake were performed during baseline (B) and following the infusion of 0.6 mg/kg of dipyridamole (D) in each patient using 15 slice PET and F-18 deoxyglucose (FDG).In both studies all pts underwent 12 to 15 hours fasting.3 pts had chest discomfort during D but only one of them showed >1 mm ST depression in the EKG.Over 60 regions of interest were drawn on an average of 10 cross-sectional images of the heart in each study and grouped into myocardium supplied by normal (N) and stenosed vessels (S).Myocardial FDG concentration was then normalised to the integral of the arterial FDG from the time of the tracer injection to mid-scantime (FDGm).Baseline FDGm in N and S was 1.02+/-.24 and 1.34+/-.21 resp(NS). Following D FDGm in N was not different than baseline (1.41+/-.4) whereas in S increased to 6.64 +/-3.4. FGDm in S was significantly higher when compared with that performed during B and with FDGm in N following D (p ≤.01 and ≤.005 resp. Student t test). Thus,PET showed a marked increase in glucose uptake in the territory of stenosed arteries following (D) even in the absence of EKG changes .This metabolic signal may be used as a noninivasive tool to localise transient myocardial ischemia.

FUNCTIONAL LEFT VENTRICULAR ANEURYSM AFTER ANTERIOR Q-WAVE MYOCARDIAL INFARCTION: INCIDENCE, CONTRIBUTING FACTORS AND NATURAL HISTORY.

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Sixty-two consecutive pts with CKMB-confirmed anterior Q-wave MI underwent 24-hour holter, radionuclide ventriculography (RVG), exercise TL-201 and coronary angio at 10±3 days. A functional aneurysm (i.e., diastolic deformity with akinesis or dyskinesis) was present on RVG in 19 patients (31%). The presence vs absence of aneurysm did not identify differences in Norris index, Lown ≥3 grade ectopy, presence or extent of TL-201 ischemia, or angio jeopardy scores. Pts with aneurysm had lower LVEF (34vs42%; p<.01), larger myocardial scar areas by RVG (p = .004) and by TL-201 (p = .0001), and a lower LAD patency rate (11vs37%; p=.038).

At one year, aneurysm pts had a higher rate of CHF (37vs9%; p<.05) but total mortality (11vs5%), sudden cardiac death ([SCD]),5vs5%) and incidence of sustained VT (5vs2%) were similar in the two groups. Long-term outcome (mean 4.5 yrs) revealed more CHF (42vs21%); however, SCD (11vs7%) and incidence of VT (11vs2%) remained low (p NS). Overall, mortality was higher in aneurysm pts (32vs14%; p<.05) secondary to recurrent MI and pump failure. Using Kaplan-Meier life table analysis, there were no between group differences in survival from SCD (.95vs.95) or in event-free survival from all arrhythmic events (SCD and VT; .83vs.95).

Thus, aneurysm formation after uncomplicated anterior Q-wave MI is common (31%) and is associated with greater global and regional LV dysfunction resulting in a higher incidence of early CHF. However, the 1-year mortality rate is not significantly increased and the incidence of VT and SCD is low both at 1 and 4.5 years of follow-up.

BIMODAL TIME COURSE OF COLLATERAL DEVELOPMENT IN ACUTE MYOCARDIAL INFARCTION.

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The prevalence of collaterals to the infarct artery was assessed in 267 patients who had angiography within 14 hours of onset of infarction. Collaterals were significantly more common in patients with complete (33%; 64/196) than in those with subtotal obstruction of the infarct vessel (11%; 8/71) (p<0.001). In patients with complete obstruction, the relation between collaterals and time interval from onset of pain to angiography was:

| Time to Angio (Hrs.) | 2-4 | 4-6 | 6-8 | 8-14 | ALL |
|---|---|---|---|---|---|
| Patients (n) | 40 | 56 | 48 | 52 | 196 |
| Collaterals (%) | 33 | 30 | 29 | 38 | 33 |

Repeat angiography 10-14 days later in 98 patients with complete obstruction at baseline angiography showed:
1. In those patients with persistent total occlusion (n=42) an increase in the prevalence of collaterals from 33% to 90%. 2. In those patients who experienced sustained recanalization during thrombolytic therapy (n=56) a decrease of collaterals from 38% to 7%.
Conclusions:
1. Within 4 hours of acute total coronary occlusion collaterals can be visualized in 1/3 of patients. It is likely that these patients had developed collateral channels prior to the infarct which were recruited as a result of the abrupt drop in pressure distal to the total coronary artery occlusion.
2. Delayed appearance of collaterals in almost all remaining patients with persistent total occlusion after more than 14 hours and before angiography on day 10 to 14, probably involves cell proliferation in the walls of minute collateral channels which are congenitally present.

FACTORS THAT INFLUENCE THE REPRODUCIBILITY OF VENTRICULAR REFRACTORINESS

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The degree of variability in the determination of ventricular refractoriness and the factors affecting such variability are unknown. Thus, we measured RV effective refractory periods (ERP) in 4 groups of 10 pts. each using 8 $S_1$'s, 3 sec. pause and 2 msec. decrements. In each group, one variable was altered and VRP's determined 10 times during Conditions A and B. Condition A's were 1) output-2 x threshold 2) no atrial pacing (pts. with AV dissociation) 3) $S_1$ delay-off 4) 1 min. pause between trials to vary the number of trains. Condition B's were 1) output-10 mA 2) AV simultaneous pacing 3) $S_1$ delay - 500 msec. 4) no pause between trials. Coefficients of variance (CV) were calculated in each pt. and compared by paired t-tests. The mean maximum difference between shortest and longest VRP's in each pt (MDif) was also computed. Mean Results:

| | Condition A | | | Condition B | | |
|---|---|---|---|---|---|---|
| Group | ERP | CV | MDif | ERP | CV | MDif |
| 1 | 247.3 | 1.16% | 8.6 | 219.8* | .94% | 6.2 |
| 2 | 232.6 | 1.78% | 12.2 | 231.6 | .96%+ | 6.8 |
| 3 | 235.7 | 1.01% | 7.0 | 237.7 | .75% | 5.6 |
| 4 | 232.5 | 1.51% | 10.8 | 231.5 | .74%* | 4.8 |

*p<0.01 vs Condition A; +p<0.05 vs Condition A
We conclude: 1) Mean differences of 5-12 msec. may be found on repeated determinations of ERP. 2) The number of trains prior to reaching VRP and the control of AV synchrony significantly affect the reproducibility of refractoriness. 3) Of the variables tested only stimulation current affects the absolute value of ERP.

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**PRESERVATION OF VENTRICULAR PERFORMANCE WITH REDUCED ISCHEMIC DYSFUNCTION BY INTRAVENOUS NISOLDIPINE DURING RAPID ATRIAL PACING**

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To evaluate the effects of nisoldipine, on systemic hemodynamics, ventricular performance and ischemic LV dysfunction, we studied 10 subjects, mean age 56 yrs (range 45-72 yrs), prior to diagnostic coronary arteriography. Hemodynamic measurements included arterial pressure, LV end-diastolic pressure and cardiac output (thermodilution), with standardized quantitative LV angiography, utilizing non-ionic contrast media (Iohexol-350), at baseline ($B_1$), and after rapid atrial pacing to moderate, typical angina ($P_1$). Intravenous nisoldipine (3.5 ug/kg total, 5 min) was administered, with repeat systemic hemodynamics and standard LV angiography before ($B_2$) and after ($P_2$) an identical rapid pacing protocol. Absolute LV volumes, ejection fractions, and regional wall motion analysis (fractional radial shortening, FRS) were determined using an image processing computer (Kontron Cardio-200). Load-independent global and regional contractility indices were calculated via peak systolic pressure/end-systolic volume (PSP/ESV) and peak systolic pressure/end-systolic radial length (PSP/SRL) ratios, respectively.

Hemodynamic data is presented below (mean, ±SD):

| | Experimental stages | | | |
|---|---|---|---|---|
| | $B_1$ | $P_1$ | $B_2$ | $P_2$ |
| mBP(mmHg) | 112(±16) | 123(±12) | 94(±10)* | 101(±12) |
| CI(L/min/m²) | 3.3(±0.7) | 3.5(±0.6) | 4.3(±0.8)# | 4.8(±1.3) |
| LVEDP(mmHg) | 13(±6.0) | 21(±10)# | 17(±7.0) | 15(±10)@ |
| EF(%) | 72(±9.0) | 67(±16) | 78(±9.0)* | 78(±10) |

*$p<0.05$, #$p<0.01$, $B_2$ vs $B_1$; @$p<0.05$, $P_2$ vs $P_1$

Potentially ischemic LV segments, supplied by significantly stenosed coronary arteries (>50% diameter stenosis, n=12), demonstrated reduced FRS after pacing, with subsequent reversal by nisoldipine [pre-6.5(±14)%, post+3.8(±14)%, $p<0.1$]. Load-independent global contractile indices were improved following nisoldipine [pre-0.82(±1.0), post+0.25(±1.4), $p<0.05$], with regional indices revealing amelioration of ischemic segmental LV dysfunction [pre-15.3(±24), post+8.7(±24), $p<0.05$]. Conclusions: During pacing-induced ischemia, nisoldipine maintains LV performance by a combination of systemic vasodilation and reduction in pacing-induced myocardial ischemia, as determined by load-independent global and regional contractile indices.

SURVIVAL AMONG PATIENTS WITH FLASH PULMONARY EDEMA: A RETROSPECTIVE REVIEW OF SURGICAL AND MEDICAL MANAGEMENT.

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We recently reported a retrospective analysis of angiographic and clinical findings in patients (pts) with sudden onset of acute pulmonary edema without preceding history of progressive congestive symptoms - "flash" pulmonary edema (FPE). Here we report follow-up and survival data for a cohort of 54 pts hospitalized with FPE without transmural infarction who were subsequently catheterized. Mean age was 68.5 years. Coronary disease was present in 51 pts (94%). The majority of pts had preserved ventricular function with mean LV ejection fraction of 42% ± 17%. Pts were managed surgically (36) and medically (18) at the discretion of attending physicians. Surgical management included coronary artery bypass (26), valve replacement/repair (4), combined bypass/valve replacement (4), and other (2). Among medically managed patients, 8 (44%) had non-surgical disease and 10 (56%) were considered inoperable because of anatomy or co-morbid disease.

Of the 54 FPE pts, 46 (83%) survived acute hospitalization. In-hospital deaths occured in 5 surgical and 3 medical pts. Follow-up data were obtained on 44 of 46 hospital survivors with a mean follow-up period of 15.4 months. Deaths occurred in 6 surgical pts (19%) and 11 medical pts (53%). Among all pts who survived hospitalization, 81 ± 5% and 74 ± 6% were alive at one and two years by life table analysis. Among surgical pts, survival was 89 ± 6% and 84 ± 7% for the same time period.

We conclude that the majority of pts with FPE can be managed surgically with a good prognosis at 2 years.

EPIDURAL SPINAL STIMULATION IN PATIENTS SUFFERING FROM INTRACTABLE ANGINA.

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Epidural spinal cord stimulation (ESCS) is a recognised technique in Europe for the treatment of severe peripheral vascular disease and it has been established that it relieves pain and increases blood flow. However, it has not been used to any extent in patients with angina. Recently we have implanted ESCS units in seven patients with intractable angina, mean age 61 (range 47 to 72 years). Six patients had had coronary artery bypass surgery (x 2 in two patients and x 3 in one patient), one inoperable, and all were on full medical treatment. The technique involves implanting under local anaesthetic a stimulating electrode (Medtronic Sigma) in the epidural space at the level of T1-T2, positioned to produce parasthesia across the chest and into the left arm (i.e. the area of angina pain) and connected to the stimulator (Medtronic Itrel) which was implanted in the axilla. There were no complications with implantation.

Post-operatively all patients noted a significant improvement in symptoms, exercise duration was increased and pain intensity was reduced. GTN consumption was reduced from average 8.5/day (4-20) pre-operatively to nil in 5 patients and average of 3/day in 2 patients post-operatively. Right atrial pacing showed an increase in the threshold of angina pain. However, the reduction in ischaemic ECG changes was small and did not correlate with symptomatic relief. ESCS appears to relieve angina but it is not clear whether this is entirely through reduction in ischaemia.

## Monday, March 20, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 4:00PM–5:00PM
## Pacific Room, Anaheim Convention Center
## Cardiovascular X-Ray, NMR and CT

A RANDOMIZED TRIAL OF IONIC VERSUS NON-IONIC CONTRAST FOR CARDIAC ANGIOGRAPHY: EFFECT ON COMPLICATIONS AND COSTS.

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In order to examine the relative efficacy and cost of ionic and non-ionic contrast media for cardiac catheterization, we randomized 443 patients to receive either iopamidol or diatrizoate for cardiac angiography. All complications acutely and within 24 hours of the procedure were recorded prospectively by study personnel and classified according to previously determined criteria. Major complications were defined as life threatening, requiring a procedure to treat, or both (e.g. ventricular fibrillation, pulmonary edema, bradycardia requiring a pacemaker, or prolonged chest pain). Minor complications were non-life threatening (e.g. bradycardia responding to cough, angina, or vomiting). Costs were assigned to medications and procedures used to treat complications based on estimated marginal costs.

A total of 22 patients (5%) had major and 141 (32%) had minor complications after catheterization with diatrizoate, while 10 patients (2%) had major and 53 had minor (12%) complications after iopamidol ($p = 0.07$ for major complications; $p < 0.0001$ for total complications). Laboratory complications occurred in 148 patients given diatrizoate (11 major, 137 minor) as compared with 38 patients given iopamidol (2 major, 36 minor). Most complications were treated fairly easily, however, and median cost of catheterization and treatment of complications was $190 higher with non-ionic contrast than with ionic contrast ($p < 0.002$).

Thus, non-ionic contrast substantially reduces the rate of complications after cardiac angiography. This reduced morbidity is associated with a significantly higher cost, primarily due to the cost of non-ionic contrast.

SURGICALLY RESECTABLE LEFT VENTRICULAR ANEURYSM: SPECIFIC CHARACTERISTICS BY ULTRAFAST COMPUTERIZED TOMOGRAPHY.
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Conventional diagnostic criteria (regional dyskinesis by contrast ventriculography (CLV)) do not reliably identify pts with a surgically resectable LV aneurysm (SRLVA). To determine if SRLVA could be identified preoperatively by ultrafast computerized tomography (UCT), we retrospectively reviewed UCT and CLV studies of 8 pts who had SRLVA confirmed by pathological findings of dense myocardial scar tissue. LV volume measurements with UCT in pts with SRLVA showed decreased LV EF (20±7% [$\bar{x}$±SE]); increased LV end-diastolic volume (273±82 ml); and an increase in LV mass (178±53 gm/M2). The aneurysms were located anterolaterally and involved the anterior septum. In 6/8 pts a large thrombus was demonstrated by UCT and confirmed in 5/6 at surgery. Quantitative segmental analysis of the UCT data revealed that pts with SRLVA demonstrated predominantly regional akinesis, involving 21±7% of the LV surface area. The abnormal area had a very thin wall (aneurysm end-diastolic wall thickness (EDWT): 4±1 mm, remote EDWT: 11±1 mm). CLV revealed evidence of diastolic distortion in 5/8 pts and predominant akinesis in 8/8. Retrospective analysis of UCT studies of 2 pts who did not have SRLVA at surgery despite a definite diagnosis of aneurysm by CLV revealed a restricted mainly hypokinetic segment involving 8±2% of LV surface area, with only a mild decrease in EDWT (8±0.2 mm) of the abnormal segment. In conclusion, although SRLVA cannot be reliably identified by conventional angiographic criteria, they can be detected with UCT by the presence of a large akinetic, thin-walled segment and a high incidence of thrombus.

NEPHROTOXICITY OF NONIONIC CONTRAST MEDIA: IMPORTANCE OF DOSAGE IN HIGH RISK PATIENTS.
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Nonionic radiocontrast agents with low osmolality have been recently introduced and are now extensively used in cardiac catheterization. The prevalence of and risk factors for contrast nephropathy (CN) due to nonionic contrast media are not established. We studied the nephrotoxicity of iohexol (Omnipaque 350) over a 20-month period from 5/86 to 12/87. Sixty pts at higher risk for CN because of baseline serum creatinine (Cr) ≥ 2.0 mg/dL underwent cardiac angiography with subsequent follow-up of renal status. Mean pt age was 68 years (range 29-94) with 65% male and a median baseline Cr of 2.5 mg/dL (range 2.0-9.4). There was Class III or IV heart failure in 32%. Mean dosage of iohexol was 110 mL (range 40-235). CN, defined as a rise in Cr ≥ 1.0 mg/dL over baseline, occurred in 9 (15%) pts with 3 pts requiring dialysis. Median baseline serum creatinine was 2.6 mg/dL in those developing CN. Iohexol dosage was significantly associated with CN. Mean dose was 148 mL in pts developing CN compared to 104 mL in those without CN ($P = 0.008$). CN developed in 3% of pts (1 of 34) receiving < 125 mL compared to 32% (8 of 25) receiving ≥ 125 mL. Other factors, including diabetes mellitus, coexistent heart failure, surgery following angiography, and treatment with calcium channel blockers, did not influence the occurrence of CN in this pt cohort.
In summary, nephrotoxicity occurred in 15% of high risk pts following cardiac angiography with iohexol and was directly related to dosage administered.

IMPROVED DIASTOLIC FUNCTION AFTER AORTIC VALVE REPLACEMENT ASSESSED BY ULTRAFAST COMPUTED TOMOGRAPHY (UFCT).
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Improvement in diastolic function(DF) is expected to accompany regression in ventricular mass after successful aortic valve replacement(AVR) in aortic stenosis and/or insufficiency. Using UFCT we assessed the LV mass and concurrent peak diastolic filling rate(PFR) in 16 Pts before AVR(n=15) or valvuloplasty(n=1), and postoperatively at 4 and 8 months. The PFR was normalized for end-diastolic volume(EDV) and derived during early diastole using a third order polynomial curve fit(17 frames/sec,r>0.95). The Pts were grouped into those with(n=13) and without(n=3) significant LV mass regression (>10% change).

| | REGRESSION | | NO REGRESSION | |
|---|---|---|---|---|
| | Mass(g/m²) | PFR(EDV/s) | Mass(g/m²) | PFR(EDV/s) |
| Baseline | 160±11 | 2.10±0.18 | 164±18 | 2.38±0.70 |
| 4 months | 107±5* | 1.93±0.21 | 159±18 | 1.72±0.75 |
| 8 months | 97±6* | 2.62±0.24* | 154±18 | 2.26±0.63 |

mean±SEM, * p<0.05 vs baseline

The Pts with regression demonstrated serial normalization of LV wall mass over the 4 and 8 month periods, although PFR only normalized during the later 4 months. Time to PFR and heart rate did not change, while EDV decreased and ejection fraction increased. Pts without regression had no improvement in PFR.
Conclusions: 1, UFCT provides an accurate method to assess changes in LV mass; 2, improvement in DF occurs after intervention for aortic valve disease and appears to follow rather than parallel LV mass regression.

CAN IN-PATIENT CARDIAC CATHETERIZATION BE ELIMINATED BY OUT-PATIENT PROCEDURES?
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To determine the potential of out-pt cardiac catheterization to replace in-pt procedures, we studied 986 consecutive pts undergoing cardiac cath in a 3 month period. Pts were stratified by eligibility for out-pt cath, using published guidelines. Group I consisted of 240 pts who underwent an out-pt cath, group IIa was 279 in-pts who were eligible for out-pt cath, and group IIb was 467 in-pts who were ineligible for out-pt cath. Among all pts catheterized, 519 (53%) had out-pt cath or were eligible for out-pt cath. Among group IIb pts, 221 (47%) had congestive heart failure, 150 (32%) had unstable angina, 105 (22%) had recent infarction, 139 (30%) had other cardiac disease, and 85 (18%) had severe non-cardiac disease. Among all in-pts, one exclusion criterion was present in 269 pts (36%), 2 in 163 (22%), and 3 in 35 (5%). Eligible in-pts (Group IIa) appeared to have more severe illness than out-pts in that they were older (p=.002), had lower ejection fractions (p=.009), and were more likely to have 3-vessel disease (p<.0001). The cost of the procedure was not different between in-pts and out-pts.

We conclude that out-pt cath is feasible in approximately half of all pts who undergo this procedure. Using currently accepted guidelines, in-pt procedures will continue to be needed for a substantial number of patients.

## LONG TERM CHARACTERIZATION OF LEFT VENTRICULAR DIASTOLIC COLLAPSE DYNAMICS POST INFARCTION

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High resolution analysis of left ventricular (LV) conformational changes during the cardiac cycle reveal that the anterolateral LV wall undergoes a brief (50-70 msec) inward displacement (D) or diastolic collapse (DC) during early diastole. Using a closed-chest canine model, high resolution cardiac surface velocity and displacement maps (CMAP) are constructed by a non-invasive technique analyzing scattered x-rays off the heart surface. These maps show that DC occurs after systolic ejection and prior to surface expansion in the normal heart. Fourier analysis of D over time permits calculation of a maximum (Max) and average (Avg) inward velocity (V, mm/sec) during DC. Serial measurements of D, MaxV, AvgV were made over 30 days in 9 dogs with infarction induced via closed-chest embolization of an epicardial artery. (%Infarct=16.4±6.0 SD).

**Results** (mean+SEM):

| | Baseline | 2 Hrs | 4 Days | 11 Days | 30 Days |
|---|---|---|---|---|---|
| HR | 122±12 | 119±10 | 127±11 | 104±10 | 129±11 |
| D (mm) | 1.2±.2 | .8±.2 | 6±.1* | .9±.1 | 1±.2 |
| Max V | 22.3±3 | 11.2±1* | 12.5±2* | 16.2±2 | 20.2±3 |
| Avg V | 12.4±1.5 | 6.06±.7* | 6.8±9* | 9.7±1.4 | 11.9±1.8 |

(*=p<.01 vs. Baseline, Newman-Keuls)

Diastolic collapse velocities are significantly reduced (50%) within 2 Hrs post-embolization but gradually return to baseline over approximately 30 days. The non-invasive measurements of collapse dynamics thus provide a sensitive quantitative measure of changes in cardiac dynamics subsequent to myocardial infarction.

## DETECTION OF MYOCARDIAL HEMORRHAGE USING $^1$H NMR IMAGING AT 1.5 T

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Proton ($^1$H) NMR imaging appears to be a useful approach for identifying zones of myocardial infarction (MI) due to increase in $T_1$ and $T_2$ resulting in increased signal intensity (SI). In the present study, ex-vivo $^1$H NMR imaging at 1.5T was performed in 14 dogs: 24 hours (6 dogs) and 72 hours (8 dogs) after coronary occlusion. In 7 dogs zones of decreased SI (zone I) were seen adjacent to or within the central zone of increased SI (zone II). Gross inspection of sliced myocardium disclosed hemorrhage in the zones with decrease SI, which was later confirmed by histology. Image-derived relaxation times ($T_1$ and $T_2$) for the different zones revealed that the decrease in SI resulted from enhancement of $T_2$ and not $T_1$ relaxation rates:

| | control(c) | zone(I) | zone(II) | c vs.I | I vs.II |
|---|---|---|---|---|---|
| T2 msec | 54±4.8 | 44±8.4 | 63±2.8 | p<.01 | p<.01 |
| T1 msec | 969±50 | 918±49 | 962±99 | p=ns | p=ns |

Such a selective enhancement is consistent with the paramagnetic effect of deoxyhemoglobin (DHb), and becomes apparent only at high magnetic fields. In 5 of the remaining 7 dogs, very small hemorrhages were observed, with no apparent effect on SI. This can be attributed to opposing effects of edema and hemorrhage on $T_2$. In conclusion, hemorrhagic zones associated with MI, demonstrate significantly reduced SI caused exclusively by T2 reduction. This observation should help to diagnose and further characterize the pathological process associated with MI.

## DETECTION OF CORONARY STENOSES BY HIGH SPEED NMR IMAGING:THE UTILITY OF DYSPROSIUM-DTPA

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Dysprosium-DTPA (Dy) has a low relaxivity but is a potent myocardial T2 contrast agent by virtue of its high magnetic moment. Its usefullness in detecting coronary stenoses has been examined with a prototype NMR imager(Advanced NMR Systems Inc, Woburn, MA), generating each image in less than 40ms. Using a canine model of LAD coronary stenosis, seven animals were examined with the following protocol:1) control, 2)stenosis, 3)dipyridamole(dipyr), 4)dipyr+release of stenosis. Images were obtained every 1.2-1.8s (set of 80) using a spin echo sequence with TE of 30ms. A rapid intravenous contrast injection (0.19 mmol/kg) was performed after the 10th image. The results shown below demonstrate a significant difference in signal reduction between two cardiac zones in the control and dipyr&stenosis studies. The coronary stenosis reduced the Dy effect on the LAD zone(NS), and the addition of dipyr accentuated the perfusion difference.

| | % Signal reduction after Dy-DTPA | | | |
|---|---|---|---|---|
| | control | stenosis | dipyr+sten | dipyr |
| **LAD** | 47±3 | 33±8 | 29±6 | 62±5 |
| **REMOTE** | 30+4 | 42±5 | 54±6 | 52±3 |
| | p<0.05 | NS | p<0.05 | NS |

**Conclusion**: We have demonstrated that high speed NMR imaging with Dy-DTPA and dipyr, is capable of detecting the effect of a coronary stenoses.

## BLOOD-VELOCITY IMAGING BY MAGNETIC RESONANCE PHASE-DIFFERENCE TECHNIQUES FOR QUANTITATIVE MEASUREMENT OF STROKE VOLUME, CARDIAC OUTPUT AND VENOUS RETURN: COMPARISON WITH DOPPLER ULTRASOUND.

Albert C. van Rossum M.D., Michiel Sprenger Ph.D, Kathinka H. Peels M.D., Frans C. Visser M.D., Jaap Valk M.D., Free University Hospital, Amsterdam, The Netherlands.

As the phase of the magnetic resonance (MR) signal is very sensitive to flow, special pulssequences have been designed to induce phase-shifts that are directly related to blood velocity (V). Measurement of these shifts allows non invasive quantification of V on a pixel-by-pixel base at multiple intervals in the cardiac cycle (RR). We used such a technique in 17 subjects to measure V in a plane perpendicular to the ascending aorta and superior vena cava (SVC), and to the inferior vena cava (IVC) on 16 velocity images acquired at equal intervals (dt) over RR. The transverse area (A) of the vessels was determined on anatomic images and mean V over this area on corresponding velocity maps. Calculations: volume per interval (Qi) = A x mean V x dt; volume per RR = sum of the 16 Qi values. Aortic measurements yield LV stroke volume (SV) and CO (LVSV x heartrate). Measurements in SVC + IVC yield venous return per RR. LVSV and CO were compared to measurements made by Doppler echocardiography (D). Results obtained by regression analysis are:

LVSV (ml) MR = -7.5 + 1.1 D r = 0.76 (n=17)
CO (L/min) MR = 0.3 + 0.9 D r = 0.86 (n=17)
MR venous return = 1.3 + 1.0 MR LVSV r = 0.91 (n=13)

Conclusion: 1)Non invasive determination of blood flow by MR is reliable, as a good correlation was found between LVSV and venous return. 2) MR velocity imaging shows a good correlation with Doppler ultrasound for assessment of LVSV and CO.

IMPROVED ASSESSMENT OF ACUTE MYOCARDIAL INFARCTION BY MAGNETIC RESONANCE IMAGING AND GADOLINIUM-DTPA

Paul R.M. van Dijkman M.D., Ernst E. van der Wall M.D., Joost Doornbos Ph.D., Arnoud van der Laarse Ph.D., Sandra Postema M.D., Albert de Roos M.D., Ad E. van Voorthuisen M.D., Albert V.G. Bruschke M.D.
University Hospital Leiden, The Netherlands.

To assess the usefulness of Gadolinium(Gd)-DTPA in Magnetic Resonance Imaging (MRI) of acute myocardial infarction (AMI), we studied 25 Pts after a first AMI (13 anterior, 12 inferior) by ECG-gated MRI and Gd-DTPA after 93±49 hrs from the onset of symptoms. MRI was performed using a Philips Gyroscan (0.5 Tesla) and spin-echo measurements (echo-time 30 msec) were made before and 20 min after intravenous injection of 0.15 mmol/kg Gd-DTPA. In all Pts contrast enhancement of the infarcted areas was observed after Gd-DTPA. Signal intensities were determined from 10 regions of interest in adjacent myocardial areas of the optimal LV slice. The signal intensities of the infarcted versus normal areas were used for calculation of intensity ratios. Intensity ratios before Gd-DTPA were 1.15±0.18 and after Gd-DTPA 1.54±0.30 ($P<0.001$). When Pts were stratified according to early MRI studies (<72 hrs, 10 Pts, Group I) and late MRI studies (>72 hrs, 15 Pts, Group II), the intensity ratios before Gd-DTPA were 1.05±0.12 (Group I) and 1.21±0.19 (Group II) ($P<0.05$). After Gd-DTPA the intensity ratios were 1.37±0.12 (Group I) and 1.65±0.34 (Group II) ($P<0.02$). Conclusions: 1, Gd-DTPA improves visualization of acutely infarcted myocardial areas by MRI; 2, infarcted areas show increased signal intensity compared to non-infarcted areas; 3, maximal contrast enhancement is obtained >72 hrs after onset of AMI indicating increased uptake of Gd-DTPA in a more advanced stage of the infarction process.

## Monday, March 20, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 2:00PM–3:00PM
## Pacific Room, Anaheim Convention Center
## Echo Doppler: General I

**DOPPLER HARMONIC SPECTRAL SIGNALS ("STRIPES"): IN VIVO AND IN VITRO EVIDENCE OF AN ARTIFACT DUE TO LEAFLET REVERBERATIONS**

Mikel D. Smith, M.D., F.A.C.C., Edward A. Harlamert, M.D., Kevin L. Sublett, M.D., Helga Miles, Oi Ling Kwan, B.S., Annette Cater, Charles Knapp, Ph.D., Michael R. Harrison, M.D., F.A.C.C., Anthony N. DeMaria, M.D., F.A.C.C., University of Kentucky Medical Center, Lexington, Kentucky.

Although high-frequency striated Doppler signals thought to be due to leaflet vibrations have been described in torn prosthetic valves, few reports exist with native valve lesions. We studied 24 patients with 25 lesions in whom pulsed (PW) and continuous (CW) Doppler of regurgitant native lesions without evidence of degeneration or tears (15 MR, 7 AR, 3 TR) revealed dense parallel bands above and below the zero line throughout regurgitation. The bands were spaced at multiples of the fundamental velocity, which ranged from 30-80 cm/s; were recorded only with PW sampling directly on or adjacent to the leaflet; and disappeared with catheters across the valves in 2 cases. Color flow imaging done in all patients showed a homogeneous bright green turbulent signal localized to the leaflet. The severity of regurgitation ranged from mild (13), moderate (5), to severe (7). Identical audio and spectral signals were reproduced in vitro by movement of a specular reflector perpendicular to the transducer. Thus, parallel Doppler harmonic signals appearing as horizontal "stripes" may rarely be seen in native valvular disease. These signals do not appear to be related to the etiology or severity of the lesion. Localization of these signals to the valve leaflets and in vitro simulation by target motion suggest that "stripes" are an artifact related to reverberation.

**INTRAVASCULAR ULTRASOUND IMAGING CATHETER ACCURATELY MEASURES AREA OF STENOTIC AORTIC VALVES IN VITRO**

Debra Heldman, M.D.; John Mallery, M.D.; Gerald Spear, M.D.; James Gessert; James Griffith, Ph.D.; Jonathan Tobis, M.D., F.A.C.C.; Walter L. Henry, M.D., F.A.C.C.; University of California, Irvine, CA.

The measurement of aortic valve area in aortic stenosis in vivo has been difficult. The limitations of the Gorlin technique are well recognized. Likewise, the use of external 2-D echo is limited because shadowing and reverberation caused by calcification prevents adequate visualization of the orifice. An ultrasound imaging technique that permits visualizing the aortic valve orifice from inside the orifice would overcome these difficulties. In this study, we evaluated a 1.2 mm diameter intravascular ultrasound imaging catheter with a single 20 mHz transducer which is hand-rotated to paint a cross-sectional image on a computer screen. To assess the usefulness of this device, 3 calcific, stenotic intact human aortic valves were imaged by both external 2-D echo and the intravascular ultrasound imaging catheter. The aortic valve orifice could not be visualized adequately by external 2-D echo. In contrast, acceptable images of the valve orifice were obtained by the ultrasound catheter in all 3 specimens and were planimetered. The smallest lumen area was compared with valve area determined by planimetering photographs of the gross tissue.

| Valve # | Ultrasound (cm2) | Gross Specimen (cm2) |
|---|---|---|
| 1 | 0.21 | 0.25 |
| 2 | 0.40 | 0.39 |
| 3 | 0.84 | 0.71 |

Thus, intravascular ultrasound imaging provides a potentially useful new avenue for quantitation of stenotic aortic valves.

## Monday, March 20, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 3:00PM–4:00PM
## Pacific Room, Anaheim Convention Center
## Echo Doppler II

QUANTITATION OF ACUTE AORTIC INSUFFICIENCY WITH COLOR DOPPLER FLOW MAPPING: IN VITRO STUDIES IN A FLEXIBLE MODEL OF THE LEFT VENTRICLE

Byron F. Vandenberg, MD, FACC, Kevin C. Dellsperger, MD, PhD, Ian Law, BS, Krishnan B. Chandran, DSc and Richard E. Kerber, MD, FACC, University of Iowa, Iowa City, IA

Previous in vitro studies of the quantitation of aortic insufficiency (AI) with color Doppler flow imaging (CD) have been limited to pulsatile studies in an axi-symmetric (tube) aortic valve chamber. Our purpose was to evaluate the quantitation of acute AI with CD in a compliant left ventricular (LV) chamber mounted in a pulse duplication system. The compliant LV chamber was made of polyurethane permitting adjustment of LV end diastolic pressure (EDP). Two bioprosthetic Hancock valves were used in the "mitral" and "aortic" positions. CD was performed with an Aloka 880 CD System and a 2.5 mHz transducer oriented at the apex of the LV chamber, parallel to outflow through the aortic valve. Transvalvular defects were created in the aortic bioprostheses. Jet area was measured from frames that did not include contamination of the AI jet by mitral inflow. Regurgitant volume and fraction were measured with an electromagnetic flow probe.
RESULTS: (n=27) EDP ranged from 23-37 mmHg (mean±SD, 26±3), regurgitant volume ranged from 0.3-9.6 ml/beat (mean, 2.7±2.3), and regurgitant fraction ranged from 0.5-24.5% (mean, 9.3±7.6). Jet area measurements were compared to actual regurgitant volumes. Actual regurgitant volume=0.85 (CD jet area) + 0.6; R=0.90, SEE=1.06 ml, $p<0.0001$.
CONCLUSION: Color Doppler flow mapping and jet area measurement may provide an accurate estimation of regurgitant volume in the presence of acute aortic insufficiency.

VARIABILITY IN MITRAL REGURGITANT JET AREA SIZE DURING SYSTOLE AND ITS RELATION TO MITRAL REGURGITATION SEVERITY

Steven J. Lavine, MD, F.A.C.C., Luis Tami, MD, Rom Reddy, MD, Daniel Dubay, MD, Vicki Johnson. Harper Hospital, Wayne State University, Detroit, MI.

Although good correlations have been noted between maximal mitral regurgitation (MR) jet area (JA) size indexed to LA size and MR severity, there is overlap among the grades of MR and variability in the timing of maximal JA/LA. To determine whether the variability in JA size during systole (S) was related to MR severity, we obtained 2-D echo's, pulsed and continuous wave Doppler and color flow mapping on 12 pts with mild MR, 21 pts with moderate MR, and 12 pts with severe MR (none with mitral valve prolapse). MR severity was assessed by pulsed Doppler regurgitant fraction (RF): RF<20% in mild MR, RF= 20-40% in moderate MR, and RF>40% in severe MR. JA/LA's were obtained on a frame by frame basis during S from parasternal long axis and apical 4 chamber views and averaged. JA/LA were then determined at 25%, 50% and 75% S.

| | Mild MR | Moderate MR | Severe MR |
|---|---|---|---|
| 25% S | 0.17 ± 0.09 | 0.24 ± 0.13 | 0.38 ± 0.12*" |
| 50% S | 0.17 ± 0.11 | 0.39 ± 0.18* | 0.49 ± 0.17* |
| 75% S | 0.07 ± 0.06 | 0.28 ± 0.19* | 0.45 ± 0.17*" |

*p < .05 vs mild MR "p < .05 moderate vs severe MR

In mild MR, JA/LA was smallest at 75% S as compared to 25% and 50% S (p<.05). In moderate MR, JA/LA at 50% of S was greater than 25% or 50% S (p<.05). In severe MR, JA/LA at 50% S was greater than 25% S (p<.05). JA/LA during 75% S best differentiated among MR groups. 10 of 12 pts with mild MR had JA/LA < 13.2% and 18 of 21 pts with moderate MR had JA/LA > 13.2% (p<.05). 17 of 21 pts with moderate MR had JA/LA < 26.7% and 10 of 12 pts with severe MR had JA/LA > 26.7% (p<.05). Conclusion: (1) Extent of MR throughout S is related to severity and (2) JA/LA during late S can differentiate MR severity.

**Three-Dimensional Echocardiography : A Feasible, Non-Invasive Method to Measure Cardiac Volume**

Hugh A. McCann, M.D., K.Chandrasekaran, M.D., Eric A. Hoffman, Ph.D., Lawrence J. Sinak, M.D., James B. Seward, M.D., FACC and James F. Greenleaf, Ph.D., Mayo Clinic, Rochester, MN, Hahnemann Univ. and University of Pennsylvania, Philadelphia PA.

The detailed evaluation of cardiac anatomy in three-dimensions (3D) without using gross geometric assumptions remains a major challenge in medical imaging. In this study we utilized a conventional sector scanner. We incrementally rotated the transducer around its central beam axis to obtain 50 angles of view 3.6 degrees apart, thus overcoming the limited acoustic access which has frustrated 3D echocardiography. We inserted the images into a 3D matrix at their respective angles of view, preserving the original myocardial backscatter data. To establish the accuracy of the method we scanned 6 balloons and 4 excised hearts in a water bath. The reconstructed volumes of the balloons matched the estimated volumes [y = 0.998X + 1.575; r = 0.99; S.E.E. = 1.67 mls] and a similarly good correlation was found for the excised heart study [y= 0.919X + 3.187; r= 0.92; S.E.E. = 1.548 mls]. We then estimated the left ventricular (lv) volume from a healthy volunteer in the same manner and compared the volumes to those estimated utilizing 3D magnetic resonance imaging.

| | $V_{ed}$ | $V_{es}$ | SV | EF |
|---|---|---|---|---|
| 3D ECHO | 107 ml | 47 ml | 59 ml | 56 % |
| 3D MRI | 109 ml | 46 ml | 58 ml | 58 % |

*$V_{ed}$: end-diastolic lv volume; $V_{es}$: end-systolic lv volume*
*SV: stroke volume; EF: ejection fraction*

We conclude that 3D echocardiography is a feasible method to obtain information on cardiac volume.

EFFECT OF AGE ON PULMONARY VENOUS FLOW VELOCITIES IN NORMAL SUBJECTS.

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Pulmonary venous (PV) flow velocity (VEL) profiles are being frequently utilized for assessment of left ventricular (LV) diastolic function; however, the effect of age on PV VEL in normal subjects is unknown. We performed pulsed-wave Doppler studies of PV VEL and of the mitral inflow (MV) with respiratory monitoring in 40 normals (age, 47±17 yr; 31 women). PV peak systolic (S), diastolic (D), and atrial reversal (AR) VEL, % systolic forward flow velocity integral (% FFVI syst) and MV (E) and (A) VEL, deceleration time (DT) were measured during inspiration, expiration, and apnea. The patients were divided into 2 groups: age < 50 yr (n = 21) and ≥ 50 yr (n = 19).

| | PV VEL, cm/s | | | % FFVI | MV | |
|---|---|---|---|---|---|---|
| Age | S | D | AR | syst | E/A | DT, ms |
| <50 | 48 | 52 | 19 | 56 | 1.99 | 172 |
| ≥50 | 62 | 37 | 23 | 65 | 1.19 | 196 |
| P | 0.0001 | 0.0001 | 0.03 | 0.0001 | 0.001 | 0.001 |

Normals ≥50 yr have increased PV S, decreased D, increased AR VEL, and increased % FFVI syst. Analogous changes seen in the MV in normals ≥50 yr were decreased E/A and prolonged DT. There was no significant change in PV VEL and MV VEL during inspiration, expiration, and apnea. Conclusions: 1, Significant changes in PV VEL occur with aging; 2, these factors must be considered in the assessment of LV diastolic function; 3, respiratory changes in PV and MV VEL profiles are negligible.

SERIAL ASSESSMENT OF MITRAL REGURGITATION IN PATIENTS UNDERGOING AORTIC VALVULOPLASTY.

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Mitral regurgitation (MR) was serially assessed by pulsed Doppler echocardiography in 144 patients undergoing balloon aortic valvuloplasty (BAV) for symptomatic aortic stenosis. Scores of 0, 1, 2 and 3 were assigned to pulsed Doppler patterns corresponding to no, mild, moderate, and severe MR. Before BAV, MR score correlated significantly ($p < 0.005$), but weakly, with aortic valve area ($r = -0.24$) and with left ventricular ejection fraction ($r = -0.34$). There was no significant correlation between MR score and either mean catheterization or mean Doppler aortic valve gradient. BAV produced decreases in both catheterization and Doppler mean transvalvular aortic gradients (56±19 to 31±12 and 60±19 to 48±16 mm Hg, respectively; both $p < 0.0001$) and an increase ($p < 0.0001$) in aortic valve area (0.6±0.2 to 0.9± 0.3 $cm^2$). Left ventricular ejection fraction did not change. Pulsed Doppler findings of MR were present pre-BAV in 102 of the 144 patients. Eighty-eight patients had scores compatible with at least mild MR, and 49 had scores indicative of moderate or severe MR. In the 88 patients with mild or greater MR, MR score decreased from 1.8±0.7 to 1.5±0.8 ($p < 0.0001$). In the 49 patients with Doppler patterns of moderate or severe MR before dilatation, regurgitant score decreased in 38, remained unchanged in 8 and increased (by only 0.5 grade) in 3. Conclusions: 1) MR is commonly present in adult patients undergoing BAV; 2) it is weakly and inversely correlated with left ventricular ejection fraction and aortic valve area; 3) its severity improves following BAV; 4) a decrease in the severity of MR may be an important mechanism for symptomatic improvement following BAV.

EFFECT OF DECREASED AFTERLOAD ON DOPPLER INDICES OF LEFT VENTRICULAR FILLING IN PRESSURE OVERLOAD HYPERTROPHY.

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Pressure overload hypertrophy (POH) is frequently associated with an impairment of LV relaxation and early diastolic filling. To determine if excessive afterload is a major contributor to this diastolic impairment in patients with POH due to aortic stenosis, we analyzed transmitral pulsed Doppler inflow patterns 1-2 days pre and post balloon aortic valvuloplasty (BAV). Of 190 consecutive patients undergoing BAV, 163 were excluded from analysis because of other factors known to influence transmitral Doppler signals (CAD, mitral/aortic regurgitation, irregular rhythms). Eight patients did not have serial Doppler studies. The 19 remaining patients (10M/9F, age 75±14 years) had a mean LV wall thickness of 18±3 mm. Baseline radionuclide LVEF was 0.73±0.15. Following BAV, peak LV systolic pressure fell from 212±32 to 185±22 mmHg ($p<.0001$) and mean aortic gradient fell from 65±13 to 50±14 mmHg ($p<.001$). Peak E and A wave velocities, % atrial contribution to LV filling, time for 50% LV filling, and % filling in the first 1/3 of diastole did not significantly change, nor was there any correlation between changes in Doppler indices and mean aortic gradient or LV systolic pressure. Analysis of a subgroup of 12 patients with the same inter-study heart rate (±10%) was similar.

Conclusion: In the aortic stenosis model of POH, an acute decrease in afterload following balloon aortic valvuloplasty is not associated with early improvement in Doppler indices of LV diastolic filling.

IMPROVED DOPPLER ASSESSMENT OF NORMAL ST. JUDE'S PROSTHETIC AORTIC VALVES USING THE CONTINUITY EQUATION.

Edward R. Chafizadeh, B.A., William A. Zoghbi, M.D., F.A.C.C., Baylor College of Medicine, Houston, Texas.

Doppler echocardiography (DE) has provided accurate measurements of stenotic aortic valve area using the continuity equation. We postulated that the continuity equation is superior to gradients in the evaluation of prosthetic aortic valves (PrV). Accordingly, DE was performed on 67 pts (41 M, 26F, mean age 58±14 yrs) within 1 month following aortic valve replacement with St. Jude's valves (mean 10 ± 6 days). All pts were clinically stable and without evidence of valve dysfunction. Valve size ranged from 19 to 31mm, mean 23.6 mm. LV ejection fraction ranged from 30 to 75%. Using the parasternal long axis view, the LV outflow diameter was measured just proximal to the PrV. A good correlation was observed between valve size and LV outflow diameter measurements ($r=0.92$). Doppler-derived maximal PrV gradients ranged from 9-71 mmHg (mean 29), mean gradients from 5-30 mmHg (mean 14) and cardiac output from 2.8-12.3 l/min (mean 5.3). Effective PrV area by the continuity equation averaged 1.63 $cm^2$ (range 0.73 $cm^2$ for a 19 mm valve to 4.23 for a 31 mm valve). Using analysis of variance, PrV area differentiated better the various valve sizes ($p<0.000001$) than did gradients ($p=0.003$). Furthermore, PrV area correlated better with valve size ($r=0.82$) than did either maximal or mean gradients ($r=-0.46$ and $-0.4$, respectively).

In conclusion, the calculation of effective valve area using the continuity equation is superior to the use of gradients in assessing normal St. Jude's prosthetic aortic valves. These data warrant the application of the continuity equation to the evaluation of prosthetic aortic valve stenosis.

**IMPACT OF TRANSESOPHAGEAL ECHOCARDIOGRAPHIC EXAMINATIONS: COMPARISON BETWEEN TRANSTHORACIC AND TRANSESOPHAGEAL APPROACH**

**Krishnaswamy Chandrasekaran, M.D., Ramesh C. Bansal, M.D., John J. Ross, RCPT, Pravin M. Shah, M.D., FACC, Gary S. Mintz, M.D., FACC, Hahnemann Univ., Philadelphia, PA, Loma Linda Univ., Loma Linda, CA.**

**We evaluated the usefulness of transesophageal echocardiography (TEE) in 80 patients in whom the transthoracic echocardiography (TTE) provided insufficient information for optimal patient (Pt) management. 6% (80/1340) of pts who had TTE required TEE. All these pts were awake during TEE. TEE played a significant role in pt management in 32 of 34 patients with aortic disorders (including 4 aortic root abscess, 2 left ventricular outflow tract to left atrial fistula, and 3 aortic dissection), 28 of 33 pts with mitral disorders (including 11 periprosthetic regurgitation, 2 endocarditis) 5 pts with congenital disorders (including partial endocardial cushion defect with aneurysm of the cleft, ventricular septal defect) and 7 of 8 intracardiac masses (including 3 interatrial septal mass, 4 left atrial appendage thrombus). Based on additional TEE information in 3 aortic dissection, 4 aortic abscess, 9 mitral regurgitation surgical treatment was planned. In the rest, TEE provided necessary information to manage medically, obviated catheterization, or indicated need for catheterization. We conclude that although TTE is adequate in majority of patients, there is a small group in whom it is not and TEE is necessary. This group include pts with all forms of heart disease especially those with aortic root disease and mitral prosthesis.**

THE CONTRIBUTION OF TRANSOESOPHAGEAL ECHOCARDIOGRAPHY IN THE ULTRASOUND ASSESSMENT OF PERCUTANEOUS MITRAL VALVULOPLASTY.

Bertrand CORMIER MD, Alec VAHANIAN MD, Pierre-Louis MICHEL MD, Bernard VITOUX MD, Charles STARKMAN MD, Lionel ENRIQUEZ MD, Alain KULAS MD, Jean ACAR MD.
Tenon Hospital, Paris, FRANCE.

The aim of this study is to assess the interest of transoesophageal echocardiography (TEE) compared with that of transthoracic (TTE) in selecting candidates and evaluating results of percutaneous mitral valvuloplasty (PMV). Between June and September 1988, 31 patients (pts) were examined by TEE and TTE before PMV.

PMV was not performed in 3 pts in whom a thrombus in the left atrial appendage was detected by TEE but not by TTE. Before PMV, TEE was also better than TTE in showing spontaneous contrast of the left atrium (20 vs 0, $p \leq .001$), in assessing subvalvular lesions (correct visualisation in all patients vs 26 by TTE, $p \leq .02$) and in detecting mild mitral regurgitation (MR) (18 vs 10, $p \leq .05$). On the contrary planimetry of valvular area was only possible with TTE. This technique was also superior in visualising the commissural area. During PMV, TEE enabled the puncture of the interatrial septum to be made in one pt. Echocardiographic study was repeated 24 to 48 hours after PMV in 28 pts. MR $\geq$ 2+ was observed in 2 pts where only TEE was able to show the causal mechanism : rupture of chordae in one and valvular mutilation in one. Color Doppler showed a trivial shunt at the atrial level in 16 cases with TEE vs 5 cases with TTE ($p \leq .01$). In the same way a small atrial septal defect was directly found in 10 cases only by TEE.

From this preliminary study we conclude that TEE provides additional information in echocardiographic assessment of PMV in :
- detecting the presence of left atrial thrombi
- determining the degree and mechanism of MR
- assessing small atrial septal defects.

## CARDIAC CYCLE-DEPENDENT VARIATION OF INTEGRATED BACKSCATTER: AN INDEX OF CONTRACTILE PERFORMANCE THAT IS NOT DISTORTED BY PARADOXICAL SEPTAL MOTION.

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We have previously shown that canine and human myocardium exhibit a cardiac cycle-dependent variation of integrated backscatter (CV) that depends on regional myocardial contractile performance and that is altered promptly by ischemia and by reperfusion.To determine whether CV provides an index of regional contractile performance that is not distorted by altered wall motion per se, we studied 8 children (age 10.6 ± 4 yrs) with congenital cardiac lesions including 5 with surgically corrected defects who exhibited paradoxical septal motion evident with conventional 2-D and M-mode echocardiography. Controls were 6 healthy children (age 9 ± 0.6 yrs) with normal echocardiograms. CV was measured in parasternal long-axis views from multiple septal sites (2.5 ± 1 in the study group; 2.8 ± 0.8 in controls) for each subject. The average magnitude of septal CV was 8.3 ± 0.8 dB (SD) compared with 5.7 ± 1.0 dB in the study and control groups (P = 0.05) consistent with right ventricular volume overload in the study group. Systolic septal thickening was 46 ± 12.7% and 42 ± 14.5% in the study and control groups (P = NS). Regional CV was in phase with electromechanical events of the cardiac cycle in both groups. These results indicate that CV quantifies regional contractile performance manifest also by physiologic wall thickening. Furthermore, CV remains in phase with physiologic regional systolic wall thickening despite paradoxical wall motion and may therefore be less prone to error in detecting regional tissue viability compared with analysis of the phase of wall motion alone. Thus, ultrasonic tissue characterization appears to provide a sensitive and quantitative index of regional tissue viability regardless of the presence of altered wall motion that may be seen in transiently ischemic but still viable myocardium.

## ESTIMATION OF PULMONARY PRESSURE IN VENTRICULAR SEPTAL DEFECT: DOPPLER AND COLOR FLOW APPLICATION.

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Quantification of pulmonary artery pressure ($PA_P$) in children with ventricular septal defect (VSD) is essential in clinical management. Continuous wave Doppler (CWD) can estimate the pressure drop ($\Delta P$) across the VSD. Eccentricity of VSD jets may allow CWD interrogation to underestimate true gradients and thereby overestimate $PA_P$. Color flow Doppler (CFD), however, accurately displays the area of maximal transseptal flow and allows for direction of the CWD beam through the VSD jet. Thirty-seven patients, aged 5 wks to 6 yr (Mean 3.2 yr) with VSD were studied by 2D echo/CWD/CFD at the time of cardiac catheterization (CC). Maximal trans-VSD velocities were identified by directing the CWD beam across the VSD both without and subsequently with CFD display. Velocities (V) were converted to gradients ($\Delta P$ LV-RV) by a modified Bernoulli equation ($\Delta P = 4V^2$). LV pressure was assumed equal to systolic right brachial artery pressure. $PA_P$'s measured during CC were regressed on the values obtained from both "black and white" and CFD CWD examinations. Estimation of $PA_P$ (no CFD) correlated well with CC-measured PAp ($r=0.96$, $p < .001$). The best-fitting regression line differed significantly from the line of identity. Use of CFD to "angle-correct" CWD provided a better prediction of PAp ($r=0.99$) which did not differ significantly from the line of identity. Estimation of PAp by trans-VSD CWD is accurate: CFD improves CWD measurements by allowing visualization of trans-VSD flow.

## THE ECHO-DOPPLER EVALUATION OF PERCUTANEOUS MITRAL VALVULOPLASTY CORRELATES POORLY WITH INVASIVE MEASUREMENTS BUT IS PREDICTIVE OF SUCCESS

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The utility of echo-Doppler measurements pre and post percutaneous mitral valvuloplasty (PMV) were assessed in 76 pts. Their mean age was 52±14 years and 66 were women. Poor correlations with invasive measurements were found:

| | | Echo-Doppler | Catheterization | R | p |
|---|---|---|---|---|---|
| Mitral area: | pre | 1.1±0.4 | 1.07±0.3 | 0.1 | NS |
| ($mm^2$) | post | 2.0±0.6 | 2.2±0.9 | 0.1 | NS |
| | 6 mo. | 1.8±0.3 | 1.8±0.3 | 0.1 | NS |
| Gradient: | pre | 10±2 | 16±5 | 0.5 | <.001 |
| (mmHg) | post | 5.4±2 | 6±2.7 | 0.3 | <.001 |
| | 6 mo. | 5.2±2.1 | 6.5±2 | 0.6 | <.01 |
| Mitral regurg. | | 45 → 57 pts | 35 → 45 pts | 0.6 | <.01 |

Success was classified by catheterization criteria as optimal (valve area >1.5 and gain >25%: 53 pts) and suboptimal (area ≤1.5 and gain ≤25%: 15 pts). The echocardiographic factors predictive of optimal success by univariate analysis were left atrial diameter (50±8 vs 56±7 mm, p=.001), leaflet thickness (p=.002), leaflet mobility (p=.002) and echocardiographic mitral valve score (p=.009). By multivariate analysis with hemodynamic parameters, left atrial size and pulmonary vascular resistance were selected as independent predictors of optimal success.

Thus, although echocardiographic parameters correlate poorly with invasive measurements, they are useful both to select optimal candidates for PMV and as a baseline for non-invasive long-term follow-up.

# Monday, March 20, 1989
# Poster Displayed: 2:00PM–5:00PM
# Author Present: 4:00PM–5:00PM
# Pacific Room, Anaheim Convention Center
# Advances in Coronary Angioplasty

## PRESERVATION OF MYOCARDIAL FUNCTION BY A CORONARY PERFUSION CATHETER.

Abel E. Moreyra, M.D., F.A.C.C., Peter M. Scholz, M.D., Angelo Macris, John B. Kostis, M.D., F.A.C.C., UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ.

We studied the effectiveness of a coronary perfusion catheter (CPC) in an animal model of acute coronary occlusion (Occ). Hemodynamic variables, regional myocardial blood flow (RMBF) in the subepicardium (epi) and subendocardium (endo) and regional systolic function (by ultrasonic crystals) of the circumflex (Cx) perfused area were measured in 7 anesthesized dogs. After baseline measurements, the Cx artery was occluded with a silk snare and measurements repeated after 5 minutes of ischemia (Occ #1). The snare was released and 1 hour later the snare occlusion was repeated after placement of a CPC with 40 pores in the Cx artery (Occ #2).

Results:

| | Baseline | Occlusion #1 | Occlusion #2 |
|---|---|---|---|
| Heart Rate | 154±28 | 152±32 | 143±57 |
| SBP mm Hg | 125±32 | 103±67 | 112±32 |
| LVEDP mm Hg | 9±2 | 11±2 | 8±2 |
| RMBF epi ml/min/g | 1.37±.54 | .24±.16* | .86±.44 †* |
| RMBF endo ml/min/g | 1.54±.68 | .16±.15* | .67±.27 †* |
| Δ L% | 7±4 | -4.8±5* | 3±4† |

SBP=systolic blood pressure; LVEDP=left ventricular end-diastolic pressure; ΔL%=percent systolic segmental shortening; *P <0.01 from baseline;†P <0.05 from Occ #1. Conclusions: In anesthesized dogs CPC returned values of epi RMBF to 63% and endo RMBF to 44% of baseline. Although both values were significantly lower (P<0.01) from baseline levels, flow was adequate to preserve regional systolic function (ΔL%).

PERCUTANEOUS LEFT ATRIAL - FEMORAL ARTERY BYPASS WITH A PULSATILE PUMP: INITIAL HUMAN EXPERIENCE IN CARDIOGENIC SHOCK.

Jacob Shani, MD, FACC, Gerald Hollander, MD, FACC, Ira Nathan, PhD, Alvin Greengart, MD, FACC, Bruce Toporoff, MD, Israel Jacobowitz, MD, Ephraim Glassman, MD, Joseph Cunningham, MD, Edgar Lichstein, MD, FACC, Maimonides Medical Center, SUNY, Health Science Center at Brooklyn, Brooklyn, NY.

Experimental data suggests that prompt unloading of the left ventricle prevents ongoing myocardial damage during acute infarction and reperfusion. We inserted a percutaneous left atrial-femoral artery (LA-FA) bypass device into 6 pts in cardiogenic shock, undergoing CPR. A cannula was inserted through the femoral vein transseptally into the left atrium. Blood drained from the left atrium was ejected by a pulsatile pump into the femoral artery, thus, bypassing and completely unloading the left ventricle while maintaining systemic circulation. Coronary angiography and angioplasty were performed subsequently. Two pts lived for 2 days; both were alert until the time of expiration. One patient in cardiac standstill was maintained 4 hours with adequate systemic pressures on the pulsatile pump. LVEDP and wedge pressure decreased, systemic pressures were normalized and lactate levels decreased in all pts while on the pump. Conclusions: The LA-FA bypass can be inserted percutaneously. The pulsatile pump is effective in supporting the systemic circulation and unloading the left ventricle.

INCREASE IN MYOCARDIAL SALVAGE BY COMBINING CORONARY SINUS OCCLUSION AND RETROPERFUSION.

Alice K. Jacobs M.D., F.A.C.C., Paul Simon M.D., Victoria Hogfeldt, David P. Faxon M.D., F.A.C.C., Alyson Owen M.D., Thomas J. Ryan M.D., F.A.C.C. Boston University Medical Center, Boston, MA.

Both synchronized retroperfusion of arterial blood (SRP) and pressure-controlled intermittent coronary sinus occlusion (PICSO) are known to reduce experimental infarct size. To test whether their effects are additive, 49 open-chest anesthetized dogs were randomly assigned 30 min. after LAD occlusion to Group I (CONTROL, n=14), Group II (PICSO, n=14), Group III (SRP, n=8) or Group IV (PICSO+SRP, n=13). PICSO was achieved by the timed inflation of a balloon-tipped catheter (∿10 sec inflation, ∿4 sec deflation) and SRP by the retroperfusion of femoral artery blood into the coronary sinus in diastole. In group IV, PICSO was combined with SRP so that SRP was performed during each 10 sec balloon inflation. Infarct size was measured by triphenyltetrazolium chloride staining and risk region was determined by Rhodamine B perfusion after 6 hours.

Infarct size/risk region (%) (mean ± SE)

| CONTROL | PICSO | SRP | PICSO+SRP |
|---|---|---|---|
| 54.7±3.9 | 38.0±5.7* | 39.0±7.6* | 21.5±4.2** |

* p< 0.05 vs Group I

** p< 0.02 vs Group II + III, p< 0.001 vs Group I

In conclusion, both PICSO and SRP significantly reduced infarct size equally. Combining PICSO with SRP reduced infarct size more than either technique alone, salvaging approximately 80% of the region at risk. This enhanced salvage is likely due to improved delivery of oxygenated blood to the ischemic territory.

CARDIOPULMONARY BYPASS SUPPORTED CORONARY ANGIOPLASTY IN INOPERABLE PATIENTS

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Some pts with severe symptomatic coronary artery disease(CAD) are not surgical candidates. Of 48 pts who underwent PTCA using percutaneous cardiopulmonary bypass support(PCPS),12(ages 47-79 yrs) were felt to be inoperable because of poor LV function, only one target vessel supplying the remaining viable myocardium(M) and/or associated noncardiac diseases. 11 had prior myocardial infarction; 8 had prior coronary bypass surgery. Ejection fraction ranged from 11-35%(mean 26). All pts had critical 3 vessel CAD and one had left main CAD. In 6, the target artery was the only remaining vessel serving viable M. 8 pts had congestive heart failure. Noncardiac disease included severe chronic lung disease(4); renal failure(2); diabetes(3); history of sternal dehiscence(1) and bilateral carotid stenosis(4). 20F cannulae were placed in the femoral artery and vein and PCPS was initiated. Flow rates of 2.8-4.0 L/min(mean 3.5) were obtained. Pulmonary wedge pressures were 0-5 mm Hg. PTCA of all 22 lesions attempted were sucessfully dilated. PCPS was discontinued without incident in all pts. There were no deaths. Six pts required transfusion of 1 to 3 units(mean 1.8). Other complications: transient ischemic attack(1), deep venous thrombosis(1), cannula site infection(1) and femoral nerve weakness(1). Followup 1-3 months after discharge: 9 pts were asymptomatic, 1 pt had Class I and 1 had Class II angina. In conclusion: (1) PCPS makes PTCA feasible in pts in whom coronary bypass is not feasible and(2) PCPS can be performed safely in high risk patients. Further study of this extended application of PTCA is needed to clearly establish its role in the therapy of CAD.

**AN IN VITRO COMPARISON OF EXCIMER LASER AND AN ARGON LASER HEATED PROBE**

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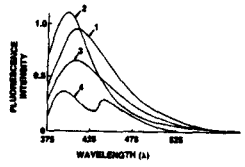
Recent studies have reported that excimer laser vaporization has a high degree of success in recanalizing complete occlusions in the femoral artery and that the incidence of arterial perforation may be less with the excimer laser than with a thermal probe. To understand the mechanism of action during recanalization of completely occluded human arteries, an in vitro study was performed with 19 arterial segments (2 to 10cm long). An Argon laser assisted thermal probe recanalized 3 segments but perforated 8 (73%) others. Histologic sections showed that the thermal probe was deflected by dense fibrocalcific plaque and dissected mechanically between the intima and media prior to perforation. An excimer laser with a 400 micron quartz fiber was pulsed at 20 Hz with 50 mj/mm$^2$ of energy. The excimer stimulated quartz fiber penetrated dense plaque in all 8 arterial segments, but perforated 4 (50%) due to deflection from calcified sections. In the arterial sections without calcification, the excimer laser cut cleanly through the intimal plaque without mechanical deflection or evidence of thermal damage on histologic section. In vitro excimer laser or thermal recanalization of dense fibrocalcific atheroma is associated with a high incidence of mechanical deflection of the delivery devices. Better guidance systems need to be developed to lower the risk of arterial perforation.

ENHANCED RECOGNITION OF PLAQUE COMPOSITION IN VIVO USING LASER-EXCITED FLUORESCENCE SPECTROSCOPY

Antonio L. Bartorelli M.D., Robert Bonner Ph.D., Yaron Almagor M.D., Richard Neville M.D., Charles McIntosh M.D., F.A.C.C., Julie Swain M.D., F.A.C.C., Martin B. Leon M.D., F.A.C.C. NHLBI, Bethesda, MD

Although we used laser-excited fluorescence spectra (FS) to successfully direct clinical laser ablation of plaque (P), recognition of P composition should improve the effectiveness of laser angioplasty. Using a nitrogen laser (337 nm @ 40μJ per pulse) for excitation and improved broadband optics, we obtained 708 FS from 177 sites, through a 200 μm optical fiber, in 25 patients (57±15 yrs.), 9 during catheterization and 16 in a bloodless field during cardiac surgery. Four highly distinct FS types were observed (see Figure): 1) normal (92 sites), 2) white fibrous plaque (34 sites), 3) yellow fatty plaque (39 sites) and 4) thrombus (15 sites). These in vivo data were compared to FS from normal and variable composition P necropsy specimens (100 sites). FS from normal aorta exhibited similar maximal intensity (.8 ± .3) and emission peaks (410 ±2 nm) whether in the cath lab, during surgery or in vitro. Compared with normal aorta, FS from normal coronaries showed similar peak position and shape, but reduced maximal intensity (.5±.3, p<.001). Tissue composition was reproducibly and accurately determined by FS shape and peak position, both in patients and in vitro for white P (peak @ 399±3nm), yellow P (peak@406±2nm) and thrombus (valley @ 431±1nm which corresponds to Hb absorption). **We conclude:** using this improved laser-excited FS system, that normal and variable composition P tissue sites manifest distinct FS patterns which are equivalent in clinical studies and in vitro. Importantly, the enhanced recognition of P composition by FS may permit ablation of specific targets (eg. thrombus in total occlusions) with optimized laser pulse energies, which should improve safety and efficacy of laser angioplasty.




rTPA VERSUS rTPA PLUS PTCA IN ACUTE MYOCARDIAL INFARCTION:
QUANTITATIVE RESULTS OF EARLY AND LATE CORONARY ARTERIOGRAPHY

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A prospective randomized study was carried out to assess whether an invasive strategy with i.v. rTPA, acetylic salicylic acid, heparin plus immediate angiography and PTCA (group 2) would be superior to a noninvasive treatment with thrombolysis alone (group 1). Coronary angiograms were obtained before and after PTCA in group 2 and 10-22 days after admission in both groups; for quantitative analysis of at least 2 views per patient and investigation, a computerized system with automatic edge detection, developed at the Thorax Center in Rotterdam, was used. Medians and 90% confidence intervals are given.
In group 2, acute angioplasty before and after PTCA revealed an improvement in diameter stenosis from 57.2 (36.4-73.1) to 38.3 (19.4-59.9)% and in obstruction diameter from 1.2 (0.8-1.9) to 1.8 (1.2-2.5) mm.
Results 10-22 days later:

| group | n | ana-lysable | diam. stenosis % | obstruct.diam. mm | plaque area $mm^2$ |
|---|---|---|---|---|---|
| 1 | 184 | 114 | 52.0(28.9-68.0) | 1.3 (0.9-2.2) | 5.8 (2.0-19.6) |
| 2 | 183 | 124 | 30.5(17.0-54.6) | 2.1 (1.3-2.8) | 3.9 (1.4-13.9) |

Conclusions: Immediate PTCA when combined with thrombolysis with rTPA is able to improve residual stenosis in the infarct related artery. The difference is still present prior to discharge 10-22 days after the acute intervention. However, this does not result in a better clinical course of these patients.

# Monday, March 20, 1989
# Poster Displayed: 2:00PM–5:00PM
# Author Present: 2:00PM–3:00PM
# Pacific Room, Anaheim Convention Center
# Balloon Valvuloplasty: Acute Hemodynamic Changes and Long Term Follow-up

BALLOON AORTIC VALVULOPLASTY: ACUTE AND CHRONIC ASSESSMENT OF LEFT VENTRICULAR HEMODYNAMICS AND PRESSURE-VOLUME RELATIONSHIPS.

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The acute and chronic changes in left ventricular (LV) performance have yet to be well defined after balloon aortic valvuloplasty (BAV). Sixty-five patients (pts) were studied before and immediately after BAV using dual sensor micromanometer catheters, digital ventriculography and aortography and Fick cardiac output. Twenty pts with similar acute changes returned for repeat catheterization at 6 ± 1.7 months (9 due to recurrent symptoms). Pressure-volume (PV) loops defined stroke work (SW).

| Results: | Pre-BAV | Post-BAV | FOLLOWUP |
|---|---|---|---|
| n = | 65 | 65 | 20 |
| LVEDP(mmHg) | 18 ± 8 | 14 ± 6[A] | 20 ± 9[B] |
| LVEDV(ml) | 148 ± 60 | 146 ± 59 | 112 ± 43[AB] |
| + dP/dt (max) | 1624 ± 452 | 1495 ± 473[A] | 1710 ± 479 |
| - dP/dt (max) | -1449 ± 427 | -1253 ± 442[A] | -1563 ± 373 |
| Mean Gradient (mmHg) | 59 ± 22 | 32 ± 11[A] | 51 ± 15[AB] |
| AVA ($cm^2$) | 0.5 ± 0.1 | 0.8 ± 0.2[A] | 0.6 ± 0.2[AB] |
| Ejection Fraction(%) | 47 ± 20 | 51 ± 19[A] | 52 ± 17 |
| SW (erg x $10^6$) | 16.0 ± 7.1 | 14.3 ± 5.7[A] | 12.2 ± 5.6[A] |
| C.O. (L/min) | 4.2 ± 1.0 | 4.0 ± 0.9 | 4.2 ± 1.2 |

A = p < 0.01 vs pre; B = p < 0.01 vs post

Initially, BAV results in complex hemodynamic changes with a shift in the PV loop to the left, a fall in both peak + and peak - dP/dt, a reduction in SW and an increase in the EF. At 6 months, despite restenosis, the PV loop shifts further to the left, and SW continues to decline, yet C.O. is preserved. This suggests ventricular remodelling has occurred that allows for maintenance of LV performance at a lower energy expenditure.

DIFFERENT IMMEDIATE AND LONG TERM OUTCOME AFTER PERCUTANEOUS BALLOON VALVULOPLASTY FOR SEVERE AORTIC STENOSIS, CONTINGENT UPON THE TYPE OF VALVE.

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From August 1985 to August 1988 Percutaneous Double Balloon Valvuloplasty (PDBV) was performed in 52 patients with severe aortic stenosis (A.S). In the overall group the transvalvular gradient (AVG) decreased from 81±34 mmHg. to 25±15 mmHg. (p<.0001) and the valve area (AVA) increased from .48±.16 cm.² to 1.14±.49 cm.² (p<.0005). Group I consisted of 34 calcific degenerative A.S, all older than 70 years of age in whom the AVG decreased from 80±36 mmHg. to 26±13 mmHg. (p<.001) and the AVA increased from .46±.14 cm.² to .89±.35 cm.² (p<.0001). Group II consisted of 13 congenital A.S younger than 35 years of age, in whom the AVG decreased from 85±30 mmHg. to 28±19 mmHg. (p<.001) with an increase in AVA from .51±.15 cm.² to 1.21±.64 cm.² (p<.01). Group III consisted of 5 rheumatic A.S, 4 younger than 35 years of age and 1 of 74 years old. The AVG in this last group decreased from 79±22 mmHg. to 14±9 mmHg. (p<.0001) and the AVA increased from .62±.17 cm.² to 2.36±.64 cm.² (p<.0001). There were 3 procedure related deaths, and all occurred in group I. At 3 years follow-up, in group I there were 2 deaths within 3 months of PDBV, 5 deaths within 1 year. One patient underwent repeat PDBV at 2 years. 7 have remained NYHA-FC I-II but the doppler AVG is the same as pre-dilatation in all but one. 3 have symptomatically (NYHA-FC III-IV) restenosed and refuse further intervention. 6 remain asymptomatic with doppler AVG under 45 mmHg. 7 were lost to follow-up. In group II, 4 underwent valve replacement (3 for restenosis and 1 for severe aortic regurgitation) within one year, 6 remain NYHA-FC I, 3 with doppler AVG under 25 mmHg. and 3 under 45 mmHg. 3 are lost to follow-up. In group III all remain NYHA-FC I, 4 with doppler AVG under 15 mmHg. and one patient had a doppler at 6 months but refused further studies. Therefore we conclude that: 1.- PDBV does not alter the outcome of degenerative aortic stenosis and should only be recommended to improve conditions for an immediate valve replacement. 2.- PDBV could be offered to young congenital A.S to gain time for a valve replacement. 3.- PDBV seems to be an effective procedure up to 2 years follow-up for rheumatic A.S, however longer follow-up is needed before the procedure can be offered as a first choice alternative.

## LEFT VENTRICULAR RELAXATION IN MITRAL STENOSIS BEFORE AND AFTER VALVULOPLASTY.

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Left ventricular (LV) relaxation was analyzed in 11 patients (pts) in sinus rhythm with mitral stenosis. The 6 pts with normal end- diastolic (ED) volumes (91±15 ml/m²; Group A) had normal LV end-diastolic pressure and time-constant T of isovolumic pressure fall (8±4 mmHg and 40±4 ms, respectively). In contrast, 5 pts (Group B) had increased end-diastolic volumes (137±11* ml/m²), increased LV end-diastolic pressure (17±4* mmHg) and prolonged T (72±21* ms) when compared to normal subjects or to group A. They also had slightly reduced ejection fractions (64±10 vs 70±9% in groupe A; NS). No correlation was found between impaired relaxation and mitral valve area. After balloon valvuloplasty, mitral valve area increased from 0.8 to 1.6* cm² and valvular gradient dropped in all pts. Heart rate was lower at the end of the procedure (91 to 83* bpm) but no significant changes in LV end-diastolic pressure, (dP/dt)Max, (dP/dt)Min or T were noted in group A or B. Thus, LV diastolic function is abnormal in a large subset of pts with mitral stenosis and this appears related more to myocardial factors than to the degree of stenosis. Such abnormalities may impair LV function during atrial fibrillation and exercise or limit the functional benefit after dilatation. *P<0.05 Group A vs B

## PERCUTANEOUS MITRAL VALVULOPLASTY IN PATIENTS WITH PREVIOUS SURGICAL COMMISSUROTOMY.

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Fibrous lesions and calcifications of mitral valve and chordae tendinae are often extensive in patients with recurrent mitral stenosis after surgical commissurotomy. In order to assess whether percutaneous mitral valvuloplasty (PMV) may be a valuable alternative to mitral valve replacement in such patients we compared among 70 patients submitted to PMV the results of those with previous surgical commissurotomy (group A = 15 patients) to those without (group B = 55 patients). On average, group A patients were significantly older (61±11 vs 50±82 $P < 0.05$), had more severe mitral stenosis and more severe cardiac enlargement than group B patients.

| | MVA group A | MVA group B |
|---|---|---|
| PrePAV | 0.79±0.33 | 1.04±0.34** |
| PostPAV | 1.67±0.40* | 2.08±0.35* & ** |

* $P < 0.05$ between pre and post PAV values
** $P < 0.05$ between group A and group B

Mitral regurgitation (MR) worsening was more frequent in group A pts (4 out of 15) than in group B pts (4 out of 55 pts). Full commissural opening was less frequent in group A than in group B pts. Mitral valve area (MVA) remained below 1.5 cm² in 3 group A pts and 5 group B pts. Functionnal improvement of at least 1 functionnal class ocurred in 9 out of 15 group A pts.

These results demonstrate that PMV is feasible in patients with recurrent mitral stenosis after closed heart commissurotomy but produces less favorable results than in patients without previous surgical commissurotomy.

## FEATURES OF SEVERE MITRAL REGURGITATION FOLLOWING PERCUTANEOUS BALLOON COMMISSUROTOMY.

Alec Vahanian MD, Pierre-Louis Michel MD, Xavier Michel MD Eric Dadez MD, Bernard Vitoux MD, Jean Guérinon MD, Christian Cabrol MD, Jean Acar MD, Tenon Hospital, Paris, France.

The characteristics of severe mitral regurgitation (MR) following percutaneous commissurotomy (PC) were reviewed from a series of 250 PC, in which 9 severe MR, angiographic grade 3+/4 (Sellers criteria), occurred after the procedure.
Six patients (pts) were female and 3 male, their mean age was 48 ± 13 yrs (22 - 64); 2 pts had had previous surgical commissurotomy, all were in NYHA Class III and mitral calcifications were present in 4 (valvular 1, commissural 3). Echocardiographic examination showed extensive subvalvular disease in all 9 and valve thickening in 6. Mitral regurgitation was present in 6 : angiographic grade 1+ in 5, 2+ in 1. PC was performed using 1 balloon in 2 pts and 2 balloons in 7.
Two patients were subsequently not operated on : one improved to NYHA Class II while the degree of MR decreased to 2+ on repeated catheterization 3 months later, while in the other, who remained in Class III, surgery was contra-indicated because of cancer. Surgery was carried out in the remaining seven, 29 ± 15 days (10 - 50) after PC due to persistent or increased functional disability. The intra-operative findings confirmed the echo predictions in all as regards the extent of valvular impairment. MR was related to para-commissural tearing of the posterior leaflet in 6 out of 7 and to rupture of chordae in the seventh. Complete commissural splitting was only observed in this last case. Valve replacement was performed in 6 and repair in 1 with moderate residual MR. No further complication occurred.
Conclusions : 1. Severe post PC mitral regurgitation though infrequent (4%) may occur in cases of unfavourable anatomy 2. Valvular tearing is the major mechanism 3. Delayed surgery appears necessary in most cases.

## EARLY AND LONGTERM RESULTS AFTER MITRAL VALVULOPLASTY AS COMPARED WITH OPEN COMMISSUROTOMY

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To compare the results of successful valvuloplasty (VP) with those of open commissurotomy (COM) for severe mitral stenosis, studies were performed in 52 pats with pre-existing valve orifice area <1.0qcm/qm (1.1±0.4qcm prior to VP and 1.1±0.3 qcm prior to COM). Before, 1 week (W) and 1/2 year(Y) after VP as well as before, 2-3 W and 1/2 Y after COM resting (R) and exercise (EX) hemodynamics as well as $O_2$-saturation in the pulmonary artery (PA) were determined. Newly incurred regurgitation or increase were assessed after VP with angiography and after COM by auscultation and Doppler echo; the incidence was 33% in VP and 42% in COM pats.

| | PAPm (mmHg) | | SV (ml) | | PA-$O_2$ (sat%) | | HR (b/min) | |
|---|---|---|---|---|---|---|---|---|
| | R | Ex | R | Ex | R | Ex | R | Ex |
| pre VP | 30 | 63 | 57 | 54 | 61 | 37 | 72 | 128 |
| post VP(1 w) | 23 | 51 | 67 | 67 | 64 | 41 | 69 | 126 |
| post VP(1/2 y) | 22 | 51 | 64 | 64 | 66 | 40 | 65 | 126 |
| pre COM | 26 | 62 | 67 | 65 | 66 | 42 | 75 | 132 |
| post COM(2-3 w) | 20 | 46 | 65 | 76 | 67 | 41 | 81 | 122 |
| post COM(1/2 y) | 17 | 42 | 66 | 76 | 67 | 40 | 75 | 120 |
| p values | | | | | | | | |
| pre VP vs COM | ns | ns | .05 | .05 | .005 | .005 | ns | ns |
| postVPvsCOM(1/2-3w) | ns | ns | ns | ns | ns | ns | .005 | ns |
| postVPvsCOM(1/2y) | .005 | .005 | ns | ns | ns | ns | .01 | ns |

Thus, early after VP the hemodynamic results achieved are comparable with those of COM. 1/2 Y after the respective interventions, there are clearly more markedly pathologic changes in PA pressure after VP than COM such that after VP longterm results appear less favorable.

RESPONSE OF ATRIAL NATRIURETIC FACTOR TO PERCUTANEOUS MITRAL VALVULOPLASTY.

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In 23 pts undergoing percutaneous mitral valvuloplasty (PMV), atrial natriuretic factor (ANF) levels in femoral vein, pulmonary artery and aorta were simultaneously measured at baseline, 1 min after the first inflation and 20 min after the last inflation. ANF was also measured in a peripheral vein 1 day before and 3, 24 and 48 hrs after PMV.

| ANF (pg/ml) | Basal | First Inflation | Last Inflation |
|---|---|---|---|
| Femoral vein | 78±9 | 112±10* | 107±12* |
| Pul. artery | 116±11 | 164±13*** | 152±13** |
| Aorta | 108±12 | 168±14*** | 152±14** |

*p=.05, **p<.01, ***p<.001 vs basal values

In 9 pts in whom pulmonary artery samples were obtained 1 min before the first inflation, ANF levels had already increased (148±19 to 201±32 pg/ml, p<.001) with no further increase after the first inflation (217±18 pg/ml, p=NS). Peripheral ANF levels returned to baseline 3 hrs after the procedure (87±10 vs 84±10 pg/ml, p=NS), with no subsequent change: 93±10 at 24 hrs and 92±10 pg/ml at 48 hrs (p=NS). In 9 pts restudied 6 months after PMV, hemodynamic improvement persisted but ANF levels in femoral vein, pulmonary artery and aorta remained elevated.

Thus, during PMV technical manoeuvres before balloon inflation transiently increase ANF. Despite a decrease in intracardiac pressures ANF levels remain abnormal up to 6 months post-PMV.

THE CLINICAL VALUE OF MEASURING ATRIONATRIURETIC FACTOR AFTER BALLOON AORTIC VALVULOPLASTY

Warren Sherman MD, FACC, Charles Lazzam MD, Howard B. Eison MD, Matthew Schwinger MD, Ronnie Hershman MD, Lawrence Krakoff MD, FACC, Mount Sinai Hospital, New York, NY.

We measured atrionatriuretic factor (ANF) and hemodynamics (right heart pressures and flow) before (pre) and after (at 1/4, 1, 4 and 12-24 hr) balloon aortic valvuloplasty (BAV) in 16 pts (age 81±8, mean±SD) with aortic stenosis (AS). Pre- to post-BAV changes included: mean aortic gradient 46±20 to 24±15 mm Hg (p<0.001) and valve area 0.5±0.1 to 0.7± cm$^2$ (p<0.001).

ANF (pg/ml; mean±SD) decreased over time: pre= 345±244, 1/4 hr= 331±200, 1 hr= 276±159, 4 hr= 242±112 and 12-24 hr= 278±191 (normal= 37±7). These changes were not significant by paired analysis. While ANF was weakly correlated with baseline right atrial pressure (p=0.06, r=0.53), neither ANF nor the %change in ANF (%dANF= change in ANF/baseling ANF) correlated with any pre- or post-BAV hemodynamic variable.

%dANF at 24 hrs strongly correlated with adverse clinical outcome (return or persistence of symptoms) at 2 (p<0.005), 8 (p<0.05) and 26 (p<0.05) weeks. A %dANF at 24 hrs of >10% (increase in ANF) identified all patients who remained symptomatic at 2 weeks, 75% of those symptomatic at 8 weeks and all patients symptomatic at 26 weeks.

CONCLUSION: The very high levels of ANF in pts with AS tend to decline following BAV. A rise in ANF of > 10% after BAV is a strong predictor of poor early clinical outcome.

REGRESSION OF INFUNDIBULAR PULMONARY STENOSIS AFTER SUCCESSFUL BALLOON PULMONARY VALVULOPLASTY IN ADULTS.

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Between July 1985 and March 1988, 22 consecutive adult patients with congenital pulmonary stenosis underwent pulmonary balloon valvuloplasty (PBV). There were 10 males and 12 females, age 15-45 (mean 25) years. A double balloon technique was used in 17 patients and single balloon in 5. Fifteen paients were studied 6-30 (mean 9) months later. Student's t test was used for comparison of data. Results RV systolic pressure before dilatation was 84-200 (mean 127 ± 33.4) mmHg and the peak pulmonary gradient (PPG) was 60-176 (mean 110 ± 34.2) mmHg. Immediately after dilatation the RV systolic pressure dropped to 32 to 110 (mean 56 ± 18) mmHg ($P < 0.001$) and PPG dropped to 10-80 (mean 34.5 ± 17.3) mmHg ($P < 0.001$). At repeat catheterization the RV systolic pressure dropped to 33-66 (mean 45.5 ± 11.6) mmHg ($P < 0.05$) and PPG dropped to 0 to 48 (mean 22 ± 13.5) mmHg ($P < 0.001$). The infundibular gradient ranged from 14-80 (mean 35.6 ± 16.7) mmHg before PBV. This regressed at repeat catheterization to 0 to 25 (mean 15 ± 6.4) $P < .05$. Conclusion. (1) PBV is safe, effective and long lasting for the treatment of pulmonary valve stenosis in adults, (2) severe to moderate infundibular stenosis regresses after successful pulmonary valvuloplasty in adults.

## Monday, March 20, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 3:00PM–4:00PM
## Pacific Room, Anaheim Convention Center
## Cardiovascular Changes with Aging

AGE-RELATED CHANGES IN LEFT VENTRICULAR PERFORMANCE DURING ISOMETRIC EXERCISE

Christian J. Swinne, M.D., Jerome L. Fleg, M.D., F.A.C.C., Joao A.C. Lima, M.D., Sandra D. Lima, Edward P. Shapiro, M.D., F.A.C.C. Francis Scott Key Medical Center, A Johns Hopkins Medical Institution, Gerontology Research Center, NIA, Baltimore, MD

Whether advancing age alters left ventricular (LV) performance during isometric exercise is unknown. We performed echo-Doppler during isometric handgrip (IHG), at 30% of maximum strength for 3 min in 25 healthy, normotensive volunteers ages 23-84 from the Baltimore Longitudinal Study of Aging. At rest, systolic blood pressure (SBP), and LV end diastolic dimension (EDD) were unrelated to age, end systolic dimension (ESD) decreased with age (r=-.40, p<.05) and fractional shortening (FS) increased with age (r=.49, p=.01). The Doppler diastolic filling ratio (A/E) and planimetric atrial filling fraction (AFF) were both correlated with age at rest (r= .92, p<.0001 and r=.89, p<.0001 respectively). IHG induced the following age-related changes from baseline:

| Parameters | Age Regression Slope | r | p |
|---|---|---|---|
| SBP (mmHg) | .46 | .53 | .008 |
| ESD (mm) | .013 | .50 | .01 |
| EDD (mm) | .009 | .59 | .002 |
| FS | -.002 | -.42 | .04 |
| AFF (%) | .072 | .48 | .014 |

Thus, with advancing age IHG induces an exaggerated rise in afterload, associated with diminished systolic performance, mild LV dilatation and a greater dependence on the already augmented atrial contribution to LV filling.

**IMPROVEMENT OF RELAXATION VELOCITY BY CALCIUM BLOCKER IN AGING RABBIT MYOCARDIUM**

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Aging is associated with a reduction in the diastolic function of the heart. Because calcium channel blockers have been reported to improve diastolic function, we studied the effect of two calcium blockers (nisoldipine and nifedipine) on the diastolic performance of isolated perfused ventricular septa from 5 young (age 1-1 1/2 years) and 6 old (3-4 years) rabbits. Septa were perfused at 3 ml/min with oxygenated Ringers and paced at 48 beats/min. Maximum relaxation velocity (-dT/dt) and time of relaxation ($t_R$) were measured before and during drugs. At baseline, -dT/dt was reduced and $t_R$ lengthened by 20% in old compared to young rabbits ($p<0.05$). When either Calcium blocker was introduced into the perfusate at high doses ($>10^{-8}$M), all systolic and diastolic parameters were depressed. However, at lower doses of nifedipine ($10^{-10}$M) and nisoldipine ($10^{-9}$M), $t_R$ shortened by 20% and -dT/dt increased by 20% ($p<0.01$) in old but was unchanged in young rabbits. As a result of this differential effect, $t_R$ and -dt/dt were similar in old and young rabbits at these lower drug doses. Systolic parameters such as max tension (T), time to max tension (tm) and contraction velocity (+dT/dt) were not changed by these lower drug doses in either age group. These beneficial concentrations of the drugs are within or below the therapeutic range of $5x10^{-9}$ to $4x10^{-8}$M of plasma free drug. These data suggest that calcium blockers could potentially improve relaxation in the aging myocardium at therapeutic doses.

DOES AGE MODIFY THE HEMODYNAMIC AND CLINICAL RESPONSE TO CONVERTING-ENZYME INHIBITORS IN PATIENTS WITH CHRONIC HEART FAILURE? David J. Pinsky MD, Marrick L. Kukin MD, Milton Packer MD, FACC. Mount Sinai School of Medicine, New York, NY

Elderly pts show a diminished therapeutic response to converting-enzyme inhibitors (CEI) when these drugs are used in the treatment of hypertension, but it is unknown whether age modifies the effects of CEI in pts with heart failure (CHF). We measured cardiac index (l/min/m²), mean arterial, pulmonary wedge and right atrial pressures (MAP, PWP & RA, mm Hg), heart rate (HR, bpm), systemic vascular resistance (SVR, d-s-c), blood urea nitrogen (BUN, mg/dl) and serum creatinine (Cr, mg/dl) in 104 CHF pts before (pre) and after treatment with captopril or enalapril for 1-3 months. Pts were grouped according to their median age (65 yrs); * = $p<.05$ (pre vs CEI)

| | | CI | MAP | PWP | RA | HR | SVR | BUN | Cr |
|---|---|---|---|---|---|---|---|---|---|
| <65 | Pre | 1.7 | 84 | 26 | 12 | 87 | 2012 | 35 | 1.5 |
| (n=51) | CEI | 2.0* | 68* | 16* | 8* | 78* | 1441* | 44* | 1.6* |
| ≥65 | Pre | 1.8 | 84 | 27 | 11 | 80 | 2035 | 47 | 1.9 |
| (n=53) | CEI | 2.0* | 67* | 16* | 6* | 74* | 1518* | 60* | 2.1* |

Pretreatment hemodynamic variables in elderly pts were similar to younger pts. Although PRA was slightly lower in elderly pts (4.9 vs 6.7 ng/ml/hr), both groups showed similar hemodynamic responses to CEI after 1-3 months. Thirty-four of the 51 pts (67%) <65 years and 32 of the 53 pts (60%) ≥65 years improved clinically after 1-3 months of CEI, p=NS.

Although elderly pts had worse renal function before CEI than younger pts ($p<.05$), the ↑ in BUN and Cr following CEI in both groups was similar. A similar fraction of pts <65 yrs (12 of 51 pts) and ≥65 yrs (20 of 53 pts) had worsening azotemia during CEI. Elderly pts were less likely than younger pts to experience early symptomatic hypotension (9% vs 20%), p=NS.

In conclusion, in contrast to hypertensive pts, age does not ↓ the benefits or ↑ the risks of CEI in pts with CHF. CEI should not be avoided in elderly CHF pts who require these drugs.

AGING-RELATED DECREASE IN VASODILATORY CAPACITY IN CORONARY MICROCIRCULATION ESTIMATED BY CORONARY DOPPLER CATHETER

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Coronary flow reserve in patients with effort angina was demonstrated not necessarily to coincide with coronary stenosis. There may be great difference in the reserve capacity in coronary microcirculation level in each individual. To estimate the effect of aging on reserve capacity for vasodilation in coronary microcirculation, 30 patients without epicardial coronary lesion in the left coronary artery were studied. Peak coronary flow velocity during maximal vasodilation by intracoronary papaverine was measured by coronary Doppler catheter, and reserve capacity was calculated as the quotient of the peak coronary flow velocity and the resting coronary flow velocity. The Doppler catheter was located in the proximal left coronary arteries. The patients with hypertrophic heart and/or left ventricular asynergy as well as the patients with diabetes mellitus were excluded in this study. The average age of the patients was 60±10 (mean±SD), ranged from 33 to 78 years. And the average of reserve capacity for vasodilation in these patients was 3.6±1.2, ranged from 2.2 to 8.0. The vasodilatory reserve were less in the elder patients than in the younger, revealing a significant correlation between the vasodilatory reserve and the age ($r=0.68$). Thus, these results suggest that the vasodilatory capacity in coronary microcirculation are decreased with age.

SITE OF AGE-RELATED PR INTERVAL PROLONGATION IN NORMAL SUBJECTS.

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The mechanism for the PR interval prolongation seen with aging is unclear. Using a high resolution ECG (Marquette MAC-I) to signal average 512 cardiac cycles, we recorded His bundle potentials from the body surface of 50 young ($\bar{x}$ = 30 yr) and 64 old ($\bar{x}$ = 72 yr) healthy volunteers from the Baltimore Longitudinal Study of Aging. All subjects were free of clinical heart disease and had normal rest and exercise ECG and a PR interval ≤ 210 msec. The following intervals in msec were measured or derived: PR (PR), P wave duration (P), HV (HV), PR - HV (PH), and PH - P (Prox PR) segment. Values are mean ± S.D.

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Young (n=25) | Old (n=25) | p | Young (n=27) | Old (n=37) | p |
| PR | 159±16 | 175±22 | .01 | 156±17 | 165±15 | .05 |
| PH | 121±13 | 136±18 | .01 | 117±16 | 127±15 | .02 |
| Prox PR | 22±11 | 33±15 | .01 | 24±12 | 30±15 | .07 |
| HV | 38± 6 | 40± 9 | NS | 40± 6 | 39± 9 | NS |

Neither heart rate nor P were age-related in either sex. In a separate group of 7 older men ($\bar{x}$ = 71 yr) with PR ≥ 220 msec ($\bar{x}$ = 238 ± 14), the PH (193 ± 21) and Prox PR (82 ± 19) but not HV (45 ± 11) were longer ($p<.001$) than in the 25 old men with normal PR. Thus, a modest and similar age-related prolongation of PR interval is found in both sexes, and is localized to the Prox PR segment, probably reflecting delay within the atrioventricular junction. A similar but more striking delay in the Prox PR segment is present in older men with first degree heart block.

## Monday, March 20, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 4:00PM–5:00PM
## Pacific Room, Anaheim Convention Center
## Coronary Angioplasty Technique I

### PATTERNS OF DILATATION DURING CORONARY ANGIOPLASTY

Craig Monsen, MD, John A. Ambrose, MD,FACC, Susan Borrico, BS, Marc Cohen, MD,FACC, Warren Sherman, MD,FACC, Richard Gorlin, MD,FACC,Valentin Fuster, MD,FACC, Mount Sinai Hospital, New York, NY.

There are little in-vivo data concerning the mechanisms of balloon inflation during angioplasty (TCA). To characterize how lesions dilate we used videodensitometry to measure the diameter (D) of the inflated balloon across 27 coronary lesions in 25 patients. Pressure-diameter (P-D) curves for each lesion were derived utilizing a standardized incremental inflation protocol between 2 and 6 BAR with 3mm low profile balloons that approximated normal vessel D. D of coronary stenoses pre and post TCA were also measured.

P-D curves showed that the most improvement in lumen caliber occurred at low inflation P. A distensibility factor (dis) defined as the ratio of D at 2 BAR compared to D at 6 BAR showed that eccentric-irregular lesions (n=11) had greater dis (.49±.17) than lesions (n=16) without this morphology (.33±.14) p<.02. The former were soft presumably due to thrombus in these lesions. Also P-D curves often showed a loss of lumen calibre when balloon D at 6 BAR was compared to D post TCA. This was defined as elasticity or recoil and we found a significant direct correlation between the amount of elasticity and the extent of balloon inflation at 6 BAR. That is, lesions more fully dilated at 6 BAR showed more elasticity. This relationship was most striking for eccentric irregular lesions (r=0.8,p<.001) and was unchanged by nitroglyerine. Thus, P-D curves analyzing distensibility and elasticity provide information about mechanisms of TCA that probably reflect lesion composition and geometry. This approach may have clinical relevance.

### DOES BALLOON INFLATION DURATION INFLUENCE THE ANGIOGRAPHIC RESULT OF CORONARY ANGIOPLASTY?

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The importance of the duration of balloon inflation during coronary angioplasty (CA) is undefined. We performed a randomized trial comparing 30 second (Gp1) with 60 second (Gp2) inflations in 165 patients, with 224 lesions. The study required up to 3 inflations at the randomized duration with angiographic assessment prior to alteration of inflation duration. Chest pain (duration and severity) and ST alteration was noted. Stenosis severity was measured with digital calipers from orthogonal views. Lesion and vessel characteristics were documented. Results: Gp1 comprised 107 lesions, Gp2 117. There was no significant difference between the two groups in pre-CA angiographic variables, number of protocol inflations (2.8vs2.7 p=NS), residual post-protocol stenosis (35%vs34% p=NS), total number of inflations (3.4vs3.1 p=NS), final residual stenosis (34%vs33% p=NS), incidence of dissection (14%vs18% p=NS), side branch occlusion, or vessel appearance post-CA. Total inflation time was significantly less in Gp1 (123vs184 seconds p<.001) as was pain duration (105vs203 secs p<.05) and average ST alteration (74vs135 secs p<.001). 49 lesions received additional inflations (mean 2.2) following protocol for a mean stenosis improvement of 6.8%. Only 7 of 13 with a post-protocol stenosis >50% improved to a stenosis <50% with additional inflations. Conclusions: 1. There is no difference in the acute angiographic result of 30 as opposed to 60 second inflations 2. Short inflations are much better tolerated 3. The improvement provided by inflations in excess of the initial 4 is usually minimal.

### SINGLE VERSUS MULTIPLE BALLOON INFLATIONS IN CORONARY ANGIOPLASTY: LATE ANGIOGRAPHIC RESULTS AND RECURRENCE

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A prospective study was carried out to assess wether multiple in comparison to single balloon inflations during the same PTCA-procedure could decrease recurrence rate. In 300 consecutive patients (pts., 258 m, 42f, 45±8 yrs.) 325 PTCA-procedures randomly were assigned to either a single balloon inflation (infl., gr.A) or 3 infl. (gr.B). In 97 pts of gr.A and 47 pts. in gr.B the initial randomization could not be maintained because of a residual stenosis > 50%, a pressure gradient remaining > 15 mm of mercury, or because a complication occured. Initial success rate was slightly higher in group B (94 vs. 88%, p < .05) and complication rate was comparable in both groups. In 272/325 PTCA-cases (80,4%), an angiographic follow-up 6 months after the procedure is available; recurrence rate was analysed according to the definition of the NHLBI.

| | no. of inflations random. | no. of inflations final | PTCA n | Control n | recurrence n | recurrence % |
|---|---|---|---|---|---|---|
| | 1 | 0 | 2 | 0 | 0 | -- |
| A | 1 | 1 | 70 | 61 | 9 | 14,7 |
| | 1 | >1 | 95 | 79 | 27 | 34,2 |
| | 3 | <3 | 19 | 14 | 2 | 14,3 |
| B | 3 | 3 | 111 | 94 | 29 | 30,8 |
| | 3 | >3 | 28 | 24 | 8 | 33,3 |
| Σ: A | | | 167 | 140 | 36 | 25,7 |
| Σ: B | | | 158 | 132 | 39 | 29,5 |
| Σ: A+B | | | 325 | 272 | 75 | 27,6 |

Conclusion: Multiple inflations cannot be recommended in general, because recurrence rate even tended to be higher with this approach.

### ACUTE THROMBOTIC REOCCLUSION AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY - SHOULD THROMBOLYSIS BE ATTEMPTED?

Dietrich C. Gulba, M.D., M.Sc.; Rüdiger Simon, M.D.; Werner G. Daniel, M.D.; Gert-H. Reil, M.D.; Monika Barthels, M.D.; Paul R. Lichtlen, M.D., F.A.C.C. Hannover Medical School, Hannover, FRG

One major complication of percutaneous transluminal coronary angioplasty (PTCA) is thrombotic occlusion of the vessel. In a series of 447 pts undergoing PTCA from february 1987 to july 1988, 27 experienced acute thrombotic occlusion (6%) and underwent thrombolysis with either rt-PA (14) or a combination of urokinase and pro-urokinase (13). Primary restoration of antegrade blood flow could be achieved in 22 pts (81%), however, control angiography 24h later in 12 pts revealed reocclusion (54.5%). Only 37% of all patients undergoing thrombolysis had an persitant open vessel. Thrombin-antithrombin III complex (TAT) levels were measured in 21 pts (7 with persistant open vessel/group A; 14 with reocclusion (10) or non reopening (4)/group B).
Results: TAT µg/l

| group | n | 0 | 60 | 120 min | sign. |
|---|---|---|---|---|---|
| A | 7 | 8.5 ± 11.4 | 6.4 ± 3.6 | 3.5 ± 1.5 | n.s. |
| B | 14 | 5.5 ± 2.8 | 14.0 ± 14.7 | 15.4 ± 13.8 | p< 0.05 |

Both groups were separated by the value of > 6 µg/l (sensitivity 100%, specifity 92.8%, p < 0.01). We conclude that in the majority of cases only temporary patency can be achieved by TT after PTCA. This is due to strongly increased thrombin release in patients experiencing reocclusion. TAT levels > 6 µg/l specifically predict reocclusion, therefore patients with TAT > 6 µg/l 2h after TT after PTCA should undergo emergency bypass grafting.

**INTRAVENOUS NITROGLYCERIN PREVENTS CORONARY ARTERY VASOCONSTRICTION AFTER PTCA**

Tim A. Fischell, Geraldine Derby, TM Tse, Michael L. Stadius, FACC, Stanford University Medical Center, Stanford, CA.

It has recently been observed that spontaneous coronary artery vasoconstriction occurs routinely in the dilated coronary artery segment after PTCA, despite the use of aspirin and calcium channel blockers. To determine whether or not this vasoconstriction could be prevented by intravenous (IV) nitroglycerin (NTG) given during and after PTCA we analyzed the spontaneous, and then intracoronary (IC) NTG induced changes in segmental coronary artery diameters following PTCA in patients randomly assigned to receive (+IV NTG, n=5) or not receive (- IV NTG, n=10) IV NTG. Exclusion criteria included concurrent NTG therapy, IC NTG during the PTCA, and inadequate coronary arteriography. All 15 patients were maintained on diltiazem and aspirin at the time of the study. Coronary arteriograms were obtained as follows; 1) pre-PTCA (Pre), 2) < 5 minutes after PTCA (Post), 3) 30 minutes after PTCA (30 min), 4) and then, 3 minutes after 300 μg of IC NTG (IC NTG). Serial quantitative measurements were performed at each time, in 5 mm long segments centered in the dilated segment (PTCA), and in a nonmanipulated vessel (Control). The diameters after IC NTG were defined as the maximally vasodilated state. The minimal diameter (mean, in mm) for the PTCA segment at each time is shown below for the - and + IV NTG groups; (SE) = standard error of the mean. The % vasoconstriction, vs. IC NTG diameter is shown to right (%).

| | Pre (SE) | % | Post (SE) | % | 30 min (SE) | % | IC NTG (SE) | % |
|---|---|---|---|---|---|---|---|---|
| - IV NTG | .79 .08 | - | 1.73 .16 | -3 | 1.12 .11 | 33 | 1.68 .27 | 0 |
| + IV NTG | .83 .24 | - | 1.78 .10 | 0 | 1.61 .17 | 6 | 1.79 .21 | 0 |

Significant vasoconstriction (vs.IC NTG) was seen in the PTCA segment in the - IV NTG group ($p< 0.01$) but not in the + IV NTG patients at 30 min after PTCA. The difference in % vasoconstriction between the - and + IV NTG groups at 30 minutes was significant ($p<0.01$, t-test).

**Conclusions**:1) Spontaneous post-PTCA coronary artery vasoconstriction at the site of dilatation can be prevented by the administration of IV NTG during and after PTCA. 2) These findings have implications concerning the prophylaxis of abrupt vessel closure following PTCA.

IDENTIFICATION OF ACUTE EXPERIMENTAL LEFT VENTRICULAR THROMBI USING A REAL-TIME BACKSCATTER IMAGING SYSTEM

Byron F. Vandenberg, MD, FACC, Hewlett E. Melton, Jr, PhD, Robert A. Kieso, MS, Karen Fox-Eastham, BLS, Richard E. Kerber, MD, FACC, Steve M. Collins, PhD, David J. Skorton, MD, FACC, Univ. of Iowa, Iowa City, IA

2D echo is an excellent technique for detecting LV mural thrombi (LVT) but LVT may be difficult to differentiate from extraneous echoes. We have previously demonstrated that acute LVT can be distinguished from surrounding blood and myocardium by off-line computer analysis of ultrasound gray level statistics. Our purpose was to study acute LVT with a recently developed real-time integrated backscatter (IBS) imaging system which provides on-line, immediate analysis of IBS. Transthoracic imaging was performed in 7 dogs in the presence of LVT produced by injecting thrombin into the LV apex after coronary occlusion. IBS was measured in the cavity (blood), LVT and myocardium (apex). RESULTS (mean±SD): Data are expressed in relative units (dB). ED=end-diastole, Δ=diastolic-systolic IBS.

| | Cavity (blood) | LVT | Myocardium (apex) |
|---|---|---|---|
| ED: | 0.8±0.2 | 16.9±3.4+ | 13.2±1.5* |
| Δ: | -0.5±1.1 | -0.6±1.8 | 0.6±1.3 |

+p<0.05 vs blood and myocardium
*p<0.05 vs blood and LVT.

CONCLUSION: Acute LV thrombus is characterized by: (1) an increase in backscatter compared to blood and ischemic tissue, and (2) no cyclic backscatter variability. This approach may provide a method for rapid, objective identification of LV thrombi.

## Monday, March 20, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 2:00PM–3:00PM
## Pacific Room, Anaheim Convention Center
## Echo Doppler: General III

DIASTOLIC ABNORMALITIES IN HYPERTENSION ARE NOT EXPLAINED BY LVH ALONE.

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Hypertension (HTN) and aging are both associated with abnormalities of LV diastolic filling (DF) and increased LV mass index (LVMI). To determine whether DF abnormalties in HTN are due to aging, LV hypertrophy or other factors, we studied 19 HTN patients following 4 weeks off therapy and 18 normotensives (NLS) matched for age and LVMI. All subjects had normal systolic function by echo and ejection fraction by radionuclide angiography. We measured: peak velocity of early filling (E), late filling (A) and their ratio (E/A) using pulsed Doppler echocardiography.

| | NLS (n=18) | HTN (n=19) |
|---|---|---|
| LVMI ($g/m^2$) | 112±20 | 119±22 |
| SBP/DBP (mmHg) | 126±12/79±6 | 150±11*/101±4* |
| E (m/s) | 0.96 ± 0.30 | 0.87 ± 0.20 |
| A (m/s) | 0.72 ± 0.18 | 0.91 ± 0.20* |
| E/A | 1.44 ± 0.64 | 1.00 ± 0.20* |

(* = p<.01 vs NLS)

Diastolic filling indices were significantly different in HTN compared to NLS. None of DF indices were related to LVMI. E/A was inversely related to age in both NLS ($r=-0.75$) and HTN ($r=0.-55$, both $p<0.01$). A was related to systolic BP ( $r=0.48$, $p<0.05$) only in HTN. These findings indicate that DF abnormalities in HTN are not solely caused by either LVMI or older age and therefore must be in part related to altered myocardial or chamber properties.

GRADUAL INCREASE IN LEFT VENTRICULAR DIMENSION WITH DECREASE IN PRESSURE HALF-TIME OF TRANSMITRAL FLOW FOLLOWING BALLOON MITRAL VALVULOPLASTY.

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National Cardiovascular Center, Suita, Osaka, Japan.

To investigate the serial changes in cardiac dimension and pressure half-time (PHT) of transmitral flow following balloon mitral valvuloplasty (BMV), we measured mitral valve area (MVA), left atrial (LAD), left ventricular diastolic (LVDd) and systolic dimensions (LVDs) by two dimensional and M-mode echocardiography. PHT was determined by continuous wave Doppler technique. These examinations were performed pre- and post-BMV in 12 patients with mitral stenosis.
Results: Values are mean±S.D.

| | pre | post-2hrs | -10hrs | -24hrs | -7days |
|---|---|---|---|---|---|
| MVA($cm^2$) | 1.1±0.5 | 1.9±0.6* | 1.9±0.5 | 1.9±0.5 | 1.9±0.5 |
| LAD(mm) | 52±7 | 47±7* | 46±7 | 46±7 | 46±7 |
| LVDd(mm) | 50±4 | 50±4 | 51±4# | 53±4## | 53±4## |
| LVDs(mm) | 35±4 | 34±4 | 34±4 | 35±4 | 35±5 |
| PHT(msec) | 290±80 | 190±50* | 160±60## | 150±50## | 150±50## |

*=p<0.01 vs pre. #=p<0.05 and ##=p<0.01 vs post-2hrs.
BMV decreased PHT and LAD at post-2hrs. Although LVDd was unchanged in these periods, thereafter it tended to increase until post-24hrs. PHT also showed further decrease although MVA was constant. These results suggest that improvement of transmitral flow gradually increased LV dimension, which may affect the pressure half-time of transmitral flow following balloon mitral valvuloplasty. One should take a caution when mitral valve area is determined from PHT during these periods.

ISOLATED QUADRICUSPID AORTIC VALVES; INCIDENCE, DESCRIPTION, AND FUNCTIONAL ASSESSMENT.
Barry Feldman, M.D., Carole Warnes, M.D., Bijoy Khandheria, M.D., James Seward, M.D., F.A.C.C., A. Jamil Tajik, M.D., F.A.C.C., Mayo Clinic, Rochester, Minnesota.

Necropsy incidence of isolated quadricuspid aortic valves (QAV) has varied from .0008% to .033%. To determine incidence in living pts, we reviewed archival data from the Mayo Clinic Echocardiographic Laboratory. Of 60,447 pts between June 1982 to May 1988 who had a 2D echocardiogram there were 8 cases of QAV with an incidence of 0.013%. In the latter 10 months 6 of these pts were noted from 13,805 pts giving an incidence of 0.044%. Ages ranged from 28-71 with a mean of 45. There were 3 males and 5 females. The diagnosis of QAV was based on a characteristic 2D echo appearance of the letter "X" configuration in diastole and a "squared" opening in systole. This is in contradistinction to the "Y" configuration in diastole and "triangular" opening in systole observed in trileaflet aortic valves. In 3 pts the 4 cusps were of near equal size and in 5 pts the accessory cusp was considerably smaller than the other 3. A QAV with a small accessory cusp was confirmed in 2 pts; one at the time of valve replacement for bacterial endocarditis (BE) and the other at necropsy. Doppler interrogation revealed AR in 6/8 pts (75%); mild in 4, moderate in 1, and severe in the pt with BE. One pt (the oldest) had mild aortic stenosis. Conclusions: 1. The incidence of QAV is higher than most published necropsy data and recent improved ultrasound technology suggests an incidence of 0.044%. 2. There is a high incidence of AR possibly reflecting referral bias. 3. Significant premature aortic stenosis does not occur. 4. Diagnosis is important because of the possible risk of BE. 5. High resolution ultrasound permits accurate diagnosis and functional assessment of QAV.

## Tuesday, March 21, 1989
## 8:30AM–10:00AM, Anaheim Room
## Anaheim Convention Center
## Laser Coronary Angioplasty

**"LASER WIRE" FOR PERCUTANEOUS ANGIOPLASTY COMPLETE PERIPHERAL AND CORONARY ARTERIAL OCCLUSIONS - INITIAL CLINICAL RESULTS.**
Robert J. Bowes M.D., David C. Cumberland M.D., Anna M. Belli M.D., G.D.G. Oakley M.D., Richard K. Myler M.D., F.A.C.C., Simon H. Stertzer M.D., F.A.C.C., John C. Crew M.D., Thomas J. Linnemeier M.D., Northern General Hospital, Sheffield, England and San Francisco Heart Institute, Seton Medical Center, Daly City, CA

A percutaneously introduced 2.0mm diameter thermal probe powered by laser energy has been shown to recanalize some complete peripheral artery occlusions not amenable to conventional techniques, with a low incidence of complications. A new device, the "laser wire", consisting of a metal-tipped laser fiber contained in a 0.018 inch diameter steerable guide wire which is coupled to a continuous wave argon laser generator at 3 watts power, was used to traverse 7 tibial artery and 4 coronary artery occlusions not associated with acute ischemia/infarction, all of which could not be traversed with a conventional guidewire. Five of seven (71%) tibial arteries and 3 of 4 (75%) coronary arteries were successfully recanalized prior to balloon dilation. There were no complications.

The laser wire shows promise in improving the results of angioplasty in chronic, smaller artery occlusions, and thus possibly extending the applicability of the angioplasty technique in peripheral and coronary arteries.

USE OF DOPPLER ECHOCARDIOGRAPHY IN DETERMINATION OF LEFT VENTRICULAR Dp/Dt MAX. ANTHONY HUNT MRCP, RAPHAEL PERRY MRCP., ASHOK SETH MRCP, PATRICA LOWRY MD. MRCP. MAN FAI SHIU MD. FRCP. QUEEN ELIZABETH HOSPITAL, BIRMINGHAM, UK

Doppler echocardiography is emerging as a powerful tool in measuring indices of left ventricular contractility. In human subjects peak acceleration been shown to be correlated closely to ejection fractions and in dogs peak aortic flow velocity has been shown to be correlated closely to maximum Dp/Dt. Our study verifies the correlation of peak velocity with Dp/Dt max in human subjects and validates our theoretically derived formula which showed a better correlation with Dp/Dt max. Using the concept for conservation of energy, by assuming sinusoidal aortic flow and pressure patterns and a constant of proportionality between the area of LV outflow and ascending aorta, the following is derived:

$$\frac{Dp}{Dt}\ max = K\frac{Vp^2}{T} + \frac{pulse\ pressure}{TC}\quad (pulse\ p)$$

K = constant T = time to peak velocity
Vp = peak velocity TC = corrected ejection time

The validty of this equation was tested in 12 patients undergoing diagnostic catheterisation using a catheter tip micromanometer in the LV for Dp/Dt max and a 2MHz continuous wave Doppler transducer for aortic flow signals. Whilst Vp and mean acceleration (MA) correlated with Dp/Dt max (r=0.765 and 0.86 respectively) a better correlation (r=0.882 p<0.001) was found for $KVp^2/T$ + pulse P/TC and a correlation of (r=0.85 p 0.001) found for Vp2/T against Dp/Dt max. This method may prove useful in the non-invasive estimation of Dp/Dt max in differing clinical situations. Particularly in conditions of rapidly changing (beat to beat) variation in contractility.

DIRECT ARGON LASER IRRADIATION OF HIGH-GRADE STENOSES AND TOTAL OCCLUSIONS IN NATIVE HUMAN CORONARY ARTERIES AND BYPASS GRAFTS: INITIAL CLINICAL EXPERIENCE.
A.E. Foschi, M.D., C.A. Zapala, R.N., St.Francis Hospital, Evanston, IL
A clinical trial of an argon laser delivery system (IASTAC® System, GV Medical) for treating atherosclerotic coronary arteries and bypass grafts is underway. By using a multi-lumen balloon catheter to coaxially align an optical fiber and lens assembly, which diverged the laser beam to 40°, and by infusing Ringer's solution and monitoring lens fluorescence, laser delivery without tissue contact was possible despite systaltic motion. Standard PTCA technique was used under fluoroscopic guidance to treat 9 lesions in 8 Pts. (7 male, 1 female; 41-73 yrs. old), who all gave informed consent. Two native right coronary arteries (RCA), 3 native left anterior descending (LAD) arteries and 4 saphenous vein by-pass grafts were treated. Each native vessel and one graft were totally occluded; all stenoses exceeded 90%. The mean filling defect was of 18.7 mm (range 10-30 mm). Exposures consisted of 1 to 2 second exposures; total energy delivered ranged from 30 to 510 Joules. The laser allowed subsequent penetration of the lesion with a guidewire(previously impossible), followed by balloon dilation. All lesions were reduced to less than 50% stenosis; no perforations, arterial spasm, ventricular fibrillation, post-treatment myocardial infarction or emergency surgery occurred. All Pts. remained hemodynamically stable, without elevated CK (MB) enzymes: pain did not increase upon lasing. Clinical improvement (relief from symptoms, supported by post-treatment angiography) was evident in each case. Laser energy may thus augment coronary angioplasty, but more follow-up and further non-invasive assessment of patency are obviously needed.

**PERCUTANEOUS CORONARY EXCIMER LASER ANGIOPLASTY IN ANIMALS AND HUMANS**

Frank Litvack, MD, FACC, Warren Grundfest, MD, Ann Hickey, MD, Andrew Jakubowski, MD, Fred Mohr, MD, Jacob Segalowitz, MD, Lisa Hestrin, MPH, Tsvi Goldenberg, PhD, James Laudenslauger, PhD, Hugh Narciso, MS, James Forrester, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, California.

We report animal testing and the first human experience with a percutaneous coronary excimer laser angioplasty system. The system operates at 308 nm, 35-45 mJ/mm$^2$, 150 nsec, 20 Hz. The catheter has twelve 200 micron fibers concentrically arranged around a moveable .018 inch PTCA guidewire. In 8 pigs, a guide catheter was placed in the coronary ostium via the carotid artery. The guidewire was advanced to the distal portion of an epicardial artery. During multiple passes, 1,000 to 10,000 pulses were delivered to 2-3 arteries per pig. In all cases, the catheter advanced easily through tortuosities into distal vessels. With the catheter in motion, no perforation, spasm or occlusion occurred. Occlusion without perforation occured when the catheter was placed in a 1 mm obtuse marginal. To test tolerance to perforation the catheter was left stationary for 5 minutes in 1 pig. This caused no angiographic effect after 3,000 pulses, however, after 5,005 pulses (4.2 minutes) dye extravasation was seen. Histology revealed medial ablation and slight periadventitial hemorrhage but no perforation. Subsequently, percutaneous coronary excimer laser angioplasty was used in our first patient, reducing the stenosis from 95% to 30% with the laser alone. **CONCLUSIONS:** 1. The "over-the-wire" percutaneous excimer laser angioplasty catheter tracks effectively through tortuous coronary arteries without vascular injury. 2. This system permits percutaneous angioplasty of obstructed human coronary arteries.

**EARLY CLINICAL EXPERIENCE WITH PERCUTANEOUS TRANSLUMINAL ARGON LASER CORONARY ANGIOPLASTY.**

**Gilles Côté, MD, Simon H. Stertzer, MD, FACC, Richard K. Myler, MD, FACC, Raoul Bonan, MD, FACC, W. Scott Andrus, PhD, Lary Roth, MEng, John Lane, BSc, Mike Dumont, BSc, Mike Maden, BSc, Benito O. Hidalgo, Montreal Heart Institute, Montreal, Canada and San Francisco Heart Institute, Daly City, CA.**

**The purpose of this study was to evaluate the feasibility and safety of percutaneous transluminal coronary recanalization using argon laser energy (454.5-528.7 nm). All lesions attempted were first crossed with a 0.014 inch guide wire to assure coaxial delivery of laser energy. A specially designed laser recanalization catheter (LRC) was subsequently advanced, over the wire, at the obstruction. Pulsed argon laser energy (15 Watts) was delivered percutaneously at 0.1 sec pulses, through 4 flexible optical fibers mounted inside a 1.5 mm in diameter (4.5 French) catheter. A total of 5 patients, with 5 lesions localized in the 3 major coronary arteries (3 RCA, 1 LAD, 1 LCx) were irradiated. The targeted lesions, range 95-100% diameter narrowing, were discrete (≤1.5 cm in length) and non-calcified. Significant residual stenoses (≥50%) remained after laser angioplasty in all cases. Additional balloon angioplasty was subsequently performed reducing the residual stenosis (range 0-30% diameter narrowing). Initial hemodynamic, angiographic and clinical success was achieved in all cases attempted. No arterial perforation, thrombosis, spasm or embolization occurred. No other immediate or delayed complication were seen and all patients were discharged 24 to 48 hours post laser angioplasty. This study would suggest that percutaneous transluminal coronary laser angioplasty can be performed safely and pulsed argon laser energy delivered effectively in selected patients.**

*HUMAN PERCUTANEOUS LASER-ASSISTED CORONARY ANGIOPLASTY: EFFORTS TO REDUCE SPASM AND THROMBOSIS*

*Thomas J. Linnemeier, M.D., F.A.C.C., David C. Cumberland, M.D., Donald A. Rothbaum, M.D., F.A.C.C., Ronald J. Landin, M.D., F.A.C.C., Michael W. Ball, M.D., St. Vincent Hospital, Indiana Heart Institute, Indianapolis, Indiana*

*The initial case reports of percutaneous laser-assisted coronary angioplasty (PLCA) suggested frequent complications of spasm and/or thrombosis. We present a larger pilot study of 19 patients (22 vessels), aged 47-75 years (mean 62) treated with PLCA. Fifteen saphenous vein bypass grafts and 7 native (6 restenosed) coronary arteries were treated. All patients were pretreated with ASA, Dipyridamole, calcium antagonists, IV Nitroglycerin, IV Dextran and intra-arterial Heparin. PLCA was performed using two 8-12 watt bursts of argon laser energy (Trimedyne Laserprobe®). The probe crossed 21/22 vessels (95%), and was followed by successful balloon angioplasty (PTCA) in 21/22 vessels (95%). IV Nitroglycerin was continued for 24 hours, IV Heparin drip for 24-48 hours and ASA, Dipyridamole and calcium antagonists as an outpatient. Problems related to spasm or thrombosis occurred in three vessels (14%) including one distal embolization (successfully treated with PTCA), closure of a side branch vessel in the native left circumflex during PLCA, and late closure of an LAD graft 6 days post PLCA (stenosis unable to be reduced to <50% by PTCA). The remaining 19 vessels (86%) showed no evidence for laser-related spasm or thrombosis, suggesting a lower incidence of these complications than the initial case reports. Complications related to this protocol included one femoral artery hematoma(4.5%). In summary, we feel that with the use of this regimen, thrombosis and spasm can be minimized with PLCA and that other important issues such as restenosis and efficacy of PLCA as compared to conventional PTCA may be addressed.*

PERCUTANEOUS CORONARY LASER BALLOON ANGIOPLASTY: PRELIMINARY RESULTS OF A MULTICENTER TRIAL.

J.Richard Spears,MD,FACC, Vincent Reyes,MD, I. Nigel Sinclair,FRACP, Barry Hopkins,MD, Leonard Schwartz,MD, Harold Aldridge,MD, H.W.Thijs Plokker,MD,PhD. Harper Hospital/Wayne State University, Detroit, MI

Laser balloon angioplasty(LBA), wherein the arterial wall surrounding an inflated balloon is heated to a tissue subvaporization threshold with laser energy, has been shown experimentally to have utility in the treatment of potential causes(dissection, recoil, thrombus) of complications following PTCA. To test the hypothesis that LBA may be similarly effective clinically, 25pts in 4 centers were treated with a LBA balloon identical in size(3.0mm x 20mm) to a balloon used for PTCA performed immediately prior to LBA. Coronary angiography was repeated at 1 day (n=23) and 1 month(n=13) after the procedure, and computerized processing was used to quantitate lumen diameter (D). 1-3 laser doses of either 450 or 380 joules of 1.06μm cw Nd:YAG laser radiation were given over 20 sec/exposure under brief anesthesia. High risk lesions treated included 3 ostial RCA stenoses, 3 long recurrent restenoses and 5 proximal LAD stenoses. Results:Acutely and 1 day after LBA, no significant adverse effects on the arterial lumen or on angiographic LV function was noted. Suboptimal PTCA results from suspected thrombus (n=2), recoil(n=3), and dissection(n=2) were all successfully reversed with LBA. Mean minimum D increased from 1.28±48mm pre PTCA to 2.19±48mm post PTCA ($p<0.05$) with further improvement to 2.44±.50 acutely post LBA($p<0.05$). No change in D at 1 day (2.53±56mm) or at 1 month (2.54± 45mm) was found. However, restenosis has occurred in 3 patients with proximal LAD lesions ca 4 months post high dose LBA. Conclusions: LBA is effective in the acute treatment of common causes of a poor PTCA result. Optimal laser dosimetry needs to be defined to prevent late recurrence.

# Tuesday, March 21, 1989
# 8:30AM–10:00AM, California Pavilion D
# Anaheim Hilton Hotel
# Cardiac Transplantation

## CYCLOSPORINE AND CONCOMITANT KETOCONAZOLE AFTER CARDIAC TRANSPLANTATION: INTERMEDIATE TERM FINDINGS AND POTENTIAL SAVINGS

Samuel M. Butman, M. D., FACC, Joan Wild, ARTC, Paul Nolan, D. Pharm., Tim Fagan, M. D., Mary Mackie, RN, Paul Finley, M. D., Jack G. Copeland, M. D., FACC, University of Arizona, Tucson, Arizona

The use of cyclosporine (C) after transplantation has resulted in increased longevity but at an increased financial burden for the transplant patient. Ketoconazole (keto), by altering hepatic metabolism, reduces the daily oral requirement for C. In a prospective evaluation of the benefit/risk profile of keto + C in cardiac transplant recipients, 11 stable transplant pts have been given 200 mg Keto bid with C doses lowered appropriately. Baseline and follow-up ( mean 6 mos, range 1-10) trough C blood levels by fluorescence polarization, renal fxn, and 24 hr ambulatory blood pressure have been obtained. The findings are described below:

| | C only | Cyclo+Keto | p value |
|---|---|---|---|
| Mean daily C dose(mg) | 390(39) | 47(6.5) | <0.005 |
| C level (ng/ml) | 156(8.7) | 147(12) | NS |
| Mean BP (mmHg) | 104.2(3.1) | 98.9(4.2) | <0.025 |
| BUN(mg/dl) | 25.1(2.8) | 33.7(2.1) | <0.005 |
| Cr (mg/dl) | 1.4(0.1) | 1.9(0.2) | <0.005 |
| **Projected Mean Costs/yr/pt** | | | |
| Cyclosporine | $5040 | $ 617 | ( ) = SEM |
| Ketoconazole | $ 0 | $1044 | |
| Mycostatin elixir | $ 600 | $ 0 | |
| Total | $5640 | $1661 | |

Ketoconazole reduced the oral C dose by 88% with a salutory effect on mean BP. Significant changes in renal function were seen. We conclude that significant financial savings can be expected in transplanted pts treated with keto+C though careful patient selection is required.

## RESPONSE TO NITROPRUSSIDE - PREDICTOR OF EARLY POST TRANSPLANT MORTALITY

Angelika Costard M.D., Irene Hill Ph. D., John Schroeder M.D., F.A.C.C., Michael Fowler M.B., M.R.C.P., F.A.C.C., Stanford University Hospital, California.

Screening of potential cardiac transplant candidates at Stanford includes demonstration of reactivity of pulmonary vascular resistance (PVR) to nitroprusside (N) with the attempt to achieve a PVR ≤ 2.5. To test the validity of this concept we analyzed the pre-transplant right heart catheterization data, available in 291 of 301 pts who underwent cardiac transplantation between December 1980 and July 1988. The 3-month mortality (3-MM) did not differ significantly between pts with a baseline PVR ≤ 2.5 (n=149; 3-MM 8,7%) and those with a PVR > 2.5 (n=142; 3-MM 16,9%). 135 pts with baseline PVR > 2.5 received N. The response to N and subsequent 3-MM is shown in the table:

| Response to N | total | 3-MM | | Cause of death | |
|---|---|---|---|---|---|
| | n= | n= | % | pHTN | EGF |
| **Group I** (PVR > 2.5) | 31 | 13 | 41.9 | 2 | 1 |
| **Group II** (PVR≤2.5, $BP_{syst}$≤85mmHg) | 34 | 8 | 23.5[a] | 3 | 2 |
| **Group III** (PVR≤2.5, $BP_{syst}$ >85mmHg) | 70 | 4 | 5.7[b,c] | - | - |

[a] n.s. vs group I; [b] <.0001 vs group I; [c] < .01 vs group II; pHTN: pulmonary hypertension; EGF: early graft failure.

Conclusion: In contrast to baseline PVR, the response of PVR to N is of value in predicting early post-transplant mortality. High risk pts include those whose PVR cannot be reduced below 2.5 as well as those whose PVR can be reduced below 2.5 only at the expense of systemic hypotension.

## DIAGNOSTIC APPLICATIONS OF LYMPHOCYTE CULTURES FROM HEART ALLOGRAFT BIOPSIES.

John Carlquist Ph.D., Jeffrey Anderson M.D., F.A.C.C., Elizabeth Hammond M.D., John O'Connell M.D., F.A.C.C. LDS Hospital and University of Utah, Salt Lake City,Utah.

Despite advances in cardiac transplantation, acute rejection still remains the principal cause of graft failure. In an effort to assist in this problem, we evaluated the diagnostic and prognostic utility of culturing endomyocardial biopsy specimens in medium containing interleukin-2 (IL-2). This technique allows the in vitro proliferation of activated lymphocytes present in the myocardium at the time of biopsy (i.e. alloactivated lymphocytes). A comparison of the culture results (positive or negative lymphocyte growth) of 234 specimens with the histological grading of the specimen (1=no rejection; 2=can't rule out rejection; 2.5= focal mild rejection;3= mild rejection;4=moderate-severe rejection) employing a 2x5 contingency table revealed a highly significant correlation ($p<0.0005$) between the methods. The predictive value of IL-2 cultures was examined by comparing culture results for a specimen with the histological and culture results of a subsequent specimen obtained by biopsy within 21 days. A significant correlation was noted between culture results for a given specimen and the histological grade of the subsequent biopsy specimen (n=150; $p<0.02$, ANOVA). Similarly, culture results were observed to be significantly predictive of the culture results of the next biopsy (n=110; $p<0.004$, ANOVA). Cultures were of particular value when initial culture results and histology were in disagreement. A follow up of 45 patients with culture positive/histologically negative (≤grade 2) specimens, revealed that 24 (53.3%) experienced worsening rejection by one or more histological grades within 21 days, 18(40%) had no change, and 3 (6.6%) had a reduction in histological grade. Of the 24 patients showing increased rejection grade, 16 (66.6%) required treatment for acute rejection. Thus, IL-2 lymphocyte cultures can be of value in the diagnosis and prognosis of acute rejection in cardiac allograft recipients.

## PROPHYLACTIC ANTI-REJECTION THERAPY EARLY AFTER CARDIAC TRANSPLANTATION: RATG VERSUS OKT3.

James K. Kirklin MD,FACC, Robert C. Bourge MD,FACC, Connie White-Williams RN, David C. Naftel PhD, Michael G. Phillips PA, Univ of Alabama at Birmingham, AL.

The value of prophylactic monoclonal or polyclonal antibody therapy early after cardiac transplantation is controversial. Between 1/1/87 and 7/1/88, 32 consecutive patients (pts) underwent cardiac transplantation (C Tx) (cyclosporine, azathioprine, and prednisone maintenance therapy) utilizing either early prophylactic rabbit antithymocyte globulin (RATG) (n=17) or monoclonal OKT3 (10 days) (n=15), with follow-up through 9/1/88.

Data: All pts (100%) survived throughout the study period (follow-up 2-20 months). The efficacy of RATG and OKT3 prophylaxis was similar regarding median time (days) to first rejection (16 vs 21, p=0.5), number of rejection episodes during first 2 months (1.5 vs 1.3, p(chi-square)=0.8), and persisting or severe rejection in first 2 months (0.5 vs 0.5 episodes, p(chi-square) =0.4). Infections were similar in the RATG and OKT3 groups (infections in first 2 months: 0.3 vs 0.5/pt, p=.08; median time to first infection: 318 vs 250 days, p=0.5). CMV syndrome was common, with one CMV pneumonia. T-cell markers during OKT3 did not predict subsequent rejection (within 2 weeks following OKT3) as assessed by mean T3 lymphocyte count (T3-L) during OKT3 (p=0.3) or T3-L during last 3 days of OKT3 (p=0.4).

Inferences: (1) Prophylactic RATG or OKT3 with 3-drug immunosuppression yields excellent intermediate survival after C Tx. (2) These protocols for RATG and OKT3 provide similar protection against early rejection with the same low risk of early infection. (3) T-cell markers do not predict early rejection after OKT3.

HIBERNATION INDUCTION TRIGGER EXTENDED EFFECTIVE ORGAN PRESERVATION TIME IN A NEW AUTOPERFUSION MULTIORGAN PREPARATION.

Sufan Chien, MD. Peter R. Oeltgen, PhD, John N. Diana, PhD, Edward P. Todd, MD, PhD, FACC, William N. O'Connor, MD, W. Randolph Chitwood, Jr. MD, FACC. University of Kentucky Medical Center, Lexington, KY.

Plasma from hibernating woodchucks containing a hibernation induction trigger (HIT) was added to a new autoperfusion preparation. The animal was anesthetized and the heart, lungs, liver, pancreas, duodenum and kidneys were removed, while still being perfused by the heart and oxygenated by the lungs. The system was then placed in a 32°C solution bath. A respirator with a gas mixture of 50% $O_2$ and 3% $CO_2$ was used to maintain ventilation. Blood and a dextrose solution containing: KCl, insulin, $CaCl_2$, mannitol, penicillin and flagyl, were given via the portal vein. Soyacal 2 ml and prednisolone 30 mg were infused through the portal vein every 2 hours. Six dogs (G 1) were injected intravenously with 10 ml of HIT containing plasma 2 hours before the operation and 5 ml every 4 hours during the preservation. Seven dogs (G2) without HIT were used as controls. The survival time in G1 ranged from 33 to 56 hours with an average of 43.4 hours. The survival time varied between 9 to 26 hours with an average of 14.8 hours for G 2. In G 1, average urine output was 45.6 ml/hour, bile output 5.2 ml/hour, pancreatic and duodenal outputs 5.8 ml/hour. AOSP 65-90 mmHg, free plasma hemoglobin changed from 38.3 to 167 mg/dL at 44 hours. RBC varied 6.25-8.12 ($10^6$/uL) and WBC reduced from 10.4 to 0.3 ($10^3$/uL) at 44 hours ($p<.001$). Arterial blood pH was between 7.28-7.42, $PaO_2$ 164-290 mmHg, $PaCO_2$ 22-34 mmHg. Serum SGOT increased from 40 to 200 (u/L) and SGPT increased from 45 to 362 (u/L) within 44 hours. Serum amylase scaled between 750-673 u/L; BUN reduced from 15.58 to 6.60 (mg/dL)($p<.0025$), and Creatinine also reduced from 0.80 to 0.25 (mg/dL) by 44 hours ($p<.001$). In G 2, severe liver congestion, premature renal failure and pulmonary edema reduced the survival. These were not evident in G1 within 44 hours of the preservation time. Lung wet/dry weight ratio in G 1 was 4.85 at the beginning and changed to 5.34 by the 44th hour. Although the exact mechanisms are not clear, the use of HIT in the new autoperfusion preparation seems to extend organ preservation time significantaly.

A DIRECT ADMINISTRATION OF RECOMBINANT SUPEROXIDE DISMUTASE SIGNIFICANTLY PRESERVES MYOCARDIAL FUNCTION AND MITOCHONDRIAL STRUCTURES AFTER 30 MINUTES NORMOTHERMIC GLOBAL ISCHEMIA

Nobuo Hatori,MD.,Yozo Uriuda,MD.,Eriya Okuda,MD.,Hiroshi Yoshizu,MD.,Akira Senoo,MD.,Susumu Tanaka,MD.,National Defense Medical College, Tokorozawa, Japan

To determine the efficacy of direct vs. systemic administration of human recombinant superoxide dismutase (rt-SOD) in acute myocardial ischemia and reperfusion, the following experimental model was applied. 21 dogs were subjected to 30 min. global ischemia at 37°C by the occlusion of the ascending aorta followed by 60 min. reperfusion. To eliminate the collateral blood flows during ischemia, bipulmonary hilus were clamped. The dogs were randomly assigned to three groups: group A(n=7),rt-SOD (10000IU/kg) was administered by bolus injection through the aortic root into the coronary artery 1 min. prior to reperfusion, in addition to a 30 min. continuous infusion of rt-SOD (30000IU/kg) into the cardiopulmonary bypass circuit beginning just after reperfusion; group B(n=7), the treatment was similar except the bolus injection was into the cardiopulmonary bypass circuit; group C(n=7), saline was administered as in group A. Left ventricular stroke work index(LVSWI) was determined by a right heart bypass technique and expressed as a % recovery of pre-occlusion state. Morphologic structures were observed by electron microscope. Coronary sinus blood was assessed for malondialdehyde (MDA) measured by TBA method and creatine phosphokinase(CPK).Results for a % recovery of LVSWI after 60 min. reperfusion are tabulated. (*$p<0.05$)

| LA pressure | 5mmHg | 10mmHg | 15mmHg |
|---|---|---|---|
| Group A | 121±81%* | 80±43%* | 86±53%* |
| Group B | 52±21% | 62±39%* | 52±18% |
| Group C | 24±38% | 22±14% | 35±23% |

In group A, myocardial structure had a normal appearance in most areas. However, swollen mitochondrias, disrupted myofibrills, decreased glycogen particles and capillary endothelial alterations were observed in groups B and C. Serum MDA levels did not change in all groups, although CPK levels were less in group A. Conclusion:These results show that the direct infusion of rt-SOD is more effective than systemic one.It may also suggest that rt-SOD is need to be adequate concentrations in the interstitial fluid at the time of reflow.

## Tuesday, March 21, 1989
## 10:30AM–12:00NOON, California Pavilion D
## Anaheim Hilton Hotel
## PET and Receptor Imaging

QUANTITATIVE POSITRON TOMOGRAPHY DEMONSTRATES ACCELERATED GLUCOSE UTILIZATION RELATIVE TO FLOW IN ISCHEMIC HUMAN MYOCARDIUM.

Richard Brunken M.D., F.A.C.C., Freny Vaghaiwalla Mody M.D., Sanjiv S. Gambhir M.S., Christoph Nienaber M.D., Lynne Warner Stevenson M.D., F.A.C.C., S. C. Huang DSc., Heinrich Schelbert M.D., F.A.C.C., UCLA School of Medicine, Los Angeles, California.

Laboratory studies have indicated that glucose utilization is augmented relative to flow in ischemic myocardium. To determine the relationship between absolute myocardial blood flow (MBF) and glucose utilization (GU) measurements in human myocardium, 11 pts with ischemic cardiomyopathy were studied with dynamic positron tomography (PET) utilizing N-13 ammonia (NH3) and F-18 deoxyglucose as tracers of flow and metabolism respectively. Tissue time-activity curves and arterial input function were obtained by drawing 8 ROI's on 3 simultaneously acquired cross-sectional planes and LV cavity respectively. Quantitative MBF measurements were derived utilizing a two compartment NH3 model while quantitative GU rates were calculated using a modified Patlak approach. In 50 segments with flows ranging from 0.09 to 1.15 ml/min/gm, GU rates ranged from 0.068 to 1.21 μmol/min/100 gm. Ratios (R) of GU/MBF were inversely related to MBF according to the exponential formula: $R=4.39*(\exp(-3.13*flow))$ [$r^2=0.58$, corr coeff=0.76]. For flows greater than 0.45 ml/min/gm, there was little variation in R with increasing flows. In contrast, for flows less than 0.45 ml/min/gm, R increased rapidly to a maximum of 4.2 at 0.12 ml/min/gm. We conclude that GU is accelerated relative to MBF in ischemic human myocardium, consistent with increased substrate flux in glycolytic pathways.

IMPAIRED FATTY ACID METABOLISM IN POSTISCHEMIC CANINE MYOCARDIUM : A TIME COURSE STUDY WITH POSITRON EMISSION TOMOGRAPHY.

D. Vogelaers, W. Wijns, J.A. Melin, A. Bol, C. Michel, D. Labar, M. Cogneau, A. Keyeux, G.R. Heyndrickx. Univ. of Louvain, Brussels and State Univ.of Gent, Brussels.

Prolonged postischemic dysfunction was induced in 9 chronically instrumented dogs by a single 1 hr episode of graded circumflex coronary(C) artery(A) stenosis(S). Blood flow(F) was measured by microspheres and by Doppler probes. Regional left ventricular thickening was measured by transmural ultrasonic crystals (% systolic wall thickening, SWT). CAS reduced transmural F to 47±8% of baseline such that regional akinesia was obtained (SWT ranging from 27 to -15% of control). Fatty acid metabolism was studied with C-11 palmitate (CPA) and dynamic PET imaging 4-8hr after ischemia and reperfusion in 2 dogs as well as serially 24 hr and 1 week after ischemia in 7 dogs. CPA tissue wash-out curves were obtained from regions of interest in the stunned(SA) and normal areas(NA). Biexponential curve fitting yields the halftime of the early rapid phase ($t_{½}$), which is related to CPA oxidation and the size of the late slow turnover pool (LSP) related to deposition of CPA in neutral lipids. In the dogs studied 4 and 8 hr after ischemia, $t_{½}$ in SA was respectively 175 and 115% of NA; LSP was 103 and 141% of NA. In 3 dogs showing normal CPA washout at 24 hr, SWT had returned to 90% of control. In 4 dogs showing abnormal CPA washout at 24 hr, SWT was only 65% of control. In SA, $t_{½}$ was prolonged by 21% from 4.9±1.3 min in NA; LSP in SA was increased by 44% from 28±8% of peak activity in NA. At 1 week, SWT was 93% of control and CPA washout was normalized. Thus, stunning is associated with altered CPA handling i.e. decreased oxidation and increased storage. Recovery of SWT is paralleled by normalization of CPA metabolism.

QUANTITATION OF CRITICALLY ISCHEMIC MYOCARDIAL MASS DURING ACUTE CORONARY OCCLUSION IN VIVO: MEASUREMENT WITH POSITRON EMISSION TOMOGRAPHY.
Michael E. Merhige, M.D., F.A.C.C., Dahlia Garza, M.D., David Sease, M.D., R. Wanda Rowe, Ph.D., Jonathan Maclean, M.S., K. Lance Gould, M.D., F.A.C.C., Positron Research Center, University of Texas at Houston, Houston, TX

"Critical" myocardial ischemia (CI) during acute coronary occlusion has been defined as myocardial perfusion < 50% of normal because tissue ATP content and regional wall motion decline with this level of flow reduction. To determine if CI LV mass can be measured in vivo with Positron Emission Tomography (PET), we obtained myocardial perfusion images in 9 open chest dogs with IV N-13 Ammonia, during LAD coronary ligation. Left atrial injection of radiolabelled microspheres was performed during image acquisition and perfusion was subsequently calculated in each 0.5 g myocardial section of the trimmed LV.

LV mass with microsphere perfusion ≤ 50% of peak midwall flow was expressed as a fraction of total LV weight while the CI LV mass was measured from PET perfusion images after 50% background subtraction which defined the LV edges. The number of pixels with ≤ 50% of peak myocardial N-13 ammonia uptake was determined using computer assisted regions of interest. There was a linear correlation between the CI LV mass measured with microspheres in vitro and that measured in vivo with PET which approximated the line of identity ($y = 0.90x + 2.7$; $r = 0.88$). Conclusion: noninvasive myocardial perfusion imaging with N-13 Ammonia and PET permits quantitation of critically ischemic LV mass during acute coronary occlusion in vivo.

DIFFERENCES IN DISTRIBUTION OF BETA-BLOCKERS IN INFARCTED PORCINE HEARTS. A STUDY WITH POSITRON EMISSION TOMOGRAPHY (PET).
A. Waldenström, J.-A. Björkman, P. Hartwig, J. Hultman, P.-O. Sjöquist, G. Wikström, G. Antoni, J. Ulin, B. Långström, and H. Lundqvist. Uppsala University, Uppsala, Sweden.

The aim of the present study was to compare the dynamics of tissue distribution within the ischemic heart of two beta-blockers with different physicochemical properties; metoprolol (M) being more lipophilic than atenolol (A). Atenolol (A) and metoprolol (M) were both synthesized and labelled with positron emitting $^{11}C$ ($t1/2 = 20$ min). 30 min after LAD occlusion, equipotent doses (0.3 mg/kg) of either of the drugs were injected into anaesthetized pigs positioned in the PET camera. Myocardial flow before and during ischemia was measured by injection of radiolabelled microspheres, and blood flows close to zero in the ischemic region were confirmed. Normal and ischemic areas of PET pictures were delineated and drug concenterations over time estimated.
**Results:** In the ischemic region of M pigs (n = 3) a continuous increase in drug concentration was seen which was not observed in the A group (n = 6). Average drug concentreations in the ischemic area at the end of experiment (60 min after drug administration) was for A = 57 pmol/g tissue and for M = 136 pmol/g tissue. This study demonstrates that **a)** a lipophilic drug (M) penetrates more easily into an ischemic area than a hydrophilic one (A) as described by the significantly different slopes of the activity curves, M being 0.017 and A being 0.005, and **b)** that the PET technique is suitable for studying drug distribution continuously within ischemic hearts during *in vivo* conditions.

F-18 METARAMINOL UPTAKE AS MARKER FOR NEURONAL FUNCTION IN POST-ISCHEMIC CANINE MYOCARDIUM.
Markus Schwaiger, M.D., Haydee Guibourg, M.D., Karen Rosenspire, Ph.D, Thomas McClanahan, Kim Gallagher, Ph.D., Gary Hutchins, Ph.D., Donald Wieland, Ph.D., University of Michigan Medical Center, Ann Arbor, Michigan.

Myocardial ischemia has been shown to cause sustained depletion of tissue norepinephrine (NE). To study neuronal function in reperfused myocardium (REP) following 30 min (Grp 1) and 60 min (Grp 2) ischemia, regional uptake of the new catecholamine analog F-18 metaraminol (FMR) was determined in 11 intervention and 6 control dogs (Sham). Myocardial blood flow (MBF) was measured using microspheres during LAD occlusion (OCL) and prior to i.v. FMR injection 30 min after reperfusion. The animals were sacrificed 30 min after FMR injection. Tissue F-18 activity was determined by well counting and normalized to the arterial input function of FMR yielding absolute FMR uptake in control (CONT) and center of REP. Tissue NE levels were determined in CONT and REP using HPLC electrochemical methods.

| | $MBF_{OCL}$ | $MBF_{REP}$ | $FMR_{CONT}$ | $FMR_{REP}$ | $NE_{CONT}$ | $NE_{REP}$ |
|---|---|---|---|---|---|---|
| Sham | | 1.1±.3 | 30±5 | 28.3±4 | 431±99 | 441±84 |
| Grp 1 | 0.2±2* | 1.0±.4 | 28±21 | 21±17* | 363±100 | 297±84 |
| Grp 2 | 0.3±2* | 1.0±.5 | 25±8 | 18±5* | 340±88 | 273±40 |

*p <0.05; MBF=ml/min/g; FMR=arbitrary units; NE=pg/g
Thirty and 60 min IS resulted in significantly decreased FMR uptake in REP. 30 min IS resulted in decreased FMR in REP only, while 60 min produced also decreased FMR uptake in CONT ($p<0.05$). FMR paralleled changes in regional NE tissue content. Thus, F-18 metaraminol allows sensitive assessment of catecholamine uptake in ischemically injured myocardium and may be clinically useful in combination with PET for the noninvasive evaluation of neuronal function in patients with ischemic heart disease.

PORTRAYAL OF CARDIAC BETA RECEPTORS IN LIVING ANIMALS.
James Sisson, M.D., Donald Wieland, Ph.D., Jon Johnson, B.S., Gerald Bolgos, B.S., Terese Malak, B.S. Marcian Van Dort, Ph.D., David Gildersleeve, Ph.D., Markus Schwaiger, M.D, Gary Hutchins, Ph.D., University of Michigan Medical Center, Ann Arbor, Michigan.

To aid in determining the roles of beta cardiac adrenergic receptors in the development of arrhythmias and heart failure, we have developed a method to portray and quantify beta receptor binding in living animals. 125-I-iodocyanopindolol (125-ICYP), a beta antagonist, bound with high affinity to the heart in rats. Binding was inhibited by a non-selective antagonist, propranolol, to give non-specific binding (45%). Binding of 125-I-ICYP to lung was inhibited by a beta-2 selective antagonist, ICI 118,551, in doses that did not affect binding to the predominately beta-1 heart receptors.

In dogs, about 90% of 123-ICYP injected into coronary arteries was extracted. Early release from the heart was biexponential: relatively rapid over a few minutes and unaffected by propranolol; then slower over an hour and accelerated by propranolol. 123-ICYP given IV enabled scintigraphic portrayal of the dog left ventricle in planar and tomographic views. There was no gradient in the binding of 123-ICYP from base to apex which contrasts with the gradient known for adrenergic neurons. Specific binding was estimated at 2 hours after which total binding decreased slowly (T1/2: 9.8 h), and non-specific binding in the presence of propranolol only slightly faster (T1/2: 7.8 h).

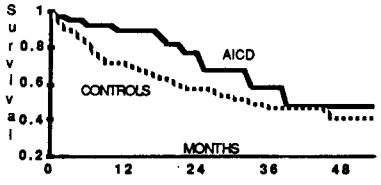
Scintigraphy of 123-ICYP may enable portrayal and quantifying of beta receptors in man. The method combined with scintigraphy of the neurons by a neuron-specific agent could define the major components of the adrenergic nervous system in the heart.

# Tuesday, March 21, 1989
# 8:30AM–10:00AM, Marriott Hall North
# Anaheim Marriott Hotel
# Implantable Defibrillators I

THE AUTOMATIC IMPLANTABLE CARDIOVERTER DEFIBRILLATOR AND PATIENT SURVIVAL: A CASE CONTROL STUDY

David Newman MD, John Herre MD FACC, Mary Jane Sauve RN, Jay Franklin MD, Melvin Scheinman MD FACC, Jerry Griffin MD FACC. University of California, San Francisco, California.

An automatic implantable cardioverter defibrillator (AICD) was implanted in 40 patients (pts) with ventricular tachycardia (VT) or cardiac arrest. Each AICD patient was matched to 2 controls according to age, ejection fraction (EF), heart disease, presenting arrhythmia, continuing amiodarone (Amio) use, Amio intolerance or clinical recurrence on drug therapy. Thirty four pts received amiodarone (Amio) prior to AICD and 17 after. In both groups the EF was (31±11.5%,mean ±SD), age (59±13 yr), and 75% had ischemic heart disease. The AICD pts and controls were followed for 19.9±12 months (range 0-52) and 17.5±10 months (range 1-92) respectively. In the first 25 mos there were no AICD sudden deaths and 4 in the control group. There have been a total of 10 and 20 deaths in the AICD and control groups respectively. The cumulative probability of survival is shown:




By interval analysis AICD improved survival between 8-21 months ($p < .05$). Overall by Cox proportional hazard model analysis there were no differences between the two survivorships. Subgroup analysis suggest that most of the AICD survival gain was seen in the group unable to take Amio. Conclusion: AICD improves survival in pts treated for life threatening VT but this benefit may be of limited duration.

INITIAL CLINICAL EXPERIENCE: ENDOTAK™ - IMPLANTABLE TRANSVENOUS DEFIBRILLATOR SYSTEM.

Stanley M. Bach, Jr., MD; Janice Barstad, BS; Nancy Harper, RN, BSN; David Mayer, BS; Suzan Moser, RN, BSN; Mark Smutka, BS; Rita Theis, RN, BSN; Jill Wollins, Ph.D.; Cardiac Pacemakers, Inc., St. Paul, MN

Between March 24, 1988 and August 31, 1988, 28 pts received the CPI ENDOTAK™ Transvenous Defibrillation Lead System. The lead system, consisting of a transvenous defibrillation catheter, submuscular or subcutaneous patch was implanted in 23 males and 5 females, mean age 63 yrs (range 46-78 yrs). Primary diagnoses for pt group were: coronary artery disease 86%, nonischemic cardiomyopathy 4%, other cardiac diseases (idiopathic ventricular arrhythmia and other valvular disease) 10%. Mean LV ejection fraction was 29% (range 12-57%). Primary clinical arrhythmia was ventricular fibrillation (VF) in 4 pts, ventricular tachycardia and fibrillation (VT/VF) in 11 pts and ventricular tachycardia (VT) in 13 pts. Two of four possible lead system configurations (configs) were randomly selected for implant testing. Additional configs were tested at investigator discretion. At conclusion of testing the lead config determined to be most efficacious was chronically implanted: 1 pt received config #1 (pos patch, neg proximal and distal spring electrodes); 23 pts received config #2 (pos proximal spring and patch, neg distal spring); 1 pt received config #3 (pos proximal spring, neg distal spring); and 2 pts received config #4 (pos patch, neg distal spring) and 1 pt received a combination ENDOTAK/2 large patch leads (pos patches, neg distal spring). During implant, pre-hospital discharge, and 8-12-week post-implant VENTAK® AICD™ cardioverter/ defibrillator arrhythmia conversion testing, the pulse generator sensed and converted induced VT/VF. To date, 5 pts have received appropriate cardioversion/ defibrillation of VT/VF episodes.

Conclusions: 1) Transvenous defibrillation lead system implantations using the ENDOTAK Lead System have occurred with good early results; 2) Use of a chronically implanted transvenous lead system for implantable cardioversion/ defibrillation is feasible in humans.

A Flexible and Effective 3 Electrode Non-Thoracotomy Defibrillation System In Man.

Gust H. Bardy M.D., F.A.C.C, Margaret D. Allen M.D., Rahul Mehra PhD., George Johnson B.S.E.E., H. Leon Greene M.D., F.A.C.C., Tom D. Ivey M.D., University of Washington, Seattle, Washington.

It is unlikely that any single pulsing method or electrode system will result in a uniformly superior defibrillation technique when used with non-thoracotomy lead systems for automatic antiarrhythmia devices. The purpose of this study, therefore, was to develop a non-thoracotomy lead system that would lend itself to a large number of alternative defibrillation methods. Using a coronary sinus coil, right ventricular coil, and a thoracic patch, we were able to test monophasic, biphasic, sequential, and/or simultaneous pulses over a variety of current pathways. In 12 sudden death survivors, defibrillation thresholds (DFT) were measured with the non-thoracotomy lead system described above and subsequently compared to DFT values obtained with 2 large epicardial patch electrodes used at the time of automatic defibrillator implantation. The multiple options available for improving defibrillation efficacy enabled defibrillation of each pt within the voltage and energy limits of presently available pulse generators. Comparison of epicardial and non-thoracotomy DFT's follow:

| | DFT Voltage | DFT Stored Energy |
|---|---|---|
| Epicardial | 264 ± 93 | 5.9 ± 3.8 J |
| Non-thoracotomy | 408 ± 134 | 13.1 ± 8.5 J |

Thus, a coronary sinus--right ventricular--subcutaneous patch lead system coupled to a flexible waveform pulse generator should allow non-thoracotomy defibrillator implantation in the majority of pts.

**Does Poor Cardiac Function Preclude Benefit from an Automatic Implantable Cardioverter Defibrillator?**

Joseph H. Levine, Adrienne Richards, David Mellits, Rosemary Baumgartner, Enrico P.Veltri, Lyle A.Siddoway, Louise Grunwald, Jean Lisek, Diana Aarons, Levi Watkins, Morton Mower, M.Mirowski, N.A.M. Estes, Lawrence S.C. Griffith, The Johns Hopkins Hospital, Baltimore, MD.

The utility of the Automatic Implantable Cardioverter Defibrillator (AICD) in patients with severe left ventricular dysfunction (LVD) is unknown; some suggest that although the device may reduce arrhythmic mortality, patients with severe LVD may succumb to other complications of heart failure. To determine whether survival in patients with AICD is dependent upon severity of LVD, we evaluated outcome as a function of ejection fraction (EF) in 199 patients with AICD. The incremental benefit of survival added by AICD was defined as the time from first appropriate firing (symptomatic, documented VT, etc) to death.

Results:

| Ejection Fraction | ≤15% | 16-25% | ≥26% | |
|---|---|---|---|---|
| Patient Number | 17 | 45 | 137 | |
| Median Survival (months) | 27.7 | 35.5 | 64.9 | p<0.01 |
| Median Time to First AICD Firing or Death | 4.8 | 5.2 | 15.8 | p=0.01 |
| Median Time from First AICD Firing to Death | 14.5 | 22.9 | 30.2 | p=.05 |

Conclusions: 1. Patients with severe LVD (EF<15%) have earlier appropriate AICD discharges but worse overall prognosis. 2.All groups had benefit from AICD as indexed as the time from first AICD firing to death. 3.The degree of benefit was dependent, in part, on ejection fraction.

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**PACEMAKER/IMPLANTABLE DEFIBRILLATOR INTERACTIONS: ARE THEY OF CLINICAL IMPORTANCE?**

Hugh Calkins, M.D., Jeffrey A. Brinker, M.D., F.A.C.C., Lyle Siddoway, M.D., Robert Hanich, M.D., Thomas Guarnieri, M.D., Joseph H. Levine, M.D., Johns Hopkins Medical Institution, Baltimore, Maryland.

Since its introduction in 1980, 176 patients have had an implantable defibrillator (AICD) placed at the Johns Hopkins Hospital. Thirty of these patients (17%) also had a pacemaker implanted either prior to (N=16), during (N=2) or following (N=12) AICD placement. To determine the incidence and clinical importance of interactions between these two devices, we reviewed our experience. Twenty-five had single chamber pacemakers (22 VVI, 1 VVIR, 2 antitach) and 5 patients had dual chamber pacemakers (1 DDDR). The 4 patients with unipolar pacemakers were revised to bipolar. Pacemaker/AICD interactions occurred in one patient whose AICD double counted the pacer stimulus and evoked QRS but did not cause false firings. No AICD inhibition during VF was seen. AICD/Pacemaker interactions occurred frequently. During AICD testing, 7 patients demonstrated transient (<60 sec) failure to capture and/or sense post discharge. Three patients demonstrated pacemaker reprogramming following an AICD discharge (2 to backup mode, 1 to off). Conclusions: 1) Pacemaker/AICD interactions including double counting and AICD inhibition are extremely uncommon with bipolar pacemakers, 2) AICD/Pacemaker interactions occur frequently and may result in transient failure to sense and capture as well as pacemaker reprogramming which may be clinically significant. With careful screening, the clinical importance of these interactions can be minimized.

**AUTOMATIC IMPLANTABLE CARDIOVERTER DEFIBRILLATOR: ANALYSIS OF SPONTANEOUS SHOCKS**

Hugh F McAlister MB, Jay Gross MD, Lon W Castle MD, FACC, John D Fisher MD, FACC, Victor A Morant MD, Anthony Mercando MD, Tony W Simmons MD, FACC, Bruce L Wilkoff MD, FACC, Seymour Furman MD, FACC, James D Maloney MD, FACC
The Cleveland Clinic Foundation; Cleveland, Ohio and Montefiore Medical Center; Bronx, New York

We analyzed the occurrence of shocks and its effect on prognosis in 125 pts implanted or followed with an automatic implantable cardioverter defibrillator (AICD) between 1982 and 1988 at 2 centers. There were 106 males, 19 females, aged 58±11 yrs; 99 had coronary disease, 20 cardiomyopathy, 6 other; ejection fraction (EF) was 33±13%, 38 (30%) were in NYHA classes III-IV. Shocks were assumed appropriate unless documented or strongly clinically suspected otherwise. At a follow-up of 20±17 mos, 66 pts (53%) had received ≥1 shock, of whom 22 (33%) had received ≥10. First shock occurred at 8±10 mos. Cumulative discharge occurrence rate at 6,12, 18,24,36 and 48 mos was 38%,53%, 61%,75%, 90% and 92% respectively. Of 18 pts without shocks at 18 mos, and followed to 36 mos, 11 (61%) received shocks during that time. Pts with shocks (GpA) and those without (GpB) had similar mean EF (33% vs 34%), no. in NYHA classes III-IV (30% vs. 31%), no. with coronary disease (79% vs. 80%), and no. initially presenting with sudden death (45% vs 43%). There were 22 deaths, 18 in GpA and 4 in GpB (p=0.005), at a mean of 12 mos after implant. Follow-up was 23±19 mos in GpA, 16±15 mos in GpB. One and 2 yr survival was 77% (n=53) and 67% (n=43) in gpA, and 91% (n=33) and 76% (n=17) in gpB (p=ns).
CONCLUSIONS: 1) Despite AICD efficacy, pts receiving shocks have a poorer prognosis. 2) 90% of pts followed 3 yrs had AICD shocks.

## Tuesday, March 21, 1989
## 10:30AM–12:00NOON, Marriott Hall North
## Anaheim Marriott Hotel
## Implantable Defibrillators II

**USE OF GRADIENT MAPS TO CREATE AN ELECTRODE CONFIGURATION WITH A MORE EVEN DEFIBRILLATION FIELD**

Anthony S. L. Tang, M.D., Patrick D. Wolf, M.S., William M. Smith, Ph.D., Raymond E. Ideker, M.D., Ph.D., Duke University Medical Center, Durham, NC

The potential gradient field produced through the ventricles by a shock is thought to be an important determinant for defibrillation efficacy. This study used potential mapping to determine the shock fields produced by three catheter and patch defibrillation electrode configurations. In 6 dogs, a catheter was inserted with RV apical (V) (2.8 sq cm) and RA (A) electrodes (1.4 sq cm). In the last 3 of the dogs, a second catheter was inserted with its distal electrode (2.8 sq cm) in the RV outflow tract (O). A cutaneous R2 patch (P) was placed on the left lateral thorax. Shock potentials were recorded simultaneously from 128 electrodes in the LV and RV subepicardium and subendocardium, the ventricular septum and the atria. After closing the chest, 50 mA shocks were given during diastole via V→A (V, cathode and A, anode); V→P; and V+O→P. Potential gradients were calculated at the subepicardium and subendocardium in mV/cm per volt of shock. The highest(H) and lowest(L) gradients (mean±SD) were:

| | V→A | V→P | V+O→P |
|---|---|---|---|
| H (mV/cm/V) | 101.3±5.7 | 82.7±34.2 | 57.2±5.7 |
| L (mV/cm/V) | 5.2±0.9 | 5.7±2.8 | 7.2±0.9 |
| ratio H:L | 20±8 | 17±8 | 8±1 |

V→A was most uneven, with low gradients at the LV apex. V→P was also uneven, with low gradients anteriorly. We attempted to raise the gradient anteriorly by adding O in the last 3 dogs. V+O→P created a more even field, decreasing the high gradient by furnishing an alternate current path and raising the low gradient by O's anterior location. This study suggests that mapping the shock potentials can guide the development of defibrillation electrode configurations which produce a more even potential gradient field.

**EFFECT OF SUCCESSFUL DEFIBRILLATION ON SUBSEQUENT DEFIBRILLATION THRESHOLD IN A CANINE MODEL OF RAPIDLY RECURRING CARDIAC ARREST.**

Sajad H. Mir B.S., Michael H. Lehmann M.D., F.A.C.C., Douglas Lang Ph.D., Russell Steirman M.D., Claudio Schuger M.D., Harper Hosp./Wayne State Univ., Detroit, MI

During implantation of the automatic cardioverter defibrillator (AICD), defibrillation thresholds (DFTs) are assessed using induced episodes of ventricular fibrillation (VF) separated by several minutes. However, AICDs may be required to function in settings of more rapidly recurring VF, when DFTs might be altered. To investigate this possibility we studied 10 open-chest, anesthetized and ventilated mongrel dogs. An external defibrillator was attached to 2 epicardial patch electrodes. In the single arrest (VFx1) protocol, VF was induced via myocardial plunge electrodes; 15 sec later, a test shock was delivered across the patch electrodes. The double arrest (VFx2) protocol modeled a scenario in which VF recurs shortly after successful defibrillation (SDF) with a 30J AICD shock. This was mimicked by first inducing VF and, 15 sec later, defibrillating with a 30J shock; then, following only a 15 sec recovery period, VF was again induced for 15 sec before the test shock. Test energy bandwidths for each protocol were centered on the initially determined conventional "DFT" (beginning with 20J shocks, and decrementing by 2J). Each shock energy was then randomly tested four more times (with 5 min rest between protocols). Data relating percent SDF to energy were used to construct sigmoidal "dose-response" curves. Mean (±SE) energies corresponding to 50% (E50) and 80% (E80) SDF were: 8.4 ± 1.2J and 10.4 ± 1.5J for VFx1 vs. 8.7 ± 1.2J and 10.2 ± 1.3J for VFx2, respectively (p=NS). Findings in this canine model suggest that with promptly terminated VF, there is no cumulative rise in DFT (E80) during rapidly recurring episodes.

## INCREASED DEFIBRILLATION THRESHOLD AND CARDIAC HYPERTROPHY IN A RAPID PACING MODEL OF CONGESTIVE HEART FAILURE IN THE DOG

S. Deborah Lucy M.Sc., Douglas L. Jones Ph.D., George J. Klein M.D., F.A.C.C., University of Western Ontario and J.P. Robarts Research Institute, London, Ontario, Canada

Patients with idiopathic congestive cardiomyopathy, prone to arrhythmia and sudden death, are candidates for an implantable automatic defibrillator. It is unknown if the progressive hypertrophy in these patients influences the energy necessary for defibrillation. We evaluated this influence of hypertrophy using a rapid ventricular pacing model of heart failure in the dog. Following electrophysiological and hemodynamic assessment, adult mongrel dogs were randomly assigned to one of two groups: 1) control, those having standard transvenous pacemaker implants set to demand pacing at 70 beats per minute (bpm), (n=6) or 2) rapidly paced, those having a custom modified pacemaker (Medtronics Inc.) set to pace at 240 bpm, (n=6). Seventeen days post implant, three evenly spaced epicardial mesh electrodes (Medtronic, TX-7) were sutured onto the basal ventricular surface for sequential pulse defibrillation. Three replicate defibrillation thresholds were obtained from each animal. Average defibrillation threshold was five times higher in the rapidly paced group, 13.3 ± 4.4 joules (mean ± SD), than the control group, 2.9 ± 1.4 joules ($p < .01$). Ventricular weight corrected for body weight was significantly higher in the rapidly paced dogs, 15.5 ± 1.4 g/kg$^{0.75}$, versus 12.5 ± 1.4 g/kg$^{0.75}$ of the control dogs ($p < .01$). We conclude that ventricular hypertrophy may profoundly increase the minimum energy required for ventricular defibrillation.

## A COMPARISON OF SINGLE AND DOUBLE CAPACITOR BIPHASIC WAVEFORMS FOR INTERNAL DEFIBRILLATION

Katherine M. Kavanagh, M.D., Anthony S.L. Tang, M.D., Dennis L. Rollins, M.S., William M. Smith, PhD., Raymond E. Ideker, M.D., PhD., Duke University Medical Center, Durham, NC

Truncated exponential biphasic waveforms have been shown to reduce energy requirements for internal defibrillation. The use of a single output capacitor for defibrillation would reduce the size of implantable devices. For double capacitor biphasic waveforms (DCBW's), the leading edge voltage of the second phase (V2l) usually equals the negative of the leading edge voltage of the first phase (V1l). For single capacitor biphasic waveforms (SCBW's), V2l equals the negative of the trailing edge of the first phase of the waveform. This study compared the defibrillation energy requirements of SCBW's and DCBW's. The cathode consisted of two 3.25 cm long transvenous catheter electrodes, one in the RV apex, the other in the RV outflow tract. The anode consisted of a 113.0 sq cm cutaneous left chest wall electrode patch. Defibrillation thresholds were established within 40 volts using a modified Bourland technique in 8 anesthetized dogs (25.6 ± 2.6 kg). All biphasic waveforms were 6/6 msec duration.

| | DEFIBRILLATION THRESHOLD | | |
|---|---|---|---|
| | V1l | V2l | Joules |
| SCBW | 258±21 | -99±13 | 5.7±0.8 |
| DCBW | 334±48 | -333±49 | 16.9±5.7 |
| p | 0.005 | 0.001 | 0.001 |

The total energy required for defibrillation using this SCBW was one third of that required for the DCBW. The use of the SCBW unexpectedly resulted in a significant reduction not only of energy, but also of V1l required for defibrillation when compared to the DCBW. In conclusion, the SCBW requires only a small amount of energy for successful defibrillation and is significantly more energy efficient than the DCBW.

## DOES ELECTRODE POLARITY INFLUENCE DEFIBRILLATION EFFICACY FOR THORACOTOMY AND NON - THORACOTOMY INTERNAL DEFIBRILLATION?

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To assess the effect of electrode polarity upon defibrillation efficacy for thoracotomy (N=6) and non-thoracotomy (N=6) lead systems, 12 dogs (23.9 ± 1.9 kg) underwent defibrillation trials using monophasic (M) and single capacitor biphasic (B) shocks of 10 msec total duration. B shocks had a 5 msec positive phase followed by a 5 msec negative phase. The thoracotomy defibrillation pathway consisted of two 13.9 cm2 patch electrodes placed on the epicardium anteriorly and posteriorly while the non-thoracotomy defibrillation pathway consisted of a 4 cm2 right ventricular catheter electrode paired with a 13.9 cm2 subcutaneous chest wall patch electrode. Each polarity configuration was tested 4 times against AC induced ventricular fibrillation at 5 different voltage levels and efficacy curves were constructed using logistic regression analysis. Energies associated with 80% probability of defibrilation (E80) were compared:

| | THORACOTOMY | | | NON-THORACOTOMY | |
|---|---|---|---|---|---|
| | Mono E80 | BI E80 | | Mono E80 | BI E80 |
| LV Post(-) | 14.1 | 9.6 | Cath(-) | 24.9 | 15.0 |
| Ant(-) | 14.4 | 9.8 | Patch(-) | 25.0 | 14.9 |

For all lead configurations, B waves were superior to M waves ($p<0.001$). Change in polarity did not affect defibrillation energy requirements for either thoracotomy or non-thoracotomy model. Conclusion: Polarity does not significantly affect defibrillation energy requirement of normal canine hearts for M or B waveforms using thoracotomy or non-thoracotomy lead systems.

## THE STRENGTH OF MONOPHASIC AND BIPHASIC SHOCKS THAT CAUSE CONDUCTION BLOCK

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Biphasic (B) shocks defibrillate at lower energy than monophasic (M) shocks. Potential gradients (PGs) >100 V/cm are created near cardiac defibrillation electrodes during shocks. We determined if such PGs cause conduction block and if conduction is impaired less with B than M shocks. In 6 dogs, simultaneous recordings were made on the upper anterior RV from 117 epicardial electrodes over a 32 x 30 mm area. S1 pacing (350 ms cycle length) from a long narrow electrode on the right side of the mapped area generated parallel activation isochrones. At 300 ms after the last S1, a 10 ms M or 5-5 ms B shock of 70 to 850 V was delivered via a mesh titanium electrode cathode on the left side of the mapped area with the anode on the RA. Eighty shocks created PGs of 1.4 to 190.3 V/cm with high PGs on the left and low PGs on the right side of the mapped area. S1 pacing from the right side was reinitiated 0.2 sec after the shock. The first post shock activation propagated as before the shock where PG was weak, but blocked without conducting into areas where PG was >64±7 V/cm for M and >72±6 V/cm for B shocks. These values are significantly different ($p<0.01$). As shown below for both M and B shocks, the higher the PG, the longer was the duration of block before conduction returned.

| Duration (sec) | 0.55 | 0.9 | 2 | 5 | 10 | 15 | 30 |
|---|---|---|---|---|---|---|---|
| PG (V/cm) M | 76 | 79 | 94 | 110 | 116 | 133 | 131 |
| PG (V/cm) B | 81 | 87 | 104 | 113 | 123 | 128 | 141 |

Thus, conduction block can follow either B or M shocks, but the PG causing block is greater for B than M shocks. This effect may partially explain the increased defibrillation efficacy of B shocks, if reentry circuits can form around regions of block and lead to the resumption of fibrillation.

# Tuesday, March 21, 1989
# 8:30AM–10:00AM, California Room D
# Anaheim Convention Center
# Transesophageal Echocardiography

TRANSTHORACIC VERSUS TRANSESOPHAGEAL TWO-DIMENSIONAL ECHO/DOPPLER FLOW IMAGING IN SURGICAL PATIENTS WITH MITRAL REGURGITATION.

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Precise determination of abnormalities of the mitral apparatus is necessary in planning mitral valve reconstruction. To date the comparison of transthoracic (TTE) to transesophageal(TEE) in assessing the mitral support apparatus has not been reported. Therefore, we compared TTE with intraoperative TEE echocardiography in 16 patients (pts) undergoing mitral valve repair. The mean age was 64 yrs (42-87), 15 patients were male. TTE transducer frequency was 2.5 mHz and TEE was 5 mHz. The echocardiographic findings were compared with surgical observations.

| Anatomy | TTE (Pt#) | TEE (Pt#) | Operative Findings (Pt#) |
|---|---|---|---|
| Prolapse | 7 | 8 | 8 |
| Flail Leaflet | 5 | 8 | 8 |
| Ruptured Chordae | 3 | 12 | 12 |
| Regurgitation Severity | | | |
| Severe | 12 | 14 | |
| Moderate | 4 | 2 | |

There was a high concordance between TEE and operative findings. Mitral valve repair was successful in all pts. Conclusions: 1) TEE was highly accurate in delineation of morphological abnormalities of the mitral apparatus. 2) TEE was superior to TTE in the diagnosis of ruptured chordae tendinae and flail segments. 3) There was a high concordance between TTE and TEE in determining the severity of mitral regurgitation.

TRANSESOPHAGEAL 2D COLOR-CODED DOPPLER ECHOCARDIOGRAPHY DURING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY.

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As transesophageal echocardiography provides stable recording positions and high-quality images, we determined at LV papillary muscles level, in 9 anesthetized pts, before and during percutaneous transluminal coronary angioplasty (PTCA), the % increase/decrease (Δ) of: percentage area reduction (PAR), regional area ejection fraction (RAEF) of area at risk, and end-systolic meridional wall stress (MWS; dyne/cm²). In addition, early (E)/atrial (A) transmitral peak flow velocity and time-velocity integral (TVI; cm) were obtained at annular level; as well as mitral regurgitation (MR) development. All pts had normal LV function and no MR at baseline; 26 ischemic periods were monitored, 18 left anterior descending artery (LAD) and 8 of right coronary artery (RCA).

| | LAD | | | | RCA | | | |
|---|---|---|---|---|---|---|---|---|
| | control | | PTCA | Δ | control | | PTCA | Δ |
| PAR | 60 ±6 | * | 48±5 | 23 | 56 ±5 | ** | 50 ±4 | 11 |
| RAEF | 57 ±6 | * | 31±10 | 96 | 51 ±9 | * | 21 ±4 | 17 |
| E/A | 1.2±.3 | * | .9±.3 | 37 | 1.2±.2 | ns | 1.1±.2 | 18 |
| TVI | 12 ±1.9 | * | 10±1.5 | 16 | 11 ±1.7 | ns | 11 ± 1.2 | 2 |
| MWS | 72 ±17 | * | 111±17 | 56 | 75 ±10 | * | 98 ±16 | 30 |

* p<.001; ** p<.01

During PTCA Δ of all variables were significantly (p<.01) different between LAD and RCA pts. MR during PTCA was only seen during RCA occlusion.

Conclusions: 1) Both global and regional LV function are more affected by LAD than by RCA occlusion. 2) Rearrangement of LV inflow and decrease of TVI during PTCA is only seen in LAD pts. 3) MR was only seen during RCA occlusion.

**TRANSESOPHAGEAL ECHO COMPUTER TOMOGRAPHY: A NEW METHOD FOR DYNAMIC 3-D IMAGING OF THE HEART**

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The limited acoustic windows of the chest wall prevent imaging of a sufficient number of parallel sections to permit complete spatial reconstruction of the heart. Transesophageal echocardiography provides unrestricted access for ultrasonic imaging of the heart, but is limited by varying transducer positions and thus different imaging planes. Therefore, we developed a new device for the acquisition of standardized parallel echocardiographic imaging planes covering the entire heart and the great vessels.

This device consists of a conventional transesophageal probe with an additional fully flexible distal portion serving as housing for the ultrasonic transducer, which is mounted on a sliding carriage. After insertion of the probe into the distal esophagus and visualization of a cross sectional view of the left ventricular apex, the housing (extending over 20 cm) is mechanically straightened to form a rigid tube, thus allowing the transducer to slide in axial direction. Thereafter, the transducer is pulled back in 0.5 mm increments by means of an ECG gated, computer controlled step motor providing exact parallel and equidistant imaging planes. At each level, a complete cardiac cycle is recorded with ECG triggering and stored in the memory of an image processing computer. 256*256*256*8 bit cubic data sets are generated in 30 msec intervals corresponding to the echocardiographic frame rate. A dedicated software for dynamic 3-D reconstruction allows the computation of any desired tomographic view of the beating heart and the great vessels.

Initial clinical application of transesophageal echo computer tomography demonstrated the applicability of this technique and resulted in high quality computed tomographic echo images of the dynamic cardiac anatomy, providing unique new views of the beating heart.

OVERESTIMATION OF REGURGITANT JET AREA BY TRANSESOPHAGEAL AS COMPARED TO TRANSTHORACIC COLOR DOPPLER

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Transesophageal echocardiography(TEE) with color Doppler flow imaging(CDFI) has been widely applied for the quantitative estimation of valvular regurgitation(REG). However, because of differences in depth, transmitting frequencies and attenuation, the existing criteria employed for estimating severity of REG by transthoracic echo(TTX) may not apply. We compared TTX and TEE for 16 regurgitant lesions. The maximal jet areas for 7 MR, 5 AR and 4 TR lesions were traced from 4 and 5-chamber views by TEE and compared with equivalent views by TTX. For TTX, imaging was performed using 2.5 MHz transducers at an average scale of 16.0 cm while a 5 MHz probe was used for all TEE studies and at average scale of 12.4 cm. Two observers traced the largest definable REG jet area for each lesion from 3 cardiac cycles and results were averaged. Jet areas for TTX studies ranged from 0.8 to 14.4 $cm^2$ (mean = 4.5 + 3.6 $cm^2$). The same lesions from comparable TEE studies ranged from 1.4 - 12.3 $cm^2$ (mean = 6.2 + 3.6 $cm^2$). TEE jet areas were larger (p = .025) than TTX areas in 14/16 lesions, with a mean difference of 1.6 $cm^2$. There was a fair correlation for jet areas by the two techniques with r = .74 but a systematic overestimation by TEE; TTX = .74TEE + .04. Thus, TEE REG jet areas are larger than those obtained from TTX images using CDFI. This finding is important in the quantitative estimation of valvular REG, especially during intraoperative monitoring. A baseline TEE study, performed intraoperatively prior to sternotomy, is indicated for comparison in patients undergoing valve surgery.

**TRANSESOPHAGEAL ECHO IN MITRAL PROSTHETIC DYSFUNCTION: ECHO - SURGICAL CORRELATION**

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Due to shielding of the LA, diagnosis of mitral prosthetic dysfunction by precordial echo is difficult. We compared transesphageal echo and color flow Doppler (**TEE**) to surgical findings in determination of the mechanism of mitral dysfunction in 60 consecutive pts who underwent **TEE** and subsequently had reoperation for mitral valve replacement. There were 37 bioprosthetic valves and 23 mechanical valves. All 30 pts with central prosthetic mitral regurgitation (**MR**) by **TEE** were confirmed at surgery. All 27 pts with periprosthetic **MR** by **TEE** were confirmed at operation. The sites of periprosthetic **MR** by **TEE** were correctly predicted in 25/27 of these pts. The most common lesion for bioprostheses was central prosthetic **MR** (26/37 pts) and for mechanical was periprosthetic **MR** (16/23 pts). 10/11 pts with predominant prosthetic stenosis by **TEE** were confirmed at surgery; 1 pt with mild stenosis by **TEE** and moderate stenosis by catheterization, had no stenosis at surgery. All 4 pts with definite vegetations by **TEE** were confirmed at operation. In 2 pts small echodensities on the prosthesis were diagnosed as possible vegetations by **TEE**, but were not confirmed as vegetations at operation. In 9 pts, LA thrombus detected by **TEE** were confirmed in all pts at operation. Only 1 pt was falsely negative for thrombus by **TEE**, however this was very small intraprosthetic laminated thrombus at surgery.

**Conclusions**: **TEE** for mitral prosthetic dysfunction is extremely accurate and reliable. **TEE** is the new diagnostic standard of accuracy in this disorder.

MITRAL PROSTHESIS MALFUNCTION: UTILITY OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY.

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Ultrasonic shadowing by prosthetic material reduces the usefulness of standard transthoracic 2-D/Doppler echo (2DE) in the assessment of mitral prosthesis (MP). Transesophageal echocardiography (TEE) allows an unobstructed window for imaging left atrium and posterior MP. We performed TEE in 55 Pt (39 females), mean age 62 yrs (range 16-86 yrs) with suspected MP dysfunction (mechanical MP 40 Pt, bioprosthetic MP 15 Pt). Indication for 2DE: abnormal clinical examination 26, thromboembolism 12, endocarditis 7, miscellaneous 10. Standard transthoracic 2DE detected MP regurgitation in 13/55 (24%) Pt. TEE, however, detected abnormal MP in 28/55 (51%) including: vegetation/abscess (4 Pt), significant regurgitation (20 Pt) [11 perivalvular, 9 valve dysfunction, (7 torn cusp, 3 partial dehiscence)], obstructed valve (2 Pt) and thrombus (2 Pt). TEE more accurately delineated the site of regurgitation in the 13 Pt identified as abnormal by standard 2DE. Operation in 23 Pt showed findings concordant with TEE in 21 (91%); 2 Pt had small thrombus [sewing ring (1 Pt), ventricular surface of ball (1 Pt)], 15/23 Pt (66%) had operation without catheterization. Conclusion: TEE is superior to standard 2DE for the assessment of MP dysfunction and is particularly suited for the diagnosis of vegetations/abscess, and for semiquantitation and accurate localization of the site of MP regurgitation.

## Tuesday, March 21, 1989
## 10:30AM–12:00NOON, California Room D
## Anaheim Convention Center
## Balloon Mitral Valvuloplasty Hemodynamic Effects

RAPID REDUCTION OF PLASMA ATRIAL NATRIURETIC PEPTIDE AFTER BALLOON MITRAL VALVULOPLASTY IN PATIENTS WITH MITRAL STENOSIS.

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To demonstrate the direct effect of the left atrial pressure (LAP) on secretion of human atrial natriuretic peptide (hANP), we studied the relationships between plasma hANP levels, neurohumonal factors and hemodynamic changes in 16 patients with mitral stenosis undergoing balloon mitral valvuloplasty (BMV). Thirty minutes after BMV, LAP fell in all patients significantly, while there were no remarkable changes in either right atrial pressure, mean arterial pressure and heart rate. Plasma hANP levels in the pulmonaly artery significantly decrease and plasma aldosterone concentration (PAC) increased 30 minutes after BMV. However there were no remarkable changes in plasma renin activity and plasma norepinephrine concentration. There was a significant correlation between the decrement of hANP levels and that of LAP ($r=0.73$, $p<0.005$). However, there was no significant correlation between the decrement of hANP and the increment of PAC.

| | pre | post | (mean±SE) |
|---|---|---|---|
| LAP (mmHg) | 13.6±1.6 | 6.2±0.6 | p<0.0005 |
| hANP (pg/ml) | 262±43 | 129±25 | p<0.0005 |
| PAC (pg/ml) | 11.0±1.3 | 15.5±2.3 | p<0.05 |

These data suggest that the rapid reduction of LAP directly influenced hANP secretion. And the reduction of hANP had no influence to other neurohumoral factor. So left atrial pressure as well as right atrial pressure had importante role in the secretion of hANP.

PERCUTANEOUS MITRAL VALVOTOMY USING THE DOUBLE BALLOON TECHNIQUE: DETERMINANT FACTORS OF MITRAL REGURGITATION.

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Percutaneous mitral valvotomy(PMV) was successfully performed in 62 (95%) out of 65 Pts (18M, 44F, mean age: 38 ±10 yrs) with mitral stenosis. There was an increase in mitral valve area(MVA) (0.9±0.2 to 2.0±0.7 cm2,$p<0.0001$), a decrease in mean mitral gradient (17±7 to 6±3 mmHg, $p<0.0001$) and a rise in CO (4.3±0.8 to 4.8±1.2 L/min, $p<0.01$).Mitral regurgitation(MR) developed or increased in severity in 26(42%). Complications included embolic episode in 2, cardiac tamponade in 2 and creation of ASD(Qp/Qs>1.5) in 12. The morphologic features of the stenotic mitral valve was evaluated using echocardiographic score (1-4 represent the severity of valve mobility,thickening, calcification and subvalvular lesions). Pts with low-score (≤8) had more effective dilation in MVA after PMV compared with Pts with high-score (>8)(0.9 to 2.2 vs 0.8 to 1.4 cm2,$p<0.001$) despite of the similar EBDA/BSA(effective balloon dilating area/body surface area, 4.02 vs 4.03). Pts with an incease in MR had relatively larger EBDA/BSA,more thickened and stiffer leaflets, and higher total score. ( * $p<0.05$, ** $p<0.01$ vs group A )

| GROUP | A.NO MR | B.INCREASE IN MR=1+ | C. MR ≥ 2+ |
|---|---|---|---|
| No. of Pts | 36 | 14 | 12 |
| EBDA/BSA | 3.8 ±0.4 | 4.1 ±0.4 | * 4.3 ±0.6 |
| Thickening | 1.9 ±0.5 | ** 2.4 ±0.5 | * 2.3 ±0.5 |
| Mobility | 1.4 ±0.5 | * 1.7 ±0.5 | 1.7 ±0.5 |
| Total score | 7.3 ±1.4 | * 8.4 ±1.6 | 8.2 ±1.2 |

Conclusion:1) PMV using double-balloon technique is safe and effective procedure in selected Pts; 2)MVA after PMV was more effectively dilated in Pts with low-score; 3) An increase in MR might be related to EBDA/BSA, valvular thickening and mobility, and echocardiographic score.

HEMODYNAMIC RESULTS AND FOLLOW-UP OF PATIENTS WITH IATROGENIC ATRIAL SEPTAL DEFECT FOLLOWING BALLOON MITRAL VALVULOPLASTY

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21 of 85 pts undergoing balloon mitral valvuloplasty demonstrated significant post-procedure atrial septal defects (ASD) by oximetry, with a mean Qp/Qs ratio of 1.4 (range 1.1 to 2.3). Compared with the other pts, those pts with an ASD had lower post-procedure systemic blood flow (SBF) ($p<.01$), less of an increase in calculated mitral valve area (MVA) ($p<.01$), and higher post-procedure right atrial and mean pulmonary artery pressures ($p<.05$). Mitral valve gradient (MVG) was identical in the two groups. Pre- and post-valvuloplasty hemodynamic data are summarized below (mean ± standard error).

| | Patients with ASD | | Patients without ASD | |
|---|---|---|---|---|
| | pre | post | pre | post |
| SBF (l/min) | 3.7±.2 | 4.0±.2 | 4.4±.2 | 5.3±.2 |
| MVA ($cm^2$) | 0.9±.07 | 1.5±.07 | 1.0±.04 | 2.0±.1 |
| MVG (mmHg) | 14.2±1.3 | 6.6±.6 | 13.8±.6 | 6.6±.4 |
| RA (mmHg) | 9.8±.9 | 11.2±1.1 | 7.7±.8 | 6.6±.8 |
| PA (mmHg) | 45±5 | 36±3 | 37±2 | 30±1 |

Development of an ASD tended to correlate with use of a large single balloon vs primary use of two smaller balloons ($P<.10$). Late follow-up (mean of 14 months, range 1-33 months) revealed no difference in mortality or symptom recurrence in the two groups. One patient with ASD (Qp/Qs of 1.5) and pre-existing tricuspid regurgitation has developed worsening right sided congestive heart failure. Conclusion: Iatrogenic ASD after balloon mitral valvuloplasty is associated with less initial hemodynamic improvement but no significant difference in clinical outcome at an average follow-up of 14 months.

BALLOON MITRAL VALVULOPLASTY : A MULTICENTRE STUDY

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Eighty patients (pts) with tight mitral stenosis who were symptomatic despite medical therapy underwent percutaneous balloon mitral valvuloplasty (PBMV). There were 57 females and 23 males. The mean age was 31 years. All pts were in NYHA functional class III or IV. Six pts had previous closed mitral commissurotomy. PBMV was performed trans-septally using a single catheter (Trefoil or Bifoil) in 48 pts and 2 single balloon (2x20mm) catheters in 27 pts. PBMV was successful in 74 pts (92%). The results were as follows (mean ± SD):

| | Pre PBMV | Post PBMV |
|---|---|---|
| Mitral valve area ($cm^2$) | 0.85 ± .19 | 2.31 ± .67 * |
| Cardiac output (l/min) | 3.46 ± .77 | 4.30 ± .85 * |
| Mean gradient (mmHg) | 13.1 ± 5.9 | 3.9 ± 2.5 * |

*p <0.0001

There was no difference in the results obtained with the single catheter vs the double catheter technique. Complications included 2+ mitral regurgitation in 7 pts. Atrial septal defect with shunt ratios < 1:1.5 were detected in 13 pts. One pt died. Cardiac tamponade developed in 2 pts. Three pts underwent MVR for persistent symptoms related to mitral regurgitation. Two pts underwent successful repeat valvuloplasty for recurrent symptoms due to valve restenosis. The remaining pts remain clinically well at a mean follow-up of 6 months and serial echo studies have not shown restenosis in this group.

Conclusion: PBMV is an effective therapy for the relief of symptomatic tight pliable mitral stenosis. The use of a single catheter (Trefoil or Bifoil) or the double balloon catheter appears to be equally effective in relieving the stenosis.

PERCUTANEOUS MITRAL VALVOTOMY INCREASES LEFT ATRIAL COMPLIANCE WITHOUT AFFECTING ITS PRESSURE-VOLUME CURVE

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In order to investigate the changes in atrial (LAC) and ventricular (LVC) compliance caused by percutaneous mitral valvotomy (PMV), we studied 10 patients prospectively immediately before and after PMV. Compliance is taken to be the instantaneous ratio of volume change to pressure change. Pressures were obtained transseptally and cardiac output by thermodilution. Mean LAC was defined as (stroke volume)/(magnitude of atrial V-wave), and thus is considered to include the pulmonary veins in a common elastic chamber; mean LVC was defined as (stroke volume)/(ventricular end-diastolic pressure). **RESULTS:** LAC increased by 130% immediately after PMV, from 3.19±1.97 $cm^3$/mmHg (mean±S.D.) to 7.34±3.95, $p<0.005$, whereas LVC was unchanged, 4.84±3.66 $cm^3$/mmHg pre-PMV to 5.01±4.08 post-PMV ($p$ = NS). Mean LAC and atrial pressure data were then used to construct postulated exponential pressure-volume relationships. The data for individual patients were well fit by the same set of curves pre- and post-PMV ($r = 0.89$). Even the pooled atrial data from all patients could be fit by a single pressure-volume curve that held equally well before and after PMV: PRESSURE = exp(VOLUME/91.9), $r=0.62$, $p<0.01$. The left ventricular data was similarly fit best by a single relationship pre- and post-PMV: PRESSURE = exp(VOLUME/35.5). **CONCLUSION:** PMV causes a significant increase in mean LAC and insignificant changes in LVC. These changes appear to result from shifts along a given pressure-volume curve, rather than any significant change in the material properties of the chambers.

RESULTS AND FOLLOW-UP OF A MULTICENTER REGISTRY FOR BALLOON MITRAL VALVULOPLASTY

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The M-Heart registry for percutaneous balloon mitral valvuloplasty (PMV) has entered 50 pts in 7 centers with a mean (±SEM) age of 53 ± 2 years (range 14-85). All pts had heart failure: NYHA class II (n=15), III (n=27), or IV (n=9). Hemodynamic results of PMV follow (*$p<0.001$, MVA = mitral valve area):

| | MVA ($cm^2$) | Gradient (mmHg) | CO (l/min) | $\overline{LA}$ (mmHg) | $\overline{PA}$ (mmHg) |
|---|---|---|---|---|---|
| pre-PMV | 0.9 ± 0.04 | 15 ± 1 | 4.1 ± 0.1, | 26 ± 1 | 37 ± 2 |
| post-PMV | 2.0 ± 0.1* | 7 ± 1* | 4.7 ± 0.2* | 17 ± 1* | 32 ± 2* |

A successful procedure defined as a final MVA ≥ 1.2 $cm^2$ and final gradient ≤ 10 mmHg was obtained in 78% of attempted PMV. Fifteen pts (30%) experienced complications including: LV perforation and death (1), cardiac tamponade (1), cardiac arrest (2), systemic embolism (4). Mitral regurgitation grade increased in 7/30 pts (23%).

Follow-up was obtained in 39 pts at 6.4 ± 0.7 months. Restenosis occurred in 5 pts (13%), and was treated with mitral valve replacement (3 pts) or re-dilation. Thirty-three pts (85%) felt improved, including 23 pts who became asymptomatic. Mean NYHA class improved from 2.9 ± 0.1 to 1.5 ± 0.1 ($p<0.0001$).

**Conclusions:** 1) PMV can be successfully performed in the majority of pts, and results in marked clinical improvement by 6 months of follow-up. 2) 78% of attempted procedures were successful, but complications occurred in 30% of pts and may limit widespread application.

# Tuesday, March 21, 1989
# 8:30AM–10:00AM, Garden Grove Room
# Anaheim Convention Center
# Valvular Regurgitation: Factors Affecting Outcome

SUPPRESSION OF CARDIAC PROTEIN DEGRADATION CONTRIBUTES TO PROGRESSIVE HYPERTROPHY DUE TO AORTIC REGURGITATION.
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To determine in vivo the contributions of protein synthesis and degradation to the progressive hypertrophy occurring after surgical induction of aortic regurgitation (AR), infusions of 3-H leucine were performed in 24 rabbits 3 days(3D) and 1 month(1M) following AR induction, in 12 sham-operated controls, and in 7 normal rabbits. Total cardiac protein fractional synthesis(Ks) and degradation(Kd) rates per day [obtained from subtraction of growth rates(Kg) from Ks] were calculated from plasma and total cardiac protein hydrolysate data. Results are expressed as mean % per day ± SD:

| | Ks | | Kg | Kd | |
|---|---|---|---|---|---|
| Normals(n=7) | 4.7±0.8 | | +0.0 | 4.7±0.8 | |
| 3D Sham(n=6) | 4.8±0.8 | p<.01 | -0.4 | 5.2±0.8 | p<.05 |
| 3D AR(n=12) | 6.5±1.3 | | +2.4 | 4.1±1.3 | |
| 1M Sham(n=5) | 5.6±0.4 | p<.01 | -0.5 | 6.1±0.4 | p<.01 |
| 1M AR(n=12) | 4.9±0.7 | | +0.7 | 4.2±0.7 | |

We conclude that an increase in total cardiac protein synthesis occurs only during the early phase of hypertrophy following acute AR induction, accounting for the more rapid hypertrophic response during this period. However, a reduction in cardiac protein degradation also occurs acutely and appears to be the primary cause of the slower, progressive hypertrophy occurring one month following AR induction.

IMPORTANCE OF CONTRACTILITY IN DETERMINING LEFT VENTRICULAR SIZE AND PERFORMANCE IN PATIENTS WITH AORTIC REGURGITATION.
Mark R. Starling, M.D., F.A.C.C., University of Michigan and VA Medical Centers, Ann Arbor, Michigan.
To determine the importance of contractility in determining LV size and performance before and following aortic valve replacement (AVR) in Pts with aortic regurgitation (AR), we studied 26 Pts with AR using micromanometer LV pressures and radionuclide LV volumes (V) during right atrial pacing. Depressed LV contractility was defined as 2 standard deviations below the mean maximum time-varying elastance slope (Emax) of 5.06±1.54mmHg/ml obtained in 25 normal Pts. Prior to AVR, Pts with AR and preserved LV contractility had higher LV systolic pressures ($p<0.05$), smaller LV end-diastolic and end-systolic Vs ($p<0.01$ for both), and higher LV ejection fractions (58±9%, $p<0.05$) compared to Pts with AR and depressed LV contractility (LV ejection fraction 48±12%). In 6 Pts with AR and preserved and 9 Pts with AR and depressed LV contractility, AVR was performed. In those with preserved LV contractility, LV end-diastolic and end-systolic Vs and ejection fraction did not change. In contrast, in the Pts with AR and depressed LV contractility, LV end-diastolic and end-systolic Vs decreased ($p<0.01$ for both) and the LV ejection fraction increased modestly from 49 to 55%. These data suggest that, in contrast to Pts with AR and preserved LV contractility, Pts with AR and depressed LV contractility may have increased LV size and reduced LV performance because of a contractile-dependent afterload mismatch. Following AVR, the afterload mismatch is alleviated and, thus, LV size and performance are no different at 3 to 6 months following AVR in Pts with AR and preoperative preserved or depressed LV contractility.

RIGHT AND LEFT VENTRICULAR RESPONSE EARLY AND LATE AFTER SURGICAL RELIEF OF MITRAL REGURGITATION.
Jeffrey Borer M.D., FACC, Clare Hochreiter M.D., FACC, Nathaniel Niles M.D., FACC, Mary Roman M.D., Richard Devereux M.D., FACC, Paul Kligfield M.D., FACC, Cornell Medical Center, New York, NY.

Previous observations indicate that left(L) ventricular (V) ejection fraction(EF) falls early after complete surgical relief (MVR) of mitral regurgitation(MR). However, late response of LVEF to MVR, and its course of development, have not been determined, while response of right(R) VEF (recently shown by us to be prognostically important in unoperated MR) is unknown. Therefore, among 21 pts with successful MVR, we used radionuclide angiography to prospectively assess LV and RVEF at rest(r) and exercise (ex) pre-op, <1yr post-op and annually thereafter for up to 7 yrs. While LVEFr decreased from pre-op to 5-12 mos post-op(50% to 47%, $p=.057$), by end of yr 2 this early value had increased (+5%,$p<.05$). Though later improvement occurred in some pts (particularly with subnormal LVEFr pre-op), av LVEFr did not vary significantly and at last follow-up was 52% ($p=.3$ vs pre-op). In contrast, pre-op RVEFr rose markedly by 5-12 mos post-op(38% to 46%,$p<.01$) and 3% further ($p<.05$) at later follow-up; RVEFr normalized in all 4 pts who were subnormal pre-op. Late ex response to MVR was even more striking: LVEFex=50% pre to 55% post ($p<.02$); RVEFex=32% pre to 45% post($p<01$). We conclude: MVR for MR can cause early deterioration in LV performance, but gradual improvement then can be expected, with normalization in most patients by 2 yrs post-op; in contrast, RV performance improves dramatically early post-op, with modest later improvement. These findings may help explain the excellent long term survival we recently reported post MVR even among pts with markedly depressed RVEFr and LVEFr pre-op.

UTILITY OF LEFT VENTRICULAR ELASTANCE FOR PREDICTING SURGICAL OUTCOME IN PATIENTS WITH MITRAL REGURGITATION.
Mark R. Starling, M.D., F.A.C.C., University of Michigan and VA Medical Centers, Ann Arbor, Michigan.
To determine whether calculating LV elastance is useful for predicting surgical outcome in Pts with mitral regurgitation (MR), we studied 16 Pts with MR using micromanometer LV pressures (P) and radionuclide LV volumes (V) during right atrial pacing. LV contractility was assessed as the maximum slope (Emax) of the linear regression of multiple, isochronal P-V data points. Depressed LV contractility was defined as 2 standard deviations below the mean Emax slope of 5.06±1.54mmHg/ml obtained in 25 normal Pts. LV contractility was depressed in 12 Pts with MR and preserved in 4 Pts with MR. The Pts with MR and preserved LV contractility had higher LV systolic P ($p<0.05$) and smaller LV end-diastolic and end-systolic Vs ($p<0.01$ and 0.05) compared to Pts with MR and depressed LV contractility. In contrast, they had LV ejection fractions (60±9%) and (+)dP/dtmax (1441±405mmHg/sec) values which were comparable to those in Pts with MR and depressed LV contractility (55±12% and 1077±337mmHg/sec). In 7 Pts with MR and depressed and 2 Pts with MR and preserved LV contractility, mitral valve replacement was performed. In those with preserved LV contractility there was no significant change in LV end-diastolic and end-systolic Vs or LV ejection fraction (63 vs. 63%). In contrast, in those with depressed LV contractility, LV end-diastolic and end-systolic Vs increased modestly and LV ejection fraction decreased (55 to 42%, $p<0.01$). These data suggest, therefore, that using the elastance concept to assess LV contractility will be useful for predicting the LV functional response to mitral valve replacement in Pts with MR.

**PREDICTION OF RISK FOR COMPLICATIONS IN PATIENTS WITH LEFT SIDED INFECTIOUS ENDOCARDITIS.**

Anthony J Sanfilippo MD, Michael H Picard MD, Ravin Davidoff MD, James D Thomas MD, Arthur E Weyman MD FACC. Massachusetts General Hospital, Boston MA.

Detection of valvular vegetations (VEGS) by echocardiography (echo) has become important in the diagnosis and management of infectious endocarditis (IE). Although the size of such VEGS has been reported to relate to prognosis, little is known about the significance of other structural characteristics.

To study the relative importance of a number of VEG characteristics a 5 year computer search was carried out to identify patients with the clinical diagnosis IE who had an echo study carried out during their hospitalization. These studies were reviewed by experienced observers blinded to the clinical data. The following morphologic features were assessed and graded; VEG size, mobility, extra-valvular extent (EVX) and texture. The occurence of the following clinical events was determined by chart review; peripheral and central embolization, heart failure, necessity of valve surgery, and death. The results of the first 53 patients (34M:19F; mean age=54.0 yrs) with left-sided native endocarditis were analysed using logistic regression analysis.

**RESULTS:** Vegetation EVX and mobility were significant predictors of complications (p=0.0019 and 0.0113 respectively) but size and texture (p = 0.15 and 0.41) were not. An echo score based on EVX and mobility predicted complications with even greater power (p=0.0007) and correctly predicted outcome in 78% of cases.

**CONCLUSIONS:** The mobility and extra-valvular extent of vegetations as assessed by echo predict the occurence of complications in patients with IE, but vegetation size and texture do not. A score can be derived which is highly effective in predicting complications.

ECHO-DOPPLER VS CARDIAC CATHETERIZATION IN THE DECISION TO OPERATE ON MITRAL VALVES

Aaron J Gindea, M.D., James Slater, M.D., F.A.C.C., Larry A. Chinitz, M.D., F.A.C.C., Robin S. Freedberg, M.D., F.A.C.C., Ephraim Glassman, M.D., F.A.C.C., Andrew Goldfarb, M.D., Barry P. Rosenzweig, M.D., F.A.C.C., Paul A. Tunick, M.D., F.A.C.C. Howard E. Winer, M.D., F.A.C.C., Itzhak Kronzon, M.D., F.A.C.C. New York University Medical Center, New York, New York.

One hundred and forty nine consecutive pts referred for cardiac catheterization (C) for mitral and/or aortic valvular disease underwent Doppler-echocardiography (DE). The decision concerning operating on the mitral valve (MV) was made twice for each pt by blinded, clinically experienced cardiologists: once using clinical plus DE data (Method A), and once using the same clinical data plus C data (method B). Using Method A, a decision was reached in 139/149 pts (93%) which agreed with the decision by Method B in 119/149 (80%). This included the decision to operate on 32 and not to operate on 84 valves. Decisions differed in 20/149 (13%) . In 10 pts (7%) a decision could not be made by Method A. Estimation of the degree of mitral regurgitation (MR) in 17 pts was the major cause of differences between the two methods (DE>C in 7, C>DE in 10).

CONCLUSION: In 139/149 (93%) of pts, decisions could be made using clinical and DE data alone which was unchanged by C data in 119/149 (80%) of these pts. Grading of MR appears to be the main reason for differences in the decision.

# Tuesday, March 21, 1989
# 10:30AM–12:00NOON, Garden Grove Room
# Anaheim Convention Center
# Valvular Heart Disease: Diagnostic Methods

THE SURGICAL FATE OF MITRAL REGURGITATION ASSOCIATED WITH SEVERE AORTIC STENOSIS: AN INTRAOPERATIVE ECHO STUDY.

Bruce P. Mindich, M.D., F.A.C.C., Theresa Guarino, RN, Scott Lazar, John Fotiades, Andrew Rothschild, Laura Andreae, M. Hasan Jethabhai, Martin E. Goldman, M.D.,F.A.C.C., St. Luke's Hospital, New York, New York.

Frequently, severe aortic stenosis (AS) is accompanied by significant mitral regurgitation (MR) which may be primary or functional due to markedly elevated systolic intracavitary pressure or LV dysfunction. Though preoperative assessment cannot determine the severity of residual MR once the AS is relieved, potentially intraoperative 2-D echo (IOE) could better define valvular pathology and assess MR at lower afterload conditions. Therefore, we performed epicardial IOE with contrast and/or color flow imaging immediately prior to the aortic valve procedure (valve replacement or decalcification), following the procedure (pt off bypass) and at 6 month follow up to determine degree of residual MR. Baseline IOE (Interspec and ATL, UM-6) MR was graded based on contrast or color filling of left atrium in long and short axis views. Fifty-five pts had both significant AS and MR; all underwent aortic surgery. 40/55 (73%) required initial mitral surgery. However, 9/55 (16%) who had mild-moderate MR and 6/55 (11%) who had moderate-severe MR by catheterization but only mild-moderate MR by IOE, did not undergo mitral surgery because of no primary pathology of the mitral valve and/less MR by IOE than by preop catheterization. At 6 month follow up, only 1/15 pts had developed more significant MR. Therefore, intraoperative 2-D echo with color or contrast can significantly alter the operative outcome of combined aortic stenosis and mitral regurgitation reducing surgical duration, risk and postoperative complications.

ALTERED LEFT VENTRICULAR DIASTOLIC FILLING DUE TO ACUTE RIGHT VENTRICULAR VOLUME OVERLOAD FOLLOWING TRICUSPID VALVULECTOMY. A PULSED DOPPLER ECHOCARDIOGRAPHIC STUDY.

Eric K. Louie, M.D., F.A.C.C., Teresa Bieniarz, B.S., Anna Marie Moore, B.A., Sidney Levitsky, M.D.,F.A.C.C., Loyola U., Maywood IL & U of IL, Chicago IL.

Tricuspid valvulectomy (TVV) for isolated tricuspid endocarditis provides the opportunity to study the effects of acute RV volume overload (RVVO) on LV filling in pts with intrinsically normal LV function. Using pulsed Doppler and 2D echo we assessed transmitral filling and LV geometry in 11 TVV pts (mean age 33±8y) and 11 age matched controls (CTRL). RVVO in TVV resulted in progressive leftward shift of the ventricular septum throughout diastole such that the eccentricity index of the LV (minor axis parallel to the septum/minor axis perpendicular to the septum) increased from 1.07±0.09 at end-systole to 1.30±0.22 at mid-diastole ($p < 0.01$) and remained significantly deformed at end-diastole (1.35±0.13). In contrast CTRL had no significant change in eccentricity index from end-systole (1.00±0.05) to mid-diastole (1.03±0.09) and at end-diastole the short axis profile of the LV remained circular in shape with an eccentricity index (1.03±0.10) significantly less than that found in TVV (1.35± 0.13, $p < 0.001$). The late diastolic compression of the LV which occured in TVV pts resulted in a significant reduction in the LV late diastolic filling fraction (0.22±0.11) when compared to CTRL (0.32±0.09 $p < 0.05$) and a redistribution of LV filling to early diastole (LV early diastolic filling fraction: TVV 0.78±0.11 v. CTRL 0.68±0.09, $p < 0.05$). Thus RVVO due to TVV results in late diastolic ventricular septal deformation and impaired late filling of the LV with atrial systole.

## THE GORLIN FORMULA FOR AORTIC VALVE ORIFICE AREA VALIDATED IN VITRO

David Sprigings MRCP, John Chambers MRCP, Thomas Cochrane PhD, John Allen MRCPath, Martin Black PhD, Graham Jackson FRCP. Cardiac Dept, King's College Hospital, London SE5 9RS, UK.

Calculation of orifice area (OA) using the Gorlin formula is regarded as the gold standard for quantifying the severity of aortic stenosis. However, the formula has rarely been tested against direct measurement of OA. We therefore studied 9 human aortic valves obtained at necropsy (ranging from normal to severely stenotic) and 4 bioprosthetic valves in a computer-controlled, positive-displacement pulse-duplicator. Maximum OA was planimetered from simultaneous video recordings. Each valve was studied at 3-5 systolic flow rates ranging from 130-340 ml/sec at a cycle rate of 70 bpm giving 57 data points. OA (range 0.3-2.8 $cm^2$) and mean systolic pressure drop (MPD) (range 3-84 mmHg) varied directly with flow (Q). For individual valves, the increase in OA from lowest to highest flow ranged from 11-107%. OA correlated well with $Q/\sqrt{MPD}$ ($r = 0.93$, $p < 0.00001$). The empirical Gorlin constant, calculated from the formula $(Q/\sqrt{MPD})/(44.3 \times OA)$, for each set of observations was $1.2 \pm 0.3$ (mean ± SD) and was only weakly correlated with flow ($r = 0.3$), MPD ($r = 0.4$) and OA ($r = -0.3$).

We conclude that orifice area is accurately predicted by the Gorlin formula over a wide range of systolic flows in aortic valves in vitro. The correction factor in common use is too low and this may explain why the Gorlin formula overestimates relative to the continuity equation.

## VALIDATION IN PHYSIOLOGIC PULSATILE FLOW OF A NEW METHOD FOR NONINVASIVE QUANTIFICATION OF VALVULAR REGURGITATION BASED ON CONSERVATION OF MOMENTUM

Edward G. Cape, BSChE, Ajit P. Yoganathan, PhD, Elias G. Skoufis, BSChE, Liisa Rihko, Robert A. Levine, MD, FACC. Massachusetts General Hospital, Boston, MA

The assessment of regurgitant volume (RVOL) from Doppler (D) flow maps is limited because visualized jet volume (JVOL) = RVOL+entrained fluid, and JVOL critically varies with driving pressure and instrument settings. An equation has therefore been derived from the principles of turbulent jet flow to quantify RVOL from velocities (VEL) directly measurable by D. Because momentum is conserved for free jets, as more mass is entrained, VEL falls. This principle yields an equation for RVOL in terms of maximum jet VEL, a distal centerline VEL and the intervening distance. This equation was derived most properly for steady flow. The purpose of this study was to determine its validity in physiologic pulsatile flows and its ability to calculate peak flow rate (Qpeak) and total RVOL, by correcting Qpeak for the time-course of orifice VEL. A physiologic pulse duplicator was used to drive flow through .08-.2 sq cm orifices at peak rates of 1.2-4.5 l/min (7-169 mm Hg gradients). Peak orifice and downstream VELs were measured by continuous (CW) and pulsed D to calculate Qpeak; RVOL was obtained from Qpeak and the time-velocity integral of orifice VEL by CWD. These were compared with electromagnetic flow probe data. **RESULTS:** By linear regression, calculated and actual flows agreed well (Qpeak: $y = 1.02x+.03$, $r = .98$, SEE = .2 l/min; RVOL: $y = 1.02x+.58$, $r = .95$, SEE = .8 ml; $n = 42$). Results were not significantly different at various downstream sites ($p > .05$). **CONCLUSIONS:** For free turbulent jet resembling many cardiac lesions, despite the presence of pulsatile physiologic flows and pressures, both Qpeak and total RVOL can be calculated from D VELs without planimetry of jet area.

## THE GORLIN FORMULA: IS THE TRADITIONAL METHOD OF CALCULATING THE PRESSURE GRADIENT ACCURATE?

John P. O'Shea, M.B.B.S., F.R.A.C.P., James D. Thomas, M.D., Vivian M. Abascal, M.D., Frank A. Flachskampf, M.D., Igor F. Palacios, M.D., F.A.C.C., Peter C. Block, M.D., F.A.C.C., Arthur E. Weyman, M.D., F.A.C.C. Massachusetts General Hospital, Boston, MA.

The Gorlin equation, the standard method for calculating mitral valve area (MVA) at cardiac catheterization, typically uses the square root of the mean pressure gradient in its denominator (Method A). However, basic principles of fluid dynamics suggest that the mean of the square roots of multiple instantaneous pressure gradients (Method B) is more accurate and that any discrepancy will be most marked when the end-diastolic gradient (EDG) is low. This prediction has been confirmed in an in-vitro model of mitral stenosis: when the EDG is close to zero, Method A underestimates a given orifice area by up to 14%, whereas in the event of the EDG being 50% of the peak gradient, this error reduces to only 2%. To investigate the practical significance of this observation, we prospectively studied 10 consecutive patients undergoing percutaneous mitral valvuloplasty (PMV), by the anterograde transseptal approach, recording simultaneous LA and LV pressure tracings immediately before and after PMV, together with cardiac outputs at each stage. The pressure tracings were digitized, the trans-mitral gradient was calculated, at 5 msec intervals and the mean gradient calculated by both Method A and Method B. Five cycles, pre- and post-PMV, were analyzed for patients in sinus rhythm and ten for those in atrial fibrillation and the resulting mitral valve areas, calculated using the Gorlin formula, were compared. **RESULTS:** Method B resulted in a significantly larger Gorlin mitral valve area than Method A, the discrepancy being more marked immediately post-PMV (mean MVA: $2.21 \pm 0.21$ cm2 vs. $1.85 \pm 0.18$, $p < 0.0008$) than pre-PMV ($0.97 \pm 0.07$ $cm^2$ vs. $0.93 \pm 0.9$, $p < 0.003$). This discrepancy resulted in a significantly greater increase in MVA post-PMV by Method B ($1.24 \pm 0.25$ cm2 vs. $0.92 \pm 0.22$, $p < 0.002$), and appeared to be related to the lower EDG in the post-PMV group. **CONCLUSIONS:** Mitral valve area may be significantly underestimated if calculated by the traditional Method A. This has important implications for procedures, such as PMV, where estimation of mitral valve area is critical in guiding clinical decision-making.

## HYPERLIPIDEMIC VALVULOPATHY; AORTIC REGURGITATION IN FAMILIAL HYPERCHOLESTEROLEMIA STUDIED BY COLOR DOPPLER ECHOCARDIOGRAPHY

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Homozygous familial hypercholesterolemia (FH) frequently showed significant valvular regurgitation associated with cholesterol infiltration to the valve leaflets. To study this "hyperlipidemic valvulopathy", 38 patients (pts) with FH, including 3 homozygotes (serum LDL level >1000 mg/dl) and 35 heterozygotes (500<LDL<700 mg/dl), ranging from 9 to 58 years, were examined by color flow imaging technique (Toshiba SSH-65 A). Clinically healthy 30 subjects were also examined as a control. Aortic regurgitation (AR) was demonstrated in 10 pts (26.3%), 2 of homozygotes and 8 of heterozygotes. Only a homozygote who was treated by plasmaexchange to maintain the cholesterol low level (<300 mg/dl) did not show AR. In contrast, AR was found in 1 of 30 controls (3.3%, $p<0.05$). Two-dimensional echocardiography showed morphological abnormalities in only 4 pts who showed slight enhancement of valvular echo images. Severity of AR was moderate in 6 and mild in 4 pts, and it was related to the serum LDL levels. None of pts with AR have any other factor resulting in AR. Mitral regurgitation was found in 15 of 38 pts (40%) and 8 of 30 controls (27%, N.S.). Conclusions: (1) The higher incidence of AR in FH was documented by color flow imaging technique. (2) Severity of hyperlipidemic valvulopathy is correlated with the serum LDL levels. (3) Color flow imaging is sensitive method to detect valve involvement in FH which was not detected by conventional 2-dimensional echocardiography.

# Tuesday, March 21, 1989
# 10:30AM–12:00NOON, California Room C
# Anaheim Convention Center
# Surgery for Congenital Heart Disease

CORONARY BLOOD FLOW AND HEMODYNAMICS DURING EXERCISE AFTER THE CORONARY ARTERY BYPASS GRAFTING WITH THE INTERNAL MAMMARY ARTERY FOR KAWASAKI DISEASE

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The subjects of the present study were 12 pediatric pts with Kawasaki disease(avg. age 8.7±3.0) who underwent coronary bypass surgery(CBS) employing the internal mammary artery(IMA). Hemodynamics during exercise(Ex) were measured with a bicycle ergometer, and coronary sinus flow(CSF) was measured by the continuous thermodilution method. The average number of coronary bypass grafts was 2.3±0.7 per pt. For all pts, the left IMA was anastomosed to the left anterior descending artery; for 5 pts, right IMA was also anastomosed to the right coronary artery. In addition, 10 saphenous vein grafts (SVG) were used. The postoperative patency rates after one month were 100% with IMA and 91% with SVG. One year after the operation, the patency rates showed 100% with IMA and 50% with SVG($p<0.05$). The results of hemodynamic measurements showed no significant differences between preoperative stroke volume index(SVI) at rest(R) and during Ex. However, postoperatively, SVI during Ex increased. The relationship between ΔLVEDP(the difference between LVEDP at R and during Ex) and ΔSWI(the difference between the stroke work index at R and during Ex) was analysed. Four pts out of 6 showed reduced cardiac function preoperatively(ΔLVEDP=plus, ΔSWI=minus). However, after the operation, 5 pts out of 6 demonstrated improvements in cardiac function during Ex(ΔLVEDP=plus, ΔSWI=plus). CSF per unit LV mass increased postoperatively from 70±46 to 87±56 ml/min at R, and 139±118 to 183±150 ml/min during Ex. Conclusion: The results of this study revealed improvements in both hemodynamics and CSF during Ex after CBS with IMA for Kawasaki disease.

BIDIRECTIONAL CAVO-PULMONARY ANASTOMOSIS.

Antonio Corno M.D., F.A.C.C., Ennio Mazzera M.D., Bruno Marino M.D., Sergio Picardo, M.D., Carlo Marcelletti, M.D.; Ospedale Bambino Gesù, Roma, Italy.

From February 86 to March 88 22 patients (pts), mean age 3 yrs 8 mos (4 mos-13 yrs), mean weight 14.3 Kg (5-36 Kg), underwent bidirectional cavo-pulmonary anastomosis for complex cyanotic congenital heart disease The diagnosis was in 4 pts left isomerism with pulmonary stenosis (PS), in 4 right isomerism with PS, in 4 pulmonary atresia (PA) with intact ventricular septum, in 4 univentricular heart with PS, in 3 congenitally corrected transposition of the great arteries with PA, in 2 double outlet RV with PS, in one tricuspid atresia with PS. Nine pts had persistent left superior vena cava and 2 pts azygos continuation. The choice for this palliative approach was due in 8 pts to the age (less than 2 yrs), in 5 anomalous venous return, in 4 distortion of the pulmonary arteries, in 3 a-v valve regurgitation, in 2 failure or a Fontan procedure. In 15 pts a bidirectional cavo-pulmonary anastomosis was performed, in 7 pts the anastomosis was bilateral bidirectional. There were no hospital deaths and 2 late deaths (2/22 = 9.1%) in a mean follow-up of 15.7 mos (4-28 mos). All survivors are clinically improved, with a mean arterial $O_2$ saturation increased from 75.2% to 85.3%; 11/19 (= 58%) pts are taking digoxin and/or diuretics. Lung scintigraphy was performed in 13 pts and cardiac catheterization in 9, in all of them showing bilateral lung perfusion. Conclusions: in pts requiring increase of the effective pulmonary blood flow with reduction of the cardiac volume overload, the bidirectional cavo-pulmonary anastomosis, with low mortality and morbidity, warrants clinical improvement avoiding distortion of the pulmonary arteries and allowing normal venous pressure in the coronary, hepatic and renal system, and maintains the possibility for further surgical procedures.

DOUBLY-COMMITTED SUBARTERIAL VENTRICULAR SEPTAL DEFECT: AN ELEVEN-YEAR EXPERIENCE

Merrick, S.H., Verrier, E.D., Hanley, F.A., Turley, K.T., Ebert, P.A., University of California, San Francisco

From 1977 to 1988, 36 patients underwent surgical repair of a doubly-committed subarterial ventricular septal defect(DCS VSD); this group represented 5.2% of 689 VSD repairs performed at our institution during that interval, (23 males and 13 females, aged 2 months to 46 years). Eight patients(22%) were repaired during the first year of life due to progressive congestive heart failure and pulmonary hypertension, secondary to significant left-to-right shunting. After age 1 year, pulmonary hypertension was uncommon, but aortic insufficiency(AI) was present in 18 patients(50%) and cusp prolapse in 13 patients(36%). A significantly wider pulse pressure and severity of AI was seen in the second decade of life. Two-dimensional echocardiography correctly identified the pathophysiology in all but 1 patient. The DCS VSD was repaired with a Teflon patch in 32 patients(89%); other procedures were primary repair(1), aortic valvuloplasty(1), valve replacement(1) and palliative PA band(1). Two patients required a patch and aortic annuloplasty to restore aortic competence. No operative or late deaths occurred. Postoperatively, there was 1 residual VSD and 2 patients had mild AI. Our results confirm the DCS VSD is unlikely to close spontaneously. Echocardiography has replaced catheterization at our institution for diagnosis and follow-up of these patients. Surgical repair can be done safely in infants to prevent failure and irreversible pulmonary hypertension. In older children and adults, correction is justified to prevent valvular damage and progressive AI. Simple patching of the VSD, with or without annuloplasty, will give excellent results in the majority of patients and valve replacement is rarely required.

**NEONATAL REPAIR OF FALLOT'S TETRALOGY WITH AND WITHOUT PULMONARY ATRESIA**

Roberto DiDonato M.D., Richard A. Jonas M.D., Peter Lang M.D., Jonathan J. Rome M.D., John E. Mayer M.D., Aldo R. Castaneda M.D., Children's Hospital, Boston, MA

Neonatal repair is the logical extension of the trend to earlier corrective surgery for congenital heart disease and is already practised routinely for d-transposition of the great arteries at our institution. We have previously demonstrated that early repair of Tetralogy of Fallot minimizes secondary organ damage and late ventricular ectopy and particularly in the case of pulmonary atresia, may improve pulmonary angiogenesis. We examined the results of surgery among 26 symptomatic neonates who underwent repair of tetralogy with (12) or without (14) pulmonary atresia between 1973 and 1987. Mean age was 8.2 days and mean weight 2.9 kg (1.3 - 4.2 kg). Unsatisfactory palliative shunts had been placed previously elsewhere in 4 patients. Twenty-four transannular patches and two conduits were placed. There were 5 hospital deaths (2 with pulmonary atresia) including two avoidable technical problems. All deaths occurred with pulmonary artery area index < 150 $mm^2/m^2$. One premature child weighing 2.3 kg developed an absent pulmonary valve-like syndrome and died late from respiratory complications caused by aneurysmal branch pulmonary arteries. Late catheterization in 16 of 20 survivors showed RV pressure less than half systemic in 12. All patients are symptomatically well and in sinus rhythm 1-15 years after repair. We infer from this selected group of sick neonates that satisfactory short and longterm results may be achieved by neonatal repair of tetralogy of Fallot

EXPERIENCE WITH THE FONTAN PROCEDURE

Hillel Laks, M.D., Jeffrey Pearl, M.D., Barbara George, M.D., Alex Wu, B.S., Thomas Santulli, M.D., Roberta Williams, M.D., UCLA Medical Center, Los Angeles, CA.

From 11/78 to 9/88, 143 patients underwent a Fontan procedure for a variety of congenital cardiac defects. There were 50 patients with tricuspid atresia (TA), 86 patients with univentricular heart, 6 patients with pulmonary atresia and intact ventricular septum, and one patient with hypoplastic left heart syndrome who had previously undergone a Norwood Stage I procedure. The mean age was 8.7 years (8 mos- 463 mos). The mean pulmonary artery pressure was 15± 7mmHg (5-72mmHg) preoperatively with a Qp/Qs of 1.5± 0.7. The pulmonary vascular resistance was 2.0± 1.5 Wood units (0.17- 7.9 Wood units) preoperatively and mean LVEDP was 9± 3mmHg (3- 20mmHg). The early mortality, deaths less than 30 days and all hospital deaths, was 9% overall. In the TA group there were 3 early deaths among 50 patients (mortality= 6%). There were 8 early deaths (mortality= 9%) in the 86 patients with univentricular heart. In the 130 hospital survivors there have been 3 late deaths (mortality= 2.3%) in a mean follow-up of 40 months (2-117 months). Hence, the combined early and late mortality for the Fontan operation is 11%. Twenty-six pts. required the use of a venous assist device postoperatively and 3 required intra-aortic balloon pumps; the mortality among this group was 31%. Conclusions: 1, the Fontan procedure can be performed with a relatively low operative mortality; 2, late results are excellent with a late mortality of only 2.3%; 3, the use of a venous assist device can be beneficial in the early postoperative period in patients with RA hypertension and low cardiac output.

COLOUR FLOW IMAGING AS INTRA-OPERATIVE ANGIOGRAPHY IN VENTRICULAR SEPTAL DEFECTS - ADVANTAGES AND PITFALLS?

George Sutherland M.D., John Smyllie M.D., Jos Roelandt F.A.C.C., Marc van Daele M.D., Jan Quaegebeur M.D., Thoraxcenter, Rotterdam, Netherlands.

51 patients undergoing surgical repair of one or more ventricular septal defects (VSD) were studied by epicardial echo both immediately pre and post cardiopulmonary bypass. 2-D echo, contrast echo and colour flow imaging (CFI) were performed to determine whether a combination of these techniques could reliably predict 1) successful VSD closure, 2) further unsuspected VSDs, or 3) any resultant complications. 2-D echo alone detected a patch dehiscence in 1 pt. Post bypass CFI demonstrated, well localised trans or peri-patch VSD jets in 26/51 pts (multiple jets 16/26). In none did contrast echo suggest a significant shunt. Early and late post op studies demonstrated the disappearance of the narrow jets in 24/26 pts. This invariably occurred by 6 hours post bypass. In a further 4 pts broad extensive CFI VSD jets were immediately identified in all of whom contrast echocardiography suggested an interventricular shunt. In none of these cases was bypass recommenced as the defect appeared small. Post-bypass, further significant distal VSDs (undetected by pre-op angio) were noted in 2 pts and bypass was recommenced to effect closure. Late patch dehiscence was clearly defined in a further 3 pts. We conclude that a combination of 2-D echo, contrast echo and CFM can provide the surgeon with an accurate intra operative monitoring technique which can both confirm defect closure and exclude the presence of singificant and residual VSDs.

## Tuesday, March 21, 1989
## 8:30AM–10:00AM, Santa Ana Room 1
## Anaheim Convention Center
## Atrial Naturetic Factor and Inhibitors

ATRIOPEPTIDASE INHIBITORS, A NOVEL CLASS OF DRUG THAT RAISES LEVELS OF ENDOGENOUS ATRIAL NATRIURETIC FACTOR - THE PRECLINICAL PHARMACOLOGY OF UK-69,578

G.M.R. Samuels BSc PhD, P.L. Barclay BSc PhD, C.J. Peters BSc PhD, P.Ellis BSc PhD
Pfizer Central Research, Sandwich, U.K.

UK-69,578 (Cis-4-{1-[2-carboxy-3-(2-methoxyethoxy) propyl]-1-cyclopentanecarboxamido}-1-cyclohexanecarboxylic acid), (UK), is a potent, selective inhibitor (Ki 3.6 x $10^{-9}$M) of atriopeptidase (EC 3.4.24.11), the rate limiting enzyme in the breakdown of atrial natriuretic factor (ANF) by renal homogenates. We describe here some biochemical and physiological consequences of atriopeptidase inhibition in vivo. UK (3 mg/kg i.v.) prolongs the half-life of exogenous APIII in normal (0.72 min to 1.02 min) and in nephrectomised (0.96 min to 2.52 min) anaesthetised rats, indicating important extra-renal locations of this enzyme. The compound (0.3 mg/kg i.v.) potentiates the diuretic and natriuretic responses (x4) to APIII (50 ng/kg/min i.v. for 10 min) in anaesthetised rats, and (at 10 mg/kg i.v.) to endogenous ANF released by an acute saline load (20 ml/h/rat i.v.). In the latter model, this enhanced natriuresis, unlike that induced by hydrochlorothiazide, is substantially reduced by ANF antibodies, clearly indicating a different mechanism of action of the two agents. In conscious spontaneously hypertensive rats maintained on a high salt intake, UK (10 mg/kg/day via a minipump) causes an enhanced diuresis and natriuresis over the 7 day study, with a concomitant increase in plasma ANF levels (x6) and a decrease in plasma aldosterone levels (50%). Thus UK clearly illustrates the physiological impact of modest elevations of endogenous ANF.

THE EFFECT OF UK-69,578, AN ATRIOPEPTIDASE INHIBITOR, IN A CONSCIOUS DOG MODEL OF CARDIAC INSUFFICIENCY

C.T. Alabaster BSc PhD, I. Machin BSc, P.L. Barclay BSc PhD, G.M.R. Samuels BSc PhD
Pfizer Central Research, Sandwich, U.K.

UK-69,578 (Cis-4-{1-[2-carboxy-3-(2-methoxyethoxy) propyl]-1-cyclopentanecarboxamido}-1-cyclohexanecarboxylic acid) (UK) is a potent, selective inhibitor of atriopeptidase (EC 3.4.24.11) thereby reducing the breakdown of atrial natriuretic factor (ANF) both in vitro and in vivo (Samuels et al, this meeting). This study describes the renal and hormonal effects of UK administration to conscious dogs with atrioventricular heart block, a model of low output cardiac insufficiency with circulating ANF levels higher than those found in normal dogs.

UK, over the dose range of 0.5 to 3 mg/kg (i.v.) produced dose related natriuretic and diuretic responses peaking at 1 to 2 h and still evident 4 h after dose. At 3 mg/kg (n=5) there was a doubling of circulating ANF, and a ten fold increase in urinary excretion of ANF, both effects being maximal 1 h after dose. There was no change in plasma renin activity (PRA). In contrast, hydrochlorothiazide (n=3), at an equinatriuretic dose level, caused no change in ANF levels whereas PRA increased. The enhanced excretion of sodium and water, without activation of the renin axis, as demonstrated with UK, suggests therapeutic potential for this class of agent in heart failure.

## THE ACUTE AND CHRONIC ANTIHYPERTENSIVE EFFICACY OF ATRIOPEPTIDASE INHIBITION IN RATS

G.M.R. Samuels BSc PhD, P.L. Barclay BSc PhD, N.B. Shepperson BSc PhD, J.A. Bennett BSc PhD. Pfizer Central Research, Sandwich, U.K.

UK-69,578 (Cis-4-{1-[2-carboxy-3-(2-methoxyethoxy) propyl]-1-cyclopentanecarboxamido}-1-cyclohexanecarboxylic acid) is a potent, selective inhibitor of atriopeptidase (EC 3.4.24.11). It raises circulating atrial natriuretic factor (ANF) levels in vivo, and potentiates the diuretic and natriuretic responses to exogenous and endogenous ANF in rats and dogs (Samuels et al, this meeting). We describe here its antihypertensive efficacy in 1-kidney DOCA-salt rats (DOCA-R). UK-69,578 (10 mg/kg i.v.) significantly reduced blood pressure by some 30 mm Hg, the effect being well maintained through 4 h (n=9 animals). At 3 mg/kg i.v., the effect was less pronounced and of shorter duration. Using UK-74,816 (an orally active indanyl ester of UK-69,578) we investigated the effect of chronic atriopeptidase inhibition on the development of hypertension in DOCA-R. UK-74,816 (3 mg/kg p.o. once daily, first administered 24 h post surgery) substantially reduced the rate of development of hypertension, and significantly reduced the blood pressure reached 29 days post-surgery (mean increase 51 ± 7 mm Hg n=9) in comparison with vehicle treated control animals (mean increase 79 ± 8 mm Hg n=10). All blood pressures were measured 18 h post-dose. This antihypertensive effect was associated with an increase in plasma ANF levels (1038 ± 364 pg/ml vs 542 ± 190 pg/ml), but evidence of dependence on ANF awaits completion of further studies. Thus administration of an atriopeptidase inhibitor not only decreases blood pressure acutely, but on chronic administration markedly reduces the development of hypertension in DOCA-R, suggesting therapeutic potential for this class of agent.

## PHARMACOLOGICAL ELEVATION OF ENDOGENOUS ATRIAL NATRIURETIC FACTOR IN MAN USING THE ATRIOPEPTIDASE INHIBITOR (UK 69578).

Alan Jardine MB MRCP, John MC Connell MD MRCP, Stephen G Dilly MB PhD, David Northridge MB MRCP, Brenda Leckie PhD, N.J. Cussans PhD, Anthony F Lever MB MRCP, MRC Blood Pressure Unit, Western Infirmary, Glasgow, UK.

Atrial natriuretic factor (ANF) is a peptide hormone with vasorelaxant, natriuretic and diuretic properties. UK 69578 (C20,H33,NO7) is a novel compound developed by Pfizer Central Research (UK) which inhibits breakdown of ANF by the endopeptidase EC3.4.24.11 ('atriopeptidase') and elevates plasma ANF in experimental animals. In this first administration in man, 16 normal male volunteers received 3 doses of intravenous UK 69578 plus placebo in a study covering the dose range 0.025-10.0 mg/kg. UK 69578 was well tolerated in all subjects, with no adverse effects. Blood pressure, plasma electrolytes and haematocrit were unchanged. The plasma half life of UK 69578 was 1.1 hours, volume of distribution 0.25L/Kg, clearance 2.7 ml/Kg/min. There was a dose dependent increase in plasma ANF with a peak of 2-3 times basal values by 2 hours post dose returning to normal by 8 hours. After 2mg/Kg UK 69578 ANF rose from 23.4 (3.1) to 45.8 (6.2) pg/ml at 2 hours [mean(SE),P<0.01]. Plasma levels were unchanged following placebo. There was an associated diuresis and natriuresis with 8 hour urinary Na excretion rising from 88.0(8.0)mmoles after placebo to 133.6(5.3) after 2 mg/Kg[P<0.01]. Urinary K was unchanged and the natriuresis was not accompanied by a rise in renin angiotensin II or aldosterone. UK 69578 is a new class of agent which,through elevation of endogenous ANF produces diuresis and natriuresis without stimulation of the renin angiotensin system and may have a therapeutic role in a variety of conditions in man including hypertension and heart failure.

## ACUTE EFFECTS OF ATRIOPEPTIDASE INHIBITION ON PLASMA ATRIAL NATRIURETIC FACTOR IN CHRONIC HEART FAILURE.

David B Northridge MB MRCP, Iain N Findlay MB MRCP, Alan Jardine MB MRCP, Stephen G Dilly MB and Henry J Dargie MB FRCP.
Department of Cardiology, Western Infirmary, Glasgow.

Inhibition of atriopeptidase raises plasma levels of atrial natriuretic factor (ANF) in animals and normal human volunteers causing diuresis and natriuresis. We report the first study of a new atriopeptidase inhibitor (UK 69,578; Pfizer Central Research) in chronic heart failure (CHF).

UK 69,578 was administered as an intravenous infusion in a placebo controlled, cross-over fashion to 6 male patients with stable LV dysfunction (mean [range] LV end-diastolic dimension 65 [57-73] mm). Plasma ANF was elevated at baseline, mean (SD) 84 (53) pg/ml, and rose further to a peak of 275 (322) pg/ml, 1 hour after active drug administration ($p<0.05$). This was accompanied by a fall in plasma active renin from 61 (48) to 35 (21) uU/ml ($p<0.01$), and a dose dependent diuresis and natriuresis. Non-invasive haemodynamic monitoring revealed no change in heart rate, arterial blood pressure or echocardiographic LV dimensions. However, invasive measurements using a Swan Ganz catheter demonstrated falls in right atrial pressure from 6.1 to 4.2 mmHg, and pulmonary artery wedge pressure from 9.3 to 6.9 mmHg following UK 69,578, with no change in CO. No such changes occured following placebo.

Thus in mild CHF, UK 69,578 elevates plasma ANF with associated diuretic, natriuretic and venodilator effects, but without stimulating renin secretion. Atriopeptidase inhibitors therefore represent a potential therapeutic advance.

## Atrial natriuretic factor in atrial flutter and fibrillation: Role of atrial rate and cardioversion.

Sakti Mookherjee, M.D., F.A.C.C., James Longo, M.D., F.A.C.C., Harold Smulyan, M.D., F.A.C.C., Suman Vardan, M.D., Gunner Anderson, M.D., VA Medical Center and Health Science Center, Syracuse, N.Y.

To examine whether faster atrial frequency and/or associated congestive heart failure (CHF) contribute to elevated atrial natriuretic factor (ANF) in the setting of atrial flutter (AFLUT) and fibrillation (AFIB), 24 patients (pts), 16 with AFLUT and 8 with AFIB were studied. Clinical and electrocardiographic evaluation was performed and venous ANF level determined by radioimmunoassay 1 hour before and 1 hour after cardioversion (cv). Control ANF level was unrelated to atrial frequency, arterial pressure, ventriuclar rate, arrhythmia duration or left atrial size (echocardiography). Seven pts (5 AFLUT and 2 AFIB) had clinical indices of CHF with ANF values of 172.2 ± 45.7 (SE) pg/ml vs 110.6 ± 17.5 pg/ml in 17 without CHF (p-NS). AFIB pts had ANF levels of 161.6 ± 37.8 pg/ml vs 112.1 ± 20.1 pg/ml in AFLUT pts (p-NS). Two AFLUT and 1 AFIB pts converted to sinus rhythm without D.C. countershock (1 spontaneously and 2 pharmacologically). Remaining 21 pts recieved D.C. countershock (14 AFLUT and 7 AFIB) under intravenous methohexital anesthesia. Regardless of energy used or the mode of cv the ANF fell post cv in the entire group from 128.6 ± 18.5 pg/ml to 55.7 ± 9.2 pg/ml ($P<0.01$). The post cv fall in ANF correlated with control ANF level ($r = 0.83$, $P<0.01$) but not with fall in heart rate. Thus, (1) ANF level in AFIB with more frequent atrial electrical impulses may not be significantly higher than that in AFLUT, (2) presence of CHF seems non contributory to ANF levels in this setting, (3) the ANF is promptly lowered with dysrrhythmia termination and (4) its post cv reduction is independent of the mode of cv or anesthesia use.

# Tuesday, March 21, 1989
# 10:30AM–12:00NOON, Santa Ana Room 1
# Anaheim Convention Center
# Thrombosis and Thrombolysis: Mechanisms

PREVENTION OF THROMBOSIS BY RECOMBINANT HIRUDIN DURING ARTERIAL ANGIOPLASTY IN PIGS: COMPARISON WITH HEPARIN

Magda Heras, MD, James H. Chesebro, MD, FACC, Mark Webster, MB, Jozef Mruk, MD, Diane Grill, MS, Lina Badimon, PhD, Valentin Fuster, MD, FACC, Mayo Clinic, Rochester, Minnesota

The effects of heparin and 3 dosages of recombinant hirudin, a specific thrombin inhibitor, were compared for reducing $^{111}$In-platelet and $^{125}$I-fibrinogen deposition (PD,FD) and mural thrombus (TH) in arteries with deep injury during angioplasty. Hirudin, heparin or placebo was given as a bolus plus an infusion started 10 minutes before angioplasty. Dosages (mg/kg + mg/kg/h) of hirudin were 1.0, 0.7 and 0.3 and of heparin was 50 U/kg +50 U/kg/h. Pigs underwent bilateral carotid angioplasty (5 inflations for 30 sec to 6-8 atm, 60 sec apart) and were sacrificed 60 minutes later. Activated partial thromboplastin time (APTT) at angioplasty is reported in multiples of the basal value, PD and FD (mean ± SD) are reported as log platelets/cm$^2$ and log of molecules/cm$^2$, respectively. The proportion of TH in arteries with deep injury is also assessed.

| Rx | Control (n=8) | 0.3 mg/kg (n=8) | 0.7 mg/kg (n=4) | 1.0 mg/kg (n=14) | 50 U/kg (n=6) |
|---|---|---|---|---|---|
| APTT | 1.02 | 1.64 | 1.97 | 3.25 | 1.94 |
| PD | 3.7±0.9*,° | 2.9±0.6* | 1.8±0.5 | 1.7±0.5 | 3.2±0.8*,° |
| FD | 3.5±0.8* | 3.2±0.6* | | 2.4±0.3 | 3.0±0.5 |
| TH | 78% | 54% | 0% | 0% | 62% |

*p<0.05 compared with 1 mg/kg; °p<0.05 compared with 0.7 mg/kg. There was also a significant inverse relationship between hirudin dosage and PD (r=-0.8; p=0.0001).
In conclusion, at similar APTTs hirudin significantly decreased thrombosis compared with heparin. The two higher dosages of hirudin totally prevented thrombosis at therapeutic APTTs.

ASPIRIN BUT NOT STANDARD HEPARIN PREVENTS THROMBUS FIBRIN DEPOSITIO IN RABBITS TREATED WITH TISSUE PLASMINOGEN ACTIVATOR.

Giancarlo Agnelli M.D., Claudia Pascucci, Benilde Cosmi M.D., Giuseppe G. Nenci M.D., Istituto di Semeiotica Medica, University of Perugia, 06100 Perugia, Italy.

Rethrombosis after thrombolytic treatment is a crucial problem and the value of adjunctive therapy is not defined. The aim of this study was to evaluate the effectiveness of standard heparin (SH) and aspirin (ASA) in preventing fibrin deposition onto experimental thrombi partially lysed by tissue plasminogen activator (t-PA). To evaluate the fibrin deposition, standard sized non radioactive thrombi were produced in the jugular veins of New Zealand rabbits (weight: 2.5 Kg). Then 125I-fibrinogen was injected via left carotid artery, its accumulation onto the thrombi being considered as an expression of potential rethrombosis. Single chain recombinant t-PA (Actilyse, Boehringer Ingelheim, Florence, Italy), 0.5 mg, was infused over three hours in each rabbit. This dose was selected because it produces 35% thrombolysis in this animal model. In addition to t-PA rabbits received 1)saline or 2)SH 20 and 60 I.U./Kg/hour for three hours or 3)saline or ASA 20 mg/Kg as a bolus dose. The infusion of SH and t-PA started at the same time, the 10% of the doses being injected as a bolus. The saline and ASA bolus was injected immediately prior to the start of t-PA infusion. The accretion of 125I-fibrinogen was evaluated at the end of t-PA infusion. At the end of the infusion the accreted 125I-fibrinogen was 34±6 μg in the saline treated rabbits (both bolus and infusion), 33±2 and 33±6 μg in the rabbits treated with the low and high dose of SH, respectively and 8±1 μg in the ASA treated rabbits. Thus when compared with saline, ASA significantly reduced the accumulation of radioactive fibrin onto preformed thrombi (p<0.05), while SH had no effect. In the standard heparin treated rabbits the anti-Xa level was about 0.4 U./ml and 0.9 U./ml in the low and high dose, respectively. We conclude that in this animal model ASA inhibits thrombus growth while SH, at therapeutic doses, fails in achieving this goal.

THE ANTITHROMBOTIC EFFECT OF ASPIRIN IS INDEPENDENT OF STENOSIS SEVERITY.

Jules Y.T. Lam, M.D., F.A.C.C., Michael Johnstone, M.D., Garth Linton, Chantal Lachapelle, Jean-Gilles Latour, Ph.D., David Waters, M.D., F.A.C.C., Montreal Heart Institute, Montreal, Canada.

Hemorrheologic disturbances at sites of arterial stenoses promote localized platelet deposition; more severe stenoses cause more extensive platelet thrombus deposition. Whether the antithrombotic efficacy of aspirin is influenced by these rheologic disturbances is not known. Platelet deposition (x10$^6$) onto normal porcine aortic media placed in cylindrical flow chambers and exposed ex vivo to flowing, non-anticoagulated blood from control (n=8) or aspirin treated (1 mg/kg/day for 3 days, n=8) pigs was quantitated. The flow chambers were specially designed to provide 0, 50, 66 or 75% stenoses. Femoral arterial blood was circulated ex vivo through the flow chambers for 5 min. by means of a peristaltic pump set at a flow rate of 20 ml/min. Platelet deposition was evaluated using autologous $^{111}$Indium labeled platelets injected 18-24 hrs before the experiment. The following differences in platelet deposition were observed:

| Stenosis | n | Control | Aspirin | p (vs control) |
|---|---|---|---|---|
| 0% | 8 | 55.5±6.6 | 26.2±5.3 | 0.005 |
| 50% | 8 | 75.1±14.7 | 29.5±5.8 | 0.005 |
| 66% | 8 | 95.0±19.2 | 30.2±5.0 | 0.015 |
| 75% | 8 | 108.0±18.0 | 36.5±5.9 | 0.005 |

Thus, aspirin (1 mg/kg) significantly decreases platelet deposition onto aortic media exposed to flowing blood. This antithrombotic effect persists regardless of the severity of stenoses. Flow alterations caused by stenoses do not appear to modify the antithrombotic effect of aspirin.

BLEEDING COMPLICATIONS AFTER DOUBLE-CHAIN tPA: INFLUENCE OF DOSE AND DURATION OF INFUSION.

Udho Thadani, M.D., FACC for the Burroughs Wellcome tPA Study Group, OUHSC, Oklahoma City, Oklahoma.

We examined the relationship of serious bleeding complications(BC) to maintenance dose rate(MDR), duration of infusion(DI), and total dose(TD) of tPA administered to 223 patients(pts) with myocardial infarction. Burroughs Wellcome tPA(PROLYSIS®) was administered 3.4±1.1 hours after symptom onset in an initial dose of 0.64±0.16 megaunits/kg(MU/kg) over 90 min. Responders at 90 min [65% (134/207),TIMI grade 2-3] then received 1/3 the initial dose over 1.5 hrs, followed by one of several MDRs(range: 0.01-0.13 MU/kg/hr for 0.6-22.4 hrs). Repeat angiography was performed 11-26 hrs after initiation of tPA. During the 96-hour study period,40 pts(18%) experienced serious BC, primarily at catheterization sites(13%). No CNS or fatal BC were reported. Other serious BC were: GI, 2%; hematuria <1%; retroperitoneal, <1%. Transfusions were required in 34 pts(15%). Serious BC occurred with the following frequency :

| TD(MU/kg) | BC | DI (hrs) | BC |
|---|---|---|---|
| 0.19-0.73 | 7% (4/56) | 0.8-1.5 | 6% (3/54) |
| 0.75-1.02 | 16% (9/55) | 1.5-8.4 | 10% (6/58) |
| 1.03-1.47 | 14% (8/57) | 9.3-17.6 | 20% (11/56) |
| 1.49-2.61 | 35% (19/55) | 17.7-25.4 | 37% (20/55) |

No significant relationship between MDR and serious BC was found(P=0.8). When TD and DI were examined separately, both demonstrated a significant relationship to serious BC(P<0.0001). After adjustment for TD in a logistic model, DI added additional independent information for predicting the occurrence of serious BC. These data suggest that a prolonged maintenance dose following a lytic dose is associated with high risk of serious BC.

STREPTOKINASE INHIBITS PLATELET THROMBUS FORMATION IN STENOSED DOG CORONARY ARTERIES: POSSIBLE MECHANISMS.
John D. Folts, Ph.D.,F.A.C.C., Bradford S. Schwartz, M.D., Michael Kroll, M.D., Andrew I Schafer, M.D., Univ. of Wisconsin Medical School, Cardiology Section, Madison, WI and Dept. of Medicine, Harvard Medical School, Boston, MA.

We have shown that IV streptokinase (SK) inhibits periodic acute platelet thrombus formation (APTF) in our open chest dog model with mechanically stenosed coronary arteries (MSCA), and intimal damage. These thrombi are primarily platelet aggregates with very little fibrin. In 22 dogs with MSCA, (coronary blood flow measured with EMF probe) APTF periodically occurred producing cyclical coronary blood flow reductions (CFRs) as the thrombi formed and then embolized distally. SK 68,000±13,000 U/kg was given IV to generate plasmin (P) and CFRs were abolished in 20 and diminished in 2 dogs. Plasma fibrinogen levels decreased from 227±41 to 132±19 mg/dl ($p<.001$) while template bleeding time increased from 3.2±0.6 to 14±4 min ($p<.001$) after SK. Platelet thromboxane $A_2$ production (n=7) and platelet rich plasma C-AMP levels (n=5) were not significantly changed, nor was binding of $^{125}I$ antibody to the platelet GPIIb-IIIa receptor altered (n=5), after SK. Ex vivo platelet aggregation induced by ADP (n=10) or Botrecetin (n=4) was not changed but collagen induced aggregation was decreased by 34±11% (n=6, $p<.05$). We postulate that P was generated by SK and that the P inhibited APTF and thus abolished or diminished CFRs in these dogs. If SK and generated P inhibit collagen induced platelet aggregation this may account in part for abolishing CFRs, since exposed collagen, due to intimal damage, is thought to be the primary stimulus for APTF in this model. P inhibits human platelets in vitro and if it occurs in vivo in man it may enhance thrombolysis by inhibiting further platelet accumulation on the clot.

**THE EFFECT OF THE LENGTH OF TISSUE PLASMINOGEN ACTIVATOR ADMINISTRATION ON LYSIS OF FRESH AND OLD THROMBI.**
Ken Kanamasa, MD, Ikuyoshi Watanabe, MD, Bojan Cercek, MD, Juliana Yano, Michael C. Fishbein, MD, FACC, William Ganz, MD, FACC, Cedars-Sinai Medical Center and Univ. of California, Los Angeles, CA.

Serious bleeding may occur during coronary thrombolysis when a hemostatic thrombus is also lysed. On the assumption that hemostatic thrombi are likely to be older than the coronary thrombi, we explored the effect of the length of t-PA administration on lysis of 1-hr and 24-hr old clots (CL). In dogs, clots were produced with the copper coil technique in the left or right jugular and femoral vein and 23 hours later in the contralateral jugular and femoral vein. One hour later all 4 coils were removed from the veins, weighed and inserted into the adjacent carotid and femoral arteries. A 1 mg/kg dose of t-PA was given either over 30 min and 180 min. The coils were removed from the arteries and weighed to determine the degree of lysis, either upon termination of the infusion (groups I-A and II) or 45 minutes later (group I-B). The results were expressed as the ratio of lysis of 1-hr and 24-hr old clots.

Results:

| | | n | Initial weight (mg) | Lysis (%) | Average ratio Lysis: 1-hr/24-hr |
|---|---|---|---|---|---|
| | **30 min infusion** | | | | |
| I-A | 1-hr CL | (12) | 140.0±8.4 | 65.2±6.0 | 7.95±2.16 |
| | 24-hr CL | (12) | 153.5±6.5 | 16.6±3.5 | |
| I-B | 1-hr CL | (9) | 153.1±7.0 | 91.7±1.7 | 6.52±1.50 * |
| | 24-hr CL | (9) | 166.8±2.9 | 21.6±5.4 | |
| | **180 min infusion** | | | | |
| II | 1-hr CL | (9) | 143.1±7.0 | 86.1±2.5 | 1.71±0.17 * |
| | 24-hr CL | (9) | 159.1±4.9 | 53.9±4.8 | |

*=p<0.01

Conclusion: More rapid administration of a given dose of t-PA results in a significantly lesser degree of lysis of older clots and may therefore be safer.

# Tuesday, March 21, 1989
# 8:30AM–10:00AM, Santa Ana Room 2
# Anaheim Convention Center
# Cardiovascular Effects of Cocaine

COCAINE-INDUCED CONTRACTION OF VASCULAR SMOOTH MUSCLE IS INHIBITED BY CALCIUM CHANNEL BLOCKADE.
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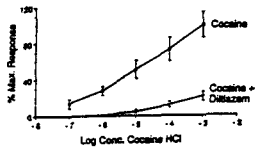
Recent in vitro studies have documented that cocaine (C) may provoke endothelium-independent contraction (CON) of rabbit and human vascular smooth muscle (VSM) in vitro, thus providing a basis for clinical reports of C-induced myocardial infarction. To investigate the mechanisms responsible for the vasoconstrictor effects of C on VSM, the potential antagonism of alpha blockers and calcium channel blockers on C-induced CON of VSM were studied in 78 ring segments of rabbit thoracic aorta mounted isometrically with 1-2 gms tension in Krebs bicarbonate buffer (37°C and pH=7.4, 95% $O_2$ - 5% $CO_2$). In 43 segments challenged with either $10^{-7}$ to $10^{-4}$ M prazosin or phentolamine prior to C ($10^{-7}$ through $10^{-3}$ M) (n=145), no consistent effect on C-induced CON of VSM was observed. In contrast, pre-treatment with diltiazem (D) markedly inhibited C-induced CON according to the dose response curve shown below:values are presented as means±SEM (for C, n=14; for D+C, n=21). Similar results were obtained with verapamil ($10^{-7}$ M) and nifedipine ($10^{-4}$ M). C-induced CON with or without antagonists was again endothelium-independent. Conclusion: C has a potent vasoconstrictor effect on VSM in vitro which is calcium-dependent and endothelium-independent. These findings suggest that in contrast to the conventional view of C as potentiator of response to norepinephrine, C-induced CON of VSM is more directly a result of enhancement by C of calcium influx across the cell membrane.




CARDIODEPRESSANT EFFECTS OF COCAINE
Sharon L. Hale, B.S., Kevin J. Alker, Shereif Rezkalla, M.D., Gerald Figures, Robert A. Kloner, M.D, Ph.D., FACC. Hospital of the Good Samaritan, Los Angeles, California

Cocaine produces diverse effects depending on such factors as the dosage and rate of administration. Smoking "crack" is currently popular in certain populations. This results in rapidly peaking, high blood levels of cocaine. Our objective was to study the effects of rapid cocaine administration. We measured hemodynamics, myocardial blood flow (MBF), and LV cavity end-systolic area (ESA) and end-diastolic area (EDA), by 2-D echocardiography, before and 15 min after a bolus injection of cocaine (10 mg/kg) in pentobarbital-anesthetized dogs. Cocaine adversely affected several hemodynamic parameters:

| | Pre-Cocaine | 15' Cocaine |
|---|---|---|
| Heart Rate (bpm) | 146±10 | 121±6** |
| LV pressure (mm Hg) | 119±5 | 115±10 |
| LV dP/dt (mm Hg/sec) | 1600±100 | 1075±125** |
| LVEDP (mm Hg) | 7±1 | 11±1* |

*p<.05, **p<.006 vs baseline

Cocaine also caused dilation of the LV: ESA increased from 2.7±.2 to 3.2±.3 $cm^2$ ($p<.03$) and EDA increased from 3.4±.4 to 4.3±.4 $cm^2$ ($p<.04$). Subepicardial MBF fell from .82±.09 to .60±.11 ml/min/g ($p<.04$). In 7 other dogs, angiographically estimated proximal circumflex artery diameter (CxD) and MBF were measured before and 3-5 minutes after the same dose of cocaine. In these animals cocaine-induced coronary artery vasoconstriction was observed: CxD was reduced 15±4% (range 2-29%, $p<.01$ vs baseline) after cocaine. Epicardial RMBF was reduced from 1.07±.23 to .83±.16 ml/min/g. We conclude that in this model, rapid administration of cocaine depresses LV function, causes LV dilation and is associated with coronary artery vasoconstriction and reduced myocardial blood flow.

## ERGONOVINE TESTING IN COCAINE INDUCED MYOCARDIAL ISCHEMIA

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Coronary spasm appears to be the underlying mechanism responsible for cocaine induced coronary ischemia. To determine propensity for spasm, provocative testing with ergonovine maleate was carried out during catheterization in 7 male cocaine abusers (26-37 years). Four had angina and 3 had sustained myocardial infarction(MI). All 7 had patent coronaries with ventricular asynergy in 3 patients. Two of 7 however, demonstrated insignificant coronary atherosclerosis in the involved vessel. Intravenous ergonovine was administered in incremental doses until there was reproduction of chest pain, EKG changes, pressor response and/or total dose of 0.5mg. Focal spasm with ergonovine was present only in the two that had pre-existing coronary disease. In contrast, 5 patients including one who required thrombolysis for MI and two others with cocaine induced ST elevation had negative ergonovine test. Thus, in the absence of underlying coronary disease, ergonovine testing is negative and in addition to spasm there may be other mechanisms responsible for cocaine induced myocardial ischemia.

## EVIDENCE THAT COCAINE SLOWS CARDIAC CONDUCTION BY AN ACTION ON BOTH AV NODAL AND HIS-PURKINJE TISSUE IN THE DOG.

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The effects of intravenous (IV) cocaine (2 mg/kg) were tested on several indices of electrical activity in conscious, sedated dogs. These included sinus rate, AH interval (paced and unpaced), HV interval (paced and unpaced), AV nodal effective refractory period (AVNERP), ventricular effective refractory period, QRS duration and the QT interval (during sinus rhythm and at a constant pacing rate ). No significant effects were observed in 6 control animals after IV cocaine. However, after blockade of sympathetic nervous system effects on the heart with propranolol (0.5 mg/kg IV), cocaine increased the PR interval (+15 ± 4 msec, $p<0.05$). The effect on the PR interval was related to slowing at the AV node level as AH prolongation was observed at a constant paced rate (+23.3 ± 8.71 msec, $P<0.05$). No significant change in HV interval was noted either during sinus rhythm or during constant pacing. There was a significant increase in the QT interval (+56 ± 18 msec, $p<0.05$). Cocaine administered to 6 animals subjected to pharmacological blockade of both divisions of the autonomic nervous system (with IV propranolol plus propantheline) resulted in similar significant increases in PR and AH intervals. In addition, there were significant increases in AVNERP (+29 ± 5.9 msec, $p<0.05$) and HV interval (+6.7 ± 1.7 msec, $p<0.05$) during constant pacing. These data suggest that cocaine impairs cardiac conduction by acting directly on the AV node and His-Purkinje system, presumably by blocking the entry of calcium and sodium into these cells, respectively.

## COCAINE MEDIATED IMPAIRMENT OF CARDIAC CONDUCTION IN THE CONSCIOUS DOG

J. Scott Kabas, M.D., Susan M. Blanchard, Ph.D., Yuzuru Matsuyama, M.D., Samir Gupta, Ph.D., Everett H. Ellinwood, M.D., Peter K. Smith, M.D., Harold C. Strauss, M.D. Duke University Medical Center, Durham, NC

Previous studies of the physiologic effects of cocaine (C) have focused on variables likely to be affected by changes in autonomic tone including blood pressure (BP), heart rate (HR), cardiac output, and coronary blood flow. However, cocaine also produces a local anesthetic effect which may slow cardiac conduction. To assess this possibility, 10 conscious mongrel dogs were randomly assigned to receive either 3 or 5 mg/kg cocaine HCl intravenously over 30 sec. His bundle electrograms and serum cocaine levels were obtained in the control state and at 0.5, 1.0, 1.5, 5, and 15 min following cocaine administration. At both doses, significant prolongation of His to ventricle (HV) intervals occurred as early as 0.5 min (15% and 17% increases) and progressed to maximal delays of 40% and 52%. HV prolongation followed the rise in serum cocaine and persisted for 5 min. Mean BP and HR also increased with cocaine infusion by 2-40% and 2-57%, respectively, and remained elevated throughout the study. While arterial $pO_2$ and $pCO_2$ stayed within physiologic limits, mild metabolic acidosis developed at both doses (minimum pH: 7.27 for 3 mg/kg and 7.26 for 5 mg/kg). Despite marked cardiac effects, only one animal experienced seizures.

| *Time:* | *0.5 min* | *1.0 min* | *1.5 min* | *5 min* | *15 min* |
|---|---|---|---|---|---|
| *3 mg/kg:* [C] ng/μl | 30±6 | 14±4 | 4±1 | 1±0 | 0±0 |
| %ΔHV | 15±4* | 40±4* | 32±3* | 14±4* | 1±1 |
| %ΔBP | 10±7 | 5±4 | 40±12* | 29±11* | 15±9 |
| %ΔHR | 18±13 | 32±12* | 57±36 | 49±27 | 26±14 |
| *5 mg/kg:* [C] ng/μl | 47±9 | 17±7 | 6±2 | 2±1 | 0±0 |
| %ΔHV | 17±1* | 49±9* | 52±6* | 23±3* | 3±3 |
| %ΔBP | 2±2 | 13±7 | 19±9 | 31±7* | 30±5* |
| %ΔHR | 2±12 | 29±16 | 33±17 | 29±12 | 17±11 |

Mean±SEM; * $p<0.05$ from control (paired t-test on raw data)

These data indicate that cocaine significantly prolongs cardiac conduction which may contribute to cocaine-induced mortality.

## COCAINE INDUCED DELETERIOUS EFFECTS ON THE CANINE CORONARY CIRCULATION

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Cocaine abuse has been associated with cardiovascular complications (myocardial infarction, sudden death), but its effects on the coronary circulation have not been well characterized. Accordingly, the coronary vascular effects of cocaine were assessed in 7 sufentanil sedated dogs. Cocaine (2 mg/kg IV) produced a decrease in the diameter of the left anterior descending (LAD, coronary angiography) of 19±3% $p<0.05$; and an increase in coronary vascular resistance (microspheres) of 55±20% $p<0.05$. These effects were noted 2 min after cocaine and were associated with significant ($p<0.05$) increases in heart rate (from 76±9 to 100±14 beats/min), mean arterial pressure (from 106±6 to 128±10 mm Hg), and cardiac output (from 3.7±0.7 to 5.4±1.7 L/min). In 2 other groups of dogs (n=5 each), lower doses of cocaine (0.5 and 1.0 mg/kg) produced similar changes but of lesser magnitude. Dogs (n=5) pretreated with the alpha-adrenoceptor antagonist phentolamine, did not exhibit the deleterious effect of cocaine (2 mg/kg IV) on either LAD diameter (+1±8%), or coronary resistance (-11±30%), (both p=NS vs pre-cocaine baseline).

**Conclusions:** 1) Despite marked augmentation of myocardial oxygen demand, cocaine produces constriction of both epicardial and coronary resistance vessels; 2) These deleterious effects are mediated by alpha-adrenoceptor stimulation; 3) These data suggest that an imbalance between myocardial oxygen supply and demand may play a role in the cardiovascular complications associated with cocaine abuse.

## Tuesday, March 21, 1989
## 10:30AM–12:00NOON, Santa Ana Room 2
## Anaheim Convention Center
## Coronary Artery Disease/Myocardial Ischemia and Infarction

POSTOPERATIVE MONITORING OF REGIONAL LEFT VENTRICULAR FUNCTION IN MAN. Craig J. Hartley, PhD; Raphael S. Rabinovitz, PhD; Hee Shik Lee, BS; Luc J. Suignard, MS; Bharat S. Patel, MD; Jacques E. Chelly, MD, PhD; George P. Noon, MD, FACC; Roberto Bolli, MD, FACC; Baylor College of Medicine, Houston, TX.

To monitor the recovery of regional ventricular function after cardiac surgery, we developed an ultrasonic sensor which can be sutured loosely to the epicardium during surgery to measure LV thickening (LVT). The silastic sheathed leads are exteriorized near the chest tube, and when measurements are no longer needed, the sensor is removed by pulling on the leads. LVT is sensed by tracking the phase of echoes from a sample volume (SV) range-gated to any depth in the myocardium. Thickening fraction (TF) is determined by dividing systolic LVT by the SV depth. Sensors have been implanted on the anterior LV wall in 23 coronary bypass patients with normal pre-op LV function (EF>35%) for 24 to 48 hours. No data was obtained from 6 patients because the sensor failed (2) or detached from the LV (4). All sensors were removed successfully in the intensive care unit. Two patients developed sustained systolic thinning (-10%) during the recovery period (one confirmed by echo), but neither had ECG changes or other symptoms of ischemia. In one patient placed on an intra-aortic balloon pump, TF improved progressively from 5% to 18% in 48 hours. In the other patients TF averaged 26% (range 2-48) before bypass, 30% before chest closure, 22% after chest closure, 27% after 24 hours, and 34% (range 12-55) after 48 hours. In general, regional TF is highly variable, is depressed after surgery ($p<.01$), but recovers to pre-op control levels by 24 hours. We conclude that the epicardial thickening sensor can follow the recovery of regional myocardial function and is valuable for detecting ischemia and for assessing the effects of therapeutic interventions during the postoperative period.

ENDOCARDIAL TRABECULATION: A MARKER FOR HIBERNATING MYOCARDIUM

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Detection of hypocontractile yet viable myocardium is important in coronary disease. We evaluated a new easily derived angiographic parameter: endocardial trabeculation (T) as an index of hibernating (H) myocardium. 75 consecutive pts with wall motion abnormalities (WMA) in the anteroapical segments on LV grams were evaluated. T was graded 0=none or minimal and 1 = moderate or normal, and WMA was graded 0-4; 0 = normal or mild hypokinesis, 1= moderate, 2 = severe, 3 = akinesis and 4 = dyskinesis. T, WMA and precordial R wave sum on ECG were compared to post PVC potentiation as an index of H myocardium.

T grade was inversely related to WMA ($R = -0.6$, $p\leq.01$) and positively related to the sum of R waves ($R = .4$, $p\leq.01$). The correlation between WMA grade and R wave sum was less significant ($R = .2$, $p\leq.05$).

In pts with WMA grade ≥1 (n = 54), a T grade = 1 was predictive of post PVC potentiation ($chi^2 = 9.9$, $p=.002$). Even in pts with reduced R wave sum ≤40 mV and WMA grade ≥1, TG = 1 predicted post PVC potentiation ($chi^2 = 4.0$, $p \leq .05$). In contrast, neither WMA grade nor R wave sum correlated with post PVC potentiation.

In conclusion, preservation of endocardial trabeculation appears to predict viable myocardium in pts with wall motion abnormalities.

SYSTOLIC SHORTENING DETERMINES DIASTOLIC DISTENSIBILITY OF ISCHEMIC MYOCARDIUM DURING PACING INDUCED ANGINA AND TRANSLUMINAL CORONARY OCCLUSION.

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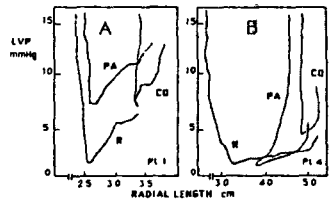
Low flow-high oxygen demand ischemia of pacing induced angina (PA) and no flow ischemia of coronary occlusion (CO) have different effects on LV diastolic (D) distensibility (Dt). D Dt of the same LV anterior wall segment (AWS) was studied during PA and during CO by PTCA in 8 patients (pts) with a LAD stenosis. D LV pressure (P)-radial length (RaL) plots of the AWS were derived from tipmicromanometer LVP and digital subtraction LV angiograms at rest (R), during PA after cessation of pacing and during CO. Fig. A and B show D LVP-RaL plots for 2 pts. Shortening (Sh) of the AWS was lower during CO (8±4%) than at rest (39±15%;$p<0.01$). During CO there was no shift of the D LVP-RaL plot (fig. A and B). During PA Sh of the AWS varied from 33% to 14% (mean:25±11%). When Sh was preserved during PA, the D LVP-RaL plot was shifted upward (fig. A). When Sh was reduced during PA there was no shift of the D LVP-RaL plot (fig. B).

Conclusion: PA decreases D Dt when Sh is preserved. Reduced Sh during CO or PA prevents this decrease of D Dt.




RELATION BETWEEN LEFT VENTRICULAR HYPERTROPHY, FILLING, AND PERFUSION IN ASYMPTOMATIC HYPERTROPHIC CARDIOMYOPATHY.

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Previous studies in our laboratory have shown that exercise-induced thallium perfusion defects are common in asymptomatic or mildly symptomatic pts with hypertrophic cardiomyopathy. To assess the relation of these perfusion defects to LV hypertrophy (LVH) and LV filling parameters, we studied 29 such pts with 2-D echocardiography, exercise and rest thallium tomography, and radionuclide angiography. Maximum wall thickness and an LVH index were used to score the magnitude and extent of LVH by echocardiography. Reversible perfusion defects developed in 14 pts with exercise. Pts with inducible perfusion defects had a higher LVH index (94±14 vs 60±10, $p=.001$), lower peak filling rate at rest by radionuclide angiography, normalized either to end-diastolic volume (3.3±0.9 vs 4.2±1.0 EDV/s, $p<.04$) or to stroke volume (4.2±1.2 vs 5.7±1.3 SV/s, $p<.01$), and longer time to peak filling rate (241±87 vs 185±26 ms, $p<.04$) compared to pts with normal perfusion. Ejection fraction and heart rate did not differ between the two groups. In addition, maximum wall thickness correlated with peak filling rate ($r=.4$, $p<.05$), and LVH index correlated with both peak filling rate ($r=.58$, $p<.002$) and time to peak filling rate ($r=.48$, $p<.02$). Thus, the rate and timing of rapid LV filling are influenced by the magnitude and extent of LVH in asymptomatic or mildly symptomatic pts with hypertrophic cardiomyopathy, and both LVH and impaired LV filling are related to inducible myocardial ischemia. These data suggest that LVH, impaired LV filling, and myocardial ischemia (even when clinically silent) are interrelated pathophysiologic features of hypertrophic cardiomyopathy.

CORONARY ARTERY DISEASE IS ASSOCIATED WITH INADEQUATE LEFT VENTRICULAR HYPERTROPHY IN AORTIC STENOSIS.

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Pts with severe aortic stenosis (AS) develop widely variable patterns of left ventricular hypertrophy (LVH). We postulated that limitations in coronary flow imposed by atherosclerosis (CAD) may lead to ineffective LVH in pts with AS and no previous MI. LV mass and volumes were quantitated from the 2-D echo using the 5/6 short axis area x length method and correlated with coronary angiography in 41 pts with severe AS (0.3-0.8 $cm^2$), no more than mild ($1^+$) insufficiency, and no regional wall motion abnormalities. 8 pts (Group I) had smooth coronary arteries, 15 pts (Group II) had <50% atheromatous irregularities, and 18 pts (Group III) had obstructive CAD with ≥50% stenoses. The magnitude of hypertrophy in relation to cavity size, given by the mass:systolic volume ratio ($M/V_{sys}$), and ejection fraction (EF) were higher in pts with no CAD compared to pts with CAD (ANOVA). Pt age, sex, or degree of AS did not influence the $M/V_{sys}$.

| CAD Score: | I | II | III | p |
|---|---|---|---|---|
| LV mass | 252 ± 35 | 274 ± 23 | 312 ± 22 | NS |
| $M/V_{sys}$ | 10.0 ± 1.7 | 6.0 ± 0.9 | 5.6 ± 0.6 | 0.01 |
| EF (%) | 67 ± 4 | 55 ± 5 | 49 ± 4 | 0.03 |

These data indicate that angiographically normal coronary arteries in AS are associated with concentric LVH, better LV function and normal cavity size, whereas early and particularly obstructive CAD is associated with inadequate LVH with chamber dilatation and abnormal function. Coronary blood flow may play a permissive role in effective LVH development in AS.

**IMPROVEMENT IN LEFT VENTRICULAR EJECTION FRACTION DURING THE FIRST POST-INFARCTION YEAR IN PATIENTS WITH INFERIOR AND NON Q-WAVE INFARCTS.**

**Shmuel Gottlieb M.D., Menahem Gordin M.D., Andre Keren M.D., Dan Tzivoni M.D., F.A.C.C**
**Bikur Cholim Hospital, Jerusalem, Israel.**

**Radionuclide ventriculography (RNV) was performed in 164 consecutive pts recovering from acute myocardial infarction (MI) prior to discharge and 6-12 months (mean 8.7) later. No pt received streptokinase during the acute MI. No pt had new cardiac event between the two studies. Pts were divided according to infarct site and predischarge LVEF (LVEF1). 57 pts had anterior, 48 inferior, 32 non-Q wave and 27 had previous MI. 72 pts had LVEF1 ≥ 51%, 64 LVEF1=30-50% and 28 LVEF1 ≤ 29%. Repeated RNV revealed improvement of ≥ 10% (relative to baseline value) in LVEF in 57 (35%) pts, worsening in 42 (26%) and no change in 65 (40%) pts. Improvement was more marked in pts with LVEF1 30-50%, 47% (30 pts) of them improved their LVEF by more than 10%, and 31% (20 pts) by more than 20%, during the first post MI year.**
**In the whole group LVEF did not change between the two studies (47.6% vs 48.9%, p=NS). However, when the pts were divided into subgroups, a significant improvement was noticed in those with LVEF1 30-50%, from 40.2% to 43.3% (p<0.02). In this subgroup, of 64 pts, the improvement was mainly observed in those who had either inferior or non-Q wave MI (20 pts), from 43.7% to 51.4% (p<0.01). On the other hand, LVEF did not change between the two studies in pts with LVEF1 ≥51% or ≤29%. LVEF1 was higher in 42 pts whose LVEF deteriorated as compared to 57 pts whose LVEF1 improved (50.6% vs 41.5%, respectively, p<0.02). Conclusion: Improvement in LVEF during the first post infarction year is seen mainly in pts with LVEF1 30-50%, with inferior or non-Q wave MI.**

# Tuesday, March 21, 1989
# 8:30AM–10:00AM, California Room B
# Anaheim Convention Center
# Hormonal Influences in Hypertension

ATRIAL NATRIURETIC PEPTIDE AND ELEVATED RIGHT HEART PRESSURES IN ESSENTIAL HYPERTENSION.

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High, normal, and low levels of atrial natriuretic peptide have been reported in human essential hypertension. To explain these apparent contradictions we studied the relationship of atrial natriuretic peptide (ANP) and right heart pressures in 40 essential hypertensives (HT) and in 60 normotensives (NT). ANP was 42(3) pg/ml in NT and 59(5) pg/ml in HT (p<0.05). The regression line between mean right atrial pressure and ANP was significantly steeper in HT than in NT. Therefore, at low atrial pressures no significant differences were observed in ANP levels in HT versus NT whereas at high right atrial pressures HT had significantly higher ANP values. To eliminate the possibility that raised LVEDP in HT influenced ANP via raised pulmonary and right heart pressures, HT and NT with identical LVEDP in the normal range (<13 mm Hg) were matched. For each level of LVEDP mean pulmonary and right atrial pressure were higher in HT than in NT. The same applied to ANP levels. For all matched patients mean right atrial pressure was 3.1(0.2) versus 4.5(0.3) mm Hg in NT and HT, respectively (p<0.05). ANP was 40.2(4.3) pg/ml in NT and 57.9(5.8) pg/ml in HT after matching for LVEDP. Conclusion: The elevation of ANP is best explained by raised right atrial and pulmonary pressures independent of left heart involvement. Differences in ANP become apparent only at high levels of pulmonary and right atrial pressures in HT.

INFLUENCE OF ANTIHYPERTENSIVE THERAPY ON PLASMA HORMONES IN CARDIAC TRANSPLANT RECIPIENTS: MEASUREMENTS AT REST AND DURING EXERCISE

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After cardiac transplantation (HTX) systemic hypertension develops in most patients on cyclosporine A and steroids. To investigate the influence of an antihypertensive regimen(T) with enalapril (20mg/d) and furosemide (20-40 mg/d) alone or combined with verapamil (120-360 mg/d) on resting and exercise blood pressure (BP,mmHg) and plasma hormones, 14 hypertensive patients after HTX (44+9 yrs.,12+11 months pop.) were evaluated. Systolic and diastolic BP, plasma renin activity (PRA,ng AI/ml/h), atrial natriuretic factor (ANF,pg/ml)and its 2nd messenger cyclic guanosin monophosphate (cGMP, pmol/ml), adrenaline and noradrenaline (A,NA, pg/ml) were determined. Blood was taken at rest (control) and during supine bicycle exercise (25 and 50 W). Measurements before and during antihypertensive T were compared. Results (mean values, **/*: p<0.05/0.001 before T vs. T):

| | BPs | BPd | PRA | ANF | cGMP | E | NE |
|---|---|---|---|---|---|---|---|
| Control | 160 | 105 | 2.9 | 128 | 7.42 | 20 | 195 |
| 25 W | 163 | 104 | 3.2 | 165 | 8.10 | 24 | 331 |
| 50 W | 175 | 101 | 3.4 | 244 | 9.34 | 28 | 542 |
| Control (T) | 129** | 84** | 9.8* | 107 | 5.98* | 23 | 275 |
| 25 W (T) | 144* | 89* | 10.2* | 132* | 6.84 | 32 | 380 |
| 50 W (T) | 161* | 93* | 11.8* | 171* | 7.96 | 46 | 612 |

Conclusion: T normalizes resting and exercise BP in hypertensive HTX-patients, but causes marked changes in plasma hormones: PRA increases during T; ANF and cGMP, which are elevated at rest and during exercise after HTX, decrease under T, possibly as a consequence of lower peripheral and probably intraatrial pressures.E and NE do not change significantly, but there is a trend to higher levels under T.

DECREASED ADRENERGIC RESPONSE IN HYPERTENSIVE PATIENTS WITHOUT LEFT VENTRICULAR HYPERTROPHY.

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LV mass fractional shortening (FS) and end-systolic wall stress (ESS) measured by echocardiography and the response of FS and ESS to the infusion of isoproterenol (ISP) (0.02 μg/kg/min for 5 min) were studied in 84 patients who had essential hypertension for 5 years, and 13 age-matched normal volunteers (N). Twenty-seven hypertensive patients had no LV hypertrophy (LV mass <240 g) (H(-)), and 57 patients had LV hypertrophy (H(+)). Blood pressure was not different between H(-) and H(+). When ESS was >12 g/cm$^2$, this variable showed a significant inverse linear relation with FS in all the subjects before ISP. The inotropic response to ISP was measured as the increase of FS corrected for the decrease of ESS (ΔFS/-ΔESS). The M±SD change in ΔFS/-ΔESS was significantly smaller in H(-) (0.52±0.16 cm$^2$/g) than in normal (0.65±0.17 cm$^2$/g) ($p<0.05$), and than in H(+) (0.95±0.54 cm$^2$/g) ($p<0.01$). The response to ISP was decreased in the patients with severe LV hypertrophy in H(+), too. Conclusions: In the hypertensive patients without LV hypertrophy (H(-)), adrenergic response is depressed, compared to normal control and H(+). This depression might be etiologically related to the phenomenon that LV hypertrophy did not develop in H(-) in spite of the same level of pressure overload as in H(+).

BLOOD PRESSURE, LEFT VENTRICULAR MASS AND INTRACELLULAR CALCIUM IN PRIMARY HYPERPARATHYROIDISM.

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Primary hyperparathyroidism is associated with left ventricular hypertrophy which is said to be out of proportion to mild hypertension. The mechanisms are not well understood but intracellular free calcium may affect vascular tone and cell growth. We measured blood pressure, left ventricular mass and platelet cytosolic free calcium ($Ca^{2+}$)i, using Quin 2 in 23 patients with untreated primary hyperparathyroidism and in 30 normal controls. 13 out of 23 patients underwent parathyroidectomy and all measurements were repeated 6 months later. Blood pressure was higher in the hyperparathyroid patients than in controls (141±5(SE)/85±2mmHg vs 125±2/78±2mmHg, $p<0.01$) and parathyroidectomy had no effect on blood pressure. LV mass index was also higher in hyperparathyroid patients (123±9 vs 99±5g/m$^2$, $p=0.02$) and surgical treatment did not lower it significantly (133 vs 144g/m$^2$, $p=0.1$). Median platelet ($Ca^{2+}$)i was slightly but not significantly lower in patients than in controls (82nM vs 88nM; 95% CI (-0.7, 17.7), $p=0.07$). Following parathyroidectomy median ($Ca^{2+}$)i tended to increase (77nM vs 88nM; 95% CI (-2.1, 20.1), $p=0.07$). There was a negative correlation between ($Ca^{2+}$)i and diastolic pressure in the hyperparathyroid group ($n=23$, $r=-0.46$, $p<0.05$). Conclusions: 1, In primary hyperparathyroidism LV mass is consistent with mildly raised blood pressure. 2, In contrast to essential hypertension, patients with high blood pressure and hyperparathyroidism show low levels of ($Ca^{2+}$)i and this cellular abnormality seems to be at least partially corrected by surgical removal of parathyroid adenoma.

LEFT VENTRICULAR DIASTOLIC FUNCTION IN PHEOCHROMOCYTOMA: RELATION TO PLASMA CATECHOLAMINES.

Fetnat Fouad-Tarazi, M.D., FACC, Hassan Nagi, M.D., Manoel Saragoca, M.D., Emmanuel Bravo, M.D., Cleveland Clinic, Cleveland, Ohio.

Plasma catecholamines may reflect adrenergic activity and therefore influence LV systolic function and relaxation indices. To evaluate this question, we studied 11 pheochromocytoma pts and 11 essential hypertensive pts matched for age, sex, BSA, and blood pressure. LV function was evaluated by gated blood pool scanning with derivation of LV ejection fraction, peak ejection rate (PER), peak filling rate (PFR), time to PER and time to PFR. Despite differences in plasma norepinephrine (PNE), LV functional indices were not significantly different between the two groups:

| | Pheochromocytoma | Essential Hypertension |
|---|---|---|
| PNE (pg/ml) | 3340±2451 | 301±134* |
| Ejection fraction (%) | 65±12 | 61±9 |
| PER (Hz) | 2.86±0.75 | 2.62±0.77 |
| PFR (Hz) | 2.47±0.72 | 2.28±0.53 |
| PFR/PER | 0.86±0.09 | 0.89±0.13 |
| Time to PER (msec) | 138±32 | 133±36 |
| Time to PFR (msec) | 516±54 | 515±52 |

(mean ± SD, *$p<0.01$ between groups)

PNE did not correlate in either group with PFR or PER. However, PNE correlated with time to PFR in pheochromocytoma ($r=-0.92$, $p=0.001$) but not in essential hypertension. We conclude that although mean values of LV functional indices were similar in pheochromocytoma and essential hypertension, the relationship of PNE to indices of diastolic LV function differed in the two groups; in pheochromocytoma but not in essential hypertension PNE influenced time to PFR. The lack of correlation of PNE with PFR may be related to factors other than adrenergic activity influencing LV filling.

CAPTOPRIL PRETREATMENT AND MYOCARDIAL FIBROSIS AND STIFFNESS IN RENOVASCULAR HYPERTENSIVE RATS.

Jorge E. Jalil M.D., Joseph S. Janicki Ph.D., Sanjeev G. Shroff Ph.D., Ruth Pick M.D., Karl T. Weber M.D., F.A.C.C., Michael Reese Hosp., Cardiovascular Institute, Univ. of Chicago Pritzker Sch. of Med., Chicago, Illinois

Although converting enzyme inhibition (CEI) has been shown to induce regression of LVH in different models of hypertension, its effects on myocardial stiffness and collagen concentration in renovascular hypertension (RH) have not been examined. We tested the hypothesis that in rats with RH, CEI pretreatment would prevent collagen accumulation, or fibrosis, and alter systolic and diastolic stiffness. Three groups were studied: control (CTRL); RH created by abdominal aorta and right renal artery constriction for 8 weeks (H); and rats treated with oral captopril (0.5 g/L) 2 days before RH and 8 weeks thereafter (H-CAP). At sacrifice, systolic blood pressure (SBP, mmHg); LV to RV weight ratio (LVW/RVW); LV collagen volume fraction (CVF, %); and slopes (gm/cm$^2$) of LV systolic (m-Sys) and diastolic (m-Dia) stress-strain relations in isolated, perfused hearts were measured. (Data: mean±SD, * $p<0.05$ versus CTRL; @ $p<0.05$ versus H)

| | CTRL (n=11) | H (n=10) | H-CAP (n=8) |
|---|---|---|---|
| SBP | 132±8 | 185±21* | 128±20 |
| LVW/RVW | 3.75±0.26 | 4.75±0.71* | 3.95±0.47 |
| CVF | 2.97±0.50 | 6.57±2.20* | 4.79±1.20* @ |
| m-Sys | 359±7 | 533±16* | 517±6* |
| m-Dia | 130±17 | 215±53* | 200±33* |

Thus, in this model of RH, pretreatment with captopril prevented hypertension and LVH and attenuated, but did not abolish, myocardial collagen accumulation. These effects were not associated with significant modifications in LV myocardial stiffness given that fibrosis occurred in the absence of LVH.

# Tuesday, March 21, 1989
# 10:30AM–12:00NOON, California Room B
# Anaheim Convention Center
# Vascular Reactivity in Hypertension

POTENT PRESSOR EFFECTS OF ENDOTHELIN IN SPONTANEOUSLY HYPERTENSIVE RATS AND WISTAR KYOTO RATS

Takashi Miyauchi, M.D., Tomohisa Ishikawa Ph.D., Masashi Yanagisawa M.D., Sadao Kimura Ph.D., Yasuro Sugishita M.D., F.A.C.C., Iwao Ito M.D., Katsutoshi Goto Ph.D. Tomoh Masaki M.D., Ph.D., University of Tsukuba, Tsukuba, Ibaraki, Japan

Endothelin (ET) is a potent vasoconstrictor peptide produced by vascular endothelial cells. To investigate its involvement in the pathogenesis of hypertension, pressor effects of ET were studied in spontaneously hypertensive (SHR) and Wistar Kyoto rats (WKY) (12 w old) after treatment with autonomic blockade (atenolol 1, bunazosin 1, atropine 0.25 mg/kg), under urethane anesthesia. The blood pressure (BP) was measured from the carotid artery and drugs were injected intravenously. ET showed dose-dependent (0.125 ~ 2 nmol/kg) pressor actions. ET-induced pressor responses consisted of the first (transient) and the second (long-lasting, continued about 3 hours at 2 nmol/kg) phases. The maximum increase in BP (2 nmol/kg) was significantly greater in SHR than WKY in both the first (76.5 ± 6.2 vs 60.8 ± 3.1 mmHg, n=6, $p<0.05$) and the second (70.8 ± 6.2 vs 60.8 ± 3.1 mmHg, N=6, $p<0.05$) phases. From the pharmacological analysis in WKY, nicardipine ($Ca^{2+}$ antagonist, 0.1 mg/kg) attenuated largely the second phase (37.0 ± 5.8 mmHg at 2 nmol/kg, n=5, $P<0.001$) but only slightly the first phase. However, a higher dose of nicardipine (1 mg/kg) inhibited greatly both phases (n=6). Neither saralasin (angiotensin II blocker) nor indomethacin (PG synthesis inhibitor) attenuated the pressor effects of ET. Conclusions: 1. ET produced potent pressor effects. The maximum responses were significantly larger in SHR. 2. Pressor effects of ET were blocked by $Ca^{2+}$ antagonist. 3. These results suggest that ET may contribute to the pathogenesis of hypertension in SHR.

ANF BLUNTS FOREARM VASOCONSTRICTION TO LOWER BODY NEGATIVE PRESSURE IN ESSENTIAL HYPERTENSIVE PATIENTS

ROBERTO PEDRINELLI,MD,STEFANO TADDEI,MD,STEFANIA FAVILLA,MD, ANTONIO SALVETTI,MD
HYPERTENSION UNIT,I CLINICA MEDICA,UNIVERSITY OF PISA,ITALY

Contrasting human data exist about the modulation of sympathetic outflow by ANF,particularly at low concentrations. Therefore,the interference by a synthetic human ANF analogue(WY,47663)on sympathetic forearm vasoconstriction was studied in 5 male patients with essential hypertension.Non hypotensive lower body negative pressure(LBNP,-10 mmHg x 5min) was used to stimulate sympathetic tone reflexogenically; forearm blood flow (FBF,strain gauge venous plethysmography,ml/dl/min), intraarterial MAP and HR were monitored,and venous immunoreactive (IR) ANF ,PRA, aldosterone(ALDO)and Norepinephrine(NE) measured at the end of each experimental period.ANF was given at either a low or high concentration,preceded and followed by vehicle infusion(Haemacell x 30 min)either systemically or locally at at least 8 hrs intervals.

Graded systemic infusion(.005 and .05 μg/kg/min x 60min) increased IR-ANF from 37.8±8. to 112.6±20.and 644.4±65 pg/ml,while basal MAP,FBF,HR,PRA,NE did not change and ALDO dropped (from 20±5 to 12±4 and 10±2 ng/ml respectively $p<0.05$). LBNP decreased FBF during preinfusion and recovery periods by 38±4 and 46±5% respectively,but it was ineffective in presence of ANF at either rate(-4 +2.and -2.7±4 %). To dissect a peripheral from a more central site of action,ANF was also infused into the brachial artery at rates(.005 and .05 μg/dl tissue/min x 30 min each)raising local (from 32.4±7 to 184±51 and 470±89 pg/ml respectively) but not systemic venous IR-ANF.The analogue increased FBF dose-relatedly,from 3.2±.3 to 3.8±.5 and 6.2±.4 ml/dl/min on the infused side($p<.01$) without changes in systemic MAP and HR or contralateral FBF.Under these experimental conditions,LBNP vasoconstricted forearm arterioles to a similar extent,irrespective of the presence(.005:-33±5, .05:-42.8±6%) or absence of ANF(preinfusion:-54±4; recovery:-40±7%, NS vs ANF).

Therefore, exogenous ANF, even at low doses, counteracts sympathetic-mediated vasoconstriction in man,an effect exerted at a site other than the neurovascular junction,at least in the forearm vasculature.Sympathetic modulation may be relevant to the physiological and pharmacological action of ANF.

EFFECT OF ORAL ADMINISTRATION OF ANTIHYPERTENSIVE AGENTS ON ENDOTHELIUM DEPENDENT AND ENDOTHELIUM INDEPENDENT VASCULAR RELAXATION.

Pamela Shultz, M.D., Jon Tolins, M.D., Leopoldo Raij, M.D., VAMC and U. of Minnesota, Minneapolis, Minnesota.

We have shown that in hypertension (HPN) both endothelium dependent (EN-D) as well as independent (EN-I) responses to vascular relaxants are depressed. In these studies we investigated whether anti-HPN agents affect EN-D and/or EN-I responses to agonists of vascular relaxation. Normotensive Sprague-Dawley rats were given for 2 weeks either tap water (W) or W containing captopril (CAP) enalapril (EPL) or hydralazine (HYZ) in concentrations shown to be equihypotensive in hypertensive rats; these concentrations did not significantly lower BP of normotensive rats. Aortic rings (with and without EN) were suspended in organ chambers for isometric tension recording. The % relaxation induced by the EN-I agent Na nitroprusside ($10^{-8}$M) was significantly but similarly enhanced in rats given CAP, EPL and HYZ compared with rats given W (75±8%, 81±6% and 80±6% vs 50±5%, respectively, $p < 0.05$). In all rats acetylcholine (Ach), $10^{-9}$-$10^{-4}$M, caused relaxations in rings with, but not in those without EN. EN-D relaxations were significantly enhanced in CAP rats but not in W, EPL or HYZ rats: the concentration of Ach (-log M) required to evoke 50% relaxation (IC50) was reduced in rats given CAP (7.9±0.1) vs W (6.2±0.2), HYZ (7.1±0.2) or EPL (6.8±0.2) $p<0.05$. Indomethacin $10^{-5}$M did not prevent the effect of Ach while both pyrogallol $10^{-4}$M and Hb $10^{-5}$M, inhibitors of the endothelium derived relaxing factor NO, inhibited Ach induced relaxations. These studies suggest that anti-HPN agents differentially affect vascular relaxations in response to EN-D and EN-I agonists. This may influence the overall beneficial effect of anti-HPN agents in cardiovascular pathology.

CYCLOSPORIN THERAPY IMPAIRS ENDOTHELIUM-DEPENDENT RELAXATIONS IN THE RENAL CIRCULATION.

Dennis Diederich M.D., Zhihong Yang M.D., Fritz R. Bühler M.D. and Thomas F. Lüscher M.D., Dept. of Research and Medicine, University Hospital, Basel/Switzerland.

Cyclosporin A (CyA) is an immunosuppressive substance which causes structural and functional changes of endothelial cells. The endothelium can modulate vascular tone by the release of endothelium-derived relaxing (EDRF) and constricting factors (EDCF). Functional changes of the endothelium could contribute to hypertension, arteriolopathy and premature atherosclerosis occurring during chronic CyA therapy. Male Wistar Kyoto rats (20-24 weeks) were treated with CyA 50 mg or 30 mg s.c./day, the solvent or saline for 1 or 2 weeks, respectively. CyA did not cause significant increases in blood pressure. Renal artery rings were suspended in organ chambers filled with physiological salt solution (37°C; 95% $O_2$/5% $CO_2$); isometric tension was recorded. In saline treated rats, acetylcholine (ACh) induced relaxations in rings with (71±7%; n=9), but not in those without endothelium. The sensitivity and maximal response to ACh was impaired in rats receiving either 30 mg CyA for 2 weeks or 50 mg for 1 week (13±10% and 31±11%; $p<0.05$; n=9 and 22, respectively). The solvent also tended to reduce the relaxations. Inhibition of cyclooxygenase with either indomethacin or meclofenamate ($10^{-5}$M) augmented the response in CyA rats. Thus, (1) ACh releases EDRF in the rat renal artery; (2) chronic CyA therapy blunts endothelium-dependent relaxations in the renal circulation and (3) an endothelium-derived cyclooxygenase product interferes with the action of EDRF in CyA treated rats.

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TRANSIENT MYOCARDIAL ISCHEMIA IN HYPERTENSIVE CORONARY MICROANGIOPATHY.

Wolfgang Motz M.D., Sibylle Scheler M.D.,Martin Vogt M.D., Bodo E. Strauer M.D., F.A.C.C.,Dept. of Medicine, University of Duesseldorf, W.Germany.

In hypertensive patients with a normal coronary angiogram coronary regulating capacity is usually impaired due to coronary microangiopathy. To determine whether episodes of transient myocardial ischemia can be documented in patients with coronary microangiopathy,coronary reserve was measured and ST-Holter-analyses were performed in 20 pts (age: 55.6 ± 8.1 years) with essential arterial hypertension (systolic/diastolic blood pressure: 170±11/95±15mmHg). Coronary reserve (Rcor/Rmin) was determined by measuring the coronary resistance before (Rcor) and after dipyridamole (0.5mg/kg body weight intravenously:Rmin).Coronary blood flow was measured by the gaschromatographic Argon method. ST-segment changes were evaluated by Holter-monitoring (Marquette-Holter) over 24 hours. Horizontal or downsloping ST-segment depressions ( ≥1.0 mm, duration ≥1.0min) were considered to be of pathological value. Results:In 75% (15/20) of the patients studied ST-segment depressions were detected by Holter-monitoring.In patients with ST-segment depressions Rmin was 46% higher than in patients without ST-segment depressions (0.50± 0.18 vs 0.23 ± 0.02mmHg·min·100g/ml, $p < 0.01$). Coronary reserve (Rcor/Rmin) was markedly impaired in patients with ST-segment depressions (2.60±1.15 vs 4.68±0.18, $p< 0.01$). Maximum coronary blood flow per weight unit myocardium after dipyridamole was significantly lower in patients with (245 ± 25 ml/min·100g) than in those without ST-segment depressions (344 ± 36 ml/min·100g; $p<0.05$) Conclusions: (i) Hypertensive patients with a normal coronary angiogram have coronary microangiopathy as shown by an impaired coronary vasodilator reserve. (ii) The frequent episodes of ST-segment depressions in these patients indicate that hypertensive coronary microangiopathy implies a chronic ischemic risk inspite of the abscence of coronary macroangiopathy.

INDUCTION BY LDL OF GROWTH RELATED METABOLISM IN VASCULAR SMOOTH MUSCLE CELLS.

Tim Scott-Burden Ph.D., Thérèse J. Resink Ph.D., Alfred Hahn Ph.D., Fritz R. Bühler M.D., Department of Research, University Hospital, Basel, Switzerland.

The implication of LDL in the pathophysiology of atherosclerosis has been long recognized but its direct effects on vascular smooth muscle cell (VSMC) metabolism are less clear. We have shown that LDL stimulates a number of intracellular metabolic events normally associated with proliferation in cultured human and rat VSMC. When quiescent (serum-deprived) VSMC are exposed to LDL there is a time- and dose-dependent ($10^{-10}$-$10^{-7}$ M) stimulation of $S_6$-kinase and ornithine decarboxylase activation, phosphoinositide breakdown, elevation of intracellular pH and the induction of the nuclear proto-oncogenes c-fos and c-myc. Under the serum-free conditions employed we did not see growth stimulation by LDL alone, however, in the presence of EGF (5 ng/ml) both growth and DNA synthesis were enhanced significantly. Similar studies with VSMC from spontaneously hypertensive rats (SHR) and their normotensive Wistar Kyoto (WKY) counterparts yielded essentially the same date as that obtained with human VSMC except that cells from SHR sources showed an enhanced responsiveness to LDL in combination with EGF. Prolonged (48 hrs) preincubation of VSMC from the two speicies (rat/human) with TPA ($10^{-7}$ M) obliterated all subsequent stimulatory effects of LDL by itself. A direct effect of LDL on human VSMC 'proliferative' responses may be relevant to atherogenesis.

## Tuesday, March 21, 1989
## 8:30AM–10:00AM, California Room A
## Anaheim Convention Center
## Coronary Vasoconstrictor Substances

INTRACORONARY ENDOTHELIN INFUSION INDUCES TRANSMURAL MYOCARDIAL ISCHAEMIA IN THE DOG

S. Larkin BSc, J. Clarke MRCPI, B. Keogh FRCS, L. Araujo MD, C. Rhodes PhD, J. Brannan, K. Taylor FRCS, G.Davies MD, and A. Maseri FACC.
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A 21 residue endothelium-derived vasoconstrictor peptide, endothelin (ET), has recently been isolated and studied in vascular preparations in vitro. We have investigated the effects of locally infused ET in the dog coronary circulation in vivo. Six anaesthetised, open chest greyhound dogs were studied. Recordings were taken from electromagnetic flow probes applied to the proximal left anterior descending (LAD) and circumflex (CX) arteries, LA and AO pressure lines, and the epicardial ECG. Normal saline vehicle or incremental doses of ET (3 to 100 pmol/min) were infused via a fine cannula positioned in the proximal LAD. In three animals radiolabelled microspheres were also given to determine regional myocardial blood flow, and in two coronary arteriography was performed to assess changes of epicardial coronary (EC) calibre at the maximum dose of ET. ET induced a significant dose-dependant reduction of LAD coronary blood flow (CBF) reducing it by 70% from 60±8 to 19±7 ml/min (mean± SEM, $p<0.005$) at 100pmol/min. Reductions of LAD CBF below 50% of basal were associated with the onset of gross ischaemic ECG changes and raised LA pressure. Microsphere distribution showed transmural flow reduction in the LAD territory. No significant changes of AO pressure, heart rate, or CX CBF were seen until severe ischaemia persisted, and no EC constriction was seen during angiography. In conclusion we have shown picomolar doses of a novel endothelium-derived peptide can induce myocardial ischaemia predominantly by small vessel constriction.

ENDOTHELIN IS A POTENT CONSTRICTOR OF FOREARM RESISTANCE VESSELS AND VEINS IN MAN

John Clarke MRCPI, Nigel Benjamin MRCP, Simon Larkin BSc, David Webb MRCP, Graham Davies MD, Attilio Maseri FACC. Royal Postgraduate Medical School, London, U.K.

Endothelin (ET) is a 21 amino acid peptide synthesized by cultured mammalian endothelial cells. Studies in vitro suggest that it is a potent constrictor of vascular smooth muscle and may act as a final mediator for a number of constrictor agents. We have studied the effect of brachial artery infusion of ET (5pmol/min) on forearm blood flow (FBF) using strain gauge plethysmography, and of local infusion on dorsal hand vein diameter in normal volunteers. ET produced a progressive reduction in FBF in the infused arm over 60 mins to a maximum 39±7% (n=9) similar to that with the same molar dose of angiotensin II (40±7%; n=8). The effect of ET was prolonged on stopping the infusion ($t_{1/2}$ = 50min) and was rapidly reversed by co-infusion of nicardipine (10μg/min). No effect was seen in the non-infused arm. ET similarly produced a progressive constriction in veins over 60 mins (53±12%; n=9), again with delayed offset but here nicardipine failed to reverse the effect. The kinetics of ET-induced constriction in human vessels make it unlikely that the effects of other recognised constrictor agents are mediated by this peptide. However it may have an important role in long-term modulation of peripheral resistance and venous capacitance in man.

**ENDOTHELIN IS A POTENT CONSTRICTOR OF HUMAN CORONARY ARTERIES IN VITRO**

Adrian Chester BSc, John Clarke MRCPI, Sham Kauser, Simon Larkin BSc, Graham Davies MD, Magdi Yacoub FRCS. The Cardiothoracic Institute, Harefield Hospital, U.K.

Endothelin (ET) is a 21 amino acid peptide derived from vascular endothelial cells in culture and is a potent constrictor of mammalian vascular tissue in vitro. It has been suggested that ET may be an endogenous antagonist of voltage-dependent calcium channels. We have investigated the dose-response relationship of ET in isolated human epicardial coronary arteries. Human epicardial coronary arterial ring segments of 2-3mm diameter from 4 patients undergoing cardiac transplantation were suspended on L-shaped hooks and studied in 5ml organ baths at 37°C in a modified tyrode solution gassed with a 95% $O_2/CO_2$ mix. An initial tension of 50mN was applied to each segment which resulted in a resting tension of 5-25mN at one hour. All segments were challenged with 90mM $K^+$ to assess viability. After washing and recovery, cumulative log doses of ET ($3x10^{-10}$ to $3x10^{-7}$) were added. ET induced a concentration dependent constriction of rapid onset but with a protracted development of maximum tension of 67.7mN ± 9.9. The maximum contraction was consistently greater than that induced by 90mM $K^+$ (163%). The dose response curve was shifted to the right by 1mg nicardipine while the constriction was reversed by substance P ($10^{-7}$ M), adenosine ($10^{-6}$ M) and isoprenaline ($10^{-6}$ M), but not by acetylcholine or indomethacin. We have shown that an endothelium derived peptide is a potent constrictor of human coronary artery inducing a maximum contraction greater than that inducible with serotonin (30mN) or $K^+$ (30mN) and that the effect is inhibited by a calcium channel blocking agent.

EFFECTS OF ENDOTHELIN, A NOVEL VASOCONSTRICTOR PEPTIDE, ON THE ISOLATED HUMAN MESENTERIC ARTERIES

Takashi Miyauchi M.D., Yoko Tomobe B.S., Masashi Yanagisawa M.D., Yasuro Sugishita M.D., F.A.C.C., Iwao Ito M.D., Sadao Kimura Ph.D., Katsutoshi Goto Ph.D., Tomoh Masaki M.D., Ph.D., University of Tsukuba, Tsukuba, Ibaraki, Japan

Endothelin (ET) is a novel potent vasoconstrictor peptide, which consists of 21 amino acids and is produced by vascular endothelial cells. To investigate the physiological significance of ET in the regulation of human vascular tone, we studied the effect of ET on the isolated human mesenteric arteries (HMA), and compared with that of noradrenaline (NA). HMA were obtained from patients undergoing segmental resection of the intestine. Ring segments (4 mm long) of HMA were mounted in a Krebs-Ringer's solution (37°C, bubbled with 95%$O_2$ + 5%$CO_2$), and contractile tension was measured. Both ET and NE produced dose-dependent contractions. The maximum response to ET was 85.9±4.2% (n=7) of that to NA. However the ED50 value of ET ($2.8 \times 10^{-9}$ M, n=7) was about two orders of magnitude less than that of NA ($3.8 \times 10^{-7}$ M, n=7, $p<0.001$). Vasoconstrictor effects of ET were not affected by α-adrenergic, β-adrenergic, muscarinic and serotonergic antagonists but were significantly reduced by nicardipine ($3 \times 10^{-9}$ M), a $Ca^{2+}$ antagonist, thereby the ED50 value of ET being $1.7 \times 10^{-8}$ M, n=4, $p<0.05$). Conclusions: 1. ET showed potent vasocostrictor effects (about 100 times more potent than NA) on the isolated human mesenteric arteries. 2. The effects of ET were specifically blocked by $Ca^{2+}$ antagonist. 3. These results suggest that ET may participate in regulation of the human vascular tone and is implicated in certain types of hypertension as well as vasospasm.

**ACETYLCHOLINE IS A POTENT VASOCONSTRICTOR IN HUMAN CORONARY ARTERIES EARLY AFTER CARDIAC TRANSPLANTATION.**

Tommy C. Lee M.D., Ulrich Nellessen M.D., Tim A. Fischell M.D., Tohru Masuyama M.D., Edwin L. Alderman M.D. FACC, John S. Schroeder M.D. FACC, Stanford University, Stanford, CA.

The reliability of intracoronary (IC) acetylcholine (ACh) to monitor the accelerated atherosclerosis seen in cardiac transplant patients (pts) is controversial. We have previously shown that IC ACh consistently constricts coronary arteries of pts 1 to 8 years after transplantation. In order to determine early responses, we infused IC ACh in increasing log doses (10-6 M to 10-2 M) in 6 pts soon after transplantation (mean ± SD = 18 ± 8 days). All had angiographically normal coronary arteries and were free of rejection at the time of study. ACh was infused via a 3 Fr catheter placed into the mid-portion of the left anterior descending coronary artery through a guiding catheter. Angiograms after 4 minute infusion periods at each ACh dose were obtained to assess coronary vasomotion. Analysis of the angiograms was performed by a computer-assisted quantitation system. No vasodilation was observed in any pt. Five of 6 pts had significant vasoconstriction at 10-3 M ACh with mean diameter reduction of 34 ± 7% ($p < 0.001$). No change was observed in the sixth pt. There were no changes in blood pressure or heart rate with the drug infusion. Sublingual nitroglycerine caused significant vasodilation in all pts. We conclude that ACh is a potent vasoconstrictor in coronary arteries of pts even very early after transplantation and that ACh mediated vasomotion is not a useful assay for accelerated atherosclerosis in transplant pts.

**ACETYLCHOLINE CAUSES VASOCONSTRICTION IN PRE-CONTRACTED HUMAN CORONARY ARTERIES IN VIVO.**

Tommy C. Lee M.D., Ulrich Nellessen M.D., Tohru Masuyama M.D., Edwin L. Alderman M.D. FACC, John S. Schroeder M.D. FACC, Tim A. Fischell M.D., Stanford University, Stanford, CA.

The role of acetylcholine (ACh) on coronary vasomotion is controversial. Although ACh causes endothelial dependent vasodilation in organ baths, results from human studies are mixed. To optimize the detection of vasodilation mediated by ACh, we studied the dose response of normal coronary arteries to ACh after phenylephrine (PE) induced contraction in 6 patients (pts). All had normal coronary arteries angiographically. Increasing doses of PE (10-6 M to 10-4 M) was infused over 4 minute periods via a 3 Fr catheter placed into the mid-portion of the left anterior descending coronary artery through a guiding catheter. These incremental infusions produced a 19 ± 10% reduction ($p < 0.001$) in coronary diameter without causing significant changes in blood pressure or heart rate. Incremental log doses of intracoronary ACh (10-6 M to 10-2 M) were then infused simultaneously with PE. Angiograms after 4 minute infusion periods at each ACh dose were made to assess coronary vasomotion. Analysis of the angiograms was performed by a computer-assisted quantitation system. No vasodilation was observed in any of the pts. Five of the 6 pts had vasoconstriction beyond the pre-constricted diameters at 10-4 M ACh with further mean diameter reduction of 27 ± 21% ($p < 0.01$). No change was observed in the sixth patient. All 6 pts had a negative ergonovine provocation test following the ACh drug studies. We conclude that ACh is a potent vasoconstrictor in angiographically normal coronary arteries despite a pre-contracted state produced by PE.

# Tuesday, March 21, 1989
# 10:30AM–12:00NOON, California Room A
# Anaheim Convention Center
# Systolic Function: Left Ventricular Mechanics

## A Geometric View of Cardiac "Efficiency"

Eric A. Hoffman Ph.D., John Rumberger M.D., Larry Dougherty, Nathaniel Reichek M.D., and Leon Axel M.D., Ph.D.. Univ. of Pennsylvania, Philadelphia., PA. and Mayo Clinic, Rochester, MN.

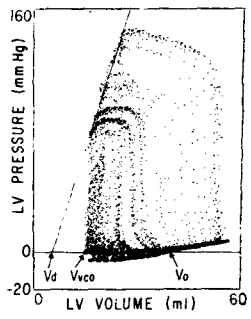
It has been previously demonstrated (AJP 249: H883-H890, 1985) that the total heart volume (THV: pericardial sac contents) in dogs remains within 5% of the end-diastolic volume throughout the cardiac cycle. We have hypothesized that this constancy of THV minimizes the work load particularly for the right heart and that, the maintenance of a constant center of mass would further minimize cardiac work load. To evaluate this hypothesis in humans, we have volumetrically scanned 6 volunteers via cine-CT and 4 volunteers via a new magnetic resonance (MR) myocardial tagging technique. Change in THV between end-diastole ED and end-systole ES as per cine-CT scans was 8±0.76% (SEM) while the % change in total chamber volume was 20±2.4 %. Data closely parallel previous dog studies which suggested possible intra-cardiac cycle alterations of myocardial blood aiding the maintenance of a constant THV. Shift of the THV center of mass between ED and ES was only 3±0.8 mm along the LV long axis with no change along orthogonal axes. MR tagging, whereby "stripes" are added to the myocardium via spatial modulation of magnetization (SPAMM), has allowed for evaluation of the contribution of segmental myocardial contraction to the interaction between the four chambers leading to a constant THV. Stripe motion parallel to the mitral valve plane demonstrate a tethering of atrial dome and epicardial apex. Transmural warping of stripes demonstrate regional inhomogeneities of myofibril contributions to wall thickening and motion. Motion of the mycardial stripes relative to pericardial sac stripes demonstrate the strong role of the pericardial sac in facilitating low resistance to cardiac positional and shape changes.

*Supported in part by NIH HL-29886; Dr. Hoffman is an established investigator of the American Heart Association.*

## ON IMPORTANT VOLUMES IN THE LEFT VENTRICLE

Srdjan Nikolic, MS, Michael P. Feneley, MD, Octavio Pajaro, MS, Robert W.M. Frater, MD, FACC, J. Scott Rankin, MD, FACC, Edward L. Yellin, PhD
Albert Einstein College of Medicine, Bronx, N.Y., and Duke University Medical Center, Durham, N.C.

In 7 anesthetized dogs, LV pressure (P) was measured with micromanometers, and LV volume (V) was calculated from 3 orthogonal ultrasonic diameters. Relationships were investigated between 3 important ventricular parameters: volume intercept of the end-systolic P-V relationship (Vd), "unstressed" end diastolic volume determined at maximal vena caval occlusion (Vvco), and "equilibrium" volume (Vo) obtained by end-systolic occlusion of an implanted Bjork mitral valve (MVO). Single beat MVO's were performed every 6-8 cycles during VCO to transiently prevent filling, and minimal LVP and V during MVO determined the non-filling P-V relationship (dashed line) with volume intercept Vo. The end-diastolic P-V relationship also was computed (solid line) with volume intercept Vvco. Observed values (mean±SD) relative to Vd were: Vvco= 28.6±7.7 ml and Vo=48.6±8.1 ml (p<.01). Thus, Vvco and Vo measured in the same preparation seem to represent different physiologic phenomena. The conceptual relationship between these volume parameters, especially as to which represents true myocardial "slack length," needs to be assessed in further studies.




## COMPARISON OF THREE INDICES OF LEFT VENTRICULAR PERFORMANCE DERIVED FROM PRESSURE-VOLUME LOOPS IN CONSCIOUS DOGS.

Michael Mumma, M.D., Che-Ping Cheng, M.D., Ph.D., Jakob Vinten-Johansen, Ph.D., William E. Johnston, M.D., William C. Little, M.D., F.A.C.C. Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC.

Three load-insensitive indices of left ventricular (LV) performance derived from pressure (P)-volume (V) loops have been proposed: the end-systolic P-V ($P_{ES}$-$V_{ES}$) relation, the stroke work-end-diastolic V (SW-$V_{ED}$) relation and the maximum dP/dt-$V_{ED}$ ($dP/dt_{max}$-$V_{ED}$) relation. We evaluated the variability and inotropic sensitivity of the slopes of these relations in 9 conscious dogs. LV V was determined from three orthogonal LV diameters measured by sonomicrometry. Three to five sets of variably loaded P-V loops were generated by transient caval occlusions before and after inotropic stimulation with dobutamine (6±1 mcg/kg/min, mean±SD). The variability of the slopes were assessed at constant inotropic state using the coefficient of variation. The SW-$V_{ED}$ relation was less variable (5±3%) than either the $P_{ES}$-$V_{ES}$ relation (9±6%, p<0.05) or the $dP/dt_{max}$-$V_{ED}$ relation (11±9%, p<0.05). The SW-$V_{ED}$ relation had a smaller increase with dobutamine (125±29% of control, p<0.05) and the $dP/dt_{max}$-$V_{ES}$ relation a greater increase (233±57%, p<0.05) than the slope of the $P_{ES}$-$V_{ES}$ relation (187±60%) . The position of the $P_{ES}$-$V_{ES}$ relation, quantitated by $V_{100}$, the $V_{ES}$ at $P_{ES}$=100, showed less variability (4±5%) than the slope of the $P_{ES}$-$V_{ES}$ relation (9±6%, p<0.05). $V_{100}$ consistently decreased with dobutamine (88±7% of control, p<0.05).

Conclusion: In conscious dogs, the slope of the SW-$V_{ED}$ relation is less variable but also less sensitive to changes in inotropic state than the slope of the $P_{ES}$-$V_{ES}$ relation, while the slope of the of the $dP/dt_{max}$-$V_{ED}$ relation is more sensitive and more variable. $V_{100}$ has less variability than the slope of the $P_{ES}$-$V_{ES}$ relation and responds consistently to inotropic stimulation.

## DELETERIOUS EFFECTS OF VOLUME LOADING AFTER ACUTE PULMONARY EMBOLISM.

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Volume loading (VL) is used to treat hypotension due to pulmonary embolism (PE). We studied 10 closed chest, anesthetized and ventilated dogs to test the hypothesis that VL after PE would decrease LV stroke work (SW) by causing a leftward septal shift and decreased LV transmural pressure (P). PLV, PRV (Millar®), PRA and P pericardium (balloon) plus septum-to-RV free wall, septum-to-LV free wall (DSLV) and LV anteroposterior (DAP) diameters (sonomicrometry) were measured. Repeated PE (RPE) was produced with autologous clot. VL was done before PE, after one PE and after RPE. LV area (ALV = DAP x DSLV) was used as an index of LV volume. SW was calculated as the area of the LVP x ALV loop.

| | ALV ($mm^2$) | | SW(mm Hg x $mm^2$) | |
|---|---|---|---|---|
| | C | VL | C | VL |
| Before PE | 2870±430 | 3080±520* | 188±85 | 260±101* |
| After 1 PE | 2850±470 | 2870±500 | 188±39 | 203± 52 |
| After RPE | 2760±440 | 2660±420* | 133±64 | 45± 27* |

* p <.05 vs C (ANOVA).

VL after RPE decreased the transseptal gradient (-3±2 to -5±0 mm Hg; p<.001) with a leftward septal shift. Preload, as reflected by LV transmural P, also decreased (1±2 to -1±2 mm Hg; p<.01). Thus, despite similar increases in LVEDP with each VL, the response after RPE was quite different from before PE and after 1 PE.

We conclude that volume loading in this model of pulmonary embolism can cause a marked reduction in LV stroke work by decreasing diastolic filling secondary to ventricular interaction. This suggests that the responses to VL in patients with PE may also be variable and potentially deleterious in some circumstances.

LEFT VENTRICULAR SYSTOLIC PRESSURE-VOLUME AREA AND OXYGEN CONSUMPTION OF HYPER-AND HYPOTHYROID RABBITS.
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$O_2$ consumption per beat ($VO_2$) in isolated left ventricle (LV) is linearly correlated with pressure-volume area (PVA). The reciprocal of the slope (m) of the $VO_2$-PVA relationship indicates the mechanical efficiency of the contractile machinery, while the $VO_2$-intercept (Int) reflects the energy cost of EC coupling and basal metabolism. A variety of acutely administered inotropic drugs have been shown to alter the $VO_2$-Int, but none has had any effect on mechanical efficiency. In rabbits, hyperthyroidism increases the $V_1/V_3$ ratio of myosin isoforms, thereby altering the kinetics of the actin-myosin interaction. To determine what effect this has on the $VO_2$-PVA relation, we quantified contractility by Emax (slope of the end-systolic PV relation) and mechanical energy output by PVA in blood perfused hearts isolated from normal (N, n=7), hyperthyroid (Hr, n=5), and hypothyroid (Ho, n=7) rabbits. LV weight and normalized Emax were similar among the groups. However, both m and $VO_2$-Int of the $VO_2$-PVA relation were greater ($p<.05$) in Hr (m, $3.1 \times 10^{-5}$ ml $O_2$/[mmHg·ml]; Int, 0.051 ml $O_2$/beat/100 g) than in N (m, $2.1 \times 10^{-5}$; Int, 0.040) and Ho (m, $2.1 \times 10^{-5}$; Int, 0.035). Isoproterenol increased Int but not m in each group, indicating that m changes in Hr are not due to increased beta-receptors. We conclude that in Hr the LV has both decreased contractile efficiency (due to increased $V_1/V_3$ ratio) and increased energy cost of E-C coupling + basal metabolism. Both contribute to higher $VO_2$ in Hr.

MYOCARDIAL METABOLIC TO MECHANICAL ENERGY TRANSFER CHARACTERISTICS FROM SINGLE VENA CAVAL OCCLUSIONS IN CONSCIOUS DOGS
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Myocardial energetics have been quantified by linear energy transfer (ET) curves relating steady-state total LV oxygen consumption per beat (coronary blood flow x $AVO_2$ difference) on the abscissa to total mechanical energy expenditure (stroke work plus the product of end-diastolic LV volume and mean ejection LV pressure) on the ordinate. ET characteristics have been shown to be insensitive to alterations in afterload and inotropism, and link myocardial metabolism to mechanical function. However, a clinically applicable method for determining ET relationships has not been available. Accordingly, dynamic ET curves obtained during rapid vena caval occlusion (VCO) were compared with those from steady state preload reduction in 8 autonomically blocked conscious dogs. LV volume was measured with ultrasonic transducers, LV pressure with micromanometers, coronary blood flow with Doppler probes, and coronary $AVO_2$ difference with high fidelity fiberoptic catheters. Highly linear (mean R=.95±.03) ET curves were observed both for rapid VCO and for multiple steady state preloads. The slopes and intercepts of the dynamic ET curves (1.32 ± .24; .14 ± .07) were not significantly different from steady state coefficients (1.34 ± .20; .13 ±.06) by analysis of covariance ($p>.6$). Thus, metabolic adjustments to changing LV energy demand occur rapidly, and transient vena caval occlusion may be a simple, practical, and clinically useful technique for examining myocardial energetics in patients undergoing cardiac catheterization.

# Tuesday, March 21, 1989
# Poster Displayed: 9:00AM–12:00NOON
# Author Present: 9:00AM–10:00AM
# Pacific Room, Anaheim Convention Center
# Myocardial and Pericardial Disease

CAN PRE-OPERATIVE PEAK CORONARY FLOW PREDICT SYMPTOM AND METABOLIC BENEFIT AFTER OPERATIVE RELIEF OF OBSTRUCTION IN HYPERTROPHIC CARDIOMYOPATHY?
Richard O. Cannon, M.D., F.A.C.C., Charles L. McIntosh, M.D., F.A.C.C., Stephen E. Epstein, M.D., F.A.C.C., NHLBI, Bethesda, Maryland.

Operative relief of left ventricular (LV) outflow obstruction improves symptoms in most, but not all, patients with hypertrophic cardiomyopathy (HCM). We have hypothesized that small vessel coronary disease may contribute to symptoms in HCM: this abnormality would impair peak coronary flow, and would not be improved by surgery. To ascertain whether pre-op peak coronary flow predicts operative benefit, we measured great cardiac vein (GCV) flow during rapid atrial pacing in 20 HCM patients with LV outflow obstruction. Group A includes 6 patients with peak GCV flow >175 ml/min during pre-op pacing and Group B includes 14 patients with peak GCV flow <175ml/min. Values=mean±1S.D.

| | | Peak GCV Flow | Pacing Lactate | Lactate Production | Chest Pain |
|---|---|---|---|---|---|
| **Group A** | Pre-op | 216±18 | -32.8±30.5 | 5/6 | 6/6 |
| | Post-op | 151±46* | 28±23.9* | 0/6* | 3/6 |
| **Group B** | Pre-op | 138±19 | -10.4±52.8 | 8/14 | 14/14 |
| | Post-op | 123±43 | -6.0±26.2 | 6/14 | 10/14 |

*$p<.05$ vs pre-op: Lactate=mM·ml/min.
All Group A patients had a 10 beat/min or greater improvement in pacing angina threshold with no lactate production, whereas 5/14 Group B patients had no improvement. Thus, a higher peak flow response to stress pre-op consistently predicts post-op symptom and metabolic improvement to pacing stress. Results in patients with lower peak flow responses are variable, suggesting mechanisms other than obstruction, such as small vessel disease, may contribute to symptoms.

ENHANCED CARDIAC ADRENERGIC RESPONSE IN CARDIOMYOPATHIC HAMSTER AT A PRE-CONGESTIVE FAILURE STAGE.
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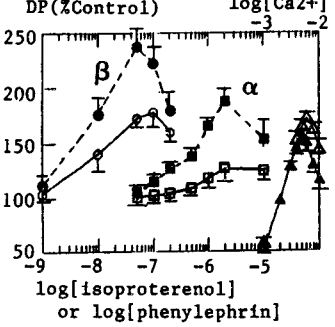
Previous studies suggest that the pathogenesis of the Syrian hamster cardiomyopathy(CMH) may be related to an exaggerated responsiveness to catecholamines. In order to differentiate the response to adrenergic stimulation from that due to increased cell $Ca^{2+}$ per se, we used 35-60 day old male CMH (filled symbols) and age-matched F1B strain control (C; open symbols) hearts. Isolated, isovolumic and AV blocked hearts were perfused with Hepes buffer at constant pressure and stimulated at 2 Hz at 37°C to investigate the effect of changes in bathing $[Ca^{2+}]$ (1-10 mM; n = 6 of each; ▲,△), β-adrenergic (isoproterenol, 0.001-0.5 μM; n = 6 of each; ●,○) and α-adrenergic (phenylephrine, 0.05-10 μM plus propranolol, 5 μM; n = 6 of each; ■,□) agonists on developed pressure (DP). Results (Figure) are % of DP in 2 mM $[Ca^{2+}]$ prior to drug, which were 61.2±5.5 and 81.2±4.2 mmHg (mean ± SEM) in CMH and C respectively. In CMH both α- and β-adrenergic responsiveness is markedly enhanced (Figure); this is not due to an enhanced response to $Ca^{2+}$ per se (Figure), but may be due to greater cell $Ca^{2+}$ loading by catecholamine stimulation.



## PATHOGENESIS OF SYSTOLIC ANTERIOR MOTION OF THE MITRAL VALVE - CAN THE PAPILLARY-MITRAL APPARATUS PLAY A PRIMARY ROLE CLINICALLY?

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The pathogenesis of systolic anterior motion (SAM) of the mitral valve remains controversial, as patients with hypertrophic cardiomyopathy have two potential primary causes of SAM: asymmetric septal hypertrophy (ASH) and abnormalities of the papillary-mitral apparatus (PMA). In order to explore whether SAM can occur clinically due to PMA abnormalities in the absence of ASH, we searched the records of our laboratory and referrals for all patients (PTS) with 2-dimensional echo studies (2DE) demonstrating leaflet SAM. **RESULTS:** 95 PTS with SAM were identified, of whom 90 had septal hypertrophy. Of the remainder, in addition to 2 pts with tumors of the PMA prolapsing into the LV outflow tract (LVOT), there were 3 distinct mechanisms evident for SAM: 1)tumor of the posterobasal myocardium displacing the papillary muscles (PMs) and mitral leaflets anteriorly into LVOT flow (n=1), 2)anomalous fusion of redundant chordae (n=1) and 3)anomalous PM position (n=1). In this series, the ratio of septal to posterior wall thickness was normal (1.01 $\pm$ 0.15) as was the LVOT diameter (2.3 $\pm$ 0.4 cm) and area (6.46 $\pm$ 0.7 $cm^2$). Nevertheless, SAM in this series was accompanied by elevated LVOT velocities (up to 3.2 m/s), abnormal LVOT gradients at catheterization (up to 45mm Hg at rest) and clinical evidence of pre-syncope. **CONCLUSION:** In the absence of ASH, SAM can occur clinically as a result of PMA abnormalities. These spontaneous experiments of nature illustrate the primary role that abnormalities of the PMA can play in generating LVOT obstruction, by alterations in leaflet redundancy and chordal tension.

## ELECTROCARDIOGRAPHIC CHANGES DURING DIPYRIDAMOLE STRESS AS POTENTIAL MARKERS OF ACUTE CARDIAC REJECTION.

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It has been hypothesized that acute cardiac rejection, Syndrome X and arterial hypertension can induce small vessel damage and therefore restriction of coronary reserve in the presence of normal epicardial coronary arteries. We have previously described in Syndrome X and arterial hypertension a characteristic response pattern to dipyridamole (DIP) infusion: ST segment depression without any measurable systolic dysfunction. Aim of this study was to establish whether acute cardiac rejection might induce electrocardiographic alterations during DIP infusion. Changes in 12 lead electrocardiogram and 2-D echocardiogram during high dose DIP infusion (up to 0.84 mg/kg in 10') were evaluated within 24 hrs of endomyocardial biopsy in 11 transplanted Pts: a total of 40 biopsy controlled DIP studies were performed within 5 weeks after cardiac transplantation. For each Pt, at least 7 days elapsed between 2 consecutive studies. Electrocardiographic and echocardiographic tracings were analyzed without prior knowledge of endomyocardial biopsy findings. No remarkable side effects occurred in any case, so that the DIP study could be completed in all Pts. In all studies a synergic contraction pattern of all ventricular walls was detected in resting conditions and after DIP. A diagnostic (> 0.1 mVolt) ST segment depression was found in 13 studies. The sensitivity and specificity of DIP-induced ST segment depression for the detection of biopsy proven acute rejection was 72% and 90% respectively. These data show that DIP stress is feasible and safe in transplanted Pts, and that acute cardiac rejection can be accompanied by DIP induced ST segment depression, without detectable impairment in systolic function. These changes might provide non invasive markers for surveillance of rejection.

## NOVEL CARDIAC-SPECIFIC CIRCULATING AUTOANTIBODIES IN DILATED CARDIOMYOPATHY

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Organ-specific autoimmunity is characterized by circulating autoantibodies (Abs) which are specific to the diseased target organ and do not cross react with other tissues. Organ-specific cardiac Abs have not been reported. To determine whether organ-specific cardiac Abs are present in dilated cardiomyopathy (DCM) we tested 55 sera from patients (pts) with DCM, 249 with other cardiac disease (OCD) and 200 normals by indirect immunofluorescence (IFL) on human atrium (HA) and human skeletal muscle (HSM). Positive sera were then titrated by IFL before and after absorption with homogenates of HA, HSM and rat liver as control tissue. Sera were classified as cross-reactive when Ab titer dropped significantly ($\geq$ 2 doubling dilutions) after absorption with both HA and HSM and as organ-specific when the Ab titer fell only with HA absorption. Organ-specific cardiac Abs were more frequent in DCM (13/55, 24%), than in pts with OCD (2/249, 1%) and normals (3/200, 1.5%, p<0.001). Organ-specific cardiac Abs were IgG (titer range pre-absorption: 1/10 - 1/40) and gave a cytoplasmic IFL staining on atrial myocytes only. Conversely, cross-reactive sera were similarly detected in DCM (4/55, 7%), OCD (15/249, 6%) and normals (15/200, 7.5%, p=NS) and gave the previously described striated and/or sarcolemmal IFL pattern both on HA and HSM. These results provide novel evidence for the existence of organ-specific cardiac Abs in DCM and suggest an autoimmune pathogenesis in some pts with this condition.

## T LYMPHOCYTE SUBSETS AS THE NONINVASIVE MARKER OF CARDIOMYOPATHY

Tsugiyasu Kanda M.D., Tomoyuki Yokoyama M.D., Tadashi Suzuki M.D., Kuzuhiko Murata M.D., Gunma University, Gunma, Japan.

Eighty-five patients with unexpained congestive heart failure were examined T lymphocyte subset in the peripheral blood as the noninvasive diagnosis by two-color laser flow cytometry. The final dianosis was performed catheterization and endomyocardial biopsy. The patients were diagnosed as dilated cardiomyopathy (DCM), (n=24), myocarditis (MC) by Dallas criteria(n=11), Coronary heart disease(CHD) (n=17). The results were as follows: $CD8^+CD11^-$(cytotoxic T) subset was significantly lower, $CD4^+2H4^+$(suppressor/inducer T) subset was higher in patients with DCM than MC and CHD. CD4/CD8 and $CD4^+2H4^+/CD8^+CD11^-$ ratios were examined and compared with normal control(NC).

| | DCM | MC | CHD | NC |
|---|---|---|---|---|
| mean age | 47±10 | 43±9 | 46±11 | 49±12 |
| $CD4^+2H4^+$ | 13.4±5.7* | 22.5±9.2 | 22.1±8.4 | 19.6±4.6 |
| $CD8^+CD11^-$ | 26.9±9.3* | 20.6±7.9 | 16.3±8.1 | 17.9±9.7 |
| $CD4^+2H4^+$ /$CD8^+CD11^-$ | 2.2±1.3** | 1.2±0.7 | 0.6±0.4 | 0.8±0.6 |
| CD4/CD8 | 2.4±1.7* | 1.5±0.8 | 1.5±0.7 | 1.6±0.7 |

*p<.05, **p<.01, *p<.02 compared with NC.

A ratio of $CD4^+2H4^+/CD8^+CD11^-$>1.6 was defined as a 83% specificity and 79% sensitivity for the diagnosis of dilated cardiomyopathy, although CD4/CD8>1.8 was a 67% specificity and 65% sensitivity. There were no significance in the ratio between MC and CHD, however, $CD8^+Leu7^+$ (natural suppressor)subset in MC was statistically higher(19.2±8.3% p<.02) than DCM, CHD and NC. Conclusion: An elevated ratio of $CD4^+2H4^+/CD8^+CD11^-$ in the lymphocytes of peripheral blood may be a useful diagnostic marker of dilated cardiomyopathy versus myocarditis and coronary heart disease.

PREVALENCE AND DIRECTION OF MITRAL REGURGITATION IN HYPERTROPHIC CARDIOMYOPATHY.

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To study the presence and direction of mitral regurgitation (MR) and its relationship to LV outflow tract obstruction we performed 77 color flow imaging studies in patients with Hypertrophic Cardiomyopathy. Obstruction (OBS) was present in 18, no obstruction at rest (NO) in 30 and 29 were studied post-myectomy (M). The prevalence and direction of mitral regurgitation were as follows:

| | MR% 0-triv | MR% mild | MR% >mod | Posterior Jet% | Central Jet% |
|---|---|---|---|---|---|
| OBS | 17 | 44 | 39 | 93 | 7 |
| NO | 70 | 27 | 3 | 33 | 67 |
| M | 66 | 31 | 3 | 38 | 62 |

In the OBS patients with at least mild MR, 93% had jets originating from the anterior portion of the mitral valve plane. These jets were directed posteriorly in an eccentric fashion and often were layered against the posterior left atrial wall. This was due to the anterior direction of both mitral leaflets. Following myectomy only 34% had at least mild MR with 63% of jets being centrally directed. Patients without obstruction and post myectomy behaved similarly.

In most patients, MR is related to the presence and degree of obstruction. The posterior direction of the MR jet appears due to the funnel effect of systolic anterior angulation of the mitral leaflet tips.

**RELATIONSHIP BETWEEN THE EXTENT OF MUSCULAR HYPERTROPHY AND DIASTOLIC FUNCTION IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY WITHOUT LEFT VENTRICULAR OUTFLOW GRADIENTS OR MITRAL REGURGITATION.**

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Multiple factors have been postulated to cause diastolic dysfunction in patients with hypertrophic cardiomyopathy (HCM), including the extent of myocardial thickening produced by the myopathic process. We evaluated the relationship between the extent of myocardial thickening and diastolic function in 16 pts with HCM (aged 15-75 yrs) using M-mode, 2-D and Doppler echo. Six of 16 pts had LV outflow gradients and 8 had mitral regurgitation (MR). Because of the known influence of MR on early diastolic filling, the 8 pts with MR were excluded. In the remaining 8 pts without MR or LV outflow gradients, the severity and extent of muscular hypertrophy were assessed from 2-D echo by Wigle's index. Diastolic function was evaluated by measuring the ratio of late-to-early diastolic peak mitral flow velocity from Doppler and maximum early diastolic velocity of the LV posterior endocardium from M-mode echo. Doppler mitral flow velocity data were adjusted for age using previously derived regression equations. In HCM pts without MR, Wigle's index correlated directly with the ratio of late-to-early diastolic peak mitral flow velocity ($r=0.69$, $p<0.05$) and inversely with the maximum early diastolic velocity of the LV posterior endocardium ($r=-0.79$, $P<0.05$). These data suggest that the extent of myocardial thickening reflected by Wigle's index and the degree of LV diastolic dysfunction are significantly associated in pts with HCM who do not have LV outflow gradients or MR.

**ANTIBODY MEDIATED DISTURBANCE OF MYOCARDIAL FUNCTION - A MODEL FOR DILATED CARDIOMYOPATHY.**

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Recently, autoantibodies (AB) against the ADP/ATP carrier, which inhibit the nucleotide transport in vitro were demonstrated in DCM. To establish whether AB against the ADP/ATP carrier might be of pathophysiological relevance by altering myocardial function, guinea pigs were immunized with the isolated carrier protein. After 24-30 weeks the haemodynamic function of the hearts was measured by isolated perfused working heart preparations, the metabolic status by non-aqueous fractionation. In immunized animals mean aortic pressure (53±12 vs. 93±8 mmHg), stroke work (0.4±0.3 vs. 1.7±0.3 mJ/g) and external heart work (62±82 vs. 375±58 mJ/g/min) were significantly decreased, the lactate release (4.4±1.9 vs. 1.7±0.4 µM/g/min) increased. Parallel the ADP/ATP ratio as well as the phosphorylation state of ATP were significantly lower in the cytosol, while in the mitochondria a substantial increase was observed. Consequently the difference between the mitochondrial and the cytosolic phosphorylation potential of ATP (ΔG) was only 0.7 kJ/mol (controls: 4.6 kJ/mol) ($p<0.001$). These findings prove the suspicion that AB against the ADP/ATP carrier, causing an imbalance between energy delivery and demand, might be an essential component of the pathophysiological mechanism involved in dilated cardiomyopathy.

PREVALENCE OF CARDIAC ABNORMALITIES IN A LARGE KINDRED WITH MYOTONIC DYSTROPHY.

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Myotonic dystrophy is the most common muscular dystrophy affecting adults. Clinical manifestations may not become evident until late adulthood. The incidence of cardiac involvement in large families with myotonic dystrophy has not been determined. We prospectively performed echocardiographic studies as well as neurologic and opththalmologic examinations on 85 blood line members of a single large kindred with myotonic dystrophy (43 M, 42 F; mean age 31 ± 18 yrs). Sixteen individuals were clinically affected with myotonic dystrophy; of these, 6 had mitral valve prolapse (MVP) by both M-mode and 2D echo, 2 had diffuse LV hypokinesis (ejection fraction 40% and 45%) and 3 had segmental wall motion abnormality. In contrast, in the 69 unaffected members who are still at risk for developing myotonic dystrophy, MVP was present in 12 and no other cardiac abnormality was observed. Overall, the presence of any cardiac abnormality of MVP and/or cardiac function was significantly more prevalent in affected (11/16 or 69%) than in unaffected members (12/69 or 17%; $p=0.0001$). Conclusions: Cardiac abnormalities are prevalent in a large kindred with myotonic dystrophy, predominantly involving affected individuals. Of interest is the high incidence of mitral valve prolapse (17%) in individuals at risk for developing myotonic dystrophy, compared to the general population. This raises the possibility of subclinical involvement with myotonic dystrophy and warrants a prospective follow-up of these patients.

## Tuesday, March 21, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 10:00AM–11:00AM
## Pacific Room, Anaheim Convention Center
## New Aspects of Experimental Myocardial Infarction

**POST-HYPOPERFUSION REPERFUSION: ORCHESTRATED RECOVERY FROM MYOCARDIAL SUPPLY/DEMAND IMBALANCE MAXIMIZES HEART FUNCTION.**

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To determine whether hypoperfusion-induced augmentation of mitochondrial function is an adaptive response to myocardial supply/demand imbalance, 19 experimental isolated perfused rat hearts were subjected to 30 min hypoperfusion (coronary perfusion pressure [CPP] decreased to 20 mm Hg) followed by reperfusion (CPP returned to 80). During early reperfusion LV pressure increased to 88 ± 2 mm Hg, greater than baseline pre-hypoperfusion pressure (78 ± 2; p<0.005). Mitochondria isolated from 5 hearts in early reperfusion during LV functional augmentation showed an increase in state 3 respiration (470 ± 49 ngram atoms O/min/mg) compared to 5 time-matched non-hypoperfused controls (327 ± 33; p<0.05). In 14 experimental hearts mitochondria were isolated after 30 min reperfusion when LV pressure had returned to baseline levels. State 3 was 321 ± 32, equivalent to that found in 7 time-matched control non-hypoperfused hearts (380 ± 47; p=NS). Thus, hypoperfusion-induced augmentation of mitochondrial function persisted during increased LV function in early reperfusion but not into late reperfusion, after the period of increased LV function. The simultaneous enhancement of LV and mitochondrial functions therefore may be components of an orchestrated response to supply/demand imbalance which maximizes post-hypoperfusion recovery.

**ISCHEMIC VENTRICULAR FIBRILLATION IS DISTINGUISHED BY PRESERVED HISTAMINE-STIMULATED ADENYL CYCLASE ACTIVITY**

Andrew Wolff, MD, FACC, Dawn Hines, Joel Karliner, MD, FACC, VAMC and CVRI, UCSF, San Francisco, CA.

We have shown that adenyl cyclase activity (ACA) mediated by β-adrenergic receptors is preserved during ischemia by enhanced coupling of β-receptors to the stimulatory guanine nucleotide binding protein, Gs. To see if ischemic histamine (Hst) H2 receptors behave similarly, we compared net ACA (i.e., ACA in the presence of agonist and 10 μM GppNHp minus activity due to 10 μM GppNHp alone; pmol cAMP/mg prot/min) stimulated by Hst or (-)-isoproterenol (Iso) in membranes from non-ischemic (NI) vs ischemic (I) myocardium from rabbits surviving 30 min of coronary occlusion, and from rabbits which succumbed to ventricular fibrillation (VF) within 30 min of coronary occlusion. Net Iso-stimulated ACA (5 concentrations, 10 nM through 10 μM) was not different in NI vs I from non-fibrillating rabbits, nor was the Iso dose-response curve shifted (EC50s: 9 vs 20 nM; n=6). In contrast, net Hst-stimulated ACA at both .1 and 1 mM was depressed by 30 min ischemia (33 ± 17 [SD] vs 9 ± 17, p=.01 and 35 ± 26 vs 14 ± 12, p=.05, respectively; n=8); EC50 rose after 30 min ischemia from 12 to >80 μM (n=8). Remarkably, this divergent ischemic response between Iso- and Hst-stimulated ACA was not seen with VF; ACA was preserved during ischemia with VF, whether stimulated by Iso or by Hst, each over 4 logs of agonist concentration. (Iso EC50s: 27 vs 50 nM; Hst EC50s: 3 vs 8 μM; n=3). We conclude that β-receptors and Hst H2 receptors respond differently to ischemia without VF, but respond similarly when VF complicates ischemia. The pathogenesis of VF may involve the dichotomy between the Hst responses of adenyl cyclase in ischemic membranes from fibrillating vs non-fibrillating hearts.

**PROTECTIVE EFFECTS OF GLUTATHIONE ON COMPLIANCE AND CORONARY RESISTANCE**

Alvin S. Blaustein M.D., Ruth I. Stolz M.D., Nancy A. Healey B.S., Deborah Baxter B.S., Susan M. Deneke Ph.D., VA Medical Center, Boston, MA.

We hypothesized that glutathione (G) is an important defense against ischemia (I)/reperfusion (R) radical injury within the vasculature. Isovolumic buffer-perfused (constant flow) rat hearts underwent 20 or 40 min I and were reperfused for 30 min with standard (B) or 2mM G-enriched (B+) buffer. We compared changes in G levels, compliance (k values), and coronary perfusion pressure (PP, mmHg). G levels were 1.42±0.65 umol/heart after 20 min equilibrium (EQ). With B, there were no changes in G levels after I/R. With B+, levels increased to 4.66±0.50 (20 min I/R) and 3.72±0.67 (40 min I/R) (p<0.05 vs EQ); after 5 min washout, levels fell to 1.54±0.39. G levels in bovine pulmonary artery endothelial cells incubated 2h with 6mM G increased from 1.97±0.07 to 15.2±1.67 nmol/$10^6$ cells.

| | | EQ | 20 I/R | EQ | 40 I/R |
|---|---|---|---|---|---|
| B | k | 2.4±0.6 | 2.4±1.0 | 1.6±0.3 | 6.5±2.5* |
| | PP | 77±8.3 | 102±22.4* | 87±6.1 | 116±16.3* |
| B+ | k | 1.3±0.4 | 1.2±0.3 | 1.4±0.6 | 2.2±0.6 |
| | PP | 82±6.3 | 88±18.7 | 80±7.1 | 86±13.4 |

*p<0.05 vs EQ; data are mean ± SD, n=5-10.

Reperfusion with B+ prevented increases in myocardial stiffness and coronary resistance. Although most of the increase in G represented extracellular trapping, protection of coronary vasculature may also represent endothelial G uptake resulting in only small increases in myocardial levels.

**STUNNED MYOCARDIUM: A FORM FRUSTE OF ELECTROMECHANICAL DISSOCIATION?**

Robert F. Hanich, M.D., Joseph H. Levine, M.D., Charles Prood, Ph.D, Joseph F. Spear, Ph.D., F.A.C.C., E. Neil Moore, D.V.M., Ph.D., F.A.C.C. The Johns Hopkins University School of Medicine, Baltimore, MD

Brief periods of ischemia (I) and reperfusion (R) lead to prolonged mechanical dysfunction, the electrophysiologic (EP) correlates of which are uncertain. Eighteen dogs anesthetized with pentobarbitol (30 mg/kg IV) underwent thoracotomy, 15 min proximal anterior descending occlusion, and 20 min R. At baseline (B), peak I, and 20 min R, electrogram durations (D), refractory periods (ERP) and conduction velocity (CV) were measured from 12 standardized sites spanning the border zone between ischemic (IZ) and less or nonischemic (LIZ) myocardium. Echocardiographic percent thickening (T) confirmed normal preischemic and markedly reduced postischemic function.

| | | B | I | 20 min R |
|---|---|---|---|---|
| D (msec) | IZ | 37.2±12.1 | 110.0±35.9** | 39.2±11.5 |
| | LIZ | 38.4±12.0 | 42.0±14.2 | 37.8±11.0 |
| CV (M/s) | IZ | 0.68±0.15 | 0.19±0.31** | 0.65±0.15 |
| | LIZ | 0.64±0.18 | 0.74±0.18* | 0.73±0.19 |
| ERP (msec) | IZ:LIZ | 132±6 | | 134±11 |
| I (%) | IZ:LIZ | 42±21 | | -13±8** |

(mean±SD; **p<0.001 versus B; *p<0.05 versus B)

With R, return of CV toward normal in IZ versus LIZ is slightly blunted. Nonetheless the EP of SM has largely renormalized (p>0.05: 20 min R versus B), despite ongoing hemodynamic compromise. SM thus appears to represent a forme fruste of electromechanical dissociation.

EFFECTS OF ASPIRIN ON IN VITRO LYSIS WITH UROKINASE OF COMBINED PLATELET AND FIBRIN THROMBI

Wolfram Terres, M.D., Christian Beythien, Christian W. Hamm, M.D., Wolfram Kupper, M.D., Walter Bleifeld, M.D., F.A.C.C., Department of Cardiology, Eppendorf University Hospital, Hamburg, West-Germany.

We could recently show that the addition of platelet deaggregating prostaglandin $E_1$ to urokinase (UK) improved the in vitro lysis of combined platelet and fibrin thrombi. To further evaluate the possible role of platelets in thrombolysis, we studied the effects of pretreating plasma with aspirin before thrombus formation, and of adding aspirin to UK after completion of thrombus formation. Thrombi (n = 144, mean weight 20 mg) were produced in vitro by adding $CaCl_2$ and collagen (1 µg/ml) to citrated platelet rich plasma (PRP, 250,000 platelets per µl). After 10 min, thrombolysis with UK (2000 U/ml for 30 min) was started. The addition of aspirin (10 - 200 µg/ml) to PRP prior to thrombus formation resulted in a dose dependent improvement of thrombolysis. This effect was optimal at a concentration of 20 µg/ml of aspirin. After pretreatment of the PRP with aspirin 20 µg/ml, thrombus weight after 30 min of thrombolysis was by a mean of 47 % lower than in the control experiments ($p < 0.0001$). However, when aspirin (10 - 200 µg/ml) was added to PRP after completion of thrombus formation, no significant effect on thrombolysis with UK was noted. Thus, the in vitro lysis with UK of combined platelet and fibrin thrombi was found to be enhanced when the thrombi were produced under the influence of aspirin, but not when aspirin was added to UK after completion of thrombus formation.

EFFECT OF THE CHOLINERGIC AGONIST CARBACHOL AND CYCLIC GUANOSINE MONOPHOSPHATE ON SUDDEN CARDIAC DEATH: PROTECTION FROM VENTRICULAR FIBRILLATION

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Previous studies have demonstrated that a reduced cardiac vagal tone correlates with a greater susceptibility to ventricular fibrillation (VF). If reductions in vagal tone contribute to VF, one would predict that interventions that increase vagal tone should protect against these lethal arrhythmias. To test this hypothesis, VF was induced in 11 mongrel dogs with healed myocardial infarctions by a 2 min. coronary occlusion during exercise. This exercise plus ischemia test consistently elicited VF on each placebo (normal saline) presentation. On a subsequent day, the cholinergic agonist carbachol (20 ug/kg, i.v.) was injected 3 minutes before the coronary occlusion (i.e., while the animal was running). Carbachol elicited significant (analysis of variance, $P < 0.001$) reductions in heart rate (control 227.6 ± 9.3 versus carbachol 150.9 ± 9.3 beats/min.) and prevented VF in 9 of 11 dogs. This protection was still present even when heart rate decline was prevented by ventricular pacing (n=3). Cyclic guanosine monophosphate (cyclic GMP) is believed to act as an intracellular messenger of cholinergic activation; therefore, 8-Bromo-cyclic GMP, a compound that enters the cell and resists breakdown by phosphodiesterases, was infused (100 ug/kg/min., i.v.) throughout the exercise plus ischemia test, beginning 30 minutes before exercise (to allow time to enter the cardiac cells). This dose of 8-Bromo-cyclic GMP did not affect heart rate (control 232.9 ± 13.3 versus cyclic GMP 234.5 ± 9.7 beats/min.) yet prevented VF in 5 of 5 dogs tested. These data suggest that cholinergic agonists and cyclic GMP can prevent VF independent of heart rate change.

RANDOMIZED CONTROLLED TRIAL OF NEUROLEPTANALGESIA INFUSION IN THE EARLY TREATMENT OF ACUTE MYOCARDIAL INFARCTION.

Alfredo Balvanera M.D. FACC., Victor Alvarez M.D., Omar Fuentes M.D., Alberto Zamora M.D., Humana Hospital and La Salle University, Mexico City, Mexico.

Forty patients (Pts) with acute myocardial infarction (MI) were admitted to the hospital within 4 hours of symptoms. Pts were randomly assigned, 20 to the control (C) group, and 20 to the Neuroleptanalgesia (NLA) group 10 inferior and 10 anterior in each group. The C group received 5% dextrose solution in water and meperidine. The NLA group received 1 amp of 10 ml of fentanyl and 1 amp of 10 ml of droperidol dissolved in water to be administered within 8 hours. In both groups all Pts registered 3+ or 4+ of chest pain score, Killip Class I-II and important ST segment elevation. In the NLA group all Pts were completely relieved of chest pain within 10 ± 4 min after infusion (P 0.001) vs 120 ± 72 min in 3 ± 1 divided doses for the C group. In the NLA group the mean pulmonary capillary wedge pressure decreased 36% for the group with anterior MI and 26% for the inferior MI group (P 0.001) vs 10% or less reduction in this parameter for the C group. The radionuclide ejection fraction improved 10% for the group of Pts with anterior MI and 12% for the group with inferior MI, one week after NLA administration (P 0.05). In contrast Pts in the C group showed a consistent decrease in radionuclide ejection fraction. Angiography was performed in 5 of 20 Pts on the NLA group as well as the C group. In the NLA group we could observe in 3 cases the reopening and reperfusion of infarct related artery vs no change in the C group. Overall mortality for the C group was 15% and 5% for the NLA group (P 0.05 ). Conclusions: NLA possess an action of augmenting blood flow in ischemic myocardium, releasing the spasm, and thus it may improve chest pain, myocardial energetics, ST segment elevation and decrease myocardial damage and mortality rate.

## Tuesday, March 21, 1989
## Poster Displayed: 9:00AM–12:00NOON
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## Pacific Room, Anaheim Convention Center
## Myocardial Infarction Clinical Studies

### OBSERVER VARIABILITY IN TIMI FLOW GRADING: COMPARISON TO A NEW COMPUTER METHOD FOR MEASUREMENT OF REPERFUSION KINETICS

Steven E. Nissen MD FACC, John C. Gurley MD, Cindy Grines MD David Booth MD, Marc Branco MD, and Anthony N. DeMaria MD FACC University of Kentucky & VA Hospital, Lexington, Ky

The Thrombolysis in Acute Myocardial Infarction (TIMI) study utilized a subjective scale for grading reperfusion following acute MI which is now widely employed to assess the results of thrombolysis and to guide therapy. However, the TIMI flow scale is subjective and may be compromised by variability in interpretation. Therefore, we designed this study to evaluate the interobserver variability of TIMI flow grading and to compare the subjective TIMI scale of reperfusion to an objective method based upon computer analysis of the contrast decay rate in the infarct vessel in comparision to a non-involved artery. Films from 21 successfully reperfused patients (4 patients-TIMI grade I, 9 patients-II, 8 patients-III) were assigned TIMI flow grades by three other experienced angiographers (total = 4 observers). The films were digitized using a 512 x 512 x 8 bit pixel matrix. A region of interest (ROI) was placed over the infarct artery (IA) and a non-involved adjacent vessel (NIA) and time-density curves generated. The time from peak opacification until decay to 1/2 peak density was determined for the IA and NIA and the ratio IA/NIA was computed. A difference of at least 1 TIMI grade among the 4 observers was present for 2/4 arteries originally graded TIMI I, 6/9 for TIMI II, and 3/8 TIMI III. Decay half-times ranged from 1.07-2.03 sec for TIMI III (mean-1.5), 1.67-2.67 sec for TIMI II (mean-2.14) and 1.83 to 3.13 sec for TIMI 1 (mean-2.76). Ratios of NIA/IA ranged from 1.8-4.5:1 (mean-2.7), 1.1-3.0:1 mean-1.65), and .8-1.6:1 (mean 1.18) for TIMI I,II, and III respectively. These data demonstrated that there is considerable interobserver variability in TIMI grading and actual contrast decay rates overlap substantially between grades. This phenomenon must be considered in evaluating the results of thrombolytic studies. Contrast decay rates obtained by digital image processing provide a more objective means for evaluating reperfusion.

## SELECTIVE NEUROHUMORAL ACTIVATION IN THE RECOVERY PHASE OF ANTERIOR MYOCARDIAL INFARCTION IN MAN.

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Neurohumoral activation is readily apparent in patients with symptomatic CHF and in the acute phase following myocardial infarction (MI), but its profile in asymptomatic patients in the early convalescent phase post-MI is less clear. We measured plasma catecholamines, renin (PRA), aldosterone (ALDO), and angiotensin II (A2) levels and performed hemodynamic measurements, coronary angiography, and biplane left ventriculography in 35 patients with LV dysfunction but no clinical evidence of CHF 18±4 days post-anterior MI. Plasma catecholamines were not significantly elevated and did not correlate with hemodynamic or angiographic variables. The renin-angiotensin-aldosterone system was activated, as anticipated, in patients on diuretics. As well, however, in the 27 patients not on diuretics plasma A2 levels were elevated in correlation with the extent of systolic wall motion abnormality [% Akinesis, Dyskinesis (AD)].

| | n | NE | EPI | A2 | PRA | ALDO |
|---|---|---|---|---|---|---|
| AD<30% | 19 | 266±110 | 43±25 | 21±8 | 1.6±1.0 | 9.6±9.7 |
| AD≥30% | 8 | 211±132 | 42±30 | 30±7* | 2.5±0.8* | 22.5±20.8* |

Patients not on diuretics. mean±SD, *p<0.05.

Thus, in these asymptomatic patients in whom catecholamines were not significantly elevated 3 weeks post-AMI we found that not only in the presence of diuretics, but even in the absence of diuretics or hemodynamic imbalance, that the renin-angiotensin-aldosterone system was activated, the extent of which was related to the degree of myocardial damage.

## THE PIVOTAL ROLE OF MULTIVESSEL CORONARY ARTERY DISEASE AND THE REMOTE ZONE IN THE REPERFUSION ERA.

EJ Topol MD, FACC, SG Ellis MD, FACC, BS George MD, DJ Kereiakes MD, FACC, RJ Candela MD, FACC, RS Stack MD, FACC, CW Abbottsmith MD, FACC, K Sigmon, K Lee PhD, B Pitt MD, FACC, RM Califf MD, FACC and the TAMI Study Group, Univ. of Michigan Medical Center, Ann Arbor, MI.

The role of multivessel disease (MVD) in pts receiving reperfusion therapy has not been amply studied. Of 855 consecutive pts enrolled in the TAMI trials, all received i.v. thrombolysis, had emergency cardiac cath ± angioplasty, and 7 day repeat cath; 92% achieved reperfusion. Using a 75% non-infarct vessel stenosis criterion, 233 (27.3%) pts had MVD and 622 (72.7%) pts had single vessel (SVD). Age, sex, time to reperfusion, MI location and intervention were similar for the 2 groups. Results for ejection fraction (EF), infarct zone (IZ), and regional wall motion (RWM) were as follows:

| | MVD (n=233) | SVD (n=622) |
|---|---|---|
| EF (initial %) | 47.7±12.5 | 51.5±10.9 |
| EF (7 day %) | 50.8±11.8 | 52.1±10.8 |
| Non IZ RWM (acute; SD/cd) | -0.53±1.7 | +0.65±1.5 |
| Non IZ RWM (day 7; SD/cd) | -0.47±1.5 | +0.53±1.4 |
| IZ RWM (acute; SD/cd) | -2.76±1.0 | -2.51±1.1 |
| IZ RWM (day 7; SD/cd) | -2.12±1.3 | -2.19±1.2 |
| Death (in-hospital) | 11.6%* | 4.2%* |

*p=0.0001

Using a stepwise logistic regression model, non-infarct zone wall motion, was the most powerful predictor of in-hospital survival (p=0.0057); no. of diseased vessels was second (p=0.04). In conclusion: 1) perfusion and function of the contralateral wall is critical; 2) methods to rapidly detect and rectify the condition need scrutiny.

## DETERMINANTS OF IMPROVED GLOBAL LEFT VENTRICULAR FUNCTION AFTER tPA AND DEFERRED PTCA FOR ACUTE MI

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To determine variables predictive of improved rest and exercise LV function in patients receiving tPA and/or deferred PTCA, multiple regression analysis was applied to 138 patients with acute MI randomly assigned to tPA or placebo, and from these, 85 angioplasty candidates randomly assigned to PTCA on day 3 or no PTCA during the 10 days of the study. Treatment with tPA increased resting EF by 3.6 percentage points (P<0.01). This increase was inversely related to day 1 EF (r=-.31,P<.02) but independent of age, infarct location, initial heart rate or BP, Q waves on entry ECG, or PTCA.

Although deferred PTCA had no effect on resting EF, it was associated with an increase in EF from 53% to 61% during exercise (P<0.01). This increase in exercise EF was directly related to an angiographic estimate of the % LV distal to ≥90% stenoses (P<.05). Response to PTCA was not dependent on resting EF, treatment with tPA, peak CPK or Q waves on day 2 ECG.

These data support treatment of large and intermediate sized MI's with tPA. Benefit from PTCA is related to extent and severity of CAD and cannot be predicated by ECG.

## INTRACORONARY THROMBOLYTIC THERAPY IN PATIENTS WITH REFRACTORY THROMBUS AFTER INTRAVENOUS TREATMENT

JK Samaha, M.D., P Quigley, M.D., DJ Kereiakes, M.D., FACC, B Griffin, RS Stack, M.D., FACC, K Sigmon, R Candela, M.D., FACC, RM Califf, M.D., FACC, EJ Topol, M.D., FACC, Baptist Memorial Hospital, Memphis, Tennessee

Although the majority of patients (pts) achieve adequate reperfusion with intravenous (iv) thrombolytic therapy (TT), some pts have resistant intraluminal thrombus. In the TAMI 2 and 3 trials we prospectively applied intracoronary (IC) TT in 21 pts with angiographically documented persistent thrombus. IC t-PA in a dose of 30 mg was used in 11 pts, IC urokinase was used in 3 pts in a dose of 750,000 units and 7 pts received both agents IC. Specific indications for IC therapy were visible thrombus alone in 7 pts, intermittent reocclusion in 3 pts, poor flow despite patency in 2 pts, distal emboli in 2 pts, both visualized thrombus and distal emboli in 4 pts and other reasons in 3. Pts treated with IC therapy had worse LV ejection fractions (46.2 vs 49.4%) and required more balloon inflations with angioplasty (6.8 vs 3.9 inflations). prior to IC therapy, 9 pts had TIMI Grade 0 or 1 perfusion, while after IC therapy only 3 had TIMI Grade 0 or 1 flow. Visible filling defects cleared in 13 pts. At one week followup, 13 pts had TIMI Grade 3 flow; 1 had TIMI Grade 2 flow and 2 had TIMI Grade 0 flow (5 pts did not have followup angiography, 3 because of death). During the hospitalization 3 reocclusions occurred, 4 pts required urgent bypass surgery and 2 required repeat emergency angioplasty. Bleeding complications were not significantly different in pts with IC therapy despite the higher total thrombolytic therapy dose. In conclusion, while pts requiring adjunctive IC thrombolytic therapy remained at high risk for reocclusion or recurrent ischemia, direct administration led to improvement in acute phase patency without apparent incremental bleeding risk.

## IN-HOSPITAL ANGINA WITH TRANSIENT ECG CHANGES PREDICTS POOR ONE-YEAR SURVIVAL ONLY IN PATIENTS WITH ST DEPRESSION

Kenneth B. Schechtman, Ph.D. William E. Boden, M.D., F.A.C.C., Robert E. Kleiger, M.D., F.A.C.C., Robert S. Gibson, M.D., F.A.C.C., Robert J. Capone, M.D., F.A.C.C., David J. Schwartz, M.D., F.A.C.C., Robert Roberts, M.D., F.A.C.C., and the Diltiazem Reinfarction Research Group. Washington University, St. Louis, MO.

We have previously documented the importance of post infarction angina with ECG changes (PIA) and of admission and/or discharge ST ↓ in risk stratification of patients with non Q-wave MI. Analysis of admission and discharge ECG's in 484 patients with non Q-wave MI yields the following mortality rates.

| | No PIA | PIA | p-value |
|---|---|---|---|
| No ST ↓ | 6.6%(N=167) | 0.0%(N=32) | NS |
| ST ↓ -one ECG | 9.0%(N=145) | 17.4%(N=23) | NS |
| ST ↓ -both ECG's | 16.7%(N=84) | 36.4%(N=33) | .021 |

Among patients without ST ↓, mortality is non-significantly higher in those without PIA. However, in non Q-wave MI patients with ST ↓ at both admission and discharge, mortality is lower in patients without PIA (16.7%) than in those with PIA (36.4%, p=.021). When all patients with ST ↓ at one or at both time points are analyzed, mortality without PIA is 11.8% (27/229) vs 28.6% (16/56) with PIA (p=.002). We conclude that PIA after non Q-wave MI is a risk factor for 1-year mortality only in the presence of ST ↓. With ST ↓ at both admission and discharge, PIA is associated with 36.4% 1-year mortality.

## COMPARISON OF THE EFFECT OF UPRIGHT POSTURE AND EXERCISE ON PLATELET AGGREGABILITY AND FIBRINOLYTIC ACTIVITY

Kai Winther, M.D., Geoffrey H. Tofler, M.B., Alfredo Jimenez, M.D., Damian Brezinski, Joseph Loscalzo, M.D., Ph.D., James E. Muller, M.D., F.A.C.C., Harvard Medical School, Boston, Massachusetts

There is increasing evidence that daily activities may trigger the onset of coronary thrombosis. This triggering could be mediated in part by alterations in the balance between the thrombogenic and thrombolytic components of the blood. We compared the effects of assumption of the upright posture (AUP) and exercise on platelet aggregability (PA) and fibrinolytic activity (t-PA antigen, plasminogen activator inhibitor [PAI], and euglobulin clot lysis time [ECLT]) in 11 male volunteers. PA was assessed as the minimum concentration of epinephrine required for biphasic platelet aggregation in vitro. Values are mean ± SEM.

| | SUPINE | UPRIGHT | | EXERCISE | |
|---|---|---|---|---|---|
| | | 10 min | 90 min | pre | post |
| t-PA antigen (ng/ml) | 3.8 ±0.3 | 5.8* ±0.5 | 4.6 ±0.4 | 4.0 ±0.3 | 13.5** ±1.5 |
| ECLT (minutes) | 136 ±4 | 98* ±10 | 120 ±11 | 100 ±11 | 41** ±4 |
| Platelet agg. (μM epi) | 3.5 ±0.4 | 1.8* ±0.3 | 1.5* ±0.3 | 1.0 ±0.3 | 1.1 ±0.3 |

Wilcoxon *p < .05 vs supine; **p < .01 vs pre-exercise

PAI did not change significantly at any time.

AUP increased PA and caused only a moderate increase in fibrinolysis which did not persist at 90 min when PA remained increased. In contrast, during exercise PA did not increase and t-PA levels increased more than 3-fold. Thus, changes in t-PA and PA, major determinants of the thrombogenic potential of blood, are less favorable during AUP than during exercise.

## ATRIAL NATRIURETIC FACTOR IN PATIENTS WTIH RIGHT VENTRICULAR INFARCTION

Benjamin Robalino M.D., Richard Petrella M.D., Emmanuel Bravo M.D., Fuad Jubran M.D., Bernadine Healy M.D., F.A.C.C., Patrick Whitlow M.D., F.A.C.C., The Cleveland Clinic Foundation, Cleveland, Ohio

Right ventricular infarction (RVI) is often associated with inappropriate diuresis and protracted hypotension in the setting of normal left ventricular function. To determine the possible role of atrial natriuretic factor (ANF) in this syndrome, we performed serial measurements of peripheral plasma ANF in Pts with inferior myocardial infarction with associated RVI (Group I, n=8) and without associated RVI (Group II, n=13). All Pts underwent enzymatic, ECG, echocardiographic, and coronary arteriographic studies, and diagnosis of RVI was made by at least 2 of the following: ECG changes, echocardiograms, and coronary arteriography. Ten Pts had right heart hemodynamic measurements. Enzymatically measured infarct size, presence of left heart failure and arrhythmias were similar in both groups. Group I had evidence of RV dysfunction by echocardiography and elevated RV pressures. ANF results (mean±SEM in pg/ml):

| | Day 1 | Day 2 | Day 3 | Day 7 |
|---|---|---|---|---|
| Group I | 152±30 * | 165±48 † | 199±27 ** | 189±32 ** |
| Group II | 55± 9 | 55±11 | 61±13 | 77±20 |

*P < 0.05, **p < 0.01, † = not significant

ANF levels above 100 on day 1 were seen exclusively with RVI. Conclusions: The data shows that (1) pronounced ANF elevation is part of the neurohumoral response to RVI; (2) ANF is also elevated in inferior infarction without RVI at a markedly less extent. These findings suggest that elevated ANF may play a pathophysiologic role in the right ventricular infarct syndrome.

## MECHANISM OF MYOCARDIAL INFARCTION IN PATIENTS WITH PRIOR CORONARY BYPASS SURGERY: THERAPEUTIC IMPLICATIONS

Cindy Grines, M.D., Steven Nissen, M.D., F.A.C.C., David Booth, M.D., F.A.C.C., Marcelo Branco, M.D., F.A.C.C., John Gurley, M.D., Kim Bennett, R.N., Anthony DeMaria, M.D., F.A.C.C., University of Kentucky and VA Medical Centers, Lexington, Kentucky.

Although acute myocardial infarction (AMI) is usually due to thrombotic occlusion when involving a native coronary artery, the mechanism responsible for AMI in pts with previous bypass surgery (CABG) is not clear. Since knowledge of pathophysiology of AMI may alter subsequent management, we reviewed angiograms obtained within 1 hr - 7 days of AMI (median = 1 day) in 43 pts at least 1 year after CABG. The culprit lesion was identified by the presence of residual stenosis and/or thrombus in the vessel supplying the infarct zone or by reviewing previous angiograms. Infarction was produced by a recent occlusion of a vein graft in 27 (63%), critical graft stenosis in 5 (12%), recent occlusion of a native vessel in 8 (19%), and could not be accurately determined in 3 (7%). Among the 32 vein grafts suspected as the culprit vessel, unequivocal angiographic evidence of residual thrombus (filling defect/persistant staining) was present in 24 (75%) and was >3 cm in length in 10 pts. Successful thrombolytic reperfusion occurred in only 3/9 (33%) grafts after IV and/or intragraft drug administration. Angioplasty was successful at restoring flow in 3 grafts after failed thrombolysis. Thus, in pts who have undergone previous CABG: 1) acute myocardial infarction is usually caused by recent graft thrombosis, 2) conventional thrombolytic approaches may be inadequate to restore flow and 3) the large mass of thrombus and absent flow in the graft may require subselective drug infusion, a higher thrombolytic dose, or a mechanical means of recanalization.

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# Pacific Room, Anaheim Convention Center
# Thrombolysis and PTCA in Acute Myocardial Infarction

## THE WESTERN WASHINGTON TISSUE PLASMINOGEN ACTIVATOR EMERGENCY ROOM STUDY

Ralph Althouse MD, MPH, Charles Maynard PhD, Michele Olsufka RN, James Ritchie MD FACC, J. Ward Kennedy MD, FACC and their clinical colleagues, University of Washington, Seattle, WA.

To evaluate starting IV tissue plasminogen activator (tPA) in the emergency room (ER), we prospectively screened 1028 consecutive MI pts admitted to 8 hospitals. 160 pts ≤ 75 yrs old with ST elevation and chest pain for ≤ 6 hrs were treated with 150 mg (10 pts.) or 100 mg (150 pts) of tPA over 6 hrs: all received IV heparin. Pts had nuclear studies of ejection fraction (EF) and thallium infarct size. 98% had documented MI. Although not a randomized control group, we compare outcome with control and treated pts from our previous trial of IV streptokinase (SK), which had the same entry criteria and core labs as the present study. The groups were nearly identical in age, sex, MI location, Killip class, peak CPK and number of diseased vessels. Time to treatment was shorter in the ER group (141±69 vs 209±84 mins; p=0.0001).

| | tPA % (n) | SK % (n) | Control % (n) |
|---|---|---|---|
| Number | 160 | 191 | 177 |
| Mortality | 5.0 (8) | 6.3 (12)‡ | 9.6 (17) |
| EF-anterior | 43±17 (38)* | 43±19 (31)‡ | 37±15 (33) |
| EF-inferior | 56±10 (62)* | 54±12 (79)‡ | 52±12 (62) |
| Infarct size-anterior | 19±12 (37)† | 23±15 (31)‡ | 27±13 (34) |
| Infarct size-inferior | 10±9 (62)* | 12±11 (79)‡ | 14±12 (63) |
| Complications | 1.9 (3) | 0.5 (1)‡ | 0 (0) |

*p<0.05 tPA vs Control, † p<0.01 tPA vs Control, ‡ tPA vs SK all n.s.

We conclude that starting tPA in the ER reduces time to thrombolysis. Furthermore, within the limits of using historical controls, early tPA is as effective as later IV SK in decreasing mortality, preserving LV function and reducing infarct size. There was a slight although not statistically significant (p=0.33) increase in ICH in tPA pts compared to those given SK.

## ACUTE OUTCOME AND LONG TERM FOLLOW-UP OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND SINGLE VESSEL DISEASE TREATED WITH ANGIOPLASTY WITHOUT THROMBOLYTIC THERAPY

Gregg W. Stone MD, Barry D. Rutherford MD, FACC, David R. McConahay MD, FACC, Warren L. Johnson MD, FACC, Lee V. Giorgi MD, FACC, Robert W. Ligon MA, Geoffrey O. Hartzler MD, FACC, Mid-America Heart Institute, Kansas City, MO.

We studied 211 consecutive pts (age 57±11 yrs, 75% male) with acute myocardial infarction (AMI) and single vessel disease who underwent PTCA as primary therapy. The infarct related vessel was identified as the LAD in 89 pts (42.2%), the LCX in 26 pts (12.3%), the RCA in 92 pts (43.6%), the LMain in 1 pt (.5%), and a saphenous vein graft in 3 pts (1.4%) resulting in 92 anterior (43.6%) and 119 inferior (56.4%) MIs.

PTCA was successful in 208 pts (98.6%). There were no procedural deaths, though 2 pts (.9%) died prior to discharge. Two pts (.9%) required bypass surgery (CABG) after failed PTCA. Follow-up data was available in 210 pts (99.5%) at a mean interval of 21.7±14.3 months. There were 12 late deaths (survival 93.3%), 3 of which were non-cardiac. The actuarial 3-year survival was 95.0%. Univariate correlates of cardiac death were anterior MI, shock and peak CPK. Six pts (2.9%) sustained a late nonfatal MI, and 8 pts (3.8%) underwent subsequent CABG. Considering cardiac death, MI and CABG as events, the actuarial 3-year event free survival was 94.4%. Repeat PTCA was performed in 69 pts (32.9%), before discharge in 20 pts (9.5%) and after discharge in 49 pts (23.3%). At late follow-up, 174 pts (82.9%) were free of angina.

Conclusions: 1) In pts with AMI and single vessel disease, PTCA without thrombolysis can be performed with a very high success rate and few procedural complications. 2) This approach results in an excellent early and late (3-year) event free survival.

## PRIMARY ANGIOPLASTY THERAPY IN PATIENTS EXCLUDED FROM THROMBOLYTIC THERAPY OF ACUTE MYOCARDIAL INFARCTION.

Anil Bansal, M.D., Gerald C. Timmis, M.D., F.A.C.C., William O'Neill, M.D., DART & AGED Study Group, William Beaumont Hospital, Royal Oak, Michigan.

Conclusive evidence now exists that timely reperfusion significantly reduces mortality during acute transmural myocardial infarction (MI). Nevertheless, reperfusion therapy is withheld from some patients (pts) admitted with MI due to advanced age or late presentation after onset of chest pain (CP). We therefore determined the number of pts excluded from the TIMI II-B study for the above reasons; from October 1987 through April 1988 54 MI pts were considered for inclusion in this trial. Only 36 pts (66%) were eligible (<76 years of age, presenting 0 to 4 hrs after chest pain); ten pts were excluded due to age and 8 pts due to late presentation. Therefore, two new acute PTCA protocols were initiated. Thirteen pts were prospectively enrolled in the Delayed Arterial Recanalization Trial (DART; <76 yrs and presenting 3 to 24 hrs after CP with high risk MI, e.g., anterior MI, inferior MI with reciprocal changes or second MI); 11/13 underwent successful PTCA (defined as residual stenosis of 50% or less); 2/13 had urgent bypass due to left main or equivalent disease. There was no in-hospital mortality. Five pts were enrolled in the Aged trial (i.e., age >76 yrs presenting with CP from 0 to 12 hrs); all 5 underwent successful angioplasty. One pt with a MUGA EF of 11% died within 24 hrs due to progressive heart failure. Conclusion: Reperfusion is withheld from fully 34% of MI pts due to age or delayed presentation. Our initial experience indicates that over 80% of these pts (16/18) can be successfully treated with PTCA.

## MYOCARDIAL RUPTURE COMPLICATING TISSUE PLASMINOGEN ACTIVATOR THERAPY OF ACUTE MYOCARDIAL INFARCTION.

Karin L. Loukinen, M.D., William O'Neill, M.D., Nathan Laufer, M.D., F.A.C.C., Alan Lew, M.D., F.A.C.C., Gerald C. Timmis, M.D., F.A.C.C., William Beaumont Hospital, Royal Oak, Michigan.

To characterize the incidence and clinical predictors of myocardial rupture following thrombolytic reperfusion therapy for acute myocardial infarction, 198 patients receiving tissue plasminogen activator (t-PA) between January 1986 and April 1988 were studied. Among this group, there were three cases of myocardial rupture (MR). For purposes of comparison with survivors of thrombolytic therapy, these cases were added to three MR cases collected from other institutions. Rupture was documented by necropsy (4) or ventriculography (2; one early death and one delayed beyond 30 days). Clinical differences between patients with and without MR follow:

| | MR | No MR | p |
|---|---|---|---|
| Number | 6 | 195 | |
| Age | 68.2±6 | 57.5±10 | 0.01 |
| Sex M:F | 2:4 | 159:39 | 0.02 |
| MI Area Ant/inf | 3:3 | 85:110 | NS |
| Initial B/P | 106/67 | 130/82 | NS |
| Prior MI | 1 | 15 | NS |
| CPK peak | 1415 | 2399 | NS |
| t-PA dose | 103.5mg | 110.5mg | NS |
| Time to t-PA | 40±41 hrs | 2.9±0.9 hrs | <0.001 |
| Hospital mortality | 83.3% | 5.5% | <0.001 |

CONCLUSIONS: The incidence of MR following t-PA therapy of myocardial infarction is 1.5% at this institution. Predictors of myocardial rupture include advanced age, female sex, and delayed initiation of t-PA therapy. Rupture must be added to the list of concerns in designing delayed reperfusion protocols.

## OVERRIDING HEIGHTENED RISK, PRIOR ANGINA DENOTES A FAVORABLE RESPONSE TO MYOCARDIAL REPERFUSION.

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To examine the importance of previous angina in pts with acute MI who receive reperfusion therapy, we analyzed 727 pts in the TAMI trials who had prior angina ≥ 7 days (n=196) or no prior angina (n=531). All pts received i.v. thrombolysis, emergency cardiac catheterization ± angioplasty, and follow-up cath. The age, sex, race, infarct vessel, frequency of reperfusion and thrombolytic and angioplasty intervention were similar for the 2 groups. But, pts with prior angina had a substantially higher risk profile (hypertension 53.6 vs. 37.2%, p<0.0001; diabetes 22.5 vs. 12.1%, p<0.0001; hyperlipidemia 19.4 vs. 9.8%, p=0.001, cerebrovascular disease 4.6 vs. 1.5%, p=0.015; multivessel coronary disease 57.8 vs. 39.7%; p<0.0001, and longer time to reperfusion, 190 vs. 174 min; p<0.01).

| | + Angina | - Angina | P |
|---|---|---|---|
| No. Pts. | 196 | 531 | |
| Reocclusion | 16 (8.2%) | 72 (13.6%) | 0.048 |
| Death | 9 (4.6%) | 38 (7.2%) | 0.21 |
| Ejection fx (acute %) | 48.8±11.9 | 51.3±11.3 | 0.02 |
| Ejection fx (7 day %) | 51.2±11.0 | 52.0±11.3 | NS |

This benefit may relate to preconditioning or an adaptive endothelial response, but was not correlated with ↑ collaterals. Thus, despite a multiplicity of increased risk factors, more multivessel disease, and worse baseline ventricular function, pts with previous angina demonstrated more recovery of ventricular function, less reocclusion and lower mortality.

## BIPHASIC RELEASE OF CARDIAC MYOSIN LIGHT CHAINS IN PATIENTS WITH SUCCESSFUL THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

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It has been shown that serum cardiac myosin light chain (MLC) levels are useful to estimate the infarct size more accurately than cardiac enzymes, however, the intracellular source and release kinetics of MLC from irreversible injured myocardium are not known with certainly. We measured the serum MLC levels by enzyme linked immunoadsorbent assay (ELISA) using monoclonal antibodies (mAb), then studied the serial changes of serum MLC levels in 17 patients with successful thrombolysis in acute myocardial infarction. The MLC release showed the biphasic pattern; that is, the early rapid release reaches the peak concentration of 32±18 ng/ml at 18-24 hr. and the subsequent release reaches the peak concentration of 47±24 ng/ml at 3-5 days after the onset. The peak concentrations of the first and second released MLC have significant correlations with not only % abnormally contracting segment calculated by left ventriculography ($r=0.72, p<0.05$ and $r=0.81, p<0.01$, respectively) but also peak creatinine kinase activity ($r=0.69$, $P<0.05$ and $r=0.67, p<0.05$, respectively). MLC I&II complexes measured by ELISA utilizing two monoclonal antibodies specific to MLC I and II respectively in a sandwich assay were detected at both peaks. Thus there were no different characteristics and meanings between MLCs at both peaks. These results showed that MLCs at both peaks released from the degradation of myofibrils itself and biphasic release of MLC represent the process of myocardial cell necrosis in myocardial infarct zone . The measurement of the MLC release may be useful to monitor the cell necrosis as well as to estimate the infarct size.

## REDUCTION OF INFARCT SIZE BY INTRAVENOUS APSAC IN MYOCARDIAL INFARCTION (MULTICENTER RANDOMIZED TRIAL VS HEPARIN).

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In a series of 231 patients with a first myocardial infarct (MI) who were randomly treated by heparin (hep) or acyl plasminogen streptokinase activator complex (APSAC) within 5 hours following the onset of symptoms, the infarct size (IS) was measured by a thallium 201 myocardial single photon emission tomography (SPECT).

Coronary arteriography and LV angiography were performed between day 1 and day 7 ; radionuclide (RN) angiography and Tl 201-SPECT were performed between day 14 and day 21. The tomographic defect was measured by 2 independant blinded observers : the inter and intra observer reproductibility was excellent ( > 0.95). The defect size was expressed in percentage of the total myocardial volume.

Results (m±sd) were :

| | LVEF | RNEF | IS |
|---|---|---|---|
| Heparin | 47±12 | 39±12 | 19±14 |
| APSAC | 53±13*** | 43±12* | 13±11** |
| Occluded Vessel | 45±14 | 36±13 | 21±15 |
| Patent Vessel | 53±14*** | 45±11*** | 12±9*** |

*p < 0.05 **p < 0.01 ***p < 0.001

Beside value in detecting and localizing a defect, Tl 201 SPECT is a reproductible method to quantify IS, that can be used to evaluate the efficacy of drugs.

A significant limitation of IS was observed in APSAC patients, resulting in a significant improvement of the LV function.

## THROMBOLYSIS-INDUCED LIMITATION OF INFARCT SIZE IN RELATION TO TIME FROM PAIN ONSET AND INFARCT LOCALIZATION: RESULTS FROM THE I.S.A.M. STUDY.

Rolf Schröder M.D.,F.A.C.C., Karl-Ludwig Neuhaus M.D., Thomas Linderer M.D., Ulrich Tebbe M.D., Thomas Brüggemann MSc, Karl Wegscheider PhD, Klinikum Steglitz, Free University Berlin, FRG

The ISAM study was a double-blind, placebo-(PLA)controlled trial, in which within 6 h of AMI in 1741 Pts aged ≤ 75 y the effect of 1.5 M STK on limitation of infarct size was tested by 3 different parameters: 1) QRS score (QRS)(93 Pts with BBB=5.8% and 64 Pts =4% without the required amount of ST elevation on the prerandomization ECG were excluded). 2) Cumulative CK-MB release(CK) (80 Pts=5.3% with insufficient samples and 34=2.2% early deaths were excluded). 3) Global and regional EF (R EF) from contrast angiography 3 weeks after AMI in 52% of Pts (it was a subset of younger Pts who had angiography without any selection as to whether treated with STK or PLA). For all 3 parameters there was a significant limitation of infarct size as compared with PLA for the total group and for Pts treated within 3 h of symptom onset.

Subgroup analyses revealed a significant limitation of infarct size for anterior MI (ANT) for the first 4 h after onset of pain: QRS 25% ($p<0.002$), CK 14% ($p<0.02$), EF 57.7 vs 52.1 ($p<0.005$), R EF 23% ($p<0.01$). (First hour 38 to 46%, similar effects 2nd to 4th h). Inferior MI (INF) similar for the first 2 h: CK 28% ($p<0.003$), EF 61.4 vs 56.8 ($p=0.06$), R EF 31% ($p<0.03$). According to the ischemic area at risk at baseline limitation of infarct size was significant in Pts with moderate or large infarction but also substantial in Pts with a small ischemic area (sum of ST elevations on the prerandomization ECG 1-6 mm). Angiography at 3 weeks revealed improved LV function also in Pts treated later, i.e. who had no effect in QRS or CK.

Conclusion: Thrombolysis limits infarct size within 4 h of symptom onset in ANT MI and within 2 h in INF MI. Limitation of infarct size is significant in Pts with moderate or large ischemic areas but may be worthwhile also in Pts with smaller infarcts. Pts may benefit by a subsequent improvement in LV function, even if limitation of infarct size could not be assessed in the acute phase.

**NO DIFFERENCE IN LONG TERM LEFT VENTRICULAR FUNCTION AFTER STREPTOKINASE AND TISSUE PLASMINOGEN ACTIVATOR THERAPY IN ACUTE MYOCARDIAL INFARCTION.**

Hylton J. Miller MB, Arie Roth MD, Avraham Parades MD, Boris Shagarodsky MD, Gabriel Barabash MD and Shlomo Laniado MD. Tel-Aviv Medical Center, Tel-Aviv, Israel.

In a sequential non-randomised study using similar protocols, 76 patients (pts) were were treated with SK (GrI) and 96 with tPA (GrII) within 4 hrs of the onset of MI. There was no difference between groups regarding time to therapy, peak creatine kinase,coronary anatomy, mortality, bypass surgery and non-Q wave infarction. In Gp.I, 70% of infarct arteries (IA) were patent, 83% in Gp.II. 72% of pts in Gp I underwent PTCA, and 54% in Gp. II. Mean IA stenosis was 92±14% in Gr.I and 82±10% in Gr.II (p<.01). Pts with inferior (inf) MI and anterior (ant) MI were analysed separately and global LVEF (%) serially measured.

| Results | 24 hours | | 12 months |
|---|---|---|---|
| inf MI SK | * 47±9 | NS | 46±10 * |
| inf MI tPA | 53±13 | NS | 56±11 |
| ant MI SK | NS 38±10 | * | 48±12 NS |
| ant MI tP | 39±15 | * | 48±14 |

NS = p non-significant * = p<0.01

Conclusions: Both SK and tPA are effective and safe thrombolytic agents. Pts with inf MI did not show a significant late improvement in LVEF, regardless of type of thrombolytic therapy. However, in pts with ant MI, there was a significant LVEF improvement in both groups but no difference between both agents. Despite evidence of apparant improved thrombolytic efficacy with tPA, long term global LVEF is not different from SK treated pts.

## Tuesday, March 21, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 10:00AM–11:00AM
## Pacific Room, Anaheim Convention Center
## Ambulatory Ventricular Function and Miscellaneous Myocardial Imaging

**AUGMENTATION OF EJECTION FRACTION DURING AMBULATORY MONITORING IN THROMBOLYSIS PATIENTS WITH CONCOMITANT SILENT VENTRICULAR DYSFUNCTION: MECHANISTIC IMPLICATIONS**

David S. Kayden, M.D., Frans J. Wackers, M.D., F.A.C.C., Barry L. Zaret, M.D., F.A.C.C., and TIMI. Yale University, New Haven, CT.

We have shown that silent left ventricular dysfunction (LV dys) detected by ambulatory radionuclide LV function monitoring (VEST) during routine clinical activity following thrombolysis predicts adverse cardiac events. The mechanisms underlying this LV dys are not known and the ability of these pts with transient LV dys to augment LV function in response to increased demand is unclear. Consequently, we studied 27 MI pts following thrombolysis with VEST monitoring and submaximal supine bicycle exercise equilibrium radionuclide ventriculography (ExT) at hospital discharge. Pts were monitored with the VEST for an average of 184±59 mins during routine hospital activity. 11/27 pts demonstrated transient falls in LV ejection fraction (EF) >5%, lasting ≥1 min, occurring without increase in heart rate (HR). 8/11 of these pts and 11/16 pts without LV dys also had episodes of ↑LVEF ≥10% with ↑HR during the same monitoring period. There was no difference between the 2 groups in number of episodes ↑LVEF/pt (2.8±2.3 vs 2.5±2.7), ΔLVEF (+13±4% vs +12±3%), ΔHR with ↑LVEF (+14±11 vs +10±10 b/min) or duration of episodes (5.7±4.1 vs 7.1±4.3 mins). In contrast, during ExT at ≥same HR as VEST activity only 4 pts had ↑LVEF ≥10% (p<0.0001).

Thus, following thrombolysis, transient LV dys occurs during routine activity in the apparent absence of increased myocardial demand. Many of these pts can augment LVEF at other times, suggesting that the mechanism of silent LV dys following thrombolysis is a decrease in myocardial supply. In addition, changes in LVEF during supine ExT do not necessarily parallel relevant LVEF augmentation during routine activity. Ambulatory monitoring of LVEF during routine activity may provide additional important functional clinical information.

**AMBULATORY LEFT VENTRICULAR FUNCTION MONITORING: ARE THE EJECTION FRACTION MEASUREMENTS REPRODUCIBLE?**

Ling de Yang, M.D., C. Noel Bairey, M.D., Daniel Berman, M.D., FACC, Ken Resser, B.S., Ken Nichols, PH.D. Alan Rozanski, M.D., FACC, Cedars-Sinai Med Ctr., LA, CA

We previously reported a validation of the ambulatory left ventricular (LV) function monitor (VEST) by comparing exercise (EX) LV ejection fraction (EF) to gamma camera (C) measurements (J Nucl Med 29(5):741,1988), but the reproducibility of LVEF by VEST measurements during serial activity is not known. Hence, Tc-99m RBC EX LVEF responses were compared for VEST vs VEST (V-V) in 9 volunteers who exercised 3 times, twice wearing the VEST and once during gamma camera (C) imaging. V vs C EFs during repeat EX were also compared in 27 other subjects who exercised twice. V vs V measurements for EF were compared at matched heart rates for 2 minute and 30 second intervals for each level of exercise (N=36) as well as for peak EX only (N=9):

| | Duration | EF | | Δ EF | |
|---|---|---|---|---|---|
| V-V comparisons | (seconds) | ICC | Diff | ICC | Diff |
| All EX levels | 120s | 0.88 | 1.9±1.5 | 0.88 | 1.8±1.4 |
| All EX levels | 30s | 0.94 | 1.7±1.3 | 0.94 | 1.8±1.5 |
| Peak EX only | 30s | 0.88 | 1.8±1.2 | 0.94 | 1.3±0.9 |

ICC=intra-class correlation coefficient. Diff=average absolute difference in EF (±SD). By comparison, the correlation coefficient for EF for V vs C was 0.85 (SEE=3.98) and for Δ EF was 0.73 (SEE=3.95) for 138 matched EX stages in the total of 36 subjects.

Conclusion: Measurements of LVEF during repeat EX are highly reproducible by VEST measurements, even for measurements obtained over brief 30 second intervals during peak exercise. These results underscore the usefulness of the VEST for assessing continuous LV function during ambulatory activities, short time periods and strenuous exercise.

**INITIAL VALIDATION OF A NEW PATIENT-BORNE MINIATURE DEVICE FOR CONTINUOUS MONITORING OF LEFT VENTRICULAR FUNCTION AND ST-SEGMENT**

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A new portable bedside monitoring system has been developed for continuous monitoring of left ventricular (LV) function using a miniature CsI/photodiode scintillation detector (45x40mm) and an Olivetti M24 computer (CsD). Special purpose modules inside the computer perform signal processing and gated or beat-to-beat LV activity curves are continuously displayed together with an averaged ECG from which ST-segment values are obtained. At the end of each acquisition the ejection fraction (EF), relative volumes, diastolic filling parameters and ST level are displayed, can be trended and/or stored on disc. Validation was performed on 15 patients undergoing gamma camera (G) radionuclide ventriculography within 20 min and 6 hours later. The mean ±SD difference between CsD and G was 5.6±7.9% (early) and 4.5±7.3% (late), (range of EF: 20%-78%). The small size and low cost of this system make it suitable for long-term monitoring and rapid response time allows accurate LV function assessment following acute interventions.

**NITROGEN-13 AMMONIA MYOCARDIAL UPTAKE AT REST AND WITH EXERCISE IN NORMAL VOLUNTEERS: QUANTIFICATION OF CORONARY FLOW WITH DYNAMIC POSITRON EMISSION TOMOGRAPHY**

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To assess the utility of using the flow tracer nitrogen-13 ammonia (NH3) with dynamic positron emission tomography (PET) to quantitate coronary flow, we injected NH3 at rest and during supine exercise into 11 normal volunteers and obtained dynamic PET images for 10 min. The net extraction of NH3 was calculated as the myocardial uptake of NH3 at 10 min divided by the input function obtained from a left ventricular blood pool region of interest. Net extractions of NH3 were .35±.02 for rest and .40±.02 for exercise. The ratio of exercise/rest extractions was 1.14±.06. Average flows obtained from application of a 2 compartment model fit to the initial 90 sec of PET data were .81±.43 and 1.53±.69 ml/min/g for rest and exercise. The ratio of exercise/rest flows was 2.06±.68 which correlated with a 280% increase in double product. The lack of significant increase in net extraction of NH3 with exercise is due to a decrease in extraction fraction with increasing flow and limits the usefulness of net extractions to quantitate flow changes. We, however, conclude that coronary blood flow can be quantitated using dynamic PET images and a 2 compartmental model.

Quantitative measurement of myocardial blood flow and coronary flow reserve in patients with CAD employing O-15 water and positron emission tomography (PET)

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We previously validated a method to measure MBF with a continuous inhalation of O-15 CO2 and dynamic PET scanning in a dog model performing simultaneous measurements of MBF with gamma labelled microsphers (r=0.98).In the present study we studied 6 patients with severe single vessel disease ,positive exercise test and no evidence of myocardial infarction (MI) (group1) and 4 patients with q-wave MI(group2).Measurements of MBF were performed during baseline (B)in all pts and following the administration of 0.6 mg/kg of dipyridamole (D) in group1.Over 60 regions of interest were drawn on an average of 10 cross-sectional images of the heart to generate time /activity curves of the myocardium and left ventricular chambers(arterial input function). MBF was obtained by fitteing to a 2 compartment model.MBF results were then grouped in regions of myocardium supplied by normal arteries (N) and those supplied by stenosed arteries(S) .The following results are expressed in ml/g/min

| GROUP | B | | D | |
|---|---|---|---|---|
| | N | S | N | S |
| 1 | 0.93+/-.21 | 0.86+/-.2 | 2.6+1.3 | 1.31+/-.71 |
| 2 | 0.86+/-.26 | 0.35+/-.2 | - | - |

(group1:B N vs D N p≤.05,B S vs D S NS;group2:N VS S p≤.001).Coronary flow reserve in the distribution of S was 57+/-12% of that of N in patients of group1(p<.001 one way ANOVA). Thus,PET measurment of MBF was found to be consistent with the presence of MI and an impaired flow reserve in those pts with single CAD and no MI.

Predictive value of In-111 Antimyosin uptake for improvement of left ventricular wall motion after thrombolysis in acute myocardial infarction.

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In 19 patients (pts.), who were treated with thrombolysis for transmural acute myocardial infarct (AMI), the degree of myocardial uptake (MU) of Indium-111 Monoclonal Antimyosin (IMA), injected within 24 hours after onset of AMI, was compared with the degree and extent of regional asynergy (RA) on admission and discharge as assessed by 2D-echo. 2mCi IMA was injected on day 1 of AMI and planar images were made 24 hours later. IMA-MU was evaluated for count density index (CDI=count density of infarct zone/left lung count density) in the left anterior oblique projection, which optimally displayed infarct zone in all patients. Using 2D-echo, LV was divided in 13 segments and evaluated for RA. RA was considered severe (akinesis or dyskinesis) or mild (hypokinesis). RA extent was measured by the number of asynergic segments. All 19 pts. had severe RA on admission; 7/19 showed only mild RA on discharge, 12/19 had persistent degree of RA.

RA ON DISCHARGE

| | MILD | | SEVERE | |
|---|---|---|---|---|
| CDI | 1.71±0.25 | * | 2.50±0.47 | * P<0.01 |

In 13 pts. a decrease in the number of akinetic segments was seen between admission and discharge. In 6 this number was unchanged.

EXTENT OF SEVERE RA

| | DECREASED | | UNCHANGED | |
|---|---|---|---|---|
| CDI | 1.93±0.37 | * | 2.72±0.40 | * P<0.01 |

Thus, early CDI predicts wall motion improvement in AMI treated with thrombolysis.

## Tuesday, March 21, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 11:00AM–12:00NOON
## Pacific Room, Anaheim Convention Center
## Myocardial Perfusion Imaging

PROGNOSTIC IMPLICATIONS OF NUCLEAR EXERCISE TESTS IN AN UNSELECTED OUTPATIENT POPULATION.

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To assess the efficacy of nuclear exercise tests in predicting mortality (M), 235 pts with suspected or proven coronary disease (CAD) were prospectively enrolled and followed for 5 yrs. 121 pts were referred for exercise thallium scintigraphy and 114 for radionuclide ventriculography. Since there were no significant differences in clinical characteristics or survival of patients sent for exercise thallium scintigraphy or radionuclide ventriculography, combined results are presented below. There were 192 men, 43 women, median age 55 years. Pretest probability of CAD was <.10, .10-.90, and >.90 in 15%, 39%, and 14% of pts respectively. The remaining 32% had known CAD (prior infarction or CAD at angiography). Only 4% had heart failure, and 6% had rest ejection fractions <50%. Followup for M was complete. Overall survival was 94.5% at 5 years. M rates were as follows: Men 8%, women 1% (p< 0.04); anginal symptoms present 8%, absent 1% (p<0.03); probability for CAD >.90 9%, =<.90 3% (p=0.05); ST segment depression during exercise present 8%, absent 3% (p=NS). Ischemia on either exercise thallium scintigraphy (defined as a transient exercise related perfusion defect) or radionuclide ventriculography (defined as an exercise related regional wall motion abnormality) was highly predictive of an increased M (10%) when compared with the absence of ischemia (1.6%) (p<0.007). Conclusions: Five year survival was good among unselected outpatients referred for nuclear exercise tests. Nuclear exercise test results further identified low and higher risk subgroups, and were superior to ECG stress testing for this purpose.

**SUPERIORITY OF Tc-99m METHOXYISOBUTYL ISONITRILE COMPARED TO THALLIUM-201 FOR THE TOMOGRAPHIC ASSESSMENT OF CORONARY ARTERY STENOSES.**

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To test the hypothesis that tomography (SPECT) with Tc-99m 2-methoxyisobutyl isonitrile (MIBI) accurately identifies coronary stenoses, we compared stress-rest Tc-99m MIBI with stress-redistribution thallium (Tl-201) imaging in 38 pts with coronary artery disease documented by angiography (≥50% diameter stenoses). Tracer distributions were quantified and compared to lower limits (mean - 2.5 S.D.) from 12 healthy volunteers. Tc-99m MIBI images were visually superior to Tl-201 in 84% of pts. Heart/lung and heart/liver ratios were similar for MIBI and Tl-201. Tc-99m MIBI identified 36 pts compared to 32 pts with Tl-201 (p=0.2). Compared to Tl-201, Tc-99m MIBI identified more stenoses (59 vs. 45 of 75,p<.05), a similar number of uninvolved vessels (28 vs. 27 of 39,p=NS), and had greater accuracy (76% vs. 63%,p<.05). More non-infarct related stenoses were detected with Tc-99m MIBI (38/54 vs. 25/54,p<.05). Quantitative perfusion defect severity was equivalent for MIBI and Tl-201. Tc-99m MIBI identified 134 reversibly ischemic segments in 33 pts compared to 104 segments in 28 pts with Tl-201 imaging (p<.05). Thus, Tc-99m MIBI SPECT myocardial perfusion imaging provides superior detection of stenoses and reversible ischemia compared to Tl-201.

PLANAR AND TOMOGRAPHIC MYOCARDIAL IMAGING WITH SQ 30217, A NEW TECHNETIUM LABELED AGENT

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In evaluation of SQ 30217 (SQ), a new neutral lipophilic technetium labeled myocardial perfusion agent with rapid clearance, we studied 22 patients referred for coronary arteriography. Treadmill exercise was performed to 80% of maximal predicted heart rate or symptoms and SQ (12-20mCi) was injected at peak exercise. Planar imaging was performed in the first 15 patients in three views starting in 2 minutes in the anterior (3 min), 45 LAO (6 min), and left lateral (9 min) views. A dose of SQ was repeated 120 minutes later at rest. Images were evaluated by 3 observers blinded to the cath results. Eight patients had significant coronary disease (≥50% stenosis). SQ scans identified 5/8 (63%) patients with CAD and 5/11 (45%) abnormal vessels with no false positives. Two patients with single vessel circumflex and one with only right coronary disease were not detected possibly because SQ hepatic activity obscured the inferior wall on the lateral view. All but one abnormal region (100% occlusion), in a non-infarct location, normalized at rest. In order to improve accuracy, SQ SPECT was performed post exercise and at rest in the final 7 patients, 6 of whom had CAD. SQ SPECT identified all 6 patients with CAD and 8/11 (72%) abnormal vessels with no false positives. Conclusion: SQ is a promising imaging agent for the identification and localization of CAD, particularly using SPECT. The rapid myocardial washout of SQ allows for the sequential performance of both rest and exercise studies.

QUANTITATIVE ANALYSIS OF STRESS TC-99M METHOXY ISOBUTYL ISONITRILE(MIBI) SPECT: PRELIMINARY DEVELOPMENT AND VALIDATION OF AN OPTIMIZED COMPUTERIZED METHOD.

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A method was developed to objectively quantitate MIBI based on our quantitative SPECT Tl-201(Tl) method. SPECT MIBI imaging used 32 projections over 180°. After low-pass filtering and reconstruction, maximum count circumferential profiles were generated and normalized to each short- and vertical long-axis slice. Short-axis and the apical portion of long axis profiles were plotted on a 2-dimensional polar display. Using 10 pts(5 male(M) and 5 female(F)) with <5% likelihood of coronary artery disease(CAD), average counts of Tl and MIBI in 4 myocardial regions were:

| | Anterior Tl/MIBI | Lateral Tl/MIBI | Inferior Tl/MIBI | Septum Tl/MIBI |
|---|---|---|---|---|
| M: | 84/84 | 91/93 | 74/76 | 78/81 |
| F: | 86/87 | 93/93 | 83/86 | 81/85 |

Relative increase in counts observed in the inferior and septal regions in F was presumably due to breast attenuation of opposite walls. Normal limits for MIBI were then developed from 14 M with <5% likelihood of CAD. Sensitivities and specificities for overall CAD detection and identification of diseased vessels (≥50% stenosis) in 12 M pts were:

| | Overall | LAD | LCX | RCA |
|---|---|---|---|---|
| Sensitivity: | 8/8(100%) | 5/6(83%) | 6/6(100%) | 4/5(80%) |
| Specificity: | 3/4( 75%) | 4/6(68%) | 4/6( 68%) | 5/7(71%) |

We conclude:1) gender matched normal limits are required for SPECT MIBI, 2) this objective quantitative method for SPECT MIBI offers promise for the overall detection of CAD and identification of disease in individual coronary arteries.

KINETICS OF THE NEW Tc-99m LABELED BLOOD FLOW MARKER (SQ30217) IN CANINE MYOCARDIUM.

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SQ30217 (SQ), a boronic acid adduct of technetium oxime complex, is a neutral lipophilic myocardial blood flow (MBF) tracer introduced for cardiac imaging. To characterize myocardial retention and clearance, a small bolus of SQ was injected into the LAD in 5 open chested dogs (8 experimental runs). Myocardial time activity curves were recorded using a NaI (Tl) probe placed over the left ventricle. Myocardial activity cleared in a biexponential pattern following i.c. injection. Curve fitting was employed, yielding first pass retention fractions (RF), clearance halftimes (T 1/2) and relative proportions (RP) of each exponential to the RF. Prior to each injection, radiolabeled microspheres were injected to determine MBF. SQ kinetics were assessed over a wide MBF range utilizing i.v. dipyridamole (D). At baseline, (GI) MBF averaged .43 ± .17 ml/min/g, while MBF increased (GII) to 3.1 ± 1.5 ml/min/g following D (0.3-0.5 mg/kg).

| | n | RF | T 1/2(1) (min) | T 1/2(2) (min) | RP(1) % | RP(2) % |
|---|---|---|---|---|---|---|
| GI | 3 | .80 ± .07 | 2.5 ± .7 | 20 ± 11 | 70 ± 2 | 30 ± 2 |
| GII | 5 | .84 ± .06 | 1.8 ± .2 | 37 ± 8 | 78 ± 1 | 22 ± 1 |

SQ has a high first pass retention fraction, which is stable over a wide flow range. Myocardial tracer kinetics are characterized by biexponential clearance. The rate and proportion of the fast component, which represents approximately 75% of total clearance, is related to blood flow. Thus, the high RF favors SQ as a suitable MBF tracer, but the fast clearance seen in canine heart challenges conventional SPECT imaging procedures.

**REVERSE REDISTRIBUTION FOLLOWING MYOCARDIAL INFARCTION IS RELATED TO SEVERITY OF CORONARY STENOSIS.**

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We evaluated the infarct-related territory (IRT) and artery (IRA) to test the hypothesis that, in comparison to reversible defect (RD), apparent worsening (reverse redistribution, RR) on exercise thallium single photon emission computerized tomography (SPECT) may be due to rapid washout (WO) of thallium in segments supplied by IRA with less severe flow limiting stenosis. Accordingly we studied 58 pts (age 54±1 yrs, $\bar{x}$±SEM) who were part of a randomized, double-blind, placebo controlled trial of IV tPA for myocardial infarction (MI, 34 pts received tPA and 24 placebo). All pts had an open (TIMI grade II or III) IRA at 10±.3 days and underwent symptom-limited, Bruce protocol exercise with SPECT at 9±.4 days following admission. Quantitative coronary angiography (QCA) was used to calculate minimal cross-sectional area (MCSA) of IRA. Presence of normal perfusion (N), fixed defect (FD), RD, and RR in IRT was determined by two independent observers blinded to the results of QCA.

| | N | FD | RD | RR | |
|---|---|---|---|---|---|
| All pts n= | 2 | 9 | 23 | 24 | |
| tPA pts n= | 1 | 5 | 14 | 14 | *p<.01 |
| MCSA($mm^2$) | .8±.6 | .9±.4 | .7±.1 | 1.6±.3* | vs RD |

The WO rates in IRT were assessed by quantitative analysis and were more frequently above normal in pts with RR than in those with RD (17/24 vs 3/23, p<.005).

We conclude that reverse redistribution is frequently seen in pts with patent IRA following MI. RR is associated with faster thallium washout and a lesser degree of luminal obstruction and may be useful in identifying vessels with less severe flow limiting stenosis.

**CHARACTERIZATION OF PATIENTS WITH ABNORMAL STRESS REDISTRIBUTION TL-201 SPECT AND NORMAL CORONARY ARTERIES.**

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To assess the potential causes of abnormal(abnl) stress redistribution Tl-201(Tl) SPECT in patients(pts) with normal(nl) coronary arteriograms(NCA), 46 pts with these findings tested from 1983-1988 were identified. Their SPECT studies and those of 27 randomly selected additional pts - 17 with coronary disease ≥50% stenosis(CAD) and 10 with low likelihood of CAD(LL) - were reinterpreted blindly by 3 experienced observers as nl, equivocal or abnl. Excellent agreement was found between the original(1 expert) and consensus reading for LL(90%) and CAD(94%) pts. Agreement was lower for NCA pts with 10/46(22%) being reclassified as equivocal(N=7) or nl(N=3), attributed to experience in identification of nl variant Tl SPECT patterns(eg., breast and inferior wall attenuation). An additional 9/46(20%) pts had technical artifacts explaining positive Tl SPECT: 5 had motion or "upward creep", 2 had "hot spots" and 2 had "vertical heart", the latter causing nonreversible septal defects. Of the other 27 pts, definite cardiac abnl was present in 18: LBBB with septal reversible defects(N=4), marked(≥ 20 mmHg) elevation of LV end-diastolic pressure(LVEDP) and/or moderate to severely abnl wall motion(N=13), and severe mitral regurgitation(N=1). The remaining 9 NCA pts had possible occult cardiac pathology with ST depression (N=7), and/or moderate elevation of LVEDP(N=6).

In conclusion, pts with abnl Tl and NCA can be categorized into 2 groups: 1) over-reading and technical errors(solved by experience and quality control), and 2) definite or possible occult organic cardiac pathology.

**IODINE-123-PHENYLPENTADECANOIC ACID TOMOGRAPHY FOLLOWING DIPYRIDAMOLE INFUSION FOR THE DETECTION OF CORONARY ARTERY DISEASE.**

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Myocardial uptake of iodine-123-phenylpentadecanoic acid (IPPA), a synthetic fatty acid, is directly related to blood flow and aerobic metabolism. Dipyridamole results in flow differences and often ischemia (anaerobic metabolism) in pts with coronary artery disease (CAD). Thus, myocardial uptake of IPPA after dipyridamole should be reduced in myocardial regions supplied by stenosed coronary arteries and permit localization of CAD. The diagnostic accuracy of dipyridamole IPPA imaging for the detection of CAD was evaluated in 55 pts with chest pain (35 with and 20 without CAD defined as ≥70% diameter stenosis by quantitative coronary angiography). Pts were imaged tomographically (3 serial 16 minute studies) after dipyridamole and IPPA injection. Rapid IPPA clearance permits redistribution imaging immediately after initial imaging. Results for detection of CAD by decreased uptake of IPPA are below.

| | SENSITIVITY | SPECIFICITY | DIAGNOSTIC ACCURACY |
|---|---|---|---|
| CAD | 0.94 | 0.80 | 0.89 |
| LAD | 0.82 | 0.82 | 0.82 |
| LCX | 0.60 | 0.94 | 0.82 |
| RCA | 0.87 | 0.70 | 0.75 |

Dipyridamole IPPA tomographic imaging has high sensitivity, specificity and diagnostic accuracy for detection of CAD. Redistribution imaging immediately after initial imaging results in greater patient and laboratory convenience. Dipyridamole IPPA imaging may be a superior alternative to stress thallium imaging.

## Tuesday, March 21, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 9:00AM–10:00AM
## Pacific Room, Anaheim Convention Center
## Cardiac Function: General

**LEFT VENTRICULAR DIASTOLIC FUNCTION - DOPPLER CHANGES IN EARLY POST CARDIAC TRANSPLANT RECIPIENTS.**

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Left ventricular diastolic function is altered in acute cardiac transplant rejection and a restrictive ventricular filling pattern occures. Doppler echocardiographic indices have been proposed as sensitive markers of the rejection process. As rejection progresses the restrictive ventricular filling pattern is reflected by a shortening of the isovolumic relaxation time (IVRT) and mitral valve pressure half time (PHT) and an increase in the early transmitral filling velocity (M1). It is also known that left ventricular filling undergoes characteristic changes suggestive of improving diastolic function in the early post operative period in non transplant cardiac surgery patients. We examined the progression in Doppler derived mitral filling indicies in a group of cardiac transplant recipients (10 patients) who demonstrated no histological evidence of transplant rejection. IVRT, PHT and M1 were measured on a weekly basis for the first post operative month on the day that surveillance right ventricular endomyocardial biopsies were performed. A gradual improvement over time in LV diastolic function and a decrease in the restrictive filling pattern was demonstrated by all three measured Doppler parameters.

| Week Post Op | IVRT (ms) | PHT (ms) | M1 (m/s) |
|---|---|---|---|
| 1 | 69.3 +/- 12.8 | 37.4 +/- 9.2 | 0.75 +/- 0.13 |
| 2 | 74.7 +/- 16.5 | 37.9 +/- 6.2 | 0.74 +/- 0.16 |
| 3 | 82.1 +/- 12.8 | 43.5 +/- 12. | 0.68 +/- 0.23 |
| 4 | 82.8 +/- 11.6 | 43.9 +/- 6.2 | 0.62 +/- 0.18 |

**Conclusions:** This Doppler data confirms the improvement in LV diastolic filling in the early post operative period in the absence of rejection. Knowledge of these characteristic changes is important for the application of these indices for rejection surveillance.

**RESTING AND SUPINE EXERCISE HEMODYNAMICS IMPROVE 1 AND 3 YEARS AFTER ORTHOTOPIC CARDIAC TRANSPLANTATION**

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To assess the changes in resting and exercise central hemodynamics that occur with time, 74 heart transplant recipients have had serial resting hemodynamic studies at 1 wk, 3 mo, and 1 yr, and 12 patients have also had studies at 3 yr. Hemodynamic measurements during symptom limited graded supine exercise were obtained serially in all patients at 3 mo, 1 yr, and 3 yr. **Results:**

**Resting Hemodynamics**

| | HR | CO | PCWP | RAP |
|---|---|---|---|---|
| 1 wk | 87±14 | 5.3±1.3 | 16±6 | 9±6 |
| 3 mo | 95±12* | 6.2±1.2* | 14±4 | 6±2* |
| 1 yr | 92±11* | 6.0±1.2* | 12±4* | 5±2* |
| 3 yr (n=12) | 86±12 | 6.5±1.3* | 11±3§ | 5±2* |

means ± SD; *p<.01 vs 1 wk, §p<.01 vs 1 wk and 3 mo.

**Exercise Hemodynamics**

| | PCWP | | | RAP | | |
|---|---|---|---|---|---|---|
| | 3 mo | 1 yr | 3 yr | 3 mo | 1 yr | 3 yr |
| EX 1 | 23±6 | 21±6 | 20±6 | 14±5 | 10±4* | 9±2* |
| PEAK | 27±7 | 25±7 | 27±6 | 17±4 | 14±4* | 12±4§ |

means ± SD; *p<.01 vs 3mo, §p<.01 vs 3 mo and 1 yr; EX1=25 W supine exercise, PEAK=maximum exercise.

At 1 and 3 yr, exercise heart rate response became more physiologic as did deceleration post exercise. Peak exercise cardiac output (97% increase) was maintained to 3 yr. Thus, although ventricular filling pressures increase strikingly during exercise from 3 mo on, there is no evidence of progressive LV dysfunction with time. RV performance during exercise continues to improve to 3 yr.

BETA ADRENERGIC BLOCKADE BLUNTS COMPENSATORY HYPERKINESIS DURING ACUTE INFARCTION.

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Compensatory hyperkinesis (CH) in acute MI has been attributed to adrenergic stimulation, the Frank-Starling mechanism, and intraventricular interactions that unload the normal segments. To assess the role of adrenergic stimulation in CH, nine men, age 52±13 yrs were given 15 mg IV metoprolol (MET) <1.5 hours after PTCA for acute MI. All had 1 vessel CAD. Measurements were obtained before IV MET (PRE), immediately after (POST), and after 9.1±1.2 days of 100mg MET PO BID (LATE). Regional motion (RWM) was scored in a masked fashion: 0=dyskinetic; 1=akinetic; 2=hypokinetic; 3=normal; 4=hyperkinetic.

| | Heart Rate | | | Blood Pressure | | | EF | | |
|---|---|---|---|---|---|---|---|---|---|
| | PRE | POST | LATE | PRE | POST | LATE | PRE | POST | LATE |
| MEAN | 88 | 71* | 62* | 125 | 125 | 111 | 55 | 45* | 54+ |
| S.D. | 14 | 13 | 12 | 10 | 15 | 16 | 14 | 15 | 10 |

*=p<0.005 vs PRE, +=p<0.05 vs POST IV MET.

In a control population, IV MET produced no change in RWM. Among pts, IV MET did not change infarct zone RWM, 1.6±0.7 to 1.3±0.7, but normal zone RWM declined from 3.6±0.5 (hyperkinetic) to 2.7±0.5, (normal) (p<0.05). This resulted in a 10 unit fall in the global EF. At LATE study, normal zone RWM remained normal, while infarct zone RWM improved to 2.4±0.7, p<0.02. This improved infarct zone RWM resulted in a 9 unit rise in the global EF from POST to LATE, or only a 1 unit fall from PRE to LATE. Conclusions:Adrenergic stimulation causes CH in acute MI. By blocking normal zone CH, IV MET can influence the directional change in global EF, independent of its effect on infarct zone recovery.

RIGHT VENTRICULAR RESTRICTIVE/CONSTRICTIVE PHYSIOLOGY ACCOMPANIES HEART TRANSPLANT REJECTION.

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Conflicting reports have evaluated changes in indices of both systolic and diastolic LV function with heart transplant (TX) rejection (RJN). Therefore, in 10 TX Pts, intravenous digital subtraction RV angiograms based on densitometric analysis and micromanometer RV pressure were prospectively assessed at endomyocardial biopsy. 13 episodes of RJN (myocyte necrosis) were compared to preceding negative biopsies. Heart rate (HR,bpm), RV systolic (SYS), minimum (MIN) and end-diastolic (ED) pressures (mm Hg), ejection fraction (EF%), peak filling rate (PFR, ED vol/s) and time to PFR (tPFR, ms) were (mean ± SEM):

| | HR | SYS | MIN | ED | EF | PFR | tPFR |
|---|---|---|---|---|---|---|---|
| - RJN | 83±2 | 28±2 | 0±1 | 7±1 | 58±2 | 2.45±.10 | 132±5 |
| + RJN | 86±3 | 34±3* | 4±1* | 10±2* | 62±2 | 2.82±.19* | 140±5 |

*p< .05 vs. - RJN

Dip and plateau changes in RV diastolic volume and pressure curves were noted with RJN. No significant changes in stroke volume,pulmonary capillary wedge pressure, pulmonary vascular resistance or RV peak positive dP/dt occurred. Thus TX RJN may effect RV diastolic performance secondary to either changes in myocardial mechanics or loading. RV diastolic function may be a better index of graft viability than systolic function.

QUANTITATIVE REGIONAL CURVATURE ANALYSIS: DETERMINATION OF ABNORMAL SYSTOLIC AND DIASTOLIC FUNCTION BY ASSESSING SHAPE THROUGHOUT THE CARDIAC CYCLE.

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Quantitative Regional Curvature Analysis (QRCA) was developed to measure left ventricular (LV) regional function independent of volume and reference, coordinate or indexing systems. QRCA was based on calculation of shape (curvature) from LV cines at end-diastole and end-systole. Curvature was normalized to dimensionless units by incorporating perimeter length thereby allowing comparison of ventricles of different sizes. QRCA was enhanced so that systolic and diastolic shape abnormalities could be quantitated throughout the full cardiac cycle. Frame-by-frame outlines of 30 normal and 40 abnormal patients were analyzed. To account for differences in cycle length, interpolation was used to create 100 "frames" per cardiac cycle such that frame 1 and frame 100 corresponded to end-diastole and frame 50 corresponded to end-systole. Results were displayed in a color-modulated graph containing 100x100 pixels (color = deviation from normal curvature values, X axis = perimeter location, y axis = phase of the cardiac cycle). Percentage of pixels with abnormal deviations, mean deviation per pixel and total deviation per region were worse in areas of dysfunction compared to normal zones (44 ± 2 vs 55 ± 3, 0.14 ± 0.05 vs -0.11 ± .08, and 594 ± 200 vs -598 ± 296, respectively, all p < .004). QRCA is an innovative technique for comprehensively measuring both systolic and diastolic function independent of volume and reference frames.

## ACUTE AND CHRONIC RESPONSE TO ORAL ENOXIMONE IN SEVERE CONGESTIVE HEART FAILURE: SUSTAINED HEMODYNAMIC IMPROVEMENT AND PREFERENTIAL EFFECT ON RIGHT VENTRICULAR SYSTOLIC PERFORMANCE

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We examined acute and chronic responses to oral enoximone to determine 1) effect of chronic therapy on baseline hemodynamics and ventricular performance; 2) effect of chronic therapy on acute drug effect; 3) relative acute and chronic effects on RV and LV performance. Eleven patients with severe congestive heart failure [LV ejection fraction (EF) 0.17 ± 0.02, mean ± SE] underwent hemodynamic and radionuclide ventriculographic study before and 2 hours after a single oral dose (mean 1.2 mg/kg). All patients were restudied after an average of 7 weeks of enoximone therapy, with enoximone discontinued 24 hours before study. Enoximone increased CI and reduced PA wedge pressure (PAWP). Enoximone improved RVEF, but not LVEF. At follow-up study, pre-drug parameters were unchanged from the initial study. Response of all parameters to enoximone was similar to the response observed at the initial study. (*p<0.05 vs. rest.)

| | Initial Study | | Follow-up Study | |
|---|---|---|---|---|
| | Rest | Enoximone | Rest | Enoximone |
| LVEF | .17 ± 02 | .17 ± .02 | .16 ± .02 | .17 ± .03 |
| RVEF | .33 ± .02 | .40 ± .04* | .32 ± .02 | .41 ± 04* |
| CI(l/min/m2) | 2.0 ± .2 | 2.3 ± .2* | 2.0 ± .2 | 2.2 ± .2* |
| PAWP(mmHg) | 21 ± 2 | 17 ± 3* | 20 ± 3 | 17 ± 3* |

Conclusions: In patients with severe congestive heart failure: 1) Enoximone preferentially augments RV systolic performance, with no detectable effect on LVEF. 2) Chronic enoximone therapy does not alter baseline (off enoximone) hemodynamics or ventricular performance. 3) Effects of enoximone on hemodynamics and on RV performance are maintained after chronic therapy.

## HETEROGENEITY OF REGIONAL MOTION AND SHAPE IN RESPONSE TO ALTERED LOAD.

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Left ventricular (LV) regional wall motion (RWM) has been used to evaluate interventions despite the fact that such measures are load-dependent. To assess whether LV shape, an important aspect of mechanical function, is also load-dependent, 10 normal patients and 12 patients with either aortic or mitral regurgitation were studied with ventriculography and high-fidelity pressures during control and infusions of methoxamine (M) and nitroprusside (N) at a constant heart rate. RWM and regional shape (RS) were derived using the "centerline" and "quantitative regional curvature" methods, respectively. In normal subjects, LV end-diastolic and systolic pressures ranged between 12-20 and 102-179 mmHg, respectively and LV end-diastolic volumes ranged between 102-179 ml. In valve patients, the respective ranges were 4-38 and 87-208 mmHg and 134-408 ml. RWM in normal subjects showed load-dependency that was greatest in the inferior wall (-.19 ± .9 during N vs -1.06 ± 1.22 standard deviations per chord during M, p< .05). RS of the anterior and inferior walls showed no load-dependency. In valve patients, RWM of both the anterior and inferior walls showed a similar degree of load dependency whereas RS showed no load dependency. Thus, in patients with normal LVs, load dependency of RWM is greatest in the inferior wall, whereas in valve patients both the anterior and inferior walls show similar load dependency. RS is independent of load. RS may, therefore, be more suitable than RWM for assessing interventions.

## PROPAGATION OF TURBULENCE IN AORTIC STENOSIS

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Turbulence produces high-frequency oscillations of pressure and velocity waveforms immediately above the stenotic aortic valve (AS). While turbulence is key to the physical findings of AS, in vivo data are scant to understand it's origin and propagation. The speed and extent of distal propagation of turbulence in the aorta were studied in 23 pts with AS (valve area 0.6 ± .2 $cm^2$) using multisensor catheters (3 pressure, 1 velocity). The onset of turbulence (fall in pressure, arrows in figure) was timed at 2 sensors 5 cm apart. Turbulence velocity (TV) was calculated and contrasted to the velocity of pressure wave transmission (PWV).


Turbulence was progressively delayed and attenuated at more distal sensors. TV was 0.8 ± 0.3 m/sec and PWV was 7.8 ± 4.2 m/sec. In pts with valve area ≤0.5 $cm^2$ turbulence persisted further downstream. No signs of turbulence were present in any patient at 25 cm downstream. The blood velocity waveform was turbulent in the ascending aorta, but laminar in the descending aorta. Conclusions: 1) Turbulence is propagated downstream at a velocity typical of blood, thus distinguishing its physical basis from pulse wave transmission. 2) Turbulence is transient during systole and the extent of propagation is variable and dependent on the severity of AS.

## IN VIVO ASSESSMENT OF THE INDEPENDENT EFFECTS OF HEART RATE, CONTRACTILITY AND SYSTOLIC LOADING CONDITIONS ON MYOCARDIAL OXYGEN CONSUMPTION.

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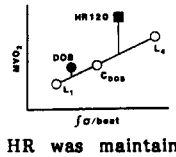
The dependence of myocardial oxygen consumption ($MVO_2$) on HR, contractile state and LV fiber load [i.e., integral of wall stress during ejection ($\int\sigma$)] is well recognized. However, a method for determining the relative importance of each factor in vivo does not exist. Accordingly, 7 atrially paced closed chest dogs were imaged with 2D targeted M-mode echo and instrumented with coronary sinus and Ao/LV microtip catheters. Data were acquired during: 1) load (L) manipulation with nipride and/or volume at HR90, 2) increased contractility [dobutamine (Dob), 5 μg/kg/min, HR90] and 3) increased HR (90 → 120 bpm). For each dog, a reference line of $MVO_2$ vs $\int\sigma$/beat (r = 0.92) was generated at a HR of 90 under basal contractility conditions using 4 points ($L_1 \rightarrow L_4$) acquired over a 73% change in $\int$/beat. The independent effects of ↑HR and ↑contractility on $\Delta MVO_2$ were assessed using the vertical deviation from this reference line, thereby eliminating changes in systolic load as a confounding variable.

| | Δ LOAD | Δ DOB | Δ HR |
|---|---|---|---|
| $\Delta MVO_2$ | 29% | 5% | 32% |




The isolated change in systolic load ($L_1 \rightarrow L_4$) resulted in a 29% change in $MVO_2$. The ↑ in contractility resulted in only a minimal change in $MVO_2$ when HR was maintained constant and $\int\sigma$/beat was normalized to the reference line. In contrast, the ↑ in HR resulted in a marked ↑ in $MVO_2$ relative to the $\int\sigma$/beat reference line. Thus, (1) a method for assessing the importance of each of the major determinants of $MVO_2$ now exists, (2) in the normal LV, a moderate increase in contractility alone does not significantly alter $MVO_2$.

NON-INVASIVE DETERMINATION OF CARDIAC OUTPUT DURING ACUTE MYOCARDIAL INFARCTION USING ELECTRICAL BIOIMPEDANCE CARDIOGRAPHY.
Iain N Findlay MRCP, David Northridge MRCP, John T Wilson, Esther Henderson, James Christie, Henry J Dargie, FRCP. Cardiac Department Western Infirmary Glasgow Scotland.

A reliable non-invasive technique for measuring cardiac output in acute myocardial infarction is described. We measured CO in 26 patients, within 12 hours of the onset of chest pain, using the technique of electrical bioimpedance. CO determined by the change in transthoracic impedance (TTI) was compared with Swan-Ganz thermodilution (TD). Mean (SD) CO by TD was 4.1 (1.1), range 2.1-6.2 l/min and by TTI was 4.1 (1.2), range 1.1-6.2 l/min (p=NS), r=0.86, p<0.0005, y=1.06x-0.4, SEE = 0.7 l/min. Mean stroke volume by TD was 50 (18) vs 48 (20) mls by TTI (p=NS), r=0.93, p<0.0005, TTI = 1.06TD-4, SEE = 8mls. Since stroke volume determined by TTI makes assumptions on thoracic volume and body surface area this was corrected for; stroke volume index showed a similar close relationship, stroke volume index by TD was 27 (9) vs 26 (11) mls/$m^2$ by TTI, p=NS, r=0.93, p<0.0001, TTI = 1.05TD-2, SEE=4mls/$m^2$. Reproducibility of CO by TTI was determined in 10 patients with repeat assessment after 30 minutes. CO was 4.2(1.5) vs 4.1(1.4) l/min, mean difference = 0.13 l/min, 95% confidence limits 0.24 l/min, co-efficient of variation 2.7%, r = 0.99, y = 0.96x+0.1, SEE = 0.14 l/min.
Thus CO by electrical bioimpedance is highly reproducible, comparable with thermodilution and offers the possibility of rapid non-invasive determination of cardiac function during acute myocardial infarction.

LEFT VENTRICULAR ISOVOLUMIC CONTRACTION PERIOD VANISHES DURING INTENSE EXERCISE
Joe M. Moody, Jr., M.D., F.A.C.C., Ares Pasipoularides, M.D., Ph.D., F.A.C.C., Joseph P. Johns, M.D. Brooke Army Medical Center, Fort Sam Houston, TX.
There is an inertial delay (ID) between atrioventricular (A-V) pressure crossover and mitral closure (MC). Mathematical modeling of this ID showed that LV pressure (LVP) at MC should be inversely related to the product (PRO) of diastolic filling time (DFT) and ID. If PRO falls sharply in exercise, LVP at MC could match/exceed levels inducing aortic opening (AO), phasing out isovolumic contraction (ICP=MC-AO). To test this, 9 NL adults were studied during graded bicycle exercise (EX) with dual M-mode for simultaneous echo of MC and AO. Interval measurements follow ($\bar{x} \pm$ SD, ms; * NS vs 0 ms):

| STAGE | R-R | DFT | LVET | ICP |
|---|---|---|---|---|
| RL | 867±137 | 491±122 | 269±23 | 53±16 |
| EX | 484± 29 | 215± 25 | 242±17 | 19± 9 |
| PK EX | 376± 30 | 176± 19 | 195±15 | 4± 6* |

In intense EX (PK EX), DFT falls to 1/3 and LVET to 2/3 their resting levels (RL). If ID responds as LVET, PRO should drop to 2/9 its RL. LVP at MC should then rise to 4.5 its RL, i.e. to 70-80 mm Hg. Diastolic BP in PK EX was 75± 10 mm Hg. Beats were identified in three instances where AO clearly preceded MC. Thus, our finding of ICP ∽ 0 ms in intense EX is consistent with the model prediction and has important physiological and clinical implications.

## Tuesday, March 21, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 10:00AM–11:00AM
## Pacific Room, Anaheim Convention Center
## Metabolism or Ischemia and Reperfusion

OXIDATIVE METABOLISM DURING CARDIAC ALLOGRAFT REJECTION STUDIED BY NADH LASER FLUORIMETRY.
Denis Duboc M.D., Martine Muffat-Joly Eng., Patrick Perrier M.D., Philippe Abastado M.D., Marcel Toussaint M.D., Thomas Lavergne M.D., François Guérin M.D., Michel Degeorges M.D., Alain Carpentier M.D., Université René Descartes, Hôpital Cochin, Paris, France.

Using NMR spectroscopy, decrease in high energy phosphate compounds has been described during early phase of cardiac graft rejection. To investigate the behaviour of myocardial oxidation-reduction states during rejection, we studied NADH fluorescence ($F_0$) on 12 non rejecting (NR: Lewis donnor/Lewis recipient) and 19 rejecting (R: Fisher donnor/Lewis recipient) heterotopically transplanted rat hearts. Six days after transplantation, $F_0$ (arbitrary units) was recorded, at base-line, during 30 s of complete ischemia (I:donnor aorta transiently occluded), and during reperfusion. At base-line $F_0$ was not significantly different in both groups (NR :0.45±0.04, R:0.45±0.05). During I, no significant difference was evidenced between both groups (NR: 1.11±0.05, R: 0.87±0.10, p#0.06). However in 7 R presenting myocardial necrosis and fibrosis histologically evidenced, $F_0$ level during I was signicantly lower than in NR (0.49±0.09, $p<10^{-3}$), reflecting a lower content of NAD to be reduced probably due to the myocardial tissue loss in these cases. For the other 12 R, with moderate histological rejection score, $F_0$ level during I was 1.08±0.10 (NS versus NR). The rate of FO decrease after I was significantly lower in the overall R group than in NR (0.024±0.001 vs 0.038±0.002 $F_0.s^{-1}$, $p<10^{-3}$) reflecting a lower rate of NADH reoxidation in rejecting myocardium. This suggests a mitochondrial impairment during rejection process. Energetic metabolism disturbancies may contribute to myocardial dysfunction during cardiac allograft rejection.

GLUCOSE METABOLISM IN STUNNED REPERFUSED MYOCARDIUM.
Britta Renstrom, Ph.D., A. James Liedtke, M.D., F.A.C.C., Stephen H. Nellis, Ph.D., Section of Cardiology, Univ. of Wisconsin, Madison, WI

We have previously determined that oxidation of fatty acids (FA) recovered to at least aerobic values during early myocardial reflow while pyruvate metabolism was suppressed. To further characterize use of carbohydrates during this condition, rates of glucose oxidation were measured in two groups of hearts (n=18), one of which (n=9) received treatment with the FA blocker, oxfenicine. Experiments were performed using extracorporeally perfused, intact swine hearts infused with Intralipid and heparin (average serum FA levels: 1.1±0.1 μmol/ml), [6-$^{14}$C]-glucose, and unlabeled glucose as needed (average serum levels 6.3±1.2 μmol/ml). All hearts were perfused aerobically for 30 min (average anterior coronary flow 7.6±0.4 ml/min/g dry), rendered regionally ischemic (-60Δ % in anterior flow) for 45 min, and reperfused for 50 min. Appreciable mechanical stunning was evident during recovery in both groups (-50Δ% in systolic shortening, p< 0.05 from aerobic values in control hearts; -32Δ%, p< 0.05 in treated hearts) and was associated with comparable reductions in myocardial oxygen consumption (-18Δ%, p < 0.02 from aerobic values). Glucose oxidation as estimated from $^{14}CO_2$ production from labeled glucose was no different in recovery than during ischemia in control hearts (14 μmol/hr/g dry) but doubled (p< 0.01) in hearts treated with oxfenicine which blocked access to FA utilization. Tissue glycogen recovered to 55% of aerobic levels in reperfused hearts in both groups. Thus early myocardial reperfusion is characterized by preference for FA oxidation as a primary energy source without any evidence of accelerated use or need of carbohydrates. Indeed, glycogen is preserved in this condition.

IMPROVEMENT OF POST-ISCHEMIC MYOCARDIAL METABOLISM AND FUNCTION BY INOSINE IN 31P-MRS STUDY.
Minoru Yoshiyama, Hirozumi Sakai, Masakazu Teragaki, Kazuhide Takeuchi, Tadanao Takeda. Osaka City University, Mari Ikata, Makoto Ishikawa, Iwao Miura. Otsuka Pharmaceutical co. ltd., Tokushima, Japan.

Perfused guinea-pig hearts, which were analyzed, by 31P-MRS, were subjected to 30 and 60 minute ischemia and reperfused using two perfusates, one containing 200 μM inosine, and the other without inosine (Control). Inosine, hypoxanthine, xanthine, and uric acid were detected in the coronary effluents of post-ischemic hearts by HPLC, however, adenosine was not found.

ATP

| Reperfusion | | 5 minutes | 1 hour | 4 hours |
|---|---|---|---|---|
| A | Control | 63.3±3.3% | 69.0±4.2% | 72.2±1.8% |
| | Inosine | 63.1±3.2% | 73.7±1.7% | 95.5±3.1%* |
| B | Control | 41.1±4.7% | 45.7±4.9% | 46.9±4.9% |
| | Inosine | 43.0±2.1% | 54.1±3.6% | 73.4±3.8%* |

(Preischemic value=100%) (*:p<0.01)

Left Ventricular Maximal Positive dp/dt

| Reperfusion | | 20 minutes | 1 hour | 4 hours |
|---|---|---|---|---|
| A | Control | 100.0±2.7% | 84.4±2.4% | 78.8±5.9% |
| | Inosine | 102.8±7.4% | 90.0±3.7% | 81.8±4.7% |
| B | Control | 95.7±9.2% | 77.6±6.5% | 51.1±4.7% |
| | Inosine | 93.7±3.5% | 76.8±7.3% | 80.9±7.3%* |

(A:30 minute ischemia, B:60 minute ischemia)

Administration of inosine was very useful for increasing myocardial gross energy product and improving cardiac function.

POSSIBLE DIFFERENCE OF METABOLICAL CONDITION IN PATIENTS WITH DILATED CARDIOMYOPATHY AND SEVERE CORONARY ARTERY DISEASE: EVALUATION BY POSITRON EMISSION TOMOGRAPHY.
Tetsuro Fudo, M.D., Hirofumi Kambara M.D., F.A.C.C., Masataka Hayashi M.D., Tetsuo Hashimoto, M.D., Ryuji Nohara M.D., Nagara Tamaki M.D., Keiji Yamashita M.D., Junji Konishi M.D., Chuichi Kawai M.D., F.A.C.C., Kyoto University, Kyoto, Japan.

To examine the alteration of metabolism and perfusion in patients with dilated cardiomyopathy (DCM) and severe coronary artery disease (CAD), positron emission tomography (PET) was performed with N-13 ammonia and F-18 deoxyglucose as an indicator of blood flow and exogenous glucose utilization, respectively. Eighteen patients with DCM and 20 patients with CAD, who had multivessel disease and reduced left ventricular ejection fraction (≤40%), were selected for the study. Discrete perfusion defects were observed in 19 of 20 patients with CAD, whereas DCM showed imhomogenous distribution of flow tracer and only 3 discrete perfusion defects ($p<0.01$). In CAD, FDG imaging showed increased uptake in hypoperfused area ("mismatch") in 14 of 20, and concordant decrease in 5. On the other hand, in DCM, concordant increase of F-18 deoxyglucose and N-13 ammonia was observed in 10 of 18 patients. The remaining 8 showed increased F-18 deoxyglucose uptake with normal $NH_3$ distribution (6: lateral, 2: anteroseptal), suggesting the regional alterations of metabolism with no relation to myocardial blood flow. Thus, PET findings with N-13 ammonia and FDG shows different metabolical and flow pattern between DCM and CAD and would give us new insights into the pathophysiology of the two disease entities.

VALIDATION OF A TRACER ANALOGUE METHOD FOR THE ASSESSMENT OF GLUCOSE METABOLISM IN ISOLATED WORKING RAT HEART.
Van T.B. Nguyen B.A., Donna Shaffer, Heinrich Taegtmeyer, M.D., D. Phil., F.A.C.C., University of Texas Medical School at Houston, Houston, Texas.

In order to assess whether the tracer analogs, 2-deoxy-D-glucose (2-DG) and 2-fluoro-2-deoxy-D-glucose (2-FDG) are valid markers of glucose metabolism, we perfused working rat hearts for specified time periods and at different work loads (WL) with either 2-DG or 2-FDG. To determine the time dependence of tracer accumulation, hearts were perfused for 30' or 90' at intermediate WL (10 mM glucose) with 2-DG. To determine the work dependence of tracer accumulation, hearts were perfused for 60' at either low or high WL (5 mM glucose) with 2-DG. Rates of glucose utilization were 365, 813 and 965 (umol/hr/g dry) for low, intermediate and high WL, respectively and correlated well with the accumulation of radioactivity in the tissue. Concentrations of intracellular free and phosphorylated tracer were also measured. Although 2-DG accumulated as a function of perfusion time and work load, the percent of nonphosphorylated tracer remained constant (12±2%). To determine the uptake and retention of 2-FDG, hearts were perfused at intermediate WL (10 mM glucose) with 2-FDG for 60' followed by a 40' washout period with non-radioactive perfusate. 2-FDG activity in the heart rose linearly with time. Conclusions: 2-DG and 2-FDG appear to be valid markers of glucose metabolism. Superior temporal resolution resulting from external detection of 2-FDG permits more accurate assessment of changes in glucose uptake induced by metabolic perturbations. In contrast to previous observations, there was a detectable pool of intracellular, non-phosphorylated 2-DG supporting the countertransport (k2) process across the sarcolemmal membrane.

## Tuesday, March 21, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 11:00AM–12:00NOON
## Pacific Room, Anaheim Convention Center
## Hypertension

HIGH DOSE DIPYRIDAMOLE-ECHOCARDIOGRAPHY TEST IN HYPERTENSIVES: CORRELATION WITH EXERCISE-ELECTROCARDIOGRAPHY TEST AND CORONARY ARTERIOGRAPHY.
Alessandra R. Lucarini, MD, Eugenio Picano, MD, Fabio Lattanzi, MD, Antonio Salvetti, MD, Alessandro Distante, MD. University of Pisa, Pisa, Italy.

The value of exercise-electrocardiography test (EET) in the detection of coronary artery disease (CAD) in hypertensives is limited. Recently, the high-dose dipyridamole-echocardiography test (DET: 2-D echo monitoring during i.v. dipyridamole infusion, up to 0.84 mg/Kg over 10') has been proposed as an alternative to exercise for the diagnosis of CAD. In order to establish the relative diagnostic usefulness of EET and DET for the detection of CAD, the 2 tests were performed in 114 consecutive hypertensive pts evaluated for chest pain syndrome. Of these 114, 41 had echocardiographic evidence of LV hypertrophy; 22 had ST segment and T wave changes on resting ECG; 40 had a previous myocardial infarction. Positivity of DET was based on detection of a transient asynergy of contraction, absent or of a lesser degree in resting conditions; an EET (by upright cycloergometer) was considered positive in case of ST segment shift >0.1 mVolt, 0.08 sec. after the J point. Coronary angiography showed significant CAD (>70% diameter reduction of at least 1 major coronary vessel) in 84 pts. (* = $p<0.05$)

| | EET | | DET |
|---|---|---|---|
| Sensitivity | 68% | | 77% |
| Specificity | 52% | * | 90% |
| Accuracy | 62% | * | 79% |
| Predictive value of a positive test | 79% | * | 96% |
| Predictive value of a negative test | 34% | * | 58% |

Thus, DET appears to be of greater diagnostic value than EET for non-invasive detection of CAD in hypertensives with chest pain.

COUPLING OF LEFT VENTRICULAR LOAD AND HYPERTROPHY IN HYPERTENSION.

Antonello Ganau, M.D., Mary J. Roman, M.D., Thomas G. Pickering, M.D., Ph.D., Peter L. Schnall, M.D., Richard B. Devereux, M.D., FACC. Cornell Medical College, New York, N.Y.

The weak relation of systolic blood pressure (SBP) to LV mass in hypertensive pts suggests a mismatch between pressure load and muscle growth. To analyze this discrepancy we studied 50 untreated H and 50 normal adults by independently read M-mode and 2-D echocardiograms. Theoretical optimal LV mass (LVMt) was calculated as a function of SBP and M-mode LV diastolic diameter, to allow each subject to achieve a constant normal peak LV wall stress; 2-D echo was used to calculate LV end-diastolic volume (EDV) and stroke volume (SV); the end-systolic stress/volume index ratio (ESS/ESVI) was calculated from M-mode measurements and SBP as an index of contractile performance; and observed LV mass was measured by the Penn method. In spite of the adequacy by design of LVMt to hemodynamic load, relation of SBP to LVMt was not close ($r=.46$; $p<0.001$), and was similar to that with observed LV mass ($r=.45$; $p<.001$). On the other hand, LVMt was more closely related to 2-D echo LVEDV ($r=.72$; $p<.001$). Observed LV mass was more closely related to SV ($r=0.60$, $p<0.001$) and ESS/ESVI ($r=-0.48$, $p<0.001$) than to SBP; all 3 contributed independently ($p<0.001$) to prediction of LV mass (multiple $R=0.81$, $p<0.0001$). Multiple regression equation showed equivalence of 10ml of LV volumes and 10mmHg of SBP in inducing a change of about 20g in LVMt.

Thus, the lack of close relation of SBP to LV mass is due to concomitant effects of LV chamber size on optimal LV load-mass coupling, rather than reflecting the effect of non-hemodynamic factors; chamber size in turn is determined by both LVSV and contractile performance.

COMPARISON OF PHARMACOLOGICAL AND NONPHARMACOLOGICAL TREATMENT OF HYPERTENSION. A RANDOMIZED PLACEBO CONTROLLED STUDY.

John B. Kostis, M.D., F.A.C.C., Raymond Rosen, Ph.D. Lynn S. Taska, B.A., Alan K. Tannenbaum, M.D., Liz Brondolo, M.S., Delia Smith, M.S., UMDNJ-Robert Wood Johnson Medical School, New Brunswick, New Jersey.

Although it is known that nonpharmacological therapy (NP) is effective in lowering blood pressure in some patients, well-controlled studies comparing this therapy with pharmacological treatment are not available.

In a randomized placebo controlled study 86 male patients age 57.1±8.9 with mild hypertension (DBP 95-105 mm Hg) were randomly assigned to NP (n=34) and double blind pharmacological therapy (n=52) consisting of 3 months administration of propranolol titrated to 80 mg bid in a randomized cross-over design.

Nonpharmacological therapy consisting of dietary modification (calorie, sodium, alcohol), exercise training and stress management resulted in blood pressure reduction (-12.7/-7.4 mm Hg) similar to PR (-8.2/-7.0 mm Hg) monotherapy and significantly more pronounced than placebo (-4.5/+0.2 mm Hg) ($p=0.0001$). NP, however, was associated with a greater improvement ($p=0.005$) in exercise tolerance (+1.2±1.4 METS) than PR (0.0±1.1 METS) or PL (+0.3±1.4 METS). In addition, NP decreased LDL cholesterol (-10.8±19.3), triglycerides (-35.6±65.6) and body weight (-13.4±10.9) while PR increased these variables (+5.0±29.0,+11.5±70.0,+1.2±5.5, $p=0.0001$). Conversely, HDL increased on NP (+1.9±6.3) and decreased on PR (-0.1±7.9).

The data of this randomized trial indicate that appropriately structured NP is superior to propranolol monotherapy in treating mild hypertension.

TREATMENT OF HYPERTENSION ALTERS THE RELATIONSHIP BETWEEN PLATELET CALCIUM AND SENSITIVITY TO AGGREGATORY AGENTS.

J.Wilson MB, M.W Baig MB, A.D Lees, M.A Orchard PhD, E.J Perrins MD FACC, J.A Davies MD, and C.R.M Prentice MD. Univ.Dept Medicine,The General Infirmary,Leeds,Engl.UK

Previous investigators have reported that platelet intracellular calcium ([Ca2+]i and platelet aggregation are increased in hypertension. In a study with severely hypertensive patients, we have investigated the relationship between these two platelet parameters and have compared the effect of two different dihydropyridine calcium antagonists. 10 patients, whose blood pressures were poorly controlled with metoprolol, were blindly randomized to receive either nifedipine (Nif.) or felodipine (Fel.) as second line agents.At each treatment phase, venous blood samples were collected for whole blood aggregation to ADP and collagen and measurement of [Ca2+]i using fura 2. Dose response curves to ADP and collagen were constructed and the concentrations required to produce 70% aggregation (ED70) calculated. Control of blood pressure induced a decrease (Wilcoxon, $p<0.05$) in median [Ca2+]i from 122 to 81 nM with Nif. and from 112 to 67 nM with Fel. such that after treatment, [Ca2+]i for both groups was within 2 standard deviations of the mean value obtained from 14 normotensive subjects. Overall [Ca2+]i correlated with mean blood pressure ($r=0.45$, $p<0.03$). Neither Nif. nor Fel. affected the ED70 to collagen, but Fel. selectively desensitized the platelets to ADP such that ED70 to ADP increased from a mean(sd) of 2.0 (1.4)uM to 4.7 (2.2)uM, $p<0.05$. These results confirm that effective treatment of hypertension significantly reduces [Ca2+]i into the normotensive range but question whether an elevation in basal [Ca2+]i modulates the sensitivity of platelets to aggregatory agents.

PROGNOSIS OF OBESITY-RELATED HYPERTENSION: FRAMINGHAM STUDY

William B. Kannel M.D., Robert J. Garrison M.S., Tingjie Zhang M.D., Boston University Medical Center, Boston, Massachusetts and National Heart, Lung and Blood Institute, Bethesda, Maryland

It has been claimed that obesity-related hypertension is relatively innocuous. To explore this, cardiovascular events over 32 years were examined in relation to biennial weights and blood pressures using time-dependent covariate proportional hazards analysis. Participants were also classified by age, cigarette smoking and antihypertensive treatment at each of four baseline exams, with 8 year follow-up. Age and smoking-adjusted risks of cardiovascular events were uniformly high in hypertensives of all ages when subjects with prior cardiovascular disease were excluded at baseline.

Risk of CV Events by Hypertensive and Obesity Status

CV Risk Ratios (Def. HBP/Normal)

| | 35-64 | | 65-94 | |
|---|---|---|---|---|
| Obesity Status | MEN | WOMEN | MEN | WOMEN |
| Lean (<112 MRW) | 2.7 | 2.6 | 3.8 | 1.8 |
| Obese (>126 MRW) | 2.6 | 3.9 | 2.6 | 2.4 |

Hypertension is dangerous in both lean and obese. Only when diagnosed cardiovascular disease at baseline is included do leaner persons appear to have a higher hypertension-associated relative risk (1.7 vs. 1.1).

VENTRICULAR ARRHTYHMIAS IN PATIENTS WITH ESSENTIAL HYPERTENSION

Vasilios Papademetriou M.D., F.A.C.C., Aldo Notargiacomo, M.S., Donald Heine M.D., Ross Fletcher M.D., F.A.C.C., Edward Freis M.D., F.A.C.C. Georgetown University and VA Medical Center, Washington, D.C.

Left ventricular hypertrophy (LVH) has been identified as a bad prognostic indicator in patients (pts) with essential hypertension (HTN). Previous studies indicated an increased incidence of arrhytmias in pts with LVH. In this study the relationship of the degree of LVH with the severity of ventricular arrhythmias was assessed in 55 black pts (age 56±10 years) with uncomplicated HTN. After discontinuing medications for 3 weeks all Pts had a 48-hr holter monitoring, an echocardiogram, an ECG and routine blood work. Of these pts 33 had LVH by echo and 22 did not. In these two groups results were as follows:

| | LVPW | LVS | LVM | PVC/hr | COUPL/48hr | VT/48hr |
|---|---|---|---|---|---|---|
| LVH | 14.7 | 15.5 | 371 | 14.4 | 3.97 | 0.30 |
| NoLVH | 10.8* | 10.9* | 229* | 2.7** | 0.27** | 0.09*** |

*=p<0.001, **=p<0.08, ***=p<0.05

Of the same 55 pts, 28 had evidence of LVH on the ECG's. However, ECG LVH was not associated with higher incidence of arrhythmias. Linear regression analysis revealed no correlation at all of any arrhythmia type and any of the echo parameters, or with ECG LVH, age, body weight, plasma potassium, or resting blood pressure. We conclude that in these Pts: 1) echocardiographic LVH predicts arrhythmias better than ECG LVH; 2) there is no close association between the degree of LVH and severity or frequency of arrhythmias and 3) it appears that other variables contribute to arrhythmogenicity in these pts.

INCIDENCE OF SERIOUS VENTRICULAR ARRHYTHMIAS DURING SURGERY IN HYPERTENSIVES WITH LEFT VENTRICULAR HYPERTROPHY.

Jadwiga Szlachcic, M.D., Martin London, M.D., Julio F. Tubau, M.D., Brian O'Kelly, M.D., Dennis Mangano, Ph.D., M.D. VAMC and University of California, San Francisco,CA

Hypertensives (HTN) with left ventricular hypertrophy (LVH) are at increased risk for sudden death and are known to have higher incidence of ventricular arrhythmias (VA). To assess whether this electrical instability is further enhanced by the presence of myocardial ischemia (I), we studied the incidence of VA, >30 PVCs/hour or VT( ≥4beats) during non cardiac surgery in a cohort of HTN patients (PTS) with or without LVH. All subjects had known or were at high risk for CAD(>2 risk factors) but had no previous myocardial infarction. I by transesophageal echocardiography was defined as the development of new segmental wall motion abnormalities and by continuous ambulatory ECG monitoring using bipolar leads CC5, CM5 or ML and defined as an ST segment depressed > 1mm compared to the preceding baseline lasting at least 1 minute.

| | >30 PVCs/hour | VT | ISCHEMIA |
|---|---|---|---|
| LVH (n=17) | 8/17(47%) | 6/17(35%) | 10/17(58%) |
| noLVH(n=17) | 5/17(29%) | 2/17(12%) | 10/17(58%) |

The presence of either ischemia or LVH were good predictors for the development of VA. PTS with both LVH and ischemia had the highest incidence of VA (6/10 60%) and of VT (5/10 50%). Thus, PTS with HTN and LVH are at high risk for developing severe VA during stressful conditions and the presence of ischemia further enhances their electrical instability.

MICROPROTEINURIA - AN EARLY MARKER FOR TARGET ORGAN DAMAGE IN ESSENTIAL HYPERTENSION

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Dept. of Medicine and Gynecology, Univ. of Bonn, FRG

The heart and the kidneys are primary target organs of hypertensive disease. Whereas left ventricular hypertrophy (LVH) indicates the onset of hypertensive heart disease, similar markers for hypertensive nephropathy are missing. To investigate the clinical importance of microproteinuria, we examined the prevalence of microproteinuria and its relation to cardiac structural adaptation in 80 male, middle-aged patients with essential hypertension. Patients with secondary causes of hypertension were ruled out.

14 out of 80 hypertensives (18 percent) were found to have microproteinuria defined as "negative" for urinary protein excretion in the conventional test, but "positive" (above the upper normal limit) in the 24-hour urine samples. Patients with microproteinuria had a similar age and body weight, but a higher systolic and diastolic pressure (161 ± 14/104 ± 12 vs 148 ± 14/97 ± 9 mmHg, $p < 0.01$) than those with normal protein excretion. Also, hypertensives with microproteinuria had a greater left ventricular mass (241 ± 57 vs 207 ± 45 g, $p < 0.05$) and greater cross sectional area (22.2 ± 2.8 vs 20.5 ± 2.9 $cm^2$, $p < 0.02$) evaluated by 2-D guided M-mode echocardiography than the control group. A positive Sokolow-index was more prevalent in patients with microproteinuria than in those without ($x^2 = 6.2$, $p < 0.02$).

Patients with essential hypertension and microproteinuria (prevalence 18 per cent) were characterized by a higher arterial pressure, by a higher degree of echocardiographic and electrographic evidence of LVH. Thus, microproteinuria might serve as a marker for early target organ damage in essential hypertension.

RISK OF VENTRICULAR ARRHYTHMIAS ACCORDING TO ANATOMICAL CATEGORIES OF LEFT VENTRICULAR HYPERTROPHY

Joanne M. Murabito M.D., Daniel Levy M.D., F.A.C.C., Keaven M. Anderson Ph.D., Jane C. Christiansen M.P.H., William P. Castelli M.D., William B. Kannel M.D., F.A.C.C. Framingham Heart Study, Framingham, MA.

The Framingham Study recently reported a powerful association between left ventricular hypertrophy (LVH) determined by echocardiography (echo) and risk for ventricular arrhythmias (VA). We studied risk for VA on 1-hour Holter recordings in 843 subjects with echo LVH. Subjects were stratified according to presence of LV dilatation and/or increased LV wall thickness. Age adjusted rates of complex-or-frequent VA are shown below according to LVH anatomical grouping.

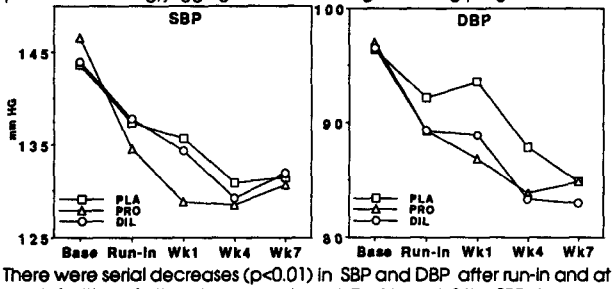
| | LV WALL THICKNESS | | | |
|---|---|---|---|---|
| | NOT THICKENED | | THICKENED | |
| | MEN | WOMEN | MEN | WOMEN |
| NONDILATED | 10.4% N=73 | 15.2% N=63 | 15.2% N=154 | 13.8% N=307 |
| DILATED | 31.2% N=83 | 17.4% N=63 | 49.0% N=31 | 11.9% N=69 |

In men LV dilatation confers increased risk for arrhythmias ($P<0.001$), while increased wall thickness does not. These findings were not observed in women.

EXERCISE TRAINING VERSUS EXERCISE TRAINING WITH DILTIAZEM OR PROPRANOLOL: EFFECTS ON RESTING BLOOD PRESSURE IN MEN WITH MILD HYPERTENSION

Kerry J. Stewart Ed.D., Mark B. Effron M.D., F.A.C.C., Stephen A. Valenti M.D., F.A.C.C., and Michael H. Kelemen M.D., F.A.C.C. Johns Hopkins School of Medicine, Baltimore, Maryland.

To determine whether exercise combined with drug therapy provides additive benefits in BP control compared with exercise and placebo, 52 sedentary men, ages 25-59, with DBP of 90 to 105 off drugs, and negative stress tests, were randomized in a double blind manner to diltiazem SR(DIL), propranolol (PRO), or placebo (PLA). Supine resting BP after a 4 week single blind placebo period, after 2 weeks of drug run-in, and at weeks 1, 4, and 7 of intense exercise training are shown below. During run-in daily doses were increased to 240 mg PRO and 360 mg DIL. 51 patients (DIL n=17, PLA n=19, PRO n=15) completed the 1 hour, 3 times per week walking/jogging and circuit weight training program.




There were serial decreases ($p<0.01$) in SBP and DBP after run-in and at week 4 with no further decrease at week 7. At week 1 the SBP decrease from baseline was greater for exercise with PRO versus exercise with DIL or PLA ($p<0.05$). The DBP decrease at week 1 was greater for DIL and PRO groups versus PLA ($p<0.05$). No between group differences were seen in BP decreases at weeks 4 and 7. Thus, there was more immediate BP control with exercise combined with active drug. However, exercise and placebo was as effective for BP control after 4 weeks of training.

## Tuesday, March 21, 1989
## 4:00PM–5:30PM, Anaheim Room
## Anaheim Convention Center
## Coronary Artery Stents

CHRONIC ENDOVASCULAR RESPONSES AFTER STENT IMPLANTATION IN VEIN GRAFTS

Martin B. Leon M.D., F.A.C.C., Renu Virmani M.D., F.A.C.C., Steven D. Lenhard, Yaron Almagor M.D., Antonio L. Bartorelli M.D., Louis G. Prevosti M.D. NHLBI, Bethesda, MD.

Although balloon expandable stents (S) may reduce restenosis after PTCA, the chronic effects of S in arterialized vein grafts (VG) are unknown. We implanted 13 slotted tubular steel S on balloon catheters (4-8 mm) in 13 femoral interposition VG (8 months after insertion) in 11 sheep and analyzed angiography, light, transmission, and scanning electron microscopy at 3 wks, 8 wks, and 5 mos. Prior to S deployment, the VG were either normal in size (n=5) or contained regions of aneurysmal dilatation (n=8). **Results:** 1) In 5 S placements without dextran treatment, large angiographic thrombi were present acutely in 3 (60%). By 3 wks, 1 of these VG was occluded and another had residual thrombus. In contrast, no dextran treated VG (n=8) had angiographic evidence of thrombus formation. 2) In normal VG, endothelialization (E) over S progressed from proximal to distal S segments and was completed by 8 wks. There were remnants of organizing microthrombi beneath E, and platelets with fibrin were seen over S with partial E. 3) S placed in aneurysmal VG manifested delayed or absent E in regions of poor S-vessel wall contact and more extensive thrombi were found in the S-vessel wall space. E over organized thrombi was seen at 5 mos only in aneurysmal VG with closer S-vessel wall spaces. 4) By 5 mos, VG media showed reduced smooth muscle cell density with replacement fibrosis. 5)Neo-intima thickness over S averaged 140 μm at 3 wks, 280 μm at 8 wks, and 130 μm at 5 mos. **We Conclude** that S placement in VG 1) requires dextran treatment to prevent early thombosis, 2) manifests delayed or absent E in areas of poor S-vessel wall contact, and 3) results in modified transmural VG architecture including an overlying neointima which becomes thinner with time and media which is replaced by fibro-collagenous tissue. Thus, chronic in vivo responses to S implantation in VG are favorable, but close S-vessel wall contact in aneurysmal segments is fundamental to ensure proper E.

THE SELF-EXPANDING PARALLEL WIRE METALLIC STENT.

Raoul Bonan, M.D., F.A.C.C., Krishna Bhat, M.D., Tack Ki Leung, M.D., Jules Lam, M.D., F.A.C.C., Lise Lemarbre, M.D., Rod Wolff, B.S., Montreal Heart Institute, Montreal, Canada.

Parallel wire stents were implanted over exchange guide wires at PTCA sites in 7 canine circumflex coronary arteries dilated with slightly oversized balloons. Stents are stainless steel, self-expandable, 3.5 to 4.0 mm in diameter, 9 to 12 mm in length and are made of 10 wires longitudinally laser welded in a zig-zag design. The compressible stent is delivered by the withdrawal of a Teflon outer catheter (4.5 to 5F) and the push of a polyethylene inner catheter. Aspirin 90 mg/day was given from the day prior to, and heparin (150 U/kg) during implantation. Pathologic and quantitative angiographic studies were performed immediately and at 2, 5 and 12 wks post-implantation. During a mean of 5.2 wks of follow-up the coronary arteriographic diameter at the stent site remained unaltered: 3.40±0.08 vs 3.60±0.06 mm (p =NS), with no stent displacement. At microscopy the wires were oriented perfectly, compressed the media, and by 2 weeks were covered by mucopolysaccharide ground substance, myofibroblasts and an almost complete monolayer of neoendothelial cells. Scanning electron microscopy showed these cells to be large, immature, ovoid and oriented with the blood flow. At 5 wks the monolayer was complete with tight intercellular junctions.

This study demonstrates that a self-expanding parallel wire stent can easily be implanted with this new delivery system. Although it is short, it has good stability, tolerability, patency and low thrombogenicity 3 months post-implantation. The perfect imbedding with mild neointimal proliferation and a complete monolayer covering offers promise for potential human application.

*Balloon Expandable Intravascular Stents (BEIS) in Human Coronary Arteries: A Follow-Up Report*

*Richard A. Schatz, MD, FACC, Julio C. Palmaz, MD, Ian M. Penn, MB,FRACP, Sally L. Levine, RN, Arizona Heart Institute Foundation, Phoenix, AZ.*

*Early reports of BEIS in coronary arteries showed high short-term patency rates. Follow-up in this series now includes 28 successfully delivered stents (20 rigid, 8 "flexible") in 18 patients. Twenty-four were placed in the right coronary artery (RCA) and 4 in the left anterior descending (LAD). The patients were pretreated with aspirin, persantine and calcium channel blockers before stenting and three months after stenting, and heparin and dextran during the procedure. Percent stenosis decreased from 94% to 0 while gradients were reduced from 54 to 3mmHg. Only one patient was discharged on warfarin for 30 days for suspected nonocclusive thrombus within the stent. There was no abrupt closure in this group, nor were there any complications. Clinically, in 17 patients and angiographically in one patient, there was no restenosis in follow-up (range 1-9 months, mean 3 months). Four rigid stents in four patients could not be delivered to the target site as a result of inflexibility. There were no complications in the group of patients that received the "flexible" stent design.*

*We conclude that when successfully delivered, BEIS are relatively nonthrombogenic and high patency rates can be expected short-term. Although delivery failure is a potential problem with the original rigid prototype, this appears to be resolved with the new "flexible" version. Whether or not BEIS will decrease long-term restenosis rates following PTCA remains to be seen.*

## STENT IMPLANTATION FOR THE TREATMENT OF CORONARY ARTERY BYPASS GRAFT STENOSIS

Patrick W. Serruys, M.D., F.A.C.C. Kevin J. Beatt M.R.C.P, Pim J. de Feyter M.D, Harry Suryapranata M.D, Marcel van den Brand M.D, Rene Geuskens M.D.
Thoraxcentre, Erasmus University, Rotterdam, The Netherlands.

The long term success of balloon angioplasty in coronary artery bypass grafts is limited by the high recurrence rate of the initial stenosis.
18 self-expanding intravascular stents were implanted in 11 patients following balloon dilatation of a coronary artery bypass graft stenosis, and the immediate results assessed by quantitative coronary angiography.

The mean age of the group was 61.1 (43-75) years and the age of the bypass graft 90.2 (2-128) months. In 10 patients the procedure was elective as a measure to prevent restenosis and in one the stent was implanted following dissection and the dislocation of atheteromatous material in order to improve the immediate hemodynamic result, and so avoid or delay the need for bypass surgery. The mean unconstrained diameter of the stent was 4.1 (3.5-5.0) mm, implanted into grafts with a mean diameter of 3.3 (2.1-4.7) mm. The implantation was proximal in 6 cases and in the middle of the bypass graft in 7 cases. In 5 cases the implanted position was in the distal portion either prior to or distal to the first jump and in two patients the device was positioned so as to involve the distal anastomosis; one straddling an end-to-side anastomosis and one a side-to-side anastomosis. The minimal lumen diameter was 1.4 (0.9-2.2) mm pre-PTCA, 2.0 (1.4-2.7) mm post-PTCA and 2.6 (2.1-3.20) mm post-stent implantation.

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So far there have been more than 36 stents implanted into the coronary artery vein grafts in five centers in Europe. This has been achieved without technical difficulty or procedure related complication, and the implanted device appears to further improve the hemodynamic result. Detailed follow-up studies are needed to determine how effective this device will be an in the long term treatment for coronary bypass stenosis.

## IMPLANTATION OF 100 CORONARY ARTERY STENTS: LEARNING CURVE FOR THE INCIDENCE OF ACUTE EARLY COMPLICATIONS.

Ulrich Sigwart M.D. F.A.C.C., Philip Urban M.D., Hossein Sadeghi M.D., Lukas Kappenberger M.D. CHUV, Lausanne, Switzerland.

Between april 86 and august 88, 100 coronary self-expanding mesh stents were implanted in 78 patients during 85 procedures. The indications were abrupt post-angioplasty occlusion (20 stents) and prevention of restenosis or recurrent restenosis (80 stents). In 72 procedures 1 stent was implanted, in 11 procedures 2 stents and in 2 procedures 3 stents. For the first 50 stents (unconstrained diameter 3.5 ± 0.5 mm, implanted length 17.9 ± 3.3 mm), the incidence of in-hospital thrombotic stent occlusion was 7/45 procedures (16%). Of these, 5 (71%) were treated by angioplasty and/or intracoronary thrombolysis and patency was restored in all cases. 3 of the 7 patients had an enzyme rise and 2 developped new Q waves on their ECG. 2 patients had emergency CABG and there was 1 post-operative death. For the last 50 stents (diameter 4.1 ± 0.8 mm, length 22.6 ± 3.4 mm), only 1 of 40 procedures (3%) was complicated by temporary stent occlusion and patency was restored with angioplasty and thrombolysis. There was a rise in cardiac enzymes, but no new Q wave developed on the ECG. No patient died or required emergency CABG.
Early thrombotic stent occlusion has become less frequent with the use of longer and larger stents, together with increased experience in patient selection, implantation technique and post-implant medication. Patency can be reliably restored in most cases of thrombotic occlusion with a combination of intracoronary thrombolysis and balloon angioplasty.

## RESTENOSIS WITHIN CORONARY STENTS: POSSIBLE EFFECT OF PREVIOUS ANGIOPLASTY.

Philip Urban M.D., Ulrich Sigwart M.D. F.A.C.C., Urs Kaufmann M.D., Lukas Kappenberger M.D., CHUV, Lausanne, Switzerland.

During a 29 months period, 104 self-expanding mesh coronary stents were implanted during 87 procedures in 80 patients. Until now, 53 (61%) procedures have been controlled angiographically after a median follow-up of 5 months (range 2 to 27 months). These 53 procedures were aimed either at a primary lesion (12 cases of abrupt post-angioplasty closure + 7 elective procedures), or at a restenotic lesion after prior balloon angioplasty (34 elective procedures).
Restenosis within the stented segment(s) was observed in 5 cases (9%) and late total occlusion in 4 cases (8%). Considering subgroups, there was 1 case of late stent occlusion after 19 procedures for primary lesions (5%) and 8 cases of restenosis or occlusion for 34 procedures on a res enotic lesion (24%). For restenotic lesions, within-stent restenosis or occlusion were observed more often when the delay between previous angioplasty and stent implantation was $\leq$ 3 months (7/17 = 41%) than > 3 months (1/17 = 6%), $p<0.05$.

These preliminary data would seem to suggest that elective stenting for restenosis early after previous angioplasty carries an increased risk of restenosis within the stent. It could be that the active fibrocellular proliferation associated with the early phase of restenosis after balloon angioplasty is further stimulated by stent implantation.

# Tuesday, March 21, 1989
# 2:00PM–3:30PM, California Pavilion D
# Anaheim Hilton Hotel
# Coronary and Peripheral Arterial Athrectomy

## Clinical follow-up in 40 patients treated with peripheral percutaneous atherectomy

A. von Pölnitz M.D., D. Backa B.S., B. Höfling M.D., J.B. Simpson M.D.
Med. Klinik I, Klinikum Großhadern, Ludwig-Maximilians-Universität, Munich, W. Germany

40 patients with a total of 72 stenoses (the majority complicated: 40.3% calcified, 26.4% totally occluded, 25% concentric and 48.6% eccentric) of the superficial femoral (n=62), popliteal (n=5) and iliac (n=5) arteries underwent atherectomy with the Simpson catheter on 45 limbs. There was technical success in 91% of stenoses. The mean stenosis was reduced from 87.2 ± 13.9% to 16.6 ± 15.5%; at 6 month angiographic follow-up 35.7 ± 30.9 % (n=43) with angiographic re-stenosis (>70%) found in 9 stenoses (21%), coincident with clinical deterioration in 8/9 cases.

| | Doppler index | Walking distance (meters) |
|---|---|---|
| pre- | 0.57 n=45 | 80.47 ± 65.74 n=40 |
| post- | 0.81 n=45 | 152.80 ± 80.27 n=40 |
| 3 mo. | 0.80 n=35 | 165.27 ± 81.62 n=30 |
| 6 mo. | 0.78 n=27 | 169.33 ± 80.64 n=25 |
| 12 mo. | 0.77 n=17 | 166.22 ± 99.01 n=15 |
| 18 mo. | 0.74 n=11 | 148.50 ± 127.38 n=9 |
| 24 mo. | 0.76 n=7 | 135.33 ± 110.21 n=5 |

7 patients (3 with baseline total occlusions) have undergone repeat atherectomy and 2 patients surgical bypass procedures at 6.3 ± 1.8 months after initial treatment.
Conclusion: Doppler index and walking distance showed a good correlation with angiographic results. The majority of patients (84%) treated by atherectomy required only one procedure in follow-up up to 2 years.

**The Acute Outcome of Atherectomy in Peripheral Arterial Obstructive Disease**

Gerald Dorros M.D. F.A.C.C. Naveen Sachdev, M.D., Ruben Lewin, M.D., Lynne Mathiak, R.N., St. Luke's Medical Center, Milwaukee, WI

Between 10/87 and 7/88, 107 patients (pts), mean age 63 ± 9 years, underwent peripheral atherectomy with the Simpson Atherocath due to claudication (86%), gangrene (4.6%), rest pain (5.6%) or non-healing ulcers (3.7%). Peripheral atherectomy was successful in 104/107 (97%) stenoses (3/6 iliac, 70/70 femoral, 27/27 popliteal, and 4/4 tibial arteries), and 42/42 occlusions (3/3 iliac, 38/38 femoral, 6/6 popliteal). Failures were due to too small a catheter (2), and a tortuous iliac vessel (1). Angiography before and after atherectomy confirmed that the lesions were successfully opened (stenoses: 86 ± 10% to 11 ± 14%; p<0.05; and occlusions: 100% to 16 ± 10%; p<0.05). A mean of 65 ± 41 passes were required to adequately remove sufficient plaque. Atherectomy was used in combination with angioplasty in 16/42 (34%) of occluded vessels. Complications included insignificant contrast extravasation in 7 (6.5%), distal embolization in 4 (3.7%), and groin hematoma in 2 pts (1.9%). Within 24 hours, 102/107 pts (95%) were improved and discharged clinically improved. Ankle-brachial indices significantly increased from 0.59 ± 0.13 before to 0.73 ± 0.18 after (p< 0.001). Thus peripheral atherectomy can be safely and efficaciously utilized to relieve arterial obstructions (stenoses and occlusions) with excellent angiographic and immediate clinical success, and a low incidence of complications.

**GREATER IMPROVEMENT IN CORONARY FLOW VELOCITY WITH ATHERECTOMY COMPARED TO ANGIOPLASTY**

N White Jr. M.D., S Denardo M.D., E Johnson M.D., P Yock M.D, FACC, V Hargrave B.S., P Hui, M.D., J Srebro M.D., M Selmon M.D., G Robertson M.D., B McAuley M.D.,FACC, T Hinohara M.D.,FACC, J Simpson M.D., FACC. University of California, San Francisco and Sequoia Hospital, Redwood City, California

We have previously validated a new Doppler catheter method for accurate assessment of flow restriction in a coronary stenosis based on the ratio of the velocity in the stenosis to the velocity in a normal proximal segment (the coronary stenosis velocity ratio, CSVR). In a canine model the CSVR predicted the true cross-sectional area (CSA) of the implanted stenoses with accuracy exceeding results of prior studies with quantitative angiography. A stenosis:proximal ratio 1:1 indicates no narrowing; larger ratios indicate formation of a stenosis jet, and correlate precisely with the ratio of stenosis to proximal CSA.

We compared CSVR in 5 patients undergoing PTCA with 5 patients undergoing coronary atherectomy (C-ATH). Pre-procedure all patients had CSVR indicative of a severe stenosis (CSVR greater than 5:1). Post-procedure, PTCA patients had a CSVR of 1.67:1 ±0.5 while C-ATH patients had a CSVR of 0.95:1±0.1 (p≤0.01). Post-procedure angiographic estimates of area corroborated the CSVR measurements, with less residual CSA for C-ATH versus PTCA.

**Conclusion:** CSVR, previously shown to be an accurate measurement of relative CSA, is useful in monitoring the success of catheter interventions. Based upon CSVR determinations, coronary atherectomy appears to be more effective than PTCA in completely removing obstruction to coronary flow.

PERCUTANEOUS CORONARY ATHERECTOMY: EARLY EXPERIENCES OF MULTICENTER TRIAL

Cass Pinkerton, MD, FACC; John Simpson, MD, FACC; Matthew Selmon, MD; Gregory Robertson, MD; Tomoaki Hinohara, MD, FACC; Jay Hollman, MD, FACC; Donald Baim, MD, FACC; St. Vincent Hospital, Indianapolis, IN.

To evaluate the efficacy and safety of percutaneous coronary atherectomy (PCA), a multicenter trial is currently underway. Since June 1988, PCAs were attempted in 80 lesions in 71 patients (pt) at 4 centers. Lesion distribution was as follows; left main (3%), left anterior descending (46%), right coronary (28%), left circumflex (2%) and vein graft (21%). The device was successfully placed in 94% of the lesions and tissue was removed in 98% of stenoses with median sample number of 9 (range 0-30). A successful result ( < 50% residual stenosis) was obtained in 68 lesions (success rate of 87%). Median stenosis was reduced from 90% to 10%. Eleven patients with failed PCA underwent attempted coronary balloon angioplasty (PTCA) with a success rate of 36%. Emergency bypass surgery was performed for acute occlusion in 4 patients (5%), 2 of which had recent thrombolytic therapy. Other complications included myocardial infarction in 3 pts (4%), angiographic evidence of distal embolization in 2 pts (3%), loss of small side branch in 5 pts (7%) and repair of femoral access site in 2 pts (3%). There were no perforations and no deaths. Conclusion: This multicenter trial confirms that PCA can be used to remove coronary atheroma with a high success rate and an occlusive complication rate similar to PTCA.

COMPARISON OF EARLY AND RECENT EXPERIENCE IN PERCUTANEOUS CORONARY ATHERECTOMY

John Simpson, MD, FACC; Tomoaki Hinohara, MD, FACC; Matthew Selmon, MD; Gregory Robertson, MD; Neil White, MD; Michael Rowe, MD; Lissa Braden, Sequoia Hospital, Redwood City, CA.

Percutaneous Coronary Atherectomy (PCA) is a new investigational procedure which is evolving rapidly in both equipment and operator's experience. This study compares our early and more recent experiences with PCA. Since October 1986, 83 patients (pts) underwent PCA. The pts were divided into two groups: Group A consists of initial 41 pts and Group B consists of the latest 42 pts. PCAs were performed between October 1986 and May 1988 in Group A and between May and August 1988 in Group B. The lesion distributions for groups A and B respectively were 16% and 8% for left main, 33% and 43% for the anterior descending, 21% and 27% for the right coronary, 7% and 0% for the circumflex and 23% and 22% for the vein grafts. Mean pre PCA stenosis was 89% in Group A and 84% in Group B. Results were as follows.

| | Group A | Group B | P Value |
|---|---|---|---|
| Lesions attempted | n= 44 | n= 49 | |
| Successful primary crossing | 66% | 92% | .005 |
| Successful placement | 86% | 94% | N.S. |
| Successful tissue removal | 68% | 94% | .005 |
| Specimens per lesions | 4.9 | 8.8 | .005 |
| Success rate ( 50% stenosis) | 52% | 90% | .001 |
| Post PCA stenosis | 22% | 12% | .003 |
| Emergency bypass surgery | 2% | 0% | |

In conclusion, comparison of early vs. recent experience reveals significantly improved outcomes of PCA, presumably due to advances in equipment and operator's experience.

CORONARY ATHERECTOMY FOR THE TREATMENT OF UNFAVORABLE PTCA LESIONS

Gregory Robertson, MD,; Tomoaki Hinohara, MD; Matthew Selmon, MD; John Simpson, MD, FACC; Sequoia Hospital, Redwood City, CA.

Despite an overall high primary success rate with percutaneous transluminal coronary angioplasty (PTCA), many lesions are not ideal for PTCA because of the higher complication rate and lower success rate. The newly developed procedure, percutaneous coronary atherectomy (PCA), is designed to overcome some of these limitations. Since March 1988, with availability of currently designed equipment, PCA was attempted in 48 lesions thought to be unfavorable for PTCA in 43 patients. The lesion characteristics were marked eccentricity (22), heavy calcification (14), ulceration (1), bifurcation lesions (1), aorto-ostial (6), ostial LAD (2), post-PTCA intimal flap (1), graft stenosis (15), markedly long lesions (1), and previously failed PTCA (5). Successful results, defined as <50% residual restenosis, were obtained in 38 lesions (79%). In 8 patients, PTCA was attempted following unsuccessful PCA crossing, with a success rate of 25%. Complications include PTCA related abrupt closure requiring emergency CABG (1), a coronary occlusion requiring surgery (1 pt), distal embolization (1 pt) and side branch occlusion (2 pt), and transient thrombosis resolving with lytic therapy (1 pt). In conclusion, early experience suggests that 1) PCA is a favorable approach for the treatment of selected unfavorable PTCA lesions, and 2) PTCA following failed PCA has a low success rate.

## Tuesday, March 21, 1989
## 4:00PM–5:30PM, California Pavilion D
## Anaheim Hilton Hotel
## Reperfusion Injury: Cases and Consequences

**PRESERVATION OF MYOCARDIAL FUNCTION AND TOPOGRAPHY BY LATE REPERFUSION AND SUPEROXIDE DISMUTASE THERAPY.**

**Bodh Jugdutt M.D., F.A.C.C., Shimin Wang M.D., Jack Demare, Terry Liu, John Henriksen, Mohammad Ibrahim M.B.B.S., Marc Poznansky Ph.D., University of Alberta, Edmonton, Canada.**

Salvage of ischemic myocardium and preservation of function by reperfusion (RP) within 2 hours is frequently not possible in the clinical setting. To determine whether late RP and therapy with the free-radical scavenger superoxide dismutase (SOD) after 2 hours of mid left anterior descending coronary artery ligation in instrumented dogs can preserve left ventricular function and topography, 24 dogs were randomized to permanent ligation (controls, C), RP and RP + SOD. SOD was given at the beginning of reperfusion (300,000 IU left atrial bolus and 300,000 IU by intravenous infusion over 2 hours). Infarct size relative to left ventricular mass and risk region (coronary arteriography), expansion index (ratio of infarct to non-infarct containing segment length) and left ventricular ejection fraction (LVEF by Simpson's rule on echocardiography) were measured at 5 days. Results (mean ± SD) were:

| | C(n=8) | RP(n=8) | RP+SOD(n=8) | |
|---|---|---|---|---|
| Infarct as %LV | 38±3 | 25±3 § | 12±1 | §,† |
| Infarct as % risk | 65±6 | 50±6 § | 25±2 | §,† |
| Expansion index | 2.52±0.29 | 1.74±0.21 § | 1.42±0.17 | §,† |
| LVEF (%) | 43±2 | 52±2 § | 58±2 | §,† |

§p<0.001 vs C; †p<0.01 vs RP (MANOVA)

Thus, RP and SOD after 2 hours coronary ligation can decrease infarct expansion and improve function more than RP alone. Late RP+SOD might prolong the period for salvage of ischemic myocardium, topography and function.

POST-ISCHEMIC OXYGEN RADICAL PRODUCTION DETECTED BY CHEMILUMINESCENCE VARIES WITH DURATION OF ISCHEMIA.

Timothy D. Henry M.D., Stephen L. Archer M.D., Daniel P. Nelson B.S., E. Kenneth Weir M.D.,F.A.C.C., Kamil Ugurbil Ph.D., Arthur H.L. From M.D., Minneapolis VAMC and University of Minnesota, Minneapolis, Minnesota.

Chemiluminescence (CL) is a sensitive continuous, indicator of oxygen radical generation. We have previously found CL decreases during ischemia and increases with reperfusion . We studied the effect of duration of ischemia on oxygen radical generation and mechanical dysfunction. CL was measured during 38°C global ischemic periods of 5, 11.5, or 40.8 + 4 min (10 min post ischemic contracture) and during a 20 min reperfusion period in three groups of five Langendorff perfused isovolumetric rat hearts. Lucigenin ($10^{-5}$M), a CL enhancer specific for $O_2^{\cdot-}$, was added to 10mM pyruvate/glucose perfusate. Hearts were paced at 300 beats/min. Mechanical dysfunction was assessed by the change in systolic blood pressure from baseline to end of reperfusion (% Δ SBP).

| | CL Basal | CL Ischemia | CL Reperfusion | % Δ SBP |
|---|---|---|---|---|
| 5 min | 200±11 | 134±8 | 328±21∞ | -12%* |
| 11.5 min | 220±11 | 142±7 | 540±56 | -13%* |
| 40.8 min | 206±11 | 100±7 | 286±26∞ | -37% |

∞ p <.01 vs. 11.5 min; * p <.02 vs. 40.8 min; CL in counts per second (mean ± SE).

The finding of higher CL with 11.5 vs. 5 min ischemia may be due to depletion of cellular protective mechanisms during longer periods of ischemia. Lower CL after 40.8 min may reflect cell damage and decreased ability to produce oxygen radicals. We conclude oxygen radical generation measured by CL varies with duration of ischemia. The level of oxygen radical production may not correlate with the severity of mechanical dysfunction.

TIME COURSE OF REPERFUSION INDUCED REVERSAL OF EARLY MYOCARDIAL EXPANSION.

Edward J. Brown, Jr., M.D., F.A.C.C., John A. Mannisi, M.D., F.A.C.C., Oneida I. Lillis, B.S., Peter F. Cohn, M.D., F.A.C.C. SUNY Health Sciences Center, Stony Brook, New York.

Reperfusion of ischemic myocardium can reverse early infarct expansion. Our purpose was to establish the time course and quantify the degree of reperfusion's effect on infarct expansion. Twenty-one dogs underwent left anterior descending coronary occlusion. Infarct size was measured with triphenyltetrazolium chloride incubation and expressed as a percent of the area-at-risk. Early myocardial expansion was measured as end-diastolic separation of ultrasonic crystals implanted in the midmyocardium of the infarct zone. Dogs were reperfused for 60 minutes after 3 (n=9), 5½ (n=5) or 9 (n=7) hours of ischemia. The table shows expansion expressed as a percent change over baseline. Results are mean±SEM:

| | 3 hrs. | 5½ hrs. | 9 hrs. |
|---|---|---|---|
| Ischemia | 18±2 | 24±5 | 21±3 |
| Reperfusion (1 Hr) | -9±6* | 2±5* | 14±3+* |

*significant compared to ischemia (p<0.001)
+significant compared to 5½ hrs. (p<0.001)

Infarct size was reduced in the 3 hr. reperfusion group but not in the 5½ or 9 hr. groups. Thus, expansion can be completely reversed by reperfusion after up to 5½ hrs. of ischemia. Reperfusion following 5½ to 9 hrs. of ischemia will partially reverse expansion. However, some infarct expansion persists.

DETECTION OF HYDROXYL RADICALS IN THE REPERFUSED ISOLATED MONKEY HEART.

Daniel R. Margulies M.D., Steven M. Schwartz M.D., Whitney M. Limm M.D., Lawrence Piette Ph.D. and J. Judson McNamara M.D., F.A.C.C., Cardiovascular Research Lab, University of Hawaii School of Medicine, Queen's Medical Center, Honolulu, Hawaii.

Oxygen Free radicals have been indirectly implicated in myocardial reperfusion injury. Using EPR analysis, investigators have recently demonstrated oxygen radical proliferation in the reperfused isolated rabbit and rat heart. In this study, a primate isolated heart model was used to demonstrate the production of hydroxyl radicals in the postischemic period. Macaque monkey hearts were excised and immediately perfused with warmed Krebs-Hensleits solution of $pO_2$ between 140 and 160 mmHg. The spin trap 5,5-dimethyl-1-pyroline-*n*-oxide (DMPO) was circulated at 100 mM prior to sampling. The LAD artery was isolated and its corresponding vein cannulated. Regional ischemia was induced for 20 minutes, and serial samples were obtained from the right ventricle and the coronary vein. EPR studies of the coronary effluent demonstrate the formation of DMPO-OH, $a_N=a_H=14.9$ G, peaking at 30 seconds and disappearing after 2 minutes. No radicals were detected from the right ventricular effluent. Hydroxyl radicals were demonstrated in primates in the regional postischemic myocardium. Maximal production was noted within the first minute of reperfusion. This finding in primates lends further support to the possibility that free radical generation may play a part in reperfusion injury in man.

SUPEROXIDE DISMUTASE (SOD) PREVENTS REPERFUSION-INDUCED DETERIORATION IN CORONARY VASODILATOR RESERVE (CVR) AND REGIONAL MYOCARDIAL FUNCTION.

Jawahar Mehta, M.D., F.A.C.C., Wilmer Nichols, Ph.D., F.A.C.C., Menno ter Riet, B.S., Linda Thompson, B.S., Dan Lawson, B.S., Tom Saldeen, M.D., Ph.D., University of Florida, Gainesville, Florida.

CVR and regional myocardial function deteriorate following coronary artery occlusion and reperfusion (O-R), due to release of superoxide radicals. To determine the effects of a superoxide scavanger SOD, 10 dogs underwent circumflex (Cx) coronary artery occlusion for 1 hr. and reperfusion for 1 hr.; 5 dogs were given saline (Group A) and the other 5 SOD (2mg/kg bolus followed by 4mg/kg i.v., beginning just before reperfusion and continuing for 20 min. (Group B). Cx blood flow (CBF) response to acetylcholine (ACh) and regional segmental myocardial function (ultrasonic crystals) were measured before and after O-R. In all animals, CBF increased prior to O-R (ACh 0.5µg-132±13%, 1.0µg-151±24%). Following O-R, increase in CBF was reduced (ACh 0.5µg-53±13%, 1.0µg-55±10%, both $P<0.01$) and myocardial segment length change was paradoxical (-6±2% vs. +10±2% before O-R, $P<0.01$) in Group A animals. In contrast, in Group B animals, CBF following O-R was preserved (ACh 0.5µg-118±18%, 1.0µg-149±21%, P-NS, compared to before O-R) and myocardial function was reduced (segment length change: 5±1% vs. 10±1%, $P<0.05$) but was not paradoxical. Thus SOD given before reperfusion prevents deterioration in CVR and myocardial function.

EFFECT OF REPERFUSION ON POST-MYOCARDIAL INFARCTION ANEURYSM FORMATION AT ONE WEEK

Carolyn M.Connelly,Ph.D. Soeun Ngoy, Scott Davis, Carl S.Apstein, M.D., F.A.C.C., Boston University School of Medicine and Boston City Hospital, Boston, MA.

To cause post-myocardial infarction aneurysms, aortic insufficiency (AI) was induced in rabbits at the time of coronary occlusion. The effect of reperfusion (R) was assessed by releasing the coronary occlusion after one hour or three hours. Aneurysm formation was assessed in these R groups and in non-reperfused completely occluded groups by measuring infarct thickness and the regional short axis diameter of the infarcted apex. At one week post-infarction AI caused significant aneurysm formation in animals without reperfusion. For AI (n=17) vs. no-AI (n=15), thickness was 1.2±0.1 vs. 2.2±0.1 mm (P=.001) and diameter was 6.2±0.3 vs 3.9±0.3 mm (P=.001), respectively. Both the R and the non-reperfused groups had transmural infarcts as determined by TTC staining. R protected against AI induced aneurysm formation as indicated:

| | Thickness (mm) | Diameter (mm) |
|---|---|---|
| no R (n=17) | 1.2±0.1 | 6.2±0.3** |
| R at 1 hr (n=15) | 1.9±0.2 * | 5.0±0.4 |
| R at 3 hr (n=8) | 1.4±0.1 | 5.0±0.3 |

Mean ± SEM. * P=.01 vs no R, **P=.03 vs R groups

Conclusion: Reperfusion at one hour although too late to prevent transmural infarction may reduce aneurysm formation by reducing wall thinning and dilatation while reperfusion at three hours may not prevent wall thinning but will nonetheless resist aneurysmal expansion.

## Tuesday, March 21, 1989
## 2:00PM–3:00PM, Marriott Hall North
## Anaheim Marriott Hotel
## Cardiac Pacing and Defibrillation

ELECTROPHYSIOLOGIC AND HISTOPATHOLOGIC COMPARISON BETWEEN APICAL AND TRANSEPICARDIAL SEPTAL VENTRICULAR PACING IN THE IMMATURE CANINE MYOCARDIUM: EVALUATION OF A NEW METHOD

Peter Karpawich M.D., Chung-Ho Chang, M.D., Lawrence Kuhns M.D., Children's Hospital of Michigan, Detroit, MI

Ventricular (V) pacing (VVI) originating from an apical (Ap) implanted electrode (E) alters normal V stress vectors and depolarization (DP) patterns producing histopathologic changes (HC) of myofibrillar disarray, calcium deposits (CD) and mitochondrial changes (MC) in the immature myocardium. To determine if HC can be prevented, more normal V DP and contraction (C) patterns were attempted using a transepicardial septal (TS) approach and compared with standard epicardial Ap V pacing. In 13 beagle puppies (age 3 mos), V DP and C sequences were determined using epicardial V electrodes and multigated acquisition nuclear imaging. Ten underwent complete atrioventricular block. In 5, a Medtronic model 6917A-35T E was attached to the right V apex. In 5, a modified model 4951 E was inserted into the aortoatrial groove and positioned in the proximal V septum (S). After 4 mos VVI pacing, V DP and C pattern studies were repeated and matched tissue samples were obtained from the paced and remaining 3 control puppies and studied using light and electron microscopy. The Ap paced group demonstrated left bundle branch DP and C patterns with cellular disarray, CD and MC. The TS paced group showed nearly normal QRS, intracardiac DP and C sequences and normal cellular arrangements without CD or MC. Conclusions: Although VVI pacing per se remains non-physiologic, the HC observed with typical Ap pacing can be prevented by maintaining relatively normal V DP and C patterns achievable with the new TS approach to V pacing.

## PACEMAKER SYNDROME IS ASSOCIATED WITH VERY HIGH PLASMA CONCENTRATIONS OF ATRIAL NATRIURETIC PEPTIDE (ANP)

Christopher M Travill MRCP, T D Meurig Williams MRCP, Panos Vardas MD, Ann Ingram, Julie Chalmers HNC, Stafford Lightman FRCP, Richard Sutton FRCP FACC, Westminster Hospital, London SW1P 2AP, UK.

Pacemaker syndrome (PMS) occurs in some patients with intact retrograde atrio-ventricular conduction (RAVC) when paced in the ventricle. It is associated with reduced cardiac output and systemic pressure due to loss of atrial contribution to ventricular filling. Contraction of the atria against closed atrioventricular valves causes elevated atrial pressures and ANP release. The latter causes vasodilatation and reduction in intravascular volume both of which would tend to worsen the haemodynamics seen in PMS.

We investigated 5 patients aged 77±3 (mean ± SE) years with a history of pacemaker upgrade for PMS complicating VVI pacing. Diagnoses were intermittent A-V block (1), Sick Sinus Syndrome (1), Carotid Sinus Syndrome (2) and Vasovagal Syndrome (1). Pacing was switched from DDD to VVI at time 0 for 120 mins at 10 ppm above the intrinsic atrial rate and plasma ANP and blood pressure were measured at intervals before, during and after this procedure. Results: *p<0.05, **p<0.01 compared with time 0

| TIME (min) | PACING MODE | BP (mmHg) | ANP (pmol/l) |
|---|---|---|---|
| -15 | DDD/SR | 101± 5 | 79± 2 |
| 0 | ↓ | 98± 7 | 73±15 |
| 15 | VVI+RAVC | 93± 8 | 147±46* |
| 30 | | 91± 8 | 341±49** |
| 60 | \| | 88± 8 | 298±50** |
| 90 | \| | 83± 5** | 311±69* |
| 120 | ↓ | 83± 7* | 235±53* |
| 150 | DDD/SR | 73±12 | 188±23* |
| 180 | ↓ | 94±6 | 131±10* |

Conclusion: Patients with pacemaker syndrome have very high circulating ANP concentrations which return to normal with dual chamber pacing. ANP may contribute to the pathophysiology of the condition.

## SPONTANEOUS CHANGES IN VENTRICULAR TACHYCARDIA CYCLE LENGTH: RELEVANCE TO ANTITACHYCARDIA DEVICE DEVELOPMENT.

Kent J. Volosin, M.D., Lou-Anne M. Beauregard, M.D. F.A.C.C., Rosemary Rudderow, B.S.N., Howard Mattingly, and Harvey L. Waxman, M.D., F.A.C.C. Robert Wood Johnson Medical School, Camden, NJ.

Understanding spontaneous fluctuations in ventricular tachycardia (VT) cycle length (CL) is required to develop VT detection and pacemaker termination algorithms. We analyzed variations in VTCL, time to stable VTCL, and range of VTCL. Seventy-four episodes of sustained monomorphic VT induced on no antiarrhythmic agents were studied. VTCL variability (VAR) was calculated as one standard deviation of the mean VTCL for every 10 beats for each episode. VTCL was considered stable when it varied <10 msec. Fifty beats were analyzed for each episode.

RESULTS:

1. VAR: Linear regression revealed VTCL VAR to decrease over time (41±24 msec to 17±19 msec, p<.001), slower VT had more VTCL VAR than faster VT (p<.001) and VT which started out more variable tended to remain more variable (p<.001).
2. STABILITY: Fifty-four percent of episodes were stable after 15 beats, 75% by the 30th beat, and 93% by the 50th beat. The number of beats to stable VTCL was independent of VTCL (p=ns).
3. RANGE: The average range in VTCL per episode was 127± 72 msec. Twelve percent of VT varied by less than 50 msec, 45% by less than 100 msec, and 70% by less than 150 msec. The maximum range in VTCL for any given episode was 290 msec.

CONCLUSIONS: 1. VT demonstrates a wide range of cycle lengths and has time dependent changes in variability and stability. 2. These cycle length changes must be considered in the algorithms for VT detection and termination by automatic antitachycardia devices.

## IS ATRIAL ACTIVATION BENEFICIAL IN HEART TRANSPLANT RECIPIENTS?

Mark G. Midei, MD, Christopher Leggett, MD, Kenneth L. Baughman, MD, FACC, William Baumgartner, MD, Gary D. Walford, MD, FACC, Jeffrey A. Brinker, MD, FACC, The Johns Hopkins Hospital, Baltimore, MD.

The unique architechture of the transplanted heart has led to speculation that atrial contraction does not contribute significantly to ventricular (V) pump performance. To study the effect of atrial activation on LV function in such pts, we compared cardiac output (CO) and mean arterial pressure (MAP) in five cardiac transplant recipients during both AAI and VVI pacing.

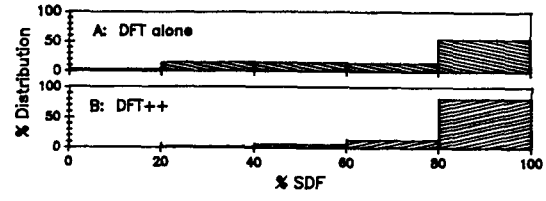
All pts received temporary epicardial donor atrial and V pacing wires at the time of their transplantation. At the time of their first biopsy (9 ± 1 d post transplantation), an arterial cannula and a PA catheter were placed; CO was measured using thermodilution. In random order, pts were paced from either the atrium or the V at a rate at least 10% faster than their sinus rate, but not slower than 100/min (mean = 105 ± 5). CO and MAP were recorded following two minutes of equilibration. Next, the pacing mode was changed to the alternate pacing site at the same heart rate, and measurements were repeated.

CO and MAP averaged 5.4 ± 1.5 l/min and 101 ± 20 mmHg respectively during atrial pacing while these values were significantly lower during V pacing at the same rate (4.1 ± 1.8 l/min, p<0.03; and 89 ± 15 mmHg, p<0.03). Changes were present despite the absence of demonstrable LV dysfunction, elevated EDP, or rejection, and no evidence of hypertrophy at the time of study. We conclude that atrial activation contributes to V pump performance in the transplanted heart. It is possible that this role might be magnified later if rejection and LV dysfunction occur. Finally, we believe that atrial pacing is superior to V pacing in heart transplant recipients who require subsequent permanent pacemaker implantation.

## PROTOCOL FOR EVALUATION OF INTERNAL DEFIBRILLATION SAFETY MARGINS.

Douglas J. Lang, Ph.D.; Elizabeth L. Cato; Debra S. Echt, M.D. Cardiac Pacemakers, Inc., St. Paul, Minnesota.

The safety margin (SM) of an automatic implantable cardioverter-defibrillator (AICD) is the difference between the AICD output and the minimum energy for consistent defibrillation (DF). Determination of a single DF threshold (DFT) by testing decreasing energy levels may overestimate the SM for DF, since the relationship between percent successful defibrillation (% SDF) and energy is a DF curve. We evaluated whether a single DFT protocol followed by 2 extra shocks at the DFT would clarify the SM. An expanded DFT protocol was performed in 154 dogs using spring lead/LV patch electrodes to construct DF curves and to determine single DFTs and the success (+) or failure (-) of 2 extra shocks at the DFT energy. The distribution of % SDF for the single DFT (Figure A) was different ($p < 0.01$) from those of the extra-shock DFTs: DFT++ (Figure B, n=79); DFT+- (n=54); DFT-- (n=21).




One-third of the DFTs lay below 60% SDF, overestimating the SM by ≥ 40% of the DF curve width. The DFT+- and DFT-- were distributed to middle and lower % SDF, indicating a possible overestimation of the SM. With 81% of the DFT++ above 80% SDF, the DFT++ were distributed higher on the DF curve than the DFT alone. Thus, a DFT that yields successful conversions for 2 extra trials results in a more accurate determination of the safety margin.

EFFECT OF PERICARDIAL EFFUSION ON ENERGY REQUIREMENTS FOR DEFIBRILLATION USING EXTRAPERICARDIAL PATCH ELECTRODES.

Joseph Souza, Ranjan Thakur M.D., Paul Troup M.D., F.A.C.C., Jule Wetherbee M.D., Peter Chapman M.D., F.A.C.C., Medical College of Wisconsin, Milwaukee, Wisconsin.

To determine if pericardial effusion (PE) influences defibrillation energy requirements with extrapericardial patch electrodes placed via median sternotomy, 6 anesthetized mongrel dogs (24.5 ± 2.2 kg) underwent defibrillation trials comparing monophasic (M) and single-capacitor biphasic (B) shocks with and without PE. A median sternotomy was performed and two 13.9 cm2 patch electrodes were sewn onto the outside of the pericardium. Three cc/kg of .9% NaCl was instilled through an intrapericardial catheter used to create a hemodynamically insignificant pericardial effusion. Four trials of 5 leading edge voltages (200, 300, 400, 500 and 600 volts) were performed for M and B shocks of 10 msec total duration (capacitance 150 uF) and defibrillation efficacy curves were determined by logistic regression analysis. Baseline impedance declined from 67 ± 9 ohms to 51 ± 8 ohms with PE (p <0.0001). Energies associated with 80% probability of successful defibrillation were compared:

| | | BASELINE* | WITH PE* | |
|---|---|---|---|---|
| | M | 13.4 J | 19.5 J | * p=0.18 |
| E80 | B | 9.7 J | 11.7 J | |

Although there was a tendency for higher defibrillation energy requirements for both M and B shocks with PE, this did not achieve statistical significance. Conclusion: Pericardial effusion is associated with a decline in impedance and a trend for higher defibrillation energy requirements, which conceivably could result in reduction in the margin of safety for defibrillation in the clinical setting.

**INITIAL CLINICAL EXPERIENCE WITH A DUAL CHAMBER RATE MODULATED PACEMAKER.**

Jeffrey Brinker, M.D. F.A.C.C., Roy Jutzy, M.D., F.A.C.C., David Hayes, M.D., F.A.C.C., Richard Gentzler, M.D., F.A.C.C.,Kenneth Austin, M.D., F.A.C.C., Tom Hee, M.D., F.A.C.C., Paul Levine, M.D., F.A.C.C., James Higgins, M.D., F.A.C.C., Charles Byrd, M.D., Stephen Schaal, M.D., F.A.C.C., Bryant McElroy, B.M.E., Johns Hopkins Medical Institute, Baltimore, Maryland.

We report the early experience with the first dual chamber activity based rate modulated pacemaker. Pacesetter model 2020T (Synchrony) was implanted in 64 patients (pts) age 61+16 yrs (23-88) for sino-atrial disease (46) and/or A-V block (18). Paired exercise tests (DDDR vs DDD) were performed in a single blind randomized fashion within a month of implant in 33 pts. Maximum heart rate (MHR) and exercise duration was increased with DDDR pacing (125+3.7/min vs 110+4.1/min, P<.002; 10.2+.7 minutes vs 9.6+.7 minutes, P<.03 repectively). During DDDR MHR was sensor driven in 23/33 (70%). Nine patients (27%) failed to increase their sinus rate > 100 during treadmill testing. These chronotropic impaired (CI) pts had a MHR in DDD of only 85/min compared with 125/min achieved by the other 24 pts (P<.0001). The CI patients increased their MHR to 109+6.1/min when programmed to DDDR (P<.006). Follow-up data on the entire group of 64 pts is 110 +40 days. All but 9 remain in DDDR (6 DDIR and 1 DVIR because of atrial tachyarrhythmia, 2 VVIR because of lead dysfunction). Thus DDDR pacing appears beneficial in prolonging exercise effort by allowing a greater MHR. For the CI patient the sensor driven MHR is significantly increased but does not equal the sinus response of the non CI patient. The ability to program the device to non-tracking rate-modulated modes is beneficial in selected patients.

## Tuesday, March 21, 1989
## 4:00PM–5:30PM, Marriott Hall North
## Anaheim Marriott Hotel
## Cardiac Pacing

ACUTE CLINICAL TESTING AND FOLLOW-UP OF A RATE-VARIABLE PACEMAKER CONTROLLED BY CENTRAL VENOUS OXYGEN SATURATION.

Svein Fœrestrand, M.D., Britt T. Skadberg, M.D., Ken Anderson, M.Sc., Ole-Jørgen Ohm, M.D., F.A.C.C., University School of Medicine, Bergen, Norway and Bakken Research Center, Maastricht, The Netherlands.

We studied a new rate-variable pacemaker (PM), that uses central venous oxygen saturation ($O_2$Sat) to control PM rate during rest and following 3 minutes supine arm exercise periods in 7 patients (mean age, 76 years) with atrioventricular block and bradycardia. The sensor, which is incorporated in the PM lead, emits red and infrared light in the RV and measures the reflection, from which $O_2$Sat is derived. The calculated $O_2$Sat, which can be transferred via telemetry to the PM programmer, is translated into a pacing rate using 1 of 20 programmable response settings (R1 to R20). The $O_2$Sat, heart rate (bpm) and CO (l/min; thermodilution) were measured during bradycardia and for three reponse settings (R5, R10 and R15) in an $O_2$Sat-controlled pacing mode (Table below). Blood samples were obtained from the RV to verify $O_2$Sat. Heart rate response to changes in $O_2$Sat was rapid and increased the cardiac output with increasing work loads. The $O_2$Sat measured by the PM correlated closely with $O_2$Sat obtained from RV sampling (n = 165, r = 0.95, p < .001).

| Parameter | Rest (mean ± sem) | Exercise (mean ± sem) |
|---|---|---|
| $O_2$Saturation, % | 62 ± 1 | 47 ± 1 |
| Heart rate, bpm (baseline) | 39 ± 2 | 53 ± 7 |
| Heart rate, bpm (R5) | 74 ± 5 | 97 ± 2 |
| Heart rate, bpm (R10) | 84 ± 7 | 112 ± 9 |
| Heart rate, bpm (R15) | 106 ± 6 | 136 ± 2 |
| CO, l/min (baseline) | 4.3 ± .2 | 4.9 ± .7 |
| CO, l/min (R5) | 4.9 ± .2 | 6.5 ± .9 |
| CO, l/min (R10) | 5.1 ± .6 | 6.9 ± 1.2 |
| CO, l/min (R15) | 4.9 ± .8 | 7.2 ± .6 |

Based on the favorable results obtained during acute studies, two patients have received permanent PMs implanted for 3 and 2 months, thus far. Initial results assessed by exercise testing and Holter recordings at different R suggest that $O_2$Sat can be measured by the PM on a long-term basis. Furthermore, the heart rate can be physiologically adapted from central venous $O_2$Sat when the optimal R is selected in an individual patient.

INVESTIGATION OF A NEW ACTIVITY SENSING RATE RESPONSIVE DUAL CHAMBER PACEMAKER

Stuart T. Higano M.D. and David L. Hayes M.D., F.A.C.C., Mayo Clinic, Rochester, MN

The importance of atrial contraction to resting and exercise hemodynamics remains controversial. This is of clinical importance in pacemaker selection, as either rate responsiveness (VVIR) or AV synchrony (DDD) may be selected. A new device incorporates activity sensing rate responsiveness with AV synchrony (DDDR).

This device is ideally suited for Pts with AV block and sinus node dysfunction. To assess the functional advantage of AV synchrony vs. rate responsiveness, we performed 1 month post-implant cardiopulmonary exercise tests in 7 Pts in each of 3 modes (VVIR, DDD, DDDR). Each Pt performs 3 separate randomized tests and thereby acts as their own control. In addition to the usual exercise parameters (HR, BP, ECG, Duration), oxygen consumption and cardiac output are determined by respiratory gases and acetylene rebreathing techniques:

| | VVIR | | DDD | | DDDR | |
|---|---|---|---|---|---|---|
| | Rest | Peak | Rest | Peak | Rest | Peak |
| HR | 61 | 120 | 74 | 118 | 71 | 124 |
| $VO_2$, ml/min | 271 | 1413 | 313 | 1454† | 282 | 1485* |
| CI, l/min/m$^2$ | 2.2 | 3.9 | 2.3 | 4.3† | 2.1 | 4.4* |
| SVI, ml/m$^2$ | 36 | 33 | 32 | 37 | 28 | 35 |
| $O_2$ Pulse ml | 4.4 | 11.8 | 4.4 | 12.8 | 4.0 | 11.7 |
| AV-$O_2$Diff ml/l | 70 | 196 | 80 | 184 | 83 | 184† |
| Duration, min | | 10:31 | | 11:00† | | 11:03* |

Versus Peak VVIR: * P<0.05, † P<0.10

Conclusion: Compared to VVIR, DDDR exhibited enhanced exercise cardiac index, oxygen consumption, and duration, with smaller AV-$O_2$ differences. Although DDD did not exhibit chronotropic incompetence, DDDR did improve function at peak exercise, due to atrial contribution to exercise stroke volume and slightly increased peak HR.

INITIAL EXPERIENCE WITH AUTOMATIC SLOPE SETTINGS FOR META MV AND RHYTHMYX RATE RESPONSIVE PACEMAKERS

M.W. Baig MB, R. Sutcliffe, A. Green, J. Perrins MD, FACC
The General Infirmary at Leeds, Leeds, England.

Patients with first generation rate responsive pacemakers often require repeated exercise tests to ensure optimal settings of the rate response algorithm. The Meta MV and Rhythmyx units incorporate mechanisms for automatic algorithm setting. The aim of this study was to evaluate the performance of these new features. The Meta senses minute volume by measuring changes in thoracic impedance (TI) with a transvenous bipolar pacing electrode. To set the algorithm, the TI measured at rest is compared with that at peak exercise and the advised slope is computed automatically. The reproducibility of the advised slope when measured after intervals greater than 24h was high in 5 out of 6 pts, that is, the value after the second test varied by less than 2 steps from the first. The sensor used by Rhythmyx is the endocardial paced QT interval. The difference in the QT intervals of successive beats determines the pacing rate according to the slope setting of the algorithm. The pacemaker computes the value of the slope at the base rate every 24h and adjusts its value as necessary. 10 Rhythmyx units have been implanted. Interrogation of the slope settings was done at 48h intervals for 14 days after enabling the automatic slope to record initial changes and to check its subsequent stability. The mean time for slope stabilisation was 20 days (range 8-32) and initial poor T wave sensing in 1 pt. accounts for the wide range. Subsequent stability of the slope has been confirmed (max. follow-up time is 8 months). Conclusion: both systems have achieved automatic slope adaptation leading to a satisfactory rate rise on exercise. This represents an important development in rate responsive pacing.

A DOUBLE BLIND CROSS-OVER STUDY ON THE SYMPTOMATOLOGY AND QUALITY OF LIFE IN PATIENTS WITH RATE RESPONSIVE PACEMAKERS

Chu-Pak Lau, MB, Julia Rushby, BSc, Michelle Leigh-Jones, Carven YF Tam, Jan Poloniecki, Ann Ingram+, Richard Sutton+, MD, FACC, A John Camm, MD, FACC
Department of Cardiology, St. George's Hospital; +Westminster Hospital, London

The hemodynamic advantages of rate responsive pacing (RRP) are well established, but the symptomatic benefit on patients (Pts) receiving RRP remains controversial and the effects on the quality of life have not been assessed. 16 Pts (6 Meta, 4 Sensolog 703, 3 Biorate, 2 dp/dt sensing and 1 Activitrax) with RRP and a mean age of 56 (range 22-77) yrs were involved in a double blind cross-over study designed to assess their exercise capacity (treadmill testing), symptoms and quality of life (structured questionnaires). During the trial, the pacemakers were randomly programmed into the RRP or constant rate pacing (VVI) modes for four-week study periods. All Pts exercised longer in the RRP mode (570±29 s vs 437±17 s, P<0.001). Symptoms were assessed in the Pts and also reported by their close relatives using a 10-point scale:

| | PATIENT SCORE | | | RELATIVE SCORE | | |
|---|---|---|---|---|---|---|
| | VVI | RRP | P | VVI | RRP | P |
| Dyspnea | 6.9±0.9 | 8.2±0.7 | 0.02 | 6.8±0.8 | 8.0±0.5 | 0.01 |
| Energy | 6.9±0.5 | 7.8±0.5 | 0.02 | 7.1±0.5 | 7.9±0.4 | 0.03 |
| Preference | 7.3±0.4 | 8.0±0.2 | 0.03 | 7.7±0.4 | 8.2±0.2 | 0.08 |
| Well being | 7.6±0.5 | 8.1±0.3 | 0.3 | 7.4±0.5 | 8.0±0.4 | 0.17 |

Non-disease specific 'quality of life' was studied in 11 Pts using the Nottingham Health Profile which showed a trend for a better quality of life in 5 of the 6 dimensions of perceived health (pain, sleep, emotional reaction, social isolation and physical mobility) during RRP compared to VVI, although none of the changes was statistically significant. CONCLUSION: RRP improves symptomatolgy of Pts but the differences are not large enough to affect the general well being nor a non-disease specific quality of life measure.

UNIQUE UPPER RATE BEHAVIORS IN DUAL CHAMBER, RATE MODULATED PACEMAKERS

Stuart T. Higano M.D., David L. Hayes M.D., F.A.C.C., Mayo Clinic, Rochester, Minnesota.

The dual chamber, rate modulated pacemaker (DDDR) is ideally suited for those with combined sinus node and AV node dysfunction. In combining dual chamber with single chamber, rate modulated technologies, DDDR developed a hybrid of upper rate behaviors (URB) utilizing intrinsic atrial activity and sensor driven pacing. We sought to analyze the observed DDDR URB in 12 Pts during one month post-implant exercise tests.

Three new URB, unique to DDDR, were observed: 1. "Pseudo-Rate-Smoothing"--Although standard dual chamber modes may have large cycle length variations at the maximum tracking rate (MTR) because of 2:1 or Wenckebach-type block, DDDR displays "pseudo-rate-smoothing" during this time. This occurs because the Wenckebach interval is not allowed to exceed the sensor driven rate interval. Like true rate-smoothing, marked cycle length variations are prevented during exercise. Pseudo-rate-smoothing will only occur at the MTR, or after ectopics, during exercise. 2. Discrepant Upper Rate Limits--The maximum sensor rate and MTR, must both be programmed in a DDDR. Programming discrepant MTR and maximum sensor rate is useful in pts with supraventricular tachycardias because rapid tracking of the tachycardia is thus prevented while sensor driven rate responsiveness is maintained. 3. P-Wave Tracking Above The MTR--At atrial and sensor rates above the MTR, appropriately timed P-waves can result in A-spike inhibition and runs of apparent P-wave tracking. This should not be mistaken for malfunction.

Conclusions: Analysis of URB in DDDR in 12 Pts has led to 3 unique responses. These will be widely seen as DDDR comes into widespread clinical use.

## Tuesday, March 21, 1989
## 2:00PM–3:30PM, California Room D
## Anaheim Convention Center
## Echocardiography in the Evaluation of Balloon Valvuloplasty

DOPPLER-ECHOCARDIOGRAPHIC EVALUATION OF THE RESULTS OF SURGICAL ULTRASONIC DECALCIFICATION OF THE AORTIC VALVE.

David Nagelhout, M.D., Anthony C. Pearson, M.D., FACC, Vallee L. Willman, M.D., Hendrick B. Barner, M.D., FACC, Arthur J. Labovitz, M.D., FACC, St. Louis University Medical Center, St. Louis, Missouri.

Surgical decalcification of the aortic valve (AV) using Cavitron Ultrasonic Surgical Aspirator (CUSA) has recently been introduced as an alternative to AV replacement for severe calcific AV stenosis. We studied 17 patients before and 7-10 days after AV (CUSA) decalcification using M-mode (MM), two-dimensional (2D) and Doppler-echocardiography. Pressure gradient (PG) across the AV was measured by continuous wave Doppler using the modified Bernoulli equation. AV area was calculated using the continuity equation. Aortic insufficiency (AI) and mitral regurgitation (MR) were quantitated using conventional and color flow Doppler. MM and 2D studies revealed marked decrease in AV calcification and increase in leaflet mobility following the procedure. All patients had a significant reduction in peak and mean gradient (63+17 to 20+7mmHg and 37+12 to 9+4mmHg p<.0001). There was also a significant improvement of aortic valve area (AVA) from 0.7cm$^2$+0.2 to 1.5cm$^2$+0.5 (p<.0001). LV systolic function measured by MM shortening fraction (SF) was not significantly changed (34+7 to 32+7%). Mild AI was initially present in 7 patients with one patient having moderate AI. AI was unchanged in 9 patients, improved in 3 (by 1 grade) and worsened in 5 patients (by 1 grade). MR was present in 8 patients and improved in 7 by 1 grade. Two patients developed mild MR after the procedure. We conclude that CUSA effectively decalcifies and mobilizes AV leaflets in patients with senile calcific AS resulting in a doubling of AVA. MR improved in 7/8 patients following the procedure probably as function of decreased afterload. AI is improved or not changed in the majority of patients.

## ECHO EVALUATION OF IMMEDIATE AND LATE FAILED MITRAL VALVE REPAIR

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Mitral repair has distinct advantages over replacement in pts with mitral regurgitation (**MR**). Intraoperative echo (**IOE**) provides immediate assessment of integrity of repair. The aim of this study was to identify by echo the mechanism of failed mitral repair. Mitral repair for **MR** was performed in 270 pts over a 26 month period. Immediate failure (**IF**) of the mitral repair was diagnosed by **IOE** in 15 pts during the initial repair allowing a second pump run for further surgery. Late failure (**LF**) occured in 11 pts requiring a second thoracotomy (interval before reoperation of 1 week to 18 months). Etiology of **MR** was prolapse in 14/15 (93%) **IF** pts and 6/11 (55%) of **LF** pts. ($p = 0.05$). The primary repair included leaflet resection in 12/15 **IF** pts and 5/11 **LF** pts ($p = 0.01$); ring insertion in 10/15 **IF** pts and 11/11 **LF** pts ($p = 0.05$). All **IF** pts had residual **MR**; **IOE** diagnosed mitral valve systolic anterior motion in 6, suture line dehiscence in 5 and inadequate leaflet coaptation in 4. The second pump run consisted predominantly of ring removal in 5, further leaflet repair in 7 and valve replacement in 3. All **IF** pts left the operation with successful surgery documented by **IOE**. In **LF** pts, etiology of failed repair was suture dehiscence in 2, ring dehiscence in 1 and disease progression in 8. Reoperation in **LF** pts was prosthesis insertion in 10 /11 **LF** pts and repeat repair 1/11 pts.

**Conclusions:** The causes of failed repair differ between **IF** and **LF** pts. The mechanism of **IF** is most commonly related to technical problems that can be identified by **IOE** and corrected during the same thoracotomy. **LF** are most commonly related to disease progression.

## DO HEMODYNAMICS OVERESTIMATE THE RESULTS OF BALLOON MITRAL VALVULOPLASTY ?

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Post balloon valvuloplasty (BV), Doppler (DOP,area=220/T1/2) evaluation of mitral valve area(MVA) is estimated inacurate because large discordances with immediate hemodynamic (H, Gorlin formula "gold standard") were published in short series. We studied the correlations between H and Dop or 2D Echo (2DE) assessments of MVA in 73 patients (Pts), age 44±18, before and after BV.

Before BV : Significant correlations between H and 2DE ($r=0.57$, $p<0.001$) and H and DOP ($r=0.59, p<0.001$) were found. The mean values of MVA were similar ($H= 1.09±0.3$ $cm^2$, $2DE= 1.04± 0.26cm^2$, $DOP= 1.02±0.2cm^2$, NS). All the Pts were correctly diagnosed as having M stenosis (MVA-$<1.8cm^2$) by the 3 methods.

After BV : Immediate H correlated less well with 2DE ($r=0.49, p<0.001$) or Dop($r=0.30, p<0.02$) performed 24 hours after BV. Aortic insufficiency (n=12) and increased mitral regurgitation (n=8) specifically denatured the correlation between H and DOP. VA was significantly larger with H ($2.26±0.51cm^2$) than with 2DE ($1.94±0.44cm^2, p<0.001$) or DOP ($1.83±0.38cm^2$, $p<0.001$). On the contrary, 2DE and DOP VA were similar and highly correlated ($r=0.70, p<0.001$) which seems to validate the results obtained by these 2 methods. Moreover, in our 25 Pts with 6 months follow-up 2DE and DOP VA were unchanged confirming the post-BV results.

Conclusions : As opposed to pre-BV, immediate post BV H evaluation of MVA oversizes DOP or 2DE MVA and thus overestimates the results of balloon mitral valvuloplasty. Therefore, only comparisons with post-BMV non invasive data have to be taken into consideration for the evaluation of a possible restenosis.

## DOPPLER-ECHO EVALUATION OF MITRAL STENOSIS PRE- AND POST-BALLOON VALVULOPLASTY

Joseph Kisslo, MD, FACC, for the NHLBI Balloon Valvuloplasty Registry, Coordinating Center, University of Washington, Seattle, WA

In a 23 center national registry, 101 patients underwent Doppler (DOP) and echo pre- (<30 days) and post- (24-72 hours) mitral balloon valvuloplasty (MPLASTY). Mean age was 57±16 years with 24 males and 77 females. Following MPLASTY, DOP mean transmitral gradient decreased (10±5 to 7±6 mmHg); planimetered echo mitral valve area (MVA) increased (1.2±.3 to 1.7±.5 $cm^2$); pressure half-time MVA increased (1.1±.4 to 1.8±.5 $cm^2$)(all $p<.001$). Invasively, mean mitral gradient decreased (14±6 to 6±4 mmHg) and MVA increased (1.0±.4 to 2.0±.8 $cm^2$)(both $p<.001$). Mitral regurgitation (MR) severity assessed by DOP color flow imaging increased post-MPLASTY in 31% with an increase greater than one grade in only 8%. Pulmonary artery (PA) systolic pressure did not change significantly when estimated from tricuspid regurgitant jet velocity (47 to 50 mmHg)($p=.10$). Invasively measured mean PA pressure dropped slightly immediately pre- and post-MPLASTY (39±12 to 31±10 mmHg)($p<.001$).

These data indicate that post-MPLASTY: DOP and echo accurately reflect changes that occur in MVA and gradient; MR does increase slightly in nearly one-third of patients; PA pressures change little in the immediate post-MPLASTY period. Such findings increase the likelihood that DOP and echo may be used to reliably follow patients in the long term post-MPLASTY.

## DOPPLER-ECHO EVALUATION OF AORTIC STENOSIS SEVERITY PRE- AND POST-BALLOON AORTIC VALVULOPLASTY.

Patricia C. Come, M.D., for the NHLBI Balloon Valvuloplasty Registry, Coordinating Center: University of Washington, Seattle, WA.

In a 23 center national registry, 240 patients, enrolled over 8 months of a planned 24 month enrollment, underwent Doppler echocardiography pre- (within 30 days) and post- (24-72 hrs) aortic balloon valvuloplasty (ABV). Mean age was 79 ± 9 years, with 104 males and 136 females. Doppler mean transaortic pressure gradient ($\Delta P$) decreased from 49 ± 19 to 35 ± 15 mmHg. Continuity equation aortic valve area (AVA) increased from 0.6 ± 0.3 to 0.8 ± 0.3 $cm^2$ (both $p < 0.001$). Similar directional changes were noted in invasive measurements immediately pre- and post-ABV for mean $\Delta P$ (58 ± 24 to 30 ± 13 mmHg) and AVA (0.5 ± 0.2 to 0.8 ± 0.3 $cm^2$, both $p < 0.001$).

Aortic insufficiency (AI) severity, evaluated by Doppler flow mapping, increased post-ABV in 16% of patients with an increase by more than one grade in only 2%. LV systolic function was depressed on 2D echo pre-ABV in 52% of patients (mildly in 18%, moderately in 15% and severely in 19%), and improved acutely post-ABV in only 19% of these patients (10% of total group).

We conclude that aortic-BV results in an immediate modest decrease in mean $\Delta P$ and increase in AVA as measured by both Doppler and catheter techniques. AI severity usually is unchanged as is LV systolic function.

ONE-YEAR CLINICAL AND DOPPLER ECHOCARDIOGRAPHIC FOLLOW-UP OF PATIENTS HAVING DOUBLE-BALLOON CATHETER BALLOON VALVULOPLASTY FOR MITRAL STENOSIS. Cheryl L. Reid, M.D., F.A.C.C., David T. Kawanishi, M.D., F.A.C.C., Shahbudin H. Rahimtoola, M.D., F.A.C.C. LAC/USC Medical Center, Los Angeles, CA.

Of the first 27 pts, age 43±15 yrs (mean±SD) having successful double-balloon catheter balloon valvuloplasty (CBV) for mitral stenosis, clinical and Doppler follow-up have been obtained in 21 pts. Evaluation including NYHA Functional Class (FC) and Doppler mitral valve area (MVA) and mitral regurgitation (MR) were made pre-, immediate post (immed), 3 mos, and 364±50 days (12 mos) post CBV. Based on reproducibility of day-to-day measurements of MVA in these pts, a change of ≥22% was considered significant.

RESULTS: MVA increased from 1.0±.2cm$^2$ pre-CBV to 2.1±4cm$^2$ immed (p<.05). Follow-up at 3 mos MVA was 1.9±.4cm$^2$, at 12 mos 1.8±.4cm$^2$ (p<.05 Immed vs 3 and 12 mos). At 3 mos, 3 pts (12%) had a decrease in MVA which was unchanged at 12 mos; an additional 8 pts (38%) had a decrease at 12 mos. Two pts returned to within 22% of pre-CBV MVA at 12 mos. MR decreased by 1 grade in 7 pts, in 5/7 pts (71%) decrease in MR was associated with decrease in MVA. Pre-CBV, 89% of pts were FC 3-4. At 3 and 12 mos, 92% and 86% of pts were FC 1-2. FC deteriorated by 1 class at 12 mos in 3 pts; all had decrease in MVA.

CONCLUSIONS: 1) 12 mos post CBV, 86% of pts maintain initial improvement in FC. 2) Decrease in MR is often associated with decrease in MVA. 3) Although MVA decreases in 52% of pts, an early decrease may not be progressive and the decrease from 3 to 12 mos is minimal. Only 10% of pts returned to pre-CBV MVA. In most pts, decrease in MVA is not of sufficient magnitude to result in deterioration of FC.

## Tuesday, March 21, 1989
## 4:00PM–5:30PM, California Room D
## Anaheim Convention Center
## Contrast/Coronaries

### MYOCARDIAL CONTRAST ECHO WASHOUT CURVES: THE INFLUENCE OF ISCHEMIA AND HYPEREMIA.

Shimon A Reisner MD, Janine R Shapiro MD, Antonio F Amico MD, Richard S Meltzer MD, PhD, FACC. U. of Rochester, Rochester, NY

To determine the influence of different coronary blood flow levels on myocardial contrast washout curves, 8 open chest dogs underwent intracoronary contrast injections of sonicated 5% human albumin. Regional ischemia was induced by ligation of a coronary artery and hyperemia by intravenous infusion of 0.75 mg/kg of dipyridamole. Blood pressure, pulmonary capillary wedge pressure and heart rate were kept at baseline level with fluids, neosynephrine and pacing. Washout curves were generated from the area of interest using beat-by-beat analysis of end-diastolic frames. Background subtracted peak contrast intensity (PCI, gray scale units/pixel) was defined as the highest value obtained. Washout half time (T1/2) was calculated from the decay phase of the curve by the equation T1/2=ln(2/k) (k = exponential decay rate). Each value of PCI and T1/2 was averaged from 2 successive injections. High quality contrast time-intensity curves, (r>0.8, correlation of exponential decay), were obtained in 5 dogs. PCI in the ischemic area was 44±14 (mean±1SD) at baseline, 43±6 after coronary artery occlusion and 51±9 during hyperemia. In the nonischemic area, PCI was 32±11 at baseline and 40±9 during hyperemia. All PCI changes were statistically insignificant. T1/2 (in number of cycles) and percent change in T1/2 from baseline after coronary occlusion and during hyperemia were:

| | Baseline | Occlusion | Hyperemia |
|---|---|---|---|
| Ischemic area: | 3.8±0.9 | 4.2±1.1 (+10%) § | 4.4±0.5 (+16%) * |
| Nonischemic area: | 3.2±0.1 | 3.3±0.9 (+3%) | 4.6±0.4 (+43%) * |

* T1/2 was significantly longer (p<0.02, by paired Student's t-test ), during hyperemia compared to baseline for both the ischemic and nonischemic areas. § T1/2 was significantly longer (p<0.05) after occlusion compared to baseline in the ischemic area. Conclusions: 1. Both ischemia and hyperemia prolong washout time, probably by different mechanisms. 2. The greater prolongation with hyperemia is partially obscured in the ischemic area. 3. There is no significant change in PCI with ischemia or hyperemia.

### MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY CAN NOT BE USED TO ASSESS ENDOCARDIAL/EPICARDIAL BLOOD FLOW RATIO.

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Two preliminary reports have claimed that endocardial/epicardial blood flow ratio (EER) can be assessed using myocardial contrast echocardiography (MCE). Based upon our experience, we postulated that EER can not be determined with MCE. Accordingly, we studied 2 groups of open-chest anesthetized dogs. In group I (n = 6) we placed a hydraulic occluder on the left anterior descending coronary artery (LAD). In group II (n = 6) we produced a critical stenosis of the left circumflex artery. Sonicated microbubbles were injected into the left main artery in all dogs and 2D echo images obtained. In group I dogs, injections were performed during baseline and following severe stenosis of the LAD. In group II dogs, injections were performed following intracoronary injection of 6 mg of papavarine to enhance endocardial steal. Time-intensity plots were obtained from the endocardium and epicardium of digitized end-diastolic 2D echo images. A gamma-variate function ($Axe^{-\alpha t}$) was fitted to the plots and curve width ($\alpha$), height ($A/\alpha^2$), and areas ($A/\alpha$) were derived. These parameters were correlated with endocardial blood flow and EER obtained using radiolabeled microspheres. The EER varied in these dogs from 0.08 to 1.4. In neither group of dogs did any MCE parameter derived from the endocardium correlate with endocardial flow or EER. The best correlations (ratios of areas under the curves from epicardium and endocardium vs EER) were 0.57 and 0.17, respectively (p=NS) in the two groups of dogs.

We conclude that EER cannot be assessed using MCE. The inability of MCE to assess the transmural distribution of blood flow may be related to tissue 'cross-talk' resulting from scatter of ultrasound from the microbubbles.

### REPRODUCIBILITY OF WASHOUT CURVES DERIVED FROM MYOCARDIAL CONTRAST ECHO.

Shimon A Reisner MD, Janine R Shapiro MD, Antonio F Amico MD, Richard S Meltzer MD, PhD, FACC.
University of Rochester, Rochester, NY

To investigate whether peak contrast intensity and washout half time (T1/2) derived from myocardial contrast time-intensity curves are reproducible, we performed repeated, paired left intracoronary injections of contrast in 8 open chest dogs. Sonicated 5% human albumin (bubble size 5.2±2.6 microns) was the contrast agent. Pairs of injections were performed 1) at baseline, 2) after ischemia induced by ligation of a coronary artery, and 3) during hyperemia produced by intravenous infusion of 0.75 mg/kg of dipyridamole. Blood pressure, pulmonary capillary wedge pressure and heart rate were kept at baseline level with fluids, neosynephrine and pacing. Time-activity curves were generated for the area of interest by beat per beat analysis of a frozen end-diastolic frame. Peak contrast intensity with background subtracted (PCI, gray scale units/pixel) for each injection was determined as the highest point of the curve. T1/2 was calculated from the decay phase of the curve using the least square fit by the equation T1/2=ln(2/k) (k = exponential decay rate). Thirty six paired high quality contrast washout curves were obtained in 6 dogs. PCI (mean±1SD), T1/2 (mean±1SD; units of T1/2 are cycles), p (by paired Student's t-test), correlation coefficient (r), and standard error of the estimate (SEE) were:

| | Injection 1 | Injection 2 | p | r | SEE |
|---|---|---|---|---|---|
| PCI | 45±8 | 45±10 | 0.97 | 0.80 | 6.8 |
| T1/2 | 4.2±0.6 | 4.0±0.7 | 0.09 | 0.86 | 0.3 |

Conclusion: Peak contrast intensity and washout half time derived from high quality myocardial contrast washout curves are reproducible at different coronary blood flow levels.

CURRENT MYOCARDIAL PERFUSION ECHO METHODOLOGY PRECLUDES AN ACCURATE ASSESSMENT OF CORONARY VASCULAR RESERVE.

Folkert J TenCate M.D., Patrick W Serruys M.D., Paul R Silverman M.D., Pieter D Verdouw Phd, Nico de Jong MSc., Thoraxcenter, Erasmus University, Rotterdam, The Netherlands.

Myocardial contrast echoperfusion (MCE) has recently been introduced into clinical cardiology. Among its possible applications is determination of coronary vascular reserve (CVR). To test this hypothesis we studied MCE and CVR in 10 patients (pts) and experimentally in 12 pigs (P). MCE was studied using intracoronary (i.c.) injections of sonicated iopamidol (microbubble size 9 ± 3$\mu$). For CVR, 0.42 mg/kg papaverine (i.c.) (Pap) was used and MCE measured after 30 seconds. In pts and P MCE images were digitized and time intensity parameters (TIP) calculated, including peak I (%I) from baseline before and after Pap. In P simultaneous electromagnetic coronary flow and myocardial wall thickness (MWT) (by epicardial ultrasound transducer) were measured. In P MWT increased significantly (>1mm) after Pap if coronary flow increased by >30%. However, in pts and P no correlation was found between %I or TIP and severity of the stenosis. Conclusions: In pts and P, MCE was unable to quantitate changes in bloodflow after Pap. This may be due to increased myocardial blood volume (as shown by increased MWT), current lack of standarization for TIP measurements and inability of current imaging systems to determine absolute Rf amplitudes.

TRANSTHORACIC TWO-DIMENSIONAL ULTRASONIC HIGH FREQUENCY (7.5 MHZ) VISUALIZATION OF THE DISTAL LEFT ANTERIOR CORONARY ARTERY

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Previous transthoracic two-dimensional echocardiographic (2DE) imaging techniques could look only at the proximal coronary artery anatomy within the focal zone of standard imaging frequencies of 2.5 to 3.5 MHZ. We hypothesized that new higher frequeny (7.5 MHZ) mechanical 2DE transducers would not only improve nearfield resolution, but also allow visualization of the distal left anterior descending (LAD) artery normally masked by near field artifacts of standard transducers.

Prospectively , we studied 35 patients (PTS) using a modified apical window and visualized the long and short axis of the distal LAD in 28 patients. This was confirmed by guide wire detection during LAD coronary angioplasty. Length, diameter and circumference were measured on line:

| | |
|---|---|
| Length - | 2.4 cm ± 0.89 |
| Diameter - | 0.2 cm ± 0.17 |
| Circumference - | 0.32 cm ± .008 |

We conclude that the improved nearfield resolution of high frequency (7.5 MHZ) 2DE transducers allow visualization of the distal LAD which is one of the most anterior structures of the heart. In the future it may be possible to detect distal LAD disease, flow, and response to pharmacologic and mechanical intervention. This approach may also be useful in detecting other distal coronary arteries.

NONINVASIVE EVALUATION OF THE INTERNAL MAMMARY ARTERY BY ULTRASONIC DUPLEX-SCANNING.

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To evaluate the feasibility of ultrasonic duplex-scanning (i.e. combined display of a 7.5 mHz 2D-echo and 5.0 mHz pulsed Doppler) of both left and right internal mammary artery(IMA), we studied 20 normals (mean age 30 yrs). In all pts both left and right IMA were imaged, either from the supraclavicular fossa, the third and fifth intercostal space. Only 2 left IMA's could not be found in the fifth intercostal space. At origo level the diameter of both IMA's was 3.1±0.6mm (mean ± 1SD), and at the fifth intercostal space 2.1±0.3mm. The peak systolic(S) velocity was 1.1±0.2 m/sec, the diastolic(D) velocity 0.3±0.05 m/sec. in both IMA's (ratio S/D 3.7). In 15 asymptomatic pts post IMA-bypass surgery a peak systolic velocity of 0.8±0.4 m/sec and a peak diastolic velocity of 0.7±0.5 m/sec was measured (ratio S/D 1.1).
Conclusions:
(1) Ultrasonic duplex-scanning can be of help to properly select the internal mammary arteries for coronary artery bypass grafting and
(2) may provide, as a noninvasive method, useful information about left and right IMA patency in the postoperated patient.

## Tuesday, March 21, 1989
## 4:00PM–5:30PM, Garden Grove Room
## Anaheim Convention Center
## Hypertrophic, Dilated and Restrictive Myocardial Disease

SPECTRUM OF RESTRICTIVE CARDIOMYOPATHY: A MULTICENTER STUDY

Yuzo Hirota, M.D., Gen Shimizu, M.D., Yoshio Kita, M.D., Yasushi Nakayama, M.D., Keishiro Kawamura, M.D., Seiki Nagata, M.D., Toshitami Sawayama, M.D., Toru Izumi, M.D., Takeshi Nakano, M.D. and Morie Sekiguchi, M.D.
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This report describes clinical profiles of 23 Pts with restrictive cardiomyopathy (RCM) from 12 institutes based on the criteria of 1) congestive heart failure (CHF) due to stiff LV, 2) normal LV size and systolic function, 3) absence of LV hypertrophy, and 4) etiology unknown. There were 7 cardiac deaths; 1 died within 1 year, 1 at the 5th year, and 5 after 10 years. Three had family history of RCM and hypertrophic cardiomyopathy (HCM), respectively. Thromboembolism was observed in 7 Pts. Echocardiogram showed normal LV wall thickness and contraction, and pericardial effusion was common in Pts with severe CHF. The square root sign (SRS) of RV pressure was seen in 11 whose RA pressure was higher than those without SRS ((+):13±6 vs (-):6±3mmHg, p<0.005). This sign was seen in LV, and LA pressure was not different between Pts with and without SRS. RVEDP was higher in Pts with tricuspid regurgitation (TR) than that of Pts without TR ((+):15±5 vs (-):7±3mmHg, p<0.005), and equalization of RV and LV filling pressures was seen in Pts with severe TR. Interstitial fibrosis (19/20) and endocardial thickening (11/18) were the most common histological findings. Severe myocardial dysarray consistent with HCM was seen in 2 cases. Conclusions: 1) the clinical course of RCM is long, 2) RV and LV filling pressures could be equal with severe TR, 3) SRS is not diagnostic, and 4) thromboembolism is common. Some of them may be an atypical manifestation of HCM.

## REDUCING LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY BY PACING-INDUCED INTERVENTRICULAR SEPTAL PRE-EXCITATION.

Lameh Fananapazir, M.D., Judith Winkler, B.S., Bill Schenke, B.A., Deborah Barbour, M.D., Arshed Quyyumi, M.D., NHLBI, Bethesda, MD.

In some pts with hypertrophic cardiomyopathy, the inward systolic movement of the thickened interventricular septum and anterior movement of the mitral valve (SAM), cause LV outflow tract (OT) obstruction. In these pts., atrioventricular pacing (DOO) may increase LV OT dimensions by inducing paradoxical septal motion. This would reduce SAM and thereby LVOT obstruction, but also maintain the atrial contribution to cardiac output. We compared the effects of DOO pacing on LV OT gradients and aortic pressures with atrial pacing at identical heart rates, during cardiac catheterization in 16 pts. The results were:

| | Pacing Mode (Atrioventricular Delay, ms) | | | |
|---|---|---|---|---|
| Heart | Atrial | DOO(80) | DOO(100) | DOO(120) |
| Rate | | (LV OT Gradient, mmHg) | | |
| 100 | 73 ± 31 | 54 ± 21* | 58 ± 27* | 58 ± 26* |
| 120 | 78 ± 31 | 53 ± 23* | 54 ± 26* | 49 ± 24* |
| 150 | 61 ± 46 | 32 ± 27* | 27 ± 23* | 36 ± 20* |
| | | (Aortic Systolic Pressure, mmHg) | | |
| 100 | 105 ± 14 | 99 ± 15 | 99 ± 18 | 103 ± 16 |
| 120 | 94 ± 17 | 95 ± 18 | 98 ± 17 | 99 ± 15 |
| 150 | 84±25 | 89 ± 31 | 98 ± 26 | 87 ± 23 |

*=p<0.05 compared with atrial pacing.

Conclusion: Ventricular septal pre-excitation during DOO pacing results in significant relief of LV OT obstruction - an effect that is not associated with hypotension and is exaggerated at higher heart rates. This intervention may have clinical utility in some pts with with obstructive hypertrophic cardiomyopathy.

## EVIDENCE FOR AN ABNORMAL VASODILATOR RESPONSE IN HYPERTROPHIC CARDIOMYOPATHY.

Micheal P. Frenneaux, M.B., Peter J. Counihan, M.B., David Webb, M.D., William J. McKenna, M.D., F.A.C.C. St George's Hospital Medical School, London, U.K.

Sudden death is common in hypertrophic cardiomyopathy (HCM) but the mechanism(s) have not yet been established. To identify those at risk of hemodynamic collapse, 103 pts with HCM, age 12-70 (mean 40) yrs underwent symptom limited treadmill exercise with standard cuff blood pressure recording (BP) at each minute of exercise and every 15 seconds during recovery for 3 minutes on at least 2 occasions. The test was repeated in 25 with direct arterial pressure measurement. Fifty one had a normal and 52 an abnormal BP response with either hypotension during recovery or a fall during exercise of ≥ 20 mm Hg (range 20-100, mean 45 mm Hg) from the peak value to that recorded immediately before stopping. A family history of sudden death was more common in those with an abnormal exercise BP response (24/52 vs 3/51, p<0.001). To assess the mechanism of the hypotensive response 10 with an abnormal and 7 with normal exercise BP response underwent exercise hemodynamic studies, with continuous direct arterial pressure recording and measurement of cardiac output each minute. Systolic BP fell by 25-95 (mean 50) mm Hg in all 10. The rise in cardiac index on exercise ($l/min/m^2$) was similar in those with normal (2.3±0.5 to 8.8±2.4) and abnormal BP response (2.1±0.5 to 7.2±1.1). Systemic vascular resistance in the 2 groups at rest and at 2 mins exercise was similar, but at peak exercise fell significantly more in the hypotensive vs normal BP responders (22±6% vs 42±4% of resting values, p<0.01). To assess the mechanism of this abnormal vasodilation, forearm plethysmography was performed during supine bicycle exercise in 11 hypotensive pts and 10 normal volunteers. Forearm vascular resistance fell by 18±45 % in the hypotensive pts, but increased by 131±45 % in the normals (p=0.003). In conclusion: Exercise hypotension is common in HCM, is strongly associated with a family history of sudden death and is due to an inappropriate vasodilation of non exercising vascular beds.

## BENEFICIAL EFFECTS OF LONGTERM BETA-BLOCKADE WITH BUCINDOLOL IN PATIENTS WITH IDIOPATHIC DILATED CARDIOMYOPATHY.

Jeffrey Anderson, MD, FACC, Edward Gilbert, MD, John O'Connell, MD, FACC, Dale Renlund, MD, FACC, Frank Yanowitz, MD, FACC, Marian Bartholomew, BS, Marianne Murray, RN, Patricia Mealey, RN, Kirk Volkman, RN, Michael Bristow, MD, PhD, University of Utah, Salt Lake City, Utah.

Beta-blockade represents a promising but controversial therapeutic approach to idiopathic dilated cardiomyopathy (DCM). Bucindolol (B), a novel new beta-blocker, showed favorable effects in a shortterm trial in DCM, but longterm response is unknown. In order to assess this, 20 study pt (7/9 placebo, 13/14 B pt) received chronic B and were followed for 21 ± 4 mo (range, 15-28). Mean age was 49 y (range, 29-66), and mean functional class (FC), 2.6 (2-4); disease duration averaged 11 mo (1-190); 15 pt were men. At most recent followup (9/88), all 20 were alive, 17 continued on B (mean dose, 157 mg/d, range, 25-200), and 2 were transplanted. Paired endpoints were (mean ± SD):

| STUDY | Rest EF(%) | FC | ET(min) | VO2 max (ml/kg/min) |
|---|---|---|---|---|
| Baseline | 25.4±8.2 | 2.5±0.5 | 9.4±3.1 | 19.1±5.1 |
| Followup | 34.8±13.4 | 2.0±0.8 | 9.1±3.5 | 18.6±5.5 |
| mo f/u | 15.2 | 19.6 | 14.7 | 14.1 |
| N pt | 19 | 18 | 19 | 19 |
| p | 0.001 | 0.03 | 0.62 | 0.53 |

EF=ejection fraction, ET=exercise time, VO2 max=maximum oxygen consumption.

Thus, longterm B leads to striking increases in EF and improved FC while maintaining stable exercise performance. Also, similar or better EF (mean, +1.5 percentage points) and ET (+0.4 min) were observed after longterm than shortterm (3 mo) B. Given this excellent tolerance, survival, and functional efficacy result, longterm B therapy deserves further evaluation in DCM.

## SURVIVAL OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY SUCCESSFULLY RESUSCITATED FROM SUDDEN CARDIAC ARREST.

Franco Cecchi, M.D., Barry J. Maron, M.D., F.A.C.C., Stephen E. Epstein, M.D., F.A.C.C., NHLBI, Bethesda, Maryland.

While sudden death is the most devastating complication of hypertrophic cardiomyopathy (HCM), the long-term outcome of that unique subgroup of Pts successfully resuscitated from cardiac arrest (CA) is not known. This study describes long-term outcome of 33 such Pts with HCM. Cardiac arrest occurred at ages 9 to 62 years (mean 32); 5 Pts survived multiple arrests (i.e., 2 or 3). A variety of treatments were administered; 18 Pts with outflow obstruction had myotomy-myectomy or mitral valve replacement and also drug therapy, while 15 Pts received medical therapy alone. To date, 22 of the 33 Pts (67%) have survived after CA for 1.5 to 22 years (mean 7); 12 have survived >5 years. Of the 22 survivors, 16 have remained asymptomatic or only mildly symptomatic; 6 others have become severely symptomatic with cardiac failure, including 3 with LV wall thinning and cavity enlargement. Eight Pts died of cardiac causes (suddenly or progressive heart failure) 7 months to 8 years (mean 5 years) after CA. Actuarial Pt survival was 97±%, 74±9% and 61±11% after 1, 5 and 10 years. Event free rate (without recurrent cardiac arrest or SD death) was 83±7%, 65±9% and 53±11%. In conclusion, long-term outcome of Pts with HCM after SD was variable. Recurrent CA or premature death (sudden or due to congestive failure) occured in about one-third of Pts, most commonly in the first 5 years after initial CA. Conversely, most Pts survived and remained free of CA and marked symptoms. Aborted episodes of sudden death do not necessarily convey an ominous prognosis in HCM and in some Pts appear to be isolated events in the natural history of their disease.

Growth Factors Identified in Myocardium of Patients with Hypertrophic Cardiomyopathy. Pamela Karasik, M.D., S. Ward Casscells, M.D., Charles L. McIntosh, M.D.,Stephen E. Epstein, M.D. NHLBI, Bethesda, MD.

Acidic and basic fibroblast growth factors (aFGF, bFGF) have been identified in many tissues of mesenchymal origin Because both aFGF and bFGF have a strong affinity for heparin, we applied the technique of heparin-sepharose chromatography to determine if these factors were present in myocardium obtained at the time of left ventricular myomectomy in pts with hypertrophic cardiomyopathy (HCM). Fresh tissue was homogenized in phosphate buffered saline with protease inhibitors, and centrifuged at 48,000 g x 60 minutes. The supernatant was applied to a heparin-sepharose column, washed, and eluted with 10mM Tris, EDTA, and increasing concentrations of NaCl. Crude homogenate, supernatant, and column fractions were tested for mitogenicity on quiescent Balb/c 3T3 cells. The homogenate, supernatant, and column fractions eluted at 1.0-2.0M NaCl (which are known to contain aFGF and bFGF, if present) were potent mitogens, stimulating DNA synthesis two to six fold. Mitogenicity of the homogenate and of the column fractions eluted at 1.0-1.5M NaCl were potentiated 50-100% by the addition of heparin, in the 10-20ug/ml range (a characteristic of aFGF). Thus myocardium derived from pts with HCM contains potent mitogens, most likely aFGF and bFGF. These data suggest a potential role of growth factors in the pathophysiology of HCM.

ELEVATED RIGHT VENTRICULAR PRESSURE INCREASES COLLAGEN IN VENTRICULOTOMY SCARS IN CANINES.
Susan W. Denfield, M.D., Debra Kearney, M.D., Kathleen Sprague, B.S., Arthur Garson Jr., M.D., F.A.C.C., Baylor College of Medicine, Texas Children's Hospital, Houston, Texas.

Ventricular arrhythmias (VA) are a significant problem in patients who have had repair of tetralogy of Fallot. The VA may be associated with increased right ventricular systolic pressure (RVSP) and are mapped in the electrophysiology laboratory adjacent to large areas of scar. It was our hypothesis that increased RVSP would alter healing and scar formation. Eight adult beagles of either sex weighing 9-14 kg had right ventriculotomy only (N=4) or right ventriculotomy and pulmonary artery band placement (N=4). RVSP was initially normal (<22 mmHg) in all dogs prior to band placement. The RVSP averaged 55±24 mmHg (SD) (range 38-90) after banding. The scars were allowed to mature for a minimum of 2 months. The hearts were removed and scars examined by hematoxylin and eosin and Gomori's trichrome stains for collagen. The amounts of dense and loose collagen and fat in each scar were estimated by light microscopy using the following scale: 0 = absent, 1 = 1-25%, 2 = 26-44%, 3 = 45-55%, 4 = 56-75%, 5 = 76-100%. The scars that healed with high RVSP had more dense collagen (all had score ≥4) and less fat (all ≤2) than those healing with normal RVSP - dense collagen (all ≤3), fat ( all ≥2) (P <0.03). It is possible that differences in scar composition may alter the arrhythmogenic potential of scar and surrounding myocardium and may contribute to the VA seen in some patients with high RVSP following repair of tetralogy of Fallot.

## Tuesday, March 21, 1989
## 2:00PM–3:30PM, California Room C
## Anaheim Convention Center
## Basic Science and Clinical Advances in Pediatric Cardiology

NONCARDIAC DEFECTS ASSOCIATED WITH CONOTRUNCAL ABNORMALITIES-FURTHER IMPLICATIONS OF NEURAL CREST INFLUENCE

Todd W. Ussery,B.S., Frederick W. Arensman,M.D.,F.A.A.C., Linda Leatherbury,M.D.,F.A.A.C., David B. Flannery,M.D., John D. Harmon,M.D., Margaret F. Guill,M.D., Mary S. Leffell,PhD., Ronald A. Bell,D.D.S., William B. Strong,M.D.,F.A.A.C., Medical College of Georgia,Augusta,Georgia.

Previous animal research has demonstrated that ablation of chick neural crest (NC) results in both a high incidence of cardiac conotruncal abnormalities and associated noncardiac malformations. Because the NC influences the development of many noncardiac structures in humans, we chose to assess the incidence and severity of abnormalities associated with Tetralogy of Fallot (TOF) and Persistent Truncus Arteriosus (PTA). 26 Patients (Pts) were evaluated by otolaryngologic, audiologic, facial dysmorphism, immunologic and cephalometric criteria. The mean number of NC abnormalities was 2 ± 1 including those of brow, ptosis, iris and palpebral fissures. Mean pharyngeal arch abnormalities numbered 5 ± 2 including pinnae, mandible, nasal bridge and alae, nares, philtrum and malar flatness. Total cutaneous anergy was present in 65% of the Pts, while low T cell number was observed in 75% of the TOF Pts and 100% of the PTA Pts. Even when %CD3 was normal, 60% had low %CD4. The incidence of associated abnormalities was not significantly different between TOF and PTA groups, but the total group had many more abnormalities than a normal population (p <.00001). Thus abnormal neural crest influence is implicated in human conotruncal malformations by the high incidence of associated noncardiac abnormalities. Pts with conotruncal abnormalities should undergo multidisciplinary screen to assess their need for complete noncardiac diagnosis and potential intervention.

Depressed Myocardial Function and Ventricular Wall Stress in Neural Crest Ablated Chick Embryos
David S. Braden M.D., Linda Leatherbury M.D., F.A.C.C., William F. Jackson Ph.D., Harold E. Gauldin. Medical College of Georgia, Augusta, Georgia.

Microcinephotography was used to study a model of persistent truncus arteriosus created in chick embryos by cauterizing premigratory neural crest destined for the fourth aortic arches and truncal septum. When embryogenesis reached the looped cardiac tube stage, 15 experimentals and 15 control embryos were evaluated. Previous data demonstrated a significantly decreased ventricular shortening fraction (SF%) in experimental embryos with similar cardiac outputs. This decreased SF% was hypothesized to be due to increased ventricular wall stress secondary to increased resistance in the aortic arch arteries. Peak-systolic meridional stress (PSSm) and peak-systolic circumferential stress (PSSc) were calculated using peak-systolic ventricular pressures (PSVP). (Data as means ± S.D.)

| | SF% | PSVP (mmHg) | PSSm ($g/cm^2$) | PSSc ($g/cm^2$) |
|---|---|---|---|---|
| Controls | 76±8 | 1.85±0.52 | 2.93±1.47 | 4.27±1.55 |
| Experimental | 53±12 | 1.85±0.48 | 3.35±1.86 | 4.57±1.25 |
| % Change | -30% | 0 | +14% | 7% |
| p value | <0.001 | NS | NS | NS |

Approximately 50% of experimental embryos have aortic arch anomalies. Although both PSSm and PSSc stresses were greater in experimental embryos, this difference was not statistically significant. Likewise, there was no difference in PSVP between experimental and control embryos. Therefore, the previously documented decrease in SF% in experimental embryos is probably due to myocardial dysfunction and not due to difference in wall stress from aortic arch artery anomalies.

MECHANICAL FUNCTION AND PALMITATE OXIDATION IN THE NEONATAL PIGLET HEART DURING NORMOTHERMIC ISCHEMIA AND REPERFUSION.

Robert J. Ascuitto, M.D., Ph.D., Nancy T. Ross-Ascuitto, M.D., Kathleen H. McDonough, Ph.D., Tulane and Louisiana State University Schools of Medicine, New Orleans, LA.

Information is limited regarding substrate utilization by the neonatal heart during ischemia and reperfusion. Left ventricular peak systolic pressure (PSP), end-diastolic pressure (EDP), coronary flow (CF), $0_2$ consumption ($MVO_2$) and palmitate oxidation (Ox) were studied in isolated hearts from pigs less than 2 days of age. Paced, isovolumically-beating hearts were perfused with a non-recirculating, oxygenated buffer (37°C) containing: erythrocytes, Hct 15%; glucose, 5mM and $^{14}C$ palmitate, 0.5mM palmitate bound to 2% albumin. Ox was determined from $^{14}CO_2$ production. Each heart was studied for 30 minutes with the perfusion pressure (PP) 60 mmHg (control): 30 minutes with PP 12 mmHg (normothermic ischemia) and 30 minutes with PP returned to baseline (reperfusion). Control values averaged: PSP, 101±7 mmHg; EDP, 1.3±0.4 mmHg; CF, 3.7±0.2ml/min/g; $MVO_2$, 81.5±8.5 ul/min/g and Ox, 28.8±2.1 nmol/min/g. During ischemia, these parameters decreased to 32±3 mmHg, 0.8±0.1 mmHg, 0.9±0.2 ml/min/g, 29.5±3.4 ul/min/g and 11.4 ±1.0 nmol/min/g, respectively. Upon reperfusion, CF increased two-fold and PSP 20% above control values and then returned to baseline. No significant increased in EDP was observed. Ox rates increased to control values by the end of reperfusion. The influence of lactate concentration on palmitate Ox has also been examined. Thus, the neonatal pig heart can utilize palmitate during low-flow ischemia and reperfusion, and recovers mechanical function following such an insult.

THE IMPORTANCE OF ANALYZING INSPIRATORY GASES WHEN CALCULATING OXYGEN CONSUMPTION AND CARBON DIOXIDE PRODUCTION DURING EXERCISE.

Gerald Barber, M.D. and Charles T. Heise, C.R.T.T. The Children's Hospital of Philadelphia, Philadelphia, PA.

Accurate breath-by-breath (BBB) determination during exercise of $O_2$ consumption ($VO_2$) and $CO_2$ production ($VCO_2$) is valuable in: 1) determination of the anaerobic threshold, 2) non-steady state exercise (ramp) protocols, and 3) determination of the time constants of the $VO_2$ and $VCO_2$ response to rapid changes in workload. We compared 1161 BBB $VO_2$ and $VCO_2$ values from 6 normal patients calculated using 3 different algorithms. In I (reference method), measured inspiratory and expiratory $O_2$, $CO_2$, and $N_2$ content were used to calculate $VO_2$ and $VCO_2$. In II, $VO_2$ and $VCO_2$ were calculated ignoring inspiratory and expiratory $N_2$ contents (which reflect changes in functional residual capacity) and, in III, $VO_2$ and $VCO_2$ were calculated ignoring all 3 inspiratory gases. A paired t-test was used to compare II and III to I.

There was no statistical difference in the mean $VO_2$ or $VCO_2$ at rest or any workload between the 3 algorithms. Methods II and III, however, result in significantly greater BBB variability.

| | % BBB Variability | | | | | |
|---|---|---|---|---|---|---|
| Workload | $VO_2$ | | | $VCO_2$ | | |
| | I | II | III | I | II | III |
| Rest | 39 | 206 | 35 | 37 | 37 | 34 |
| 1st | 17 | 54 | 22 | 17 | 22 | 23 |
| 2nd | 14 | 40 | 18 | 13 | 17 | 17 |
| 3rd | 9 | 33 | 12 | 9 | 11 | 11 |

We conclude that, due to the high BBB variability of methods II and III, only Method I appears to be acceptable for BBB determination of $VO_2$ or $VCO_2$.

**The Impact of Medical and Surgical Therapy on the Cardiovascular Prognosis of the Marfan Syndrome in Early Childhood.**

Kenneth G. Zahka, M.D., Cathy Hensley, Marshall Glesby, Reed E. Pyeritz, M.D. The Johns Hopkins Hospital, Baltimore, Maryland

We determined the cardiovascular natural history and the effects of beta blockade and surgery on 53 children presenting in the first 4 years of life with the Marfan syndrome. There were 24 sporadic (age 2.1±0.3 yrs) and 29 familial (age 1.9±0.2 yrs) cases. The mean follow-up for both groups was 4.0±0.9 yrs. Ao root and LV dimensions measured from M-mode echocardiograms were normalized for age and body surface area by calculating the Ao ratio (observed Ao/predicted Ao) and the LV ratio (observed LV/predicted LV). Data: The Ao ratio at the time of presentation was greater in the sporadic (1.43±0.33) than the familial (1.28±0.21) cases ($p<0.025$). The Ao ratio increased during follow-up in both sporadic (1.59 ±0.42 $p<0.05$, n=22) and familial (1.35±0.14 $p<0.025$, n=21) cases. There was no change in the Ao ratio in the 4 familial and 6 sporadic cases on beta blockers for 3.3 ±0.7 yrs (1.36±0.27 to 1.35±0.21). The Ao ratio in those on no therapy increased (1.30±0.31 to 1.50±0.36, $p<0.01$). The LV ratio in cases with no / mild mitral regurgitation (MR) (all the familial and 15/24 sporadic) was 0.99±0.09. The LV ratio was markedly increased (1.31±0.25) in 9/24 sporadic cases with moderate or severe MR. Of these 9, 5 had mitral valve (MV) replacement with one death, 1 had MV and tricuspid valve (TV) repair and 1 had MV and TV repair and aortic homograft replacement. The LV ratio in the 6 survivors decreased to 1.08±0.11, $p<0.001$.
Conclusions: The cardiovascular complications of the Marfan syndrome are often more severe in young children with new mutations. Beta blockade has a preventive role and cardiovascular surgery can be effective in the treatment of young children with the Marfan syndrome.

## Tuesday, March 21, 1989
## 4:00PM–5:30PM, California Room C
## Anaheim Convention Center
## Interventional Cardiology and Cardiac Surgery in Children

**USE OF BALLOON-EXPANDABLE STENTS TO TREAT EXPERIMENTAL PERIPHERAL PULMONARY ARTERY AND SUPERIOR VENA CAVAL STENOSIS:PRELIMINARY EXPERIENCE.**

Albert P Rocchini MD, Jon N Meliones MD, Robert H Beekman MD,FACC,C S Mott Children's Hospital, Univ of Michigan, Ann Arbor,Mi

Current therapy for congenital or acquired stenoses of the peripheral pulmonary arteries (PPA) and superior vena cava (SVC) is frequently ineffective. This report describes our initial experience with the use of a balloon-expandable stent to treat experimentally created PPA and SVC stenosis. Seven adult mongrel dogs had surgically created stenoses of either a PPA or SVC ( 5 Rt PPA, 1 Lt PPA and 1 SVC). A balloon-expandable stainless steel (0.076 mm) 3 cm long, intravascular stent was used in all animal ( provided by Johnson and Johnson Inc). Percutaneous placement of the stents was performed using a 12-16 French 75 cm long sheath and a 8 or 18 mm balloon angioplasty catheter. Stents were successfully placed in 4/7 animals ( 2 Rt PPA, 1Lt PPA and 1 SVC) with hemodynamic and angiographic relief of stenoses in all. We were unable to successfully place the stents in 3 animals with very distal Rt PPA stenosis due to inability to cross the stenotic site with either the large sheath or angioplasty catheter. Repeat catheterization performed six month following placement of the stents, documented persistent gradient relief and angiographic evidence of unobstructed flow through the stent without evidence of thrombus formation. Our preliminary experience suggests that balloon-expandable stents are a potential alternative for the treatment of PPA and SVC stenoses.

## TRANSCATHETER UNBRELLA CLOSURE OF ATRIAL DEFECTS

James E Lock MD, Jonathan J Rome MD, Stanton B Perry MD, John F Keane MD. Children's Hospital, Boston Mass,

We have modified the Rashkind double umbrella PDA technique to attempt closure of atrial defects (ASD) in 14 pts. All but 1 had had prior surgery (Fontan, TOF repair, Glenn, etc); one pt had an ASD 2° and severe LV myopathy. Defects were ASD 2°(n=5); SVC/RA defects post-Glenn(n=5) and post-Fontan ASD(n=4). ASD size (Balloon sizing) ranged from 5 to 27mm; umbrellas(17-34mm) were chosen to have a stated diameter of nearly 2x ASD diameter or larger. Twelve of 14 pts were cyanosed, 2 pts had atrial arrhythmias (post-Fontan) and 3 had strokes or brain abscess pre-umbrella.

Two defects(11, 27mm) were too large to close with the umbrellas available; the procedure was terminated without umbrella release. All other ASDs were closed with a single umbrella: no umbrella became dislodged, no arrhythmias occurred, and no pt had vascular compromise. Angio/echocardiography suggested complete closure in 11/12 defects; 1 pt (post-Fontan) appeared to have multiple defects. All but 1 (immediate postop) pt were discharged within 48 hrs.

Followup ranged from 2-39 months (m=18 mos) for a total of 18 pt-yrs. No pt has had umbrella migration, umbrella-induced dysfunction of great vessel or cardiac valve, endocarditis, brain abscess, or stroke. Two pts have had late arrhythmias, both post-Fontan: 1(with 2 limited episodes of flutter) had atrial arrhythmia pre-umbrella, and 1 (with L-loop and an umbrella in the LSVC-LA junction) developed A-V block 2½ years postop. No pt has had evidence of recanalization. There have been no deaths.

These data suggest that modified double umbrellas to close atrial defects are not associated with frequent late complications. Trials of modified double umbrellas in patients with uncomplicated ASD secundum would now appear warranted.

## SURGICAL MANAGEMENT OF AORTIC ARCH OBSTRUCTION AND TRANSPOSITION OF THE GREAT ARTERIES.

John E. Mayer, Jr., M.D., F.A.C.C., Gil Wernovsky, M.D, Richard A. Jonas, M.D. and Aldo R. Castaneda, M.D., Ph.D., F.A.C.C.
The Children's Hospital, Boston, MA

Aortic arch obstruction (AAO) is an uncommon associated anomaly in pts with transposition of the great arteries (TGA). Between 1/1/83 and 7/1/88, 14 pts with TGA and AAO underwent surgical management by an arterial switch operation (ASO) and aortic arch repair. Two pts had intact ventricular septum (IVS) and 12 had ventricular septal defect (VSD) or double outlet right ventricle (DORV). AAO was due to isolated coarctation (CoA) in 11, CoA plus severe transverse arch hypoplasia in 2 and type B interruption (IAA) in 1.

Both pts with IVS and 1 with small VSD had neonatal CoA repair and ASO at 6d, 17d and 2 mos of age; 1 pt died. The two pts with arch hypoplasia, CoA, and VSD were managed as neonates by one-stage ASO, VSD closure and arch reconstruction via midline sternotomy; both survived. Of the remaining 9 pts, 8 had neonatal CoA or IAA repair with pulmonary artery banding (PAB) and subsequent ASO at 4-28 mos of age, and 1 had neonatal PAB, CoA repair at 3 1/2 mos and ASO at 4 mos. All but 1 (with multiple VSD's) of these 9 pts survived.

Seven of 12 survivors have had follow-up cardiac catheterization. None has significant (>15 mmHg) residual AAO, residual VSD or "aortic" valve regurgitation. The remaining 5 pts have no clinical or echocardiographic evidence of residual AAO or VSD.

The combination of TGA and AAO can be successfully managed by an ASO and aortic arch reconstruction. Recent experience has shown that ASO and arch reconstruction can be performed as a single procedure for more severe arch anomalies or by staged procedures during the same hospitalization for isolated CoA. Follow-up has shown satisfactory early results up to 5 years postoperatively.

## EARLY EXPERIENCE WITH PULMONARY AUTOGRAFT USE FOR AORTIC VALVE REPLACEMENT IN PEDIATRIC PATIENTS

Kent E. Ward, M.D., FACC; Edward D. Overholt, M.D., FACC; Jerry D. Razook, M.D.; Webb M. Thompson, Jr., M.D., FACC: Paul Stelzer, M.D., FACC; Ronald C. Elkins, M.D., FACC, University of Oklahoma, Oklahoma City, Oklahoma.

Initial results with use of pulmonary autografts (PA) for aortic valve replacement (AVR) have been successful in adults. We have used PA for AVR with combined homograft replacement of the pulmonic valve in 15 children (age range 2.6-17.1 yrs., mean=11.7 yrs.) since 11/86. Indications for AVR were severe aortic stenosis (AS)(n=2), aortic insufficiency (AI)(n=6) or both (n=7). Six patients (pts) had undergone one or more previous aortic valvulotomies and 5 had undergone prior valvuloplasties.

PA's were performed using hypothermic circulatory arrest with a mean aortic cross-clamp time of 119 min. and a mean bypass time of 195 min. Most pts were extubated within 24 hrs. (mean=12 hrs.) and the average hospital stay was 8 days. There have been no deaths nor early thromboembolic events. Postoperative echocardiographic assessment was performed in each pt from 0.1 to 15.4 mos. after AVR. Aortic obstruction was significantly reduced from 67±22 mm Hg (pre-op) to 6±10 mm Hg (post-op) ($p<0.001$). One patient had significant residual transpulmonary obstruction. Significant AI was found in 4 of the first 5 pts and one of the following 10. Significant pulmonic insufficiency was present in 1. Other major complications were early cardiac tamponade in 1 and postoperative complete heart block in 1. Our results show PA replacement of the aortic valve in children can be accomplished with a low mortality and morbidity. PA's showed good function after a short follow-up period. Significant AI may be a long term problem, but appeared to be related to early surgical technique.

## ISCHEMIC TIME AND GRAFT FUNCTION IN HUMAN INFANT CARDIAC TRANSPLANTATION

Mark M. Boucek, MD, Mohammad S. Kanakriyeh, MD, Eugene L. Petry, MD, Leonard L. Bailey, MD, FACC
The Neonatal Cardiac Transplant Program
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Donor availability and the sensitivity of neonatal myocardium to ischemic injury may interact to limit the supply of infant cardiac allografts. To evaluate graft function as related to ischemic time, we studied 21 consecutive infants (<1 year) using echo indices of LV function post transplantation. All grafts were preserved similarly and all patients were on cyclosporine immunosuppression without evidence of rejection. Fifteen grafts harvested locally with a mean arrest time of 102±8.7 min were compared to 6 distantly procured grafts with a significantly longer arrest time 282±57 min (276%, $p<0.05$). Grafts were studied 7 and 30 days after transplantation and LV shortening fraction (LVSF), ejection phase ratio (PEP/ET), isovolumic relaxation time (IVRT), mass, and dimension were determined. In the local grafts the mean LVSF at 7 days was 39±6%, the mean PEP/ET ratio was .32 ±0.6 and the IVRT was 55±18 msec. These values were not significantly different from the respective distantly procured graft values of 37±7%, .39±0.5 and 69±48 msec. At 30 days, graft function was still normal in the local group with a mean LVSF of 40±6%, a PEP/ET ratio of .28± .05 and an IVRT of 53±16 msec, and these values were not significantly different from the data on the distant organs. There were 4 deaths (19%). Graft failure occurred with a similar frequency in both groups (13% vs 16%), but was unrelated to ischemic time. We conclude that the infant donor myocardium can tolerate an ischemic time as long as 5 hrs and 40 min and still acutely function adequately as an allotransplanted organ. These data indicate a potential procurement range of 1500 - 2000 miles.

VENTRICULAR SEPTAL DEFECT WITH AORTIC REGURGITATION: A 35 YEAR EXPERIENCE

L. Rhodes MD, J.F. Keane MD, J.P. Keane, K.E. Fellows MD FACC, R.A.Jonas MD FACC, A.R. Castaneda MD FACC: The Children's Hospital/Harvard Medical School, Boston, MA.

The purpose of this study was to review our experience with 91 pts (33 females) with ventricular septal defect (VSD) and audible aortic regurgitation (AR). Median age of AR onset was 5 years (range 0.5-17). VSD location was subpulmonary (SP) in 26% and subcristal (SC) in 65%. AO valve was tricuspid in 88% and bicuspid in 10% (2 pts with SP). Right coronary cusp (RCC) prolapse alone was present in 60% (83% of SP, 59% of SC), noncoronary cusp (NCC) alone in 12% (all with SC), and both RCC and NCC in 15% (13% of SP, 19% of SC). AR progressed in 28 pts (40% of SP, 33% of SC). 19 pts (7 with SP) have been followed medically (median 15 years), degree of AR remaining unchanged in 71% (including 2 with SP, each followed over 30 years). 72 pts underwent VSD closure, with valvuloplasty (VP) in 47, valve replacement (AVR) in 15, and alone in 10. There were 14 perioperative deaths, all prior to 1973. Following VP, AR was absent in 13%, less in 30%, unchanged in 21%, and more in 10% (3 pts required AVR). AR improvement occurred in 58% of those < 10 years old compared to 31% in those older. In those with AVR, AR was absent in 60% and less in 27%; reoperation was required in 3. In 8 survivors of VSD closure alone, AR was absent in 4, less in 2, unchanged in 1, and more in 1. Endocarditis (BE) occurred on 14 occasions in 13 pts.

Conclusions: VSD with AR is more common in males, VSD location SC in most, median age of AR onset 5 years, and BE is common. NCC prolapse alone is seen only in those with SC. Degree of AR may remain mild for many years in some, and complete relief is more common following AVR. VP is more effective when undertaken in the first decade.

PORTABLE BYPASS DOES NOT IMPROVE SURVIVAL IN CARDIAC ARREST PATIENTS

Renee Hartz, M.D., Joseph LoCicero, M.D., John Sanders, M.D., James Frederiksen, M.D., Lawrence Michaelis, M.D., Northwestern University Medical School, Chicago, Illinois.

Technical improvements in portable bypass systems have led to a rekindling of interest in the use of cardiopulmonary bypass as a resuscitative tool. In 16 months, 24 pts undergoing in-hospital CPR were placed on bypass within 9 minutes (mean) from phone request (range 7-35). An average flow of 4.3 liters per minute (3-5.2), was achieved using right femoral cutdowns and the Bard ® CPS system. Etiology of cardiac arrest was cardiogenic shock in 15 pts, metabolic in 2, septic shock in 1, arrhythmogenic in 1, iatrogenic in 1, pulmonary or amniotic fluid embolus in 3, and aortic dissection in 1. Of the 24 arrests, 18 occurred in the hospital. Subsequent diagnostic/therapeutic procedures carried out in 15 pts were: cardiac catheterization (7), other supportive devices (5), coronary bypass (4), pulmonary artery exploration (4), valve replacement (2), angioplasty (2), dialysis (1), and rewarming (1). Although 12 pts pts initially regained brief cardiac activity, only one (4%) achieved long-term survival. Five additional pts (20%) were successfully weaned from bypass and survived 2-10 days. Causes of death in the remaining 18 pts were biventricular failure, brain death, or a combination of these factors.

The dismal results in this series of resuscitations using portable cardiopulmonary bypass indicate that despite rapid implementation even for witnessed, in-hospital events, survival is negligible if the technology is employed after cardiac arrest occurs.

## Tuesday, March 21, 1989
## 2:00PM–3:30PM, Santa Ana Room 1
## Anaheim Convention Center
## Cardiac Surgery: Devices and Complications

FIRST HUMAN USE OF THE HEMOPUMP, A CATHETHER-MOUNTED VENTRICULAR ASSIST DEVICE

O.H. Frazier MD FACC, Richard K Wampler MD, J Michael Duncan MD FACC, Wayne E Dear MD FACC, Michael P Macris MD, Stephen M Parnis, John M Fuqua Texas Heart Institute, St. Luke's Episcopal Hospital, Houston, TX

The Hemopump is a catheter-mounted, temporary ventricular assist device. It consists of an external electromechanical drive console and a disposable, intra-aortic axial flow pump (21 French). Power is transmitted to the pump percutaneously by a flexible drive shaft within the catheter. The device is positioned in the left ventricle using a femoral artery cut-down or via the ascending aorta. Blood is withdrawn from the left ventricle through the transvalvular inlet cannula and pumped into the aorta. As of May, 1988, we have successfully used the Hemopump in three cases of cardiogenic shock. The first patient was a 61 year old male cardiac allograft recipient with severe rejection; the second patient was a 61 year old male with hypotension and congestive heart failure following a myocardial infarction; the third patient was a 72 year old female with post-cardiotomy syndrome after emergency aorto-coronary bypass. These patients were supported by the Hemopump for 2, 4, and 2 days, respectively. No device-related complications were encountered, including no evidence of hemolysis, thrombosis, or endothelial injury. In the first and third patients, cardiac function recovered allowing their eventual discharge.

**Conclusions:** The Hemopump provides effective, temporary circulatory support in patients with potentially reversible cardiac failure. It may be introduced without a major surgical procedure, and was well tolerated in our first human subjects.

CHARACTERISTICS OF PATIENTS REQUIRING EPICARDIAL VS ENDOCARDIAL Nd:YAG LASER PHOTOABLATION FOR VENTRICULAR TACHYCARDIA - A THREE YEAR STUDY.

Robert H. Svenson MD, FACC, Laszlo Littmann MD, FACC, John J. Gallagher MD, FACC, Jay G. Selle MD, Samuel H. Zimmern MD, FACC, John M. Fedor MD, FACC, Kathleen T. Seifert, George P. Tatsis, Francis Robicsek MD, FACC, Sanger Clinic, Carolinas Heart Institute, Heineman Medical Research Center, Charlotte, NC.

Intraoperative map-guided laser photoablation (LP) during ventricular tachycardia (VT) was performed on 72 VT morphologies in 30 pts. Epicardial presystolic activity was recorded during VT and epicardial LP was required to ablate at least one VT in 10 pts (33%). The purpose of this study was to define anatomic variables (infarct vessel and presence of aneurysm) associated with the necessity of epicardial LP to terminate VT. Only pts surviving 3 months were included.

Results:

| Infarct Vessel | | Total | Lased Surface Endo | Lased Surface Epi |
|---|---|---|---|---|
| LAD | | 16 | | |
| Aneurysm | 12 | | 11 | 1 |
| No aneurysm | 4 | | 4 | 0 |
| LCX/RCA | | 14 | | |
| Aneurysm | 3 | | 3 | 0 |
| No aneurysm | 11 | | 2 | 9 |
| TOTAL | | 30 | 20 | 10 |

Map guided epicardial LP was performed in 10/72 VT's (14%). However, epicardial LP was required in 9/11 pts (88%) with LCX/RCA infarction and no aneurysm vs in only 1/16 pts (6%) with LAD infarct. Conclusions: The data suggest that VT ablation procedures directed at the endocardium alone will have a high failure rate curing all VT's in patients with inferior infarction and no aneurysm.

## PREDICTORS OF DEEP STERNAL WOUND INFECTIONS AFTER CARDIAC SURGERY

William S Weintraub, M.D., F.A.C.C., Ellis L Jones, M.D., F.A.C.C., Joseph M Craver, M.D., F.A.C.C. and Robert A Guyton, M.D., F.A.C.C. Departments of Medicine and Surgery, Emory University School of Medicine, Atlanta, GA

Deep sternal wound infections (DSWI) are a serious complication of open heart surgery leading to further complications. To understand the clinical characteristics that give rise to DSWI, all 34 patients with DSWI noted between 9/1/86 and 3/31/88 were compared with 105 randomly selected undergoing cardiac surgery during the same time period. Results:

| | Infection | No Infection | P Value |
|---|---|---|---|
| Age | 58±14 | 61±12 | NS |
| % Male | 85 | 72 | .09 |
| % Post OP MI | 8.8 | 3.8 | NS |
| % Re-open for Bleeding | 8.8 | 1.0 | .02 |
| % Prior Surgery | 20.6 | 2.9 | .0005 |
| % IABP | 14.7 | 1.9 | .003 |
| # Grafts | 2.6±1.4 | 2.8±1.6 | NS |
| % IMA | 69 | 69 | NS |
| Cross Clamp Time | 44 | 43 | NS |
| % Mortality | 21 | 2.9 | .0005 |

DSWI post-operatively represent one of the most serious complications of cardiac surgery and are associated with a significant mortality. DSWI is associated with reoperation for bleeding and the use of the intra-aortic balloon pump. Of great significance, DSWI are strongly associated with previous cardiac surgery.

## OPERATIVE (30-DAY) MORTALITY FOLLOWING IMPLANTATION OF THE AUTOMATIC IMPLANTABLE CARDIOVERTER DEFIBRILLATOR.

Robert D. Mosteller M.D., Claudio D. Schuger M.D., Andra C. Thomas R.N., Russell T. Steinman M.D., Michael H. Lehmann M.D., F.A.C.C., Harper Hospital and Wayne State University, Detroit, Michigan.

Of 1545 pts undergoing initial implantation of an automatic implantable cardioverter defibrillator (AICD) at 17 centers, we analyzed peri-operative (op) deaths which occurred in 35 (2.3%) during the first 30 days after surgery. Among op-death pts, 91% were male; mean age was 60±12 years; underlying heart disease was atherosclerotic (ASHD) in 82%, dilated cardiomyopathy in 12%, and miscellaneous in 6%; mean ejection fraction (EF) was 26±12% (range 10-55%); and concomitant cardiac surgery (concom surg) was performed in only 11% (and consisted of revascularization [CABG] alone). A group of 440 random non-op-death control pts had similar characteristics except for higher EF (34±15%, p<0.01), and more concom surg (44%, p<0.005, with CABG alone in 29%, aneurysmectomy alone in 4%, and both in 11%). Among the op-deaths, 9 (26%) were sudden/cardiac, 16 (46%) non-sudden/cardiac and 10 (29%) non-cardiac; 30 (86%) occurred during hospitalization. All 8 in-hospital sudden op-deaths were due to ventricular tachycardia/fibrillation (VT/VF), and in 3 (38%) cases the AICDs were in a deactivated state at the time of arrest. Conclusions: 1) The 30-day op-death mortality following AICD implantation was fairly low (2.3%) in this large pt population; 2) op-death was related to a more depressed EF and to less concom surg (CABG) vs non-op-death cases, despite similar prevalence of ASHD; and 3) one-quarter of op-deaths were sudden, due to VT/VF, and associated with intentionally deactivated AICDs in several cases.

## CENTRAL NEUROLOGICAL COMPLICATIONS AFTER CORONARY ARTERY BYPASS: INFLUENCE OF MULTIPLE AORTIC CROSS-CLAMPING.

Abel Garibaldi, M.D., Joel Guillory, M.D., Aloysius Chen, M.D., Zev Davis, M.D. Cardiovascular-Renal Consultants, Blue Island, Illinois and Rush Medical College Chicago, Illinois

A recent increase in the incidence of neurological complications after coronary artery bypass (CAB) has been reported and attributed to the increasing age of the patient population being submitted to this procedure. We randomized our patients into two groups to study the influence of some surgical techniques in the incidence and seriousness of postoperative neurological complications. Patients were comparable as far as sex, age, clinical condition, left ventricular function and magnitude of the surgical procedure. Patients with cerebrovascular pathology, intracavitary clots and those requiring associated procedures were not included. Group I consists of 231 patients operated on by the traditional technique of multiple intermittent aortic cross-clampings (MIACC). Group II consists of 180 patients operated on with a single aortic cross-clamp (SACC). There were five major and one minor strokes in Group I (2.59%). Four patients with major strokes died. Two minor strokes occurred in Group II (1.11%). There were no deaths. The difference in major strokes between the groups is both statistically ($0.05 > p > 0.02$) and clinically significant. Although the patient population being submitted to CAB is growing older and, therefore, more susceptible to a neurological complication, we believe that technical factors are still important in the incidence and severity of this complication. The use of a SACC in CAB has a significantly smaller incidence of severe central neurological complications when compared to MIACC. This difference is possibly due to less aortic trauma and to the easier handling of intra-cavitary air.

# Tuesday, March 21, 1989
# 4:00PM–5:30PM, Santa Ana Room 1
# Anaheim Convention Center
# Surgery for Valvular Heart Disease

## CYSTIC MEDIAL NECROSIS OF THE AORTA: NATURAL HISTORY AND LONG-TERM FOLLOW-UP

Dominic L. Marsalese, MD, Douglas S. Moodie, MD, M. Goormastic, MPH, A. Kovacs, BS. Cleveland Clinic Foundation, Cleveland, Ohio.

Few studies have dealt with the natural history and long-term follow-up of pts with cystic medial necrosis (CMN). Ninety-three pts were diagnosed as CMN at the Cleveland Clinic from 1963 to 1987 (72% males, mean age 55 yrs, range 26-77 yrs). All pts had a pathologic diagnosis of CMN and none met the standard criteria for the Marfan syndrome (MS). Seventy-three percent of patients presented with a diastolic murmur and CXR revealed a dilated aortic arch (49%) and cardiomegaly (67%). Eighty-seven percent underwent cardiac catheterization which demonstrated aortic root dilatation (88%), aortic regurgitation (81%), aortic dissection (47%), and CAD (36%). Ninety pts underwent surgery which included aortic reconstruction and/or composite graft repair (79%), AVR (72%), and CABG (23%). Follow-up was obtained on 90 of 93 pts (97%) with a length of follow-up of 0-137 months (mean 29 months). Thirty-four of 90 pts expired (range 29.9-74.9 yrs, mean age 60.4 yrs). Ninety-four percent of the known causes of death were related to the cardiovascular system. Sixty-five percent were the result of aortic dissection, rupture, or sudden death. Ninety-six percent of 55/59 survivors were NYHA Functional Class I or II. Overall estimated survival at 5 yrs was 57.4%. The presence of a diastolic murmur at initial presentation was associated with a poor prognosis (p=0.03). Because these pts lack the external stigmata of the MS and hence identifiable markers for aortic root disease, they present at an older age and with advanced disease.

## UTILITY OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN PATIENTS UNDERGOING CARDIAC VALVE SURGERY.

Khalid H. Sheikh MD, Norbert deBruijn MD, J. Scott Rankin MD, Tom Stanley MD, Fiona Clements MD, Walter Wolfe MD, Joseph Kisslo MD, FACC, Duke University Medical Center, Durham, N.C.

The utility of intraoperative transesophageal echocardiography (TEE) was assessed in 154 pts, out of a total 686 having cardiac valve surgery between October 1985 - July 1988. All had 2-D TEE imaging pre and post cardiopulmonary bypass (CPB) with 103 also having TEE Doppler color flow (CF) imaging. Surgical decisions based on TEE were categorized as: (1)Preoperative unsuspected findings leading to modification of planned surgery, 18/154(12%); or a different operation, 11/154(7%); (2)Identification of inadequate initial repair resulting in further operation, 10/154(7%); (3)Inotropic support for post CPB LV dysfunction, 12/154(8%). Major surgical decisions based on TEE were made in 41/154(27%) cases with greatest impact seen with TEE+CF in mitral valve surgery, 27/64(42%). Risk of postoperative complications (CXS) and death (DTH) were related to post CPB LV function (LVF) and residual valvular defects (RVD) noted by TEE:

| | LVF stable | LVF decrease | No RVD | RVD |
|---|---|---|---|---|
| CXS | 13/131(10%) | 17/23(73%)* | 17/95(18%) | 6/7(86%)* |
| DTH | 7/131(5%) | 6/23(26%)* | 5/95(5%) | 3/7(43%)* |

(*p<.05 for LVF decrease v. LVF stable and for RVD v. No RVD). These data indicate that pre and post CPB transesophageal color flow imaging is useful in formulating surgical plan, assessing surgical results and identifying patients at risk for post operative complications.

## THE PULMONIC VALVE AUTOGRAFT: ECHOCARDIOGRAPHIC FACTORS PREDICTING POSTOPERATIVE VALVE PERFORMANCE

Sunil B. Lulla, MD, Steve M. Teague, MD, FACC, Mukesh K. Sharma, MD, Wyatt F. Voyles, MD, FACC, Paul Stelzer, MD, FACC, Kent Ward, MD, FACC, and Ronald C. Elkins, MD. University of Oklahoma School of Medicine, Oklahoma City.

Autologus transplantation of pulmonic valves for stenotic (AS) or regurgitant (AR) aortic valves is an attractive alternative to prosthetic or heterograft valve replacement, but predictors of surgical outcome have not been explored. We hypothesized that preoperative (PRE) echocardiographic match between the diameters of aortic and pulmonic anuli would predict postoperative (POST) valve performance. Seventeen patients (3 with pure AR) of age 31±18 years underwent echo Doppler studies PRE (4±4 days) and POST (62±60 days) to determine AS severity (peak Doppler gradient), AR grade (Doppler halftime and/or mapping; 1 to 4+), diameters of aortic (AVAN) and pulmonary valve (PVAN) anuli, and DELTA (PVAN - AVAN) (*p<.001):

| | AS (mmHg) | AR (+) | AVAN (MM) | PVAN (MM) | DELTA POST AR GRADE 0,1+ | DELTA POST AR GRADE 2,3+ |
|---|---|---|---|---|---|---|
| PRE | 52±31 | 1.8±1.3 | 23±4 | 26±4 | 5.5±4 | -5±2* |
| POST | 9±4* | 1.2±0.8 | 21±3 | 26±4 | | |

All AS patients had relief of obstruction, but POST AR was recorded in all but two patients: 1+;11, 2+;2, 3+;2, 4+;0. Significant (2+,3+) POST AR was confined to patients with significant PRE AR where AVAN>>PVAN. Two patients with acute severe PRE AR (4+) had minimal POST AR where AVAN<<PVAN (delta +10,+7). We conclude that preoperative echo assessments of aortic and pulmonic anuli diameters identify patients at risk for significant postop pulmonary autograft regurgitation.

## A COMPARISON OF THE GORLIN, CANNON, ANGEL AND HAKKI EQUATIONS FOR THE DETERMINATION OF PATHOLOGIC STENOSIS IN PORCINE XENOGRAFTS

Steven Khan, MD, Ray Cheng, Lawrence Czer, MD, FACC, Richard Gray, MD, FACC, Aurelio Chaux, MD, Jack Matloff, MD, FACC.

In order to separate normal (N) from stenotic (S) Hancock and Carpentier-Edwards mitral valves, we compared the hemodynamics of 131 measurements on 37 patients with N valves, evaluated postoperatively, and 16 measurements of 10 patients with S valves, evaluated at catheterization. Effective orifice areas (EOA's) were calculated from the Gorlin (G), Cannon (C), Angel (A), and Hakki (H) equations. Valve resistance (R=mean dias. pressure (P)/mean dias. flow, was also calculated.

| Results: Size | Avg. EOA's (cm2) (normal/stenotic) Gorlin | Cannon | Angel | Hakki | Rx100 |
|---|---|---|---|---|---|
| 27 | 1.8/.79 | 1.6/1.3 | 1.7/.84 | 1.7/.84 | 3.6/16 |
| 29 | 2.0/1.1 | 1.6/1.3 | 1.9/.99 | 1.9/1.1 | 3.1/9.1 |
| 31 | 2.4/.97 | 1.7/1.3 | 2.1/.88 | 2.1/1.0 | 2.8/14 |
| # overlp: | 3 | 0 | 3 | 6 | 0 |

N and S EOA's were significantly different (P<.008). Only the Cannon equation and valve R separated the valves without overlap. The Cannon EOA's, however, were significantly higher than the other EOA's for stenotic valves (P<.04). We conclude that parameters using the simple ratio of flow and P are superior to those based on the square root of P in separating normal from stenotic valves. The use of the square root of P in evaluating EOA (as done in G,H,A equations) diminishes the ability to distinguish N and S values.

## IS ULTRASONIC DEBRIDEMENT OF AORTIC STENOSIS A RELIABLE ALTERNATIVE TO VALVE REPLACEMENT?

Bruce P. Mindich, M.D., F.A.C.C., Theresa Guarino, B.S. Edward A. Fisher, M.D., Heidi K. Krenz, M.D., Enrico Gonzales, M.D., Warren Sherman, M.D., F.A.C.C., Martin E. Goldman, M.D., F.A.C.C., St. Luke's Hospital, NY NY

Ultrasonic debridement of stenotic aortic valves with the Cavitron Ultrasonic Surgical Aspirator (CUSA) effectively reduces transvalvular gradients and increases valve area. However, since the longevity of this procedure is unknown and because balloon aortic valvuloplasty (BAV) begins to restenose at 6 months, surgical debridement may also fail. Therefore, we evaluated 17 pts who had CUSA for severe aortic stenosis, 15 pts who had aortic valve replacement (OMNI) and 18 pts who had BAV by clinical and echo color Doppler exam. 11/18 BVA pts restenosed within 7.7 months. Late (6 month) followup was compared to early (6 week) followup in the CUSA and OMNI groups for a change in gradient (GRAD,mmHG), regurgitation on scale of 0-4+ (REG), valve area (AVA, $cm^2$), and NYHA Class.

| | # | GRAD | AVA | REG | NYHA |
|---|---|---|---|---|---|
| CUSA | 17 | 25→26 | 1.8→1.8 | 1.3→1.3 | 1.3→1.3 |
| OMNI | 15 | 31→31 | 1.8→1.6 | 0.8→0.9 | 1.3→1.1 |

One CUSA pt had a TIA at 6 weeks, 1 OMNI pt had a paravalvular leak, and 2 BAV pts required aortic valve replacement. All other pts are well. At the critical 6 month point at which balloon valvuloplasties fail, CUSA debridement is successful without increasing stenosis or regurgitation. If these results extrapolate to long term followup, CUSA will be an important alternative to valve replacement for aortic stenosis.

PULMONARY HYPERTENSION IN SEVERE AORTIC STENOSIS: SIGNS, SYMPTOMS AND SURVIVAL.

James Slater M.D.,F.A.C.C., Evan Sehgal M.D., James Post M.D., Alfred Roston B.S., James Albanese B.S., Howard A. Levite M.D.,F.A.C.C., Larry Chinitz M.D., F.A.C.C., Howa Winer M.D.,F.A.C.C., Aubrey Galloway M.D., Frank Spencer M.D., Ephraim Glassman M.D., F.A.C.C., New York Universi Medical Center, New York, New York.

To assess the potential adverse effects on operative mor· tality of pulmonary hypertension (PH) in pts with severe aortic stenosis (AS), 112 pts with a systolic PA pressur( greater than 50 (Grl) were compared to 112 randomly sele( ted age and sex matched pts with severe AS without PH (Gr 2). The incidence of diabetes, hypertension, renal and pulmonary disease was similar in both groups.

| | Group 1 | Group 2 | p |
|---|---|---|---|
| Peak systolic gradient | 95±25 | 82±25 | <0.001 |
| LVEDP | 30±8 | 20±7 | <0.001 |
| PA systolic pressure | 69±16 | 32±7 | <0.001 |
| Cardiac index | 2.4±0.6 | 2.7±0.6 | <0.001 |
| Heart rate | 83±17 | 72±13 | <0.001 |
| Aortic valve area | 0.51±0.21 | 0.57±0.23 | 0.202 |

Gr 1 pts had more dyspnea and edema and less angina. LV function was worse in Gr 1. There was no difference in coronary disease severity or history of prior infarction. Neither operative mortality nor long-term survival by life table analysis differed between groups (1 Yr Gr 1 = 69% Gr 2=74%; 5 Yr Gr 1=52% Gr 2=61%). The presence of severe PH identifies pts with more severe AS and worse LV function, though the excellent operative and long-term survival would encourage surgical intervention.

Recent Exposure to Cigarette Smoke Increases Myocardial Infarct Size

Robert C. Prentice M.D., Richard Carroll M.D., Patrick J. Scanlon M.D., FACC, John X. Thomas Jr., Ph.D. Loyola University Medical Center, Maywood, IL.

Cigarette smoking has been reported to increase the incidence of myocardial infarction. To assess the influence of a recent exposure to cigarette smoke on infarct size, dogs (CS) were exposed to the smoke of 10 cigarettes in an inhalation chamber 1 Hr daily for 10 days. Mean blood nicotine (N) and carboxyhemoglobin (CH) levels following 1 Hr exposure to smoke were 45±4 ng/ml (mean±SEM) and 27±3% respectively. After 24 Hrs, N and CH levels had decreased significantly to 4±1 and 3±1, respectively. Control (CTRL;n=5) and CS (n=5; 24 Hrs. after the 10th smoke exposure) dogs were anesthetized with α-chloralose. Through a left thoracotomy, the circumflex artery was isolated and ligated 1.5 cm from its origin. After 6 Hrs, the area at risk was defined by dye injection and the infarct size was determined using standard triphenyl tetrazolium chloride staining techniques. The area at risk (% LV) was similar between groups (CTRL:35±2, CS:37±3). Infarct size (% of area at risk) was 24±5 in CTRL, vs. 46±6 in CS ($p<0.025$). Conclusions: 1) Recent exposure to cigarette smoke significantly increases myocardial infarct size. 2) This effect is present despite the absence of elevated levels of N and CH at the time of infarction. Thus, the increased infarct size in the CS group was not due to elevated circulating levels of N or CH. The mechanism by which a recent history of smoke exposure produces larger infarct size demands further study.

## Tuesday, March 21, 1989
## 2:00PM–3:30PM, Santa Ana Room 2
## Anaheim Convention Center
## Cardiac Necrosis: New Insights into Modulating Factors and Compensatory Response

ENHANCED β-ADRENERGIC ACTIVITY IN NON-INFARCTED MYOCARDIUM MAY CAUSE EXERCISE-INDUCED ST-SEGMENT ELEVATION IN OLD MYOCARDIAL INFARCTION

Keizo Yamashita,M.D., Makoto Ohno,M.D., Yoshihide Sakaguchi,M.D., Toshio Miyazaki,M.D., Kozo Takada,M.D., Hitoshi Kawabata,M.D., Kinji Ishikawa,M.D., Ryo Katori, M.D., Kinki University School of Medicine, Osaka, Japan.

The exact mechanism behind exercise-induced ST-segment elevation in old myocardial infarction (OMI) is still unknown. In 7 closed-chest dogs transmural anterior wall infarction was induced by inserting a gelatin sponge embolus into the left anterior descending artery. One week following recovery, three interventions were performed; right atrial pacing (AP) alone, AP combined with noradrenaline (NA) infusion and AP with methoxamine (MT) injection. ECG, LV angiogram and blood pressures were taken. AP alone did not result in any ST changes, but AP+NA resulted in marked ST elevations. AP+MT again did not result in any ST changes in spite of large increases in LVEDP. AP+NA significantly improved LV ejection fraction (Δ12.3%, $p<0.01$), while AP+MT resulted in marked decreases (Δ21.6%, $p<0.01$). In the analysis of regional wall motion, AP+NA strongly enchanced radial shortenings (Δ19.5%, $p<0.05$) in the non-infarcted area, but AP+MT reduced these shortenings (Δ11.6%, $p<0.05$). The wall motion of infarcted area did not show any changes by the three interventions. Based upon these experimental results, we performed isoproterenol (ISO) infusion in 5 OMI patients who exhibited exercise-induced ST elevation and suffered from single vessel disease. ISO exhibited marked ST elevations equivalent to exercise-induced ST elevations in all patients. These results suggest that ST-segment elevation may be a result of hyperkinesia of the non-infarcted areas, probably due to enhanced β-adrenergic activity in normal myocardial cells.

**THE EFFECT OF TPA ON MYOCARDIAL CELLS, THE NO-REFLOW PHENOMENON, AND INTRAMYOCARDIAL HEMORRHAGE**

Robert A. Kloner, M.D., Ph.D., F.A.C.C., Kevin Alker, Andrew Eisenhauer, M.D., F.A.C.C. Colin Campbell, Ph.D., Heart Institute, Hospital of The Good Samaritan, L. A., CA

While tissue plasminogen activator (TPA) is being widely used for the treatment of acute myocardial infarction, there is little information on the effect of TPA on the myocardium. Some studies showed that TPA reduced infarct size independent of its thrombolytic action; others suggested TPA could worsen intramyocardial hemorrhage. We assessed the effect of TPA in a 2 hour mechanical coronary occlusion - reperfusion model in the anesthetized dog. Either high-dose TPA (1.3 mg/kg) or saline was infused for 2 hours starting 30 minutes after coronary occlusion. The extent of necrosis as a percent of the risk zone was similar in TPA (44 ± 12%) and control groups (46 ± 12%). Regional myocardial blood flow assessed with microspheres remained depressed post reperfusion in both control dogs (.27 ± .11 ml/min/gm in previously ischemic region versus .75 ± .08 in nonischemic zones) and TPA-treated animals (.20 ± .05 vs. .76 ± .11). Hemorrhage occurred following reperfusion in both groups. Intramyocardial hemoglobin levels were 16 ± 5 ug/mg in control and 12 ± 3 ug/mg in TPA-treated infarcts compared to values of 6.5 - 7.0 in noninfarcted regions. Microscopic evaluation revealed intramyocardial hemorrhage in both groups without extension of hemorrhage beyond zones of contraction band necrosis. Neutrophil infiltration was prominent in both groups. These results suggested that TPA does not have any direct beneficial effects on myocardial cells (other than its ability to lyse proximal thrombi), does not improve the no-reflow phenomenon by lysing microthrombi; but importantly does not exacerbate intramyocardial hemorrhage compared to mechanical reperfusion.

DEFIBRINOGENATION REDUCES INFARCT SIZE IN A CANINE MODEL OF ACUTE MYOCARDIAL INFARCTION

Mun Kyung Hong, MD and Thomas Aversano, MD
Johns Hopkins Hospital, Baltimore, MD.

It has been suggested that in the treatment of myocardial infarction streptokinase (SK) may have beneficial effects independent of its thrombolytic action. Since SK is also a fibrinogenolytic agent, we studied the effect of defibrinogenation (DF) alone on infarct size (ISZ). 18 open-chest dogs were pretreated either with 4 units/kg of Arvin IV (a defibrinogenating extract of Malayan Pit Viper venom) or with saline IV over one hour (N=9 in each group). The left anterior descending artery was then occluded for 4 hours. The fibrinogen level in the Arvin-pretreated (APT) group was undetectable. Otherwise there were no differences in heart rate, blood pressure, or the hemogram between the two groups. Coronary flow was measured with microspheres. The risk region was defined as the mass of myocardium whose flow at the onset of occlusion was < 50% of pretreatment flow and infarct was defined by lack of triphenyltetrazolium staining. ISZ expressed as a percent of risk region was 44 ± 9 % in controls and 14 ± 6 % in APT dogs (P<.02). In the control group ISZ was related to flow in the most ischemic regions of the infarct (Qinf) (ISZ = -3.5Qinf+69, P<.05), while in the APT group infarts were almost uniformally small. We conclude that preocclusion DF with Arvin reduces infarct size in this 4 hour occlusion-no reperfusion model of myocardial infarction. While improvement in coronary collateral flow in defibrinogenated animals cannot be completely ruled out as a contributing mechanism of salvage, it does not fully account for the profound infarct size reduction observed.

DELAYED SWITCH OF MYOSIN HEAVY CHAIN GENE EXPRESSION IN THE RIGHT VENTRICLE AFTER EXPERIMENTAL INFARCTION IN THE RAT

Stanley A. Rubin M.D., F.A.C.C., Adele El Kareh M.D., Ph.D., Cedars-Sinai Medical Center and UCLA School of Medicine, Los Angeles, CA.

Infarction imposes an immediate hemodynamic burden on the LV, but the effects on the pulmonary circulation and RV are delayed. We examined the effects of myocardial infarction (MI) on LV and RV cardiac myosin heavy chain (MHC) gene expression. Mature female rats were sacrificed one week after MI (5 rats) five weeks after MI (5 rats) or after sham procedure (4 rats). Cardiac expression of the beta and alpha mRNA transcripts of MHC was examined in the uninfarcted portion of the LV and in the free wall of the RV by solution hybridization/S1 nuclease protection assay with a radiolabelled DNA rat probe specific for MHC, electrophoresis in polyacrylamide gels, autoradiography and densitometry.

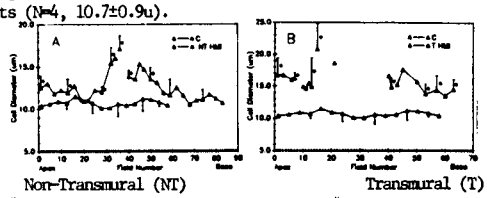
| Group | Fraction of MHC | | | |
|---|---|---|---|---|
| | LV | | RV | |
| | α | β | α | β |
| Sham | 0.66 | 0.34 | 0.80 | 0.20 |
| 1 week | 0.37 | 0.63 | 0.88 | 0.12 |
| 5 week | 0.38 | 0.62 | 0.59 | 0.41 |

In the LV the switch of MHC gene expression was within 1 week, whereas the switch in the RV was delayed.
Conclusion: There are early shifts in MHC gene expression after MI that are specific to the LV and only subsequently involve the RV. This suggests that locally acting factors (possibly humoral or hemodynamic) are capable of specific alteration of MHC gene expression after MI.

MORPHOMETRIC MAPPING OF REGIONAL DIFFERENCES IN MYOCYTE DIAMETERS AFTER HEALING OF MYOCARDIAL INFARCTION.

Marilyn Cox M.D. Irwin Berman Ph.D., Marcel Smets, R.J. Myerburg M.D., FACC, Patricia Kozlovskis, Ph.D. University of Miami, Miami, FL.

This study was designed to measure myocyte diameters in 2 healed myocardial infarct (HMI) models to test the hypothesis that myocyte hypertrophy is a function of proximity to the infarct. LV transmural (T, n=3) or non-transmural (NT, n=2) MI's were produced in cats. At 13-20 months after surgery the LV free wall was cut into longitudinal sections. Myocardial cell diameters were measured from apex to base through the infarct. No regional differences were found in control (C) hearts (N=4, 10.7±0.9u).




Non-Transmural (NT) Transmural (T)

| Field# | Tissue | Cell Diameter (u) | Field# | Tissue | Cell Diameter (u) |
|---|---|---|---|---|---|
| 1 | NI | 12.5±1.4* | 1 | I | 16.3±2.7* |
| 13 | NI | 11.9±1.7* | 7 | I | 16.2±0.9* |
| 28 | I | 11.8±0.6* | 13 | I | 14.9±4.5* |
| 32 | I | 15.3±1.8* | 15 | I | 20.8±6.4* |
| 36 | I | 16.8±1.6* | 41 | I | 14.8±1.4* |
| 40 | I | 13.5±0.8* | 53 | NI | 13.8±1.5* |
| 50 | I | 13.2±1.4* | 57 | NI | 14.3±2.3* |
| 59 | I | 11.3±1.9 | 63 | NI | 14.4±1.6* |

In the NT preparation (panel A) cell diameters were significantly increased (P<0.05, Table) in apical non-infarcted tissues (NI), and in cells from infarcted areas (NI) relative to C. Cells in fields towards the base were not different from C. In the T preparation (panel B), all fields had significantly increased cell diameters (Table). It is concluded that T and NT HMI create a gradient increase in myocyte diameter, and that the increase is greatest in tissues adjacent to the HMI.

## Tuesday, March 21, 1989
## 4:00PM–5:30PM, Santa Ana Room 2
## Anaheim Convention Center
## Non Invasive Diagnosis of Coronary Artery Disease

LIMITATIONS OF EXERCISE THALLIUM SINGLE PHOTON TOMOGRAPHY EARLY AFTER MYOCARDIAL INFARCTION

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Assessment of perfusion after thrombolytic therapy for myocardial infarction (MI) is key to evaluation of this and subsequent therapy. We performed symptom-limited Bruce exercise (time 7.2±2.7 min, peak double product 22.5±6.6x10$^3$ mmHg/min, mean±SD) thallium tomography (Tl-SPECT) on day 8 and coronary angiography on day 9 in 47 patients randomized to tissue plasminogen activator or placebo. Tl-SPECT was analyzed visually by 2 blinded observers and quantitatively by comparison of polar plots to normal data. Defects were localized to anterior descending, circumflex and right coronary distributions. Sensitivity and specificity for detection of stenoses ≥50% in MI and nonMI vessels (per ECG) were compared to those in 107 angina patients (CONTROL):

| | CONTROL | STUDY VESSELS | |
|---|---|---|---|
| | VESSELS | MI | nonMI |
| SENSITIVITY - visual: | .75 | .93 | .31* |
| - quantitative: | .84 | .95 | .35* |
| SPECIFICITY - visual: | .82 | .50 | .84 |
| - quantitative: | .82 | .14 | .79 |

*p<0.005 compared to CONTROL

Early after MI Tl-SPECT has reduced sensitivity for localization of CAD in nonMI vessels. Possible mechanisms include inadequate exercise by some patients and that defects arising from nonMI vessels can be contiguous with MI segments. Reduced specificity in MI vessels is to be expected when MI's are followed by clot lysis leaving ~50% residual stenoses.

## DIPYRIDAMOLE-INDUCED MALPERFUSION MAY NOT INDICATE ISCHEMIC VENTRICULAR DYSFUNCTION.

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Dipyridamole (D) produces myocardial malperfusion, but malperfusion may not cause ischemia. To evaluate this disparity we compared signs of ischemia on D-radionuclide ventriculography (D-RVG) to malperfusion on D-thallium (D-TL) in 28 patients (pts), 19 with coronary artery disease (CAD) (≥50% stenosis, no Q waves) and graded results blindly. Seventeen of these pts had severe CAD (≥50% left main (LM) or ≥70% other vessel (V) stenosis). Failure to increase ejection fraction (EF) ≥4%, decrease in regional wall motion (RWM) (6 point scale) or reduction in TL score (RTS) by ≥ 1 unit (4 point scale) were abnormal responses. Sensitivity (sens) and specificity (spec) for severe CAD were calculated:

| ABNORMAL RESPONSE: | N | RTS ≥1.0 | RTS ≥1.5 | RVG EF | RVG RWM |
|---|---|---|---|---|---|
| ≥1V CAD≥70% %sens/spec: | 17 | 88/27 | 41/91 | 63/91 | 53/91 |
| 3VCAD,LM %sens/spec: | 5 | 80/17 | 40/74 | 100/73 | 60/70 |

Markedly abnormal D-TL (RTS≥ had low sensitivity but high specificity for severe CAD. Definitely abnormal D-TL (RTS≥1) had high sensitivity, but very low specificity. Malperfusion was common (23/28 pts) but overestimated ischemia as defined by RVG: of 23 positive TL, only 13 had abnormal RVG; but 12/13 had CAD. Thus, malperfusion on D-TL overestimates the frequency of severe CAD, and reduced perfusion on D-TL does not always indicate myocardial ischemia. D-RVG can identify severe CAD with good sensitivity and high specificity using the principles of ischemic ventricular dysfunction rather than malperfusion.

## EXERCISE RADIONUCLIDE ANGIOGRAPHY YIELDS PROGNOSTIC INFORMATION EQUIVALENT TO CARDIAC CATHETERIZATION

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To determine the prognostic importance of exercise radionuclide angiography (RNA) testing relative to non-invasive clinical assessment (Clin) and the results of cardiac catheterization (Cath), we studied 571 consecutive medically treated patients (PTS) with coronary artery disease (≥75% stenosis) who had rest and exercise RNA within three months of Cath. All PTS were followed ≥3 years, and 90 PTS have died from cardiac causes. Using the Cox proportional hazards model, 17 RNA variables were examined, including rest and exercise ejection fraction (EF), heart rate, wall motion, blood pressure, exercise ECG changes, exercise induced angina, and exercise time.

The most important RNA predictor of survival was exercise EF ($X^2$=81, p<.0001). Also contributing independent information were resting end systolic volume index and change in heart rate with exercise. The relative prognostic value of RNA, Clin and Cath were:

| | $X^2$ (cardiac death) |
|---|---|
| Clinical Variables | 65 |
| RNA | 103 |
| Cath (alone) | 102 |
| Clinical and Cath | 121 |
| Clinical and Cath and RNA | 134 |

RNA provided prognostic information equivalent to Cath alone, and 85% of the combined information provided by Clin and Cath. In conclusion, descriptors from RNA are powerful predictors of survival. Furthermore they can help define risk even when clinical and Cath variables are known.

## PROGNOSTIC VALUE OF INTRAVENOUS DIPYRIDAMOLE THALLIUM IMAGING IN ASYMPTOMATIC PATIENTS WITH CORONARY DISEASE AND NO PREVIOUS MYOCARDIAL INFARCTION.

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We studied the prognostic value of I.V. dipyridamole thallium imaging (DPT) in 60 asymptomatic pts without previous myocardial infarction who had angiographically documented coronary disease (≥50% narrowing) and who underwent the test as part of a preoperative risk assessment or inability to exercise. The DPT was normal in 28 pts (group 1) and abnormal in 32 pts (group 2); 22 and 10 group 2 pts had a reversible and fixed defect respectively. The average follow-up duration was 13±10 months. Cardiac events were defined as death (D), nonfatal myocardial infarction (MI), angina (A), or a revascularization procedure (R). The cardiac event rates were:

| Event | D | D+MI | R | A+R | Total |
|---|---|---|---|---|---|
| Group 1 | 0 | 0 | 7% | 14% | 14% |
| | | <.05 | | <.01 | <.001 |
| Group 2 | 3% | 13% | 19% | 56% | 44% |

Of the 4 group 2 pts who died or had an MI, 3 had a reversible and 1 a fixed thallium defect.

Thus, a normal I.V. dipyridamole thallium test in an asymptomatic pt with documented coronary disease is associated with an excellent prognosis and no need for revascularization therapy. An abnormal test is associated with a significantly increased risk of cardiac events raising the possibility of silent myocardial ischemia in these otherwise asymptomatic pts.

## COMPUTER ANALYSIS REDUCES INCIDENCE OF FALSE POSITIVE EXERCISE TESTS IN MIDDLE AGED WOMEN.

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The frequent occurrence of false positive treadmill exercise (TE) ECG tests in women limits their value for the detection of coronary artery disease (CAD). In men, computer derived ST area measurements [Hollenberg TE score (HTES)] improve diagnostic accuracy of TE, but this commercially available analysis program has not been evaluated in women. Thus, we studied 40 women aged 54±8 (SD) years, without prior myocardial infarction with suspected CAD because of chest pain syndromes. The majority (75%) were hispanics with a history of typical angina (69%) and were menopausal with 2 or more risk factors for CAD. All underwent Bruce protocol TE and coronary angiography. The HTES was invalid in 11 (27.5%) because of insensitive leads due to ECG low voltage. The mean percent ideal body weight in women with a valid HTES was 142% compared to 179% in those with insensitive leads (p<.001). In the remaining 29 coronary arteriography revealed normal coronaries in 14 and stenosis diameter <50% in 4 (normals, n=18); 1 vessel disease in 2 and 2-3 vessel disease in 9 (CAD pts, n=11). Below are the results of HTES versus standard ECG analysis for ≥ 1 mm horizontal ST depression:

| TE Criteria | Specificity | Sensitivity |
|---|---|---|
| Standard ECG | 10/18 (55%) | 7/11 (64%) |
| HTES score | 16/18 (89%)* | 6/11 (55%) |

*p<.02, McNemar test

We conclude that in middle-aged women obesity limits the applicability of HTES, but in those with valid tests, HTES reduces the incidence of falsely positive treadmill exercise tests in comparison to standard ECG criteria.

## EXERCISE SEISMOCARDIOGRAPHY FOR DETECTION OF CORONARY ARTERY DISEASE: A PRELIMINARY REPORT

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Seismocardiography is a new noninvasive test for the detection of myocardial ischemia. Based on techniques from the field of seismology, the method analyzes the compression waves transmitted from the heart during its movement. We hypothesized that patients with significant coronary artery disease would develop a change in left ventricular function during exercise that would alter the compression waves recorded by the seismocardiograph. To test this hypothesis, we recorded the seismocardiogram before, immediately after, and 5 minutes after exercise in 32 patients (age 61 ± 9, 25 males) undergoing graded treadmill exercise with 12-lead ECGs obtained each minute. The patients also had coronary angiography, enabling calculation of sensitivity and specificity for the detection of coronary disease (≥ 60% stenosis). We detected reversible changes in the seismocardiographic waves in some patients immediately after exercise, defined as abnormal. Abnormal ECGs had ≥ 1 mm horizontal or downward ST depression.

| | | Sensitivity | Specificity |
|---|---|---|---|
| Seismocardiography | (reader #1) | 96 | 67 |
| " | (reader #2) | 88 | 67 |
| Electrocardiography | (reader #3) | 69 | 50 |
| " | (reader #4) | 46 | 50 |

Seismocardiography was more reliable than electrocardiography for the identification of significant coronary artery disease ($p = 0.011$ for reader #1 vs reader #3, $p = 0.055$ for #2 vs #3, $p = 0.0005$ for #1 vs #4, and $p = 0.007$ for #2 vs #4).

We conclude that exercise produces a change in the seismocardiographic waves in most patients with significant coronary artery disease. Exercise seismocardiography was superior to electrocardiography for the detection of coronary artery disease in this group of patients.

# Tuesday, March 21, 1989
# 2:00PM–3:30PM, California Room B
# Anaheim Convention Center
# Electrophysiologic Changes Produced by Ischemia

## RATE-DEPENDENT CELLULAR UNCOUPLING CONTRIBUTES TO THE CONDUCTION CHANGES IN ACUTE ISCHEMIA AND IS PREVENTED BY VERAPAMIL

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The purpose of our study was two-fold: 1) to determine if the cellular uncoupling associated with acute ischemia was rate-dependent and contributed to the associated rate-dependent conduction slowing; and 2) to determine if the known abilities of verapamil pretreatment to prevent ischemia-induced conduction slowing and to prevent ventricular fibrillation were related to effects on cellular uncoupling. We recorded simultanously internal longitudinal (coupling) resistance ($r_i$), $\dot{V}_{max}$ of the action potential upstroke, and conduction velocity ($\theta$) in superfused guinea pig papillary muscles exposed to 30 minutes of simulated ischemia (SI: $K^+ = 9$ mM, pH = 6.5, $pO_2 < 30$ mmHg, glucose = 0) and driven at rates of 0.5 Hz and 2.0 Hz. The mean results before (B) and after (A) $1 \times 10^{-6}$ M verapamil are shown as % change (n = 17).

| | $\dot{V}_{max}$ | | $r_i$ | | $\theta$ | |
|---|---|---|---|---|---|---|
| Hz | B | A | B | A | B | A |
| 0.5 C→0.5 SI | -17.3 | -20.0 | +16.0 | +22.1 | -13.0 | -12.5 |
| 2.0 C→2.0 SI | -29.4† | -29.5† | +72.9† | +26.2* | -21.7† | -14.2* |

C = 9 mM $K^+$ tyrode † = $p < .05$ cf 0.5 Hz * = $p < .05$ cf B

Before verapamil, the increases in $r_i$ and decreases in $\dot{V}_{max}$ and $\theta$ caused by SI were significantly greater at 2.0 Hz than at 0.5 Hz (i.e., were rate-dependent). Verapamil did not influence any of the SI-induced changes at 0.5 Hz or the rate-dependent change in $\dot{V}_{max}$, but significantly lessened the rate-dependent changes in $r_i$ and $\theta$. The results indicate that a rate-dependent increase in $r_i$ contributes to the ischemia-induced conduction slowing. Verapamil's ability to lessen the rate-dependent changes in $r_i$ without influencing the changes in $\dot{V}_{max}$ may underlie its prevention of the conduction slowing of acute ischemia and contribute to its antifibrillatory effect.

## NONHOMOGENOUS REDISTRIBUTION OF REGIONAL MYOCARDIAL BLOOD FLOW AND POTASSIUM DURING REPERFUSION OF ISCHEMIC MYOCARDIUM

Robert J. Hariman, M.D., F.A.C.C., Eric K. Louie, M.D., F.A.C.C., Abe F. Goldbaum, B.S., Rick L. Krahmer, M.S., Darrell P. Prechel, M.S., James L. Ferguson, Ph.D., University of Illinois, Chicago, Illinois

To better understand the mechanism of reperfusion (RP) arrhythmias, we measured left ventricular mid-wall extracellular potassium concentration ($[K^+]_o$) using up to 15 Hill K-sensitive electrodes and correlated the data with regional myocardial blood flow (RMBF) measured using multiple 15 μ radioactive microspheres during control, 20 minutes of left anterior descending (LAD) coronary artery occlusion, and after 1 minute of RP in 9 dogs. RMBF was calculated in up to 30 pieces of 0.5 to 1.5g full thickness myocardial tissue in and around the left ventricular area supplied by the LAD. At the end of 20 minute LAD occlusion, an area of ischemia (ISCH) with RMBF <50% of normal RMBF resulted in an increase in $[K^+]_o$ from 4.5 ± 0.7 mEq/l to 13.5 ± 5.8 mEq/l ($p < 0.001$), with a trend towards higher $[K^+]_o$ in the center of ISCH and lower $[K^+]_o$ in areas adjacent to the areas with normal RMBF. Electrograms in the area of ISCH showed diminution of amplitude and fractionation. After 1 minute of RP, RMBF map showed islands with various degrees of increase in RMBF ranging from three to six times of normal RMBF. The nonhomogenous RMBF during RP caused different rates of normalization in $[K^+]_o$ resulting in areas of high $[K^+]_o$ in juxtaposition with areas of lower $[K^+]_o$ and an increase in $[K^+]_o$ gradient between adjacent areas. Different rates of normalization in $[K^+]_o$ also resulted in different rates of normalization of fractionated electrograms. Nonhomogenous reactive hyperemia during RP and the concomitant variability in clearance of $[K^+]_o$ (and other metabolites of ISCH) may be important in the genesis of RP arrhythmias.

## REPERFUSION ASSOCIATED VENTRICULAR FIBRILLATION: POTENTIATION BY LEFT VENTRICULAR HYPERTROPHY DESPITE LIDOCAINE PRETREATMENT.

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While left ventricular hypertrophy (LVH) has been associated with an increase in sudden death during coronary artery occlusion (CAO), an influence of left ventricular hypertrophy (LVH) on reperfusion (R) arrhythmias has not been previously noted.

Hypothesis: LVH potentiates reperfusion arrhythmias.

Protocol: Fourteen awake, unsedated dogs with renovascular hypertension LVH and 9 control (C) dogs underwent 15 min CAO and R. Prior to CAO, all dogs were pretreated with four lidocaine (L) boluses (1.5, 1.0, 0.8, 0.8 mg/kg) at 15 min intervals followed by continuous IV infusion (2 mg/min) during CAO. Hemodynamics and ECG were measured continuously and regional myocardial blood flows were obtained.

Results: 1. Reperfusion ventricular fibrillation (RVF) immediately at reflow was increased in LVH versus C (5/14 vs 0/9, p=0.059). 2. L pretreatment abolished arrhythmias during ischemia in 9/9 C and 13/14 LVH, and prevented RVF in C dogs but not in LVH. 3. The ratio of heart weight (g) to body weight (Kg) was increased in LVH compared to C (5.0±0.7 vs 4.2±0.7, p=0.014). 4. Significantly increased heart rate at 15 min CAO was the only hemodynamic variable differentiating survivors (LVH or C) from those with RVF.

Conclusions: 1. LVH potentiates RVF in this model, and, 2. lidocaine pretreatment protected all C dogs and 13/14 LVH dogs from VF during CAO, but it did not prevent RVF in LVH dogs.

**DELAYED VENTRICULAR ARRHYTHMIAS (PHASE 1B) RESULTING FROM MIDMYOCARDIAL REENTRY**

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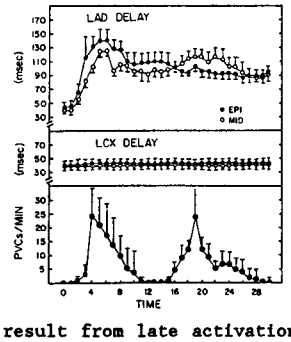
Composite bipolar electrodes were used to record from epicardium (EPI) and midmyocardium (MID) during ventricular arrhythmias observed after anterior descending coronary artery ligation (CAL) in dogs (N=13). Ventricular arrhythmias observed during the first 10 min after CAL were preceded by progressive activation delays in EPI and were accompanied by continuous electrical activity in EPI. Arrhythmias resolved with the loss of late EPI activation. Delayed ventricular arrhythmias (DVA) observed 15 to 30 min after CAL were preceded by progressively delayed activation in ischemic zone MID exceeding delays observed on the corresponding EPI. Premature ventricular beats, couplets, and tachycardia during DVA were accompanied by continuous electrical activity in MID bridging the preceding diastolic interval. DVA were observed only when delays in MID were greater than 130 msec. DVA subsided with a partial resolution of delayed activation in MID. Delayed activation in MID was distinct from delay in EPI since MID delay always exceeded delay in EPI during DVA. The data suggest that DVA after CAL result from late activation and localized reentry within acutely ischemic midmyocardium.




THE REGIONAL ELECTROPHYSIOLOGICAL EFFECTS OF STELLATE STIMULATION ON INFARCTED MYOCARDIUM

David Newman MD, Luisa Munoz MD, Michael Chin, John Herre MD FACC, Michael Franz MD, Elias Botvinick MD FACC, Melvin M.Scheinman MD FACC, Michael Dae MD. University of California San Francisco, California.

Denervation due to myocardial infarction (MI) may relate to the development of post MI arrhythmias. To examine the effects of coronary occlusion on necrosis and sympathetic denervation we studied 8 open chest dogs 2 weeks after left anterior descending artery ligation. The monophasic action potential (APD) at multiple epicardial sites was recorded before and after left stellate ganglion stimulation (SS). Heart slices were imaged after the administration of $I^{123}$-metaiodobenzylguanidine (MIBG) and $Tl^{201}$ to detect denervated but viable myocardium. Results: All had small sized infarctions (mean 3% of total heart weight). In all cases denervated regions extended beyond the planimetered infarct margins, reaching 18% of total area. In the absence of SS there were no differences in APD between normal and denervated areas. SS induced shortening of APD at 20% ($p<.05$) but not at 90% repolarization (APD90) in normal areas only. In denervated areas there was no SS induced change in either APD measure. There was a trend for ERP shortening to be greater in normal than denervated areas during SS. SS induced lengthening of APD90 was frequently due to afterdepolarizations delaying final repolarization. During SS ventricular ectopy occurred in all dogs and ranged from single ectopic beats to fibrillation in 2. Conclusions: 1. Myocardial infarction (MI) produces scintigraphic demonstration of denervation that exceeds the anatomical area of infarction. 2. The effects of SS on APD heterogeneity and on induced afterdepolarization may be important in understanding post MI arrhythmogenesis.

SUSTAINED REENTRANT ACTIVATION ORIENTS AROUND ARCS OF ABRUPT FUNCTIONAL CONDUCTION BLOCK IN THE CANINE POST-INFARCTION HEART.

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Sustained monomorphic ventricular tachycardia due to circus movement reentry could be induced in the surviving epicardial layer 3-5 days following left anterior coronary artery occlusion in the dog heart. The reentrant circuit has a figure 8 configuration in the form of two circulating wavefronts oriented around two sepearate arcs of functional dissociation. The arcs are usually aligned parallel to epicardial fiber axis. The arcs has been ascribed to functional conduction block or to "pseudo block" created by very slow conduction across fiber axis relative to faster conduction along fiber axis, i.e. anisotropic conduction properties. Both conclusions were based on relatively low density mapping of epicardial activation (3 to 8mm interelectrode distance). We investigated the nature of the arc using high density recording (1mm interelectrode distance ) and found evidence of abrupt (within 1 mm) conduction block across the arc. Two distinct deflections were seen in electrograms recorded on opposite sides of the arc; one represented local activation and the second, an electrotonus corresponding to activation recorded 1 mm away. Both deflections were separated by a variable isoelectric period which correlated with the isochronal difference across the arc. In recordings obtained from the center of the arc, local activation and electrotonus were separated by 90 to 110 msec. This interval successively decreased towards both ends of the arc. We conclude that in the canine post-infarction heart circus movement reentry is sustained around a continuous arc of abrupt functional conduction block and not very slow conduction across fibers.

## Tuesday, March 21, 1989
## 4:00PM–5:30PM, California Room B
## Anaheim Convention Center
## Basic Electrophysiology: Cardiac Conduction

EVIDENCE FOR TWO TYPES OF SODIUM CURRENTS IN ISOLATED NEONATAL AV NODAL HEART CELLS.

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Enhanced AV nodal conduction, observed in newborn animals, may result from developmental differences in the types of inward depolarizing currents present. Sodium (Na) channels have previously been identified in AV nodal cells. Our purpose was to further characterize the properties of the sodium current present in isolated AV nodal cells from the newborn rabbit heart. AV nodal cells were prepared by enzymatic isolation and cultured in DME-F12 media. Whole cell voltage clamp was performed using the gigaseal technique. Na currents were examined in a bath solution containing in mM: 107 NaCL, 1 $MgCL_2$, .02 $CaCL_2$, 10 glucose, 10 Hepes, 30 TEA, and 5 4-AP. The pipette contained in mM: 124 $CsCL_2$, 1 $CaCL_2$, 2 $MgCL_2$, 10 Hepes, and 11 EGTA.

Our results showed: 1) Under these conditions, a rapidly activating inward current was present in 95% of the cells. 2) A second component to the Na current was identified after TTX application. The remaining Na current (TTX-resistant) was 12% of the peak Na current in 10-5M TTX. 3) The TTX-resistant Na current was suppressed by Cd 0.1 mM, and nimodopine 10-6 to 10-7M. The response to nimodopine 10-8M was biphasic, consistent with a mixed agonist/ antagonist effect. In 50% of the cells studied, nimodopine 10-8M increased the TTX-resistant Na current, in the other half it decreased the TTX-resistant Na current.

We conclude that there are two components to the Na current in neonatal AV nodal cells; one TTX sensitive, and the other resistant.

IDENTIFICATION OF PUTATIVE INTRAMURAL CONDUCTION CELLS IN CANINE LEFT VENTRICLE

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We have identified morphologically distinct cardiac myocytes in canine epicardium and mid-myocardium that differ markedly from common ventricular myocytes by light and electron microscopy. These structurally specialized myocytes were arranged in loose bundles of long (138±36 μm vs. 98±53 in common myocytes, p<.01), thin (12±4 μm vs. 17±5 in common myocytes, p<.01) cells separated by sparse collagenous septae. The most striking feature of specialized myocytes was frequent lateral interconnections with small intercalated discs and gap junctions at 15-20 μm intervals along the cell body, a finding never seen in common ventricular myocytes. The unique distribution of side-to-side connections between specialized myocytes was associated with decreased surface density of intercalated discs ($2.8\pm0.8 \times 10^{-2}$ $\mu m/\mu m^2$ section area vs. 3.6±1.0 in common myocytes, p<.04) and gap junctions ($5.4\pm1.2 \times 10^{-3}$ $\mu m/\mu m^2$ vs. 6.9±2.6 in common myocytes, p=.09). Although specialized myocytes contained T-tubules, their structural specializations otherwise resembled those typical of subendocardial conduction cells. Moreover, specialized myocyte bundles terminated with extensive connections to common myocytes. Specialized myocyte connections with subendocardial Purkinje or transitional cells have not yet been investigated. However, the unique morphologic features and distribution of specialized myocytes suggest that they may be distal, intramural components of the conduction system which slow or modulate transmural activation.

CYTOPLASMIC AND JUNCTIONAL COMPONENTS OF ANISOTROPIC INTERNAL RESISTANCE IN CANINE MYOCARDIUM

Robert H. Hoyt, M.D., Jeffrey E. Saffitz, M.D., Ph.D., F.A.C.C., Washington University, St. Louis, MO

Internal resistance ($R_i$) is a major determinant of myocardial conduction velocity. Previous studies of cytoplasmic and junctional components of $R_i$, based on models of myocytes as simple cylinders packed end-to-end, have ignored important contributions of anisotropic myocyte shape, packing geometry, and gap junction distribution. Accordingly, we used morphometry and immunohistochemistry to delineate the surface areas and locations of all gap junctions and thereby construct anatomically accurate two-dimensional maps of canine myocardium. Cytoplasmic and gap junctional components of $R_i$ were determined in directions longitudinal (L) and transverse (T) to the long myocyte axis. Cytoplasmic resistivity and single channel resistance were assumed to be 200 Ω cm and $2 \times 10^{10}$ Ω, respectively. The cytoplasmic:junctional resistance ratio was linearly related to % open channels (slopes=11.2 and 3.8 in the L and T directions, respectively). Cytoplasmic resistance equaled junctional resistance at 8% and 30% open channels in the L and T directions, respectively. With physiologic coupling (5% open channels), the anisotropic resistance ratio ($R_{i(T)}/R_{i(L)}$) was 9:1, sufficient to account for directional differences in conduction velocity. With improved coupling (100% open channels), the anisotropic resistance ratio decreased to 4.8:1. Uncoupling (0.25% open channels) caused a modest increase in $R_{i(T)}/R_{i(L)}$ to 10.7:1 but a 16-fold increase in $R_i$ (4-fold slowing of conduction velocity). Thus, both cytoplasmic and junctional components of $R_i$ are anisotropic. $R_i$ is determined by gap junction distribution and elongated myocyte shape. The degree of anisotropy of $R_i$ is modulated by the extent of myocyte coupling.

MASKING OF TISSUE ANISOTROPY - A COMPUTER MODEL OF THE INTERACTION BETWEEN ACTIVATION WAVEFRONT AND FIXED BARRIERS: **Michael D. Lesh, M.D. and Joseph F. Spear, PhD., F.A.C.C. University of Pennsylvania, Philadelphia, PA**

Normal myocardium is anisotropic: resistivity is greater transverse (T) than longitudinal(L) to fiber axis and therefore conduction is faster parallel to fibers. We hypothesized that the observed pattern of conduction in anisotropic myocardium depends not only on intrinsic anisotropic propertities but also on how an activation wavefront encounters the tissue. We constructed a computer model of 5000 cells in a two-dimensional sheet. Activation could be initiated by pacing from any point(s) on the sheet. Activation times for each resting cell were calculated based on the conduction time from each currently activated cell. We could also specify fixed barriers (scar) through which no activation was possible except at holes in the barrier. "Intrinsic" L and T conduction velocities($V_L$,$V_T$) were defined as those which would occur if conduction were a plane wave in the respective direction.

***Results*** for $V_L$:$V_T$ = 0.6:0.3 m/s are shown. ***A***: Pacing from 1 site at the edge of the sheet yields elliptical 10 msec. isochrones with conduction slower T than L to fiber axis. ***B***: Simultaneous multiple site pacing along one edge produces activation with parallel isochrones; slow T conduction is masked. ***C***: The activation wave encounters an interrupted, fixed barrier; isochrones are parallel proximal to the barrier, but the presence of a hole in the barrier allows slow T conduction to again become manifest beyond the barrier.

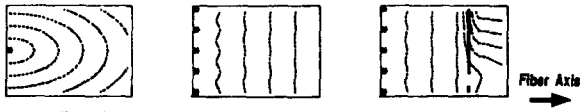


*fig. A* *fig. B* *fig C*

**Conclusion:** 1) The presence of a broad activation wavefront masks underlying tissue anisotropy. 2) A fixed, interrupted barrier allows slow T conduction to be manifest distal to the barrier. 3) Therefore, in infarcted myocardium the interaction of fixed barriers and intrinsic tissue anisotropy may be important in allowing slow conduction, required for reentry, to occur.

SYMPATHETIC-INDUCED CHANGES IN ATRIAL EXCITATION SEQUENCES INFLUENCE AV NODAL CONDUCTION.

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Recently, it has been reported that the expected shortening of AV nodal (AVN) conduction time in response to sympathetic stimulation is attenuated if the degree of sinus node (SN) tachycardia is restricted. We examined this paradoxical effect and its relationship to sympathetic-induced changes in SN-atrial activation. In 13 SN-atrial-AVN preparations superfused with Tyrode solution containing $3x10^{-6}$M atropine, bipolar electrograms were recorded from crista terminalis (CrT), interatrial septum (IAS) and His (H) along with action potentials of AVN cells. The intervals CrT-IAS and CrT-H (AVN conduction time) were monitored on a beat-to-beat basis. In control, the cycle length was 390±33ms and CrT was depolarized 26±8ms before IAS. Postganglionic sympathetic stimulation (PGSS;20-40Hz,1-3s) was introduced locally in the SN and produced transient cycle length shortening of 123±33ms. PGSS-induced tachycardia was consistently accompanied by a transient shortening of the CrT-IAS interval (by 32±11ms), including a reversed sequence of atrial activation in 10/13 preparations. In all cases, the IAS-input of AVN was depolarized progressively earlier and AVN conduction time shortened despite the tachycardia. When a feedback-programmed pacing protocol was utilized to mimic the exact pattern of tachycardia but without PGSS, the CrT-IAS interval remained constant and, as expected, AVN conduction time only prolonged. Propranolol or surgical isolation of the IAS abolished PGSS-associated changes in AVN engagement and the shortening of AVN conduction time. Thus, the effect of localized sympathetic-induced sinus tachycardia can be associated with an unexpected shortening of AVN conduction time due to a reorientation of the timing of the atrial inputs to the AVN at the CrT and IAS.

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MECHANISMS OF ELECTROTONIC UNCOUPLING OF MYOCARDIUM INDUCED BY HYPOXIA

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To delineate mechanisms of electrotonic uncoupling induced by hypoxia, we characterized electrophysiologic and ultrastructural alterations in canine left ventricular myocardium in vitro after selected intervals of superfusion with hypoxic ($pO_2$=28 mmHg) glucose-free media. Space constants, determined by current injection, were unchanged after 15 min of hypoxia (1.7±.3 mm vs 1.8±.4 in paired controls; n=5) but declined significantly after 30 min of hypoxia (p<.02, n=8), reflecting a 65% increase in gap junctional resistance. Uncoupling after 30 min of hypoxia was irreversible. Quantitative ultrastructural analysis demonstrated no significant derangements after 15 min of hypoxia. However, focal disruption of intercalated discs, resulting in a 22% reduction in gap junction surface area, and focal irreversible myocyte injury were observed after 30 min of hypoxia. Gap junction P-face particle diameters measured in freeze-fracture replicas were unchanged after 15 min (8.4±1.5 nm vs 8.5± 1.6 in controls). In contrast, particle diameters decreased to 7.3±1.3 nm after 30 min of hypoxia (p<.01 vs control) consistent with partial closure of the 1.5 nm junctional channel. Thus, impaired myocyte coupling induced by hypoxia is due to both decreased gap junction surface area and increased single channel resistance related to a conformational change in the intramembranous channel.

**EFFECT OF EARLY DIASTOLIC LOADING ON MYOCARDIAL RELAXATION IN THE INTACT CANINE LEFT VENTRICLE.**

Srdjan Nikolic M.S., Edward L. Yellin Ph.D., Koichi Tamura M.D., Takako Tamura M.D., Robert W.M. Frater M.D., F.A.C.C.
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Early transmitral flow (MiF) patterns depend strongly on the rate of fall of LVP: determined by both the active decay of pressure (Pa) due to myocardial relaxation (MyoR), and the increase in pressure due to stretch of passive elements during filling (Pp). This study was designed to uncouple filling from deactivation in order to reveal the instantaneous rate and duration of MyoR by assuming a parallel combination of passive and active elements: LVP(t) = Pa(t)+Pp(t); and without assuming any form of Pa(t). Pp(V) was determined by a retrospective analysis of data obtained in 8 anesthetized dogs instrumented for volume clamping with a remote controlled Mi valve, with LA and LV micromanometers, and with a MiF probe. The passive P-V relation (both positive and negative portions) was determined by clamping at ESV or after various filling volumes, and fit to logarithmic functions. Pp(t) was then calculated from Pp(V) and V(t) (integral of MiF). Time to end relaxation (Ter) was measured as time from Mi valve opening (MiVO) to LVPmin during isovolumic relaxation. dP/dt at the moment of MiVO when dPp/dt=0, gave the max relaxation rate, dPa/dtmax. **RESULTS, (n = 51 runs):** In completely isovolumic relaxations, asymptote $P_\infty$= -5 ± 4mmHg, (thus, Pa is 5mmHg>Pm at MiVO) and Ter = 38 ± 13ms. During normal filling, Ter = 120 ± 32ms. At any time, dPa/dt during isovolumic relaxation was ***always*** greater during filling, indicating a delay in end relaxation. Pa increased with LV volume and dPa/dtmax decreased with LVPmin. **CONCLUSIONS:** Internal restoring forces and diastolic loading in the intact LV exert a profound effect on the ***rate and duration*** of myocardial deactivation.

## Tuesday, March 21, 1989
## 2:00PM–3:30PM, California Room A
## Anaheim Convention Center
## Diastolic Function: Left Ventricular Mechanics

MITRAL OPENING PRESSURE STRONGLY INFLUENCES LEFT VENTRICULAR PEAK RAPID FILLING RATE.

Dennis Morgan, M.D., Alan Pearlman, M.D., F.A.C.C., Catherine Otto, M.D., F.A.C.C., Carolyn Gardner, R.D.M.S., Jeff Hanson, M.S., Hidetoshi Tsuboi, M.D., Yoshima Shoji, M.D., Gregory Misbach, M.D., F.A.C.C., University of Washington, Seattle, Washington.

Peak rapid filling rate (PRFR) is often used to describe diastolic LV function, yet its sensitivity to LA pressure at mitral opening (atrioventricular pressure crossover, PCO) requires further clarification. To assess the relation of PRFR to PCO, we studied 5 open-chest dogs instrumented with LA and LV micromanometer-tip pressure catheters and LV sonocrystals. Heart rate was maintained constant by sinus node crush/RA pacing and CO was controlled by a roller pump (input from cavae, output to RA). Sonocrystal-derived peak rate of change of LV volume (PRFR, ml/s) and PCO (mmHg) were measured on a beat-to-beat basis during rapid flow reduction (analogous to a vena caval occlusion). The results of linear regression analysis are shown for each dog (PRFR=dependent variable, m=slope of regression equation):

| Dog | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Correlation (r) | .95 | .96 | .84 | .94 | .98 |
| m (ml/s/mmHg) | 27.2 | 30.3 | 40.9 | 7.6 | 25.6 |
| S.E.E. (ml/s) | 26.3 | 22.5 | 29.6 | 9.9 | 15.1 |
| P value | <.001 | <.001 | <.001 | <.001 | <.001 |

Conclusions: 1) There is a steep linear relation between PRFR and PCO; 2) if alterations in PRFR are to be used as a marker of LV diastolic function, knowledge of concomitant atrial loading conditions is mandatory.

ENHANCED RECOVERY OF DIASTOLIC FUNCTION AFTER GLOBAL MYOCARDIAL ISCHEMIA IN THE INTACT ANIMAL.

Kevin Tveter, M.D., John St.Cyr, M.D., Joseph Schneider, M.D., Richard Bianco, B.A., John Foker, M.D., Ph.D., University of Minnesota, Minneapolis, MN.

The relationship of myocardial ATP levels and postischemic dysfunction remains controversial. In an intact animal model of global ischemia (Isc) and recovery, we have found ribose (R) or adenine (A) and R accelerated the return of ATP levels (84% and 80% recovery by 24 hrs). The purpose of this study was to determine the effects of enhancing ATP recovery on postIsc function. Following 20 min of Isc on cardiopulmonary bypass, dogs received either R (80mM)(n=5), A (20mM) and R (80mM)(n=5) or saline (NS)(n=6) for 24 hrs. The end-systolic pressure-volume ratio ($E_{max}$, mmHg/ml), dP/dt (mmHg/sec) and diastolic circumferential stress ($\sigma$, dynes x $10^3/cm^2$)-strain ($\epsilon$) relationships were determined from sonomicrometry and micromanometry data during transient vena caval occlusions. The results (mean±SEM, *p<0.05 vs PreIsc, **p<0.05 vs NS):

| | | PreIsc | 4 hrs | 24 hrs |
|---|---|---|---|---|
| dP/dt | NS | 2235±59 | 2212±145 | 2277±174 |
| | R | 2680±169 | 2459±199 | 2879±237 |
| | A/R | 2452±250 | 2212±173 | 2277±146 |
| $E_{max}$ | NS | 3.12±0.30 | 2.74±0.70 | 3.03±0.73 |
| | R | 2.46±0.43 | 3.02±0.25 | 2.27±0.26 |
| | A/R | 2.33±0.31 | 2.05±0.28 | 2.47±0.57 |
| $\epsilon$ at $\sigma$ =20 | NS | 0.213±0.02 | 0.100±0.02* | 0.128±0.01 |
| | R | 0.282±0.03 | 0.164±0.02* | 0.266±0.02** |
| | A/R | 0.278±0.04 | 0.171±0.03* | 0.242±0.04** |

We conclude: (1) recovery of systolic function is essentially complete by 4 hrs. (2) Return of diastolic function is enhanced similarly to ATP recovery by R or A/R. (3) Because A did not further enhance ATP recovery, R appears to be the rate limiting ATP precursor.

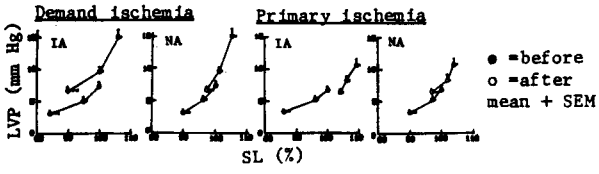
REGIONAL DIASTOLIC MECHANICS OF ISCHEMIC AND NONISCHEMIC AREAS IN THE PIG HEART

Toshiyuki Takahashi, M.D., Marc J. Levine, M.D., William Grossman, M.D., F.A.C.C., Harvard-Thorndike Laboratory, Beth Israel Hospital, Boston, MA

Diastolic dysfunction has often been observed during ischemia(IS), but differences between ischemic(IA) and nonischemic(NA) areas, and between demand(D) and primary (P) IS remain to be elucidated. We created regional D and P in the pig heart(chest and pericardium open). D was made by creating a 75-90% luminal stenosis on left anterior descending artery(LAD) plus rapid pacing(1.8x resting rate) for 3-5 min(n=7). P was made by a total LAD occlusion for 1.5 min(n=6). LVP, LV segment lengths (SL), time constant of LVP fall(T) and systolic shortening of SL(%ΔL) were obtained. Results:*p<.01, **p<.05, mean±SEM.

| | LVEDP(mmHg) | | T(msec) | | %ΔL(%) IA | | NA | |
|---|---|---|---|---|---|---|---|---|
| | pre | post | pre | post | pre | post | pre | post |
| D | 7±1 | 15±1* | 34±3 | 46±6** | 20±2 | 14±2* | 15±3 | 14±2 |
| P | 7±1 | 11±1* | 32±3 | 38±3* | 17±2 | -4±1* | 14±3 | 16±2 |

During D, dynamic diastolic LVP-SL relation shifted upward and rightward in IA, but mainly rightward in NA. During P, LVP-SL shifted more rightward in IA(Figure). During D, peak +dSL/dt(mm/sec) increased in NA(22±3 to 35±4*) without changes in IA(33±5 to 34±4). Conclusions: Regional IS causes differences in both diastolic and systolic behavior between IA and NA. Regional mechanics of IA varies with the types of IS.




DILTIAZEM IMPROVES DIASTOLIC FUNCTION DURING HYPOXIA IN HYPERTROPHIED RAT HEARTS

Ellen O Weinberg BS, W Mark Vogel PhD, Carl S Apstein MD FACC, Boston Univ. School of Medicine, Boston, MA

This study examines the effect of diltiazem on the exaggerated rise of diastolic stiffnesss during hypoxia that we previously observed in hearts with LV hypertrophy (LVH). We used 8 weeks of deoxycorticosterone-salt treatment to cause hypertensive LVH in rats. Hearts were perfused for 20 min with oxygenated buffer followed by 5 min hypoxic perfusion, paced at 4 Hz throughout. Treated hearts received 150 nM diltiazem 10 min before and during hypoxia. LV volume was held constant with a balloon adjusted to produce an initial LVEDP of 10 mmHg; thus, increases of LVEDP indicate increases of chamber stiffness. Results were tested by 2-way factorial analysis of variance. LV mass was 1.0 ± 0.03 g in 13 normal hearts and 1.3 ± 0.04 g in 13 hearts with LVH ($p < .001$). Initial aerobic LV developed pressure was 122 ± 5 mmHg in normal hearts and 156 ± 4 mmHg with LVH ($p < .001$). During aerobic perfusion, hearts with LVH were more sensitive to diltiazem, which decreased +dP/dt by 13 ± 2 % in 6 normal hearts and by 20 ± 1 % in 7 hearts with LVH ($p < .005$ normal vs LVH), while O2 consumption decreased by 7 ± 2 % in normals and by 12 ± 2 % with LVH ($p < .007$ normal vs LVH). Systolic function during hypoxia was similar in all groups. Without diltiazem LVEDP after 5 min hypoxia increased to 30 ± 3 mmHg in normals and to 60 ± 7 mmHg with LVH ($p < .001$). With diltiazem LVEDP increased to 26 ± 4 in normals (p = NS vs untreated normal) and to 34 ± 5 with LVH ($p < .001$ vs untreated LVH, p = NS vs either normal group). CONCLUSION: A modest negative inotropic dose of diltiazem normalized the exaggerated increase of LVEDP during brief hypoxia in hypertrophied hearts.

VENTRICULAR DIASTOLIC INTERACTION IN INTACT DOGS ASSESSED BY CONDUCTANCE CATHETER

Chester M. Boltwood, Jr., M.D., F.A.C.C., Stanton A. Glantz, Ph.D., Wadsworth VA/UCLA, Los Angeles and UCSF, San Francisco, CA

Previous studies of ventricular interaction have required surgical instrumentation, which may cause pericardial artifacts. The purpose of this study was to analyze ventricular diastolic interaction using the conductance catheter, which may provide a useful measure of relative LV volume without surgical instrumentation. In 7 closed chest dogs we recorded LV conductance volume (CV) and LV, RV pressures during control, and balloon occlusions of inferior vena cava (IVCO), aorta (AO), and pulmonary artery (PAO). We fit LVDP from single diastoles (ie. LVDP nadir to LVEDP at 200 Hz) to:

$$LVDP = a_0 + a_1\,CV + a_2\,CV^2 + a_3\,CV^3 + k\,RVDP.$$

In theory, if pericardial constraint pressure (PP) < RVDP then k < 1; if PP ≈ RVDP then k ≈ 1; and if PP > RVDP then k > 1.

Results: In each experimental episode this regression model showed high correlation ($R^2$ 0.88-0.96). Combining all episodes, k = 1.09 ± 0.10 during control, but changed from control by -0.30 ± 0.11 during IVCO ($p<0.05$), by 0.40 ± 0.11 during AO ($p<0.001$), and by -0.41 ± 0.12 during PAO ($p<0.001$). To validate this application of the conductance catheter, we derived k from simultaneous angiographic LV volume and CV over multiple control and intervention episodes, and obtained similar results.

Conclusions: Our findings support the PP ≈ RVDP approximation during control in the intact state. However, our data suggest that PP > RVDP during AO, and PP < RVDP during PAO. Thus, as suggested by recent experimental literature, there are significant deviations from the PP ≈ RVDP approximation during asymmetric loading of the LV or RV.

## Tuesday, March 21, 1989
## 4:00PM–5:30PM, California Room A
## Anaheim Convention Center
## Coronary Artery Stenosis and Vasomotor Tone

INCREASED FLOW VELOCITY IN THE HUMAN CORONARY STENOSIS: A SIMPLE ASSESSMENT OF STENOSIS SEVERITY.

Alan C Yeung MD, Joseph A Vita MD, Peter Ganz MD FACC, Andrew Selwyn MD FACC, Kathleen Reagan MD, and John A Bittl MD FACC, Brigham and Women's Hospital, Boston, MA.

Coronary stenoses are characterized by complex geometry, particularly after angioplasty, making angiographic assessment difficult. Since blood flow velocity increases at sites of arterial narrowing, we evaluated a flow velocity-dependent, nonangiographic method to assess stenosis severity. Validating the method, we perfused 14 segments of 3.2-mm polyethylene tubing with whole blood at 80 ml/min at an average pressure of 130/80 and found excellent correlation ($y = 1.01x + 0.23$; $r^2 = 0.95$; $p = 0.001$) between the absolute values for luminal diameter reduction (%) and the flow velocity-dependent value measured with a No. 2.5 Fr Doppler catheter using the continuity equation: $A_s = A_n \cdot V_n/V_s$, where A = the cross-sectional area and V = flow velocity in normal (n) and stenosed (s) segments. The Doppler catheter is easily used in Pts. During angioplasty, we advanced the tip of the catheter to the stenosis and measured the value for $V_n/V_s$ while estimated flow remained constant. Low noise, high quality signals demonstrated as much as a 20-fold increase in flow velocity in the stenosis compared to the normal segment, permitting a measurement of stenosis severity that is independent of angiography. In conclusion: 1) *In vitro* studies show excellent correlation between absolute and Doppler-derived values for stenosis severity; 2) This technique already exists for application in Pts, thus providing a simple complement to angiography, particularly when angioplasty produces complex luminal geometry but immediate assessment of dilation is important.

## EFFECTS OF ADENOSINE ON THE CORONARY CIRCULATION IN HUMANS

Robert F. Wilson MD, Betsy Christensen BSN, Stevan Zimmer MD, David Laxson MD, and Carl W.White M.D.,FACC. University of Minnesota, Minneapolis, MN

Although adenosine(ADN) has been used widely in studies of the coronary circulation in animals, its safety and dose response characteristics have not been defined in humans. To do so, we measured coronary blood flow velocity(CBFV) in a normal left coronary artery in 10 patients using a 3F Doppler catheter. CBFV, mean arterial pressure(AP), heart rate(HR), and the ECG (PR,QRS,and QT intervals) were recorded after intracoronary(IC) papaverine(P, 8-12mg boluses), IC ADN (4-14μg boluses) and intravenous(IV) ADN infusions.

***Results:*** ***Intracoronary Adenosine***

| (MEAN±SEM) | 4 μg | 8 μg | 12 μg | 14 μg | P |
|---|---|---|---|---|---|
| ΔCBFV | 3.9±.3 | 4.3±.2 | 4.6±.3 | 4.7±.4 | 4.8±3 |
| ΔAP(mmHg) | -3±1 | -4±1 | -5±1 | -3±1 | -7±1 |
| ΔHR(bpm) | 0±1 | 0±1 | 0±1 | 0±1 | +3±1 |

The duration of maximal hyperemia (14μg ADN: 10±2s; P 29±4s) and the time for CBFV to normalize (ADN:37+2s;P: 118±5s) were shorter after ADN than P (p<.01). The ECG intervals were unchanged after ADN, but P increased the QT (mean Δ +96±18 msec).

***Intravenous Adenosine***

| Dose | 70μg/kg/min | 100μg/kg/min | 140μg/kg/min |
|---|---|---|---|
| ΔCBFV | 2.9±.6 | 4.5±.7 | 4.4±.5 |
| ΔAP(mmHg) | -5±2 | -9±4 | -11±3 |
| ΔHR(bpm) | +7±3 | +13±6 | +18±3 |

CBFV increased maximally 123±25s after infusion onset and returned to basal levels 113±13s after discontinuation. At submaximal doses, CBFV fluctuated markedly. 1 patient had submaximal ΔCBFV at 140μg/kg/min.The ECG was unchanged at any dose.

***Conclusion:*** Maximal coronary hyperemia, equivalent in magnitude to IC P but of ultra-short duration, can be safely produced with either IC or IV ADN. Its brief duration of action and lack of effect on the ECG should facilitate studies of the coronary circulation in humans.

## THE COMPARISON OF ACETYLCHOLINE AND ERGONOVINE IN THE PROVOCATION OF CORONARY VASOSPASM.

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Provocative testing of coronary spasm is required for the diagnosis of vasospastic angina (VSA) in chest pain patients. In order to evaluate the provocating methods of coronary spasm, we performed coronary arteriograms by Judkins tecnique after the injection of acetylcholine (ACH method) and ergonovine (EM method) in 8 VSA patients and 12 patients with atypical chest pain (ACP). In ACH method, acetylcholine (ACH) was injected with incremental dose of 20, 50, and 100 micro gram to the left coronary artery, 20 and 50 micro gram to the right coronary artery, until coronary spasm was introduced. In EM method, ergonovine meleate (EM) was injected up to 0.4 mG intravenously until coronary spasm was provocated. Coronary spasm was defined as spasm of more than 90 % or total occulusion associated with an attack of chest pain and/or ischemic ST segment changes on the ECG. In VSA patients with ACH method, coronary spasm was induced 88% to the left coronary artery and 100 % to the right coronary artery. In VSA patients with EM method, coronary spasm was induced in 57%. In ACP cases with ACH method, vasospasm was induced in 17% only in the right coronary artery but with EM method, vasospasm was not induced. With both ACH and EM methods no major complication was observed. Spontaneous regression of the vasospasm was observed within 5 minutes in all cases with ACH method in which coronary spasms were observed but not with EM method. In conclusion, ACH method is easier and more sensitive however less specific than EM method in the induction of coronary vasospasm.

## CORONARY HEMODYNAMIC EFFECTS OF ATRIAL NATRIURETIC PEPTIDE

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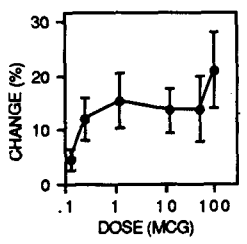
University of Pennsylvania, Philadelphia, PA

To determine if atrial natriuretic peptide (ANP) is a direct coronary vasodilator, we compared the effects of synthetic ANP (rat 103-126) and nitroglycerin (NTG) on coronary hemodynamics in 8 pts with coronary artery disease. Increasing doses of ANP (0.125 to 100 mcgs) or NTG (0.5 to 200 mcgs) were administered directly into the left coronary artery and peak total coronary sinus blood flow (CBF, ml/min) was measured by continuous thermodilution technique using a Webster catheter. Coronary vascular resistance (CVR, mmHg-min/ml) was calculated as mean arterial pressure/CBF. All pts received both ANP and NTG in random sequence with repeat baseline measurements between the drugs. No untoward effects were observed with either agent. CBF and CVR at the two baselines (differences not significant) and at the largest dose of ANP and NTG given are shown (mean±SEM; *p<0.05 drug vs baseline):

| | Baseline | ANP (100 mcg) | Baseline | NTG (200 mcg) |
|---|---|---|---|---|
| CBF | 129±9 | 155±9* | 131±7 | 167±12* |
| CVR | 1.00±.10 | 0.84±.07* | 1.00±.08 | 0.79±.08* |

The maximal effects of ANP and NTG on CBF were similar (+20% vs +27%, p=NS), and CVR fell slightly more with NTG (-16% vs -21%, p<0.05). The CBF dose-effect curve for ANP is shown. **Conclusions:** 1) ANP is a potent direct coronary vasodilator, whose maximal coronary hemodynamic effects are similar to those of NTG. 2) The administration of ANP to pts with coronary disease is safe and well tolerated.




## PRESERVED FLOW-MEDIATED VASODILATION DESPITE ACETYLCHOLINE-INDUCED VASOCONSTRICTION IN ATHEROSCLEROTIC CORONARY ARTERIES IN MAN

Andreas M. Zeiher, MD, Helmut Drexler, MD, Helmut Wollschläger, MD, Hanjörg Just, MD. Medical Clinic, Dpt.of Cardiology, University of Freiburg, F.R.G.

Recent experimental studies have demonstrated different mechanisms of vasodilation in response to nitric oxide, believed to be EDRF, and acetylcholine(ACh). We compared the vasomotor response of human coronary arteries to increased coronary blood flow and to the endothelium-dependent dilator ACh in 7 patients with normal coronary arteries(normal CA) and in 9 patients with coronary atherosclerosis (lesions < 30%, CAD). Flow-mediated coronary dilation was evaluated before and 80 sec after selective injection of 7 mg papaverin into the midportion of the LAD via a Doppler catheter. CA diameter measurements(automated quantitation of digitized cine-frames) were obtained at the proximal LAD segment exposed to increased flow, but not to papaverin. ACh ($10^{-8}$M, $10^{-7}$M, $10^{-6}$M) was infused into the proximal LAD via the Doppler catheter. LAD blood flow velocity was continuously measured and CA diameters of identical LAD segments were obtained at the end of each 3 min infusion period.

Results: Flow-mediated vasodilation was observed in all patients, although somewhat reduced in patients with CAD. In contrast, ACh caused dilation in all normal patients, but profound vasoconstriction in all patients with CAD (* p<0.001 vs flow-mediated).

| % change | normal CA | | patients with CAD | |
|---|---|---|---|---|
| | flow-mediated | ACh | flow-mediated | ACh |
| flow velocity | 340±116 | 89±25 * | 211±69 | 140±74 * |
| CA diameter | +9.1±4.3 | +9.8±4.6 | +5.7±2.9 | -21.2±4.9 * |

Thus, flow-mediated dilation of atherosclerotic human CA is preserved despite acetylcholine-induced vasoconstriction. These results suggest that, in contrast to pure EDRF-mediated flow-dependent coronary dilation, additional mechanisms may be involved in the coronary response to ACh, e.g. hyperpolarization.

## CONTRASTING EFFECTS OF ACETYLCHOLINE ON CORONARY CONDUCTANCE AND RESISTANCE VESSELS IN PATIENTS WITH CORONARY ARTERY DISEASE

Helmut Drexler, MD, Andreas M. Zeiher, MD, Helmut Wollschläger, MD, Thomas Meinertz, MD, Hanjörg Just, MD. Medical Clinic, University of Freiburg, F.R.G.

Acetylcholine (Ach) has been shown to induce paradoxical vasoconstriction of epicardial atherosclerotic coronary arteries, however its effects on coronary resistance vessels in this setting remains to be elucidated. Therefore, we evaluated the hyperemic response to contrast medium during angiography before and after intracoronary Ach infusion ($10^{-7}$ M, $10^{-6}$ M), given into the LAD via an intracoronary Doppler catheter. Coronary flow reserve was assessed as the ratio of pre-injection intracoronary blood flow velocity to contrast-induced peak hyperemic flow velocity. Intracoronary injection of contrast medium was used as a mean for coronary arteriolar dilatation and estimation of coronary reserve. For determination of the epicardial response, LAD diameters were measured by an automatic contour detection system. Contrast mediated hyperemic response (coronary reserve) decreased from 2.9±0.5 during control to 1.7±0.8 ($10^{-7}$ M) and 0.8±0.4 ($10^{-6}$ M) during Ach infusion in all 12 patients (NL = normal coronary arteries, n=6; CAD = coronary artery disease with non flow-limiting stenoses, n=6). Ach slightly increased epicardial LAD diameters in NL (7±4%), however significantly reduced LAD diameters in CAD (-20±8%). Ach mediated intracoronary flow velocity was somewhat more pronounced in CAD (140±73%) compared to NL (81±33%), due to simultaneous epicardial vasoconstriction.
Thus, hyperemic response to contrast was blunted during Ach infusion both in NL and CAD indicating substantial Ach induced dilatation of resistance vessels. These results suggest, that paradoxical vasoconstriction in CAD was confined to epicardial conductance vessels.

## CLIMATOLOGICAL VARIABLES AND ACUTE MYOCARDIAL INFARCTION: A TIME COURSE STUDY.

Barry A. Franklin, Ph.D., Susan Wetherbee, R.D., Donovan Bakalyar, Ph.D., William O'Neill, M.D., William Beaumont Hospital, Royal Oak, Michigan.

Exposure to cold or heat stress has been shown to produce transient increases in platelet and red cell counts, and blood viscosity levels. Such findings seem to reinforce the notion that fluctuations in selected climatological variables (CV) may be involved in the precipitation of acute myocardial infarction (AMI). To further clarify the effects of temperature, wind chill, heat index, relative humidity and barometric pressure on the incidence of AMI, we retrospectively surveyed 9 Detroit hospitals to determine if these hospitals simultaneously experienced an influx of documented AMIs on given admission dates over a 2-year period (1986-1987). Four hospitals provided a daily listing of the number of AMIs, yielding an extensive data base (n = 3,924 AMIs):

| | AMIs/Day | | | |
|---|---|---|---|---|
| Year | Mean | SD | Range | Total/Year |
| 1986 | 5.38 | 2.36 | 0-15 | 1963 |
| 1987 | 5.37 | 2.41 | 0-13 | 1961 |

The incidence rates for 1986 vs 1987 were remarkably similar. Moreover, the frequency of AMI was characterized by a Poisson distribution, suggesting that a small number of days would, by chance, have a significantly higher number of AMIs. Over the 2-years, 14 days were identified in which 11 or more AMIs occurred (> 2 SD). These nonconsecutive days showed no consistent relation to the aforementioned CV. In addition, there was no apparent seasonal or daily variation in the incidence of AMI.
Conclusion: These findings, although regionally specific, suggest that AMIs occur randomly over time, irrespective of common CV, seasonal change, or day of the week.

# Tuesday, March 21, 1989
# Poster Displayed: 2:00PM–5:00PM
# Author Present: 2:00PM–3:00PM
# Pacific Room, Anaheim Convention Center
# Epidemiology of Coronary Disease

## Time Of Onset Of Acute Myocardial Infarction (AMI) After Awakening.

Robert Goldberg, Ph.D., Priscilla Brady, R.N., Zuoyao Chen, M.D., Joel Gore, M.D., Athan Flessas, M.D., Josh Greenberg, M.D., George Theodosiou, M.D., James Dalen, M.D., James Muller, M.D. Univ of MA Medical School, Worcester, MA, Harvard Medical School, Boston, MA

Several recent studies have reported an increased incidence of AMI during the morning hours. These studies, however, failed to determine the relationship between AMI onset and time after awakening in relation to occurrence of AMI. We examined this association in 148 pts with AMI admitted to four Worcester, MA, teaching hospitals during the past year. There was a marked association of time of onset of first AMI symptoms and time after awakening. Forty-one percent of hospitalized pts had their initial AMI symptoms within the first four hours after awakening with 63% of these pts having their initial AMI symptoms within 2 hours after awakening. This percentage declined to 21 % of pts having their first MI symptoms within five to eight hours of awakening, 16 % between nine and twelve hours after awakening, 13% between thirteen and sixteen hours, and 9% 17 hours or greater after awakening. Further studies of the mechanisms responsible for this observation are needed and to assist in the development of prevention strategies.

## INCREASED MORNING INCIDENCE OF MYOCARDIAL INFARCTION: EXPERIENCE IN THE ISIS-2 TRIAL

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To investigate the circadian pattern in the incidence of acute myocardial infarction (MI), time of day of MI was prospectively determined in 12,160 patients, who were consecutively randomized for the ISIS-2 trial (International Study of Infarct Survival). Local time of randomization, interval between onset of clinical MI symptoms and randomization, and information on aspirin therapy in the 7 days prior to MI were recorded by the randomization centers.

| | Time of Day (0-24 hrs) | | | | |
|---|---|---|---|---|---|
| Country | 0-6 | 6-12 | 12-18 | 18-24 | Total |
| UK / Ireland | 1098 | 1684* | 1319 | 1206 | 5307 |
| Australia/N Zealand | 455 | 605* | 508 | 423 | 1991 |
| Scandinavia | 595 | 946* | 809 | 564 | 2914 |
| USA / Canada | 196 | 277* | 251 | 203 | 927 |
| West Germany | 225 | 325* | 250 | 221 | 1021 |
| Total | 2569 | 3837* | 3137 | 2617 | 12160 |

* $p < 0.001$ vs. other times of day

In the subgroup of 1693 patients (14% of total) who reportedly used aspirin in the 7 days prior to MI, the circadian pattern in the incidence of MI was similar to that observed for the total study population, suggesting that aspirin does not blunt the morning surge in the incidence of MI.
Conclusion: Prospective investigation of time of MI confirmed the finding of increased morning incidence of MI in a large international study population.

TELEPHONE-MAIL MEDIATED DIETARY INTERVENTION FOR HYPERCHOLESTEROLEMIA

Mia Clark, R.D., Mark Johannsson, M.P.H., David Hyman, M.D., Candace Corsetto, B.S., Jane Borchers, R.D., Robert DeBusk, M.D., F.A.C.C., Stanford University School of Medicine, Stanford, California.

Multiple face-to-face counseling sessions for hypercholesterolemia are often impractical. To test a more convenient method for individualized dietary counseling, 229 middle-aged (49±10 years) men and women with total plasma cholesterol (TC) exceeding 200 mg/dl were randomized in a 4-month-long worksite-based trial of dietary intervention (INT, n=114) or a control condition (n=115). INT consisted of: 1) a baseline food frequency questionnaire requiring 10 minutes for completion, 2) a 40-minute counseling session with a registered dietitian (RD) to set individual dietary goals, 3) a food manual presenting behavioral goals and tips, 4) RD's written revision of dietary goals based on 2 followup questionnaires completed at 4 and 9 weeks and 5) RD-initiated telephone contacts of approximately 10 minutes at 5 and 10 weeks to review revised dietary goals. Duplicate measurements of TC on fingerstick blood obtained at baseline and 4 months were corroborated by indirect beta quantification of venous blood. After 4 months, TC values for the INT group fell from 238±25 to 223±33 mg/dl compared to 237±24 to 235±30 in controls ($p<0.002$ for intergroup difference); the median decrease in INT was 15 mg/dl. CONCLUSION: Telephone and mail-mediated followup of initial face-to-face dietary counseling facilitates reduction of hypercholesterolemia through dietary change. The system, which enhances the convenience of dietary counseling and requires as little as 1 hour of RD time, can be widely implemented in worksites.

CARDIOVASCULAR RISK REDUCTION THROUGH WORKSITE HEALTH PROMOTION.

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Worksite health promotion has been proposed as a means to reach and motivate individuals for cardiovascular risk reduction. To test this proposition, we developed an experimental program to include: a) screening for lipoproteins, blood pressure, obesity, smoking, and behavioral risk factors b) individual counseling c) 4-hour overview of cardiovascular risk reduction d) group programs for smoking cessation, weight loss, and stress management and e) 21-month sequence of workshops and activities to promote risk reduction. 1004 employees from 17 sites of a large communication company enrolled in the program. 322 participants (83% of eligible) have completed two-year follow-up in 7 sites to date. Among smokers, 32.4% quit. For hypertension, 72.7% of those with BP over 140 and/or 90 reduced below 140/90 (mean reduction for those at risk 12.4 sbp and 9.1 dbp). For cholesterol, 54.9% of those over 200 mg/dl (or 180 if under 30 yrs), reduced at least 5 mg/dl (mean reduction for those at risk = 9.9 mg/dl). Among those at least 110% ideal body weight at baseline, 25.1% lost at least 5 lb. Among those over the 75th percentile on the JAS measure of Type A behavior pattern, 38.2% were below the 75 %ile at the end of the program (means for those at risk: pre = 85.5 %ile, post = 75.3 %ile). Among those at risk on at least one factor at screening, 54.8% reduced at least one factor by the criteria indicated. Greatest public health benefits may rest in moderate reductions by large numbers at moderate risk. Worksite programs can instigate such reductions.

SMOKING CESSATION POST MYOCARDIAL INFARCTION: EFFECTS OF A NURSE-DIRECTED INTERVENTION

Nancy H. Miller, R.N., Mary Adornato, R.N., Nancy Fitch, R.N., Robert F. DeBusk, M.D., F.A.C.C., C. Barr Taylor, M.D., Stanford University Medical Center, Stanford, California and Kaiser-Permanente Medical Centers.

Mortality in patients continuing to smoke after a myocardial infarction (MI) is twice that of those who stop. The efficacy of a relapse prevention program was evaluated in 173 patients treated for MI in 4 Kaiser-Permanente Medical Centers: 86 were randomized to a nurse-directed intervention (ND) consisting of 2 face-to-face counseling sessions beginning 5 days post-MI focusing on avoidance of high-risk situations, a relapse prevention manual and audiotapes and nurse-initiated telephone followup in the 6 months post-MI, or to usual care (UC). Nicotine gum (n=5) and mild aversive smoking (n=3) were provided for patients continuing to smoke. UC (n=87) consisted of standard messages about cessation by health care professionals. Patient refusal rate was 21% (47 of 220). Smoking status, confirmed by expired carbon monoxide and serum thiocyanate and psychological measures, intention to quit and self-efficacy were assessed at 3, 26 and 52 weeks. At 26 weeks the dropout rate was 9% (15 of 173); mortality was 3% (6 of 173) and nonsmoking rates in ND and UC groups were 71% (55 of 77) and 52% (39 of 75) respectively ($p<0.03$). This trend continued at 12 months. Predictors of smoking at 6 months included smoking at 3 weeks, alcohol intake ≥21 oz/wk, and low self-efficacy and lack of stated intention to quit measured at baseline. CONCLUSION: A nurse-directed intervention commencing in hospital significantly increased smoking cessation in the 6 months after acute MI, primarily by preventing early relapse during the transition from hospital to home care.

## Tuesday, March 21, 1989
## Poster Displayed: 2:00PM–5:00PM
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## Pacific Room, Anaheim Convention Center
## Pediatric Cardiology Follow-Up Methods

**LINEAR GROWTH IN PEDIATRIC CARDIAC TRANSPLANT PATIENTS.**

**Linda J. Addonizio, MD, FACC, Daphne T. Hsu, M.D., Eric A. Rose, M.D., Welton M. Gersony, MD, FACC, Columbia University, New York, NY.**

**Do children using steroid immunosuppression grow after cardiac transplantation? 17 children (11 cardiomyopathy, 6 congenital heart disease) ages 3 mo. to 18 yrs. were followed for linear growth from 6 to 51 mos. post-transplant. The patients were divided into 4 groups according to their growth potential at the time of transplantation. In Groups I (children <5 yrs.) and II (young adolescents) are patients with a normal growth potential at the time of transplant. In Group III are adolescents whose growth potential might be impaired because of pre-transplant high-dose steroid administration, chemotherapy or irradiation. In Group IV are young adults who had achieved near maximal growth pre-transplant. The patient data is summarized below:**

| Group | #pts. | Mean Age (yrs.) | Followup (mo.) mean | Followup (mo.) range | Hgt (%tile) |
|---|---|---|---|---|---|
| I | 4 | 1.8 ± 1.8 | 23 | 6 - 31 | 5 - 25 |
| II | 6 | 13.1 ± 0.8 | 24 | 15 - 32 | 5 - 75 |
| III | 3 | 14.9 ± 1.3 | 25 | 17 - 33 | 5 - 10 |
| IV | 4 | 18.0 ± 0.4 | 17 | 13 - 18 | 10 - 50 |

**In Group I(young children) and Group II(adolescents) 9 of 10 patients had normal growth rates for age and maintained their preop height percentiles(hgt %tile). One patient had too short a followup to assess growth rate. In Group III(adolescents with preop growth impairment) 2 patients did not grow and 1 patient had a normal growth rate and maintained his preop hgt%tile. In Group IV(young adults) no significant growth occurred. In summary, normal growth rates can be achieved in most young children and adolescents on steroid immunosuppression following cardiac transplantation. However, pre-transplant noncardiac risk factors for growth failure may continue to affect their potential for growth.**

## CARDIOPULMONARY EXERCISE RESPONSE IN ADOLESCENTS FOLLOWING CARDIAC TRANSPLANTATION.

Lee A Pyles M.D., Marcus J. Mianulli M.S., Maria T. Olivari M.D., Elizabeth Braunlin M.D. (FACC) University of Minnesota, Minneapolis, MN

Six adolescents (14-16 years,4M, 2F) have undergone cardiac transplantation (CT) in the past 2 years for end stage cardiomyopathy. Cardiopulmonary exercise testing (Bruce protocol) and right ventricular endomyocardial biopsy were performed 6 months after CT. Right heart catheterization was performed 6 to 12 months after CT. Parameters (mean ± SEM) at rest and during maximal exercise (EX) are compared to 6 healthy age,sex and weight matched controls (NL):

| | | HR beat/min | VO2 ml O2/kg-min | O2 PULSE ml O2/beat | Mean BP mm Hg |
|---|---|---|---|---|---|
| REST | CT | 96 ±6 * | 5.9 ±1.6 | 3.6 ±1.1 | 96 ±5 |
| | NL | 59 ±5 | 4.2 ±0.4 | 2.0 ±0.8 | 91 ±4 |
| EX | CT | 134 ±8 * | 24.3 ±1.9 * | 11.7 ±1.4 * | 95 ±3 # |
| | NL | 192 ±14 | 56.2 ±3.0 | 19.4 ±1.4 | 105 ±4 |

* $p < 0.001$ # $p < 0.05$

*HR=heart rate, VO2=O2 consumption, O2 Pulse=VO2/HR*

During EX, CT pts achieved no increase in mean BP, with only 70% HR, 43% VO2, and 60% O2 pulse increase compared to controls. EX duration was 8.5 (CT) vs. 15.2 (NL) min ($p<0.001$). Anaerobic threshold occurred at similar fractions of maximum VO2 (CT: 74%, NL: 69%). HR 5 min post EX remained elevated in CT (85% max) vs. NL (51% max). Same day heart biopsy showed no rejection. CT resting hemodynamics were normal except elevated HR. EX response in adolescents 6 months after CT is abnormal with attenuated BP, HR and VO2 Max consistent with the denervated state and previous adult experience.

## EBSTEIN'S ANOMALY OF THE FETUS AND NEONATE; ANATOMIC DETAILS OF PROGNOSTIC IMPORTANCE

David A. Roberson M.D. and Norman H. Silverman M.D. University of California, San Francisco;San Francisco CA.

Ebstein's anomaly (EA) presenting in the newborn period has a high mortality. The purpose of this study was to determine which anatomic features of EA are predictive of death at less than 3 months old. We examined complete echocardiograms (ECHO) and medical records of 16 Pts with EA who were diagnosed at UCSF as a fetus or neonate. EA was diagnosed when the ECHO demonstrated distal displacement of the proximal attachments of the tricuspid valve from the AV groove and valvar dysplasia. Cardiac cath data and angiograms in 5 Pts, pathology specimens in 3 Pts, and intraoperative inspection in 3 Pts confirmed the ECHO findings in each case. 6 Pts were diagnosed in utero, five of these died. 7 Pts died between 36 weeks gestation and 3 months old. Statistical differences ($p \leq 0.05$) in the incidence of anatomic features between the early mortality group and the surviving group were determined by the Fisher's exact test. Anatomic features which correlated with early death included bound-down distal attachments of the anterosuperior tricuspid valve leaflet (86%vs11%), RV wall thinning and dyskinesis (86%vs0%), LV compression by right heart dilatation (71%vs11%), and the combined area of the RA and atrialized RV being greater than the combined area of the functional RV, LA, and LV (57%vs0%) measured in the apical 4-chamber view. The amount of valve leaflet dysplasia, number of leaflets displaced, the distance the proximal valve attachments were displaced from the AV groove, and the incidence of associated cardiac lesions was not different between the 2 groups. 86% of Pts with bound-down distal attachments had RV thinning and dyskinesis. 86% of Pts with RV thinning and dyskinesis had bound-down distal attachments. CONCLUSION: Death of the fetus or neonate with EA is likely in the presence of bound-down distal attachments of the anterosuperior tricuspid valve leaflet and RV thinning and dyskinesis. These features commonly coexist. LV compression and marked RA dilatation also correlate with early death.

## PATTERNS AND DETERMINANTS OF EXERCISE PERFORMANCE IN FONTAN PATIENTS

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46 patients (age 12.5 ± 5.2 years) underwent graded supine bicycle exercise tests at levels equivalent to normal daily activity (maximum 1.5 watts/kg), 4.5 ± 3.5 years after a Fontan (F) repair. Results were compared to 28 age matched controls. Cardiac output was assessed by doppler echocardiography. At rest, cardiac index, stroke index and systolic blood pressure were comparable in both groups but increases with exercise were smaller in the Fontan patients ($p<0.01$). The resting heart rate was higher in the Fontan group but this difference disappeared as soon as exercise commenced. To determine whether there are limitations intrinsic to the F circulation we compared the 10 best performances against age matched controls and found no differences in cardiac index, stroke index, heart rate or blood pressure at any exercise level. At the other end of the spectrum, poor performance did not result from inadequate levels of heart rate but from an inability to increase stroke volume. Multivariate analysis (using morphologic, clinical, haemodynamic, surgical and resting echocardiographic variables) demonstrated that exercise performance was limited by ventricular contractility only when it was severely impaired (ejection fraction <25%). In the majority, ventricular filling, which is determined by the properties of the pulmonary vascular bed, appeared to be the major determinant of functional result after F repair. Thus, patients after Fontan can perform normally at exercise levels equivalent to everyday activities despite the absence of a biventricular circulation.

## EVIDENCE OF ENHANCED CONTRACTILITY IN NORMAL INFANTS COMPARED TO OLDER CHILDREN AND ADULTS

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Noninvasive stress-velocity and stress-shortening analysis was used to investigate potential age-related change in LV contractile state. In 200 normal children age 7 days to 18 years (23 <6 months of age), M-mode and 2D echos were obtained with simultaneous phono and pulse tracings and peripheral blood pressure. In 154/200, long-axis dimension of the LV could be obtained from apical views for calculation of circumferential stress. Tracings were computer digitized to obtain ventricular dimension, wall thickness, and pressure throughout ejection. From these data, fractional shortening (FS), rate-corrected velocity of shortening (VCFc), and end-systolic circumferential (ESSc) and meridional (ESSm) wall stress were obtained.

FS and VCFc were inversely linearly related to ESSm as has been previously reported in older patients. ESSc was similarly related to FS and VCFc in a linear fashion, with a constant proportional relationship between the orthogonal stresses at all ages. When subjects less than 6 months of age were analyzed separately, the slopes of the ESSm-VCFc and ESSm-FS relations were not significantly different from older subjects, indicating a similar sensitivity to afterload in the two groups. However, the stress-adjusted FS and VCFc were higher in the younger group ($p = 0.01$ by analysis of variance), findings consistent with an enhanced contractile state.

OCCURRENCE OF CONGENITAL HEART DEFECTS IN OFFSPRING OF PATIENTS WITH VENTRICULAR SEPTAL DEFECT, AORTIC STENOSIS, OR PULMONARY STENOSIS: RESULTS OF THE SECOND NATURAL HISTORY STUDY OF CONGENITAL HEART DEFECTS.

David J. Driscoll, M.D., F.A.C.C., V. Michels, M.D., W. M. Gersony, M.D., C. J. Hayes, M.D., J. F. Keane, M.D., B. S. L. Kidd, M.D., W. M. O'Fallon, Ph.D., D. R. Pieroni, M.D., R. R. Wolfe, M.D., W. H. Weidman, M.D., Rochester, Minnesota (Coordinating Center).

To determine the occurrence rate of CHD (congenital heart defects) in children of Pts with VSD (ventricular septal defect, AS (aortic stenosis), or PS (pulmonary stenosis), we surveyed 341, 158, and 198 probands with VSD, AS, and PS respectively who had children.

Of probands with VSD, 151 males and 190 females had 318 and 382 children respectively. CHD occurred in 10 (3.14%) of the 318 children of males and in 11 (2.88%) of the 382 children of females. Of probands with AS, 123 males and 35 females had 227 and 66 children respectively. CHD occurred in 3 (1.32%) of the 227 children of males and 0 (0%) of the 66 children of females. Of probands with PS, 92 males and 106 females had 169 and 204 children respectively. CHD occurred in 3 (1.78%) of the 169 children of males and 8 (3.92%) of the 204 children of females.

The occurrence of CHD in siblings of probands with VSD, AS and PS, were, respectively, 0.6% (15 of 2326), 1.7% (14 of 821), and 1.1% (14 of 1328).

The miscarriage rates for all females in NHS-2 were 28.6%, 14.1% and 13.8% for VSD, AS and PS respectively.

Based upon the results of NHS-2, occurrence rates of CHD in children of probands with VSD, AS, and PS are 3%, 1.02%, and 2.95% respectively; considerably lower than recently reported rates.

LONG TERM PREVENTION OF BIOPROSTHETIC HEART VALVE CALCIFICATION: $A1^{+++}$ PRETREATMENT.

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Calcification causes failure of glutaraldehyde pretreated bioprosthetic heart valves (BPV) fabricated from porcine aortic valves or bovine pericardium. Young age has been shown to be an important risk factor for accelerated BPV calcification in the pediatric population. BPV preincubation in $A1^{+++}$ inhibits BPV calcification in the 21 day rat subdermal model. This study was designed to assess the long term ability of $A1^{+++}$ to inhibit calcification after 21 and 60 day rat subdermal implants. Glutaraldehyde pretreated BPV specimens were preincubated in 0.01M A1C13 or 0.05M HEPES (24 hrs, 25C), then implanted subdermally in weanling male rats (CD, Sprague-Dawley, 50-60 gm) for 21 and 60 days. Results showed that BPV $Ca^{++}$ was profoundly inhibited in the $A1^{+++}$ pretreated groups after 21 day ($Ca^{++}=2.33\pm0.17$ug/mg) and 60 day ($Ca^{++}=11.57\pm4.58$ug/mg) implants compared to controls ($Ca^{++}=76.88\pm9.54$ug/mg at 21 days vs $110.04\pm9.28$ at 60 days). No adverse effects were noted on rat growth or bone morphology. We conclude that $A1^{+++}$ preincubation effectively inhibits BPV calcification after both short and long term subdermal implants in the rat. We speculate that $A1^{+++}$ may prolong the clinical usefulness of BPV's, especially in the pediatric population.

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## Pediatric Cardiology

VASOPRESSIN (AVP) IS ELEVATED TO PRESSOR LEVELS AND UNOPPOSED BY ATRIAL NATRIURETIC FACTOR (ANF) FOLLOWING REPAIR OF COARCTATION OF THE AORTA (CoA).

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Systemic hypertension post CoA may result from changes in renin-angiotensin and sympathetic nervous control of BP. Since these systems interact with AVP and ANF we studied AVP and ANF related to CoA repair. 6 patients,age 7 months to 12 years ($\bar{m}$=7 yrs) undergoing CoA repair had plasma AVP and ANF measured by RIA. All were hypertensive postop requiring Nitroprusside (NP). BP and plasma AVP and ANF were measured preop, immediately postop, pre NP, post NP,at 24 hrs.postop and at 48 to 72 hrs.postop.(Table) There was no relation of AVP and ANF to HR, CVP or osmolarity. ANF levels were normal and not significantly changed by surgery. AVP levels were elevated preop, increased with surgery ($p<.05$), and peaked pre NP ($p<.05$). NP resulted in a 50% decrease in mean AVP. AVP fell by 48-72 hours but remained elevated despite antihypertensive therapy. We conclude: 1)Plasma AVP is elevated in CoA to levels sufficient to cause systemic pressor effects; 2)increases in AVP occur after CoA repair and are temporally related to postop BP; 3)NP is related to a 50% decrease in AVP; 4)ANF levels may be inappropriately low after CoA repair. Increased AVP unopposed by ANF may be in part responsible for post CoA hypertension.

| | Preop | Postop | PreNP | PostNP | POD1 | POD2-3 |
|---|---|---|---|---|---|---|
| **Systol BP** | 139±9 | 138±9 | 151±6 | 139±9 | 134±7 | 121±2 |
| **AVP pg/ml** | 18±5 | 86±15* | 138±30* | 68±24* | 24±7 | 20±3 |
| **ANF pg/ml** | 24±8 | 60±16 | 71±30 | 60±20 | 40±16 | 27±2 |

(*$p<0.05$)

MODULATION OF THE FETAL LEFT VENTRICULAR FUNCTION CURVE BY THE THORACIC TISSUES.

Daniel A. Grant, M.Sc., John E. Maloney, Ph.D., John V. Tyberg, M.D., Ph.D., F.A.C.C., and Adrian M. Walker, Ph.D., University of Calgary, Calgary, Canada.

To define the role that external ventricular restraint plays in determining the shape and magnitude of the LV function curve before birth, 6 fetal lambs (142-144 days gestation) were studied. Lambs were partially delivered by caesarean section under halothane anesthesia. We measured LV stroke volume (SV) using a flow probe on the ascending aorta, LV end-diastolic pressure (Plved) using a transducer-tipped catheter passed through the LV free wall, and intra-pericardial pressure (Pp) using a flat, liquid containing balloon transducer. LV function curves were generated after autonomic blockade (0.2 mg/kg atropine and 1.0 mg/kg propranolol) by altering fetal blood volume. Two conditions were studied: "A", the chest and pericardium closed, and "B", the lungs and pericardium widely retracted from the heart. In "A", LV function curves (SV versus Plved) displayed an initial ascending limb followed by a plateau in which the SV changed little with further increases in Plved. When LV transmural pressure (Plved*=Plved-Pp) was used as the index of preload, the plateau phase was absent. In "B", LV function curves revealed much larger stroke volumes at any given Plved ($p<0.002$). These data show that the thoracic tissues significantly influence the LV function curve in the fetal lamb. In "A", the plateau of the function curve using Plved as preload results largely from elevations in Pp which limit increases in Plved* as Plved is raised. Consequently, Plved* is a more accurate index of LV preload. The fetal LV has the ability to increase its output but is limited in the intact animal by the surrounding tissues.

POSTNATAL DEVELOPMENTAL CHANGES IN MYOCARDIAL MITOCHONDRIAL CALCIUM TRANSPORT.
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The newborn heart has a sparse sarcoplasmic reticulum and T-tubule system, yet it's an active contractile organ early in gestation. Since mitochondria are a significant membrane fraction in the newborn heart, are the principal source of ATP and actively transport Ca++, we hypothesized that newborn heart mitochondria play a greater role in maintaining intracellular Ca++ homeostasis. Heart mitochondria (HM) were isolated from 1,3,7,14,30,40 day old and adult (control) rabbits. Yields of HM protein, respiratory and Ca++ transport activity were measured. HM protein content was similar in all age groups. The Vmax of succinate-supported Ca++ uptake was significantly higher in 1, 3 and 7 day HM groups ($p < .001$) compared to controls. Vmax decreased steadily with maturation and reached adult levels by age 40 days. Apparent Km's for Ca++ uptake were less in 1 day old HM (Km=24.9 μM) compared to all other age groups (Km=35.7 μM in adults). Succinate-linked respiratory rates (State 3) were the same in 3,7 day and adult HM (392-419 natomO/min/mg), but were slightly lower at 1,14,30 and 40 days. The high rate of Ca++ uptake suggest newborn HM may play a greater role in maintaining intracellular Ca++ homeostasis during early myocardial development. These maturation changes in Ca++ uptake do not appear to relate to underlying alterations in substrate utilization.

VALIDATION OF DOPPLER ECHOCARDIOGRAPHIC CALCULATION OF DESCENDING AORTIC AND UMBILICAL FLOW IN FETAL LAMBS
Klaus G. Schmidt, MD; Mariarosaria Di Tommaso, MD; Norman H. Silverman, MD, FACC; Abraham M. Rudolph, MD, FACC. University of California, San Francisco; San Francisco, CA.

In order to substantiate the accuracy of flow (Q) calculations derived from cross-sectional echocardiography (CSE) and pulsed Doppler ultrasound in the descending aorta ($Q_{DA}$) and umbilical vein ($Q_{UV}$) of human fetuses, we studied 6 fetal lambs (gestational age 125±3 d, weight 3±0.8 kg). In these animals we placed hind limb catheters, an electromagnetic flowtransducer on the descending aorta just above the iliac bifurcation as well as on the common umbilical artery, and an occluder around the umbilical cord. After closure of all incisions, CSE and Doppler study was performed. The lower descending aorta and the common umbilical vein within the liver were imaged and pulsed Doppler interrogation was performed at these sites. Mean velocity, velocity time integral, and heart rate were calculated from Doppler tracings; vessel diameter and angle of incidence were measured from CSE. Actual flow in each animal was varied by gradual occlusion of the umbilical cord; $Q_{DA}$ ranged from 150 to 950, $Q_{UV}$ from 150 to 850 ml/min. Continuous flowtransducer readings were calibrated against the radiolabeled microsphere technique. Using linear regression analysis we compared 74 $Q_{DA}$ and 25 $Q_{UV}$ flow-transducer measurements (x-axis) with calculated values obtained from CSE and PD at the same time (y-axis). We found a good correlation both for $Q_{DA}$ ($y=77+1.04x$; $r=0.95$; SEE±71 ml/min; $p<0.001$) and for $Q_{UV}$ ($y=54+1.1x$; $r=0.93$; SEE±75 ml/min; $p<0.001$). We conclude that calculation of fetal $Q_{DA}$ and $Q_{UV}$ using CSE and Doppler ultrasound is feasible and may provide useful measurements in the human fetus. The combined CSE and Doppler method may slightly overestimate the actual flow.

EXPERIMENTAL ANIMAL INVESTIGATIONS OF THE POTENTIAL FOR NEW APPROACHES TO DIAGNOSTIC CARDIAC IMAGING IN INFANTS AND SMALL PREMATURE INFANTS FROM INTRACARDIAC AND TRANSESOPHAGEAL APPROACHES USING A 20MHz REAL TIME ULTRASOUND IMAGING CATHETER.
Lilliam Valdes-Cruz, M.D., FACC, David J. Sahn, M.D., FACC, Paul Yock, M.D., FACC, Iain Simpson, M.D., Renate Schmidt, James Arenson, David Linker, Hira Thapliyal. Univ Calif, San Diego, CA.

We performed imaging studies on small open and closed chest animals with a 20MHz real time ultrasonic imaging catheter designed for intracoronary and intraarterial studies to assess its applicability for providing imaging of the heart from either an intracardiac or transesophageal site. In 2, 10Kg dogs, intracardiac catheter placement in the LA allowed imaging and measurement of AO and mitral valve orifices and LV wall, and we verified location and size of surgically placed 7mm atrial septal defects. Detailed visualization of jugular veins and carotid arteries and their walls was obtained during catheter transit. High resolution coronary artery imaging was also obtained with catheter placement in the AO root. In 3 rabbits (3Kg) and 2 rats (6-800 gms), transesophageal placement of the catheter allowed imaging of AO valve, LA, mitral and tricuspid valves and the entire AO arch and PA. A significant potential exists for using these high frequency catheters as a guide to localization of defects or for imaging from inside the heart during balloon valvuloplasty in children and neonates. Likewise, since no devices exist currently which allow intraesophageal ultrasound studies in small premature newborns and infants, this technology has potential for allowing transesophageal studies for intraoperative monitoring of congenital heart repairs and for imaging premature babies with chest deformities, pneumomediastinum or poor quality, non-diagnostic precordial imaging studies.

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## Pacific Room, Anaheim Convention Center
## Pediatric Electrophysiology

NONINVASIVE DISCRIMINATION OF RIGHT ATRIAL ECTOPIC FROM SINUS TACHYCARDIA IN DILATED, "CARDIOMYOPATHIC" HEARTS
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When a patient with an enlarged, poorly functioning heart presents with a rapid right atrial rhythm, the diagnostic possibilities include primary dilated cardiomyopathy (CMP) with sinus tachycardia and right atrial ectopic tachycardia (RAET) with secondary cardiac dysfunction. Because RAET may be overlooked and requires an intracardiac electrophysiologic study for confirmation, we attempted to identify distinguishing features from non-invasive studies. We reviewed resting surface ECG, 24 hour ambulatory ECG (Holter), and echocardiograms (echo) of patients with the retrospective diagnoses of RAET (n=34) and CMP (n=33) seen at Texas Children's Hospital from 1980-present. Age at onset and sex were not significantly different. Atrial rates on routine ECG were higher for the RAETs ($p<.003$) with 21% of RAETs greater than 180 bpm; no CMPs had a rate over 180. Maximum Holter rates while awake and asleep, corrected for age, were significantly faster with RAET ($p<.005$ and $<.02$ respectively). The mean P wave axis in the horizontal plane was more posterior in RAET ($p<.01$) with the horizontal axis < 0° (negative in lead V2) in 8/29 AETs versus 1/31 CMPs ($p<.03$). In RAET, P wave duration in lead $V_1$ was longer ($p=.03$). Inverted, notched P waves in $V_1$ were seen in 6/27 RAETs but 0/32 CMPs ($p<.02$). PR interval was longer with RAET ($p=.01$); 2° AV block was observed on ECG and/or Holter in 12/33 AETs but 0/33 CMPs ($p<.001$). Amongst patients with abnormally increased LV end-diastolic dimension (for weight), AETs had a better shortening fraction (SF) than CMPs (26% versus 15%, $p<.01$). Severe dysfunction with SF≤10% was found in 13/33 CMPs but only 1/27 AETs ($p=.003$). Conclusions: As compared to CMP, RAET presented with faster atrial rates, with P waves of different orientation, duration and morphology, with more AV block, and with better LV function in the presence of LV dilation.

CHARACTERIZATION OF THE PHASIC RESPONSES OF THE NEONATAL SINUS AND ATRIOVENTRICULAR NODE TO BRIEF VAGAL STIMULATION
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Responses of the sinus node and atrioventricular (AV) node to single, brief trains of vagal stimuli were studied in 10 very young (3-12 days) neonatal canines. Neonates were pretreated with 1 mg/kg propranolol IV, both cervical vagosympathetic trunks divided, and the proximal ends prepared for stimulation. Single, brief trains of stimuli (143 Hz, 5 stimuli) were delivered at constant current to either the right or left vagus (RVS, LVS) and were programmed to scan the cardiac cycle. Intracardiac electrograms were recorded from catheters placed in the high right atrium and region of the His bundle. Maximal prolongation of the sinus cycle (SCL) was always observed when stimuli were delivered 10 to 20 msec after atrial depolarization, and the maximal increase in SCL was greater during RVS (144±115 msec RVS, 106±97 msec LVS, $p < .05$). SCL could not be prolonged when stimuli were delivered later than 181±39 msec after atrial depolarization for RVS and 178±36 msec for LVS. A "double inhibitory wave", reported frequently in adults, was observed in only one neonate. A single peak of inhibition occurred in most, returning to control SCL over ∿ 15 cardiac cycles. During sinus rhythm, RVS and LVS most commonly resulted in only very small (7-10 msec) increases or decreases in AV nodal conduction time (AH interval) while during constant atrial pacing small, transient increases in AH (5-22 msec, spanning cardiac cycle 3 through 6) were most often observed. AV block was only observed in two neonates. Developmental differences in the magnitude and time course of the responses of the neonatal sinus and AV node to brief vagal stimulation provides further evidence for functional immaturity of the parasympathetic nervous system at birth.

IMPACT OF COEXISTING HEART DISEASE ON OUTCOME OF SURGERY FOR THE WOLFF-PARKINSON-WHITE SYNDROME IN CHILDREN
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The effect of coexisting heart disease (HD) on the outcome of surgery for Wolff-Parkinson-White syndrome was evaluated in 53 operated pts (age 12 ± 4 years, 0.8-16) with 68 accessory pathways (AP) undergoing AP division. Nineteen pts had coexisting HD: Ebstein's (Ebs)=7, cardiomyopathy=6 (2 dilated, 2 hypertrophic, 2 tachycardia induced), corrected transposition (l-TGA)=3, ventricular septal defect (VSD)=2, and aortic stenosis=1. Of those 13 with congenital defects, surgery was performed primarily due to arrhythmias in 7, defects in 3, and both in 3. In those with HD, septal APs were more prevalent (14/26 vs 14/42), and left freewall APs less prevalent (4/26 vs 22/42) than in those without HD. Nine septal APs occurred in Ebs or l-TGA. Anesthesia, bypass, intubation, and intensive care unit times were longer for those with, than those without HD ($p < .05$). APs from 48/49 pts were successfully ablated, requiring 2 reoperations in each group. All 34 pts without and 15/19 with HD survived. Two pts with Ebs, 1 with hypertrophic cardiomyopathy, and 1 with VSD and pulmonary artery band died. Three of these had HD as their primary indication for surgery, and required extensive structural repair. Of 9 pts with acquired heart block, 8 had septal APs and the ninth had l-TGA and underwent tricuspid valve replacement. Only 2 of these 9 occurred since posteroseptal AP dissection modification. From these data, we conclude that AP ablation in children is highly successful. Our experience suggests that the increased risk observed in those with other HD is related to surgery for structural defects and not to AP ablation.

# Tuesday, March 21, 1989
# Poster Displayed: 2:00PM–5:00PM
# Author Present: 3:00PM–4:00PM
# Pacific Room, Anaheim Convention Center
# Pharmacology of Antiarrhythmic Drugs

EFFECTS OF BRB-I-28 UPON LONGITUDINAL AND TRANSVERSE CONDUCTION IN CANINE MYOCARDIUM
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BRB-I-28, an experimental bicyclononane antiarrhythmic drug, was evaluated in superfused canine epicardial tissue. Before drug administration, conduction was more rapid longitudinal (L) vs. transverse (T) to fiber orientation (0.94±.06 vs. 0.44±0.4 M/sec, L/T velocity ratio= 2.2±0.2; $p<0.01$). Vmax was larger for T vs. L stimulation (189±11 vs. 133±10 V/sec; $p<0.01$). With rapid pacing (250 and 500 msec cycle lengths), the L/T velocity ratio was increased (2.3±0.2 and 2.4±0.2, respectively; $p<0.05$). BRB-I-28 administration (3.2, 10 mg/L) produced rate-dependent decreases in Vmax at 500 and 250 msec cycle lengths for both L (19±4, 30±6%; 24±5, 49±6%) and T (25±5, 30±5%;31±5, 52 ±6%, respectively) (p=NS) stimulation. L conduction was slowed to a greater extent than T conduction at 500 msec (18±5 vs. 10±3%;25±6 vs. 20±3%) and 250 msec (29±6 vs. 18±5%;35±5 vs. 21±35) cycle lengths ($p<0.01$). Conduction and Vmax at cycle lengths 1000 msec or longer were not altered by drug. Action potential duration was unchanged at 70% (144±7 and 151 ± 9 vs. 142 ± 9 msec) and 90% (191±7 and 200 ± 8 vs. 188 ± 9 msec) of repolarization (p-NS). The slope of the linear relationship between the square of conduction velocity and Vmax was greater for T (1145±128; R= 0.89) than L (267±38 Vsec/$M^2$; R=0.94)(10 mg/L) conduction. The data demonstrate a rate-dependent depression of T and L conduction with BRB-I-28. L conduction is depressed more than T conduction despite equivalent changes in Vmax. BRB-I-28 may independently delay sodium channel recovery and decrease junctional resistivity.

QUINIDINE MYOCARDIAL PHARMACOKINETICS AND PHARMACODYNAMICS: INFLUENCE OF HYPOXIA.
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Enhanced electrophysiologic effects of some antiarrhythmic drugs have been observed during hypoxia (H). To determine whether pharmacokinetic and/or pharmacodynamic mechanisms are responsible for these changes, the time course of accumulation of quinidine (QD) and changes in electrophysiologic effects were studied in isolated rabbit hearts. The QRS duration, ventricular effective refractory period (VERP) and monophasic action potential duration (MAP) were measured during control (95% $O_2$ - 5% $CO_2$) or H (95% $N_2$ - 5% $CO_2$) prior to and during QD (3μM) perfusion. The steady state QD myocardial concentration was significantly reduced during H (14.5 ± 3.6 μg/g vs 22.8 ± 5.2 μg/g, $p < .02$). The linear QD myocardial concentration-effect relationships were enhanced by H. The slopes of these relationships are shown (msec/μg/g):

| | QRS | VERP | MAP |
|---|---|---|---|
| Control (n=6) | .45 ± .17 | 3.02 ± 1.48 | 2.13 ± 1.07 |
| Hypoxia (n=6) | .66 ± .18 | 4.66 ± 1.24 | 4.19 ± 0.69 |
| | p = .08 | p < .1 | p < .025 |

QD significantly prolonged ventricular conduction time during H compared to the control, nonhypoxic state (ΔQRS = 7 ± 6 msec, $p < .01$). QD reversed the hypoxia-induced shortening of MAP and VERP. However, prolongation of MAP and VERP compared to the control, nonhypoxic state was not observed.

Conclusions: Hypoxia alters QD myocardial pharmacokinetics and pharmacodynamics. Although QD myocardial concentration is reduced by hypoxia, QD myocardial concentration - effect relationships are enhanced.

SYNERGISTIC ACTIONS OF DISOPYRAMIDE AND LIDOCAINE ON Vmax OF ACTION POTENTIALS IN GUINEA PIG PAPILLARY MUSCLES

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A single or combined application of the class 1a and 1b antiarrhythmic agents are frequently employed in clinical practice, although their precise mechanism of actions and the rationale for the combined use have not been clarified. Therefore, effects of a single or combined application of disopyramide (Dis), as class 1a, and lidocaine (Lid), as class 1b, on Vmax of action potentials in guinea pig papillary muscles were examined using the conventional microelectrode technique. Dis (100 uM) suppressed Vmax at frequency between 0.1 and 3.3 Hz, while Lid (100 uM) did it at higher frequency than 1.0 Hz. The onset of the block was best fitted by two exponentials (fast and slow component) in both Dis and Lid. The time constants of the fast and slow component in Dis were 0.962 and 0.020 per beat, respectively, and they became 3.541 and 0.037 per beat in Dis + Lid. In Lid, the fast and slow component had time constants of 2.853 and 0.060 per beat, respectively, and they became 2.496 and 0.043 per beat. The results indicate two different processes or states for drug-receptor interactions. The use dependent block (UDB) significantly increased at 1.0 Hz or the higher frequency, when the application of Dis was changed to Dis + Lid, whereas UDB became more prominent at all frequencies except 3.3 Hz when Lid was followed by Lid + Dis. The application of Lid + Dis to Dis only did not change the degree of UDB. These results indicate that the combined application of Dis and Lid increases the block of Vmax of action potentials compared to those of a single use of either drug.

DIFFERENTIAL EFFECTS OF AMIODARONE ON $\dot{V}max$ AND CONDUCTION VELOCITY IN ANISOTROPIC MYOCARDIUM.

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Despite its widespread clinical use, the precise mechanism of action of Amiodarone (AMI) has not been completely defined. We examine the effects of the $Na^+$ channel blocking properties of AMI (20 ugr/ml) on $\dot{V}max$ and conduction velocity ($\theta$) during longitudinal (L) and transverse (T) propagation to fiber orientation in 10 canine ventricular epicardial strips. Meaned values ± standard deviations are referred to as normalized fraction (beat 48/beat 1) at two different basic cycle lengths (BCL):

| BCL | $\theta_L$ | | $\theta_T$ | | $\dot{V}max$ AMI | |
|---|---|---|---|---|---|---|
| mseg | CONTROL | AMI | CONTROL | AMI | L | T |
| 1000 | 0.092 ±0.034 | 0.092 ±0.044 | 0.979 ±0.021 | 1.009 ±0.052 | 0.892b ±0.037 | 0.926 ±0.037 |
| 300 | 0.952 ±0.084 | 0.854a,b ±0.097 | 0.953 ±0.080 | 0.967 ±0.067 | 0.518b ±0.110 | 0.645 ±0.139 |

a: $p < 0.05$ respect to control
b: $p < 0.05$ respect to transverse propagation

The lack of depression of $\theta$ during T propagation associated with a marked depression of $\dot{V}max$ either during L and T propagations suggest that together with the $Na^+$ channel blocking properties, AMI would induced a decrease in the effective axial resistivity, which will be far more apparent in the T propagation. This may account for the selective depression of $\theta$ during L propagation.

ANTI-ADRENERGIC ACTION OF ADENOSINE IN A CANINE MODEL OF CHRONIC MYOCARDIAL INFARCTION.

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The antiarrhythmic effect of adenosine has been attributed to an indirect, anti-adrenergic action. However, this action has not been conclusively shown *in vivo*. To test this hypothesis, ventricular refractory periods (VRP) at twice threshold stimulus intensity and excitability thresholds (ET) were determined in normal (n=29 sites) and infarct (n=25) zones, in the distribution of the left anterior descending coronary artery (LAD), in 16 anesthetized dogs with chronic myocardial infarction during continuous intra-LAD infusion of either saline (control) or adenosine (ADN; 5 µmol/min), before and during i.v. administration of isoproterenol (ISO; 0.02 µg/kg/min). Results:

| | VRP (ms) Zone | | ET (mA) Zone | | HR |
|---|---|---|---|---|---|
| | Normal | Infarct | Normal | Infarct | (bpm) |
| Control | 184±2 | 202±5 | 0.10±.01 | 0.50±.17 | 135±5 |
| ADN | ‡177±2* | ‡191±5* | 0.11±.01 | 0.48±.18 | 137±6‡ |
| ISO | 166±2* | 165±2* | 0.10±.01 | 0.39±.14 | ‡169±4 |
| ISO+ADN | 171±2* | 170±6* | 0.11±.01 | 0.36±.13 | 168±5 |

mean ± SEM; $p \ddagger < 0.02$; * < 0.05

Summary: 1. Local myocardial adenosine shortened VRPs in both normal and infarct zones without affecting ETs or HR. 2. Systemic ISO increased HR and shortened VRPs more markedly than adenosine. 3. Adenosine had a site specific action in attenuating the effect of ISO on VRPs. Conclusion: Adenosine exerts an anti-adrenergic action *in vivo*, which may play a role in its antiarrhythmic and putative cardioprotective effects.

PREVENTION OF HALOTHANE-EPINEPHRINE-INDUCED CARDIAC ARRHYTHMIAS WITH FRUCTOSE 1-6 DIPHOSPHATE.

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Halothane (Hal) sensitizes the heart to arrhythmogenic effects of Epinephrine (Epi). Fructose 1-6 diphosphate (FDP) reduces occurrence of ventricular arrhythmias (VA) in AMI in animals and man, and in digitalis intoxication. Thus, we assessed whether FDP will prevent the occurrence of VA in Hal (1.5%) anesthetized rabbits (n=14). The arrhythmogenic dose of Epi to produce 4 or more PVC in 5 sec for all rabbits was 6.05±0.76µg/kg. Then, randomly half of the rabbits received an IV bolus of 150mg/kg and a constant infusion of 10mg/kg/min of FDP 10%, while the rest received the same amount of glucose 10%. Thirty min following treatment, Epi infusion was given every 15 min for the next two hours. In the glucose treated rabbits, VA occurred within 0.93±0.08 min for the same dose 5.67±0.48 µg/kg every time, whereas no VA were noted in the the FDP group for the 3 min testing period, although the dose of Epi was increased to 233.93±59.24µg/kg ($p<0.0001$). After the two hour experimental period, some FDP-treated rabbits received Epi from 500 up to 1600µg/kg over 10 min and no VA could be induced. No differences in systolic or diastolic arterial pressure were observed, however, the HR in the FDP group did not increase as it did in the glucose controls (NS). Arterial pH was lower in the FDP group and lactate higher ($p<0.005$ and $p<0.01$, respectively). Arterial $pCO_2$ was higher in the FDP group (NS), whereas $pO_2$ was no different. FDP prevented Hal-Epi induced VA at doses up to 383 times greater of Epi than those administered in the rabbits treated with glucose. The mechanism by which FDP prevented Hal-Epi induced VA is not known at present but, it is thought to be metabolically mediated.

PRODYSRHYTHMIA OF O-DEMETHYL ENCAINIDE: SUPPRESSION BY COMBINATION WITH MEXILETINE

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The prodysrhythmia of Class Ic agents remains a major limitation to their widespread clinical use. The purpose of the present study was to develop a model to study this prodysrhythmia and to define methods to suppress it. Six chronically instrumented dogs were studied late following occlusion-reperfusion (MI). One week following MI all dogs had sustained ventricular tachyarrhythmias (VT) induced by programmed electrical stimulation (PES). Over 6 weeks, loss of ability to induce VT occurred in all 6 dogs. O-demethyl encainide (ODME) was then infused as a series of loading and maintenance infusions. While non-inducible prior to ODME, all had inducible sustained VT on ODME requiring repeated cardioversions and one animal died. Mexiletine (M) was then added to ODME infusion and PES was repeated in 5 dogs. Combination therapy with ODME plus M suppressed inducible VT in 3 of 5 ($p<0.05$). Electrogram QRS duration as an index of local conduction time (CT), refractoriness (VERP) and pacing threshold (thresh) were measured, in the normal, and infarct (IFZ) zones. Results: mA, msec, $x \pm SD$, *$p<0.05$ from basline

| | Baseline | ODME | ODME + Mexiletine |
|---|---|---|---|
| Inducible VT | 0/6 | 6/6 | 2/5* |
| IFZ QRS | 61±21 | 71±16* | 59±15 |
| IFZ VERP | 151±50 | 165±47 | 180±55* |
| IFZ Thresh | 2.1±1.7 | 3.1±2.1 | 3.8±1.5* |

Relatively low concentrations of ODME alone (156-360ng/mL) prolonged IFZ electrogram QRS associated with prodysrhythmia. Co-administration of M suppressed prodysrhythmia associated with shortening of IFZ electrogram QRS, and prolongation of IFZ VERP. In conclusion, combination of mexiletine with ODME alters the balance between CT and VERP required for induction of sustained VT and suppresses ODME prodysrhythmia.

SHORT TERM VARIABILITY OF VENTRICULAR ARRHYTHMIA AND RAPID ASSESSMENT OF DRUG EFFICACY.

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Acute drug testing (ADT) has been proposed to abbreviate the search for safe and effective antiarrhythmic agents. Since spontaneous variability (SV) may invalidate the results we developed statistical criteria for arrhythmia suppression and aggravation in 24 pts with high-grade ventricular arrhythmia (VA). To quantify SV 24 to 48-hour Holter recordings were obtained at least 4 half-lives after discontinuation of antiarrhythmic therapy. Two-tailed 95% confidence limits were computed for each pt by linear regression analysis of log-transformed ectopy counts where each hour served as the independent variable and its successor as the dependent variable. A single oral dose of disopyramide 300mg, flecainide 200mg, or propafenone 450 mg was given after baseline studies. Lidocaine was infused in doses up to 4 mg/min. A test was considered positive when VA fell outside the calculated limits during at least one of four hours following drug administration. In 50 ADTs the minimum decrease in VA consistent with a true antiarrhythmic effect averaged 90.9%(interquartile range: 87.7-95.2) while a proarrhythmic response required an increase of hourly VA by 947%(713-1412). Analysis of VA using individual confidence limits resulted in 34/50 positive ADTs with 1.4±1.2 hours below the calculated threshold. By contrast, when a 70% reduction was required,43/50 ADTs were positive showing arrhythmia suppression during 2.2±1.2 hours. Thus, a threshold of 70% overestimated efficacy in 9/50 ADTs when compared to individual regression analysis. We conclude that individualized assessment of SV may enhance the reliability of ADT.

INTRAVENOUS PROPAFENONE FOR CONVERSION OF ATRIAL FLUTTER OR FIBRILLATION OF RECENT ONSET.

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The efficacy and safety of i.v. Propafenone (P) in the treatment of atrial fibrillation (af) or flutter (AF) of recent onset were evaluated. P (2 mg/kg) was administered to 70 pts. (mean age 62 ± 11.9): 57 with af and 13 with AF. 36 pts. (51.4%) reverted to sinus rhythm within 95 min (mean 28.2 ± 25.6): 32/57 (56.1%) with af and 4/13 (30.7%) with AF. The efficacy of the drug was influenced by the arrhythmia duration: 31/46 (67.3%) pts in whom the onset of the arrhythmia was < 48 hrs and only 5/24 (20.8%) in whom the arrhythmia lasted more than 48 hrs, were converted ($p < 0.001$). In non converters the mean ventricular rate was reduced from 141.7 ± 28.5 to 106.5 ± 21.4/min. ($p < 0.001$). A mean 17% QRS lenghthening was observed (from 76.6 ± 31.9 to 89.5 ± 36.8 msec) ($p < 0.001$). QTc interval showed no significant change. No untoward effects were observed except for two reversible low output syndromes.

Conclusions: i.v. Propafenone is a safe and effective drug in restoring sinus rhythm in the majority of pts with af of short duration and in controlling the ventricular rate in the refractory cases.

EFFECTS OF FLECAINIDE ON ACTION POTENTIAL DURATION OF HUMAN ATRIAL FIBERS.

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In order to evaluate the effects of Flecainide ($5 \times 10^{-7}$ M) on cellular electrophysiologic properties of human atrium, we studied by the micro-electrode technique 10 preparations obtained from patients undergoing cardiac surgery. We measured action potential durations at 50 (APD 50) and 90 % (APD 90) of repolarization and cellular refractory periods (CRP) at 4 cycle lengths (CL) of 1600, 1200, 800 and 400 msec. The micro-electrode was located in a space < 1 mm from the stimulating electrode. The results were related to action potential (AP) morphologies : group A (n = 5, mean age 12 ± 2) with triangular AP, group B (n = 5, mean age 52 ± 2) with AP exhibiting a plateau and an initial notch. In group A, we observed after Flecainide no significant increase of APD 50, APD 90 and CRP at all CL. In contrast, in group B, ADP 50 were increased at 1600 (24 %, $p < .05$), 1200 (31 %, $p < .05$) and 800 msec (34 %, $p < .02$). Similarly ADP 90 were increased at 1600 (22 %, $p < .01$), 1200 (25 %, $p < .001$), 800 (26 %, $p < .01$) and 400 msec (23 %, $p < .01$). Finally CRP were increased at 1600 (18 %, $p < .01$), 1200 (20 %, $p < .01$), 800 (24 %, $p < .001$) and 400 msec (33 %, $p < .01$).

In conclusion, at this concentration, atrial effects of Flecainide depend on the morphology of AP. The increase of APD observed in "plateau cells" could suggest an effect of Flecainide on transient outward currents.

## COMBINED THERAPY WITH TYPE IC AND IB AGENTS: IS IT EFFECTIVE FOR VENTRICULAR TACHYCARDIA?

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To determine the efficacy of combining a Type IB antiarrhythmic agent with a Type IC agent in patients with sustained ventricular tachycardia (VT) refractory to a IC agent alone, we studied 18 patients (mean age 59±12 years; 16 males; 13 with ischemic heart disease) with VT unsuccessfully treated with 3.9±1.1 prior antiarrhythmic agents. Mean LV ejection fraction was 33±13%. After baseline electrophysiologic study (EPS) and unsuccessful treatment with a IC agent (10 encainide, 4 propafenone, 4 flecainide), the maximum tolerated dose of a IB agent (17 mexiletine, 1 tocainide) was added to the IC agent. Almost one fourth of the patients could not tolerate IC+IB because of side effects at the lowest possible dose of IB (3 pts) or spontaneous proarrhythmia (1 pt). Of the 18 patients, 12 (67%) had EPS off antiarrhythmic therapy, on a IC alone, and with a IC+IB combination. The addition of IB to IC did not significantly alter the PR, QRS, or $QT_c$ intervals or the effective or functional refractory periods compared to IC alone. The mean number of premature stimuli for VT initiation was not significantly different at baseline (3.2±.9), with IC (3.0±.8) or IC+IB (3.0±.9). Only 1 patient (8%) was not inducible on IC+IB. Greater difficulty inducing VT (increase of 2 premature stimuli) occurred in only 1 patient (8%) compared to IC alone (or baseline). Greater ease of VT induction (decrease by 2 premature stimuli) occurred in 1 patient (8%) compared to IC (in 2 pts compared to baseline). Mean VT cycle length at baseline (233±53 ms) was significantly ($p<0.005$) prolonged by either IC (365±97 ms) or IC+IB (376±75 ms), but the means were not significantly different between treatment groups. IC+IB increased the VT cycle length by 50 msec in 7 patients (58%) and decreased it by 50 msec n 4 (33%) compared to IC alone. Thus, in patients who have failed a 1C agent, the addition of a IB agents rarely prohibits VT induction and often causes adverse reactions necessitating its discontinuation.

## DISOPYRAMIDE INDUCES UTERINE CONTRACTIONS IN PREGNANCY

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We evaluated the effect of disopyramide (D) on uterine contractions (UC) in late pregnancy using a double-blind placebo controlled protocol. Included were 20 consecutive healthy women, referred for induction of labor after the 38th week of pregnancy. Ten randomly assigned pts received D 150 mg TID and 10 pts received placebo. If regular UC were not achieved within 48 h, conventional methods of labor induction were used. Clinical/obstetric features, maternal ECG, fetal heart rate monitoring and estimated fetal weight were similar in the groups. There were no maternal or fetal complications.

| Results: | Disopyramide (n=10) | Placebo (n=10) | P |
|---|---|---|---|
| Time to regular UC (h) | 4.2±1.7 | 56.1±5.3 | <0.001 |
| Regular UC within 48h (n) | 10 | 0 | <0.001 |
| Delivery within 48h (n) | 8 | 0 | <0.001 |
| Maternal QTc (msec) | 424±30 | 430±30 | NS |
| Newborn QTc (msec) | 375±40 | 390±30 | NS |
| Apgar, 1 minute | 8.1±1.4 | 8.6±0.7 | NS |
| Apgar, 5 minutes | 9 | 9 | NS |

At time of delivery maternal and newborn D serum levels were 0.93±0.4mg/l and 0.33±0.2 mg/l, respectively (umbilical cord/maternal level ratio 0.36; r=0.73, p<0.005). Thus: 1) D induces regular UC and labor. Therefore its antiarrhythmic use should be avoided during pregnancy 2) D should be further evaluated as an alternative therapy for induction of labor.

# Tuesday, March 21, 1989
# Poster Displayed: 2:00PM–5:00PM
# Author Present: 4:00PM–5:00PM
# Pacific Room, Anaheim Convention Center
# Cardiovascular Pharmacology: Basic and Clinical

## DIRECT CORONARY VASODILATION INDUCED BY INTRACORONARY VASOACTIVE INTESTINAL PEPTIDE IN HUMAN CORONARY ARTERIES

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Vasoactive intestinal peptide (VIP) is a neuro transmitter with wide distribution including epicardial coronary arteries. When given intravenously, VIP causes an increase in coronary blood flow, but this effect may not be due to direct coronary vasodilation since there are simultaneous systemic effects. To evaluate its direct coronary effects, graded doses of VIP (0.03, 0.1 and 0.3 ug/min.) were infused, into the normal left coronary artery of 6 pts. Coronary sinus VIP concentrations rose progressively at each infusion (10±2 [mean±SD] pg/ml at baseline (BL) to 110±17 pg/ml at 0.3 ug/min; $p<0.05$), but arterial VIP was elevated (25±8 pg/ml) only at the maximal dose of 0.3 ug/min. During all dosages of VIP, heart rate, LVEDP, RA pressure and myocardial $O_2$ consumption did not change. Coronary sinus blood flow (by thermodilution) progressively increased from 127±57 (BL) to 191±60 ml/min at 0.3 ug/min ($p<0.05$) and coronary vascular resistance progressively decreased. Myocardial arteriovenous $O_2$ difference and percent $O_2$ extraction progressively decreased (118±12 to 63±25 ml/L and 64±5% to 36±15%, respectively; both $p<0.05$ from BL to 0.3 ug/min). Neither mean AO pressure nor LV dP/dt changed significantly at doses < 0.3 ug/min, but at 0.3ug/min, mean AO pressure decreased (97±15 to 92±15 mmHg, $p<0.001$) and LV dP/dt increased (1648±220 to 1809±226 mmHg/sec, $p<0.002$). We conclude that VIP has a direct coronary vasodilating action and, thus may play a role in the regulation of coronary resistance in man.

## EXCIMER LASER IRRADIATION INDUCES ENDOTHELIUM-INDEPENDENT RELAXATION OF VASCULAR SMOOTH MUSCLE

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Recent studies have demonstrated that continuous wave laser (L) irradiation (I) induces contraction of vascular smooth muscle (VSM) except at powers (<0.1 W) far below threshold for tissue ablation. To determine the corresponding effects of pulsed LI on VSM tone, rings (n=33) of rabbit aorta were mounted isometrically with 1 g of tension in Krebs-bicarbonate buffer and irradiated with 308 or 351 nm from an excimer L via a 400-um fiber. A total of 250 exposures were performed using 1-7 mJ/pulse (fluence = 0.8-5.5 J/cm$^2$), 10-100 Hz, and cumulative exposures of 10-120 sec. Excimer L irradiation, in various combinations of pulse energy (PE), repetition rate (RR), and cumulative exposure below, at, or above threshold for tissue ablation, produced relaxation unaccompanied by contraction in every one of 250 exposures. Magnitude of relaxation (reduction in recorded tension, Rmax,)=55±4% (m±SEM) of maximum vasomotor reactivity observed in response to 5-HT. Rmax increased as a function of both PE and RR: increase in PE from 1 to 5 mJ/pulse (n=13) increased Rmax from 57±19 to 80±19% ($p<0.0001$); increase in RR from 10-50 Hz (n=10) increased Rmax from 27±8 to 46±8 ($p<0.0001$). Rmax was unaffected by status of endothelium or wavelength (308 vs 351 nm). Simultaneously recorded time-temperature profiles disclosed that during pulsed LI, tissue temperature rise was never >5°C. Thus, in contrast to continuous wave LI, pulsed LI does not cause contraction of VSM, but instead induces a relaxation response. The fact that the excimer LI does not produce contraction of VSM could represent an important advantage for attempts to perform vascular recanalization using LI.

## EFFECTS OF GLYBURIDE ON ISCHEMIA-INDUCED CHANGES IN EXTRACELLULAR POTASSIUM AND LOCAL MYOCARDIAL ACTIVATION: A NOVEL ANTIARRHYTHMIC MECHANISM

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Increased extracellular $K^+$ ($K^+$) has been implicated in depression of membrane properties, conduction disorders and malignant ventricular arrhythmias during the early phase of acute ischemia. It has been recently suggested that ischemia-induced increase in $K^+$ is due to activation of an ATP-dependent $K^+$ channel. Glyburide (G) is an oral hypoglycemic known to block this channel. We investigated the effects of G on ischemia-induced increase of $K^+$ and local myocardial activation in 9 dogs. Continuous recordings of $K^+$ by $K^+$-sensitive electrodes and local bipolar electrograms were obtained from normal (N), border (B) and ischemic (I) zones during control (C), following 10 minutes of reversible occlusion of the LAD coronary artery (control ischemia,CI), and 10 minutes of ischemia following 2 mg G intravenously (I+G).

| | N | | B | | I | |
|---|---|---|---|---|---|---|
| C | 4.2±0.3 | | 4.1±0.2 | | 4.1±02 | |
| | | NS | | p<0.001 | | p<0.001 |
| C I | 4.6±0.6 | | 8.8±2.5 | | 11.9±2.5 | |
| | | NS | | p<0.01 | | p<0.005 |
| I+G | 4.6±0.8 | | 6.8±2.7 | | 8.3±1.8 | |

During CI, local electrograms showed delay and fractionation resulting in increased total activation time from 62±20 msec during C to 117±50 msec in IZ (p<0.05). Following G, local activation times significantly (p<0.01) improved to 76±22 msec in IZ. We conclude that ischemia-induced increase in $K^+$ and associated electrophysiological changes were ameliorated by a drug that specifically blocks the cardiac ATP-sensitive $K^+$ channel. This provides a novel approach for management of malignant arrhythmias associated with early phase of acute ischemia.

## INDEPENDENT EFFECTS OF HYPOXIA AND GLUCOSE DEPRIVATION ON THE ß-ADRENOCEPTOR-ADENYLATE CYCLASE SYSTEM IN CULTURED NEONATAL RAT VENTRICULAR MYOCYTES

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We explored the effects of two components of ischemia, hypoxia and glucose deprivation, on the ß-adrenergic receptor(ßAR)-adenylate cyclase system in a model of sublethal, reversible injury in cultured neonatal rat ventricular myocytes. Buffered glucose containing medium was gassed with a 95% $N_2$/ 5% $CO_2$ mixture to a average $pO_2$ 48 Torr, pH 7.35, at 37° C. After 2 hrs. of hypoxia cell surface ßAR density ($^3$H CGP-12177) decreased from 54.8 ± 16.8 (SD) to 39.0 ± 12.5 fmol/mg protein (n=10, p<.05) while cytosolic ß-AR density ($^{125}$I-CYP) in creased 49% (n=3, p<.05). Upon re-exposure to $O_2$ for 2hrs.(reox) medium $pO_2$ and cell surface ßAR density returned toward control levels(n=5). Cells exposed to hypoxia and reox without glucose exhibited similar alterations in ßAR density. In hypoxic cells incubated with 5 mM glucose, 1 µM (-)-norepinephrine (NE)-stimulated cAMP generation increased from 29.3 ± 23.8 to 54.2 ± 36.7 pmol/well (n=5, p<.025); upon reox cAMP levels remained elevated above control levels (n=5, p<.05). In contrast, NE-stimulated cAMP content in glucose deprived hypoxic myocytes fell by 31% (n=5, p<.05) and did not return to control levels with reox. ATP levels in cells incubated in glucose-free hypoxic medium dropped from 2.58 ± 0.54 to 1.54 ± 0.36 nmol/30 mm plate (n=7, p=.02); levels were unchanged from control in cells exposed to glucose-containing hypoxic medium (n=7). ßAR-agonist affinity, 1-100 µM forskolin-stimulated cAMP generation and Gi as assessed by pertussis toxin catalyzed ADP-ribosylation using SDS PAGE were unchanged in hypoxic cells regardless of glucose content. We conclude that $O_2$ and glucose deprivation independently regulate ßAR density and agonist-stimulated cAMP accumulation.

## THERAPEUTIC LEVELS OF TOCAINIDE PRODUCE DELETERIOUS HEMODYNAMIC AND CLINICAL EFFECTS IN SEVERE HEART FAILURE.

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Tocainide (TOC) exerts minimal cardiodepressant effects in pts with normal LV function, but the hemodynamic response to TOC in heart failure (CHF) has not been assessed. We evaluated the effects of a single dose of TOC (600 mg orally) in 22 pts with severe CHF (LV ejection fraction < 40%) who were clinically stable at the time of right heart catheterization. Cardiac index (CI, l/min/m$^2$), stroke work index (SWI, g-m/m$^2$), mean arterial, LV filling and mean right atrial pressures (MAP, LVFP, & RAP, mm Hg), heart rate (HR, bpm), systemic vascular resistance (SVR, d-s-c) and serum TOC levels (ng/ml) were measured before (pre) and 1.5 to 2.5 hr after TOC; where * = p <.05 (pre vs TOC)

| | CI | SWI | MAP | LVFP | RAP | HR | SVR |
|---|---|---|---|---|---|---|---|
| Pre | 2.2 | 26 | 85 | 19 | 7 | 77 | 1836 |
| TOC | 1.8* | 18* | 84 | 24* | 10* | 81* | 2098* |

LV function deteriorated significantly after TOC, as reflected by ↓ in CI and SWI and ↑ in LVFP and RAP. TOC also ↑ HR and SVR, probably due to reflex activation of neurohormonal systems. No pretreatment hemodynamic or clinical variable predicted the hemodynamic response to TOC in these pts.

Following TOC, 8 of the 22 pts (36%) developed new-onset dyspnea at rest coincident with the deterioration in LV function. These 8 pts experienced a greater ↓ in SWI after TOC than the 14 pts who remained asymptomatic at rest (39% vs 22%, p <.05).

Serum TOC levels ranged from 2.2 to 9.2 ng/ml (mean 5.3 ± 0.4) and were all within or below the therapeutic range. There was no relation between TOC levels and the change in SWI following TOC (r = 0.06). The mean TOC level in the 8 pts who deteriorated clinically was similar to that in the 14 pts who remained stable (5.6 vs 5.2 ng/ml), p = NS.

In conclusion, therapeutic levels of TOC can cause important deleterious hemodynamic and clinical effects in severe CHF.

## THE MECHANISM RESPONSIBLE FOR LASER-INDUCED PHOTORELAXATION OF VASCULAR SMOOTH MUSCLE IS LIMITED TO ULTRAVIOLET AND VISIBLE WAVELENGTHS.

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It has previously been shown that laser (L) irradiation (I) of vascular smooth muscle (VSM) with a pulsed L at any fluence, or a continuous wave (CW) L at powers sufficiently low to avoid significant rise in tissue temperature (T) may induce reproducible reduction in vascular tone, i.e. photo-relaxation (PR). The mechanism responsible for PR, however, remains enigmatic. Accordingly, we investigated the hypothesis that PR of VSM is wavelength-dependent. Segments of normal rabbit aorta were mounted in Krebs bicarbonate buffer with resting tension=1-2 g. Isometric tension and tissue T were then recorded during LI with ultraviolet (UV), visible (Vis), or infrared (IR) L light. LI with both 308 and 351 nm from a UV pulsed L consistently (n=58) produced endothelium-independent (endo-indpt) PR (280±18mg) (m±SEM) at fluences from 1-5J/cm$^2$. LI with 488 and 514 nm from a Vis CW L at powers <0.1 watt consistently produced endo-indpt PR (128±11mg). In contrast, LI both in the near IR (1060 nm) from a CW L, and mid IR (2.1um) from a pulsed L failed to produce PR. At 1060nm, powers as low as .02 watts with exposures (n=65) of 20 sec produced only a 1°C rise in tissue T; yet vasomotor reactivity was limited to contraction or no response. At 2.1 um (n=80), pulse energies of 5 to 300 mJ/pulse with repetition rates of 5-10 Hz again produced tissue T elevations limited to <10°C, but in no case produced PR of VSM. These findings were true for segments in which the endo was intact or purposely denuded. Thus, PR of VSM is a wavelength-dependent, endo-indpt phenomenon limited to UV and Vis wavelengths.

## CORONARY OCCLUSION-REPERFUSION ATTENUATES ENDOTHELIUM-MEDIATED VASCULAR RESPONSE TO LEUKOTRIENE $D_4$ AND ACETYLCHOLINE.

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Entry of leukocytes during coronary reperfusion relates to myocardial "reperfusion injury" mediated via release of superoxide radicals and leukotrienes (LTs). To examine the effect of reperfusion on coronary vascular responses to $LTD_4$, 8 dogs were subjected to circumflex (Cx) occlusion for 1 hr. followed by reperfusion for 1 hr., while LAD was kept patent. Following reperfusion, Cx (distal to occluder) and LAD coronary arterial rings were precontracted with serotonin and then exposed to $LTD_4$ ($10^{-9}$ to $2x10^{-6}$M) and ACh ($10^{-6}$M) in an organ bath at 37°C. $LTD_4$ caused a concentration-dependent relaxation of precontracted LAD coronary rings. ACh also relaxed these rings indicating intact endothelium and release of endothelium-derived relaxing factor (EDRF). In contrast, $LTD_4$, as well as ACh, failed to induce relaxation of coronary rings from the reperfused Cx, suggesting loss of EDRF. Since superoxide radical release causes breakdown of EDRF, 3 other dogs were treated with superoxide dismutase (SOD) prior to Cx reperfusion. In these animals, relaxation of arterial rings from the reperfused Cx was preserved. These data suggest that coronary reperfusion results in loss of vasorelaxant effect of $LTD_4$ on precontracted vessels. Administration of SOD prior to reperfusion protects against loss of EDRF and thus maintains the vasorelaxant effect of $LTD_4$.

## ß-ADRENERGIC AGONISTS IN NONFAILING, FAILING, AND TRANSPLANTED HUMAN HEARTS.

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During heart failure the ß-adrenergic receptor pathways are markedly down-regulated and subsensitive to ß-agonist stimulation. In this study we used isolated RV trabeculae to compare isoproterenol, a nonselective full agonist; zinterol, a $ß_2$ selective partial agonist; dopamine, a direct partial agonist with indirect actions (releases norepinephrine, (NE)); and dopexamine, a dopamine derivative that also blocks NE reuptake. Nonfailing hearts were obtained from organ donors whose hearts were not used for cardiac transplant. Failing hearts were from patients with either idiopathic dilated cardiomyopathy or ischemic heart disease undergoing transplant. Transplanted (TX) hearts were from patients undergoing retransplantation due to graft atherosclerosis. Contractile responses to these agonists and tissue NE levels were:

Net Max mg Tension and Tissue NE, ng/g (X±SEM)

| Agonist | Nonfailing | Transplant | Failing |
|---|---|---|---|
| Isoproterenol | 1935 ± 417 | 2178 ± 839 | 1130 ± 136* |
| Zinterol | 1112 ± 173 | 894 ± 463 | 715 ± 117 |
| Dopamine | 1450 ± 600 | 443 ± 208# | 344 ± 103* |
| Dopexamine | 1260 ± 320 | 454 ± 110# | 129 ± 32* |
| Tissue NE | 1799 ± 299 | 16 ± 16* | 470 ± 106* |

*p<0.05, #p<.10 compared to nonfailing

Conclusions: Although there was reduced efficacy for all agonists but zinterol in failing vs nonfailing hearts, the reductions were greatest for dopamine and dopexamine. The responses to these two agonists were also reduced in TX hearts, indicating that denervation/lack of releasable NE may contribute to the reduced efficacy of indirect acting amines in heart failure.

## "UP-REGULATION" OF GTP BINDING PROTEINS FOLLOWING CARDIAC PARASYMPATHECTOMY - QUANTITATION BY IMMUNOBLOT METHOD.

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Functional parasympathetic denervation of the myocardium is produced by several disease processes in man. In a canine model of selective cardiac parasympathectomy, we have previously demonstrated an increase in the membrane density of the pertussis toxin substrates $G_i$ and $G_o$, but used the indirect method of ADP ribosylation to quantitate these proteins. The purpose of this study was to directly quantitate the membrane density of the ß subunit of these GTP binding proteins using a specific antibody. Sarcolemmal vesicles were prepared from normally innervated canine ventricle (NI), and from ventricle 5 days following selective cardiac parasympathectomy (PS) (Method of Randall). U-49 antiserum (gift of A. Gilman) was used to quantitate the density of ß subunit in these membranes. Sarcolemmal membrane proteins were separated on SDS-PAGE and transferred to nitrocellulose. The antiserum reacted specifically with a single protein band $M_r$=36,000. Quantitative data are summarized:

| | pmoles antibody bound/mg protein |
|---|---|
| NI (n=5) | 40.1 |
| PS (n=4) | 54.4* |

*significantly different from NI p=.009.

Increases in the density of the ß subunit quantitated by immunoblot parallel the increases determined by ADP ribosylation. These data confirm that membrane density of GTP binding proteins is increased following PS. $G_o$ has been shown to directly regulate sarcolemmal Ca channels. Increases in the density of GTP binding proteins could alter transmembrane Ca flux in canine myocardium following PS.

## IONIC MECHANISMS UNDERLYING POSITIVE CHRONOTROPIC EFFECTS OF HISTAMINE ON THE RABBIT ATRIOVENTRICULAR NODE.

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To elucidate the ionic mechanisms underlying positive chronotropic effects of histamine (HST), microelectrode and voltage clamp experiments were conducted in small preparations (0.2 x 0.2 x 0.2mm) of the rabbit atrioventricular node. HST at concentrations ranging from $10^{-7}$ to $10^{-5}$ M caused a sigmoidal increase in the spontaneous firing frequency with a $K_d$ of $3 \times 10^{-6}$ M. HST significantly increased the action potential amplitude, maximal rate of depolarization and rate of diastolic depolarization. The action potential duration remained unchanged probably due to the increased spontaneous firing rate. These effects of HST were antagonized by $10^{-4}$ M cimetidine. Voltage clamp experiments using double microelectrode method revealed that HST at $10^{-5}$ M increased the slow inward current ($I_{si}$) activated on depolarization from -40 to -10mV by 72 ± 18% ($p<0.05$, n=6) without significantly changing the kinetics of its recovery from inactivation. The same concentration of HST increased the outward K current ($I_K$) tail obtained on repolarization from +10 to -40 mV by 21 ± 2% ($p<0.05$, n=6). The hyperpolarization-activated inward current ($I_h$) was similarly increased by HST. HST at $10^{-4}$ M frequently induced a transient inward current on depolarization from -40 mV to potentials more positive to -20 mV. 2-pyridylethylamine, an $H_1$ agonist, increased $I_{si}$ in the presence of cimetidine, but required higher concentrations than HST. These results suggest that HST enhances automaticity of the rabbit atrioventricular node mainly by increasing $I_{si}$, and this action appears to be predominantly mediated by $H_2$ receptor activation by HST.

## CARDIOVASCULAR EFFECTS OF PLATELET-ACTIVATING FACTOR IN CONSCIOUS DOGS

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Platelet-activating factor (PAF) is an endogenous membrane phospholipid, implicated as a mediator of anaphylaxis and endotoxemia. We examined the effects of systemically administered PAF (.4 ug/kg as an IV bolus) in 5 unanesthetized mongrel dogs.

Results:

| Time (Min) | RAP (mmHg) | HR (B/min) | AoBP (mmHg) | CO (L/min) |
|---|---|---|---|---|
| Base | 4.2 ± 0.8 | 112 ± 12 | 86 ± 2 | 3.9 ± 0.4 |
| 1 | 0.9 ± 2.0# | 115 ± 20 | 64 ± 5# | 1.8 ± 0.3# |
| 5 | -0.4 ± 1.5# | 116 ± 18 | 73 ± 5# | 2.1 ± 0.3# |
| 10 | 0.4 ± 1.4# | 113 ± 19 | 87 ± 3 | 2.5 ± 0.3# |
| 20 | 1.0 ± 1.2# | 117 ± 17 | 85 ± 2 | 2.6 ± 0.3# |

(Mean ± SE; # $p < .05$ versus baseline)

PAF produced striking declines in intravascular volume and cardiac filling pressures, systemic hypotension, peripheral vasoconstriction, and persistent elevations of pulmonary vascular resistance. Pretreatment with SRI 63-675, a selective PAF receptor inhibitor (10 mg/kg), abolished all of these hemodynamic and cardiovascular derangements associated with PAF injection. We conclude that PAF has profound cardiovascular effects, in conscious dogs, which mimic well recognized clinical shock states. Further, selective PAF receptor antagonists such as SRI 63-675 offer promise in attenuating the hemodynamic derangements associated with endotoxemia and anaphylaxis in the clinical setting.

## EFFECT OF α-TOCOPHEROL (VITAMIN E) ON REGIONAL FUNCTION IN STUNNED MYOCARDIUM

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Oxygen free radicals have been suggested to cause myocardial damage resulting in prolonged contractile depression following brief periods of regional myocardial ischemia. In pigs we infused either the natural antioxidant α-tocopherol (TOC) as its water soluble acetate (0.3 g kg iv, n=6) or saline (n=6) three times during one week. Thereafter, thoracotomy was performed and the distal left anterior descending coronary artery occluded for 8 min, followed by 90 min reperfusion (REP). Hearts were paced at a rate of 100 /min. Regional segment shortening (SS) was measured by ultrasonic crystals in ischemic-reperfused (I-REP) and control zones. Plasma level of TOC (HPLC) was 148.91+21.47 µg/ml in the treatment group (T) and 0.51+0.14 µg/ml in the control group (C). Myocardial tissue level of TOC was elevated to 93.15+14.78 µg/g in T, compared to 4.08+0.60 µg/g in C. Malondialdehyde concentration in I-REP myocardium was lower in T (441.9+59.6 vs 500.9+72.7 nmoles/g). Systolic LVP and LV dP/dt max remained stable throughout the protocol in both groups. SS in the I-REP zone was negative during occlusion and rapidly normalized within one minute of REP in both groups. During the following 10 min, SS decreased to 52 +6 % of preischemic control in T and to 54 + 7 % in C (n.s.). SS remained at these depressed values throughout 90 min REP. Conclusion: Pretreatment with the natural antioxidant TOC reduces lipid peroxidation in I-REP myocardium, but fails to prevent the development of myocardial contractile depression after a short period of ischemia.

## INCREASED CONTRACTILITY INDUCED BY ALPHA ADRENERGIC STIMULATION IN SEPTIC RAT HEARTS

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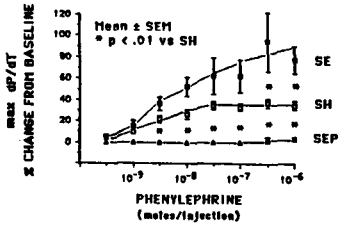
Decreased myocardial responsiveness to β agonists during sepsis has been reported, but α adrenergic response has not been studied. We used a Langendorf preparation to study the inotropic response to α agonist phenylephrine (PE) in septic rats (SE). Sepsis was induced by cecal perforation. Sham operated rats (SH) served as controls. Three hours after surgery, the hearts of 5 SE and 5 SH were excised and perfused with oxygenated buffer containing 5 x $10^{-7}$ M propranolol. An additional 5 septic rat hearts were perfused with propranolol plus $10^{-7}$ M prasozin (SEP). A latex balloon was placed in the left ventricle to measure max dP/dt at a standard preload. Hearts were incrementally bolus dosed with PE from $10^{-10}$ to $10^{-6}$ to moles. Baseline max dP/dt was 2140 ± 127 mmHg/sec in SH, 1731 ± 127 mmHg/sec in SE and 1384 ± 75 mmHg/sec in SEP ($P < 0.05$ SH vs SE, SEP). The percent increase in max dP/dt from baseline (efficacy) at higher doses was greater in SE. Efficacy was reduced at all PE doses in alpha-blocked SEP.




These data suggest that alpha adrenergic agonists may be useful inotropic agents during sepsis.

## PLASMA AND HEART TISSUE LEVELS OF FLECAINIDE AFTER SINGLE VERSUS MULTIPLE DOSES: IS THERE A RATIONALE FOR INTERMITTENT USE?

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Flecainide acetate(F), a class Ic antiarrhythmic drug, is used for chronic prophylactic treatment of various arrhythmias(A), but may also convert recent onset atrial fibrillation. To investigate the rationale for episodic versus chronic treatment with F we studied the tissue/plasma level ratio after single and multiple dose use of F. We studied plasma levels(PL) and right atrial tissue levels(TL) in 13 pts, with normal left ventricular ejection fraction, undergoing elective coronary artery bypass grafting(CABG). Six pts(group A) received 100 mg oral F prior to start of extracorporal circulation(ECC), 7 pts(group B) received 100 mg oral F b.i.d. during two days before CABG, the last dose was given as in group A. Also ECG conduction parameters( PR-interval, QRS duration and JTc-interval, written at 100 mm/sec) were obtained at baseline and together with PL and TL of F, prior to start of ECC. In group A mean PL/TL ratio was 28.8(median 20.1, SD 26.1), in group B mean PL/TL ratio was 18.9(median 17.8, SD 7.0); p=NS. Correlation coëfficient(R) of PL and TL was 0.64(A:0.61, B:0.66). R of PL and changes in PR-interval, QRS duration and JTC-interval were 0.34, 0.50 and 0.31 respectively(resp). R of TL and changes in PR-interval, QRS duration and JTc-interval were 0.60, 0.36 and 0.20 resp.

Conclusions: Plasma/tissue level ratio of F did not differ in group A and B. This supports a theoretical rationale for intermittent oral use in exacerbations of A. Furthermore R of PL and changes in cardiac conduction parameters is poor and does not improve when applying TL of F.

# Tuesday, March 21, 1989
# Poster Displayed: 2:00PM–5:00PM
# Author Present: 2:00PM–3:00PM
# Pacific Room, Anaheim Convention Center
# Thrombosis and Thrombolysis

## ANTITHROMBOTIC THERAPY: IS THE COMBINATION OF ASPIRIN AND NITROGLYCERIN BENEFICIAL?

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Aspirin and nitroglycerin are frequently used together and each possesses potent platelet inhibitor properties which may be mediated through different mechanisms. To assess their potential antiplatelet interaction, we studied platelet deposition ex vivo onto exposed aortic media prepared from normal pigs and placed in well characterized cylindrical flow chambers of 1 mm diameter. By means of a peristaltic pump, non-anticoagulated arterial blood was drawn into the flow chambers from control pigs and pigs pre-treated with aspirin (40 mg/day for 3 days), NTG or both drugs, at 20 ml/min for 5 min., for a calculated shear rate of 1690 sec-1. NTG was infused to produce a 10±4% fall in mean arterial pressure. Platelet deposition (PD X 10⁶ per media) was quantitated using autologous 111Indium labeled platelets injected 18-24 hrs before the experiment, and are shown:

| | n | Mean±SE | p (vs control) |
|---|---|---|---|
| Control | 8 | 55.5±6.6 | |
| Aspirin | 8 | 26.2±5.3 | <0.003 |
| NTG | 8 | 37.7±8.5 | <0.005 |
| Aspirin plus NTG | 8 | 17.0±4.7 | <0.003 |

NTG vs Aspirin plus NTG, p<0.03

Thus, both aspirin and NTG decrease platelet deposition onto exposed aortic media, and the antithrombotic property of the combination may be additive and beneficial. Cyclo-oxygenase inhibition may not attenuate the anti-platelet effects of NTG.

## N-ACETYLCYSTEINE POTENTIATES IV NITROGLYCERIN IN INHIBITING PERIODIC PLATELET THROMBUS FORMATION IN STENOSED DOG CORONARY ARTERIES.

John D. Folts, Ph.D., F.A.C.C., Jonathan Stamler, M.D., Joseph Loscalzo, M.D., Ph.D., F.A.C.C., Univ. of Wisconsin Medical School, Cardiology Section, Madison, WI and Dept. of Medicine, Harvard Medical School, Boston, MA

The antianginal effects of IV nitroglycerin (NTG) in Pts with coronary disease are usually attributed to a decrease in preload and coronary vasodilation, although high doses of NTG inhibit platelet aggregation in vitro. We have shown that IV NTG 10-17 μg/kg/min for 24 min inhibits acute platelet thrombus formation (APTF) in our dog model of stenosed coronary arteries. We studied the effects of combining N-acetylcysteine (Nac) with NTG on APTF in 10 open chest dogs with mechanical coronary artery stenosis and intimal damage. As periodic APTF occurs coronary blood flow is reduced (measured with EMF probe) producing cyclical reductions in coronary flow (CFRs). A low dose of NTG, 5 μg/kg/min given IV for 30 minutes decreased arterial blood pressure (ABP) 9±4 mm Hg, but diminished the size and frequency of CFRs in only one dog. Nac 100 mg/kg was then infused IV over 30 minutes with no effect on ABP, heart rate or CFR's. When the NTG infusion 5 μg/kg was repeated after Nac, for 30 minutes ABP decreased 14±5 mm Hg and the CFRs were abolished in 7 dogs and diminished in 3 dogs, after 26±4 min of infusion. We and others have shown that aspirin and other platelet inhibitors abolish CFRs in this model within 3-4 minutes, thus continuous IV NTG appears to work by a different, time dependent mechanism. We postulate that Nac potentiates the antithrombotic effects of NTG possibly by inducing the formation of S-nitrosothiols that may activate platelet guanylate cyclase. This combination, given to man may, in part, account for the antianginal effect.

## THROMBIN INHIBITION BY HIRUDIN DECREASES PLATELET THROMBUS GROWTH ON AREAS OF SEVERE VESSEL WALL INJURY.

Lina Badimon Ph.D, Juan Badimon Ph.D., Riitta Lassila M.D., Magda Heras M.D., James H. Chesebro M.D, Valentin Fuster M.D., Mount Sinai Medical Center, New York , New York and Mayo Clinic, Rochester, Minnesota.

The role of Hirudin (H) (Sigma 20U/ml) in platelet vessel wall interaction and thrombus growth on three biological vascular surfaces was studied under controlled flow conditions and compared to heparinized blood (HP) (APTT x 1.5). The vascular materials, isolated collagen type I fibrils (ICF), mildly damaged vessel wall (MDV) and severely damaged vessel wall (SDV) were perfused by flowing blood at shear rates typical of patent arteries ($212s^{-1}$) and of stenosed arteries ($1690s^{-1}$) for 5 minutes. Platelet deposition (PD) was measured by Indium-111-labeled platelets (x $10^6/cm^2$):

| Shear rate | $212s^{-1}$ | | $1690s^{-1}$ | |
|---|---|---|---|---|
| | H | HP | H | HP |
| ICF | 4.3 ± 0.7 | 7 ± 0.3 | 6.6 ± 1.0 | 6 ± 1.0 |
| MDV | 5 ± 0.6 | 5 ± 0.3 | 9.2 ± 1.5 | 10 ± 1.0 |
| SDV | 7.4 ± 1.4 | 10.7 ± 1.8 | 40 ± 7 | 87 ± 12 |

The perfusion of ICF and MDV induced the deposition of 1-2 layers of platelets (platelet-vessel wall interaction) that was not affected by hirudin. The perfusion of SDV induced significant thrombus growth mainly at high shear rate. Thrombus growth was significantly (* $p < 0.05$) reduced by hirudin (direct thrombin inhibitor) as compared to heparin (indirect thrombin inhibition). Therefore, thrombus growth is dependent on local thrombin production and hirudin seems to be more effective than heparin in preventing thrombus growth.

## PLATELET DEPOSITION IN AREAS OF STENOSIS IS STIMULATED BY HIGH PLASMA CHOLESTEROL LEVELS.

Juan J. Badimon Ph.D, Lina Badimon Ph.D., Vincent Turitto Sc.D., Valentin Fuster M.D., Mount Sinai School of Medicine, New York, N.Y.

The effect of lipids in platelet deposition and thrombosis, a common complication of advanced atherosclerosis, remains unknown. Our aim has been to study the effects of hypercholesterolemia on platelet deposition under controlled flow conditions mimicking shear rates typical of stenotic vessels ($2600\ s^{-1}$). Platelet deposition, measured by $^{111}$In-platelets and morphometry, was studied in the rabbit using the Baumgartner's perfusion chamber. Hypercholesterolemia was induced by a 0.5% cholesterol diet for 8 weeks. This diet significantly increased plasma cholesterol levels (1496±109 vs 66±4 mg/dl; X± 1SEM), and platelet membrane fluidity (0.201 ± 0.01 vs 0.217 ± 0.01 steady-state fluorescence anisotropy; X±1SEM). Whole blood aggregation in hypercholesterolemia was similar to that in normal blood (ADP and collagen). Platelet deposition on deendothelialized normal rabbit vessel wall was significantly increased in hypercholesterolemia blood compared to normal blood (plateletsx$10^6/cm^2$: 2.9±1.5 vs 0.8±0.2, $p<0.001$, at 5 min; and, 2.3±0.6 vs 0.9±0.1, $p<0.001$, at 20 min perfusion). By morphometry, we observed that both platelet adhesion and thrombi formation (>5μm) were increased in hypercholesterolemia blood but only adhesion was statistically significant. Although in vitro platelet aggregation was not modified, severe hypercholesterolemia increases platelet deposition at high shear rate conditions.

ANGIOSCOPY - MORE SENSITIVE FOR IDENTIFYING THROMBUS, DISTAL EMBOLI, AND SUBINTIMAL DISSECTION.
Christopher Johnson, M.D., D. Dennis Hansen, M.D., Rudolf Vracko, M.D., James Ritchie, M.D.,F.A.C.C., University of Washington and VA Medical Center, Seattle, Washington.

Angioscopy was compared to contrast angiography (cine) for the detection of thrombus, distal emboli, and subintimal dissection in a canine model of thrombolysis. Thrombosis was created by forceps crush injury, temporary occlusion, and thrombin injection in 15 arteries. Mechanical (rotational thrombectomy-RT) and enzymatic (tPA) thrombolysis were sequentially applied. Angioscopy and cine were performed after RT and after tPA. Later histologic assessment showed subintimal flaps or thrombi in all cases. In 27 arterial observations, subintimal dissection (seen as flaps) was present 26 times by angioscopy. Cine did not demonstrate flaps in any artery ($p<.001$). Thrombus (lining, protruding or occlusive) was present in 30/30 angioscopic observations, whereas only 11/30 had stenoses by cine ($p<.001$). Distal emboli were seen 6 times by angioscopy, versus twice by cine ($p<.06$). Conclusion: Angioscopy is a more sensitive means of detecting subintimal dissection, thrombus and possibly distal emboli following intravascular interventions.

DOES MYOCARDIAL INVOLVEMENT IN CHILDREN WITH SEVERE MITRAL REGURGITATION (MR) DUE TO ACTIVE RHEUMATIC CARDITIS (ARC) INFLUENCE THE OUTCOME OF MITRAL VALVE REPLACEMENT (MVR)?
Rafique Essop MD, Richard Marcus MD, Gillian Tweedie RN, Michael Kenyon MD, Pierre Marais MD, Pinhas Sareli MD. Baragwanath Hospital, Johannesburg, South Africa.
The role of primary myocardial involvement in LV dilatation occurring in children with severe MR due to ARC is undefined. We compared cardiac dimensions and systolic LV function echocardiographically pre and 3 months post-operatively in 32 children (mean age 13±3 yrs, mean body surface area 1,2$m^2$) with hemodynamically compromising MR and ARC referred for MVR. 17 pts had MVR only while 15 required aortic valve replacement as well (35 St Judes medical and 12 Medtronic Hall prostheses). The following table summarise the results: (mean±SD,*$p<0.05$ vs pre-op)

| | PRE-OP | POST OP |
|---|---|---|
| Functional class (FC)(NYHA) | 3,5±0,5 | 1,1±0,4* |
| Cardiothoracic ratio (CTR)(%) | 65±6 | 54±5* |
| End diastolic diameter (EDD)mm | 55±7 | 45±8* |
| End systolic diameter (ESD)mm | 35±6 | 30±9 |
| Fractional shortening (FS)(%) | 35±7 | 33±10 |

The early mortality was 3.1% (1/32). Rheumatic activity subsided completely in all pts post operatively. Conclusions: 1, MVR in pts with severe MR and ARC carries an acceptable operative mortality and is associated with significant improvement in FC; 2, Restoration of MV competence in this group of pts results in a significant reduction in CTR and EDD with no reduction in FS. This is accompanied by a rapid decline in rheumatic activity; 3, The results suggest that LV dilatation seen in our pts was largely related to volume overload rather than to significant myocardial involvement by the rheumatic process.

## Tuesday, March 21, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 3:00PM–4:00PM
## Pacific Room, Anaheim Convention Center
## Valvular Heart Disease

ENHANCED BETA ADRENERGIC RECEPTOR FUNCTION IN SYMPTOMATIC MITRAL VALVE PROLAPSE.
Azam Anwar, MD, Michael S. Katz, MD, Sarah R. Kohn, BA, Tazuko K. Hymer, BA, Gemma T. Kennedy, RN, MSN, James F. Dunn, MD, Michael H. Crawford, MD, FACC, Robert A. O'Rourke, MD, FACC. Univ of TX Health Sc Ctr & VAH, San Antonio, TX.

Mitral valve prolapse (MVP) subjects may have a hyperadrenergic state, but the mechanism of enhanced adrenergic tone is unclear. Thus, we measured catecholamines, lymphocyte beta adrenergic receptor ($\beta$AR) characteristics ([$^{125}$I] iodopindolol radioligand binding), and isoproterenol (ISO) stimulated ($10^{-5}$M ISO, 10 minutes) lymphocyte cyclic AMP production in 12 symptomatic female MVP subjects and 14 controls (C). Subsequently, physiologic responses to infusion with three increasing doses of ISO were measured in eight subjects from each group. The % of $\beta$AR which binds ISO with high affinity was greater in MVP than in C (61±7% vs 45±2%, $p<.05$). Cyclic AMP (pmol) response to ISO was higher in MVP (46±5 vs 27±5, $p<.02$). Catecholamines and $\beta$AR density were similar in both groups. In MVP but not C, ISO infusion caused arrhythmias (5/8 vs 0/8, $p<.01$) and reproduced symptoms (5/8 vs 0/8, $p<.01$). ISO also caused a greater tachycardia [ΔHR] in MVP:

| ISO (mcg/min) | 0.5 | 1.0 | 2.0 |
|---|---|---|---|
| C [ΔHR] (bpm) | 16±3 | 22±2 | 38±5 |
| MVP [ΔHR] (bpm) | 37±7 | 35±2 | 69±12 |
| p | <.005 | <.002 | <.008 |

Our studies show that in symptomatic MVP subjects $\beta$AR-catecholamine interaction and $\beta$AR-linked responses are increased, independent of catecholamine levels, and ISO infusion often reproduces symptoms. Therefore, the hyperadrenergic state of some subjects with symptomatic mitral valve prolapse may be secondary to enhanced beta adrenergic receptor function.

THE USE OF PULMONARY CAPILLARY WEDGE PRESSURE TO ASSESS THE SEVERITY OF MITRAL STENOSIS: IS A TRUE LEFT ATRIAL PRESSURE NEEDED IN THESE PATIENTS?
Richard A. Lange, MD, Donald M. Moore, Jr, MD, Ricardo G. Cigarroa, MD, L. David Hillis, MD, FACC, U of Texas Southwestern Medical Center, Dallas, TX.

There is disagreement concerning the use of the pulmonary capillary wedge (PCW) pressure (in lieu of left atrial [LA] pressure) in assessing the presence and severity of mitral valve disease. This study was done to assess the accuracy and reliability of an oximetrically confirmed PCW pressure in measuring the transvalvular pressure gradient and valve area in patients with mitral stenosis. In 9 patients (1 man, 8 women, aged 47 ± 8 [mean ± SD] years) with mitral stenosis, PCW pressure was measured through an 8 Fr Goodale-Lubin catheter with its wedge position confirmed by oximetry (oxygen saturation ≥ 95%); a transseptal LA pressure was measured through a Brockenbrough catheter; and left ventricular pressure was measured through a pigtail catheter. The mean and phasic LA and PCW pressures were similar (mean LA, 19 ± 7 mmHg; mean PCW, 19 ± 7 mmHg; NS). When the PCW pressure was used but was not adjusted for time delay, the transvalvular pressure gradient (10.1 ± 3.3 mmHg) and valve area (1.5 ± 0.5 $cm^2$) were significantly different ($p < 0.05$) than the values obtained using the LA pressure (7.5 ± 2.8 mmHg and 1.7 ± 0.7 $cm^2$, respectively). In contrast, when the PCW pressure was adjusted for the time delay through the pulmonary vasculature, the difference in gradients averaged only 1.6 mmHg, and the mitral valve areas were similar (1.7 ± 0.7 $cm^2$ using LA, 1.6 ± 0.6 $cm^2$ using time-adjusted PCW; NS). Thus, in patients with mitral stenosis, a properly obtained, confirmed, and time-adjusted PCW pressure accurately reflects LA pressure; transseptal catheterization is not needed in these pts.

## EVIDENCE AGAINST A "MYOCARDIAL FACTOR" IN RHEUMATIC MITRAL STENOSIS

Thomas Wisenbaugh MD, FACC and Kevin Sublett MD. VA and U of Kentucky Med Centers, Lexington, KY.

We tested the hypothesis that low EF in rheumatic mitral stenosis (MS) is due to chronic myocardial disease. Contractile function was assessed using frame-by-frame stress(σ) and volume (V) analysis from simultaneous LV cine and micromanometry in 19 patients with isolated MS and 23 normals (NL). Mean EF was reduced in MS (.57±.10) vs NL (.64±.07). MS patients were grouped by EF into MS1 (EF<.60, n=11) and MS2 (EF≥.60, n=8). Afterload (σes) tended to be higher than NL in MS1 (p=.07 by ANOVA) but preloads (σed) were similar. ] p<.05:

| Group | EF | EDVI ml/m$^2$ | σed kdyn | ESVI ml/m$^2$ | σes kdyn | peak LVP mmHg |
|---|---|---|---|---|---|---|
| MS1 | .50±.07 | 86±17 | 46±25 | 44±14 | 234±79 | 130±21 |
| MS2 | .65±.03 | 93±17 | 58±12 | 32± 4 | 175±32 | 118±11 |
| NL | .64±.07 | 85±17 | 49±19 | 30±7 | 192±54 | 123±14 |

An inverse relation (r=-.90) was observed between EFc (EF determined from a common preload) and σes (afterload) in the NL group. All but one patient with MS fell within the 95% prediction band of the normal EFc-σes relation. Followup 2D echo in a subgroup of MS1 showed improvement in EF from .50±.04 before to .59±.04 one year after mitral valve replacement (n=3) or balloon valvotomy (n=3), but in MS2 EF did not change (n=4). Conclusion: Normal EFc-afterload relations and normalization of EF after correction of mitral stenosis argue against a myocardial factor as an important cause of low ejection fraction in mitral stenosis.

## THE NATURAL HISTORY OF ADULTS WITH ASYMPTOMATIC, SEVERE AORTIC STENOSIS

Patricia A. Pellikka, M.D., Kent R. Bailey, Ph.D., Rick A. Nishimura, M.D., Catherine L. Taylor, and A. Jamil Tajik, M.D.; Mayo Clinic, Rochester, Minnesota

The natural history of asymptomatic, severe valvular aortic stenosis (AS) has not been well documented. From among 472 pts with AS by Doppler (peak systolic velocity > 4 M/sec) at the Mayo Clinic from Jan. 1984-Aug. 1987, 144 were asymptomatic and had isolated valvular AS. The 30 pts who remained asymptomatic but underwent aortic valve intervention (AVI), including aortic valve surgery or balloon valvuloplasty within 3 mos were excluded. The remaining 114 pts who formed the study population ranged in age from 40-90 years (mean 70 yrs). The mean velocity was 4.3 M/sec (range 4.0-6.0 M/sec). The mean ejection fraction was 64% (range 37-78%). Follow-up was available for all patients, mean period 20 mos (range 6 mos-4 yrs). The actuarial probability of remaining free of symptoms of angina, dyspnea, or syncope was 88% at 1 yr and 72% at 2 yrs. The 1-and 2-year probabilities of remaining free of cardiac events (CE), including AVI or cardiac death were 93% and 74%, respectively. Of all clinical and echo-cardiographic variables, only Doppler velocity (p=0.004) and ejection fraction (p=0.013) were independent predictors of subsequent CE. Among the 29 pts with velocity >4.5 M/sec, the relative risk of sustaining a CE by Cox regression was 2.5. There were 3 pts who sustained a cardiac death presumed to be a result of the aortic stenosis; all developed symptoms at least 3 mos prior to death. Conclusions: 1) Pts with asymptomatic, severe AS are at significant risk for CE within 2 yrs. 2) The development of symptoms precedes cardiac mortality. Thus, the asymptomatic pt requires careful follow-up for the development of symptoms.

## MECHANICAL RESISTANCE IN AORTIC STENOSIS: AN INDEX OF FUNCTIONAL CHANGE AFTER VALVULOPLASTY.

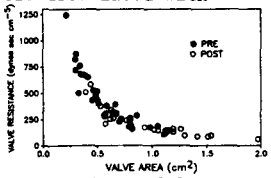
Ted Feldman MD FACC, Lincoln E. Ford MD, Y. Christopher Chiu MD, John D. Carroll MD, University of Chicago, Chicago, Il.

Balloon valvuloplasty results in small changes in valve area with great symptomatic improvement in some patients, while others have little relief with greater increases in valve area. To assess functional changes in mechanical valve obstruction, we compared Gorlin valve area with mechanical resistance in 30 aortic valvuloplasty patients. Resistance was computed as mean gradient/systolic flow, expressed as dynes/sec/cm$^{-5}$, as is peripheral resistance.

| | PRE | POST |
|---|---|---|
| Mean Gradient(mmHg) | 52±19 | 30±13* |
| Cardiac Output(L/min) | 4.3±1.4 | 4.7±1.5* |
| Area (cm$^2$) | .57±.2 | .92±.3* |
| Valve Resistance | 453±258 | 207±123* |
| Peripheral Resistance (dynes sec cm$^{-5}$) | 1660±522 | 1492±439 |

*p<.001

Area correlated with log resistance (r=0.93)(Fig). Small increases in valve area were associated with clinical improvement when fall in resistance was large, but there was not improvement with a small drop in resistance. With large increases in valve area, pts with little fall in valve resistance were not likely to improve clinically.




Conclusions: 1) Mechanical resistance is useful to characterize dynamic changes in valve obstruction because it is a functional index of opposition to flow. 2) Resistance is easily measured from clinical data and does not require an empirical constant.

## IS THERE AN IMPROVEMENT IN CORONARY VASODILATOR CAPACITY AFTER AORTIC VALVE REPLACEMENT?

Franz Eberli M.D., Manfred Ritter M.D., Otto Hess M.D., Reto Candinas M.D., Marko Turina M.D., Hans Krayenbuehl M.D., University Hospital, Zurich, Switzerland.

Coronary sinus blood flow (CSBF;ml/min) was measured by thermodilution in 6 controls (C), 30 patients (pts) with aortic valve disease before (pre) and 17 pts 29 (12-52) months after (post) aortic valve replacement (AVR) at rest (R) and after 0.5 mg/kg Dipyridamole (D) given i.v. over 15 min. Left ventricular muscle mass (LMMI;g/m$^2$) was measured by angiography. In the pts with AVR LV biopsies had been taken preoperatively and muscle fiber diameter (MFD;μ), interstitial fibrosis (IF;%) and fibrous content (FC;g/m$^2$) were determined in the subgroup with normal (n=8) and abnormal (n=9) coronary flow reserve (CFR=CSBF D/R).

| | CSBF-R | CSBF-D | CFR | CRR | LMMI | MAP |
|---|---|---|---|---|---|---|
| pre | 246 | 414 | 1.7 | 0.61 | 162 | 90 |
| post | 168* | 355 | 2.2* | 0.48* | 98*# | 105*# |
| C | 149 —* | 445 | 2.8 —*# | 0.35 —*# | 82 —*# | 102 —* |

Resistance ratio (CRR) = CR D/R;MAP = mean aortic pressure (mmHg);*P<0.05;**P<0.01. MFD, IF and FC did not differ in pts with normal and abnormal postoperative CFR. Conclusions: Regression of left ventricular hypertrophy after aortic valve replacement is accompanied by a decrease of resting coronary blood flow. Because maximal coronary blood flow after Dipyridamole was unchanged coronary flow reserve improved. Similarly coronary vasodilator capacity was enhanced. Preoperative morphometric structure had no predictive value for the degree of postoperative vasodilator capacity.

DETERMINANTS OF LEFT VENTRICULAR SIZE AND FUNCTION FOLLOWING MITRAL VALVE REPLACEMENT.
Michael H. Crawford, MD, FACC, Charles Oprian, PhD, D. Craig Miller, MD, FACC, Shahbudin Rahimtoola, MB, FACC, John C. Giacomini, MD, Gulshan Sethi, MD, Karl E. Hammermeister, MD, FACC and Participants in VA Coop Study on Valvular Heart Disease, San Antonio, TX.

To determine factors predictive of LV size and function post-mitral valve replacement (MVR) we evaluated 104 pts with isolated MVR before and 6 mos post-surgery by cardiac catheterization. In the 48 pts with mitral regurgitation (MR) the ejection fraction (EF) decreased post-surgery from .56±.15 (SD) to .45±.13 ($p<.001$). The best predictor by multivariate analysis of post-operative EF was pre-operative EF. All but one pt with a pre-op EF ≤.50 had a post-op EF ≤.50 (90% sensitivity, $p<.03$). A pre-op LV systolic pressure >120 mmHg was also predictive of a post-op EF ≤.50 (87% sensitivity, $p<.05$). LV end-diastolic volume index (EDVI) decreased post-op from 117±51 to 89±27 ml/m$^2$ ($p<.001$) in MR pts. The best predictor of post-op LV EDVI was pre-op end systolic volume index (ESVI). Only one pt with a pre-op ESVI <50 ml/m$^2$ had a post-op EDVI >101 ml/m$^2$ (95% specificity, $p<.001$). Pre-op systolic pulmonary artery pressure ≤20 mmHg was also predictive of a post-op EDVI ≤101 ml/m$^2$ (100% specificity, $p<.004$). The 23 pts with MR and mitral stenosis (MS) responded similar to the MR pts. The 33 pts with MS exhibited little change in LV size and function post-op. We conclude that preservation of LV performance following MVR for MR or MR/MS is most likely if pre-op EF is >.50, LVSP is <120 mmHg, ESVI is <50 ml/m$^2$ and systolic PA pressure is <20 mmHg. Thus these measures are important considerations in the timing of surgical intervention in MR or MR/MS pts.

## HEMODYNAMIC RESULTS AND CLINICAL FOLLOW-UP IN PATIENTS UNDERGOING REPEAT BALLOON AORTIC VALVULOPLASTY

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We examined the hemodynamic results and clinical follow-up in 22 patients (pts) undergoing repeat balloon aortic valvuloplasty (BAV) for aortic valve restenosis (mean interval between procedures 10 months). In each case, repeat BAV was safely performed with no significant difference between the complication rate following the second (BAV2) as compared with the first (BAV1) procedure. The aortic valve area (AVA), aortic valve gradient (AVG), cardiac output (CO), mean pulmonary capillary wedge pressure, and mean pulmonary artery pressure before and after each procedure, as well as the absolute and percent change in these factors, were analyzed in order to determine the efficacy of repeat valvuloplasty. Overall, there was no significant difference between BAV1 and BAV2 with respect to any of these hemodynamic variables. The pts were then divided into two groups: Group A (10 pts)--increase in AVA after BAV2 < increase in AVA after BAV1; Group B (12 pts)--increase in AVA after BAV2 ≥ increase in AVA after BAV1. Multiple linear regression analysis identified four predictive factors which significantly effected outcome ($p<.0001$): pts with a lower initial CO, higher initial AVG, higher AVG post BAV1, and larger AVA post BAV1 were more likely to be in Group A. Clinical follow-up demonstrated that 8/10 pts in Group A have either died or have required a third BAV or aortic valve replacement (AVR) (average time to death, BAV3, or AVR 4 months). In contrast, 8/12 pts in Group B are alive, and 7/8 are without symptoms; 4/12 have died (average time to death 7 months) CONCLUSIONS: 1. Repeat BAV can be safely performed in selected pts and results in similar hemodynamic improvement when compared to the first procedure. 2. Pts with an increase in AVA after repeat BAV which is not as great as that achieved during the first procedure have a poor clinical course.

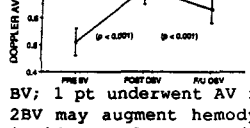
PERSISTENCE OF INCREASED DIASTOLIC STIFFNESS LATE FOLLOWING AORTIC VALVE REPLACEMENT
E. Scott Monrad M.D., Otto M. Hess M.D., Tomoyuki Murakami M.D., Hiroshi Nonogi M.D., William J. Corin M.D., Hans P. Krayenbuehl M.D., University Hospital, Zurich, Switzerland.

Patients with aortic stenosis have been shown to have an increase in passive diastolic stiffness at 1 to 2 years following aortic valve replacement (AVR), but the regression of myocardial hypertrophy has been shown to be incomplete at that time. To study the effect of further regression of myocardial hypertrophy after AVR on the passive diastolic properties of the left ventricle, we performed LV micromanometry, frame-by-frame biplane contrast ventriculography and LV endomyocardial biopsy in 15 patients before (PRE) and late (71±15 months) after (POST) AVR (8 for aortic stenosis, 7 for aortic insufficiency); the hemodynamic studies were also made in 10 controls (CON). Passive diastolic properties of the LV were assessed using the viscoelastic stress (ST) - strain (S, Lagrangian) model, where: $ST = ae^{BS} + dS/dt$.

| | WT | MMI | %FIB | B |
|---|---|---|---|---|
| CON | 0.82±0.07 | 88±14 | ---- | 10.6± 2.4 |
| PRE | 1.11±0.18* | 181±36* | 18.2± 6.7 | 19.7±11.0* |
| POST | 0.90±0.11*+ | 107±31*+ | 21.0±10.4 | 20.7± 8.9* |

- WT = LV wall thickness (cm); MMI = LV muscle mass index (g/M$^2$); %FIB = % myocardial fibrosis by light microscopy; B = dimensionless factor of myocardial stiffness as above; * = $p<0.05$ vs CON; + = $p<0.05$ PRE vs POST.
Conclusion: Despite the marked regression of myocardial hypertrophy late following AVR, there was a persistence of the elevated myocardial stiffness present preoperatively, paralleling the persistence of myocardial fibrosis.

DUAL BALLOON AORTIC VALVULOPLASTY, DESPITE AUGMENTING ACUTE HEMODYNAMIC IMPROVEMENT, FAILS TO PREVENT POST-VALVULOPLASTY RESTENOSIS
Constance D. Fields, M.D., Alexandra Lucas, M.D., Mark Desnoyers, M.D., Kenneth Rosenfield, M.D., Marjorie Caldiera, R.N., Natesa Pandian, M.D., F.A.C.C., Deeb Salem, M.D., F.A.C.C., Jeffrey M. Isner, M.D., F.A.C.C., St. Elizabeth's Hospital and New England Medical Center, Tufts Medical School, Boston, MA.
Balloon aortic valuloplasty (BV) performed with 1 or a series of single balloon catheters (1BV) has been compromised by a high incidence of restenosis. Having previously shown that use of a dual balloon technique (2BV) could augment hemodynamic improvement achieved using 1BV, we sought to determine whether such supplemental improvement would produce a more sustained result. We therefore followed (up to 15 mo post-BV) 26 pts in whom 1BV decreased peak gradient (PGr, mmHg) from 77±6 to 56±5* and increased aortic valve (AV) area (A, cm$^2$) from .43±.03 to .57±.04* (m±SEM; *=$p<.0001$); and in whom 2BV, performed immediately following 1BV, further decreased PGr to 34±3* and increased AVA to .76±.05*. Whereas 21/26 (81%) were NYHA Cl III-IV pre-BV, 14/15 (93%) were NYHA Cl I-II at 6-mo follow-up and 10/10 were Cl I-II at 12-mo follow-up . Nevertheless, non-invasive hemodynamic follow-up showed that despite initial improvement in Doppler-derived AVA (.51±.05 pre-2BV to .71±.06* post-2BV), Doppler-derived AVA




decreased to .63±.05* at mean follow-up of 7.9 mo, including 10 pts in whom AVA returned to pre-BV (baseline) value. Mortality included 3 pts who died 24 hrs, and 3 & 4 mo post-BV; 1 pt underwent AV replacement. Conclusion: although 2BV may augment hemodynamic improvement acutely, the incidence of restenosis observed post-BV using the 2BV technique remains high.

# Tuesday, March 21, 1989
# Poster Displayed: 2:00PM–5:00PM
# Author Present: 4:00PM–5:00PM
# Pacific Room, Anaheim Convention Center
# Peripheral Vascular Disease

**COMPARISON OF EXERCISE TESTING, DIPYRIDAMOLE THALLIUM IMAGING AND GATED BLOOD POOL SCANNING FOR THE PREDICTION OF CARDIAC COMPLICATIONS FOLLOWING VASCULAR SURGERY**

Terrence Ruddy, MD, FACC, Neil McPhail, MD, James Calvin, MD, FACC, Michel Sauvé, MD, Ross Davies, MD, FACC, Karen Gulenchyn, MD, Lyne Vigus, RN, Graeme Barber, MD, Clarence Cole, MD, University of Ottawa Heart Institute, Ottawa, Canada.

The value of exercise ECG testing (EX), LV ejection fraction (EF) by gated blood pool scanning and dipyridamole thallium imaging (THAL) for prediction of cardiac complications, was prospectively studied in 75 consecutive pts scheduled for vascular surgery. Ten pts with markedly abnormal tests (>2 mm ST↓, EF <20%, or THAL multivessel ischemia) were excluded, resulting in a final group of 65 pts. The attending clinicians were blinded to the noninvasive results. Complications occurred in 26 pts and included 2 deaths. EX was positive (≥1 mm ST↓) in 8/65 pts. EF was <50% in 13/65 pts. THAL showed myocardial ischemia in 35/65 pts.

| TEST | SENSITIVITY | SPECIFICITY | LIKELIHOOD RATIO | |
|---|---|---|---|---|
| | | | Positive | Negative |
| EX | 0.19** | 0.89* | 1.9 | 0.90 |
| EF | 0.31** | 0.87* | 2.4 | 0.35 |
| THAL | 0.88 | 0.69 | 2.9 | 0.17 |

(*=p<0.05, **=p<0.0001 vs THAL)

THAL had greater sensitivity for predicting cardiac complications compared to EX and EF. The specificity of THAL was less than EX and EF but reasonable. THAL had the largest positive and smallest negative likelihood ratios. Stepwise logistic regression showed THAL to be the most powerful predictor (improvement $X^2$=22.9, p<0.0001). EF had small but significant additional predictive value ($X^2$=3.9, p<0.05). Thus, THAL, with the greatest sensitivity and predictive power, is the optimal initial test for identifying high risk pts.

**ARTERIAL COLOR FLOW DUPLEX SONOGRAPHY OF THE LOWER EXTREMITIES BEFORE AND AFTER EXCIMER LASER ANGIOPLASTY**

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Nineteen patients studied by angiography prior to excimer laser angioplasty of the lower extremities were also imaged with color flow duplex sonography (CFDS). Angiography and CFDS obtained prior to angioplasty were compared for location of stenosis/occlusion and length of occlusion. In two patients with stenotic disease, 5 of 6 angiographic stenoses of >50% were correctly identified by CFDS. The remaining stenosis was identified as <50% by CFDS. The location of one stenosis was misidentified. Of 17 vessels occluded on angiography, 16 were accurately identified by CFDS. Occlusion location by CFDS was correct in all 16. In the one artery misidentified as patent, there was a >90% stenosis by CFDS. In vessels identified sonographically as occluded, estimation of occlusion length by CFDS was within 3 cm of angiographic appearance in all cases. In one patient CFDS showed a proximal occlusion of the superficial femoral artery not seen angiographically. The occlusion, confirmed at surgery, was found to be fresh thrombus. In 3 patients who experienced restenosis or reocclusion 2-4 months following laser angioplasty, the color flow duplex scan accurately diagnosed one total occlusion, and two stenoses. One restenosis was unsuspected by clinical history and both restenoses were successfully dilated.

**CONCLUSION:** 1. Color flow duplex sonography of the lower extremities correlates highly with angiographic appearance. 2. Color flow duplex sonography provides a simple, noninvasive method for following patients after laser angioplasty, allowing early detection of restenosis and therefore early treatment.

**INCIDENCE AND PROGNOSTIC SIGNIFICANCE OF EARLY POSTOPERATIVE SILENT ISCHEMIA IN PERIPHERAL VASCULAR SURGERY PATIENTS**

Pamela Ouyang, M.D., F.A.C.C., Gary Gerstenblith, M.D., F.A.C.C., William R. Furman, M.D., Peter J. Golueke, M.D., Sidney O. Gottlieb, M.D., F.A.C.C. Johns Hopkins Medical Institutions, Baltimore, MD.

Most perioperative complications in pts having peripheral vascular (PVD) surgery result from coronary disease (CAD). To see if peri-operative ST changes indicative of ischemia (STI) identifies higher risk pts, we studied 24 pts with stable CAD using 4-lead calibrated ambulatory ECG monitors (AECG) on the day before PVD surgery, intra-operatively, and for 29±10 hrs post-operatively (post-op). There were 17 men and 7 women, age 64±9 yrs; 17 pts had prior myocardial infarction (MI), 12 had prior angina, and 3 had prior coronary bypass surgery. General anesthesia was used in 19/24 pts. On blinded readings of AECG, 15/24 pts (63%) had asymptomatic STI perioperatively. All 15 had STI post-op (2.8±0.7 episodes/24 hrs, 30±7 min/episode), only 5 of these pts had intra- and only 3 pre-operative STI. Pts with and without STI did not differ as to anesthetic agent used, duration of vascular clamp time or of surgery, perioperative hyper- or hypotension, or peri-operative anti-ischemic medications. Of the 15 STI pts, 8 (53%) had inhospital ischemic events (2 MI, 2 new CHF, 4 new rest angina) compared to only 1 among the 9 pts without STI who had post-op angina (11%, p<.05).

Thus, early post-op STI is common in pts with CAD having PVD surgery and appears to predict subsequent inhospital clinical ischemic events. The immediate post-op period may be the optimum time when AECG can identify those pts who may benefit from continued close monitoring and additional anti-ischemic intervention.

Histological evaluation of "Vessel-Biopsies" obtained with the Simpson atherectomy catheter

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The Simpson atherectomy catheter enables the percutaneous removal of plaque material, thus providing the opportunity to study the process of re-stenosis. We evaluated 305 specimens from 52 primary stenoses (ST) and 9 re-stenoses (RE-S) of peripheral vessels.

Primary lesions (n= 52): a thickened, fibrotic intima was present in 100% of stenoses, media in 56% and adventitia never. Foam cells, inflammatory infiltrate and cholesterin clefts were seen in 34.6%, calcification in 15.4% and thrombi (fresh or organized) in 75%.

Re-stensoses (n=9, 5.4 ± 2.5 mo post-atherectomy): All showed a thickened intima with marked cellular proliferation; thrombi were found in 8, while foam cells and fibrosis in 7. Calcification was seen in 2. Media was present in all cases, adventitia never.

Conclusion: Obstructive tissue consists mainly of a fibrous thickened intima, although the entire spectrum of atherosclerosis could be identified; after atherectomy, the true plaque may sometimes remain deeper within the intima. Re-stenoses are characterized by marked cellular proliferation, fibrosis and the presence of foam cells. Therapy to prevent restenosis should be guided by these findings.

## Tuesday, March 21, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 2:00PM–3:00PM
## Pacific Room, Anaheim Convention Center
## Myocardial Ischemia with Normal Coronaries

### HISTOLOGICAL EVIDENCE OF CORONARY ARTERIOLOSCLEROSIS AS A CAUSE OF MYOCARDIAL ISCHEMIA IN PATIENTS WITH NORMAL CORONARY ARTERIOGRAMS

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To test the hypothesis that small-vessel disease can be a cause of clinically-defined myocardial ischemia, 20 pts with angina-like symptom and normal large coronary arteries were studied (8 men and 12 women, mean age: 55±7 years). Endomyocardial biopsy specimens were obtained from the left ventricle with a Cordis biotome introduced percutaneously through the femoral artery puncture. Three to five specimens from different sites were taken. Rapid atrial pacing resulted in ischemic ST depression associated with angina-like chest discomfort in all pts. Histologic examination of an endomyocardial biopsy specimen revealed slight to moderate interstitial fibrosis (17 of 20 pts), suggesting ischemic injury, and marked medial thickening of coronary arterioles about 30 to 100 micrometer outer diameter. The thickening was observed to be caused by proliferation of smooth muscle cells, hyaline degeneration, and an increase in collagen in the media, suggesting reduced vasodilatory reserve. Electron microscopic studies for evaluation of metabolic alterations revealed secondary lysosomes, cytoplasmic deposition of glycogen granule and intramitochondrial glycogen in viable myocytes. These might be ultrastructural responses to ischemic injury and myocardial ischemia.
These results suggest that in patients with angina-like symptoms and normal large coronary arteries, (1) there exists ultrastructural evidences of myocardial ischemia, and (2) coronary arteriolosclerosis can be one of the major mechanisms for reduced coronary flow reserve.

### LONG-TERM FOLLOW-UP AND VARIABILITY OF MARKERS OF MYOCARDIAL ISCHEMIA IN SYNDROME X

Giuseppe Pupita M.D., Juan C. Kaski M.D., Alfredo R. Galassi M.D., Margarita Vejar J M.D., Attilio Maseri M.D. FACC. RPMS, Hammersmith Hospital, London U.K.

To evaluate the long-term course of myocardial ischemia in patients (pts) with syndrome X (typical angina pectoris, positive exercise test, no evidence of coronary spasm or left ventricular hypertrophy and angiographically normal coronary arteries), we studied 13 pts, 10 f and 3 m, mean age 49±7 years. Clinical and ECG parameters as well as exercise test and Holter monitoring (H) were assessed both when the diagnosis was first established (A) and after a mean follow-up (F) of 6.3 years (range 3-9). Mean number of anginal episodes and NTG consumption/week were similar at A and F and only 2 of the pts had pain-free periods of at least 1 month. In none of the pts serious coronary events, left ventricular failure or bundle branch block developed during F. Exercise time (T), heart rate (HR) and rate-pressure product (RPP) at 1 mm of ST depression at A and F were similar:

| | +ve test | Angina | T | HR | RPP |
|---|---|---|---|---|---|
| A | 13 | 13 | 594±178 | 134±20 | 20363±5264 |
| F | 13 | 13 | 631±202 | 139±17 | 21648±6173 |

24-hour H at A and F showed similar results regarding number of episodes of ST depression ≥ 0.1 mV (31 vs 25), proportion of painful episodes (39 vs 36%) and of episodes preceded by an increase in HR (39 vs 32%). Thus, although syndrome X seems to have a benign prognosis, angina and ECGgraphic signs of ischemia tend to persist unchanged during long periods and adversily affect lifestyle in a sizable proportion of pts.

### ROLE OF α-ADRENERGIC RECEPTORS IN SYNDROME X

Alfredo R. Galassi M.D., Juan C. Kaski M.D., Giuseppe Pupita M.D., Margarita Vejar J M.D., Attilio Maseri M.D. FACC RPMS, Hammersmith Hospital, London, U.K.

Patients (pts) with syndrome X (typical angina pectoris, positive exercise test, no coronary spasm and angiographically normal coronary arteries) have a reduced coronary flow reserve due to inadequate dilatation of small resistive vessels. To assess if α-adrenergic receptors play a role in the genesis of ST ischemic changes in syndrome X, 10 such pts mean age 50±8 years underwent exercise testing (E) and 24-hour Holter monitoring (H) off treatment (OFF), and following α-blockade with prazosin (P) 2mg 12 hrly and clonidine (C) 0.20 mg 8 hrly on separate weeks. During clonidine therapy, 4 pts dropped out early, due to drug side-effects. Comparative E results regarding exercise time (T), double product (RPP) at 0.1 mV ST depression and number of pts with positive tests as well as H results, were:

| | pts | | Exercise testing | | Holter monitoring | |
|---|---|---|---|---|---|---|
| | Positive(n) | | T(secs) | RPP(mmHg/bpm) | episodes(n) | ↑HR* |
| OFF | 10 | 10 | 617±203 | 23857±6125 | 23 | 4 |
| P | 10 | 10 | 663±201 | 22098±4816 | 22 | 7 |
| C | 6 | 6 | 668±76 | 23547±2530 | 13 | 2 |

*= preceded by an increase of heart rate.

Seven patients also underwent a phenylephrine test which did not induce ST ischemic changes in any of the 7 pts although 2 had chest pain. These findings suggest that α-adrenergic receptor mediated mechanisms do not play a detectable role in the genesis of transient ischemic episodes in pts with syndrome X.

### BETA-BLOCKERS IN SYNDROME X.

R.Bugiardini,M.D.,F.A.C.C., A.Borghi,M.D., L.Biagetti,M.D., F.A.Nicolini,M.D., P.Puddu,M.D.
Institute of Patologia Medica, Univ. of Bologna, Italy.

Pts with angina pectoris and normal coronary angiograms (syndrome X: SX) have been found to have an inadequate vasodilatory capacity of the coronary microcirculation. However the mechanisms of ischemia, thus the therapeutic management of these pts, remain to be determined. We compared the effects of oral verapamil (V: 320 mg/day), propranolol (P: 160 mg/day) and placebo in 16 pts presenting with the above set of findings and documented transient myocardial ischemia during their daily life. Testing was done according to a randomized double-blind crossover,placebo-controlled trial consisting of 3 consecutive 7 day treatment periods. Pts underwent continuous 48 hour electrocardiographic monitoring during the last 2 days of each period. A total of 391 episodes of diagnostic ST↓ was recorded during the trial. Of these, 23 were symptomatic. None of the episodes occurred while asleep, 25% during exercise, 35% during minimal physical activity and 40% at physical rest. The latter occurred more during activities demanding mental arousal (conversation,reading or watching TV). Heart rate at the onset of ST↓ was higher (≥ 10 bpm) than that observed in the 5 minutes preceding ischemia in 95% of the episodes. In the group as a whole, the average number of ischemic episodes per 24 hours was significantly reduced during P, as compared to placebo (0.7±0.6 vs 3.9±1.8,p<0.005). Conversely, no significant differences were seen during V treatment. We conclude that transient myocardial ischemia in pts with SX as well as reduced coronary flow reserve is mostly precipitated by an increase in oxygen demand due to a heightened sympathetic activity. Accordingly,, beta-blockers may represent the first line of treatment.

# Tuesday, March 21, 1989
# Poster Displayed: 2:00PM–5:00PM
# Author Present: 3:00PM–4:00PM
# Pacific Room, Anaheim Convention Center
# Pulmonary Hypertension

## PATHOLOGICAL INVOLVEMENTS OF LEFT VENTRICLE IN CHRONIC COR PULMONALE

Akio Kohama, Jun Tanouchi, Ken Ishihara, Masatsugu Hori, Akira Kitabatake, Takenobu Kamada, Osaka University School of Medicine, Osaka, Japan.

To determine whether the left ventricle is involved in chronic cor pulmonale, we studied 24 autopsied hearts : 10 of chronic lung disease with right ventricular hypertrophy (RVH) in their electrocardiograms (A), 8 of chronic lung disease without RVH (B) and 6 of extracardiopulmonary disease (C). In each case other cardiovascular diseases were not complicated. In both right ventricle and left ventricle, ventricular weight, wall thickness, myocyte diameter and percent area of fibrosis (%F) were measured in the preparations. After taking photographs of Azan-Mallory stained histological sections of both ventricles, we traced the covering transparent films at the site of blue portions (collagen fiber) on the photographs. We cut off the tracing portions from the copied papers of the films and weighed the papers, then calculated the percent weight of collagen fiber which we used as the percent area of fibrosis.

| | A | B | C | |
|---|---|---|---|---|
| LV-%F(%) | 3.0±1.0 | 1.8±0.6 | 1.8±0.8 | p<0.01 |

Although there was no significant difference in left ventricular mass among the three groups, cellular hypertrophy and myocardial fibrosis were frequently observed in left ventricle in chronic cor pulmonale. In both ventricles cellular diameter was significantly correlated with percent area of fibrosis. Percent area of fibrosis of left ventricle was significantly correlated with that of right ventricle. Thus, we conclude that the left ventricle is also involved pathologically in chronic cor pulmonale and that left ventricular function can be impaired due to not only functional factors as hypoxemia and deformity of left ventricle but also organic factors as cellular hypertrophy and myocardial fibrosis in left ventricle.

## GRANULOCYTE ACTIVATION AUGMENTS HYPOXIA-INDUCED PULMONARY HYPERTENSION IN VIVO.

Nancy J. Davenport M.D., Ph.D., Linda M. Bradley M.D., F.A.C.C., Robert E. Goldstein M.D., F.A.C.C., U.S.U.H.S., Bethesda, MD.

Clinical and experimental data suggest that granulocyte activation may be a major mediator of pulmonary hypertension accompanying inflammatory lung disorders, such as adult respiratory distress syndrome. Hypoxia can also contribute significantly to pulmonary hypertension. Although granulocyte activation and hypoxia are both likely to occur in diseased lungs, the results of their interaction in vivo are unknown. We studied the effects of phorbol myristate acetate (PMA), a known potent granulocyte activator, on pulmonary hemodynamics during normoxia (systemic arterial $pO_2$ 80–150 mm Hg) and during hypoxia ($pO_2$ 30–50 mm Hg). Eight pigs had closed-chest measurement of pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) before and after PMA, 0.1 µg/kg i.v. Mean PAP (mm Hg) and PVR (dyne sec $cm^{-5}$) ± SEM were:

| | Normoxia: PAP/PVR | Hypoxia: PAP/PVR |
|---|---|---|
| Pre-PMA | 21±2/270±30 | 36±3/456±190 |
| Post-PMA | 32±2*/501±150* | 46±1*/816±170* |

*p <0.05 vs. pre-PMA

Our results show that PMA added significantly and independently to the actions of hypoxia in raising PAP and PVR. Reversal of hypoxia promptly reduced PAP and PVR to pre-hypoxic baselines in the presence or absence of PMA. The data suggest that suppression of granulocyte activation may substantially enhance hemodynamic benefits of reversing hypoxia when treating pulmonary hypertension caused by an inflammatory lung disorder.

## ECHO/DOPPLER AND CATHETERIZATION CORRELATES OF SURVIVAL IN PRIMARY PULMONARY HYPERTENSION

Susan B. Eysmann, M.D., Harold I. Palevsky, M.D. Nathaniel Reichek, M.D., F.A.C.C., Keith Hackney, Pamela S. Douglas, M.D., F.A.C.C. University of Pennsylvania, Philadelphia, Pennsylvania.

Prognosis in primary pulmonary hypertension (PPH) is highly variable and difficult to predict. To determine correlates of survival in PPH, we compared 50 echo/Doppler and catheterization variables with outcome in 26 patients. Mean follow-up was 20 months (2-52) in 10 survivors, mean survival was 5 months (0-34) in 16 nonsurvivors. Univariate Cox lifetable analysis correlated 8 variables with early death ($p \leq .05$) and the data distribution was examined to select critical values: severity of pericardial effusion, heart rate (HR; > 87bpm), pulmonic flow acceleration time (≤ 62ms), tricuspid early flow deceleration (TDec; ≤ -300$cm^2/s$), mitral early to atrial flow velocity ratio (M-E/A; ≤ 1.0), cath cardiac index (CI; ≤ 2.3 $l/min/m^2$), mean and diastolic pulmonary pressures (> 61, > 43 mmHg). Multivariate analysis showed TDec, M-E/A, CI to be independently related to death ($p = .0014$). Mortality increased with the number of critical values reached: if 0(0% mortality), 1(50%), 2(75%), 3(100%). Analysis of invasive variables alone related only CI to death ($p = .0140$), while analysis of echo variables alone related TDec, M-E/A, HR to poor survival ($p = .0016$); mortality increased with the number of echo/Doppler critical values reached: 0(20%), 1(37%), 2(88%), 3(100%).

Thus, both echo/Doppler and hemodynamic variables yield valuable information regarding outcome in PPH. The prognostic power of echo is not substantially improved by invasive testing.

## IS DIGITAL VASOCONSTRICTION A MARKER FOR REVERSIBLE PULMONARY VASOCONSTRICTION IN PATIENTS WITH PULMONARY HYPERTENSION?

Peter B. Wilson MD, David J. Pinsky MD, Gerald W. Neuberg MD, Marrick L. Kukin MD, Norma Medina RN, Madeline Yushak RN, Milton Packer MD, FACC. Mt. Sinai School of Medicine, New York, NY

Previous investigators have suggested that pts with pulmonary hypertension (PH) who have digital vasoconstriction (Raynaud's phenomenon) are likely to have pulmonary vasoconstriction as the cause of their PH. To test this hypothesis, we evaluated the responsiveness of the pulmonary vasculature to the vasodilator, nifedipine (NIF, 20 mg orally), in 20 pts with PH, of whom 10 had Raynaud's phenomenon (+Rayn) and 10 did not (-Rayn). Stroke volume index (SVI, $ml/m^2$), heart rate (HR, bpm), mean systemic arterial, mean pulmonary arterial and right atrial pressures (MAP, PA & RA, mm Hg), and systemic vascular and total pulmonary resistances (SVR and TPR, d-s-c) were measured before (pre) and 30-60 min after NIF in both groups; * = p <0.05.

| | | SVI | HR | MAP | PA | RA | SVR | TPR |
|---|---|---|---|---|---|---|---|---|
| + Rayn | Pre | 23 | 88 | 93 | 53 | 8 | 2491 | 1706 |
| | NIF | 25 | 101* | 73* | 44* | 10 | 1525* | 1160* |
| - Rayn | Pre | 23 | 83 | 90 | 63 | 15 | 1925 | 1665 |
| | NIF | 23 | 87 | 67* | 52* | 17 | 1232* | 1339* |

Pts with Raynaud's did not show more favorable hemodynamic responses to NIF than pts without Raynaud's. Both groups showed similar ↓ in PA pressure, but SVI failed to ↑ significantly in either group, despite the ↓ in RV afterload. Both groups showed similar ↓ in TPR, but the mean ↓ in SVR exceeded the mean ↓ in TPR in pts with and without Raynaud's. Individually, only 5 of 20 pts (3 +Rayn and 2 -Rayn) demonstrated a selective pulmonary vasodilator effect with NIF (%↓ in TPR > %↓ in SVR), and only 2 of 20 pts (1 +Rayn and 1 -Rayn) improved clinically.

In conclusion, PH pts with Raynaud's do not respond more favorably to vasodilator therapy than PH pts without Raynaud's. These data suggest that digital vasoconstriction does not reflect the presence of reversible pulmonary vasoconstriction in PH pts.

## Wednesday, March 22, 1989
## 10:30AM–12:00NOON, Anaheim Room
## Anaheim Convention Center
## Thrombolytic Therapy in Acute Myocardial Infarction: I

ECONOMIC ADVANTAGES OF A CONSERVATIVE STRATEGY FOR AMI MANAGEMENT: rt-PA WITHOUT OBLIGATORY PTCA.
Edgar D. Charles, PhD, William J. Rogers MD, FACC, Guy S. Reeder MD, FACC, James H. Chesebro MD, FACC, Silvio E. Papapietro MD, FACC, Larry Maske RN, Alfred A. Bartolucci PhD. UAB Med. Center, Birmingham, AL & Mayo Clinic, Rochester, MN.

In order to assess the economic impact of PTCA following rt-PA for acute myocardial infarction (AMI), we collected total hospital charges (including professional fees) in 329 patients with AMI treated within 4 h onset of symptoms in the TIMI Phase II study at Birmingham, AL, and Rochester, MN. Included were patients from the TIMI II-A and II-B sub-protocols who were randomized to receive PTCA within 2 h if feasible (II-A only), PTCA at 18-48 h if feasible, or no angiography/PTCA unless mandated by uncontrollable clinical ischemia. Employment and income status were also assessed in 210 of these patients reaching 1 yr follow-up.

| | 2 h PTCA N = 60 | 18-48 h PTCA N = 137 | No PTCA N = 132 | p |
|---|---|---|---|---|
| Days Hospitalized | 11.3 | 9.5 | 10.2 | .06 |
| PTCA Performed | 60% | 55% | 20% | .001 |
| CABG Performed | 17% | 17% | 14% | .74 |
| Total Hospital Charges | $20,301 | $18,982 | $16,076 | .01 |
| Employed at 1 year/ employed at entry | 78%(21/27) | 89%(50/56) | 92%(46/50) | .17 |
| Unchanged income at 1 year | 60%(26/43) | 73%(63/86) | 80%(64/80) | .07 |

Thus, the more conservative strategy without PTCA or CABG unless dictated by uncontrollable ischemia resulted in savings of 15-21% in total hospital charges while yielding similar 1 year employment and income profiles. The conservative strategy saved approximately $2900-$4200/patient, and, if utilized in the 0.25-1.0 million US patients with AMI each year eligible for thrombolytic therapy, would save 0.7 to 4.2 billion dollars, compared to the more aggressive obligatory PTCA strategies.

EARLY THROMBOTIC REOCCLUSION AFTER SUCCESSFUL CORONARY THROMBOLYSIS IS PREDICTABLE FROM AN INCREASED THROMBIN RELEASE TWO HOURS AFTER ONSET OF THERAPY
Dietrich C. Gulba, M.D., M.Sc.; Gert-H. Reil, M.D.; Monika Barthels, M.D.; Wolf Rafflenbeul, M.D.; Wilhelm Möller, M.D.; Paul R. Lichtlen, M.D., F.A.C.C.
Hannover Medical School, Hannover, FRG

Thrombolytic therapy (TT) in a subset of patients leads to increased thrombin release, measureable as increased thrombin-antithrombin III- blood levels. This might be related to early reocclusions after successful TT in acute MI. In 55 consecutive patients (pts) undergoing TT for MI we tested whether increased TAT-levels may predict early reocclusion. Patency was assessed by angiography 60 min and 24-36h after onset of TT.
Results: TAT µg/l

| group | n | 0 | 60 | 120 min | sign. |
|---|---|---|---|---|---|
| A | 26 | 9.7 ± 14.9 | 4.7 ± 2.6 | 3.7 ± 1.4 | p< 0.05 |
| B | 16 | 7.7 ± 10.1 | 12.6 ± 14.9 | 13.6 ± 10.3 | p< 0.1 |
| C | 13 | 5.9 ± 3.5 | 14.8 ± 15.1 | 19.0 ± 18.7 | p< 0.05 |

group A: uneventful clinical course; group B: non successful TT; group C: early thrombotic reocclusion

Group A pts were seperated at 120 min from group B and C pts by TAT values ≤ 6 µg/l (p < 0.001; sensitivity 96.2%; specificity 93.1%). In the 39 pts with primary patent infarct related coronary artery (group A+C) reocclusion was predicted by TAT levels > 6 µg/l (p < 0.001; sensitivity 96.2%; specificity 100 %). We conclude that TAT levels > 6 µg/l 2h after onset of thrombolysis are sensitiv and specific marker for an unfavourable outcome of thrombolysis while TAT levels < 6 µg/l indicate a uneventful clinical course.

PREHOSPITAL THROMBOLYTIC THERAPY - MITI PROJECT REPORT ON PHASE I: FEASIBILITY, CHARACTERISTICS OF PATIENTS
W. Douglas Weaver MD, FACC, Jenny Martin RN, Paul Litwin MS, Mickey Eisenberg MD, Mary Ho MD, Peter Kudenchuk MD, for the MITI Project Investigators, University of Washington, Seattle, WA.
During Phase I of the Myocardial Infarction, Triage and Intervention Project, pts are evaluated by paramedics and remote physiican for potential treatment with t-PA. Of the first 1871 chest pain pts, 35% were ≥75 yrs, 16% had pain >6 hrs, 16% had hypertension, 13% history of stroke/altered mental status. The time from onset of pain to medic evaluation was 52±60 (median=27) min; 17±10 min were required for evaluation and transmission of a 12-lead cellular ECG to the physician. Seventy-nine of the chest pain pts (4%), or 30% of those with acute myocardial infarction (AMI), were prehospital t-PA candidates. Initiation of t-PA by paramedics would have saved 21±9 min of transportation time plus 56±39 min from hospital admission until treatment. Of the AMI pts that medics excluded, 21% received t-PA at hospital. Mortality for the paramedic included/excluded AMI pts were 2% and 14%, respectively. Treatment in the excluded group began 76±74 min after hospital arrival; significantly later than in pts receiving prehospital ECGs (p<0.01). Conclusion: Paramedics with a remote physician can screen pts for t-PA using 12-lead cellular ECGs, saving 1-1.5 hours and allowing treatment 76±62 min after the onset of AMI.

EARLY REPERFUSION AFTER TREATMENT WITH INTRAVENOUS PRO-UROKINASE WHEN COMPARED TO INTRAVENOUS STREPTOKINASE.
F.Vermeer, J.Meyer, F.W.Bär, R.Erbel, D.Mathey, R.Uebis, M.El Deeb, J.P.Monassier, P.Westerhof, H.Boss, H.Gülker, B.Charbonnier, R.Seabra-Gomes, P.Probst, J.Heikkilä, G.Strupp, U.Schmitz-Huebner, H.J.Trampisch, I.Massberg, H.Barth. Dept. of Cardiology, University of Limburg, University Hospital Maastricht, The Netherlands.

In a randomized, double blind study (PRIMI trial) 80 mg of intravenous pro-urokinase (rscu-PA, 198 pts) was compared with 1.5 Mio IU of i.v. streptokinase (Sk, 203 pts). Treatment was given within four hours after onset of symptoms in pts with a first myocardial infarction. Coronary angiography was performed at 60 min, at 90 min, and 24 to 36 hours after the start of the infusion. Patency rates at 60 min were 71% after rscu-PA and 48% after Sk (p < 0.001). Patency at 90 min after rscu-PA was 72% vs. 64% after Sk (p = 0.09). Angiographically documented reocclusion (within 24 hours) was seen in 6 pts treated with rscu-PA vs. 5 pts in the Sk group. In-hospital mortality was low in both groups: 7 pts died in the rscu-PA group (4%) vs. 10 pts in the Sk group (5%). Four cerebrovascular accidents were reported, two in each group (1%). Reinfarctions were seen in 4% after rscu-PA vs. 3% after Sk. Significant bleeding was lower after rscu-PA (26 pts) than after Sk (49 pts; p = 0.005). Blood transfusion was required in 9 pts after rscu-PA vs 23 pts after Sk (p = 0.02). Decrease in fibrinogen was less pronounced after i.v. rscu-PA (mean 20% of baseline value) than after Sk (6% of baseline value; p < 0.001).

CONCLUSIONS: After intravenous administration of pro-urokinase in a direct comparison to i.v. streptokinase 1) patency rates are higher and reperfusion is reached at an earlier stage, and 2) bleeding complications are less frequent and less severe.

## RISK FACTORS FOR HEMORRHAGIC AND ISCHEMIC STROKE IN MYOCARDIAL INFARCT PATIENTS TREATED WITH TISSUE PLASMINOGEN ACTIVATOR

Ralph Althouse MD, MPH, Charles Maynard PhD, Michele Olsufka RN and J.Ward Kennedy MD, FACC U. of Washington, Seattle. WA.

We prospectively studied risk factors for stroke in 1028 consecutive MI pts admitted to 8 hospitals in 1988. Pts ≤ 75 yrs old with ST elevation and chest pain for ≤ 6 hrs were eligible for our tissue Plasminogen Activator (tPA) study: those with a contraindication to tPA treatment, sustained diastolic blood pressure (DBP) ≥ 120 mmHg or history of stroke were excluded. 160 pts (16%) were treated with tPA and 868 were not. Ten received 150 mg tPA and the remainder 100 mg over 6 hrs; all received IV heparin. 19/868 pts (2%) were treated with thrombolytic drugs outside of the study. Strokes were classified as intracerebral hemorrhage (ICH) or intracerebral infarction (ICI).

ICI occurred in 2/160 tPA pts (1.3%) and in 11/868 pts not given tPA (1.3%). ICH occurred in 3/160 tPA pts (1.9%) and 0/868 pts not given tPA (p=0.004). The incidence of ICH was 2/12 (17%) in pts with "transient" systolic blood pressure (SBP) ≥ 180 mmHg (which resolved rapidly prior to tPA treatment) compared to 1/147 (0.6%) with lower SBP (odds ratio=24, p=0.015 Fisher exact two-tailed). In pts with transient DBP ≥120 mmHg, the ICH rate was 2/9 (22%), compared to 1/147 (0.6%) with lower DBP (odds ratio=33, p=0.009). ICH occurred in 2/18 pts (11%) taking aspirin on admission, compared to 1/142 (0.7%) not on aspirin (odds ratio=16, p=0.03). Known risk factors for spontaneous ICH including male sex, age, black race, history of hypertension (HTN), and cigarette smoking were not associated with ICH following tPA. Known risk factors for spontaneous ICI including male sex, age, history of HTN and transient HTN were not associated with ICI in pts not treated with tPA.

We conclude that tPA treatment was associated with an excess of ICH without changing the incidence of ICI. Furthermore, risk factors for spontaneous ICH were not associated with ICH in pts treated with tPA. Pts with "transient" HTN immediately prior to tPA infusion, or who were taking aspirin were at increased risk of ICH during tPA treatment.

## TOMOGRAPHIC ASSESSMENT OF MYOCARDIAL REPERFUSION DURING ACUTE MYOCARDIAL INFARCTION USING Tc-99m METHOXY ISOBUTYL ISONITRILE (MIBI)

Raymond J. Gibbons, M.D., FACC, Mario S. Verani, M.D., FACC, Patricia A. Pellikka, M.D., Thomas Behrenbeck, M.D., John J. Mahmarian, M.D., James H. Chesebro, M.D., FACC, Frans J. Wackers, M.D., FACC

Tc-99m MIBI was injected intravenously in 15 patients during acute myocardial infarction (EARLY) and 6 to 14 days later (LATE). Ten patients were treated with intravenous thromblytic therapy after EARLY Tc-MIBI; 8 of 10 had patent arteries on subsequent angiography. Five control patients did not receive thrombolytic therapy, and had documented arterial occlusion. The absence of myocardial redistribution of Tc-MIBI permitted tomographic imaging up to 8 hours after intravenous injection to determine the extent of hypoperfused myocardium (%LVHYPO) at the time of injection. %LVHYPO was quantitated using a technique validated in phantoms (r=0.99 between true defect and measured defect). %LVHYPO measured EARLY varied from 9% to 68%, indicating a wide range of myocardium at risk. %LVHYPO measured LATE correlated significantly (r=-0.83, p=.0002) with LATE resting ejection fraction and with LATE regional wall motion score in the infarct segment (r=-0.94, p=.006 for anterior infarcts; r=-0.90, p=.02 for inferior infarcts), indicating its validity as a measure of infarct size. There was a significant decrease in %LVHYPO between the EARLY and LATE studies in the treated patients (-12% ± 12%, p=.01), suggesting myocardial salvage due to reperfusion. There was an insignificant increase in %LVHYPO in the control patients (4% ± 6%). Conclusion: The change in %LVHYPO determined by tomographic Tc-MIBI EARLY and LATE is a promising measurement tool for the assessment of the efficacy of interventions in acute myocardial infarction.

# Wednesday, March 22, 1989
# 8:30AM–10:00AM, Marriott Hall North
# Anaheim Marriott Hotel
# Pharmacology of Calcium Channel Antagonists

## EFFECTS OF LOW DOSE NIFEDIPINE ADMINISTRED THROUGH THE CORONARY SINUS IN ISCHEMIC HEART DISEASE.

Jacques Berland M.D., Jean-Christian Farcot M.D., FACC, Thierry Savin M.D., Alain Cribier M.D., FACC, Brice Letac M.D., FACC. ROUEN, FRANCE.

To determine the potential of coronary venous retroinfusion (RInf) to selectively deliver drugs in the myocardium, we assessed the effects of coronary sinus (CS) RInf low dose of Nifedipine (NIF, 200 mcg) on global and regional left ventricular (LV) function in 11 patients (Pts). After standard RAO LV angiogram and coronary arteriography, a special three lumens balloon catheter was inserted through an antecubital vein in the CS and its tip placed in the great cardiac vein. CS was occluded for one minute and 10 ml 5% glucose (control Pts, n=3) or 10 ml 5% glucose + NIF (n=8 Pts) were infused in the great cardiac vein under continuous CS pressure (P) monitoring. During RInf mean CSP increased from 7 ± 5 to 30 ± 10 mmHg p<0.001. Then a second LV angiogram was performed. Heart rate (HR), ejection fraction (EF%) and anterior wall motion shortening (AWM) before and after CS RInf were compared. In control Pts, as well as in 4 Pts without coronary disease in whom NIF was retroinfused, no changes in hemodynamic or contractility occured. On the opposite in 4 Pts with significant LAD stenosis HR increased by 21% and EF dropped by 13% which was due to a decrease in AWM by 31%.

Conclusions : 1) short term CS occlusion and 10 ml RInf of 5% glucose does not carry out adverse effects.
2) RInf of low dose NIF induces regional wall motion abnormalities only in Pts with LAD stenosis. This effect, which mimicks intracoronary NIF injection, suggests that NIF reaches the LV anterior wall and therefore that in ischemic heart disease RInf have a potential for selective delivery of drugs in this area.

## A NEW INTRACELLULAR CALCIUM ANTAGONIST, HA-1077, AN ISOQUINOLINE DERIVATIVE, INHIBITS QUIESCENT BOVINE ARTERIAL SMOOTH MUSCLE CELL PROLIFERATION.

Manabu Shirotani M.D., Yoshiki Yui M.D., Mamoru Takahashi M.D., Takeshi Aoyama M.D., Yoshiharu Murohara M.D., Hiroshi Morishita M.D., Kazushige Kadota M.D., Yoshiki Takatsu M.D., and Chuichi Kawai M.D. F.A.C.C., Third Division, Department of Internal Medicine, Faculty of Medicine, Kyoto University, Kyoto, Japan.

The effect of HA-1077 (HA), isoquinoline-sulfonyl homopiperazine, a new intracellular calcium antagonist, was examined on growth of cultured bovine vascular smooth muscle cells (BVSMC). Growth-arrested BVSMC were plated ($4x10^4$cells/dish) and stimulated with 5% fetal calf serum (FCS). Cell numbers were counted on the following days. ($x10^4$cells, M±SEM) *p<0.01 vs. control(0μM of HA)

| | Concentration of HA (μM) | | | | |
|---|---|---|---|---|---|
| DAY | 0 | 10* | 30* | 50* | 100* |
| 1 | 6.1±0.4 | 6.1±0.4 | 5.6±0.3 | 4.2±0.2 | 4.1±0.2 |
| 2 | 17.9±1.6 | 13.1±0.5 | 8.4±0.5 | 6.5±0.3 | 5.2±0.3 |
| 3 | 23.7±0.9 | 22.3±0.7 | 17.2±0.3 | 14.5±0.5 | 6.7±0.4 |
| 4 | 36.3±0.9 | 34.8±1.5 | 28.9±1.4 | 19.0±1.1 | 9.8±0.8 |

HA (10, 30, 50, and 100μM) inhibited $^3$H-thymidine uptake stimulated by 5% FCS by 20±3%*, 36±2%*, 50±1%*, and 70±1%* (*p<0.01) . HA, 10 and 30μM, also inhibited $^3$H-thymidine uptake stimulated by 1-hour exposure to platelet-derived growth factor(10ng/ml) and subsequent 23-hour incubation with 10μg/ml bovine insulin by 22±3%* and 29±3%* respectively (*p<0.01). This inhibition was observed when HA was present at the time of the initial exposure. **Conclusions**: In cultured quiescent BVSMC, HA inhibits cell proliferation and DNA synthesis dose-dependently. Since platelet-derived growth factor here worked as a competent factor, it is suggested that HA suppresses at least $G_0$-$G_1$ transition.

MODIFICATION OF MYOCARDIAL ISCHEMIA AND DYSFUNCTION BY NIFEDIPINE AND NITROGLYCERIN DURING CORONARY OCCLUSION

Ivo Amende M.D., F.A.C.C., Gunhild Herrmann M.D., Rüdiger Simon M.D., F.A.C.C., Paul R. Lichtlen M.D., F.A.C.C., Hannover Medical School, Hannover, FRG

We evaluated whether pretreatment with nitroglycerin (NTG) and nifedipine (NIF) protects the myocardium against ischemia induced by coronary occlusion during angioplasty. We studied the effects of 0.1 mg intracoronary (ic) NIF in 18 Pts and of 0.2 mg ic/iv NTG in 20 Pts during 60 sec occlusion on the ic epicardial ECG and pulmonary wedge pressure (PWP). NTG produced a significant fall in PWP before (10 to 7 mmHg) and at 60 sec occlusion (19 to 14 mmHg) and delayed the appearance of the rise in PWP >5 mmHg from 16 to 26 sec. NTG had no effects on maximal ST segment shifts of the ic-ECG (1.8 to 1.8 mV) and did not delay the onset of ischemic ST segment elevation >0.5 mV (14 to 15 sec). In contrast, NIF significantly reduced maximal ST segment shifts during occlusion (2.2 to 1.5 mV) and delayed the onset of ischemic ST segment elevation (11 to 21 sec). NIF significantly delayed the appearance of the rise in PWP (23 to 38 sec) but had no effects on PWP before (9 to 11 mmHg) and at 60 sec occlusion (23 to 22 mmHg). In conclusion, NTG delays the rise in filling pressure and limits its extent but has little effect on ischemic ic-ECG changes during occlusion. NIF delays the rise in filling pressure but does not affect its magnitude. NIF, however, delays the onset of ischemia in the ic-ECG and reduces its extent indicating protection of regional ischemic myocardium.

NIFEDIPINE DOES NOT ALTER THE VENODILATORY RESPONSE TO NITROGLYCERIN.

William P. Apollo B.S., Robert Zelis M.D. F.A.C.C., Joseph A. Gascho M.D. F.A.C.C., Penn State University School of Medicine, Hershey, Pennsylvania.

Although many patients with coronary artery disease take both calcium channel blockers and nitrates, it is not known if the calcium channel blockers alter the venodilatory response to nitroglycerin (TNG). We therefore measured the venodilatory effect of TNG (0.8 mg lingual spray) 35 minutes after placebo on one day and after the calcium channel blocker nifedipine (10 mg p.o.) on another day in 12 healthy fasting supine male volunteers, age 25±1 (SEM) yrs, on no medications. Studies were performed in a warm quiet room. In 7 of 12 subjects placebo was given on day 1 and nifedipine on day 2; in the other 5 the order was reversed. The equilibration technique was used to measure the venodilatory effect of TNG. The change in forearm volume at 30 mmHg above baseline venous distending pressure (VV[30], cc/100 cc arm) induced by TNG was considered to be the venodilatory effect of TNG.

Compared to placebo, nifedipine caused a significant fall in diastolic pressure (-3±1 mmHg) and rise in heart rate (+7±2 b/min), but did not venodilate (4.23±0.23, nifedipine; 4.03±0.34 cc/100 cc arm, Placebo, p=NS).

Effects of TNG on Hemodynamics and VV[30]

| | HR | Systolic BP | Diastolic BP | VV[30] |
|---|---|---|---|---|
| Placebo | +6±1 | -2±1 | -7±2 | +0.72±0.13 |
| Nifedipine | +8±2 | -1±1 | -6±2 | +0.70±0.09 |

n=12; x̄±SEM; *p<0.05 vs Placebo

Conclusions: (1) Nifedipine dilates arterioles but not veins; (2) Nifedipine neither attenuates nor accentuates the arteriolar dilatory or venodilatory response to TNG.

EFFECT OF DILTIAZEM ON CORONARY FLOW RESERVE IN MAN.

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Coronary flow reserve (CFR) is substantially diminished by IV calcium channel antagonists (CCA) in conscious dogs. This attenuation of coronary dilation has been postulated as one of the mechanisms responsible for the anti-anginal effects of CCA. Furthermore, use of CCA in patients could alter assessment of CFR. To determine if observations in dogs could be extended to patients, we examined the effect on CFR of diltiazem (DT) given by the IV (n=9, 125 or 250 mcg/kg bolus then 5 mcg/kg min infusion) or intracoronary (IC) (n=9, 150-600 mcg bolus) routes in patients without coronary obstruction. CFR was measured with a 3F coronary Doppler catheter as the ratio of peak to resting coronary blood flow velocity (CBFV) after a maximally dilating dose of intracoronary papaverine. CFR was measured after DT infusion when the transient increase in CBFV (IV 24±37% m±SD, IC 102%±74 of control) had returned to baseline. Results: following IV DT, the DT plasma levels (263±89 ng/ml) were higher than commonly achieved during oral therapy. MAP decreased by 12%* (*p<.05) from 96±11 mmHg and HR decreased by 7% from 76±17 bpm. With IV DT, CFR fell from 3.9±1.2 to 3.6±1.1*. After IC infusion of the largest DT dose, MAP was unchanged (99±12 vs DT 97±13 mmHg) and HR was held constant by atrial pacing. CFR with IC DT was unchanged (3.8±0.9 vs DT 3.9±1.0) despite a larger transient increase in peak CBFV. Thus, in contrast to dog studies, DT given to patients in doses larger than used clinically had no or minimal effects on CFR. Therefore, DT use should not confound interpretation of CFR measurements. Attentuation of coronary dilation by DT is not one of the mechanisms responsible for its anti-anginal effects.

VERAPAMIL AS A POTENT CARDIOPROTECTIVE AGENT FOR CORONARY ANGIOPLASTY: FIRST CLINICAL EXPERIENCE.

Gerald S. Werner, M.D., Michael Schmid, Hermann H. Klein, M.D., Volker Wiegand, M.D., Heinrich Kreuzer, M.D., Ulrich Tebbe, M.D. Dept. of Cardiology, University of Göttingen, F.R.G.

The cardioprotective effect of verapamil (Vp) was studied in 30 pts (3 groups à 10) with proximal LAD stenosis undergoing coronary angioplasty (PTCA). After one initial occlusion (oc) the groups received either Vp 1mg/2min i.c., or Vp 5mg/2min i.v., or an equivalent volume of NaCl 0.9% (5ml/2min) i.c. as control. ST segment and T wave alterations were analyzed from chest lead ECG, duration of oc and onset of angina pectoris were registered. Coronary sinus lactate, pyruvate and pH were taken before and after each oc. We observed a significantly improved ischemic tolerance after i.c. Vp as compared with i.v. and control (see Tab:x±sem;* p<0.05;** p<0.01). Coronary sinus lactate rise after oc was reduced to 48% of control (p<0.05). This effect persisted also during the third oc 5-7 min. after injection.

| | oc 1 | | oc 2 | |
|---|---|---|---|---|
| | duration(s) | ST (mV) | duration(s) | ST (mV) |
| control | 54±11 | .48±.10 | 52±8 | .48±.09 |
| Vp i.v. | 48±12 | .51±.09 | 44±10 | .51±.17 |
| Vp i.c. | 58±12 | .54±.08 | 83±20 * | .22±.03 ** |

It is concluded that intracoronary Vp improves the ischemic tolerance during PTCA; this is probably due to a local protective effect whereas the peripheral vascular actions of Vp, as assessed by unchanged systemic blood pressure and heart rate during i.c. and i.v. administration, did not contribute to this effect.

# Wednesday, March 22, 1989
# 10:30AM–12:00NOON, Marriott Hall North
# Anaheim Marriott Hotel
# Autoperfusion Catheters/Valvuloplasty

**Benefit of the "Bailout" Catheter for Emergency Bypass Surgery after Failed PTCA.**

Ponnambalam Sundram M.D., John R. Harvey M.D., Julian M. Aroesty M.D., Beverly H. Lorell M.D., Raymond G. McKay M.D., Daniel J. Diver M.D., Robert D. Safian M.D., Donald S. Baim M.D. Harvard-Thorndike Laboratory, Beth Israel Hospital, Boston, MA.

Of 2102 consecutive coronary angioplasty (PTCA) procedures, 31 patients (1.5%) were sent for emergency bypass surgery (CABG). The 11 patients (36%) who had a "bailout" (B) perfusion catheter, [including 2 who also had an intraaortic balloon (IABP)], were compared to 16 patients (52%) who had only an IABP, and 4 patients (13%) with neither B nor IABP, as regards control of ischemia and surgical outcome.

| | Bailout | IABP | Neither |
|---|---|---|---|
| Multivessel disease | 11/11 | 12/16 | 2/4 |
| Ischemia control: | | | |
| Reduced angina | 9/9 | 16/16 | 4/4 |
| Reduced ECG ischemia | 7/8 | 5/16 | 1/4 |
| Surgical outcome: | | | |
| Peak CPK (Units) | 880±699 | 1593±1362 | 1589±69 |
| Peak CPK-MB (Units) | 73±93 | 148±129 | 152±113 |
| Q-wave infarction (MI) | 1/11 | -p<.02- 12/16 | 3/4 |
| Death | 1/11 | 0/16 | 0/4 |
| Internal mammary graft | 5/11 | 2/16 | 0/4 |
| ≥2 distal grafts | 11/11 | 11/16 | 3/4 |
| Time to CPB(minutes) | 219±86 | 171±39 | 182±71 |

In conclusion, despite comparable time to cardiopulmonary bypass (CPB), patients undergoing emergency CABG with B demonstrated consistent relief of angina, reduced ECG ischemia, lower CPK, fewer Q-wave MI's, and greater use of internal mammary artery grafts than patients supported with IABP alone.

**PROLONGED AUTOPERFUSION ANGIOPLASTY: IMMEDIATE CLINICAL OUTCOME AND ANGIOGRAPHIC FOLLOW-UP.**

Peter J. Quigley M.D., Dean J. Kereiakes M.D., F.A.C.C., Charles W. Abbottsmith M.D., F.A.C.C., Robert P. Bauman M.D., James E. Tcheng M.D., Joseph B. Muhlestein M.D., Harry R. Phillips M.D., F.A.C.C., Richard S. Stack M.D., F.A.C.C., Duke Medical Center, Durham, North Carolina.

To assess the efficacy of prolonged angioplasty using a new autoperfusion balloon catheter (PBC) (Advanced Cardiovascular Systems, Inc.), the combined results in the first 122 patients (pts) (86 males; mean age 58 yrs) undergoing elective coronary angioplasty (LAD 50%; RCA 44%; CIRC 6%) from two medical centers were analyzed. The PBC is a 4.5F polyethylene catheter with multiple sideholes before and after the balloon to allow blood to flow through the central lumen during balloon inflation. PBC use was preceded by a short dilatation (60 secs) using a small (2.0 mm) balloon in 58 pts (48%). Mean PBC inflation duration was 13.8 ± 5.8 min. to a maximum of 6.5 ± .7 atmospheres. Angioplasty was successful (≤ 50% residual diameter stenosis) in 120/122 pts (98%). Mean diameter stenosis was 85 ± 11% pre- and 17 ± 14% post-angioplasty. Emergency bypass surgery was performed in one patient and one patient had late in-hospital reocclusion.

So far, 63 out of 67 pts (94%) eligible for 6 month follow-up angiography have been restudied, of whom 30% (19/63 pts) have restenosis (> 50% luminal diameter narrowing).

In conclusion, prolonged balloon dilatation can be safely and effectively performed using the PBC. The acute success rate is high and in-hospital complications are low compared to previously reported rates for standard PTCA. The restenosis rate is similar to that reported for shorter dilatations.

*USE OF THE ACS STACK PERFUSION DILATATION CATHETER IN PTCA TO AVOID CORONARY ARTERY BYPASS SURGERY*

*Zachary I. Hodes, M.D., Ph.D., Donald A. Rothbaum, M.D., F.A.C.C., Thomas J. Linnemeier, M.D., F.A.C.C., Ronald J. Landin, M.D., F.A.C.C., Michael W. Ball, M.D., and Ruth A. Giebel, R.N., B.S.N. Indiana Heart Institute, Indianapolis, Indiana*

*The success of conventional coronary angioplasty (CCA) can be severely limited by acute reclosure post CCA or ischemia during balloon inflation. The ACS Stack Perfusion Dilatation Catheter (ACS-SPDC) allows for continuous perfusion of blood during prolonged balloon inflation. This catheter was used in 22 stenoses in 21 Pts who experienced dissection and repeated subtotal or total vessel occlusion with CCA (17 Pts) or who developed profound ischemia with compromised left ventricular function with CCA (left main stenosis, 1 Pt; right coronary ostial stenosis, 2 Pts; and hypotension with LAD CCA, 1 Pt). The lesion was successfully crossed with the dilatation catheter in 19 of 21 Pts (90%). One to four inflations (mean 1.4) at 3-10 atmospheres pressure (mean 6.7) were performed. Inflation time was intended to be 20 min unless the patient developed significant ischemia earlier. The mean inflation time was 15 min (range 1-21 min) with 6 Pts requiring deflation of the balloon before 20 min. The mean predilatation stenosis was 88% (range 50-100%) reduced to a mean of 15% (range 0-40%). Four Pts developed renarrowing at the angioplasty site, although only 2 experienced total occlusion of the vessel. One Pt died in the catheterization laboratory due to failure to maintain patency of both a totally occluded LAD and subtotally occluded RCA (not CABG candidate). Three Pts required emergency CABG, however none of them experienced myocardial infarction by either ECG or CPK criteria. Therefore, 15 of 21 Pts (71%), who otherwise would have required CABG, had successful PTCA using the ACS-SPDC.*

EFFECTS OF NITRATES ON CORONARY HEMODYNAMICS AND ANGINAL THRESHOLD IN SYNDROME X.

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Patients (pts) with angina pectoris, found to have angiographically normal coronary arteries and no evidence of coronary spasm or ventricular hypertrophy (syndrome X), offer a management dilemma to the clinician. This study was undertaken to investigate the hemodynamic effects of s.l. isosorbide dinitrate (10 mg; ID) in 10 pts presenting with the above set of findings as well as spontaneous episodes of transient myocardial ischemia (anginal pain and ≥ 0.15 mV ST↓). In these pts, we measured great cardiac vein blood flow (GCVBF; ml/min) and mean aortic pressure (AoP; mmHg) at rest and peak pacing (10 bpm increments every 2 min), both off drugs and 5 min following ID. In all pts GCVBF increased by less than 50% or even decreased during pacing. This occurred both off drugs and with ID. Administration of ID caused a significant reduction (paired t-test: $p < .05$) in AoP (x±SD: 94±16 vs 104±15 at rest, and 95±18 vs 105±20 at peak pacing) and GCVBF (94±54 vs 116±60 at rest, and 83±33 vs 121±52 at peak pacing). Angina and significant ST↓ (≥ 0.1 mV) during pacing occurred after 582±110 sec off drugs and 492±93 sec ($p < .02$) following ID. We conclude that: (1) pts with syndrome X exhibit a reduced coronary flow response to pacing; (2) in such pts, ID may further reduce blood flow, thus increasing discrepancy between myocardial $O_2$ demand and supply; (3) a failure of the autoregulatory mechanisms to adequately maintain coronary blood flow during decreased AoP is suggested.

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IS BALLOON VALVULOPLASTY BENEFICIAL IN PATIENTS WITH CALCULATED CRITICAL AORTIC STENOSIS BUT LOW EJECTION FRACTION AND PRESSURE GRADIENT?

P.S. Reddy M.D. FACC, Barry F. Uretsky M.D. FACC, Alfredo Trento M.D., Karen Gallis-Davis R.N., University of Pittsburgh, PA

To determine if pts with critical aortic stenosis (AS) and severe symptoms (NYHA Class IV) have sustained improvement and survival post aortic valvuloplasty, the results of 53 pts were analyzed. Ejection fraction (EF) was ≥35% in 33 (Group A) and less than 35% in 20, of whom 13 had a mean pressure gradient >35 mmHg (Group B) and 7 had a mean pressure gradient ≤35 mmHg (Group C). Comparative data in 3 groups were as follows:

| Group | A | B | C |
|---|---|---|---|
| Age | 77±7 | 78±8 | 71±8 |
| EF | 57±14 | 27±4 o | 22±9 o † |
| Gradient | 72±19 | 54±12 o | 27±6 o † |
| CO | 3.8±0.9 | 3.6±1.0 | 2.9±1.0 |
| AVA Before | 0.44±0.2 | 0.47±0.2 | 0.53±0.2 |
| After | 0.63±0.2 * | 0.66±0.3 * | 0.64±0.1 * |
| M % | 15 | 31 | 86 o † |
| CV M % | 9 | 15 | 86 o † |

p<.05 *=post vs. pre valvuloplasty;p<.05 o=A vs B, A vs C, p<.05 †=B vs C. AVA=aortic valve area (cm2);CO=cardiac output (l/min); CV=cardiovascular;M=6month mortality (%)

All deaths in Group C but only one in Group B were from terminal heart failure. Other deaths were noncardiac. None of the 7 Group C pts had a clinical improvement post procedure, whereas 75% in Group A and 53% in Group B improved clinically (p<.05, C vs A, C vs B).

Therefore, in pts with low EF and low gradient, balloon dilatation of apparent critical AS appears to be of little clinical benefit.

## Wednesday, March 22, 1989
## 8:30AM–10:00AM, California Room D
## Anaheim Convention Center
## Echo Doppler: Ischemic Heart Disease

ECHOCARDIOGRAPHIC EVALUATION OF SEGMENTAL WALL MOTION EARLY AND LATE AFTER THROMBOLYTIC THERAPY IN ACUTE MYOCARDIAL INFARCTION.

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In 92 acute myocardial infarction (AMI) patients treated with tissue plasminogen activator (tPA) 2.3±1.2 hrs after the onset of chest pain, 2D echocardiography (2DE) was performed at 11±14 hrs (early) and, in 49 pts, again at 13±7 weeks (late). Infarct location and the LV wall motion score index (WMSI) -- the average score (normal = 1, hypokinetic =2, akinetic = 3, dyskinetic = 4) for 20 segments -- were determined by 2 blinded observers. Concordance between 2DE infarct location (anterior, inferior or lateral) and infarct related artery at angiography 4±2 days later (n=85) was 83%, compared to 75% for ECG vs angiography (both p<0.0001). The early WMSI was worse for anterior (1.7±0.4) vs inferior (1.3±0.1) or lateral (1.5±0.2) infarcts (both p<0.0001), but was not related to time to tPA or TIMI reperfusion grade. Overall, the WMSI improved from early to late 2DE (n=49, 1.5±0.3 to 1.3±0.3, p=0.004). However, improvement was confined to those with time to tPA ≤2 hrs (n=22, 1.5±0.3 to 1.2±0.2, p=0.002) vs >2 hrs (1.5±0.3 to 1.4±0.4, p=NS), TIMI reperfusion grade ≥1 (n=38, 1.5±0.3 to 1.2±0.3, p=0.002) vs TIMI grade 0 (1.5±0.2 to 1.5±0.4, p=NS), and anterior (n=17, 1.6±0.3 to 1.4±0.4, p=0.03) vs inferior infarcts (1.3±0.3 to 1.2±0.2, p=NS).

Conclusions: 2DE early after AMI identifies infarct location and usefully defines the extent of myocardium for potential salvage. Improvement in the WMSI is seen in anterior infarcts with early, successful reperfusion.

PREDICTIVE FACTORS FOR SUCCESS OF PERCUTANEOUS MITRAL VALVULOPLASTY.

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To determine whether early success of percutaneous mitral valvuloplasty (PMV) can be predicted, 76 consecutive pts were classified into 3 groups: optimal success (area >1.5 cm$^2$ and gain >25%): 53 pts (70%), suboptimal success (area ≤1.5 cm2 and/or gain ≤25%): 15 pts (20%) and failure (no effective inflations): 8 pts (10%). Univariate and multivariate analyses of 11 clinical, 20 hemodynamic, 7 procedural and 6 echocardiographic variables revealed that the strongest independent predictors of failure were LA diameter (p=.004) (61.5±8 vs 51.5±9 mm) followed by team inexperience (p=.001). Compared to optimal success, univariate analysis showed the following variables measured pre-PMV to be predictors of suboptimal success:

| | Optimal | Suboptimal |
|---|---|---|
| Cardiac output (L/min) | 4.46±1.16 | 3.1±1.39** |
| Mitral valve area (mm2) | 1.17±0.34 | 0.83±0.43* |
| Total pulmonary vasc. res. | 702±321 | 1447±1097* |
| Left atrial diameter (mm) | 50±9 | 57±9* |
| Leaflet thickness score >2 | 0/50 | 4/15* |
| Leaflet mobility score >2 | 8/50 | 9/15* |

**= p<.001; *= p<.005

By stepwise logistic regression analysis, only total pulmonary vascular resistance (p=.0001) and LA diameter (p=.01) were selected as independent predictors.

In conclusion, the results of percutaneous mitral valvuloplasty are more likely to be suboptimal in pts with higher pulmonary vascular resistance and larger left atria.

DIRECT IMAGING OF THE PAPILLARY MUSCLES DURING ISCHEMIA: IMPLICATIONS FOR ISCHEMIC MITRAL REGURGITATION.

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Although papillary muscle (PM) dysfunction is thought to cause mitral regurgitation (MR), the behavior of the PMs during ischemia has never been directly observed. Accordingly, we cannulated the left main coronary artery (LMCA) in 10 open-chest anesthetized dogs and perfused it with arterial blood. Reversible occluders were placed on the proximal left anterior descending (LAD) and left circumflex (LC) coronary arteries. 2D echo images of the LV and PMs were obtained using short axis views at a depth of 8 cms. Sonicated microbubbles were injected through the apex of the LV to assess severity of MR (0 to 4) in the 4-chamber view. Ao, LV, and LA pressures were recorded. Each animal was studied at baseline, following separate occlusions of the LAD and LC, and during global ischemia caused by reduction of flow to the LMCA. Mean end-distolic thicknesses of the anterolateral and posteromedial PMs at baseline were 0.98 cm$^2$ and 0.86 cm$^2$, respectively. Percentage systolic thickening of the two PMs was 0.36 and 0.33, respectively which was similar to the regions of the LV where the PMs were attached. During ischemia thickening of the PMs paralleled that of the corresponding region of the LV. However, the presence or severity of MR did not correlate with the degree of either PM or regional LV dysfunction. Instead it correlated best with global dysfunction (r = -0.86 with % systolic thickening, r = -0.76 with % global systolic change in LV volume, and r = -0.67 with LV dp/dt). Incomplete mitral leaflet closure was seen in all instances of MR; prolapse of the mitral leaflets was never noted.

We conclude that the PMs behave similar to the region of the LV where they are attacted. However, PM dysfunction is not the cause of ischemic MR. The severity of MR is related to degree of global LV dysfunction.

ABNORMAL DOPPLER LEFT VENTRICULAR FILLING FOLLOWING ACUTE MYOCARDIAL INFARCTION AND CHANGES DURING EARLY RECOVERY.

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Changes in LV filling during and following acute myocardial infarction (AMI) are largely unknown. To examine this, pulsed wave Doppler echo was used to evaluate LV diastolic filling in 60 pts within 24 hrs of AMI; 41 (68%) of whom had successful reperfusion. A subgroup of 13 pts had repeat Doppler at 7 days. A coronary disease (CAD) control group consisted of 15 age and sex matched pts without previous MI. Significant results are summarized below (mean±SD):

| | CAD(n=15) | AMI(n=60) | 7day(n=13) |
|---|---|---|---|
| VTI Total (m) | .120±.033 | .098±.031*** | .121±.045** |
| VTI E (m) | .068±.020 | .058±.021** | .073±.023** |
| VTI .33 (m) | .061±.020 | .040±..018** | .054±.023** |

VTI=Velocity Time Integral; *:p<.05 **:p<.01 ***:p<.001; significance values for AMI vs. CAD, and 7 day vs.AMI.

Although peak E and E/A ratios were abnormal in AMI pts., they were not different among the 3 study groups. However, AMI pts had abnormal diastolic VTI compared to CAD controls which improved by 7 days. On further subgroup analysis, significant improvement in VTI occurred in pts with initial ejection fractions < 40% (p<.05) and in pts with anterior AMI (p<.05), but not in pts with inferior AMI. We conclude that pts with AMI have impaired diastolic filling in the initial 24 hrs which improves by 7 days post-MI. This improvement is greatest in pts with anterior AMI and impaired ejection fraction. Our data suggest that diastolic filling dynamics may have greater potential for recovery following AMI than systolic dysfunction.

**LOW MAXIMUM ACCELERATION MEASURED USING AORTIC DOPPLER IDENTIFIES PATIENTS AT RISK OF CARDIAC DEATH FOLLOWING ACUTE MYOCARDIAL INFARCTION.**

Susan Gilmour BSc, David Bennett FRCP, Tim Cripps MRCP, St George's Hospital Medical School, London, England.

Doppler ultrasound was used to obtain maximum acceleration (m/s/s) (MA) from the ascending aorta using the suprasternal approach in 95 patients (pts) with acute myocardial infarction (MI). The incidence of cardiac deaths before exercise testing (within 1 month), and within 1 year were recorded:

| | Total Group | Survivors | Non-Survivors 1 month | Non-Survivors 1 year |
|---|---|---|---|---|
| n | 88 | 74 | 9 | 5 |
| mean MA | 15.8 | 16.4 | 12.9 | 11.0 |
| SE | 0.5 | 0.6 | 1.3 | 1.5 |

Both non-survivor groups had significantly lower MA than the survivors (p≤0.05). Exercise treadmill-testing (Bruce protocol) was carried out on 125 post MI pts including 46 of the above group. The pts were assessed in terms of negative (neg) or positive (pos) exercise test, a positive test being ≥1mm ST depression on exercise. The incidence of cardiac deaths (up to 18 months) were recorded. The results were assessed in terms of MA on peak exercise (peak MA).

| | Total Group | Survivors Neg | Survivors Pos | Non-survivors Neg | Non-survivors Pos |
|---|---|---|---|---|---|
| mean | 28.9 | 31.5 | 27.8 | 23 | 16.3 |
| SE | 1.1 | 1.6 | 1.6 | | 2.1 |
| n | 108 | 55 | 45 | 1 | 7 |

The non-survivors had a significantly lower peak MA than the survivors (ANOVA p≤0.05). There was a mortality of 16% in patients with a peak MA ≤23 m/s/s, no deaths have occurred in patients with peak MA >23.

MA measured acutely identifies the group at risk from early cardiac death. Similarly those with a low peak MA and positive test are at risk of cardiac death, however a positive exercise test when combined with high peak MA is not associated with cardiac death.

SERIAL CHANGES IN LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTION FOLLOWING SUCCESSFUL THROMBOLYTIC THERAPY OF MYOCARDIAL INFARCTION: ASSESSMENT BY DOPPLER ECHOCARDIOGRAPHY

Gong Yuan Xie, M.D., Oi Ling Kwan, B.S., and Anthony N. DeMaria, M.D., F.A.C.C.; University of Kentucky, Lexington, Kentucky

Few data exist regarding serial changes in LV systolic and diastolic function following successful thrombolytic therapy of acute MI. Therefore we performed Doppler-echocardiography(ECHO) in 17 pts in whom coronary reperfusion was achieved within 120 minutes. Initial studies were performed within 24 hrs, and repeated at 3, 5, and 7 days. All ECHO were performed in standard fashion from usual windows. Systolic function was evaluated by: an echo wall motion index(WMI) graded from 1(normal) to 4(dyskinetic); mean acceleration(ACL) in LV outflow tract(OT), and LVOT velocity integral(FVI). Diastolic function was assessed as mitral early(E) and atrial(A) velocity integrals Ei/Ai ratio, and pressure 1/2 time (P1/2t) at mitral annulus. Results:

| | Initial | ΔDay 3 | ΔDay 5 | ΔDay 7 |
|---|---|---|---|---|
| Ei(cm) | 5.7±3.2 | -.4±2.4 | 1.1±2.6 | .7±2.7 |
| Ai(cm) | 4.2±1.9 | -.9±1.7* | -.7±.8** | -1.1±1.8* |
| Ei/Ai | 1.4±0.6 | .3±0.5* | .8±.5** | .8±.5** |
| p1/2t(ms) | 46.4±11.6 | 3.7±15.0 | 6.9±15.1 | 7.7±17.2 |
| FVI(cm) | 13.2±3.6 | 1.5±2.2* | 2.0±3.0* | 2.7±3.1* |
| AC(cm/s$^2$) | 7.0±2.2 | 1.0±2.0 | 1.6±1.4** | 2.2±2.0** |
| WMI | 1.34±0.16 | -.09±.09** | -.12±.09** | -.16±.09** |

*p<0.05, **p<0.01 versus initial

Thus, shortly after reperfusion LV systolic function is depressed and diastolic function reveals diminished E filling. During the first week ECHO documents a significant return toward normal of LV systolic and diastolic abnormalities in reperfused MI pts.

**Can Hemodynamically Significant RV Infarction be Identified by Two-Dimensional Echocardiography?**

Ronald B. Himelman M.D., Jeffrey Goldberger M.D., Peter Hui M.D., Christopher L. Wolfe M.D., F.A.C.C., Nelson B. Schiller M.D., F.A.C.C. University of California, San Francisco, CA.

To assess 2D echocardiography (2DE) in acute RV infarction (RVMI), 19 patients with RVMI (defined by ECG and clinical criteria) were evaluated by 2DE and hemodynamics. Of 19 patients, 7 had significant hemodynamic abnormalities (Hemodyn Sig, RA pressure ≥ 13 mm Hg, ratio of RA to PCW pressure > 0.65). 2DE measurements were made in patients and 20 normal controls: systolic descent of the RV base (Descent of Base, cm), ratio of RV to LV size by single-plane area-length method in the apical four chamber view (RV/LV), and respiratory response of inferior vena cava in the subcostal view (IVC Response, fractional decrease in vena cava diameter after inspiration).

Results were (* p < 0.05 vs Hemodyn Sig):

| | Pts. | Descent of Base | RV/LV | IVC Response |
|---|---|---|---|---|
| Hemodyn Sig | 7 | 0.6 ± 0.2 | 1.12 ± 0.66 | 0.20 ± 0.17 |
| Other patients | 12 | 1.3 ± 0.4* | 0.63 ± 0.37 | 0.52 ± 0.08* |
| Controls | 20 | 2.0 ± 0.3* | 0.48 ± 0.19* | 0.64 ± 0.19* |

RV wall motion abnormalities were found in 10 of 19 patients with RVMI (3 with Hemodyn Sig RVMI) and 0 controls. An IVC Response of ≤ 0.50 was 100% sensitive for Hemodyn Sig RVMI and 56% specific, Descent of Base < 1.0 cm was 86% sensitive and 92% specific, and RV/LV > 0.80 was 57% sensitive and 67% specific.

Conclusion: 2DE signs may help predict abnormal hemodynamics in acute RVMI. Plethora of the inferior vena cava with blunted respiratory response is a sensitive marker for elevated central venous pressure, while poor descent of the RV base is specific for Hemodyn Sig RVMI. Abnormal RV wall motion and size may be diagnostic of RVMI, but do not predict hemodynamic compromise.

## Wednesday, March 22, 1989
## 10:30AM–12:00NOON, California Room D
## Anaheim Convention Center
## Exercise and Nonexercise: Stress Echocardiography

### PHYSIOLOGIC SIGNIFICANCE OF CORONARY LESIONS ASSESSED BY EXERCISE ECHOCARDIOGRAPHY AND QUANTITATIVE CORONARY ANGIOGRAPHY

Khalid H. Sheikh, MD, James R. Bengtson, MD, MPH, Sherif Helmy, MD, David S. Rendall, PA-C, Robert Burgess, BS, Thomas M. Bashore, MD, FACC, Richard S. Stack, MD, FACC, Joseph Kisslo, MD, FACC. Duke University Medical Center, Durham, NC.

To determine the geometric features of coronary lesions which relate to the development of exercise-induced wall motion abnormalities, 19 consecutive patients with single vessel, proximal coronary lesions were studied by exercise echocardiography (EE) and same-day quantitative angiography (QA). All patients had normal resting wall motion and were able to reach target heart rate or developed positive ECG changes during exercise.

Minimal luminal diameter (MLD), minimum cross-sectional area (MCSA), % diameter stenosis (% DS), and % area stenosis (% AS) assessed by QA were compared between patients developing wall motion abnormalities during exercise (positive) and those with normal wall motion (negative).

| | Negative (N=9) | Positive (N=10) | p |
|---|---|---|---|
| MLD (mm) | 1.7 ± 0.4 | 1.0 ± 0.4 | .007 |
| MCSA (mm) | 2.4 ± 1.1 | 1.0 ± 0.7 | .0001 |
| % DS | 47.8 ± 8.0 | 66.9 ± 13.1 | .0001 |
| % AS | 72.1 ± 9.0 | 87.5 ± 7.4 | .0001 |

MLD ≤ 1.5 mm or MCSA ≤ 1.9 mm identified all patients with positive EE.

In patients with limited coronary atherosclerosis, quantitative assessment of both absolute and relative coronary dimensions is related to wall motion abnormalities detected by exercise echocardiography.

### ECHOCARDIOGRAPHIC ASSESSMENT OF MENTAL STRESS INDUCED WALL MOTION ABNORMALITIES: COMPARISON WITH EXERCISE.

John S. Gottdiener, M.D., F.A.C.C., David S. Krantz, Ph.D, Adrian McGee, M.D., Marvin Oleshansky, M.D., James Myerhoff, M.D., Shera E. Raisen, B.S., Alan Rozanski, M.D., F.A.C.C., VA Medical Center, Washington DC, USUHS, Bethesda, Md and University of Maryland, Baltimore, Md.

In CAD, mental stress has been associated with transient myocardial ischemia. Therefore, we used 2D echo to continuously analyze LV wall motion (WM) in 14 men with CAD (av age 53 ± 0.6, yrs, av 1.7 ± 0.6 diseased vessels) and 6 normal men (av age 56 ± 10 yrs, pNS) during mental arithmetic (math), public speaking and upright bicycle exercise (EX). Heart rate, blood pressure, and WM abnormality (A) were assessed and compared for each stress intervention after echo digitization and display in continuous loop format. In CAD pts, av WMA increased from rest value of 1.13±0.20 to 1.37±0.41 with math, 1.31±0.42 with speech and 1.63±0.52 with EX ($p<.05$, math, speech and EX vs rest). Plasma epinephrine, (rest 101 ± 50 pg/ml, math 172 ± 91 pg/ml, speech 144 ± 53 pg/ml) and double product (rest 9.5 ± 1.9 x $10^3$, math 15.2 ± 4.4 x $10^3$, speech 14.6±3.6x$10^3$, EX 21.9±6.5) showed substantial increases with mental stress. New or worsened WMA occurred rapidly during mental stress in 8/14 pts (57%) vs 0/6 normals, while WMA during EX occurred in 11/14 (79%) pts, although at higher double product than with mental stress. ST segment depression with mental stress occurred in 4 of the 8 pts with WMA, in the absence of chest pain. **CONCLUSION:** 1) mental arousal can produce painless ischemia, probably by decrease in myocardial oxygen supply; 2) the stable body position, lower heart rate and minimal respiratory artifact with mental stress permitted easier assessment of WMA directly from the real time 2DE than possible with EX.

### EXERCISE ECHOCARDIOGRAPHIC DETECTION OF CORONARY ARTERY DISEASE IN WOMEN.

Stephen Sawada, MD, Paul L. McHenry, MD, FACC, William F. Armstrong, MD, FACC, Thomas Ryan, MD, Harvey Feigenbaum, MD, FACC, Krannert Institute of Cardiology and Indiana University Hospital, Indianapolis, IN.

The utility of exercise echocardiography (EE) for the diagnosis of coronary artery disease (CAD) has been evaluated in populations comprised largely of men who have a high prevalence of disease. To determine the diagnostic value of EE in women, 57 women who presented for evaluation of chest pain were studied with coronary angiography and EE utilizing either treadmill (n=38) or bicycle exercise (n=19). Twenty-eight of 57 patients (49%) had significant CAD (>50% reduction in luminal diameter), including 16 of 19 (84%) who had typical angina and 12 of 38 (32%) who had atypical chest pain ($p<0.001$). The overall sensitivity and specificity of EE were both 86%. There were no significant differences in the sensitivity and specificity of bicycle EE vs treadmill EE. Three of 4 pts with false positive EE had non-atherosclerotic cardiac disorders. EE correctly determined the presence or absence of CAD in 32 of 38 (84%) who had atypical chest pain and in 17 of 19 (89%) who had typical angina (p=ns). The exercise ECG was non-diagnostic in 17 pts (30%) who had resting ST segment depression or ST depression that could be induced by hyperventilation or changes in position. The correct diagnosis was made by EE in 14 of 17 pts (82%) who had non-diagnostic ECG. In conclusion, EE has good sensitivity and specificity for the detection of CAD in women. EE has diagnostic value in women who have atypical chest pain and in those who have non-diagnostic ECG.

### HIGH DOSE DIPYRIDAMOLE-ECHOCARDIOGRAPHY TEST: LARGE SCALE CLINICAL TRIAL.

Eugenio Picano, MD, Fabio Lattanzi MD, Michele Masini MD, Antonio L'Abbate, MD, F.A.C.C. C.N.R. Clinical Physiology Institute, University of Pisa, Italy.

Nine hundred fifty-two high-dose dipyridamole-echocardiography test (DET) were performed in 771 pts with history of chest pain and/or myocardial infarction. The dipyridamole infusion protocol was: 0.56 mg/kg over 4', followed by 4' of no dose, and if still negative, 0.28 mg/kg over 2'. The only criterion of DET positivity was the detection of a regional transient dyssynergy, absent or of a lesser degree in the baseline examination. Interpretable echo images during DET were obtained in all pts. The average duration of a DET was less than 30 minutes. There were no death, myocardial infarction, malignant arrhythmias, severe hypotension. Out of the 771 study pts, a subset of 580 was studied without therapy, and underwent coronary arteriography; on this subset, the sensitivity and specificity were calculated. Pts were considered to have coronary artery disease if they had at least one stenotic lesion with 70% or greater diameter reduction in the coronary angiogram. The overall sensitivity of DET was 75%; it was lower in single than in multivessel disease (54% vs 86%). The sensitivity was 84% in pts with a resting ventricular asynergy and 67% in pts with normal resting function. The overall specificity was 95%, with similar values in hypertensives and normotensives (92 vs 97%, p=ns), males and females (96 vs 93%, p=ns). Thus, high dose DET is feasible and safe, with high specificity, and acceptable sensitivity - especially in pts with multivessel disease and/or resting asynergy - for non invasive detection of angiographically assessed coronary artery disease.

DIPYRIDAMOLE-DOPPLER ECHOCARDIOGRAPHY: COMPARISON TO THALLIUM-201 IMAGING AND QUANTITATIVE CORONARY ARTERIOGRAPHY.
Paul A. Grayburn M.D., Jeffrey J. Popma M.D., Susan L. Pryor M.D., Brandy S. Walker M.D., Theodore R. Simon M.D., and Thomas C. Smitherman M.D. VA Medical Center, Dallas, TX.

This study was undertaken to assess the ability of Doppler parameters of aortic and mitral blood flow velocity to detect left ventricular functional impairment due to ischemia during intravenous dipyridamole thallium-201 imaging. In addition, we evaluated the ability of Doppler measurements to detect the presence of significant coronary artery stenoses as assessed by quantitative coronary arteriography (QCA). The study consisted of 10 normal controls and 23 patients with coronary artery disease (CAD) in whom QCA was performed (study interval 7.5±6.8 days). A flow-limiting coronary artery stenosis was defined as $<2mm^2$ in cross-sectional area by QCA. Doppler estimates of peak aortic velocity (AoV) and acceleration (Acc) were determined at baseline and post-dipyridamole as indexes of LV systolic performance. Mitral flow velocity was measured at early filling (E) and atrial systole (A) and the E/A ratio used as an index of LV diastolic function. The change from baseline to post-dipyridamole was:

| | AoV (m/s) | Acc($m/s^2$) | E/A ratio |
|---|---|---|---|
| Normal controls | 0.07±0.07 | 2.1±2.0 | -0.18±0.68 |
| CAD-thallium neg. | 0.11±0.12 | 2.9±2.3 | -0.15±0.55 |
| CAD-thallium pos. | 0.02±0.17 | 0.5±2.9 | -0.04±0.36 |

Differences between groups were not significant by analysis of variance. Moreover, AoV and Acc decreased abnormally in only 3 of 14 pts with thallium-201 evidence of ischemia. E/A ratio did not change abnormally in any pt. Similarly, no difference in Doppler parameters existed for pts with and without significant coronary artery stenoses by QCA. Thus, intravenous dipyridamole Doppler echocardiography cannot reliably detect ischemia or significant coronary artery stenoses and is of limited value in the evaluation of ischemic heart disease.

**TWO-DIMENSIONAL ECHOCARDIOGRAPHY CAN REDUCE HOSPITAL ADMISSIONS FOR ACUTE MYOCARDIAL INFARCTION BY MORE THAN ONE-THIRD: RESULTS OF A PROSPECTIVE STUDY PERFORMED IN THE EMERGENCY ROOM.** Peter Sabia M.D., Ali Atrookteh M.D., Dale Touchstone M.D., Mark Keller M.D, Sanjiv Kaul M.D., F.A.C.C. University of Virginia, Charlottesville, VA

Nationwide, less than 30% of patients admitted to the hospital from the emergency room (ER) with suspected acute myocardial infarction (AMI) actually have this diagnosis. Because regional wall motion abnormality (RWMA) is the sine qua non of AMI, we hypothesized that using 2D echo in the ER could substantially reduce hospital admissions for suspected AMI. To test this hypothesis we analyzed data from 180 pts who presented to the ER for chest pain. AMI was documented in all pts by serial cardiac enzymes. The results of the echo studies were not divulged to the physicians who admitted or discharged the pts based upon conventional criteria. Of the 40 pts discharged, 2 had AMI; of the 57 admitted to non-coronary care unit beds, 3 had AMI; while 25 of the 81 admitted to the coronary care unit (CCU) had AMI. Average cost for no admits was $247, for those admitted to non-CCU beds was $4255, and for those admitted to the CCU beds was $7605. The total cost for the 180 pts was $888,673 resulting in cost/infarct of $29,622. Of the 30 AMI pts, 29 had technically adequate studies: 27 had RWMA and 2 had normal echos neither of whom had any complications; none had diffuse global dysfunction of the LV. Of the 150 non-AMI pts, 140 had technically adequate echos, 58 were normal, 60 had RWMA and 22 had diffuse global hypokinesia. If only pts with RWMAs had been admitted, total hospital admissions would have decreased from 140 to 87 (decrease of 38%). No additional AMIs would have been discharged and hospital cost (including $300 per echo) would have been reduced to $61,1141 (decrease of 31%). We conclude that 2DE performed in the ER is a cost effective way to determine hospital admission for suspected AMI.

# Wednesday, March 22, 1989
# 8:30AM–10:00AM, Garden Grove Room
# Anaheim Convention Center
# Cardiopulmonary Bypass Support for Coronary Angioplasty and Shock

SUPPORTED ANGIOPLASTY: INITIAL EXPERIENCE WITH HIGH RISK PATIENTS
Carl L. Tommaso, M.D., F.A.C.C., Steven R. Gundry, M.D., F.A.C.C., Albert R. Zoda, M.D., J. Lawrence Stafford, M.D., F.A.C.C., Rodney A. Johnson, M.D., F.A.C.C. Robert A. Vogel, M.D., F.A.C.C., University of Maryland School of Medicine, Baltimore, Maryland

We used supported angioplasty to protect against hemodynamic collapse in high risk patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Supported angioplasty is the performing of PTCA while the patient has been placed on cardiopulmonary bypass in the catheterization lab. Ten male patients (mean age-57.7 ± 11.6 years) were placed on cardiopulmonary bypass prior to PTCA using right atrial to femoral artery bypass via cannulae placed semi-percutnaeously in a femoral artery and vein. Patients are given Heparin 400 U/kg. Six patients had unstable and 4 severe stable angina. Indication for supported angioplasty included marked reduction in left ventricular ejection fraction (<25%) in 2 patients; significant jeopardized myocardium (single coronary vessel supplying distribution of two native vessels) in 4; and both (low EF, jeoparidized myocardium) in 4. Cardiopulmonary bypass was initiated just before PTCA; flow ranged from 3.5 to 5 l/min. Balloon inflation times were 1.5 to 5 mins/inflation. We attempted 13 lesions with 12 successes. Mean EF for all patients was 25 ± 14.7%; seven had EF <30%. Complications included subsequent arterial repair in 1; late venous thrombosis in 1; and recurrent femoral hematoma in 1. One patient died because of celiac obstruction. Restenosis has occurred in two patients.

Thus, supported angioplasty permits PTCA to be performed safely in high risk patients who otherwise would not be considered candidates for PTCA.

PERCUTANEOUS INSTITUTION OF CARDIOPULMONARY (BYPASS) SUPPORT: TECHNIQUE AND COMPLICATIONS.
Fayaz A.Shawl MD,FACC, Michael J. Domanski MD, FACC, Sudhakar Punja, MD, FACC, Tomas J. Hernandez, MD, Washington Adventist Hospital, Takoma Park, MD.

Cardiopulmonary bypass support(CPS) of pts undergoing high risk PTCA may be more effective than intraaortic balloon, but has required surgical placement. We report the safety and efficacy of CPS established percutaneously in 43 pts. 8 were emergencies(group-1), 35 high risk PTCA(group-2), and 2 high risk valvuloplasty(V)(group-3). Group 1(ages 40-80 yrs) were in cardiogenic shock due to myocardial infarction(MI) with 2 in cardiac arrest(A). Pts in groups 2(ages 41-78 yrs) and 3(ages 81-82 yrs)had iliofemoral arteriography prior to CPS with iliofemoral angioplasty in 2. 20F arterial and venous cannulae were placed in the right(8) or left(35)femoral vessels. Cannulae were inserted after sequential dilatation using 8-14F dilators over a stiff .038" guidewire. CPS was then instituted using the Bard CPS system. Flows ranged from 2.8-6L/min(mean 3.8) and pulmonary wedge pressures were 0-4mm Hg. The 2 pts with A regained consciousness. PTCA was successful in 15 of 16 lesions attempted in group 1 and 85 of 86 lesions attempted in group 2. Both pts in group 3 had successful V with 4 coronary lesions dilated in one. Hemostasis was achieved in 41 by an external clamp applied for 6-18 hours(mean 12). Complications include hospital death in one, acute occlusion in one, MI in one, repair of femoral arteries in two, venous thrombosis in one, infection at the entry site in four, femoral nerve weakness in two, pseudoaneurysm in two. Mean transfusion requirements were 9 units(U) per pt in group 1, 0.5 U/pt in group 2 and 2.5 U/pt in group 3. In conclusion, CPS can be safely and effectively instituted percutaneously in selected patients with an acceptable complication rate.

PERCUTANEOUS CARDIOPULMONARY BYPASS TO SUPPORT HIGH RISK ELECTIVE CORONARY ANGIOPLASTY

Fayaz A. Shawl, MD, FACC, Michael J. Domanski, MD, FACC; Sudhakar Punja, MD, FACC; Tomas J. Hernandez, MD; Washington Adventist Hospital, Takoma Park, MD.

PTCA in pts with low ejection fraction(EF) and/or a large area of remaining viable myocardium served by the target vessel can cause hemodynamic collapse in case of acute closure. We report 35 pts in whom percutaneous cardiopulmonary bypass support (PCPS) was instituted to enhance the safety of PTCA. All pts had severe or unstable angina associated with low EF and/or a large amount of myocardium(M) perfused by the target artery. 22 males and 13 females, ages 41 to 78 yrs(mean62), with Canadian Cardiovascular Society(CCS) Class III (11) or IV (24) angina and EF ranging from 11 to 53%(mean-32) were studied. A total of 86 lesions were present(mean-2.4/pt). Severe left main and 3 vessel disease was present in 4 and 33 pts respectively. One pt had severe 2 vessel disease and one had single vessel disease. 29 had a previous myocardial infarction and 10 had bypass surgery. PCPS was instituted using 20 French cannulae. Flow ranged from 2.8-6 L/min(mean-3.7). Pulmonary capillary wedge pressures were 0 to 4 mm Hg. PTCA was successful in 85 of 86 lesions attempted. No pt had angina at the maximum flow rate with balloon inflations up to 5 min. PCPS was discontinued without complication after an average bypass time of 37 min (range 10-73). Hemostasis was achieved by external clamp compression in all but one pt who required surgical repair of the femoral artery. There was 1 hospital death. Pt followup at 1 to 14 weeks(mean 6) disclosed 4 in CCS Class II and 30 in Class 0. We conclude that PCPS can be used safely in selected high risk PTCA pts and therefore may expand the application of PTCA.

EMERGENCY USE OF PORTABLE CARDIOPULMONARY BYPASS IN PATIENTS WITH CARDIAC ARREST.

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A portable cardiopulmonary bypass system, (PCPB) was placed in 25 patients (PTS) who had sustained cardiopulmonary arrest and had not responded to the usual advanced cardiac life support (ACLS) measures. 25/25 had successful initiation of PCPB with flows in excess of 3.5 l/min obtained in all pts. 12 survived short term, 6 were discharged improved. 8 treated pts arrested in the cath lab, either after attempted PTCA (N=5) or prior to angiography (N=3). 4 survived short term, 3 were discharged, all PTCA failures. One PTCA failure, a Jehovah's Witness, survived CABG, but no blood products could be given and pt expired. 13 pts had PCPB placed after arrest in the ICU, 5 after cardiac surgery (4/5 short term survivors, 2 pts discharged); 3 with massive pulmonary emboli (0 survivors); 2 as a "bridge" to ventricular arrest device or total artificial heart (2 short term, 0/2 long term survivors); after ventricular rupture (successful return of neurologic function with surgeon/family deciding not to proceed with cardiac surgery. 4 pts had PCPB placed on ward or in ER; 1 survived. 2 morbidly obese pts had bleeding secondary to cannula side-holes being extravascular. Neither survived. Application of PCPB can salvage pts after arrest, particularly if applied early either in the cath lab percutaneously or in the surgical ICU setting. Improvements in vascular cannulae have allowed for greater success with our later experience.

IMPROVED HEMODYNAMIC AND LEFT VENTRICULAR UNLOADING DURING ACUTE ISCHEMIA USING THE HEMOPUMP LEFT VENTRICULAR ASSIST DEVICE COMPARED TO INTRA AORTIC BALLOON COUNTER PULSATION.

R. W. Smalling, M.D., Ph.D., F.A.C.C., D. B. Cassidy, M.D., M. Merhige, M.D., P. R. Felli, B.S., G M. Wise, M.S., R. L. Barrett, M.D., R. D. Wampler, M.D.

Thirteen conditioned dogs were subjected to a 2 hour mid left anterior descending (LAD) occlusion followed by a 1 hour period of reperfusion. In 7 dogs hemodynamic support was maintained by the Hemopump (HP), a 7 mm diameter axial flow pumping cannula capable of pumping 3 liters/minute from left ventricle (LV) to aorta (Ao) which was placed retrograde across the aortic valve. A conventional intra aortic balloon pump (IABP) was inserted in 6 dogs. Regional function was measured using sonomi- crometers in the control state, during LAD occlusion and with reperfusion (R) on and off left ventricular support. Left ventricular and aortic pressure (P) measurements were made simultaneously with functional measurements. Two hours after LAD occlusion during HP support the LV systolic pressure fell from 97 to 45 mmHg (P=.003) while the mean AoP rose from 79 to 87 mmHg. The LV diastolic P fell from 6 to 0 mmHg (P=.05). The LAD endiastolic diameter decreased from 17 to 13.9 mm and paradoxical systolic bulging in the LAD region decreased. During AIBP counter pulsation there was no change in any of the above parameters with LV systolic pressure maintained at 100 mmHg, mean Ao pressure maintained at 89 mmHg and LAD diastolic diameter at 16.45 mm. Conclusion: The Hemopump appears to be superior to IABP in terms of LV unloading and support of aortic pressure during interventions in acute regional myocardial ischemia.

EMERGENCY PERCUTANEOUS CARDIOPULMONARY (BYPASS) SUPPORT IN CARDIOGENIC SHOCK.

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Support of pts in cardiogenic shock(CS) with an intraaortic balloon may not provide hemodynamic stability during acute intervention. We report emergency percutaneous cardiopulmonary bypass support (PCPS) instituted in 8 pts (ages 42-80 yrs) with CS and acute myocardial infarction(MI).PCPS was instituted 30-180 min(mean 106) after onset of symptoms. 4 had previous MI & 2 were in cardiac arrest(A). 6 without A had a mean blood pressure(BP) range 43-55 and pulmonary wedge pressures(PWP) $\geq$20 mm Hg. 20F cannulae were inserted into the femoral artery and vein percutaneously. Flow rates of 3.2-5.2 L/min (mean 4.0) were achieved with mean BP 63-76 and PWP of 0-4 mm Hg. 2 pts in A regained consciousness while still in asystole or ventricular fibrillation. Angiography performed after hemodynamic stability revealed low ejection fraction,range 17-40%(mean 30), critical stenosis involving left main in 1;3 vessels in 2;2 vessels in 2 and 1 vessel in 4.One had anatomy unsuitable for either PTCA or bypass surgery, could not be weaned from PCPS, and expired. The remaining 7 underwent successful PTCA in 15 of the 16 lesions attempted and were weaned from PCPS. Total bypass time was 44-120 min(mean 66). Hemostasis was achieved by external clamp compression in all but one pt who required surgical repair of the femoral artery. There were no late MI's or vascular complications. At 1-3 month(mean 2.2) followup all pts were asymptomatic and 4 had a negative stress test. In conclusion, PCPS can:(1) be safely instituted percutaneously; (2)be lifesaving in pts with CS; (3)hemodynamically stabilize pts in A; (4)facilitate emergency complex PTCA even in pts in CS.

## Wednesday, March 22, 1989
## 10:30AM–12:00NOON, Garden Grove Room
## Anaheim Convention Center
## Myocardial Perfusion

ADENOSINE THALLIUM-201 SCINTIGRAPHY: FEASIBILITY, SAFETY AND INITIAL RESULTS IN MAN.

Richard A. Staudacher M.D., John J. Mahmarian M.D., Judy B. Hixson R.N., Terri M. Boyce B.S., Antonio Pacifico M.D., FACC, Kiyotaka Kugiyama M.D., Mario S. Verani M.D., FACC, Baylor College of Medicine, Houston, Texas.

Adenosine is a potent coronary vasodilator with a short half-life (10 sec), which makes it an ideal drug to use in combination with thallium-201 scintigraphy for the diagnosis of coronary artery disease (CAD). To test the feasibility and safety of adenosine-thallium scintigraphy, we studied 33 pts with suspected CAD. Adenosine was infused intravenously at 50, 75, 100 and 140 μg/kg/min. Thallium-201 (3mCi) was injected at the highest tolerable dose of adenosine, which was then continued for 3 additional minutes. Single photon tomography was performed immediately after the adenosine infusion and 4 hours later. Side effects occurred in 76% (25/33 pts) but were usually mild, did not require therapy, and ceased instantly after discontinuing the adenosine infusion. Chest pain occurred in 53%, headache in 34% and cutaneous flushing in 15%. Systolic blood pressure (SBP) and heart rate (HR) changes (mean ± SD) from baseline were:

| Adenosine dose$\phi$ | 50 | 75 | 100 | 140 |
|---|---|---|---|---|
| SBP (mmHg) | 1.1±5.6 | .03±6.9 | -4.6±9* | -14.4±11.3† |
| HR (bpm) | 2.5±5.5* | 2.4±6.3* | 8.1±7.6† | 14.2±8.5† |

$\phi$μg/kg/min; *p < .05; †p < .001

CAD was documented in 15 pts, all of whom had thallium defects after adenosine, which were reversible in 9 (sensitivity = 100%). Of 18 pts with either normal coronaries (n=8) or at low risk for CAD (n=10), 16 had normal scintigraphy (specificity = 89%). Thus, adenosine-induced coronary vasodilation is a safe, convenient, and potent intervention to uncover perfusion defects during thallium scintigraphy in pts with CAD.

**Superiority of Tomographic Thallium Imaging for the Detection of Restenosis After Percutaneous Transluminal Coronary Angioplasty**

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The accurate detection of restenosis following percutaneous transluminal coronary angioplasty (PTCA) continues to be a common and difficult problem. In order to address this issue, we studied 32 patients with serial tomographic and planar thallium scintigraphy performed prior to, 1 month after and 6 months after successful single vessel PTCA. Tomographic and planar imaging were performed at each study timepoint (in a randomly determined sequence) and were analyzed quantitatively for evidence of stress or washout abnormalities. All patients underwent repeat angiography at 6 months and restenosis was present in 15 (incidence of 47%). Non-invasive detection of restenosis was evaluated by comparing angiographic results to anginal symptoms, exercise electrocardiography (GXT) and tomographic and planar thallium analysis. Results (in %) are tabulated below (PV = predictive value):

| | Angina | GXT | Tomography | Planar |
|---|---|---|---|---|
| Sensitivity | 36 | 53 | 92 | 87 |
| Specificity | 94 | 58 | 77 | 50 |
| Positive PV | 83 | 62 | 80 | 62 |
| Negative PV | 64 | 63 | 93 | 80 |

Of those with restenosis, the specific vascular territory was correctly localized to the territory of the PTCA vessel in 77% of the tomographic studies as compared to only 33% of the planar studies.

These results demonstrate that tomographic thallium imaging is an accurate method for detecting and localizing restenosis in patients 6 months post-PTCA and is superior to clinical assessment, GXT and planar thallium studies in evaluating this problem.

EXPERIENCE WITH THE INTRACORONARY DOPPLER CATHETER IN PATIENTS WITH CLINICAL ISCHEMIC HEART DISEASE BUT NORMAL OR TRIVIALLY DISEASED CORONARIES.

Jan L. Houghton M.D., F.A.C.C., Martin J. Frank M.D., F.A.C.C., Albert A. Carr M.D., Thomas W. von Dohlen M.D., L. Michael Prisant M.D., F.A.C.C., Medical College of Georgia, Augusta, Georgia.

Forty-two Pts referred for cardiac catheterization because of suspicion of coronary disease and subsequently found to have normal coronaries (36) or insignificant disease in another coronary (6) underwent intracoronary (left anterior descending or circumflex) doppler measurements of flow reserve (FR) using intravenous dipyridamole (DIP). DIP thallium scans and 2D echocardiography were also performed for evaluation of myocardial ischemia and mass. Twenty-three Pts (55%) had LV hypertrophy from hypertension by echocardiography. Twenty of the 42 Pts had normal FR (augmented divided by baseline flow velocity $\geq$ 3:1, range 3.2 to 7). The remaining 22 Pts had abnormal FR (range 1.4 to 2.84) including 14 with markedly impaired FR ($\leq$ 2:1). Thallium scans were positive in 12 of 42 (29%). In spite of the fact that obstruction was absent in the instrumented coronary, FR was significantly lower in the group with positive as compared to negative DIP thallium scans (1.97 ± .79 vs 3.6 ± 1.3, p = .0002). In 11 of the 12 positives, FR was abnormal (p = .002). Neither LVEDP nor LV mass were predictive of a positive thallium scan in the low FR group. Conclusions: 1. In a population with a high incidence of hypertensive heart disease, provocative coronary vasodilator reserve testing using DIP frequently results in low measured FR and positive thallium scans in the absence of significant coronary obstruction. 2. Abnormally low FR is an important mechanism for positive thallium scans in Pts without significant coronary disease.

THE ROLE OF INTRAVENOUS DIPYRIDAMOLE THALLIUM IMAGING IN PREOPERATIVE CARDIAC RISK ASSESSMENT BEFORE RENAL TRANSPLANTATION.

Alan Camp, M.D., Judy Hoff, R.N., Leslee Shaw, M.A., Sheila Byers, R.N., Paul Garvin, M.D., Bernard Chaitman, M.D., F.A.C.C., St. Louis University Medical Center, St. Louis, MO.

The effectiveness of dipyridamole thallium imaging (DPT) in predicting cardiac events was assessed in 40 diabetic (20±6 years duration) renal transplant candidates. Of the 40 pts, whose average age was 42 (27-64) years, 34 (85%) were hypertensive and 21 (53%) were cigarette smokers. Prior cardiac history included chest pain in 6 pts and myocardial infarction (MI) in 3 pts. Cardiac events (CE), defined as cardiac death, MI, or unstable angina occurred in 6/40 (15%) pts over a mean follow-up of 17 (1-25) months. On DPT, 9 pts had reversible defects, 8 pts had fixed defects, and 23 pts had normal scans. Only pts with reversible defects had CE 6/9 (67%). Of the 6 pts with CE, 3 occurred in pts awaiting transplantation (1 sudden cardiac death, 2 MI). Of the 21 pts that had renal transplants, 3 had CE, all within 6 weeks after transplantation. Transplanted pts have been followed for a mean of 11 (1-21) months.

| Thallium Result | Reversible (p<.01) | Fixed | Normal |
|---|---|---|---|
| Cardiac Events | 6 | 0 | 0 |
| No Cardiac Event | 3 | 8 | 23 |

Thus, diabetic pts awaiting renal transplant can be safely and accurately risk stratified with DPT. Routine coronary angiography is not necessary to risk stratify this high risk clinical patient subset.

THE COST-BENEFIT ADVANTAGE OF PRIMARY SCINTIGRAPHIC EVALUATION AFTER UNCOMPLICATED ACUTE INFERIOR WALL MYOCARDIAL INFARCTION.
David C. Reed, M.D., Lorene N. Shaw, BSN, Donald L. Kaiser, DPH and Robert S. Gibson, M.D., FACC, University of Virginia, Charlottesville, Virginia

Most evaluations of cost-effectiveness utilize only initial gains and outlays and do not take into account outcome based on prospectively obtained population specific natural history data. To fully assess the cost-benefit of various risk stratification strategies after uncomplicated inferior infarction (IMI) we tested 4 diagnostic and management algorithms (A1 = cath defined, A2 = TL-201 directed, A3 = cath followed by TL-201, A4 = subgroup directed:Q-wave MI TL-201, Non-Q-wave MI cath) and compared the results with those of our natural history post-IMI population (62% multivessel disease, 36% LAD disease, 31% cardiac event rate during 39 mos follow-up). A2 is the least expensive diagnostic method (13-31% less) but leads to the highest initial treatment costs (19-30% more) due to more CABG surgery or PTCA. In contrast, its secondary costs are least because of fewer required subsequent interventions (up to 30%) and more moderate follow-up expense. A1 is least desirable, despite lower costs, due to the increased number of unprevented deaths and iatrogenic MIs. A2, A3, A4 decreased future MIs but only A2 and A4 lead to net positive lives saved with A2 saving 18 lives/1000 patients over 3 years at the lowest rate: $659.221/life saved. **Conclusion:** Patients with uncomplicated IMI should undergo initial TL-201 scintigraphy as the functional detection of ischemia leads to a more favorable cost-benefit ratio. However, identification of additional high risk variables is required to reduce the high cost of even this method.

RELATIVE CORONARY FLOW RESERVE REFLECTS STENOSIS SEVERITY MORE ACCURATELY THAN ABSOLUTE FLOW RESERVE DURING CHANGING AORTIC PRESSURE AND CARDIAC WORKLOAD.
K. Lance Gould, M.D., FACC, Richard L. Kirkeeide, Ph.D., Martin Buchi, M.D., University of Texas Medical School at Houston, Houston, TX.

Coronary flow reserve (CFR) indicates functional stenosis severity but is altered by conditions unrelated to stenosis geometry. To assess their effects on CFR, aortic pressure (AP) and pressure rate product (PRP) were altered by Phenylephrine (P) and Nitroprusside (N) in 11 acute dogs with 340 stenoses of the left circumflex by a calibrated stenoser providing % area stenosis (%S) with CFR measured by flowmeter after intracoronary adenosine. Absolute CFR (max/rest flow) with no stenosis (CFRn) was 5.9±2.5 (1SD) ranging from 2.0 to 12.1 depending on AP/PRP. However, relative CFR (CFR/CFRn) was independent of AP/PRP since their affects on both numerator and denominator cancel. The size of one standard deviation (SD) expressed as % of mean absolute CFR was ±43% without S and for each category of stenosis severity from 0 to 100% S averaged ±45% compared to ±17% for relative CFR. For example, for a 65% S, absolute CFR was 5.2±1.7, a ±33% variation whereas relative CFR was 0.9±0.09, a ±10% variation over the same range of AP/PRP. Conclusions: Absolute CFR by flowmeter is highly variable for fixed stenoses depending AP/PRP whereas relative CFR, as by PET perfusion imaging, is better suited for assessing stenoses severity independent of physiologic conditions.

## Wednesday, March 22, 1989
## 8:30AM–10:00AM, California Room C
## Anaheim Convention Center
## Antiarrhythmic Drugs/Ventricular Arrhythmias

THE SAFETY, EFFICACY AND PREDICTIVE VALUE OF DRUG TERMINATION OF VENTRICULAR TACHYCARDIA.
Michael Griffith MRCP, Nicholas Linker MRCP, David Ward MD FACC, John Camm MD FACC. St. George's Hospital, London, UK

Drug termination is frequently used in the acute management of VT. The relative merits or significance of the effects of the drugs available is not known. In this study drugs were given intravenously as bolus doses (adenosine (A) and lignocaine (L)) or infusions (disopyramide (D), flecainide (F) and sotalol (S)) during induced, sustained haemodynamically stable VT in serial trials over aperiod of a week. VT was terminated by pacing if it continued 10 minutes after end of drug administration. Re-induction of VT was attempted 15 mins after the infusions to assess suppression, defined as no inducible VT, or re-induction requiring either more extrastimuli or a faster (>20bpm) drive rate. Twenty four pts underwent 105 trials with termination of VT in 35 trials by the drug. In six pts no drug terminated VT. Adenosine did not terminate VT in any pt (so acted as a control). The number of pts whose VT was terminated by each drug are listed.

| Drug | A | L | D | F | S |
|---|---|---|---|---|---|
| Termination | 0/23 | 7/23 | 12/24 | 11/20 | 5/15 |
| Suppression+Termination | | | 6/12 | 6/11 | 3/5 |
| Suppression-Termination | | | 1/12 | 0/9 | 4/10 |

The association of termination by D and F with suppression was significant ($p<0.05$) but not specific. Serious adverse effects during VT were seen in 5/20 patients with F (4 proarrhythmic, 1 haemodynamic), in 2/15 patients with sotalol (both haemodynamic) and in 1/24 patients with D (proarrhythmic) but were not seen with L or A.
Conclusion. F was the most effective but had the most adverse effects, while L was both significantly safer and less effective ($p<0.05$). Drug termination by D and F but not S were predictors of suppression of VT re-induction.

SELECTIVITY OF A NOVEL CLASS III ANTIARRHYTHMIC AGENT
John R. Onufer, M.D., Steven M. Pogwizd, M.D., Peter B. Corr, Ph.D., Washington University, St. Louis, MO

UK-66914 is a novel class III antiarrhythmic agent which blocks competitively outward $K^+$ conductance and increases the refractory period in atrial and ventricular tissue. Since other class III agents also decrease conduction velocity (CV) in ischemic or periinfarct regions potentially modifying their antiarrhythmic efficacy, the present study was performed to evaluate whether UK-66914 altered CV in dog hearts in vivo with a previous anterior infarct of greater than 6 mo duration. CV was determined on a beat to beat basis using a 3-dimensional mapping system and recording from 240 simultaneous transmural sites. Treatment with UK-66914 (50 μg/kg) resulted in a mean increase in the ventricular refractory period of 20.8 ± 12.8 ms, $p<.001$. Total activation time for sinus beats as well as $S_1$ and $S_2$ stimulated beats were unchanged between the control interval and after treatment with UK-66914. Mean CV of $S_1$ beats (250 ms) in regions with normal CV was 76 ± 2.5 cm/s before and 75 ± 2.5 cm/s after UK-66914 ($p > .6$). In regions of slowed conduction (< 50 cm/s), CV for $S_1$ was 26 cm/s and was unchanged after treatment ($p > .39$). $S_2$ at 140 ms resulted in a CV of 80 ± 2.3 cm/s before and 80 ± 2.5 cm/s after UK-66914 ($p > .60$). In regions of slowed conduction, CV for $S_2$ was 36 ± 1.9 cm/s before and increased to 50 ± 7.4 cm/s after treatment. Premature stimuli at 180 ms also resulted in no significant changes in CV between the control and treatment intervals. In conclusion, UK-66914 does not adversely alter CV or activation time in vivo in normal or periinfarct regions although the agent significantly prolongs the refractory period indicating a specific antiarrhythmic effect not shared by other class III agents.

**COMPARISON OF ANTIARRHYTHMIC EFFICACY AND SAFETY OF CLASS 1A, 1B, AND 1C AGENTS IN SYMPTOMATIC AND POTENTIALLY MALIGNANT VENTRICULAR ARRHYTHMIA**

Prakash Deedwania, M.D., F.A.C.C., Peter Pool, M.D., F.A.C.C., Robert Zoble, M.D., F.A.C.C., and the Encainide Study Group, VAMC/UCSF School of Medicine, Fresno, CA

Recently several new class I agents with varying spectrum of electrophysiologic actions have been approved for clinical use. However, little data is available regarding their comparative efficacy and safety. In this multicenter, placebo (pl) controlled, randomized, parallel study, procainamide (P), mexiletine (M) and encainide (E) were compared in 141 pts with chronic frequent (≥30/hr) and repetitive PVCs with symptoms or organic heart disease. All antiarrhythmic drugs were discontinued and after 7-10 days pl, pts were randomized to E, M or P given in titrated doses (for 90% PVC↓) up to 50 mg TID, 400 mg TID and 1000 mg QID, respectively, for 6 wks. Efficacy was assessed by 24 hr Holter monitorings. Only tapes with ≥ 18 hrs of data were analyzed blindly at a central facility for uniformity. The interim analysis of 69 pts revealed the baseline total and repetitive PVC rates to be comparable in the 3 groups. During therapy, the median % reduction in log transformed total PVC rate was 95% with E, 55% with M and 42% with P,encainide being significantly more effective than M (p=0.004) or P (p=0.001). Using 90% PVC ↓ as a criterion, 59% of E, 25% of M and 29% of P pts achieved adequate response. The median % ↓ in repetitive PVCs was 100% for E, 96% for M and 74% for P (p=ns). An overall test for adequate response (90% ↓ in total and repetitive PVCs) revealed E to be superior to M (p=0.01) and P (p=0.02). Four % of E versus 37% of M and 33% of P pts prematurely withdrew due to adverse experiences. Conclusion: E is more effective and better tolerated than M or P in pts with symptomatic and potentially malignant ventricular arrhythmia.

ELECTROPHYSIOLOGIC AND HEMODYNAMIC EFFECTS OF SUN-1165: A NEW ANTIARRHYTHMIC DRUG

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SUN-1165 [N-(2,6-dimethylphenyl)-8-pyrrolizidineacetamide hydrochloride hemihydrate] (S) is a new antiarrhythmic drug with class Ic properties in vitro. We assessed acute electrophysiologic (EP) and hemodynamic (HD) effects of S in 18 pts with supraventricular tachycardia (SVT) (6 pts with AV nodal reentrant tachycardia (AVNRT), and 12 pts with AV reentrant tachycardia (AVRT)). All pts were free from organic heart disease. EP and HD studies were performed before and 60 min after a single oral administration of S (150 or 200 mg). S significantly shortened sinus cycle length (798±172 to 727±106 msec, M±SD, p<0.01); lengthened sinoatrial conduction time (98±21 to 112±21, p<0.01), AH interval (83±11 to 100±15, p<0.01), HV interval (42±8 to 63±17, p<0.001), and RV effective refractory period (220±28 to 231±27, p<0.05). Anterograde conduction via accessory pathway (AP) was abolished in 5/7 pts. Retrograde conduction via AP and AV node was abolished in 9/12 and 2/6 pts respectively. Induction of SVT was completely suppressed in 9/13 pts (3/5 pts with AVNRT, and 6/8 pts with AVRT). By HD studies (10 pts), decrease of stroke volume index (47±7 to 40±7; p<0.05), and increase of mean pulmonary arterial pressure (16±2 to 19±3 mmHg, p<0.05) were demonstrated. Plasma level of S at the time of these studies was ranged 0.19 to 1.88 (1.00±0.60) mcg/ml. No adverse effects were observed. In conclusion, oral S has potent EP effects on impulse propagation through AV node and AP resulting in cessation of reentry. And it will be safe and useful drug in preventing SVT. Cautions, however, may have to be paid on its negative inotropic action.

DYNAMIC RESPONSE OF CONDUCTION VELOCITY TO QUINIDINE DURING PULSE TRAIN STIMULATION IN CANINE PURKINJE FIBERS.

Douglas L. Packer M.D., F.A.C.C., Augustus O. Grant M.D., F.A.C.C., Harold C. Strauss M.D., C. F. Starmer M.D., Duke University Medical Center, Durham, North Carolina.

To determine if the relationship between squared conduction velocity ($\theta^2$) and $\dot{V}max$ remains linear during repetitive stimulation in the presence of quinidine (4-8 mg/l), 11 canine Purkinje fibers were studied with a double microelectrode technique. Conduction time was determined using $\dot{V}max$ as a fiducial point. With abrupt onset repetitive stimulation, a frequency-dependent monoexponential decline in $\theta^2$ was observed which paralleled changes in net membrane currents as reflected by $\dot{V}max$. The uptake rates and steady-state change in $\theta^2$ were both use and concentration-dependent. Quinidine apparent binding and unbinding rates derived from $\theta^2$ were $1.2 \pm .24 \times 10^3$/Msec and 63 ± 12/sec for the activated and $1.5 \pm 1.0 \times 10^3$/Msec and .16 ± .06/sec for the resting membrane states. The steady-state relationship between $\theta^2$ and $\dot{V}max$ was linear (r=.98±.02) with a 1:1 relationship in 7 fibers (mean slope= 1.02 ± .13). A concentration-independent, 1:1 relationship persisted dynamically over the course of 20 sec pulse trains (mean slope= 1.1 ± 0.3) with no deviation from linearity at any stimulation frequency. These data suggest that the linear relationship between $\theta^2$ and net membrane currents seen at steady state is maintained under the dynamic conditions of repetitive stimulation, and indirectly suggests that quinidine does not appreciably alter passive membrane properties over the course of a pulse train.

ELECTROPHYSIOLOGIC EFFECTS OF ADENOSINE FOLLOWING ORTHOTOPIC CARDIAC TRANSPLANTATION: EVIDENCE OF SUPERSENSITIVITY.

Kenneth A. Ellenbogen, M.D., FACC, Marc D. Thames, M.D., FACC, John P. DiMarco, M.D., FACC, Helen Sheehan, R.N., Bruce B. Lerman, M.D., FACC, McGuire VAMC, Med Coll of VA, Richmond, VA and U. of Virginia, Charlottesville, VA.

Adenosine (ADO) and acetylcholine (ACH) have similar electrophysiologic effects thought to be mediated by a common transduction process. Denervated sinus and AV nodes are supersensitive to ACH. We hypothesized that after cardiac transplantation (CT) the donor sinus node (Denervated, DSN) has greater responses to ADO than the recipient sinus node (Innervated, ISN). We measured changes in sinus cycle length (ΔSCL), time to peak effect, and duration of effect for DSN and ISN with boluses of ADO (25-112 ug/kg) in 21 pts with CT and 10 controls (data for 75 ug/kg dose in table; * p < 0.05).

| | SCL (ms) | %ΔSCL | Peak Onset (sec) | Duration (sec) |
|---|---|---|---|---|
| Control (n=10) | 828±88 | 4±2 | 9±2 | 4±1 |
| ISN (n=21) | 877±64 | 21±6 | 17±1* | 4±1 |
| DSN (n=21) | 706±23 | 85±20* | 6±1* | 23±1* |

DSN is markedly more sensitive to ADO than ISN. These effects are not due to hypoperfusion or surgical trauma to the ISN since responses of ISN and control are similar. Effects of ADO on ISN and DSN were not attenuated by autonomic blockade in 5 pts. The exaggerated response to ADO may be attributable to a shared messenger and may explain the bradycardia noted during episodes of CT rejection.

# Wednesday, March 22, 1989
# 10:30AM–12:00NOON, California Room C
# Anaheim Convention Center
# Antiarrhythmic Drugs in Supraventricular Tachyarrhythmias

**FLECAINIDE ACETATE FOR THE TREATMENT OF POSTOPERATIVE ATRIAL ARRHYTHMIAS.**

Samir Wafa MB ChB, David Ward MD, FACC, John Parker MD, John Camm MD, FACC. St. George's Hospital, London, UK.

The antiarrhythmic efficacy of intravenous flecainide (F) and intravenous digoxin (D) was assessed in 30 pts (27 males), aged 43 to 73 (63.2 ± 6.7) years who developed atrial arrhythmias in the first 96 hours after open heart surgery. Twenty eight had AF and 2 had atrial flutter. Pts were entered into the study if the arrhythmia had persisted for at least 15 minutes with a ventricular rate > 120 beats/minute. Pts were randomised to F (group 1, n = 15) or digoxin (group 2, n = 15). F was given as a bolus of 1 mg/kg over 10 minutes followed by an infusion of 1.5 mg/kg/hour for 1 hour and then by an infusion of 0.25 mg/kg/hour for the rest of the 24 hour study period. D was given as a bolus dose of 0.5 mg followed after 6 and 12 hours by 0.25 mg bolus doses. In both groups, intravenous verapamil 10 mg was given after 45 minutes if AF or flutter persisted with a mean ventricular rate of >100 beats/minute. The antiarrhythmic efficacy was assessed by 24 hour Holter monitoring and frequent 15 second rhythm strips. Within 45 minutes F alone achieved control of arrhythmia which was maintained for the rest of the 24 hour study period in 10/15 (9/15 reverted to sinus rhythm and 1/15 remained in arrhythmia with a controlled ventricular response rate = CVRR) compared to 2/15 achieved by D alone (both remained in arrhythmia but with CVRR) ($p<0.01$). Within one hour F either alone or combined with verapamil controlled arrhythmia in 12/15 (10/15 reverted to sinus rhythm and 2/15 remained in arrhythmia with CVRR) compared to 3/15 controlled by D either alone or combined with verapamil (all remained in arrhythmia with CVRR) ($p<0.01$). There were no serious adverse effects in both groups. Conclusion: Intravenous F was safe and more effective than conventional pharmacological therapy for recent onset postoperative atrial arrhythmias.

**FLECAINIDE FOR PREVENTION OF PAROXYSMAL ATRIAL FIBRILLATION AND FLUTTER. A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER STUDY.**

Adrian H. Pietersen M.D. and Henning Hellemann M.D. on behalf of the danish-norwegian flecainide multicenter study group, Rigshospitalet, University hospital, Copenhagen, Denmark.

Purpose: To evaluate flecainide (F) in prevention of attacks of paroxysmal atrial (A) fibrillation and flutter. Method: Inclusion criteria were at least 3 attacks in the preceding 3 months, on 3 different days, each attack lasting not more than 3 days. Forty-three Pts (23 males), mean age 53 ± 13 (1 SD) (range 21-73) fulfilled these criteria and were randomized to either F 300 mg/day (Pts < 60 kg, 200 mg/day) or matching placebo for 3 month in each period. With intolerable symptoms it was allowed to stop the treatment and cross-over, before the end of a 3 months period. Pts kept a diary for recording attacks. At least 2 of these should, in each period, be verified objectively by a mini-ECG-eventrecorder.

Results: All 43 Pts were treated at least 1 week in each period (group (G) I), of these 39 Pts were treated for at least one month (G II), while 24 Pts went through all 3 months in each period (G III). For statistical reasons each group were evaluated separately:

| | G I/1 week | | G II/1 month | | G III/3 month | |
|---|---|---|---|---|---|---|
| Treatment | Placebo | F | Placebo | F | Placebo | F |
| Sample size | 43 | 43 | 39 | 39 | 24 | 24 |
| Attack rate | | | | | | |
| Median | 2 | 0 | 6 | 0 | 10 | 0 |
| Range | 0-30 | 0-37 | 0-124 | 0-60 | 0-324 | 0-35 |
| 1.-3.quartile | 1-4 | 0-2 | 3-12 | 0-4 | 4-23 | 0-7 |
| Difference (Wilcoxon/ranks) | 2p = 0.003 | | 2p = 0.0002 | | 2p = 0.001 | |

S-F concentration were after 1 week of treatment in mean 1.24 ± 0.49 umol/l (range 0.51-2.30) and after 3 months in mean 1.03 ± 0.47 umol/l (range 0.26-2.42). In 32 of the 43 Pts a total of 51 side effects were reported: Gastrointestinal in 12 Pts, dizziness 11, eye trouble 11, tiredness 3, amenorrhea 1, others 7. Cardiovascular complaints were exercise dyspnea and weight gain in 1 Pt and bradycardia in 1. Two Pts had increase in attack rate. One developed a sustained attack of A flutter with intermittent 1:1 conduction.

Conclusion: Flecainide significantly suppresses the number of attacks in paroxysmal A fibrillation and flutter. Side effects are frequent but mostly tolerable with only 2 withdrawals.

**FLECAINIDE FOR HEART RATE CONTROL IN ATRIAL FIBRILLATION**

T. Craig Timm, M.D., Anne A. Knowlton, M.D. Nancy J. Battinelli, Rodney H. Falk, M.D., FACC. Boston City Hospital, Boston, MA.

Digoxin (Dig) may be inadequate for control of heart rate (HR) during exercise testing (ETT) in patients (pt) with atrial fibrillation (AF). To assess the efficacy of flecainide (FL) we studied 12 pt in a double blinded trial of Dig, Dig+ FL 100 bid, and FL 100 bid. FL 150 bid + Dig was given to 5 pt with inadequate HR control in blinded periods. Compared to Dig, HR was decreased by Dig+FL during ETT. Resting HR was unchanged with Dig+FL but was increased with FL alone. Peak HR was inversely correlated with FL level in patient also receiving Dig ($r=-.61$, $p=.02$).

HR Data for Modified Bruce ETT:

| | Dig | FL | Dig+FL | Dig+150bidFL |
|---|---|---|---|---|
| Rest | 81 | 92* | 76 | 77 |
| 3 min | 132 | 124 | 109* | 100* |
| 6 min | 145 | 142 | 123* | 120* |
| 9 min | 160 | 152 | 139* | 111* |
| Peak | 192 | 187 | 175* | 160* |

*p<.05 cf Dig alone

Dig+FL also reduced peak HR on Holter monitoring but not mean HR. Noncardiac side effects were rare but sustained VT occurred in 1 pt and VF in 1 pt at peak exercise. CONCLUSIONS: Digoxin is superior to flecainide for heart rate control in AF but digoxin + flecainide is superior to either alone. Significant exercise induced arrhythmia may occur with flecainide even in the absence of proarrhythmia on Holter monitoring.

**AMPLIFICATION OF DILTIAZEM'S EFFECTS ON THE AV NODE BY RAPID ATRIAL INPUT LEADS TO SELECTIVE ACTIONS DURING ATRIAL FIBRILLATION.**

Mario Talajic, MD, Monsen Nayebpour, PharmD, Wuhua Jing, MD, Stanley Nattel, MD, FACC, Montreal Heart Institute, Montreal, Canada.

Diltiazem (D) reduces the mean ventricular response (RR) in pts with atrial fibrillation (AF) at doses that have little effect on AV conduction during sinus rhythm. This could be a consequence of use-dependent enhancement of calcium channel blockade by D resulting from rapid atrial input into the AV node. To evaluate this possibility, we studied the rate-dependent effects of D on the 2 determinants of RR: concealed AV nodal conduction and AV node functional refractory period (FRP). These were evaluated at multiple cycle lengths (CL) and during AF (using RR histogram analysis) before and after D in autonomically blocked dogs. D produced small increases in FRP at long CL (means 10,18,31% for dose 1,2,3 respectively), larger increases at short CL (17,50,81%) and maximal increases during AF (39,86,154%). The rate-dependence of FRP after D was opposite to the decrease in FRP at shorter CL observed under control. Moreover, increased AV refractoriness caused by D also enlarged the zone of concealment (ZOC, measured using $S_1S_2S_3$ protocol) in a frequency-dependent manner (88±48 msec at CL 1 sec, 183±56 msec CL 500 msec, $p<0.001$). The combination of rate-dependent increases in FRP and ZOC resulted in an effect on RR (increases of 88, 197, and 300%, doses 1,2,3) which was 8-10 fold greater than that on FRP at CL comparable to sinus rhythm in man. We conclude that rate-dependent amplification of D's effects on FRP and AV nodal concealment leads to highly selective depression of AV node function during AF. This constitutes an important antiarrhythmic consequence of modulated receptor mechanisms.

INTRAVENOUS FLECAINIDE VERSUS INTRAVENOUS DISOPYRAMIDE IN THE REVERSION OF ATRIAL FIBRILLATION

Martin N Wiseman MB, Anthony W Nathan FACC, St Bartholomew's Hospital, LONDON, UK.

Drug reversion of atrial fibrillation (AF) to sinus rhythm avoids the need for direct current cardioversion under general anesthesia. Both disopyramide (D) and the newer agent flecainide acetate (F) have been used intravenously for this purpose. 25 pts with spontaneous AF were allocated randomly to double blind treatment with D (12 pts) or F (13 pts), 2mg/kg over 10 minutes. Duration of AF was 132 ± 233 days (F pts 141 ± 269 days, D pts 124 ± 200 days, p=NS). Seven pts treated with F reverted compared with only one treated with D (p<.05). All pts who reverted had AF present for 26 hrs or less, and reviewing all pts with AF present for 2 days or less there was no significant difference in the rates of reversion (F 7/8, D 1/3). In 2 pts in each group adverse events were recorded: one F pt reported a slight headache, another developed ventricular bigemini in the 2 minutes post reversion; one D pt developed a few short runs of ventricular tachycardia after injection, and another had the injection terminated after 8 minutes with the onset of ventricular tachycardia (>15 beats). DC cardioversion was immediately performed in 15 pts who had not reverted, and was successful in all cases.

Conclusions: 1) F is an effective and safe agent in the reversion of acute AF; 2) pts with AF present for less than 2 days may be candidates for drug reversion; 3) pts with AF present for longer than 2 days should be considered for elective DC cardioversion, although there may be a role for pretreatment with an intravenous antiarrhythmic.

COMPARISON OF FLECAINIDE VS PROCAINAMIDE IN DEPRESSING RETROGRADE CONDUCTION IN ATRIOVENTRICULAR NODAL REENTRY TACHYCARDIA

Russell T. Steinman M.D., Alan Olivenstein M.D., Claudio D. Schuger M.D., Michael H. Lehmann M.D., F.A.C.C., Wayne State University and Harper Hospital, Detroit, MI

Class IA antiarrhythmic agents are useful in the treatment of atrioventricular nodal reentry tachycardia (AVNRT) by depressing ventriculoatrial (VA) conduction. Class IC agents also depress VA conduction in AVNRT pts, but the relative efficacies are not well established. We compared the actions of Procainamide (10mg/kg, IV) vs Flecainide (mean 288mg/d, p.o.) on VA conduction in 8 pts with sustained AVNRT. The shortest ventricular paced cycle lengths with 1:1 VA conduction were:

| | | |
|---|---|---|
| Baseline | 291 ± 67 ms | all values |
| Procainamide | 391 ± 43 ms | mean ± SD |
| Flecainide | 492 ± 76 ms | |

Although both drugs depressed VA conduction significantly compared to baseline (p<.005), Flecainide's effect was greater than Procainamide's (p <.04). Sustained AVNRT remained inducible in 3 pts with Procainamide, but none with Flecainide; AVNRT terminated in the retrograde limb when rendered non-sustained (1 pt Procainamide, 3 pts Flecainide). During a 14 ± 7 mo follow-up on long-term Flecainide, there was no recurrent AVNRT. Conclusions: 1) Flecainide is more effective than Procainamide in depressing retrograde condtion in pts with AVNRT. 2) Flecainide represents a favorable alternative to Class IA agents as first line chronic therapy in pts with AVNRT.

## Wednesday, March 22, 1989
## 8:30AM–10:00AM, Santa Ana Room 1
## Anaheim Convention Center
## Surgery for Coronary Artery Disease

EVALUATION OF ENDOTHELIAL DEPENDENT RELAXATION IN HUMAN SAPHENOUS VEINS

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Baylor College of Medicine, Houston, Texas

Endothelial dependent relaxation factor (EDRF) activity has been observed in veins, but little is known about it. In order to evaluate its magnitude and the influence of various factors upon it strips of VG from 78 pts were contracted with phenylephrine and exposed to nitroglycerin (NTG) a non-EDRF dependent agent and ionophore A23187, an EDRF dependent agent. Interventions were compared with control strips stored in Kreb's solution: I-immediately after harvesting; II-storage in 0.9% saline (22°C) for 1 hr; III-storage in Plasmalyte (22°C) for 1 hr; without (IIIa) and with (IIIb) inflation to 400 mmHg; IV-storage in Plasmalyte for 1 hr and inflation without (IVa) or with (IVb) NTG; V- as in IV either without (Va) or with (Vb) verapamil instead of NTG. Relaxation with NTG was well preserved in all groups (68-91%). EDRF dependent relaxation was 36±4% in group I and ranged from 19 to 34% of baseline in groups II-V with the highest level in group IIIa (34 ± 4%). These results were correlated with electron microscopy. Early graft patency at autopsy in 11 pts from a series of pts subsequently operated upon using group III techniques was 97% (29/30). Light microscopy showed marked reduction in VG endothelial and inflammatory changes compared to age, sex and time matched controls which had used the group II method. Thus although venous EDRF activity is weaker than arterial EDRF, it is reproducibly present and is adversely affected by common methods of VG preservation. Because EDRF is a potent inhibitor of platelet adhesion and aggregation and is a vasodilator, EDRF may be important for good early and late VG function.

PREOPERATIVE ASPIRIN IS NOT NECESSARY TO ACHIEVE IMPROVED VEIN GRAFT PATENCY AFTER CORONARY ARTERY BYPASS SURGERY: VA COOPERATIVE STUDY #297.

Report prepared by Steven Goldman, M.D., F.A.C.C., Jack Copeland, M.D., F.A.C.C., Thomas Moritz, M.S., William Henderson, Ph.D., Karen Zadina, R.N., M.A. and VA Cooperative Study on Antiplatelet Therapy, Tucson VAMC and University of Arizona, Tucson AZ, and VA CSPCC, Hines, Illinois.

To determine if preoperative dosing with aspirin is necessary to achieve improved graft patency at one week after coronary artery bypass grafting (CABG), we compared aspirin (325 mg), given as one dose 12 hours before surgery, with placebo. Following surgery, all patients received aspirin (325 mg qd), with the first dose administered 6 hours postoperatively through the nasogastric tube. Graft patency data, determined by angiography, were obtained early (median of 8 days) after operation. In 292 patients with 954 grafts there was no difference in the early graft occlusion rate (6.3% with aspirin compared to 7.6% with placebo). Both the requirement for red blood cell replacement (1000 ml with aspirin compared to 750 ml with placebo, P<0.01) and the reoperation rate (7.9% with aspirin compared to 2.7% with placebo, P<0.03) were greater in the patients treated preoperatively with aspirin. In conclusion, early vein graft patency is not different when aspirin is started before operation compared to beginning aspirin 6 hours after surgery. Moreover, the administration of aspirin before CABG increases the rate of reoperation.

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THE ENDOTHELIUM PROTECTS AGAINST CONTRACTIONS INDUCED BY HISTAMINE AND SEROTONIN IN ARTERIAL, BUT NOT IN VENOUS CORONARY BYPASS GRAFTS.

Zhihong Yang M.D., Dennis Diederich M.D., Kurt Schneider M.D., Robert Siebenmann M.D., Peter Stulz M.D., Ludwig von Segesser M.D., Fritz R. Bühler M.D., Thomas F. Lüscher M.D., Division of Cardiology, Dept. of Research and Surgery, University Hospital Basel and Dept. of Cardiovascular Surgery, University Hospital Zürich, Switzerland.

Internal mammary artery grafts (IMA) have a higher patency rate and lower patient mortality than saphenous vein grafts (SV). Release of endothelium-derived relaxing factor (EDRF) in response to platelet-derived products and histamine may be important for graft function. IMA and SV rings with and without endothelium obtained intraoperatively were suspended in organ chambers filled with physiological salt solution (37°C;95%$O_2$/5%$CO_2$); isometric tension was recorded. In IMA rings with endothelium, histamine ($10^{-8}$-3x$10^{-6}$M) induced potent endothelium-dependent relaxations (70±5%;$IC_{50}$ 6.5±0.2) inhibited by methylene blue ($10^{-5}$M; to block guanylate cyclase) or hemoglobin ($10^{-5}$M), but not by meclofenamate ($10^{-5}$M; to inhibit prostacyclin) delineating EDRF as the mediator. The histaminergic receptor releasing EDRF $H_1$-histaminergic in nature, since chlorphenramine but not cimetidine inhibited the response. In contrast, in SV with endothelium histamine did not cause endothelium-dependent relaxations but endothelium-dependent contractions at higher concentrations. The endothelium inhibited contractions to serotonin in IMA, but not SV. In SV, contractions were enhanced as compared to IMA (n=6;p<0.005). Thus, EDRF protects against contractions to histamine and serotonin in IMA, but not SV. This may be important for improved arterial graft function and patency.

MYOCARDIAL INFARCTION COMPLICATING ELECTIVE CORONARY BYPASS SURGERY

Robert J. Burns, M.D., F.A.C.C., Peter J. Gladstone, M.D., Christopher M. Feindel, M.D., David R. Salter, M.D., Irving H. Lipton, M.D., Tirone E. David, M.D., F.A.C.C., Toronto Western Hospital, Toronto, Canada.

Standard diagnostic criteria for myocardial infarction (MI) are unreliable early after coronary bypass surgery (ACB). We employed immediate pre- and 48-hour postoperative technetium-99m pyrophosphate single photon tomography (PPi-SPECT) to detect periACB MI in 12 of 58 elective, stable angina patients (21%) and logistic regression to determine pre- and intraoperative predictive variables. Serial CK-MB's were higher in MI patients (p=0.0003); only 1/12 had new Q waves. Preoperative symptom class (NYHA 3.3 vs 2.8 (MI vs no MI), p=0.04) and smallest grafted distal vessel lumen calibre (1.3 vs 1.5mm, p=0.03) were multivariate predictors of perioperative MI. Five MI's occurred in segments revascularized using sequential vein grafts, and 7 in segments perfused by significantly stenosed epicardial vessels with distal lumen diameter and perfusion territory considered too small to warrant bypass. At 6 month follow-up LV ejection fraction had increased in negative PPi-SPECT patients (0.61 to 0.65, p=0.01) but not in perioperative MI patients.

Thus, MI is frequently detected by PPi-SPECT following successful, elective ACB for stable angina and is associated with severe preoperative angina. Our data implicate a mechanism of poor distal coronary run-off in both revascularized and nonrevascularized myocardial segments supplied by small, stenosed epicardial coronary arteries. These MI's limit postoperative recovery of LV ejection fraction.

RISK OF DEATH AFTER NONFATAL MYOCARDIAL INFARCTION IN THE VA COOPERATIVE STUDY OF CORONARY ARTERY BYPASS SURGERY.

Peter Peduzzi Ph.D., Marvin Murphy M.D., Katherine Detre M.D. Dr.P.H., James Thomsen M.D., Herbert Hultgren M.D., Timothy Takaro M.D., CSPCC VA Medical Center, West Haven, Connecticut.

The 10-year incidence of nonfatal (NF) myocardial infarction (MI) was evaluated in 686 patients (pts) who were randomly assigned to medical (M) or surgical (S) treatment. An infarction was classified as not fatal if the pt survived 4 weeks after the event. MI was defined as the development of new persistent Q-waves. The incidence of NFMI was 22.1% S vs 16.7% M (p=0.09). The higher rate in S pts was due to perioperative NFMI (7.7%) and acceleration of NFMIs after 5 years.

The risk of mortality after NFMI was 59% lower is S than in M pts (relative risk = 0.41, 95% confidence interval 0.24 to 0.71; p<0.001). In pts without MI, the RR was nearly 1.0. The reduction in post-MI mortality was most striking, in the angiographic high risk subgroup (3-vessel disease with LV dysfunction) where the relative risk of mortality (RR) was 0.08 (99% CI, 0.01 to 0.62; p=0.002).

We conclude that although S therapy does not reduce the overall incidence of NFMI, it does reduce the risk of death after MI, particularly in high risk pts who have a poor prognosis with M therapy.

LATE FOLLOW-UP OF 781 PATIENTS UNDERGOING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) OR OPEN HEART SURGERY (OHS) FOR AN ISOLATED OBSTRUCTION IN THE LEFT ANTERIOR DESCENDING (LAD) CORONARY ARTERY.

J Kramer M.D., W Proudfit M.D., F Loop M.D. F.A.C.C., M Goormastic M.P.H, K Zimmerman B.A, G Horner R.N. Cleveland Clinic Foundation, Cleveland, Ohio.

Between 1-1-80 and 12-31-84, 781 pts at the Cleveland Clinic who had either PTCA or OHS for an isolated obstruction in the LAD were followed retrospectively for survival and events. 413 pts had PTCA while 368 pts had OHS with an internal mammary artery (71.5%) or saphenous vein bypass graft (28.5%). In hospital, there were no surgical deaths and one perioperative MI while one PTCA pt died and 9 (2.2%) had MI. Six OHS pts needed reoperation while 32 PTCA pts (7.7%) needed OHS before discharge. 776 pts (99.7%) were followed 56 ± 18.4 months. At 5 years, survival was 95.3% for PTCA pts and 97.7% for OHS pts (p=0.03). Post-discharge events included recatheterization (OHS-67 pts, PTCA-229 pts, p less than 0.0001); PTCA (OHS-8 pts, PTCA-72 pts, p less than 0.001); OHS (OHS-7 pts, PTCA-24 pts, p less than 0.01). Overall, PTCA pts had lower survival and more events than OHS pts.

# Wednesday, March 22, 1989
# 8:30AM–10:00AM, Santa Ana Room 2
# Anaheim Convention Center
# Clinical Electrophysiology: Activation Sequence Mapping

ACTIVATION PATTERN DURING INDUCTION AND MAINTENANCE OF VENTRICULAR TACHYCARDIA IN PATIENTS WITH CORONARY ARTERY DISEASE.

Wilhelm Kaltenbrunner, M.D., Pierre L. Pagé, M.D., FACC, René Cardinal, Ph.D., Dominique Lacroix, M.D., Mohammad Shenasa, M.D., Ph.D., FACC. Sacré-Coeur Hosp. Université de Montréal, Montreal, Canada.

In 16 pts with remote myocardial infarction, endocardial (ENDO) and epicardial (EPI) activation mapping was performed intraoperatively during 31 morphologically distinct ventricular tachycardia (VT) induced by programmed stimulation (PS). Isochronal maps of selected cardiac cycles during induction and established VT were generated by a computerized system using 64 unipolar electrograms recorded simultaneously from both a sock electrode array (EPI) and a balloon electrode array (ENDO). In 26 VT (Group I, 14 pts) the earliest ENDO activation was detected 26 + 23 ms (mean + SD) before the onset of EPI activation, in 5 VT (Group II, 4 pts) it was 45 + 34 ms after. Evidence for reentry was found subendocardially in 6 VT (6 pts, all group I) and subepicardially in 2 VT (2 pts, all group II). The reentrant wavefront showed an ENDO figure-of-eight activation pattern in 4 VT and a circular movement in 4 VT (2 ENDO, 2 EPI). During initiation of VT, unidirectional block and a slow conduction pathway were established progressively during PS in 6 VT (5 ENDO, 1 EPI) and during the initial ventricular repetitive responses following PS in 2 VT (1 ENDO, 1 EPI). We conclude that 1) reentrant wavefront can be mapped throughout the entire VT cycle in 50% of pts and 26% of VT, 2) subepicardial as well as subendocardial layers participate in the mechanism of VT.

ENDOCARDIAL ISOCHRONAL PATTERNS NEAR THE VENTRICULAR TACHYCARDIA SITE OF ORIGIN WITH ORTHOGONAL ELECTRODE CATHETER ARRAY

Jawahar Desai, M.D., Htay Nyo, Ph.D., Zak Vera, M.D. University of California, Davis.

Recent work using balloon electrode array or electrode catheters have shown that majority of ventricular tachycardia (VT) originates from 'focal' origin with monoregional spread. We used an 8F 5 pole orthogonal electrode (E) catheter (4 peripheral, 1 central electrode, interelectrode distance 0.5 cm, 1 sq cm surface area) to study the 2-D isochronal patterns (IP) near VT site of origin. In 7 mongrel dogs, 3 to 5 plunge electrodes (PE) were randomly placed in LV. PEs paced (≥ 180 bpm) in double blind manner to simulate VT with focal origin. LV divided arbitrarily into 4 quadrants and unipolar and bipolar recordings made for each quadrant, identifying the quadrant with the earliest arrival time. PE site identified by early arrival of wavefront at one or more unipolar electrodes (≥-35 msec with ref. to earliest surface ECG). At this site radio frequency ablation was performed (all 5 E to backplate 600 KHz, 10 sec, 25 W.) All 7 dogs PE was within ablation area. IPs for area covered by 5 E were drawn for both ablation and remote sites (≤-35 msec with ref. to earliest surface ECG) from wavefront arrival times at 5 E. IP was elliptical when PE was close to central E (2), semielliptical when PE was close to one or more of peripheral Es (5). Earliest arrival time at the peripheral or central E and direction of wavefront indicates position of source. IPs remote from paced VT sites were farther apart, straighter and nonelliptical. Occasionally transverse or longitudinal velocities were identifiable by comparing unipolar electrograms to IPs. Conclusions: 1) Direction of wavefront indicated by isochronal patterns and earliest arrival times from unipolar electrograms can guide the operator to localize the site of paced ventricular tachycardia origin with orthogonal electrode catheter, 2) Elliptical and semielliptical isochrones are observed near the 'focal' site of paced ventricular tachycardia.

TRANSMURAL VENTRICULAR ACTIVATION DURING CONSECUTIVE CYCLES OF SUSTAINED VENTRICULAR TACHYCARDIA.

Nancy A. Branyas M.D., Michael E. Cain, M.D., F.A.C.C., Dennis M. Cassidy M.D., F.A.C.C., Washington University, St. Louis, Missouri.

Although computerized mapping has enabled intraoperative delineation of ventricular activation from a single complex of ventricular tachycardia (VT), beat-to-beat reproducibility of isochronic maps has not been defined. To determine the reliability of single beat analysis, epicardial, intramural and endocardial ventricular electrograms during 6 consecutive VT cycles were analyzed in each of 10 patients during intraoperative mapping of sustained monomorphic VT. Bipolar electrograms were recorded simultaneously using sock and needle electrodes from up to 96 epicardial and 160 transmural sites. In each patient, at each electrode site, local activation time, electrogram duration, and morphology were compared over 6 consecutive beats. A total of 9816 electrograms were analyzed. For each patient, the isochronic activation map during VT was reproducible with a mean beat-to-beat variation in local activation time of only 1.8+1.9 msec (p=ns). Moreover, electrogram duration did not vary significantly (1.6+3.4 msec). Epicardial electrograms, however, were significantly longer when compared to intramural and endocardial electrograms (35+22 msec vs 26+19 msec, p <.001). There were only two instances of 2:1 conduction failure, both occurred intramurally and adjacent to a site of VT origin. Thus, transmural ventricular activation during sustained monomorphic VT is reproducible regardless of electrode site or electrogram duration. These results demonstrate that single beat analysis is a reliable and expedient method to delineate ventricular activation during intraoperative mapping.

FACILITATION OF VENTRICULAR TACHYCARDIA INDUCTION BY STIMULATION AT ITS SITE OF ORIGIN.

Mohammad Shenasa, M.D., Ph.D., F.A.C.C., René Cardinal, Ph.D., Wilhelm Kaltenbrunner, M.D., Dominique Lacroix, M.D., Marc Dubuc, M.D., Pierre Pagé, M.D., F.A.C.C., Sacré-Coeur Hospital, University of Montreal, Montreal, Canada.

To determine if stimulation at the site of origin of ventricular tachycardia (VT) enhances induction of the tachycardia, we studied 16 Pts with sustained monomorphic VT during arrhythmia surgery. Induction of VT was attempted at the right and left ventricles as well as at the site of origin of VT. The site of origin of VT was determined using a computer-assisted acquisition of 63 unipolar epicardial and 63 or 32 unipolar endocardial electrograms from a sock and balloon electrode array. Stimulation at the site of origin of VT was done via the balloon electrode array. Stimulation protocol consisted of the introduction of up to 3 extrastimuli at three ventricular drive cycles. Induction of VT at the right or the left ventricular sites required stimulation at shorter cycles with up to 3 extrastimuli. Induction of VT at the site of origin was achieved during long cycles with one or two extrastimuli only. In 5 Pts, right ventricular stimulation induced only nonsustained VT while pacing at the site of origin with identical stimulation protocol induced sustained tachycardia. In 4 Pts, stimulation at the right or the left ventricle with 3 extrastimuli induced ventricular fibrillation, while stimulation at the site of origin did not. The results suggest that stimulation at the site of origin of VT facilitates the induction of sustained VT and avoids induction of nonspecific arrhythmias.

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PHASE IMAGE TRIANGULATION OF ACCESSORY PATHWAYS IN PATIENTS UNDERGOING CATHETER ABLATION OF POSTEROSEPTAL PATHWAYS

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We sought to relate findings on scintigraphic phase analysis (PhA) to electrophysiologic (EP) findings in pts prior to catheter ablation (ABL) of a posteroseptal accessory pathway (PS AP) and to prognosis after ABL. To this end, a new method was developed to triangulate on the AV valve plane, the site of earliest phase angle. The method was applied blindly to 42 preexcited pts. Among these were 21 pts with EP study indicating a PS AP, who underwent ABL. Here, we report PhA for AP localization compared to EP localization and to clinical outcome in only those having ABL.

The pre-ABL PhA localized a middle or PS AP in 16 pts, 2 with additional non-dominant right AP. In 4 other pts with a second right or left AP, PhA identified the non-PS AP correctly. PhA localization erred in 1 pt with single PS AP. The surface ECG localization of dual AP was unreliable.

Among those 15 pts with a single AP, all of 3 pts with a concentric activation of both ventricles in PhA had successful ABL, but only 6/11 pts with eccentric activation.

VA conduction time during reciprocating tachycardia failed to predict ABL outcome.

CONCLUSIONS: PhA closely localized 14/15 single PS AP. The PhA localization of a non-septal focus suggested dual AP with the non-PS AP at the site of earliest activation in PhA. In pts with single AP, a concentric activation of both ventricles in PhA suggested success of ABL.

DIRECT ENTRAINMENT GUIDED ABLATION OF THE SLOW CONDUCTION ZONE (SCZ) IN HUMAN TYPE I ATRIAL FLUTTER (AF).

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In order to avoid His bundle ablation with the subsequent creation of a pacemaker dependency state, we attempted to directly fulgurate the critical area of slow conduction of the reentrant circuit in 8 patients (pts) referred for drug resistant repetitive type I AF and His bundle ablation. Pts 1-6 had a history of symptomatic sustained AF which proved to be resistant to at least 4 antiarrhythmic agents. Pt 7 had recurrent episodes of pulmonary oedema due to AF, and pt 8 had poorly tolerated 1/1 AF. In all cases AF was induced during programmed atrial stimulation. In 7/8 pts, careful right atrial mapping during tachycardia revealed the presence of a zone of prolonged (80-130 ms) and fragmented electrograms in the low posterior right atrial septum . Other areas of fragmentation were excluded because they exhibited second degree local block either spontaneously or during fixed rate overdrive atrial pacing while entrainment criterion n°I was fulfilled. In one patient tachycardia termination was accompanied by second degree local block within the SCZ, followed by narrow local electrograms with shorter conduction time. 1 to 2 fulguration shocks (2j/kg body weight) were delivered in this area, with neither immediate nor late complications. Patients were discharged without drug therapy and AF was no more inducible in 7/8 pts immediately after the procedure, and in 4/7 pts at late control (1 and 3 months). After a mean follow up of 35,6 weeks, 3 pts experienced early (D5) and late (D80) recurrences and underwent a second ablation session which was unsuccessful in 1 pt.

In conclusion, direct entrainment guided catheter fulguration of the SCZ of human type I AF is a feasible procedure, with apparent good results, and deserves further study.

## Wednesday, March 22, 1989
## 10:30AM–12:00NOON, Santa Ana Room 2
## Anaheim Convention Center
## Catheter Ablation

CATHETER MODIFICATION OF THE ATRIOVENTRICULAR NODE: A POTENTIAL CURE FOR ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA.

Laurence M Epstein M.D., Jonathan J Langberg M.D., John M Herre M.D., F.A.C.C., Jerry C Griffin M.D., F.A.C.C., Melvin M Scheinman M.D., F.A.C.C., Univ of California, San Francisco

Recently, surgical ablation of atrioventricular nodal reentrant tachycardia (AVNRT) with preservation of antegrade atrioventricular (AV) conduction has been reported. Six patients (age 27-66) with disabling AVNRT (1/week - >25/day, for 1/2 - 20 years) who failed multiple drugs (3-10), underwent a catheter procedure to " modify " AV conduction. Earliest retrograde atrial activation during supraventricular tachycardia (SVT) was localized to the anterior low right atrial septum in all patients and dual AV nodal pathways were demonstrated in 4 of 6. The area between the His bundle electrode and coronary sinus os was divided into 3 zones and perinodal direct current shocks (1-7) of 100-300 joules were delivered in one (n=2) or each zone (n=4) without complications. The end points were induction of first degree AV block (1° AVB) and failure to induce SVT. At early restudy (1-3 days), antegrade conduction was preserved in all patients, with 1°AVB in 3 of 6. Retrograde conduction persisted in 4 of 6 patients and dual AV nodal pathways persisted in 2. No patient had inducible SVT with or without atropine and isoproterenol. Symptomatic AVNRT recurred in one patient at 3 months and required His bundle ablation. The remaining 5 patients have had no recurrences after a mean follow-up of 5.5 months (range1-10) and, of the 3 who underwent late restudy (2-6 months), 1 had inducible atrial tachycardia and AVNRT and 2 had no inducible arrhythmias. Possible mechanisms appear to be either abolition of retrograde conduction or modification of AV node function such that SVT cannot be sustained. Percutaneous catheter "AV nodal modification" appears to be a safe and potentially effective approach to the management of refractory AVNRT.

ATTEMPTED ABLATION OF LEFT SIDED ACCESSORY PATHWAYS BY RADIOFREQUENCY CURRENT

Karl-Heinz Kuck, M.D., Klaus-Peter Kunze, M.D., Manfred Geiger, M.D. and Michael Schlüter, Ph.D. University Hospital Eppendorf, Hamburg, F.R.G.

In 8 patients (5 men, 3 women, 38±10 years) ablation of a left sided (LS) accessory atrioventricular pathway (AP) was attempted with radiofrequency current (RFC). All pts had drug refractory supraventricular arrhythmias and a short (<250 ms) antegrade refractory period of the AP. 3 pts had episodes of syncope due to documented atrial fibrillation. The AP was precisely localized by direct recordings of AP potentials and by the retrograde atrial activation sequence during supraventricular tachycardia. In all pts, a dominant coronary artery close to the AP was excluded by coronary angiography. RFC was delivered 2-9 times for 10-30 seconds between an (epicardial) electrode in the coronary sinus (CS) and the tip electrode of a catheter in the LV (endocardial), directly below the mitral annulus and opposite the CS electrode. Preset voltage was 30 to 50 V with a measured current of 69±39 mA. The LS AP was located lateral in 3 pts, posterolateral in 2 pts, posterior in 2 pts and posteroseptal in 1 pt. Permanent AP block was achieved in 2 pts, prolongation of the antegrade effective refractory period of the AP in 2 pts (215->470 ms). In 4 pts, AP conduction remained unchanged. During follow-up (6±3 months) 5 pts became asymptomatic without drugs, 1 pt became asymptomatic under sotalol. 4 of these 6 pts had a normal surface ECG. 2 pts underwent surgery. Conclusion: RFC application with a bipolar epicardial-endocardial electrode configuration seems to be feasible in selected pts with a LS AP.

CATHETER ABLATION OF A POSTEROSEPTAL ACCESSORY ATRIOVENTRICULAR CONNECTION IN FORTY-TWO PATIENTS. Morady F, Scheinman MM, Kou WH, Griffin JC, Dick M, Herre J, Kadish AH, Langberg J.

Forty-two patients (pts) with a posteroseptal accessory atrioventricular connection (AAVC) and symptomatic tachycardias underwent catheter ablation of the AAVC using 200-400 joule shocks delivered by a standard defibrillator. Cathodal shocks were delivered through the proximal pair of electrodes of a 6 French quadripolar electrode catheter positioned at the os of the coronary sinus. A 16 cm patch electrode positioned on the back or anterior chest served as the anode. Two to 4 shocks were delivered (total joules 636 ± 19, mean ± SD). The ablation procedure was successful in eliminating symptomatic tachycardias in 31/42 pts (74%) over a follow-up of 29 ± 19 mos. A long-term follow-up electrophysiology study in 24 of these pts demonstrated that conduction through the AAVC was completely absent in 22 pts and present but impaired in 2 pts. The success rate was significantly higher in pts with a concealed AAVC (12/12, 100%) than in pts with manifest preexcitation (19/30, 63% p<0.001). Complications included cardiac tamponade requiring needle pericardiocentesis, AV block requiring a permanent pacemaker, and a transient atrial tachycardia in 1 pt each.

In conclusion, with the catheter ablation technique described in this study, a successful clinical outcome may be achieved in approximately 75% of pts who have a posteroseptal AAVC, with a low risk of serious complications. This technique is particularly well-suited to pts with a concealed posteroseptal AAVC, in whom the success rate is higher than in pts with manifest preexcitation.

ELECTROPHYSIOLOGIC EFFECTS OF ARGON LASER IRRADIATION DURING INTRAOPERATIVE ATRIOVENTRICULAR NODE OR ACCESSORY PATHWAY ABLATION IN MAN.

Sanjeev Saksena M.D., F.A.C.C., Isaac Gielchinsky M.D., Nicholas G. Tullo M.D. Newark Beth Israel Med Ctr - NJ Medical School, Newark, NJ.

We examined the immediate and delayed electrophysiologic (EP) effects of pulsed argon laser energy alone or combined with mechanical resection (MR) in 11 pts with refractory supraventricular tachycardia (SVT). Intraoperative map-guided laser AV nodal ablation (3 pts) or accessory bypass tract (ACB) ablation (8 pts) was performed. A 15W argon laser was coupled to a 300μ optical fiber with or without a metallic tip encasing a sapphire lens and a partial beam transmission window. Direct EP effects of laser energy alone could be examined in normothermic pts on the AV node or right/posterior septal ACB (6 pts), with MR in 2 pts with posterior septal ACB, while left-sided ACB (3 pts) required laser ablation and MR during hypothermic cardioplegic arrest.
RESULTS: Laser ablation alone of the AV node acutely resulted in 3° AV block (AVB) preceded by 1° AVB (3 pts), and associated with accelerated junctional rhythm (1 pt). Recovery of 1:1 AV conduction occurred in 2 pts (1° AVB- 1 pt; normal PR interval- 1 pt). HV interval and QRS morphology were unchanged from preoperative studies. Normothermic laser ablation alone of right-sided ACB produced immediate antegrade and retrograde ACB conduction block in all pts accompanied by transient 3° AVB in 2 pts with septal ACB. Orthodromic SVT termination with disappearance of antegrade and retrograde preexcitation during laser ablation was documented in 1 pt. Spontaneous intermittent ACB conduction occurred in 2 pts postop which became persistent (1 pt) and disappeared (1 pt). Postop EP study occasionally demonstrated slow antegrade ACB conduction during close coupled atrial extrastimulation despite elimination of delta wave (7 of 8 pts) and AV reentry (all pts). Delta wave reappeared after discharge in 2 pts with septal ACB with SVT recurrence controlled on preoperative ineffective drugs in 1 pt.
CONCLUSIONS: 1) Argon laser energy is effective in producing immediate and permanent interruption or modification of antegrade and retrograde AV nodal and ACB conduction and refractoriness in man. 2) Lens-tipped optical fibers with metallic probes should be considered for percutaneous catheter ablation systems.

**CATHETER ABLATION OF THE ATRIOVENTRICULAR JUNCTION USING RADIOFREQUENCY ENERGY**

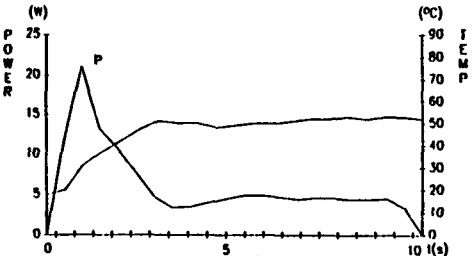
Jonathan J Langberg, M.D., Michael C Chin, B.S., John M Herre, M.D., F.A.C.C., Jerry C. Griffin, M.D., F.A.C.C.,Navneet Dullet, M.D., Melvin M Scheinman, M.D., F.A.C.C. Univ of California, San Francisco

Catheter ablation of the atrioventricular junction (AVJ) using direct current shock requires general anesthesia and may have serious side effects. Ten patients with drug-refractory supraventricular tachycardia underwent catheter ablation of the AVJ using radiofrequency (RF) energy. A standard 7Fr quadripolar electrode catheter was positioned to record the largest unipolar His potential from the distal electrode. An electrocoagulator (Microvaisive 4005) delivered continuous unmodulated RF energy at 550kHz. One to 14 applications of RF were applied between the distal electrode and a large chest wall electrode. RF of 17±4 Watts was applied for 13.5 to 120 seconds. None of the patients had pain, significant arrhythmias or blood pressure changes during RF.Five of 10 patients (Group 1) had persistent complete AV block (3°AVB) induced by RF. All of these had stable junctional escape rhythms at 46±3 BPM. His electrograms could be recorded after RF in the remaining 5 patients (Group 2), all of whom had successful His ablation with DC shock at the same session. There was no difference in unipolar His electrogram size, atrial electrogram size, atrial injury current, or energy delivery parameters (power, duration, total energy, impedance) between the two groups. The HV interval was longer in Group 1 (56±4msec) than Group 2 (42±8msec, p=.014), suggesting that a more proximal catheter position increases the liklihood of successful ablation.
CONCLUSIONS: 1. Catheter ablation of the His bundle using RF appears to be safe and painless. 2. 50% of patients had 3°AVB induced with RF, associated with a stable junctional escape rhythm. 3. All patients not ablated with RF had 3°AVB induced with DC shock.

TEMPERATURE-GUIDED RADIOFREQUENCY COAGULATION OF MYOCARDIAL TISSUE

Wilhelm Haverkamp, MD, Gerhard Hindricks, Ulrich Rissel, Thomas Budde, MD, Winfried Pfennigs, Hartmut Gülker, MD, Günter Breithardt, MD, FESC. University Hospital, Department of Cardiology, Münster, Germany (FR)

The size of lesions induced by radiofrequency energy strongly depends on the extend of tissue heating. Therefore we investigated the applicability of a new temperature-guided RF-generator (HAT 200, Osypka, FRG). The microprocessor controlled device delivers energy as a function of the preselected catheter tip temperature (TT) which is continuously monitored via an ablation catheter with a built-in tip thermistor. Energies (unipolar mode, duration: 10 - 30 s) were applied to isolated specimans (n=15) of porcine hearts which were placed in a saline bath at room temperature (24 °C).Temperature rise to preselected levels (50 - 90 °C) was paralleled by a maximum of delivered power (10.3 - 29.5 W). When TT-levels were reached delivered power decreased by approximately 70 - 80% (see graph). Total delivered energy ranged from 74 - 286 J. Lesions volume (range: 3.8 - 51 mm³) significantly correlated with the integral of the temperature curve (r = .86). Lesions revealed smooth coagulation necrosis; no crater formation, rise in impedance or catheter damage was observed. Thus, the temperature guided approach seems to improve the feasibility of RF-ablation and needs further investigation.



# Wednesday, March 22, 1989
# 10:30AM–12:00NOON, California Room B
# Anaheim Convention Center
# Pediatric Electrophysiology and Arrhythmias

LATE POTENTIALS AND INDUCIBLE VENTRICULAR TACHYCARDIA IN SURGICALLY REPAIRED CONGENITAL HEART DISEASE.

David A. Danford, M.D., Jonathan A. Stelling, John R. Windle, M.D., F.A.C.C., John D. Kugler, M.D., F.A.C.C., University of Nebraska Medical Center, Omaha, Nebraska

Episodic ventricular tachycardia (VT) appears in some pts after repair of congenital heart disease (CHD). The signal averaged electrocardiogram (SAECG) has correlated with VT by electrophysiologic study (EPS) in pts with coronary artery disease. This study compares SAECG and EPS in pts with repaired congenital heart disease to (1) select appropriate criteria for positive SAECG in this pt group, and (2) determine the accuracy of SAECG to identify pts with inducible VT by EPS. 21 pts (age 3-40, 13.7 years) with surgically repaired CHD who had EPS were studied with SAECG. Pts were classified by EPS as no VT, nonsustained VT, and sustained VT. SAECG's were examined for the duration of low amplitude (≤ 25 μV) terminal QRS signal (LAS) and the root mean square voltage in the terminal 40 msec of the QRS (RMS).

| | | LAS (msec) | | RMS (μV) | |
|---|---|---|---|---|---|
| EPS | n | range | mean | range | mean |
| Sustained VT | 4 | 16-27 | 21.8 | 22-127 | 53.5 |
| Nonsustained VT | 4 | 12-45 | 24.2 | 36-328 | 129.0 |
| No VT | 13 | 5-19 | 9.6 | 72-360 | 162.4 |

Positive LAS > 15 msec correlated highly with EPS sustained or nonsustained VT (Fisher exact p = 0.0005). Similarly, positive RMS < 70 μV was concordant with EPS (p = 0.012). This study suggests (1) SAECG is an accurate method to identify pts in whom VT is found by EPS, (2) Appropriate cutoffs for interpretation of SAECG in this pt group are 15 msec LAS and 70 μV RMS, (3) SAECG could screen asymptomatic pts at risk for VT after surgery for CHD, and help select pts for EPS.

LONG-TERM FOLLOWUP OF 109 PEDIATRIC PATIENTS TREATED FOR THE WOLFF-PARKINSON-WHITE SYNDROME

Joyce C. Pressley, M.P.H., Eric N. Prystowsky, M.D., F.A.C.C., Ronald J. Kanter, M.D., James E. Lowe, M.D., Douglas L. Packer, M.D., F.A.C.C., J. Marcus Wharton, M.D., Duke University Medical Center, Durham, NC.

Interference with normal childhood activities and the prospect of lifelong antiarrhythmic medications are factors affecting selection of therapy for pediatric patients (pts) with Wolff-Parkinson-White Syndrome (WPW). This study examined the long-term outcome of 109 consecutive pts with WPW (age 0.5-16 years) treated with surgical ablation of the accessory pathway (n=71) or with pharmacological therapy alone (n=38). Followup data were obtained in 89% by questionnaire (mean 6.0±3.8 years). At baseline, surgically treated pts had failed more antiarrhythmic drugs (2.6 vs 1.5, p=.01), had more years of arrhythmia (6.1 vs 4.1, p=.001) and had more cardiac arrests (19% vs 8%, p=.12). The distribution of accessory pathway locations, clinical arrhythmias and associated diseases were not different in the two groups. At followup, the overall mortality was not significantly different in the surgical vs medical pts (12% vs 5%) with 10/11 deaths occurring in pts with associated heart disease. Both groups reported significant improvement in the frequency (94% vs 97%) and severity (98% vs 67%) of arrhythmias post-therapy. Although 37% of pts reported palpitations and arrhythmias post-surgery, none of the surgical group required antiarrhythmic therapy. Post-therapy WPW-related hospitalizations were reduced in both groups (98% vs 93%). Surgery pts reported no post-therapy activity limitations vs 19% for pharmacologically treated pts (p=.01). In conclusion, although both groups improve significantly over baseline, surgery is superior in reducing WPW-related activity limitations and generally eliminates the need for long-term antiarrhythmic therapy.

LATE ELECTROPHYSIOLOGIC SEQUELAE OF EXPERIMENTAL RIGHT VENTRICULOTOMY WITH RIGHT VENTRICULAR HYPERTENSION.

Jeffrey P. Moak, MD, FACC; Arthur Garson, Jr., MD, FACC; Kathleen Sprague, BS
Texas Children's Hospital, Houston, Texas.

Right ventriculotomy (Vent) has been implicated as a substrate for conduction disturbances and ventricular arrhythmias. In a previous report (Pediatr Res 23:433, 1988), we observed that experimental Vent performed during low RV pressure had few electrophysiologic (EP) effects on cellular action potential (AP) characteristics or conduction on a macroscopic level. In the present study we addressed the late EP effects of Vent performed in a cyanotic model of RV hypertension. Ten animals were studied: 6 beagles served as controls. Four beagle puppies formed the study group: 3 had a PA-LA shunt and PA band, 1 had a VSD created and PA band at age 6 weeks; all had surgical Vent performed 12 months later, the PA band was left intact. All dogs had RV pressure >50 mmHg. Electrophysiologic assessment 12 months after Vent included ECG, 24 hour Holter, clinical EP and microelectrode study using standard techniques.

**Results:** 1) Marked abnormalities in AP characteristics were noted in the Vent dogs. Phase 0 upstroke velocity (543 +/- 48 vs 333 +/- 70 V/sec), AP amplitude (119 +/- 3 vs 114 +/-3 mv) and maximum diastolic potential (86 +/- 2 vs 83 +/- 1 mv) were significantly depressed in the Vent group compared with controls, p<0.05. X+SD. Post- Vent AP duration (APD) was significantly prolonged, p<0.01. For example, in the outflow septum APD 50 increased from 125 +/- 11 to 149 +/- 7 msec and APD 90 increased from 173 +/- 12 to 199 +/- 6 msec. However, lengthening of APD was less in the Vent region (APD 50= 121 +/- 16 vs 127 +/- 15 msec; APD 90= 173 +/- 18 vs 184 +/- 15 msec). 2) Delayed afterdepolarizations occurred during rapid ventricular pacing in 1 post-Vent dog. 3) In the Vent region, localized areas of conduction delay and block were demonstrated. We **conclude** that an abnormal electrophysiologic substrate develops when a Vent is healed under high RV pressure (abnormalities in conduction and refractoriness). These detrimental electrophysiologic consequences may predispose to late reentrant or triggered arrhythmias.

DETERMINANTS AND OUTCOME OF EARLY AND LATE ARRHYTHMIA AFTER FONTAN OPERATION

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Hospital for Sick Children, Great Ormond Street, London,UK

The incidence and clinical significance of arrhythmia was studied in 104 consecutive patients (pts) undergoing Fontan (F) repair from 1975-1988. 11 pts developed perioperative arrhythmia (8 atrial flutter, 3 junctional tachycardia). On multivariate analysis elevated mean perioperative pulmonary artery pressure (PAP) ($p < 0.005$) and low aortic saturation ($p < 0.05$) were significant risk factors, but not underlying morphology or surgical technique. Despite aggressive medical treatment 10 of 11 died. Clinical and annual ECG follow-up was available in all 78 hospital survivors (mean age 11.4 ± 5.4 years, interval from F 3.7 ± 3.3 years) and 63 underwent ambulatory ECG monitoring (AECG) 3.5 ± 3 years after F. 55 of 63 (87%) were in stable sinus rhythm on AECG with 2 pts in atrial flutter, 5 pts in junctional rhythm and 1 pt paced. None had significant bradycardia or ventricular arrhythmia. Actuarial survival free of supraventricular arrhythmia (SVA) 8 years after F was 82%. 11 pts had late SVA (7 atrial flutter, 1 atrial fibrillation, 3 SVT). In 9 the onset occurred early (< 4 m) after surgery during weaning from diuretics and was associated with haemodynamic upset. Multivariate analysis identified enlarged right atrium on echo ($p < 0.05$) and elevated pre-operative PAP > 20 mmHg ($p < 0.01$) as risk factors for late SVA. All pts responded to medical treatment except 1 who died at redo F. Thus, arrhythmia after F is associated with adverse haemodynamics, both early and late after surgery, rather than with underlying morphology. Medical and surgical modifications to improve the haemodynamic disturbance associated with arrhythmia are indicated.

LONG-TERM FOLLOWUP OF AMIODARONE IN THE YOUNG: CONTINUED EFFICACY, UNIMPAIRED GROWTH, MODERATE SIDE EFFECTS

Paolo Guccione, M.D., Thomas Paul, M.D., Arthur Garson Jr., M.D., F.A.C.C., Baylor College of Medicine, Texas Children's Hospital, Houston, Texas

Long-term followup on young pts receiving amiodarone (A) is lacking, especially in terms of growth and late side effects (SE). We reviewed the records of 95 young pts, mean age 12.4 yrs (3 wks-31.5 yrs), who received A. Minimum followup for those continuing to take A was 1.5 yrs; mean duration of therapy was 2.3 (max. 6.5) yrs. Mean maintenance dose was 7.7 (1.5-25) mg/kg/d. Initial success (symptoms and 24 hr-ECG) was achieved in 23/34 pts with ventricular tachycardia (VT) (9/11 pts with VT and A failure had ventricular tumor or congestive cardiomyopathy), in 32/33 pts with atrial flutter (AFL) (in 7/33 pts, AFL returned 6 mo after start of A), and in 21/28 pts with SVT. Growth continued along pre-A percentiles in all but 8, improving in 6 and worsening in 2 with severe underlying disease. Proarrhythmia occurred in 3: 1 had torsade de pointes that disappeared when A was stopped; 2 with severe anatomic heart disease died suddenly during loading period of A (1 AFL, 1 VT). SE occurred in 28/95 (29%) pts: keratopathy (11), abnormal thyroid function tests (6), chemical hepatitis (3), rash (3), peripheral neuropathy (2), behavioral changes (2), blue skin discoloration (2), headaches (2), hypertension (1), vomiting (1). All SE disappeared when A was discontinued or the dose was reduced. Conclusions: 1) A was an effective drug for young pts with tachyarrhythmias. 2) Growth was unimpaired. 3) SE were relatively common but not severe (no pulmonary SE). Therefore, we recommend A only for young pts with life-threatening arrhythmias that are resistant to conventional drugs.

EFFECTS OF POSITION AND EXERCISE ON THE QT INTERVAL IN CHILDREN

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The Children's Hospital of Philadelphia,Philadelphia, PA.

Exercise and postural change may affect autonomic tone, with reflection of these changes in the corrected QT interval (QTc). The effects of position and exercise on the QTc were evaluated in 40 patients (pts) without known cardiac disease, and in 14 pts with congenital long QT syndrome (LQTS), none on beta blockers. The groups were not significantly different in age. LQTS was defined as QTc $\geq$.45 (age<12) or $\geq$.44 (age$\geq$12) with ventricular arrhythmias or family history of LQTS. QTc's (Bazett's formula) were determined supine, standing, seated at rest, at peak exercise (PE), immediately post exercise, and at 3, 5, and 10 minutes of recovery. QTc's did not significantly change at PE in either group, nor were there significant differences between groups at PE or during recovery. QTc significantly increased with change in position from supine to standing in normals but not in pts with LQTS.

| | QTc Values (Mean ± S.D.) | | | |
|---|---|---|---|---|
| | Supine | Standing | %Change | PE |
| LQTS (14) | .451±.021* | .457±.036 | 0 | .439±.025 |
| normals (40) | .418±.020*# | .439±.032# | 4.7 | .426±.028 |

*p<0.001 t-test; #p<0.001 paired t-test.

We conclude from these data that: 1) change in QTc during exercise testing is of limited value in discriminating between normals and patients with LQTS, since the QTc varied little in either group, 2) a moderate increase in QTc occurs with change from supine to standing position in normal individuals, 3) the postural change of QTc is not present in patients with LQTS. These findings are consistent with high tonic level of left stellate ganglion input in patients with LQTS, versus more reactive fluctuations in sympathetic tone in normals.

## Wednesday, March 22, 1989
## 8:30AM–10:00AM, California Room A
## Anaheim Convention Center
## Neurohormones and Cardiovascular Function

DOES ANF INFLUENCE VENOUS RETURN?

David L. Rutlen M.D., Geir Christensen M.D., Knut Helgesen M.D., Arnfinn Ilebekk, M.D. Dr.Med.,
University of Oslo, Oslo, Norway.

Whether atrial natriuretic factor (ANF) acts on intravascular volume in the capacitance vasculature to change venous return is unknown. Furthermore, whether ANF causes transport of volume between the peripheral capacitance circulation and the central circulation is unknown. Thus, in 8 anesthetized pigs undergoing carotid denervation and cervical vagotomy, blood was drained at a constant CVP from the vena cavae to an extracorporeal reservoir and returned to the right atrium at a constant rate so that changes in venous return could be recorded as changes in reservoir volume. Transudation was measured by determining total intravascular volume from Tc labeling of erythrocytes and determining changes in hematocrit. ANF (0.1 μg/kg min) for 15 minutes to increase plasma ANF from 85±9 (SEM) to 4191±310 ρg/ml (P<.05) was associated with a total volume displacement from the reservoir to the animal of 63±13 ml (P<.05). Increased urine production accounted for only an inconsequential portion of this displacement, since ureteral flow increased only from .044±.016 to .124±.016 ml/min. Since 200±26 ml (P<.05) of transudation to the animal's extravascular space occurred, the total peripheral capacitance vasculature acted to displace 137±33 ml (P < .05) from the intracorporeal circulation to the extracorporeal reservoir. Thus, ANF's net effect on intravascular volume acts to decrease venous return. This decrease is due almost entirely to transudation of volume out of the intravascular space; however, a tendency to displace volume from the peripheral capacitance circulation to the central circulation attenuates the transudative influence on venous return.

ENDOCRINE CONVERSION OF VENTRICULAR CARDIOCYTES IN VENTRICULAR ANEURYSM

Jiang Gu, M.D., Ph.D.,
Lynn McGrath, M.D., F.A.C.C., Michael D'Andrea, B.A., Debra Graf, R.N., Sally Cull, A.A.S. Deborah Research Institute, Browns Mills, NJ 08015-1799

Normal adult ventricular myocardiocytes do not have endocrine function and contain only minute amounts of the peptide hormone, atrial natriuretic peptide (ANP). To study the effects of physical stretch on the ventricular cardiocytes, we investigated human ventricular tissues from 5 adult ventricular aneurysm patients with normal blood pressure. In these patients, the viable ventricular cardiocytes in and around the aneurysm were paradoxically over-distended during heart contractions. The tissues were collected during aneurysmectomy. The occurrence and distribution of ANP and a neuroendocrine-element marker, neuron-specific enolase (NSE), were studied with light and electron microscopic immunocytochemistry. ANP gene expression was examined with RNA-RNA tissue in situ hybridization. Large amounts of ANP-containing electron-dense granules, NSE immunoreactivity and ANP mRNA were detected in the cytoplasm of the over-stretched cardiocytes in and around the aneurysm. The scar tissues and the normal ventricles were devoid of any ANP, NSE or ANP mRNA positivities. These findings suggest that physical over-distention of the ventricular wall may be a triggering factor for the activation of ANP and NSE synthesis by the ventricular cardiocytes and the ventricles may become an important endocrine entity during over-distension, such as ventricular aneurysm, congestive heart failure and hypertension.

**EFFECT OF ATRIAL NATRIURETIC FACTOR ON LEFT VENTRICULAR DIASTOLIC FUNCTION IN HUMANS WITH HEART FAILURE**

Marc J. Semigran MD, Constantine N. Aroney MBBS, Howard C. Herrmann MD, G. William Dec MD FACC, Charles A. Boucher MD FACC and Michael A. Fifer MD FACC. Massachusetts General Hospital and Harvard Medical School, Boston, MA

To assess the effect of atrial natriuretic factor (ANF) on LV diastolic function in heart failure, we administered nitroprusside (NTP) and ANF to 9 pts (NYHA class II-IV, LV ejection fraction 14±1%) with coronary artery disease (n=5) or idiopathic dilated cardiomyopathy (n=4) undergoing cardiac catheterization. LV micromanometer pressure and simultaneous LV volume (gated scan) were obtained at baseline, on NTP, during a second baseline, and on ANF. Mean arterial pressure fell by an average of 18 mmHg on NTP and 9 mmHg on ANF. LVEDP (mmHg) and LV end diastolic volume (LVEDV, ml), time constant of isovolumic relaxation (T, ms), and peak filling rate (dV/dt, ml/s) were (mean±SEM, *p<0.05 vs. baseline):

| | LVEDP | LVEDV | T | dV/dt |
|---|---|---|---|---|
| Baseline | 26±2 | 320±29 | 61±7 | 234±19 |
| NTP | 14±3* | 284±26* | 54±8* | 210±20 |
| Baseline | 26±2 | 314±26 | 65±7 | 233±12 |
| ANF | 18±3* | 302±27* | 58±8* | 241±13 |

T decreased similarly on ANF and NTP; this may be related to the load dependence of relaxation. The LV diastolic pressure-volume (P-V) relation was shifted downward on ANF in 3 pts and on NTP in 3 pts. These effects were eliminated when the transmural P-V relation was constructed by subtracting RA pressure from LV pressure. **Conclusions:** (1) ANF has no direct effect on LV diastolic properties in humans with heart failure. (2) Some indices of LV diastolic function improve on both ANF and NTP, probably due to changes in loading conditions.

**EFFECT OF INHIBITION OF ARGININE VASOPRESSIN ON SYSTEMIC AND CORONARY HEMODYNAMICS.**

James J. Glazier M.D., Haralambos Gavras M.D., Roger M. Mills Jr., M.D., F.A.C.C., Nicholas A. Ruocco Jr., M.D. F.A.C.C., Margaret Bresnahan DSc, Thomas J. Ryan M.D., F.A.C.C., David P. Faxon M.D., F.A.C.C. Boston University Medical Center, Boston, MA.

Arginine vasopressin (AVP) is a potent vasoconstrictor of isolated arterial sements in vito but its effect on systemic and coronary vasomotor tone in man are disputed. To determine the effects of AVP, we measured blood pressure (MAP), systemic resistance (SVR), coronary sinus blood flow (CSBF) and resistance (CVR) in 6 patients (pts) with severe coronary disease (CAD) at the time of angiography. Cardiac pressures and serum osmolality (Osm), AVP, catecholamines and renin levels were measured before and after administration of hypertonic contrast dye (HC), then following intravenous injection of 0.5mg of an analogue inhibitor of vasopressin (AVPI). Results (mean± S.D.):

| | Before HC | After HC | After AVPI |
|---|---|---|---|
| MAP(mm.Hg) | 106±12 | 115±19 | 114±13 |
| SVR(d.s.cm$^{-5}$) | 1429±152 | 1419±110 | 1453±138 |
| CSBF(cc/min) | 196±49 | 206±51 | 191±67 |
| CVR(d.s.cm$^{-5}$) | 41.5±75 | 39.7±7.4 | 44.9±10.2 |
| OSM(MOSM/kg) | 295±12 | 306±7 | 297±10 |
| AVP(pg/ML) | .61±0.28 | 3.84±36 | 36.1±16.3 |

5 of 6 patients had a rise in AVP above physiologic levels. No change in hemodynamic parameters were noted in these patients. No changes were seen in catecholamines or renin levels.

We conclude that, in pts with coronary artery disease, endogenous AVP does not contribute to systemic nor coronary vasomotor tone.

ATRIAL NATRIURETIC PEPTIDE FROM THE CORONARY SINUS IS ACUTELY INCREASED FOLLOWING INDUCTION OF PAROXYSMAL TACHYCARDIA.

Bertil Kjell Øie M.D., Per Ivar Hoff M.D., Britt Skadberg M.D., Arve Tronstad M.D., Ole Myking M.D., Asbjørn Aakvaag M.D., Ole-Jørgen Ohm M.D., F.A.C.C., University School of Medicine, Bergen, Norway.

We evaluated concentrations of atrial natriuretic peptide (ANP) in plasma from the coronary sinus in 5 patients following paroxysmal tachycardia (T) induced by programmed stimulation. Coronary sinus plasma samples and mean right atrial pressure (RAP) measurements were made before (B) and every minute (min) after initiating the T. Logarithmic transformation of ANP (LANP) was done to obtain normal distribution for statistical calculations. ANP in pmol/l, LANP, and RAP (mmHg) are shown below (mean ± sem):

| Time: | B | 1 min | 2 min | 3 min | 4 min | 5 min |
|---|---|---|---|---|---|---|
| ANP | 490±109 | 885±252 | 1171±305 | 1431±360 | 1638±438 | 1846±482 |
| LANP | 6.1 ± 0.2 | 6.6 ± 0.3 | 6.9 ± 0.2 | 7.1 ± 0.2 | 7.3 ± 0.2 | 7.4 ± 0.2 |
| RAP | 4.4 ± 0.9 | 7.0 ± 2.1 | 6.8 ± 2.0 | 7.0 ± 2.1 | 7.0 ± 2.1 | 7.0 ± 2.1 |

There was a marked, statistically significant increase in ANP during every minute of induced T ($p < .001$, ANOVA). The increase in RAP from 4.4 ± 0.9 to 7.0 ± 2.1 mm Hg was not statistically significant. Heart rate increased from 75 ± 5 at baseline to 186 ± 13 beats/min ($p < 0.001$) during T. There was a significant correlation ($r = 0.89$, $p < .05$) between the increase in ANP and the increase in heart rate, while no relationship was found between the increase in ANP and the increase in RAP from baseline to 5 minutes of T ($r = 0.38$, p = ns). These data show that there is an immediate and significant increase in ANP in plasma from the coronary sinus during induced T. Furthermore, the increase in ANP is related to the increase in heart rate but is apparently not related to an increase in mean right atrial pressure.

DIRECT SUPPRESSION OF ALDOSTERONE SECRETION BY ENDOGENOUS ATRIAL NATRIURETIC PEPTIDE IN HEMODYNAMICALLY NORMAL MAN: EVIDENCE FOR PHYSIOLOGIC ROLE OF ANP

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Atrial natriuretic peptide (ANP) has been shown in vivo to reduce plasma aldosterone (ALDO) in association with reduced plasma renin activity (PRA) and in vitro to directly inhibit ALDO secretion by the adrenal cortex. It is unclear whether direct suppression of ALDO by endogenous ANP occurs in vivo. Accordingly we measured hemodynamics, pulmonary artery plasma ANP ($ANP_{PA}$), PRA and plasma norepinephrine (NE) and ALDO at control, after i-v saline 750 ml over 30 min ("peak") and again 30 min later (post) in 11 Pt with normal LV function. Results are given as mean ± SD (RAP and PCWP-right atrial and pulmonary capillary wedge pressures [mm Hg], BP-blood pressure, HR-heart rate, ANP, NE and ALDO-pg/ml, PRA-ng/ml/hr).

| | Control | "Peak" | Post |
|---|---|---|---|
| RAP | 6±2 | 9±2# | 7±2 |
| PCWP | 6±3 | 10±3# | 6±4 |
| $ANP_{PA}$ | 52±24 | 78±57# | 60±29 |
| NE | 185±84 | 306±356 | 192±96 |
| PRA | 0.74±0.55 | 0.75±0.6 | 0.52±0.35 |
| Aldo | 330±1621 | 245±101# | 244±98* |

p vs. control are*<0.05, #<0.01, (ANOVA).

RAP, PCWP and $ANP_{PA}$ increased with volume expansion. HR and BP were unchanged, as were NE and PRA, but ALDO was reduced at "peak" (-26%) and at 30 min post-infusion (-26%).

These data support the hypothesis that the response of endogenous ANP to increases in atrial pressures within the normal range may directly modulate ALDO secretion and, hence, sodium homeostasis.

## Wednesday, March 22, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 9:00AM–10:00AM
## Pacific Room, Anaheim Convention Center
## Clinical Electrophysiology

OUTCOME OF EMPIRICAL ANTIARRHYTHMIC DRUG THERAPY IN MATCHED COHORTS OF PATIENTS WITH VENTRICULAR ARRHYTHMIAS AFTER MYOCARDIAL INFARCTION.

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Serial testing (ST) has been proposed as the best approach to select antiarrhythmic drugs (AD) in Pt with ventricular tachycardia (VT) or fibrillation (VF) after myocardial infarction (MI). The purpose of our study was to determine outcome of individualized empirical treatment with antiarrhythmic drugs (AD) as an alternative to ST. Fourty-two Pt treated in Liège were compared (matched for age, LVEF, location of MI, NYHA class for dyspnea, number of diseased vessels and arrhythmia type) to 42 Pt included in the "Parallel Study" in Maastricht. Amiodarone alone or in combination with a class I AD was given to most Pt. Total mortality (TM), sudden death (SD), cardiac death (CD) and recurrences (Rec) of VT during a mean 24 months follow-up are shown below:

| | LIEGE | MAASTRICHT | P value |
|---|---|---|---|
| TM | 9 (21%) | 10 (24%) | NS |
| SD | 4 (10%) | 5 (12%) | NS |
| CD | 4 (10%) | 5 (12%) | NS |

TM, SD and CD were similar to reported series using ST. Treatment using potent AD based on clinical knowledge and experience results in survival rates similar to ST.

AV NODAL REENTRY INCORPORATING HIS BUNDLE: VERAPAMIL SENSITIVITY IN RETROGRADE FAST PATHWAY CONDUCTION

Warren M Jackman MD,FACC, John AF Yeung-Lai-Wah, MBChB, FACC, Karen J Friday MD,FACC, David M Fitzgerald MD, Carlos Roman MD, Ralph Lazzara MD,FACC, Univ. of Oklahoma Health Sciences Center and VAMC,Oklahoma City, OK

In AV nodal reentrant tachycardia, an indirect method has been used to evaluate if the ventricular (distal) end of the retrograde fast pathway (RFP) arises from the His bundle (H) or AV node and correlate site of origin of RFP with pharmacologic sensitivity. This method compares the H to atrial interval during tachycardia ($H\text{-}A_t$) and during ventricular pacing at the same cycle length ($H\text{-}A_p$). $H\text{-}A_t$ is measured from onset of the H potential. $H\text{-}A_p$ is measured from the end of the H potential, since H is activated retrogradely during ventricular pacing. End of retrograde H was identified by pacing at RV sites which prevented overlap of H and ventricular potentials. It is proposed that if RFP originates within the AV node, then $H\text{-}A_t < H\text{-}A_p$, as the reentrant impulse has entered the RFP before H is activated. If the RFP originates from H, $H\text{-}A_t \geq H\text{-}A_p$ since the tachycardia impulse must travel to H before engaging RFP. Of 33 pts, $H\text{-}A_t < H\text{-}A_p$ in only 18. In the other 15 pts (45%), $H\text{-}A_t = H\text{-}A_p$ (5 pts) or $H\text{-}A_t > H\text{-}A_p$ (10 pts). Decremental ventricular pacing was performed immediately before and after verapamil (10 mg iv) in 22 pts. Shortest ventricular pacing cycle length maintaining 1:1 VA conduction (1:1 VA) was 323 ± 39 msec in 9 pts with $H\text{-}A_t < H\text{-}A_p$ vs 299 ± 57 msec in 13 pts with $H\text{-}A_t \geq H\text{-}A_p$ ($p=0.07$). Verapamil increased the median 1:1 VA by only 40 msec in $H\text{-}A_t < H\text{-}A_p$ pts compared to 200 msec in $H\text{-}A_t \geq H\text{-}A_p$ pts ($p<0.01$).

We conclude: 1) RFP may originate from H in a large number of pts (45%); 2) conduction in RFP originating from H may be capable of conduction at faster rates, and 3) verapamil depresses RFP conduction to a greater extent in this group, but the reason for this response is unknown.

ANTEGRADE AND RETROGRADE CONDUCTION OCCURRING OVER SEPARATE, ADJACENT ACCESSORY AV PATHWAYS

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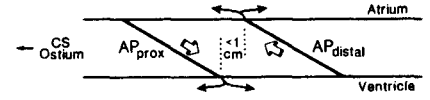
Catheter recordings of accessory pathway (AP) activation suggest that left free-wall APs have an oblique course with ventricular insertion distal (anterior) to the atrial insertion. Identification of separate AP potentials can distinguish activation of 2 close APs. In 69 patients (pts) with 85 septal and left free-wall APs, AP potentials were recorded from 67/85 APs. Antegrade and retrograde conduction occurred over two separate, but close APs in 7 pts (10%).

In 4 pts, 2 parallel left free-wall APs had opposite unidirectional conduction, antegrade in proximal (posterior) AP and retrograde in distal (anterior) AP (figure).




At surgery, earliest epicardial atrial and ventricular activation were within 1 cm, simulating a single, vertical pathway. Pressure over the coronary sinus (CS) catheter electrode recording activation of 1 AP resulted in unidirectional conduction block in 3 of 4 pts.

In 3 pts, retrograde conduction occurred over a concealed left posteroseptal AP, with AP potentials recorded from CS at least 7 mm distal to the ostium. During antegrade conduction, AP potentials were recorded across the tricuspid annulus, just anterior (1 pt) or posterior (2 pts) to the CS ostium.

We conclude that antegrade and retrograde conduction can occur over separate, unidirectional pathways (10%).

MECHANISM OF COMPENSATORY PAUSE IN ATRIAL FIBRILLATION

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The compensatory pause after premature ventricular contractions in pts with atrial fibrillation (AF) is classically explained by interception of atrial impulses and prolongation of atrioventricular nodal (AVN) refractoriness. On the other hand, retrograde conduction may also facilitate anterograde conduction. We studied the underlying mechanism of compensatory pauses in 15 pts with AF in whom single premature ventricular extrastimuli were delivered at a fixed coupling interval (RS) after each 8th spontaneous R wave. In each pt an average of 375 extrastimuli were applied. The histogram of compensatory pauses (SR) was compared with that of the other spontaneous RR intervals. In 6/7 pts in whom RS was more than 200 ms shorter than the shortest spontaneous RR interval, the SR intervals were 240±70 ms longer than the RR intervals but the shape of both histograms was not significantly different. However, in 5/8 pts in whom RS was relatively longer, the SR histogram was broader than, and significantly different from the spontaneous RR histogram. Conclusions: 1, These results suggest that during AF, early retrograde penetration can reset the AVN; 2, later penetration results in a mixed pattern of AVN resetting and interception of anterograde conduction, dependent on the timing of retrograde conduction relative to the spontaneous anterograde impulses; 3, the ability to reset the AVN during AF, challenges the classical concept that the AVN merely acts as a "passive" structure transmitting atrial impulses.

INCIDENCE AND SUBSTRATE OF SUSTAINED BUNDLE BRANCH REENTRY AS A MECHANISM OF VENTRICULAR TACHYCARDIA.

Jose Caceres, M.D., Patrick Tchou, M.D., Mohammad Jazayeri, M.D., James McKinnie, M.D., Boaz Avitall, M.D., Masood Akhtar, M.D., F.A.C.C., Sinai-Samaritan Medical Center, Milwaukee, Wisconsin.

Identification of bundle branch reentry (BBR) as a mechanism of clinical and/or induced sustained monomorphic ventricular tachycardia (SMVT) is of crucial importance since nonpharmacologic therapy is curative. The typical substrate, however, seems to be unrecognized and its incidence is not clearly defined.

Of 285 pts with inducible SMVT studied in our laboratory (1980-1987), 17 were diagnosed as BBR (6% incidence). A detailed analysis of intramyocardial and His Purkinje System (HPS) conduction was performed to identify the substrate. Nonspecific intraventricular conduction delay (IVCD) was observed in 100% of Pts with BBR and 63% of those with non-BBR. Nonspecific IVCD and prolonged HV ($\geq$60 ms) was seen in all Pts (100%) with BBR and in 11% with non-BBR ($p<0.01$). Of the Pts who had the trio of IVCD, prolonged HV and left bundle branch block (LBBB) configuration SMVT, BBR was the mechanism in 73%.

Conclusions: (1) BBR is not an uncommon mechanism of clinical SMVT and occurs in about 6% of cases. (2) The typical substrate appears to be abnormal HPS conduction. (3) The combination of IVCD, prolonged HV, and LBBB-SMVT strongly suggests BBR as the mechanism of tachycardia.

MECHANISM OF INDUCIBLE VENTRICULAR TACHYCARDIA IN PATIENTS WITH IDIOPATHIC DILATED CARDIOMYOPATHY

Patrick Tchou, M.D., Zalman Blanck, M.D., James Mckinnie, M.D., Boaz Avitall, M.D., Ph.D., Keith Atassi, M.D., Mohammad Jazayeri, M.D., Masood Akhtar, M.D., F.A.C.C. Sinai Samaritan Medical Center, Milwaukee, WI.

Sustained ventricular tachycardia (VT) is often seen in patients with idiopathic dilated cardiomyopathies. There is little data, however, on the mechanisms of tachycardia in this pathologic entity.

Over a 51 month period, 58 patients with dilated myopathies underwent electrophysiologic studies at our institution for suspected or documented VT. Of these, 17 had inducible sustained monomorphic VT. In 7 of the 17 (41%), the mechanism of tachycardia was bundle branch reentry. The 7 patients with bundle branch reentry had documented clinical VT (N=5), syncope (7) or sudden death (1).

Conclusions: 1) Bundle branch reentrant VT is a clinically important cause of sustained VT in patients with idiopathic dilated cardiomyopathies. 2) Since therapy of this entity can be apporoached with right bundle ablation, one should consider the possibility of bundle branch reentry mechanism in all patients with idiopathic dilated cardiomyopathies in whom sustained monomorphic VTs are induced at electrophysiologic studies.

EFFECT OF MYOCARDIAL REVASCULARIZATION ON INDUCIBLE VENTRICULAR ARRHYTHMIAS. Patricia A. Kelly, M.D., Charles S. Freeman, R.N., Jeremy N. Ruskin, M.D., F.A.C.C., Hasan Garan, M.D., F.A.C.C., Massachusetts General Hospital, Boston, MA. In some pts with out-of-hospital ventricular fibrillation (VF) or sustained ventricular tachycardia (SUVT) and inducible ventricular arrhythmias, surgical myocardial revascularization (CABG) suppresses arrhythmia induction. To determine what factors can be used to identify those pts in whom CABG is most likely to suppress ventricular arrhythmia induction, we analyzed data from 33 pts with $\geq$70% stenosis of $\geq$1 major coronary artery. All pts had a history of VF (n=23) or SUVT (n=10) and inducible VF or SUVT at electrophysiologic study. All pts had CABG and repeat electrophysiologic study off anti-arrhythmic drugs post-CABG. Thirteen variables of potential predictive value were chosen and analyzed. Stepwise regression analysis identified left ventricular ejection fraction ($p=0.015$) and the type of ventricular arrhythmia induced at pre-CABG electrophysiologic study ($p<0.001$) as the only variables significantly predictive of arrhythmia suppression at post-CABG electrophysiologic study. The mean LV ejection fraction was 43$\pm$10% in pts with no inducible ventricular arrhythmia post-CABG (n=13) versus 33$\pm$11% in pts with persistently inducible arrhythmias (n=20). Of 24 pts with inducible SUVT pre-CABG, 19 had SUVT and 1 had VF at post-CABG electrophysiologic study. Nine of 9 pts with VF at pre-CABG electrophysiologic study had no inducible ventricular arrhythmia post-CABG. Thus, in pts with coronary artery disease and inducible ventricular arrhythmias, SUVT induction is unlikely to be suppressed by CABG alone. VF induction is frequently suppressed by CABG alone.

DOES RESPONSE TO IA AGENTS PREDICT RESPONSE TO IC AGENTS IN PATIENTS WITH SUSTAINED VENTRICULAR TACHYCARDIA?
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In an effort to facilitate the management of patients (Pts) with sustained ventricular tachycardia (VT), we prospectively evaluated whether the response to programmed ventricular stimulation performed during treatment with with IA antiarrhythmic agents can predict response to subsequent treatment with IC antiarrhythmic agents. Each of 33 Pts (mean age = 57±11) had sustained VT at baseline electrophysiologic study (EPS) (mean VT cycle length [VTCL] = 275±88 ms) and during treatment with IA agents (mean VTCL = 317±64 ms). EPS was also performed during treatment with IC agents (mean VTCL = 333±106 ms). VT was inducible in 30/33 (91%) Pts on IC agents. The MOI of the VT induced in Pts on IC agents when compared to the MOI of the VT induced in pts on IA agents was harder [increased extrastimuli (ES)] in 7/30 (23%), the same in 11/30 (37%) and easier (decreased ES) in 12/30 (40%). The MOI of VT in Pts on IA agents did not predict the MOI of VT in Pts on IC agents. The VTCL in Pts on IC agents was compared to the VTCL in Pts on IA agents and found to be increased by 50 ms in 9/30 (30%), to be decreased by 50 ms in 5/30 (17%) and have $<$ 50 ms change in 16/30 (53%). Prolongation of the VTCL in Pts on IA agents tended to suggest a similar VTCL response in Pts on IC agents.

Conclusions: Inducibility of VT in Pts on IA agents predicts continued inducibility on IC agents. The VTCL in Pts on IC agents is not significantly different from the VTCL in Pts on IA agents.

**Retrograde Pathway in Atrioventricular Nodal Tachycardias: Nodal Tissue or Extranodal Accessory Pathway?**

James McKinnie M.D., Boaz Avitall M.D., Ph.D., Jose Caceres M.D., Mohammad Jazayeri M.D., Sergio Kershenovich, M.D., Patrick Tchou, M.D., Masood Akhtar M.D., F.A.C.C., Sinai-Samaritan Medical Center, Milwaukee, WI.

The introduction of surgical techniques in the management of patients with atrioventricular nodal (AVN) reentrant tachycardia (AVNRT) has resulted in renewed interest in the anatomic boundaries and electrophysiological properties of the reentrant circuit. Specifically, the nature of retrograde (ReT) fast pathway (FP) in Pts with AVNRT remains unclear. Fixed ReT AVN conduction (H2A2) using ventricular extrastimulus technique during a single and relatively long basic cycle length (BCL range 600-800 ms) has been interpreted as implying AVN bypass tract conduction. ReT AVN input (V1H2) remains fixed at a given BCL due to ReT His Purkinje system (HPS) refractoriness and must be shortened to appreciate AVN response. Shorter BCL (range 350-500) were therefore scanned in 17 Pts with AVNRT and H2A2 intervals at long and progressively shorter BCL were compared. RESULTS: At the long BCL the H2A2 ranged 25 to 50 ms. The H2A2 progressively increased by 25% to 83% of the baseline value as the V1H2 decreased at shorter BCL; behavior typical of AVN conduction. It is concluded that decremental properties of ReT FP conduction can be unmasked using short BCL. These new findings suggest that conduction via AVN bypass tract need not be involved to explain short and "fixed" H2A2 intervals in Pts with AVNRT.

COMPARATIVE EFFECTS OF RADIOFREQUENCY AND LASER ABLATION IN NORMAL AND DISEASED VENTRICULAR MYOCARDIUM.

Huanlin An M.D., Sanjeev Saksena M.D., F.A.C.C. Newark Beth Israel Med Ctr - NJ Medical School, Newark, NJ.

We compared the effectiveness & safety of radiofrequency (RF) energy & laser energy for ablation of normal ventricle (NV) & diseased human ventricle (DV). RF ablation in NV was performed in the unipolar mode using a 500 kHz RF generator coupled to a 6Fr USCI quadripolar ring electrode catheter (RF1) or 5Fr screw-in electrode (RF2). Laser ablation employed a 15W argon laser coupled to a 300μ core optical fiber alone (L1) or 2.5mm metal probe encasing a sapphire lens-tipped 600μ core fiber with 80% beam transmission window (L2). In DV, RF2 & L1 catheter delivery systems (CDS) were used. Lesion dimensions were obtained by microscopic examination & correlated with delivered energy using regression analysis. The ratio of lesion depth to diameter (D/D) was examined.

RESULTS: 203 lesions were analyzed. Lesion dimensions with each energy & CDS were:

| NV: | RF1 | RF2 | L2 |
|---|---|---|---|
| Mean diameter(mm): | 7.2±.9 | 5.8±.5* | 6.7±1.4 |
| Mean depth(mm): | 3.2±.3* | 2.1±.3** | 3.7±1.0 |
| Mean D/D: | 2.3±.3** | 2.8±.3** | 1.9±.2 |
| Mean energy(J): | 627 | 637 | 632 |

*p <.05; **p <.001 as compared to L2

In each catheter, D/D ratio did not change with increasing delivered energy. Correlation between lesion size & delivered energy was good for RF2 & L2 at all energies, but deteriorated for RF1 & L1 at high power/energy outputs. RF2 failed to produce lesions in DV at energies <500J, while L1 induced lesions in DV with mean diameter of 3.4mm & depth of 2.4mm at mean energy of 195J. RF2 lesion dimensions in DV were comparable at mean energies of >800J. Perforation was only observed in NV with L1 at energies >300J, but was not observed with any other laser or RF CDS in NV or DV.

CONCLUSIONS: 1) Laser ablation is more effective in DV. 2) RF energy produces shallower lesions & may be safer for ablation in thin-walled structures. 3) Metal probe-tipped optical fibers & screw-in electrodes are preferable for ventricular ablation with laser & RF energy respectively.

## Wednesday, March 22, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 10:00AM–11:00AM
## Pacific Room, Anaheim Convention Center
## Ablation, Devices, Late Potentials

HIS BUNDLE CRYOSURGICAL ABLATION USING A CLOSED HEART EPICARDIAL APPROACH.

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We report our experience with His bundle cryosurgical ablation using a closed heart epicardial approach in 5 patients. The His bundle region was exposed via the right coronary fossa (anterior septal region). The atrio-ventricular fat pad was mobilized and the tricuspid valve annulus exposed. The aortic annulus, and the subjacent atrial membranous septum were exposed. The His bundle is located at the tip of the exposed trihedron (aorta and membranous septum, right ventricle an right atrium). A cryoprobe 5mm in diameter with a 45° oblique tip (custom made by Frigitronics) is applied onto the membranous septum and cooled at -5°C (ice mapping). Cryosurgical ablation (-60°C, 2min) is carried out at the site where antegrade heart block is readily obtained.

There were 4 men and 1 woman, age 35 to 73 (median 62). The His bundle ablation was indicated for chronic atrial fibrillation (4 pts) and multifocal atrial tachycardias (1 pt) resistant to antiarrhythmia therapy. One pt had associated congestive heart failure. All pts had attempted catheter ablation. Permanent complete heart block was obtained in all pts (mean follow-up 13 months). There were no complications.

Closed heart epicardial His bundle cryosurgical ablation is an effective surgical alternative to catheter ablation avoiding cardiopulmonary bypass and/or intracardiac manoeuvers.

JUNCTIONAL TACHYCARDIA - ANATOMIC SUBSTRATE AND ITS SIGNIFICANCE IN ABLATIVE PROCEDURES.

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We studied the Conduction System (CS) by serial section in three cases of intractable junctional tachycardia (JT) who died suddenly. Case One was a six month old female, Case Two a five month old male, and Case Three a twenty-two year old female nurse. The latter had a pacemaker following surgical ablation of the atrio-ventricular (AV) node. All hearts were hypertrophied and enlarged. In Case One, the beginning of the AV node lay within the central fibrous body (CFB) and there was a left-sided bundle of His. Acute necrosis was present in the summit of the ventricular septum adjacent to the AV node and bundle. In Case Two, the coronary sinus was displaced cranially close to the CFB, resulting in abnormality of the latter and entrapment, distortion and division of the AV node within the CFB. In Case Three, there was a left AV node connected to the atrial septum, and the right AV node formed the peripheral CS. The right AV node was completely interrupted by sutures and the penetrating and branching bundle was fibrosed.

In conclusion, (1) in all cases abnormalities in the coronary sinus and/or the CFB and/or the AV node are related to JT; (2) before ablative procedures are undertaken, it might be useful to study clinically the anatomy of the atrial septum, and the coronary sinus.

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EFFECTS OF LOW ENERGY DIRECT CURRENT COUNTERSHOCK ON ATRIOVENTRICULAR NODAL JUNCTION IN DOG USING SUCTION-ABLATION CATHETER.

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The effects of low energy direct current (DC) countershock on AV nodal conduction were studied using a Cordis suction-ablation catheter in 6 dogs. DC shocks in increments of 10 joules (J) were delivered until either a partial or complete AV block occurred. A mean of 36 ± 34 J was delivered. Complete AV block occurred in 2/6 dogs. Partial AV block occurred in 4/6 dogs, defined as ≥ 50% increase in AH, or PR interval. The dogs were sacrificed at 1 (n=2), 3, 8, 14 and 42 days. The lesions were 3-22 (11 ± 6) mm in diameter and 1-4 (2.5 ± 1) mm in depth and involved the AV node, the His bundle, and adjacent atrial tissue. Immediate changes were focal coagulative necrosis and edema. At 3 days, neutrophilic infiltrate, contraction bands and interstitial edema were present. Chronic inflammatory infiltrate was seen at 8 days. Granulation tissue was seen at 2 weeks, progressing to scar at 6 weeks. Conclusions: 1) With this catheter, partial or complete AV nodal injury is possible using graded DC shocks. 2) Pathologic changes are localized to the AV node and adjacent tissue. 3) Suction-ablation catheter has a potential clinical value for partial AV nodal ablation.

SUCCESSFUL RADIOFREQUENCY CATHETER ABLATION OF RIGHT ANTEROSEPTAL ACCESSORY ATRIOVENTRICULAR CONNECTIONS.

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Accessory atrioventricular connections (AAVCs) occur least commonly (about 10%) in the right anteroseptal (RAS) area. Surgical cure rates are not as high as free wall locations and there is a high incidence of complete AV block due to the AAVCs proximity to the AV node. We successfully ablated RAS AAVCs in two patients using 625 KHz continuous wave radiofrequency current (RFC). A custom device triggered the electrosurgical unit synchronous with the QRS complex, controlled pulse duration and measured RMS voltage, current, resistance, power and energy. In both patients RFC was delivered, without general anesthesia, between a 6F catheter and an anterior indifferent chest patch electrode. Patient 1, a 15 year-old male, had drug refractory orthodromic SVT and patient 2, a 31-year-old male, had symptomatic paroxysmal atrial fibrillation with a rapid antidromic response requiring DC cardioversion. In patient one, 15 seconds of RFC (14 W, 210) successfully ablated both antegrade and retrograde AAVC conduction. In patient two, eight seconds of RFC (14 W, 112 J) delivered over an area where a Kent potential was recorded resulted in transient loss of AAVC conduction. A second pulse of RFC (12 W, 180 J) for 15 seconds permanently ablated AAVC conduction. Neither patient had any alteration in AV nodal or His-Purkinje conduction. Both patients have been asymptomatic with no overt preexcitation noted up to one month after the procedure. We conclude that unipolar catheter-delivered RFC can safely and successfully ablate AAVCs in selected patients.

RADIOFREQUENCY OR DIRECT CURRENT FOR ABLATION OF VENTRICULAR TACHYCARDIA?

Klaus-Peter Kunze, M.D., Karl-Heinz Kuck, M.D., and Michael Schlüter, Ph.D. University Hospital Eppendorf, Hamburg, F.R.G.

Transvenous catheter ablation (TCA) using radiofrequency current (RFC) was attempted in 7 patients (pts) with ventricular tachycardia (VT). 6 pts had coronary artery disease (CAD), 1 had VT from RV outflow tract. VT was incessant (inc) in 4 pts and paroxysmal (pxl) in 3. In CAD pts the site of TCA was determined by demonstration of an isolated mid-diastolic potential preceding the onset of the VT QRS complex by 80-140 ms and by pacing this site to achieve a QRS complex identical to that during spontaneous VT, but with a marked delay between stimulus and onset of stimulated QRS complex. These criteria were fulfilled in 3 pts at the proximal LV septum, in 2 pts at the posterobasal and in 1 pt at the anterolateral LV. RFC (30-40 volts for 10-30 secs) was applied in 5 pts between the LV catheter and a back paddle. In 2 pts with septal origin of VT, RFC was applied transseptally. In all 4 pts with inc VT, VT could not be terminated and VT cycle length did not change. In all 3 pts with pxl VT, VT was still inducible after RFC. After unsuccessful RFC application all pts underwent direct current (DC) TCA at the same sites. 2-3 DC shocks of 100-300 joules caused termination and noninducibility of VT in all pts. During follow-up (6±3 months) sustained monomorphic VT did not recur, but 2 pts required antiarrhythmic therapy because of symptomatic ventricular premature beats. Conclusion: DC TCA at the site of slow conduction effectively terminated and suppressed VT, whereas RFC was ineffective at the same catheter position.

CATHETER MODIFICATION OF AV NODAL CONDUCTION IN DRUG RESISTANT AV NODAL REENTRANT TACHYCARDIA (AVNRT).

Nadir Saoudi M.D., Gilbert Kirkorian M.D., Georges Atallah M.D., Jean C. Chevalier M.D., Paul Touboul M.D. Hôpital Cardiologique, Lyon, France.

Patients with drug resistant AVNRT are frequently referred for His bundle ablation with subsequent pacemaker implantation. Recent studies suggest the possibility of surgical cure of this tachycardia with preservation of normal antegrade conduction when selective destruction of atrial areas in the vicinity of the AV node is performed. We therefore attempted to "modify" AV nodal conduction by means of catheter ablation shocks in 4 patients with long lasting (12 to 27 years) drug resistant (4-7 antiarrhythmics drugs) AVNRT. During induced AVRNT all patients underwent careful mapping of the perinodal region by means of a standard bipolar catheter that was pretested for fulguration. The latter was positioned close to the His bundle recording catheter and then slightly manipulated in order to map the AV nodal region. In all cases the retrograde atrial activation was found to be synchronous with (pt 1-3), or earlier than (pt 4) that recorded in the His bundle lead, despite the lack of H wave recording. 1 to 13 cathodal shocks (mean energy 175 J) were delivered under general anesthesia in 1 to 4 sessions and were followed by a brief period of complete AV nodal block. 30 min after the shock antegrade AV nodal His Purkinje system conduction was normal in all cases, whereas retrograde conduction was abolished (3 cases) or severely impaired (1 case). AVNRT was no more inducible in 3/4 cases. At late control evaluation (day 30) AVNRT remained inducible in 1/2 pt. During a mean follow up of 5,5 months (1-10) AVNRT did not recur in 3/4 pts despite drug withdrawal.

In conclusion : catheter modification of AV nodal conduction is a feasible procedure with preservation of normal antegrade conduction. This procedure deserves further study.

RELATIONSHIP BETWEEN STIMULATION THRESHOLD VARIABILITY OF ISOLATED CARDIOMYOCYTES AND SEPARATED DEFIBRILLATION SHOCKS DELIVERED IN ORTHOGONAL DIRECTIONS.

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A marked improvement has recently been obtained in defibrillation by use of separated pulses delivered in orthogonal directions. These results suggested the possible dependence of cardiac fibres stimulation threshold on their orientation with respect to the stimulus electric axis. The aim of this work was to evidence such a variability on isolated rat ventricular myocytes. These isolated myocytes were placed in a culture box were they appeared spontaneously arranged along multiple directions. A 2ms, 1.5Hz stimulation was then delivered between two parallel electrodes. Stimulus intensity was progressively increased from zero to a given value until obtention of cells contraction. For a 2cm inter-electrodes distance, contraction has always been obtained with a 8 to 10 volts stimulus intensity for the most longitudinally disposated myocytes. A progressive recruitment was then observed by increasing the stimulus intensity up to a 18 to 20 volts value required to obtain the contraction of the most perpendicular myocytes. Conclusions: 1, These results show that the dependence of stimulation threshold on longitudinal or transversal application of stimulus appears to be a fundamental property of ventricular fibres. This threshold can vary in a ratio 1 to 2. 2, Considering that fibres are distributed along different directions in the heart, these results clearly show that after delivery of 2 orthogonal shocks, the cells undepolarized by the first one are quite easily depolarized by the second one. In these circumstances, cardiac fibres are totally depolarized using the lowest energy required which leads to an important decrease in energy required to defibrillate.

NON-INVASIVE ASSESSMENT OF IMPROVEMENT OF REGIONAL LEFT VENTRICULAR CONTRACTILITY AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY BY QRST ISOAREA MAP IN PATIENTS WITH ANGINA PECTORIS.

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The purpose is to examine whether QRST isoarea maps can detect the improvement of the regional LV contractility after percutaneous transluminal coronary angioplasty (PTCA). Left ventriculography (LVG) and ECG mapping were performed before and 6 months after PTCA in 16 angina pectoris Pts with a stenosis (>75%) of LAD. None had the prior myocardial infarction. QRST isoarea map was constructed from data recorded with 87 body surface unipolar electrodes at a sampling interval of 1 msec. The improvement of the segmental LV contractility was evaluated with the centerline method by analyzing LVGs before and after PTCA. In 7 Pts (44%), LVG showed asynergy before PTCA (Group A). LVG had no asynergy in other 9 Pts (Group N). In 5 Pts (71%) of Group A, asynergy disappeared after PTCA. In QRST isoarea maps of all these 5 Pts, after PTCA, the positive area recovered over the upper left anterior chest where the negative area was located before PTCA. However, QRST isoarea maps revealed no changes after PTCA in 10 Pts out of 11 Pts whose LV contractility showed no changes after PTCA. The recovery of the positive area over the upper left anterior chest demonstrated the improvement of the regional LV contractility after PTCA with a sensitivity of 100% and a specificity of 91%. These findings strongly suggested that QRST isoarea maps was useful to detect the improvement of the local contractility of the left ventricle after PTCA.

AUTOMATIC IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR IN PATIENTS ON CHRONIC AMIODARONE: EFFECTS ON THE DEFIBRILLATION THRESHOLD AND THE RATE OF SHOCKS.

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The role of chronic amiodarone (AM) in patients who received AICD for ventricular fibrillation (VF) (n=22) or sustained intractable tachycardia (VT) (n=16) was evaluated in 38 patients. There were 31 males and 7 females with a mean age of 56 ±12 years (range 21-74). Twenty-eight patients had coronary artery disease. The mean LV ejection fraction was 40 ±13%. Twenty patients had been taking AM prior to AICD implant (mean 3.6 ±1.5 months). These patients were unresponsive or intolerable to a mean of 3.8 ±1.6 antiarrhythmic agents before receiving AM. The average dose of AM was 360 ±24 mg/day (200-400 mg). The defibrillation threshold at AICD implant in patients on AM was 13.5 ±6.2 joules, which was not significantly different from that (12.3 ±4.4 joules) in patients (n=18) who were not on AM. At mean follow-up of 18 ±14 months, 5 of 20 patients (25%) receiving chronic AM had a total of 71 appropriate shocks in the presence of symptoms or documented VT/VF. Subsequently, 2 of these 5 patients died suddenly presumably due to generator failure (>28 months old). None of the 20 patients on AM have experienced major side effects. Of 18 patients not on AM, 4 (22%) had a total of 88 appropriate shocks. In conclusion, 1) chronic amiodarone therapy does not appear to increase the defibrillation threshold, and 2) a significant number of patients receiving chronic amiodarone continue to suffer from VT/VF requiring repeated shocks from the AICD.

**ABSENCE OF LATE POTENTIALS IN PATIENTS WITH REPETITIVE MONOMORPHIC AND EXERCISE-FACILITATED VENTRICULAR TACHYCARDIA AND NO APPARENT HEART DISEASE**

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Ventricular tachycardia occurring in the absence of heart disease may be due to mechanisms other than reentry. If so, late potentials should be absent from signal-averaged ECG's performed in patients with ventricular tachycardia and no heart disease. We examined signal-averaged ECG's (bandpass 25-250 Hz, bidirectional filter, 300 beats, noise ≤1.0 μv, sinus rhythm, QRS ≤0.10 sec, no antiarrhythmics) from 6 patients, ages 7 to 45 years, with repetitive monomorphic (5) and/or exercise-facilitated (4) ventricular tachycardia, and no symptomatic (excluding palpitations), electrocardiographic, or echocardiographic evidence of heart disease. Criteria for the presence of late potentials were signal-averaged QRS duration ≥120 msec, root mean square voltage of the terminal 40 msec ≤25 μv, or a terminal low amplitude signal (<40 μv) ≥38 msec in duration. Results: signal-averaged QRS duration, 82-110 msec; root mean square voltage, 32-148 μv; duration of low amplitude signal, 11-25 msec. Conclusion: Late potentials were absent in this group of patients with repetitive monomorphic or exercise-facilitated ventricular tachycardia and no apparent heart disease. This finding is consistent with the hypothesis that such ventricular tachycardia is due to a mechanism(s) other than reentry.

Effect of Thrombolysis on Late Potentials Incidence after Acute Myocardial Infarction.

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In order to study the effects of thrombolysis on incidence of late potentials (LPs) after acute myocardial infarction (AMI) the signal averaged ECG (SA ECG) was recorded in 202 consecutive patients (pts) during the first six weeks after an AMI (mean 21 days). In 52 pts, the AMI was treated by Streptokinase, the remaining 150 pts did not receive Streptokinase. The presence of LPs was defined as root mean square voltage during the last 40 msec of the filtered QRS (V40) $\leq$ 25 $\mu$V and filtered QRS $\geq$ 120 msec. LPs were recorded in 31 pts (15,3%); 22 of the 150 pts in the non thrombolysis group had LPs (14.7%) and, 9 of the 52 pts in the thrombolysis group had LPs (17.3%) (NS). The thrombolysis group was subsequently divided in 2 groups according to reperfusion status : myocardial reperfusion (MR) with opened infarct related artery (36 pts) 69.1%) and non MR with closed infarct related artery (16 pts, 30.8%). LPs were recorded in 5 of 36 pts in the MR group, (13.8%) and, in 4 of 16 pts in the non MR group (25%) (NS).

In contrast with previous works, our study suggests that effective thrombolysis does not change significantly the incidence of LPs in pts after AMI, but these results need to be further assessed by larger series.

ORAL ISOSORBIDE DINITRATE IN CHRONIC HEART FAILURE: TOLERANCE DEVELOPMENT TO QID VS TID REGIMEN.

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Questions have been raised recently regarding the optimal regimen of isosorbide dinitrate (ISDN) in pts with heart failure (CHF). We therefore evaluated continuously hemodynamic effect of the commonly used regimen of ISDN given every 6 hours (h) in 22 pts with CHF. 11 pts received 5 consecutive doses of ISDN (qid) and 11 pts received 4 doses at 0, 6, 12 and 24 hrs (tid), allowing a 12h nitrate-poor interval between the 3rd and last dose.

RESULTS: Effect on mean pulmonary artery wedge pressure (PAW) was markedly attenuated in magnitude and duration in both groups already after 2nd dose. PAW in mmHg at baseline (BL) and after 1st and last dose was (*p<0.05 vs $BL_1$):

| 1st Dose | $BL_1$ | 2 h | 4 h | 6 h |
|---|---|---|---|---|
| qid | 28±8 | 19±7* | 22±9* | 22±7* |
| tid | 24±6 | 15±6* | 17±5* | 21±7 |
| **Last Dose** | **$BL_2$** | **2 h** | **4 h** | **6 h** |
| qid | 24±7 | 21±7* | 25±9 | 25±7 |
| tid | 22±4 | 16±7* | 16±5* | 21±5 |

CONCLUSION: 1) Commonly used regimen of ISDN given every 6h results in early development of tolerance with attenuation and shortening of effect on PAW; 2) efficacy of ISDN can be fully restored by nitrate-poor interval of 12h; 3) these findings suggest that ISDN tid is preferred to ISDN qid in treatment of chronic CHF.

## Wednesday, March 22, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 11:00AM–12:00NOON
## Pacific Room, Anaheim Convention Center
## Congestive Heart Failure I

NEGATIVE INOTROPIC EFFECT OF NICARDIPINE IN PATIENTS WITH HEART FAILURE: DEMONSTRATION BY LEFT VENTRICULAR END-SYSTOLIC PRESSURE-VOLUME ANALYSIS

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Nicardipine, a dihydropyridine calcium antagonist, has been shown to have minimal negative inotropic effect in animal studies. To assess the inotropic effect of this agent in humans independent of its vasodilator effect, we administered equihypotensive doses of intravenous nitroprusside (NTP) and nicardipine to 15 patients with severe heart failure (NYHA class II-IV, LV ejection fraction (EF) 15±2%). LV micromanometer pressure and simultaneous LV volume (gated scan) were obtained at baseline, during NTP infusion, during a second baseline, and during nicardipine infusion. Heart rate (HR, beats/min), mean arterial pressure (MAP, mmHg), CI ($L/min/m^2$), systemic vascular resistance (SVR, $dynes\text{-}s/cm^5$) and EF (%) were:

| | HR | MAP | LVEDP | CI | SVR | EF |
|---|---|---|---|---|---|---|
| Baseline | 84±3 | 94±4 | 27±2 | 1.8±0.1 | 2131±150 | 15±2 |
| NTP | 82±3 | 73±3# | 14±2# | 2.1±0.1# | 1486±130# | 16±1 |
| Baseline | 80±3 | 91±4 | 27±2 | 1.7±0.1 | 2130±129 | 15±1 |
| Nicardipine | 80±3 | 72±2# | 23±3#* | 2.4±0.1#* | 1170±66#* | 19±1#* |

(#p<0.05 vs baseline, *p<0.05 vs NTP)

Left ventricular pressure-volume loops were constructed in 14 patients. The LV end-systolic pressure-volume relation was shifted rightward on nicardipine, indicating a negative inotropic effect, in 12 of 14 patients. Conclusions: (1) Nicardipine has a negative inotropic effect in most patients with heart failure. (2) Despite this effect, EF and CI increase on nicardipine because of afterload reduction with minimal change in preload.

## Wednesday, March 22, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 9:00AM–10:00AM
## Pacific Room, Anaheim Convention Center
## Congestive Heart Failure II

MECHANISMS OF IMPAIRED VASODILATION IN THE CORONARY MICROVASCULATURE OF PATIENTS WITH DILATED CARDIOMYOPATHY

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Dilator reserve of the coronary microvasculature is impaired in myocardial hypertrophy. Dilated cardiomyopathy (DC) is also associated with marked ventricular growth. We tested the hypothesis that a) dilator reserve is impaired in DC and b) abnormal endothelial vasodilator function could be a contributing mechanism. We infused into the left anterior descending coronary artery (LAD) the endothelium dependent vasodilator acetylcholine (ACH) (10-8 to 10-6 M) and the smooth muscle vasodilator adenosine (AD) (10-6 to 10-4 M) in 7 DC patients (mean EF 27%) and 5 controls (C) (atypical chest pain). Small vessel resistance was assessed by measuring LAD flow (CBF) at constant arterial pressure with a Doppler velocity catheter (corrected for cross-sectional area by angiography). With ACH, C patients increased CBF 254 ± 37% while DC patients only increased CBF 32 ± 26% (p<.01). With AD, C patients increased CBF 405 ± 90% and DC patients 276 ± 50% (p=NS). Microvascular vasodilation to AD in dilated cardiomyopathy patients was 68.1% (276/405) of the vasodilation seen in controls but vasodilation to ACH was only 12.6% (32/254) of that seen in controls. Thus, small vessel dilation is impaired in patients with dilated cardiomyopathy, especially to an endothelium dependent vasodilator. Defective vasodilator function of the microvascular endothelium appears to be one of the pathogenetic mechanisms involved in this abnormal coronary flow regulation found in dilated cardiomyopathy.

ALTERATIONS IN THE CATALYST OF ADENYLATE CYCLASE AND THE INHIBITORY GUANINE NUCLEOTIDE REGULATORY PROTEIN IN EXPERIMENTAL HEART FAILURE.

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Diminished contractile responses in heart failure (HF) to beta stimulation may in part be due to abnormalities in either the guanine nucleotide proteins (Gs and Gi) or the catalyst of adenylate cyclase. We utilized a canine model of HF produced by rapid ventricular pacing at 260 bpm for 4 weeks to characterize the adenylate cyclase/G protein system. Adenylate cyclase activity was determined in membranes from the left ventricular free wall. Basal, Gpp(NH)p ($10^{-4}$M) and forskolin-stimulated (30 $\mu$M) adenylate cyclase were reduced 24%, 56%, and 49%, respectively (all $p<0.05$). The functional integrity of the catalyst was determined by direct stimulation with purified $GTP_{\gamma}S$·Gs (0.1-0.8 $\mu$g/ml); maximal stimulation by purified Gs was reduced in HF (C: 110±25; HF: 42±6 pmol/mg/min; $p<0.01$). Inactivation of Gi by pertussis toxin resulted in normalization of basal (C: 6.3±0.8; HF: 5.0±0.8 pmol/mg/min) and forskolin (C: 35.7±2.7; HF: 27.0±2.8 pmol/mg/min) stimulated cyclase activity. The level of αGi, αGo, and the β-subunit common to all G proteins were assessed by enzyme-linked immunotransfer blotting. By densitometric analysis, the level of αGi was increased in HF 34±5% compared to control tissue ($p<0.05$), while there was no change in either αGo or the β-subunit. In canine HF produced by rapid pacing: 1) the catalytic component of adenylate cyclase is altered and fails to respond to purified Gs and 2) the guanine regulatory protein αGi is increased and inactivation of Gi partially restores adenylate cyclase activity.

VENTRICULAR TACHYCARDIA IS NOT THE PREDOMINANT CAUSE OF MONITORED SUDDEN DEATH IN HEART FAILURE.

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Sudden death in pts with heart failure is usually attributed to a ventricular tachyarrhythmia (VT) but the initial rhythm at cardiac arrest (CA) is rarely known. Therefore 21 consecutive unexpected CA occurring in stable pts hospitalized for cardiac transplant evaluation (mean LVEF .20 ±.10) were reviewed. In only 8 patients (38%) was the initial rhythm VT (7 pts) or VF (1 pt). In 13 (62%) pts the initial rhythm was bradycardia (BA) (11 pts) or pulseless sinus rhythm (EMD) (2 pts). Pts with VT/VF did not differ from pts with BA/EMD in mean LVEF, history of nonsustained VT (3/8 vs 6/13), antiarrhythmic drug therapy (6/8 vs 8/13), serum $K^+$, or success of resuscitation (3/8 vs 5/13). Non-ischemic cardiomyopathy and hyponatremia were more common in pts with BA/EMD.

| Rhythm | N | Coronary Disease | $K^+>6$ | $K^+<3$ | $Na^+$ |
|---|---|---|---|---|---|
| VT/VF | 8 | 8 | 1 | 0 | 133±4 meq/l |
| BA/EMD | 13 | 5 | 2 | 1 | 128±4 meq/l |
| p | | <0.005 | | | <0.02 |

12 autopsies revealed recent infarction in 5 (1 from a coronary artery embolus) and no acute structural cause of CA in 7.

Conclusions: CA in heart failure frequently occurs with bradyarrhythmias even in pts with a ventricular arrhythmia history. This is likely to limit the efficacy of antiarrhythmic drugs for prevention of sudden death in heart failure.

ENDOTHELIN CONSTRICTS THE SYSTEMIC AND CORONARY CIRCULATIONS AND DEPRESSES VENTRICULAR FUNCTION IN VIVO.

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Endothelin, an endothelium-derived peptide, demonstrates calcium-dependent contractile properties in vitro and may function in pathophysiologic states to elevate systemic vascular resistance by antagonizing the vasodilating and renin inhibitory actions of endothelin-derived relaxing factor(s). The integrated in vivo actions of endothelin on cardiac and systemic hemodynamics and cardiorenal hormones, however, have not been determined. This study was designed, therefore, to test the hypothesis in anesthetized dogs that endothelin increases mean systemic blood pressure (MAP) and resistance (SVR), decreases cardiac output (CO) and coronary blood flow (CBF) and elevates the cardiorenal hormones, atrial natriuretic factor (ANF) and renin (PRA) in vivo.

| | Control | Endothelin (50 ng/kg/min,iv) | Washout† |
|---|---|---|---|
| MAP, mmHg | 98±7 | 123±7* | 101±5 |
| CO, L/min | 3.3±0.2 | 1.1±0.1* | 2.3±0.2* |
| SVR, mmHg/ml/min | 0.03±.002 | 0.13±.017* | 0.04±.005* |
| CBF, ml/min | 60±15 | 41±13 | 55±15 |
| CVR, mmHg/ml/min | 2.16±0.05 | 6.48±3.76* | 2.48±0.65 |
| (L) AP, mmHg | 2.5±0.4 | 9.1±3.4* | 4.7±1.5* |
| ANF, pg/ml | 39±6 | 180±53* | 74±10* |
| PRA, ng/ml | 3.7±1.0 | 6.9±1.7* | 5.6±1.6 |

*p<.05; x±SEM; n=6 †1-hr post-infusion

We conclude that endothelin has potent systemic and coronary vasoconstrictor activity associated with a significant depression of cardiac inotropic function. Further, despite increases in atrial natriuretic factor, an inhibitor of renin, endothelin stimulates renin release by the kidney.

RAPID-ONSET PULMONARY EDEMA IN PATIENTS WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION: A SYNDROME RELATED TO RIGHT VENTRICULAR FUNCTION

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Patients with depressed LV ejection fraction (EF), may manifest rapid-onset pulmonary edema (ROPE), regardless of the presence of active ischemia. We studied determinants of ROPE, postulating that a failed RV serves as a capacitor, buffering pulmonary venous pressure and preventing ROPE. We analyzed 48 variables in 105 consecutive pts with congestive heart failure and LVEF < 0.40 (mean ± SE: 0.20 ± 0.01). ROPE (<3 hr progression from asymptomatic to pulmonary edema, without myocardial infarction) occurred in 17 pts (16%). A similar proportion with (59%) and without (57%) ROPE had coronary artery disease. Stepwise logistic regression showed RVEF to be the strongest independent correlate of ROPE, averaging 0.51 ± 0.04 in pts with ROPE [normal RVEF (≥ 0.45) in 65%] and 0.33 ± 0.02 in those without ROPE (≥ 0.45 in 23%) ($p<0.0001$). Pts with ROPE also had higher serum Na (141 ± 1 v. 137 ± 1 meq/L; $p<0.01$), higher pulse pressures (54 ± 4 v. 43 ± 2 mmHg; $p<0.05$), and were older (64 ± 1 v. 60 ± 1 years; $p<0.05$). Smoking was present in 67% of pts without ROPE but in all pts with ROPE ($p<0.02$). Conclusions: In patients with low LVEF, ROPE correlates with RVEF, serum Na, pulse pressure, age, and smoking. We speculate that the failed RV prevents ROPE by serving as a capacitor, buffering changes in intravascular volume and in pulmonary venous pressure.

## COMPARISON OF ELECTROPHYSIOLOGIC RESPONSES TO ISOPROTERENOL IN THE FAILING AND NONFAILING HEART

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Inotropic and chronotropic responses to beta-adrenergic stimulation are impaired in heart failure. We tested the hypothesis that the right ventricular effective refractory period (ERP) response to infused isoproterenol (ISO) would also be altered. We retrospectively examined the sinus cycle length (SCL) and ERP (constant pacing) before and during an infusion of ISO corrected for body size (μgm/min body surface area) in 11 patients (pts) with radionuclide LVEF<.30 and 27 pts with LVEF>.50 studied electrophysiologically off antiarrhythmic drugs for evaluation of known or suspected cardiac arrhythmias. Pts on beta blockers or with sinus dysfunction (abnormal sinus node studies) were excluded.

RESULTS

| Group | ISO Dose | Baseline SCL(msec) | SCL | Baseline ERP(msec) | ERP |
|---|---|---|---|---|---|
| EF>.5 | 0.9± | 793± | -174± | 216± | -16± |
| | 0.5 | 119 | 85 | 17 | 14* |
| EF<.3 | 1.4± | 710± | -116± | 263± | -20± |
| | 1.2ƒ | 155ƒ | 108*ƒ | 30ƒ | 22* |

*p<.05 vs pre-ISO, ƒp<.05 vs LVEF>.50; data are mean±SD; statistics are t-test. Group mean ages did not differ.

Conclusions: Ventricular effective refractory period responses to beta-adrenergic stimulation are preserved in the failing heart while chronotropic responses are reduced. Thus, responses to beta-adrenergic influence that likely modulate ventricular arrhythmias are operative in heart failure patients and may play a role in their occurrence.

## ALTERATIONS IN LYMPHOCYTE SUBSETS AND CATECHOLAMINES IN CONGESTIVE HEART FAILURE.

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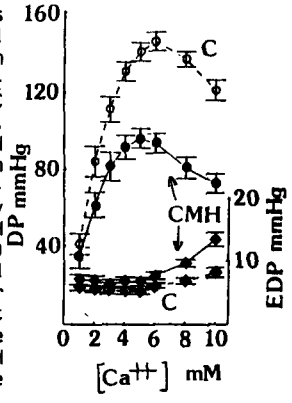
Growing evidence suggests that the sympathetic nervous system can regulate the function of the immune system. We asked whether the chronically elevated sympathetic nervous activity in patients with congestive heart failure (CHF) is associated with altered subsets of circulating mononuclear leukocytes (MNL). We measured number and subset distribution of MNL by flow cytometry using specific monoclonal antibodies, and determined plasma levels of epinephrine and norepinephrine by a radioenzymatic assay, at rest in 35 patients with CHF (NYHA I-IV) and 31 age-matched controls (C). CHF compared to C had lower relative (18±1.4% vs 29±1.5% of WBC, p<0.001) and absolute MNL numbers (1447±98/mm$^3$ vs 1953±116/mm$^3$, p<0.01). The numbers of suppressor ($CD8^+$) and natural killer (NK; Leu $7^+$, $7/2^+$, $11^+$, $19^+$) cells was reduced by 40-50% in CHF, but the number of helper cells ($CD4^+$) did not differ. Thus, the helper/suppressor cell ratio ($CD4^+/CD8^+$) was increased in CHF (2.3±0.2 vs 1.2±0.1, p<0.05). These alterations in suppressor and NK cells were more pronounced in NYHA III-IV than I-II patients but were similar whether CHF was of idiopathic or ischemic etiology. Similarly, plasma levels of epinephrine and norepinephrine were higher in NYHA III-IV than I-II patients but did not differ between etiologies. We conclude that alterations of both circulating MNL and plasma catecholamines in CHF are a secondary rather than a primary event. Since MNL have ß-adrenergic receptors that can inhibit MNL function in vitro, we hypothesize that the increased sympathetic activity may both reduce MNL numbers and alter MNL function in CHF.

## IMPAIRED MYOCARDIAL RESERVE AND CALCIUM INTOLERANCE OCCURS PRIOR TO THE CONGESTIVE HEART FAILURE STAGE IN THE CARDIOMYOPATHIC HAMSTER.

Osamu Hano, M.D., Edward Kasper, M.D., Harlan F. Weisman, M.D., Edward G. Lakatta, M.D., Laboratory of Cardiovascular Science, Gerontology Research Center, NIA, NIH, Baltimore, Maryland.

While the cardiomyopathic hamster (CMH), BIO 14.6 strain, develops congestive heart failure with aging, the evolution of compromised myocardial reserve (MR) and calcium tolerance prior to overt failure remains to be undefined. We compared MR in hearts (isovolumic via LV balloon, AV-blocked, perfused with Hepes buffer at constant pressure and stimulated at 2 Hz at 37°C) isolated from 35-60 day CMH (n = 6) and from 6 age-matched F1B strain controls (C). The maximum developed pressure (DP) with increases in perfusate [$Ca^{2+}$] was approximately 150% greater in C (p<.001) than in CMH (Fig.). Maximum DP occurred in CMH occurs at lower [$Ca^{2+}$] than in C (Fig.). End diastolic pressure (EDP) was significantly (p<.001) elevated in CMH especially at high [$Ca^{2+}$] 8-10 mM; however, coronary flow did not vary between groups nor with [$Ca^{2+}$]. Thus, a deficit in MR and calcium intolerance can be well demonstrated in CMH before the dilated congestive heart failure stage.




## PROGNOSIS OF CONGESTIVE HEART FAILURE (CHF) EVALUATED BY I-123 META-IODOBENZYLGUANIDINE (MIBG) MYOCARDIAL IMAGING

Pascal Merlet M.D., Michel Bourguignon M.D., Heric Valette M.D., Denis Agostini M.D., Brigitte Jouve, David Lellouche M.D., Anne-Marie Duval M.D., Jean-Luc Dubois Rande M.D., Alain Castaigne M.D., André Syrota M.D. ; S.H.F. Joliot, CEA, Orsay, C.H.U. Mondor, Créteil, France.

Previous studies have demonstrated the ability of cardiac MIBG scintigraphy to assess the depletion of norepinephrine stores of the failing myocardium. The prognosis value of MIBG imaging was prospectively investigated in 40 patients (age 51±11) with CHF of various etiologies treated only with digitalis, diuretics and vasodilators. Inclusion criterias were : NYHA class II-IV and radionuclide left ventricular ejection fraction (LVEF) <40 %. MIBG myocardial uptake was quantified as a cardiac to mediastinum ratio (R) computed on anterior view image recorded 4 hours after IV injection of I-123 MIBG. R values (1.11±.16) were correlated with LVEF (r=.58, p=.001) but not related with NYHA class. Seventeen patients poorly responded to medical therapy during a 1-16 months follow up period (6m±3) : 7 died, 5 had heart transplantation and 5 are waiting for transplantation. These 17 patients showed a lower R value (1.04±.1, p<.03) and LVEF (12±3 %, p<.01) when compared to the patients who presented a sustained clinical improvement with medical therapy (R=1.22±.15, LVEF=20±6 %). For the calculation of positive (+) and negative (-) predictive values (P), threshold values : R=1.11 and LVEF=14 % were choosen as the median values of the overlap of the 2 groups : P+(EF)=68 %, P-(EF)=81 %, P+(R)=68 %, P-(R)=81 %. When the 2 tests were combined, P+ and P- values were 84 % and 95 % respectively. Therefore, in this selected population, MIBG scintigraphy provided additionnal information for an accurate assessment of the prognosis in CHF.

EFFECTS OF FLOSEQUINAN ON METABOLIC AND VENTILATORY PARAMETERS DURING SUBMAXIMAL EXERCISE IN CARDIAC FAILURE

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Patients with chronic cardiac failure (CCF) demonstrate abnormal metabolic and ventilatory responses to exercise. We studied the effects of flosequinan (F), a vasodilator, and placebo (P) in 20 patients with NYHA grade III - IV CCF, aged 63 (7) years, mean (SD), and LVEF 26 (7)%. All were symptomatically stable on 92 (19) mg furosemide/day. After 3 preliminary cardiopulmonary exercise tests, patients were randomly allocated to F 100 mg daily or P, double-blind, and the test repeated after 8 weeks. In each subject the exercise stage approximating to 60% of peak achieved oxygen consumption ($PVO_2$) was identified before drug intervention (week 0), and the ventilatory and metabolic responses observed during the last minute of that stage compared at weeks 0 and 8:

| | $VCO_2$ (ml/min/kg) | $V_E$ (l/min) | Lactate (mmol/l) |
|---|---|---|---|
| P (week 0) | 11.1 (1.6) | 30.9 (6.4) | 1.30 (0.4) |
| P (week 8) | 10.9 (1.4) | 30.6 (6.9) | 1.28 (0.4) |
| F (week 0) | 10.9 (1.9) | 31.4 (7.1) | 1.44 (0.6) |
| F (week 8) | 9.5 (2.2)* | 26.2 (6.8)* | 1.06 (0.4)* |

* P<0.05 vs placebo

F increased $PVO_2$ by 2.4 (1.5) ml/min/kg (P<0.01 vs P), and $VO_2$ at anaerobic threshold from 13.2 (2.8) to 15.8 (3.7) ml/min/kg (P<0.01). F therefore improves ventilatory and metabolic responses during both submaximal and maximal exercise, and hence is likely to benefit patients with CCF during everyday activity as well as at peak exercise.

SELECTIVE $\beta$-1 ADRENERGIC RECEPTOR DOWN-REGULATION IN EXPERIMENTAL CANINE HEART FAILURE.

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John R. Wilson M.D., University of Pennsylvania, Philadelphia, Pennsylvania.

Prior animal models of heart failure (HF) do not result in down-regulation of beta adrenergic receptors ($\beta$AR), as has been reported for humans. In a canine model of HF produced by rapid ventricular pacing at 260 bpm for 4 weeks, we measured the density of $\beta$AR, dihydropyridine receptors (DH), and adenylate cyclase activity (AC) in 6 dogs with HF and 7 control (C) animals. The density of $\beta$AR determined by Scatchard analysis of ICYP binding was reduced from 46±8 fmol/mg in C to 24 fmol/mg in HF ($p<0.05$), whereas the density and Kd of DH receptors measured by $^3$HPN-200-110 was unchanged (C: 145±20 fmol/mg, 0.06 nM; HF: 145±40 fmol/mg, 0.08 nM). Competition binding of ICYP with ICI 89,406 was fitted to a computer model to determine the percentage of $\beta$-1 and $\beta$-2 receptor subtypes: (*$p<0.05$)

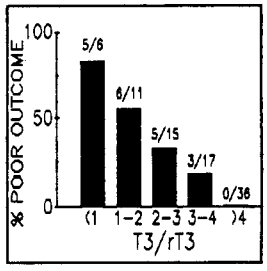
| | %$\beta$-1 | %$\beta$-2 | Bmax$\beta$-1 | Bmax$\beta$-2 |
|---|---|---|---|---|
| Control | 81±13 | 19±13 | 33±8 | 12±6 |
| HF | 51±10* | 49±10* | 13±4* | 12±4 |

Isoproterenol stimulated AC was reduced in the dogs with HF from 144±15 pmol/mg/min to 86±8 pmol/mg/min ($p<0.05$). While the density of $\beta$-2 receptors was unchanged, $\beta$-2 specific stimulation of AC was also reduced in HF (C: 76±7; HF: 46±10 pmol/mg/min; $p<0.05$). These data suggest that the canine model of HF produced by pacing results in selective down-regulation of the $\beta$-1 adrenergic receptor and subsensitivity of AC to both $\beta$-1 and $\beta$-2 stimulation. Since these changes parallel those in human HF, this model could potentially be used to study drug effects on the $\beta$AR.

**ABNORMAL TRIIODOTHYRONINE IS THE STRONGEST SHORT-TERM PROGNOSTIC FACTOR IDENTIFIED IN ADVANCED HEART FAILURE.**

Michele Hamilton, M.D., Lynne W. Stevenson, M.D., F.A.C.C., Michael Luu, M.D., William G. Stevenson, M.D., F.A.C.C., Julie Walden, R.N.. UCLA Medical Center, Los Angeles, CA.

To assess the prevalence and significance of altered thyroid metabolism in advanced heart failure, thyroxine, triiodothyronine (T3), reverse T3 (rT3), and thyrotrophin (TSH) levels were obtained in 85 pts hospitalized for heart transplant evaluation (7 pts on Amiodarone and 4 with clinical hypothyroidism were excluded). 43/85 pts (51%) had normal thyroid tests, 37/85 (44%) ↓T3 and/or ↑rT3, 4 ↑TSH, and 1 ↑T3. The strongest univariate predictor of poor outcome (death within six weeks (13pts) or placement on urgent transplant list (6pts)) was the T3/rT3 ratio ($p<.0001$). T3/rT3 <4.0 was associated with lower serum sodium (133 vs. 138, $p<.01$), ejection fraction (16 vs. 19%, $p<.01$), and CI (1.8 vs. 2.1 L/min, $p<.05$), and higher RA (17 vs. 10mm, $p<.01$), mean pulmonary artery (39 vs. 33 mm, $p<.05$)) and wedge (29 vs. 23 mm, $p<.01$) pressures. However, in multivariate analysis of these factors, T3/rT3 was the only independent predictor of prognosis.



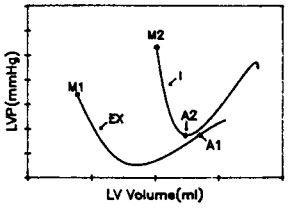

The ratio T3/rT3 is the strongest predictor yet identified for short term outcome in advanced heart failure.

## Wednesday, March 22, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 10:00AM–11:00AM
## Pacific Room, Anaheim Convention Center
## Exercise Physiology

EFFECTS OF EXERCISE-INDUCED ISCHEMIA IN PRESSURE-VOLUME RELATIONS AND FILLING DYNAMICS IN THE CONSCIOUS DOG

Shunichi Miyazaki M.D., Brian D. Guth Ph.D., Rainer Schulz M.S., Ciro Indolfi M.D., Erik Thaulow M.D., Toshiro Miura M.D., John Ross Jr M.D.,F.A.C.C. Univ. of California San Diego, La Jolla, California

The effects of exercise(EX) induced ischemia on the diastolic(D) properties of the left ventricle(LV) were examined in 8 conscious dogs instrumented with a micromanometer and sonomicrometers(LV pressure,P, LV dimensions). After recording a steady state of EX, ischemia(I) was created, during EX, by a pneumatic occluder located on the left circumflex coronary artery so that %ischemic wall thickening showed less than 10%. From EX to I, minimal DP(PDm) increased from 2.7±3.21 to 8.7±4.4 mmHg*(values are mean±SD, * indicates $p<0.05$.), volume at PDm(VDm) from 72±12 to 90±10ml*, peak filling rate decreased from 771±223 to 625±228ml/sec* and ejection fraction from 51±9 to 37±8%*. During EX induced I, disturbed ejection and reduced relaxation increased VDm and PDm, which resulted in a right and upward shift of the diastolic P-V relation (Figure). The volume increment from mitral valve opening(M1 during EX, M2 during I) up to the VDm during I(point A2) was 23% of that from M1 to A1(the volume at equivalent pressure to PDm of I during EX)(M1 to A1 vs. M2 to A2, *). Thus, markedly disturbed filling dynamics accompanied the shift of the early diastolic P-V relation during EX induced ischemia.



CATECHOLAMINE METABOLIC PATHWAYS AND EXERCISE TRAINING: PLASMA AND URINE CATECHOLAMINES, METABOLIC ENZYMES, AND CHROMOGRANIN A. Paul J. Rogers, M.D., G. M. Tyce, Ph.D., R. M. Weinshilboum, M.D., D. T. O'Connor, M.D., and A. A. Bove, M.D., Ph.D., Mayo Clinic and Foundation, Rochester, MN 55905.

The significant release of catecholamines during exercise training may alter the basal release and metabolism of catecholamines. Ten well-trained male subjects and nine minimally-trained male subjects (maximal oxygen uptake 55.2 and 42.5, respectively) were examined at rest, at submaximal and at maximal exercise to determine plasma levels of norepinephrine, epinephrine, dopamine, the sulfoconjugates of each, and chromogranin-A, a marker of exocytotic catecholamine release. Activity of catechol-O-methyltransferase (COMT) in red blood cells and monoamine oxidase (MAO) and phenolsulfotransferase (PST) in platelets was determined at rest and at maximal exercise. Urine for catecholamines was collected for 24 hours during sedentary activity. There were increased plasma levels of sulfoconjugated norepinephrine and sulfoconjugated dopamine at rest and with exercise in the well-trained subjects. Plasma levels of chromogranin-A did not change with exercise or differ between groups. There was no difference in activity of COMT, MAO, or PST between groups with exercise. There were increased urine concentrations of sulfoconjugated epinephrine and dopamine products in the well-trained group. Urine indices comparing activity of COMT, MAO, and PST showed similar activity in both groups. These results demonstrate that in well-trained individuals there is greater inactivation of plasma catecholamines by sulfoconjugation, with no difference in daily release of catecholamines, in activity of catecholamine metabolic enzymes, or in daily production of most catecholamine metabolites.

COMPARISON OF EFFECTS OF PROLONGED EXERCISE ON THE RIGHT AND LEFT VENTRICLES

Pamela S. Douglas, MD, FACC, Mary L. O'Toole, PhD, W. Douglas B. Hiller, MD, Robert Morrow, Keith Hackney, Nathaniel Reichek, MD, FACC. Univ. of PA, Phila., PA.

Since exercise increases right ventricular (RV) work more than left (LV), we compared the effects of prolonged exercise on RV and LV in 41 athletes before, at the finish (13 min) and after recovery (25 hr) from the Hawaii Ironman Triathlon (2.4 mi swim, 112 mi bike, 26.2 mi run). 2D echoes were digitized for LA, RA, LV and RV areas at end-diastole and end-systole; emptying fractions and total diastolic area (TAd=LA+LV+RA+RV) were calculated. Twenty-one athletes had Doppler assessment of mitral and tricuspid regurgitation (MR, TR)and RV and LV inflow velocities (E/A). Results were (*p<.05, **p<.01 vs pre and recovery):

| | RAs | LAs | LVd | LVs | RVd | RVs | TAd | M-E/A | T-E/A |
|---|---|---|---|---|---|---|---|---|---|
| Pre | 20 | 19 | 38 | 26 | 21 | 16 | 84 | 1.5 | 1.6 |
| Finish | 18** | 17** | 36** | 25** | 24** | 18** | 84 | 1.3* | 1.2** |
| Recovery | 20 | 20 | 38 | 26 | 22 | 17 | 83 | 1.8 | 1.9 |

RAs, LAs and LVd all decreased while RVd increased at race finish; the emptying fractions of all chambers were unchanged. RV and LV filling patterns were similarly altered at race finish, although the decrease in T-E/A was greater than in M-E/A. Both the prevalences of MR (76 to 0%) and TR (86 to 52%) were decreased at finish (both p<.01), but neither their presence nor severity correlated with chamber sizes, emptying fractions or heart rate.

Thus, prolonged exercise redistributed intracardiac volume, while ventricular filling and valvular regurgitation were substantially altered. The increase in RVd at race finish cannot be attributed to increased preload alone since RAs was decreased. Exercise may result in changes in RV diastolic shape, compliance or function.

DIAGNOSTIC STRATEGIES BASED ON CLINICAL AND EXERCISE VARIABLES: LIBERATION FROM BAYES'S THEOREMA?

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The relationship between the diagnostic properties of clinical and exercise variables was studied with logistic regression analysis. The study population comprised 295 consecutive symptomatic patients without a previous myocardial infarction, who underwent exercise testing and coronary angiography to establish the presence of coronary artery disease. All had a normal ECG at rest. Prevalence of coronary disease was 77% in males and 51% in females. Clinical variables included sex, age, risk profile and symptom classification. Exercise variables comprised achieved workload, angina during exercise and heart rate (HR) corrected ST segment amplitude changes. Logistic regression analysis revealed the mutual dependance of various clinical and exercise variables. The final diagnostic model only included age, (severe) angina, high cholesterol, cigarette smoking, HR adjusted ST segment changes and angina during exercise in males. Results obtained with this model proved to be superior to those based on Bayesian analysis. Correct diagnostic classification was substantially improved by exercise testing in males but not in females. It is concluded that logistic regression analysis is more suited to establish a diagnostic function than the Bayesian approach.

INSENSITIVITY OF THALLIUM 201 IMAGING AFTER ORAL DIPYRIDAMOLE FOR DETECTION OF REVERSIBLE MYOCARDIAL ISCHEMIA

Sakina Khan, M.D., Jashvant Thakkar, M.D., David Bushnell, M.D. and Henry S. Loeb, M.D., F.A.C.C., Hines V.A. Hospital, Hines, Illinois.

Patients (pts) with known or suspected coronary disease who may be at high risk during non-cardiac surgery may be identified by stress testing. However, for pts unable to exercise sufficiently Thallium 201 imaging (TI) following intravenous dipyridamole (D), and recently, oral D has been used in place of exercise. Since demonstration of reversible myocardial ischemia (RMI) is important in planning further workup and/or treatment we investigated the sensitivity of TI following oral D for detection of RMI in 21 stable pts selected on the basis of angiographically proven coronary disease ($\geq$ 70% diameter narrowing of a major coronary artery) and RMI ($\geq$ 1 mm ST depression during standard treadmill testing). Images (planar and SPECT) were obtained 45 minutes following oral D (300 mg suspension) at which time serum D levels were 4.7±2.1 µg/ml. Aminophylline (125 mg IV) was given and delayed images were obtained at 3 hours. RESULTS: Reversible defects by TI were present in 11 of 21 pts (52%). Five pts (24%) had only fixed defects and 5 pts (24%) had neither reversible nor fixed defects. Mean serum D was (5.4±2.1 µg/ml in 11 pts with reversible defects vs 3.9±2.8 µg/ml in the 9 pts without (p = 0.2-NS). CONCLUSION: Since almost 50% of pts with coronary disease and RMI by treadmill did not have reversible defects on TI the use of TI after oral D appears not to be a satisfactory substitute for stress testing in detecting high risk pts prior to non-cardiac surgery.

INCREASED EXERCISE CAPACITY IN HEART FAILURE PATIENTS FOLLOWING DIGOXIN ADMINISTRATION.

Michael Sullivan M.D., J. Edwin Atwood M.D., Joshua Feuer M.D., Barbara Kellerman R.N., Jonathan Myers M.A., Susan Forbes R.N., Victor Froelicher M.D., F.A.C.C., Long Beach VA Medical Center, Long Beach, California.

There is controversy regarding whether digoxin should be included in the treatment of patients with chronic congestive heart failure. Prior studies have not consistently demonstrated improvements in hemodynamics or exercise capacity in such patients due to digoxin. In order to resolve this controversy, we investigated the effect of digoxin on respiratory gas exchange variables in 11 patients with congestive heart failure. Systolic dysfunction was documented by clinical evaluation and noninvasive testing. They had a mean age of 59 (± 8 years) and a mean ejection fraction of 24% (± 9). They were tested during chronic digoxin administration and then two weeks after discontinuation. Symptoms and weight were stabilized while off digoxin by diuretics.

Results: There was no significant increase in treadmill time or workload. However, there were significant increases in maximal oxygen uptake (mean of 2.6 ml/kg/min; $p < .01$) and the gas exchange anaerobic threshold (mean of 2.2 ml/kg/min; $p < .02$) during chronic digoxin administration. In addition, there was a significant decrease in submaximal VD/VT (mean of .03; $p < .02$).

Conclusions: There is an improvement in exercise performance in heart failure patients during digoxin administration most likely due to improved matching of ventilation and perfusion. Since there was no significant change in treadmill time or workload achieved, these findings also demonstrate the need for respiratory gas analysis to measure changes in the cardiopulmonary response to exercise in patients with chronic heart failure.

TRAINING LEVEL COMPARISON STUDY: FACTORS INFLUENCING EXERCISE COMPLIANCE.

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Forty men with stable coronary heart disease were randomly assigned to a low intensity (L) level (50% $VO_2$) or to a high intensity (H) exercise level (85% $VO_2$). Characteristics at entry were assessed to determine factors predictive of compliance to the exercise routine. Each group exercised in an identical mode by walking, walk-jogging, cycling, and calisthenics for 45 to 60 minutes, 3 times per week. Compliance was defined as the percent of exercise sessions attended during the initial six months of this two-year rehabilitation study. Compliance for those randomized to L levels ($n = 21$) was 66.3% compared to 70.4% for those at the H level ($n = 19$). Regardless of randomization assignment compliance was greater for those with some college education, 70.4% compared to 22.5% for those without ($p < .05$). Smokers attended less regularly, 35.6%, than the non-smokers, 70.4%. Compliance related to time since the cardiac event qualifying patients for the study; 70.4% (< 6 mo.); 67.0% (7 to 12 mo.); and 62.9% (13 to 18 mo.). Compliance varied by previous exercise habits - 70.4% (some physical activity) compared to 41.7% (little or none). We concluded that the intensity of the exercise program had little effect on compliance, whereas educational level significantly related to attendance at sessions. Other important factors include smoking habits, time since qualifying cardiac event; and previous exercise habits.

THE USE OF THE EXERCISE TEST TO PREDICT PROGNOSIS AFTER CORONARY ARTERY BYPASS SURGERY.

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Predicting prognosis of patients who become symptomatic after coronary artery bypass surgery is an important issue since more than 200,000 patients undergo this surgical procedure annually in the USA. Evaluation is often difficult after coronary artery bypass surgery, since symptoms are often atypical and resting ECGs are often abnormal.

The objective of this study was to predict the prognosis of patients who became symptomatic after having undergone coronary artery bypass surgery using clinical and exercise test responses. A retrospective analysis was performed of all veterans referred for clinical indications to a Veterans Administration Medical Center for a treadmill test after having undergone coronary artery bypass surgery. Out of 2044 patients who were exercise tested from April 1984 to May 1987, 296 had previously undergone coronary artery bypass surgery. Clinical data considered included age, sex, medication and symptom status, history of myocardial infarction and myocardial infarction type, and the time from coronary artery bypass surgery. The following exercise test responses were considered: MET level, maximal heart rate, maximal systolic blood pressure, chest pain pattern, and ST segment response. During a two year follow-up after exercise testing, there were 15 deaths, 11 non fatal myocardial infarctions, 6 repeat coronary artery bypass surgeries, and 3 coronary artery dilations. Though MET level and maximal heart rate were significantly related to prognosis and no patient who exceeded 8 METs died, the predictive power of these exercise test responses was low and ST segment depression was not predictive at all.

Conclusions: The inability of the exercise ECG to predict cardiac events in patients after coronary artery bypass surgery requires that other methods of testing be utilized to identify those who need invasive studies and intervention.

REDUCED EXERCISE CAPACITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS EXERCISING WITH NOSECLIP/MOUTHPIECE: DECREASED RIGHT HEART PRELOAD?

Douglass A. Morrison, M.D., F.A.C.C., Michael Collins, M.D., James R. Stovall, CNMT, Geoffrey Freifeld, M.D. Denver Veterans Administration Medical Center and the University of Colorado Health Sciences Center, Denver, Colorado.

A noseclip and low resistance mouthpiece are used to monitor exhaled gases. Because the otolaryngologic literature suggests that 50% of airway resistance is in the nose and mouth, we hypothesized that patients with advanced chronic obstructive pulmonary disease (COPD) might be artifactually limited by exercise testing with exhaled gas measurement. Accordingly, 12 patients with stable COPD performed 2 symptom-limited exercise tests with simultaneous right heart hemodynamic measurements, radionuclide ventriculography, and arterial and mixed venous gas sampling. Exhaled gases were analyzed on the noseclip/mouthpiece exercise.

Comparing noseclip to room air exercises, there were significant reductions in exercise duration (397 ± 270 sec vs 300 ± 230 sec $p < 0.01$), exercise oxygen consumption (780 ± 279 vs 638 ± 200 ml $p < 0.01$), and exercise cardiac output (8.4 ± 2.7 vs 7.3 ± 2.0 L/min $p < 0.05$), an increase in right ventricular ejection fraction (RVEF) (.39 ± .08 vs .43 ± .08 $p < 0.01$) and no change in exercise heart rate (106 ± 14 vs 106 ± 14), right heart pressures, or arterial and mixed venous blood gases.

These data suggest that a noseclip/mouthpiece can limit exercise tolerance in advanced COPD patients. The cardiac output, heart rate, and RVEF data suggest that this ventilatory maneuver is associated with decreased right ventricular end-diastolic volume or decreased right heart preload (venous return).

## DEVELOPMENT OF PHYSIOLOGIC EXERCISE HEART RATE RESPONSES AFTER CARDIAC TRANSPLANTATION

Blair J. O'Neill, MD, Peter W. Pflugfelder, MD, Alan H. Menkis, MD, F. Neil McKenzie, MD, William J. Kostuk, MD, FACC, University Hospital, London, Ontario, Canada.

The chronotropic responses of the denervated heart during and after exertion are blunted, but adaptations to exercise late following transplantation have not been documented. Therefore, the cardiovascular responses of 40 age-matched normal volunteers (N) during treadmill (TM) exercise testing (Bruce protocol) were compared to 49 cardiac transplant (Tx) recipients studied serially at 3 mo and 1 yr and in a further 20 patients at 3 yr. **Results:**

| | Ex dur (secs) | Rest HR | 2 Min ExHR | Peak ExHR | Rec HR 4 min |
|---|---|---|---|---|---|
| N | 665±126 | 74±11 | 107±15 | 167±13 | 110±14 |
| 3 m | 587±170 | 101±12* | 104±13 | 141±18* | 142±16* |
| 1 y | 621±189 | 103±11* | 113±13 | 155±15* | 141±16* |
| 3 yr | 596±182 | 92±12* | 105±15 | 149±24* | 114±14 |

means±SD; *p<.01vs N; Ex dur=treadmill exercise duration, HR=heart rate, Rec=recovery.

Although resting heart rates were similar, after 3 mo, Tx heart rate rose more rapidly with the initiation of exercise and a higher peak heart rate was acheived (p<.01). Deceleration of heart rate post exercise was most pronounced 3 yr post transplant. Thus, the heart rate responses during upright exercise post cardiac Tx differ significantly from normal, but do evolve toward normal with time. In the absence of cardiac reinnervation, these data imply the development of an intrinsic cardiac mechanism responding to the onset and termination of exercise.

RISK ASSESSMENT AFTER MYOCARDIAL INFARCTION RULED OUT

Charles Dennis, M.D., FACC, Patricia Goins, R.N., Cheryl Leong, B.S., Haim Hammerman, M.D. Stanford University, Stanford, California

The purpose of this study was to evaluate a management strategy after myocardial infarction was ruled out in patients hospitalized with chest pain. Sixty men, mean age 60 ± 10 years, underwent symptom-limited treadmill testing (ETT) soon after chest pain was stabilized on medical therapy and myocardial infarction was ruled out. Patients with a normal ETT (peak workload ≥ 7 METS) were managed medically. Patients with an abnormal ETT (≥ 2 mm ST depression, workload < 7 METS) were referred for coronary angiography. Patients with an equivocal ETT (< 2 mm ST depression, workload < 7 METS) underwent rest and exercise radionuclide ventriculography (RVG). RVG was classified as abnormal if ejection fraction fell and normal if it rose. Patients were followed for cardiac events (death, non-fatal myocardial infarction, coronary surgery) for a mean of 181 ± 137 days.

| ETT Results / RVG Results | Normal | Equivocal Normal | Equivocal Abnormal | Abnormal |
|---|---|---|---|---|
| EVENT | 1 | 0 | 3 | 5 |
| NO EVENT | 16 | 22 | 8 | 5 |

Only 1 of 39 patients with a negative non-invasive evaluation had a cardiac event (sudden death at 106 days). Of the 21 patients with a positive non-invasive evaluation 8 underwent coronary surgery (p < 0.01) because of severe coronary disease on angiography.

CONCLUSION: A management strategy using ETT and RVG accurately separates patients at high risk for severe coronary disease requiring coronary surgery from patients with an extremely low risk of cardiac events while treated medically after myocardial infarction ruled out.

EFFECT OF COLD UPON ISCHEMIC THRESHOLD IN PATIENTS WITH STABLE ANGINA: MAGNITUDE AND MECHANISM.

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To investigate the influence of cold upon ishemic threshold, we performed treadmill exercise tests off antianginal medication at -8°C and 20°C in 24 pts. All had stable angina and exercise-induced ST depression (↓ST). Standardized light clothing was worn in a cold chamber for the tests at -8°C. An angina questionnaire completed before study entry identified a subgroup of 8 pts with worse angina in cold weather. Their clinical features did not differ from the other pts.

| | All Pts | | Cold Subgroup | |
|---|---|---|---|---|
| | -8° | 20° | -8° | 20° |
| Exercise duration (secs) | 396 | 381 | 420 | 413 |
| Time to angina (secs) | 306 | 313 | 292 | 346 |
| Time to 1 mm ↓ST | 222 | 252 | 169* | 244 |
| RPP at 1 mm ↓ST (x10-3) | 22.0 | 23.0 | 19.8† | 22.0 |
| Maximum ↓ST (mm) | 2.1 | 2.1 | 2.9 | 2.7 |

RPP=rate-pressure product; *=p<0.01; †=p<0.05 vs 20°.

For the entire group, none of the exercise parameters differed significantly between cold and normal temperatures. However, cold-sensitive pts developed ↓ST 75±40 secs (30%) sooner at -8° compared to 20°C. At the onset of ischemia, RPP was significantly lower in the cold.

Thus, as assessed by exercise testing, cold does not worsen ischemic threshold in most stable angina pts. However, in a subset identifiable by history, ischemic threshold is lower in the cold. This difference appears to be caused by reduced supply, not increased demand.

# Wednesday, March 22, 1989
# Poster Displayed: 9:00AM–12:00NOON
# Author Present: 11:00AM–12:00NOON
# Pacific Room, Anaheim Convention Center
# Electrophysiology, Drugs and Arrhythmias

A NEW QUANTITATIVE METHOD OF SINOATRIAL NODAL CELLS IN SICK SINUS SYNDROME.

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We have reported that pathological process either in sinoatrial node(SAN) or perinodal regions is predominantly responsible for sick sinus syndrome(SSS). To quantify the degree of cellular degeneration in SAN, we compared the percentage of sinoatrial nodal cells(%SAN) and sinoatrial nodal size(S-SAN) in histopathological sections stained with xylidine ponceau and light green, from 23 cases with SSS(age 69-94 yr;8 males, 15 females) and from 23 cases with normal sinus rhythm(age; 16-100 yrs,10 males,13 females), using computer-assisted color image analyzer at 672x magnification. %SAN was defined as mean value of different three points determined by dividing the area of nodal cells by the area of nodal cells plus fibrosis. S-SAN was measured by tracing the outlines of SAN on digitizer. Results were as follow.

| | Control(n=23) | SSS(n=23) | P Value |
|---|---|---|---|
| Age (yrs) | 70.2±26.0 | 78.7±7.1 | NS |
| %SAN(%) | 20.8±10.4 | 10.5±5.0 | P<0.01 |
| S-SAN(mm2) | 3.6±3.1 | 2.7±1.3 | NS |

A linear correlation was found between age and %SAN(r= -0.64,P<0.01) but not between age and S-SAN.

Conclusions:1)It was the %SAN, not the S-SAN, which was statistically related to age. 2)%SAN was significantly lower in SSS, compared with that of control cases.

**SIMULTANEOUS DEMONSTRATION OF EARLY- AND DELAYED AFTERDEPOLARIZATIONS IN $CA^{2+}$ LOADED CARDIAC CELLS**

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Early afterdepolarizations (EAD) have been induced by various interventions in cardiac Purkinje fibers, but not in myocardial cells. In our studies increased $[Ca^{2+}]_i$ enhanced $Cs^+$-induced EAD in Purkinje fibers. We examined the effects of high $[Ca^{2+}]_i$ in 31 disaggregated canine subepicardial ventricular myocytes pretreated in low $[Na^+]$ (115 mM + 60 mM sucrose) solutions with 5 mM $[Ca^{2+}]$ for 15 minutes. Eight cells exhibited both EAD and delayed after depolarizations (DAD) upon the readministration of 145 mM $[Na^+]$ and 1.8 mM $[Ca^{2+}]$. EAD manifested only at slow pacing rates (<0.5 Hz). DAD also were observed at slow rates, but their amplitudes increased with increasing rate. Both EAD and DAD induced triggered action potentials. Seven cells which did not produce EAD following low $[Na^+]_o$ and high $[Ca^{2+}]_o$ pretreatment developed EAD immediately in $[Cs^+]_o$ 3-7 mM. Both EAD and DAD were inhibited by acetylcholine or carbachol (1 uM) but only DAD were enhanced by 10-100 uM epinephrine. EAD but not DAD were immediately and reversibly inhibited by sudden increases in $[Ca^{2+}]_o$ (by 1-3 mM) or decreases in $[Na^+]_o$ (by 30 mM). We conclude that: 1) EAD can be induced in cells of working myocardium loaded with $Ca^{2+}$ and are enhanced by $Cs^+$; 2) Both EAD and DAD can be induced with $Ca^{2+}$ loading but they respond differently to changes in rate, $[Na^+]_o$, or $[Ca^{2+}]_o$ suggesting that $Ca^{2+}$ loading can generate different arrhythmogenic mechanisms.

**MECHANISM AND SIGNIFICANCE OF CYCLE LENGTH ALTERNANS DURING SUPRAVENTRICULAR TACHYCARDIA.**

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Cycle length alternans (CLA) is commonly observed during onset and termination of supraventricular tachycardia (SVT). Although multiple mechanisms have been proposed to explain its occurrence, experimental confirmation has been lacking. To test the hypothesis that CLA is due to feedback between tachycardia cycle length and intrinsic AV node recovery properties during AV reentrant tachycardias (AVRT), we developed computer simulations to predict sequential AH and RR intervals after onset of orthodromic AVRT based on recovery curves (AH vs A1A2) measured in 5 autonomically blocked dogs. Simulated AVRT (sAVRT) was compared to experimental AVRT (eAVRT) created by a sensing and pacing circuit mimicking a retrograde accessory pathway with a programmable VA conduction time. Results: No evidence of dual pathways was found. Steady state rate of sAVRT correlated closely with that of eAVRT ($r=0.99$, $p<0.0001$). CLA appeared consistently at the onset of both sAVRT and eAVRT at shorter VAs. Duration of CLA was always less than 10 beats and was inversely related to VA. Peak CLA amplitude was exponentially related to VA under both simulated and experimental conditions, with similar exponential coefficients for each. Abrupt accelerations in atrial pacing leading to similar rates as AVRT did not result in CLA. We conclude: 1) CLA is an expected phenomenon based on normal AV nodal conduction properties, and does not require changes in autonomic tone or dual AV pathways. 2) CLA occurrence, amplitude, and duration depend on VA during AVRT. 3) Presence of CLA suggests that the AV node is an integral part of an SVT reentrant circuit.

FREQUENCY RESPONSE OF ACTION POTENTIALS FROM HUMAN MYOCARDIUM.

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Previous experiments have suggested that a calcium overload state exists in myopathic human myocardium. We tested the hypothesis that calcium overload would affect electrophysiological parameters and associated isometric muscle tension in human heart muscle. Action potentials (AP) were studied in ventricular trabeculae from control and myopathic human hearts. Resting potential (RP) and time to 50% and 80% repolarization ($APD_{50\%}$, $APD_{80\%}$) were recorded at 30°C. Muscles from control hearts displayed a decrease in APD as stimulus frequency was increased from 0.1 Hz to 1 Hz. This was associated with a decrease in isometric twitch duration. However, there was an increase in peak tension (PT) (positive treppe effect). Myopathic heart muscles displayed a greater reduction in APD when the stimulus frequency was increased to 1 Hz. This was associated with a decrease in PT (negative treppe effect). These results are consistent with the hypothesis that an intracellular calcium overload state exists in myopathic tissue. Intracellular calcium overload could cause a greater reduction in AP duration at higher stimulus frequency by increasing $Ca^{2+}$-mediated $K^+$ efflux and/or by reducing driving force for $I_{si}$. Conclusion: These findings may explain in part why tachycardia is poorly tolerated in patients with cardiomyopathy.

| | 0.33 Hz | | 1.0 Hz | | |
|---|---|---|---|---|---|
| | RP | APD80% | RP | APD80% | PT(%) |
| Control | -80±2 | 689±3C | -75±2 | 412±16 | 200±26 |
| Myopathic | -76±3 | 775±24 | -72±2 | 338±9 | 102±13** |

* p<0.01 ** p<0.004

SURFACE ECG AND INTRACARDIAC FINDINGS WITH THE ONSET OF ENTRAINMENT IN A PACING MODEL OF PSEUDOREENTRY VENTRICULAR TACHYCARDIA.

Mark Kremers, M.D., F.A.C.C., Peter Wells, M.D., William Black, M.D., Robin Eckels, Anne Taylor, M.D., F.A.C.C., U T Southwestern Medical Center, Dallas, TX.

Ventricular (V) pacing (P) in the VAT mode with both "atrial" sensing (AS) and VP electrodes on the V was used to create a pseudoreentrant V tachycardia (T) circuit in 5 dogs with cycle lengths (CL) of 290-400 msec (mean 347±33). Entrainment from 1-4 other V sites at 2-4 PCL 20-90 msec less than VT CL was performed to investigate the effects of PCL, conduction time (CT) to the circuit, and the relationship of entraining site to circuit entrance and exit points on the surface ECG and intracardiac findings of entrainment. CT to circuit was estimated from CT to AS and VP sites measured during P at comparable CL during sinus rhythm. Entrainment sites were distal (D) if CT VP less than CT AS, proximal (PR) if CT AS less than CT VP and within (W) if between AS and VP. In 106 entrainments (45D, 57PR, 4W), we found: 1) the number of cycles to achieve an stable QRS and intracardiac circuit entrainment was directly related to PCL and CT to circuit. 2) A stable QRS and intracardiac circuit entrainment occurred on the same cycle in only 42/106 (40%). 3) At D sites, stable QRS proceeded or occurred on the same cycle as intracardiac entrainment in 38/45 (84%) but at PR and W sites stable QRS occurred after intracardiac entrainment in 46/61 (75%) ($p<0.05$). 4) AS site was always entrained before or on same cycle as VP site regardless of entrainment site. Conclusions: 1) stable QRS is a poor marker of reentrant circuit entrainment; 2) onset of entrainment may provide insight into CT to circuit and circuit localization.

IS THE PROARRHYTHMIC EFFECT OF QUINIDINE A CHAOTIC PHENOMENON? Alan Garfinkel, Ph.D, Hrayr S. Karagueuzian, Ph.D, FACC, Steven Khan, M.D., George A. Diamond, M.D., FACC. Cedars-Sinai Medical Center, Los Angeles, CA

We used dynamic markers based on recent mathematical developments in chaos theory to predict the onset of ventricular fibrillation (VF) during progessive quinidine intoxication. Three closed-chest anesthetized dogs were infused with quinidine (up to 100mg/kg over 5 hours). RV endocardial bipolar electrograms were recorded and analyzed by frequency spectra, phase plane plots, Poincare section return maps and Lyapunov exponents. In the control state and at therapeutic doses the phase plane plots were uniformly thick and showed no gaps, indicating that cycle-to-cycle variation was due to normal biological "noise". But as the quinidine dose was increased to intermediate levels (40-50 mg/kg), phase plane plots showed clear non-uniform thickening, (indicating sensitive dependence on initial conditions), and also showed marked banding (densely filled regions separated by divisions or gaps). Both these phenomena are strong indicators of deterministic chaos as opposed to random noise. At these intermediate doses, Lyapunov exponents became positive and poincare return maps also indicated non-random chaos. At still higher doses, phase plane plots became more complex. In the two dogs that did exhibit VF (and not in the other) there was a significant change in the phase plane plot at the last pre-fibrillatory dose: the development of a "funnel", a classic mechanism of chaos. The frequency spectra at all pre-fibrillatory doses were discrete, with peaks at a fundamental frequency and multiple harmonics. We conclude that chaos does in fact occur during progessive quinidine intoxication, and that phase plane plots are better indicators of chaos than frequency spectra.

FECAL ELIMINATION OF AMIODARONE AND DESETHYL AMIODARONE Suriya Sastri, MD, David Bull, MD, Nelson Mostow, MD. University of Missouri, Columbia, MO & Cleve Metro Gen Hosp. Cleveland, OH.

The importance of the fecal excretory pathway in amiodarone (AMD) metabolism is not well defined. 24 hr fecal excretion of AMD and desethyl AMD (dAMD) was measured by HPLC in 7 pts receiving chronic AMD therapy with mean cumulative dose (CD 370 gms) and in 6 pts who discontinued AMD therapy (CD 244 gms). 7 pts on AMD had mean 24 hr fecal excretion of AMD(12.5 mg) and dAMD (33.1 mg) compared to AMD(2.1 mg) and dAMD(48.4 mg) in 6 pts within 2 months of AMD withdrawal. 3 further pts had 24 hr fecal drug levels performed at 14,21 and 28 days after AMD withdrawal. While AMD levels were all <1 mg/24 hr, dAMD 24 hr excretion values were 19.5, 13.9 and 16.2 mg respectively for the 3 study days. Daily fecal excretion of AMD and dAMD in pts on AMD remained constant at approximately 5% of the ingested drug during chronic AMD therapy. Interpatient variability was more marked in pts withdrawn from AMD than in pts on AMD. CONCLUSIONS: 1) In pts on chronic AMD therapy, about 5% of the ingested drug is excreted daily in feces. 2) Fecal excretion of the metabolite dAMD was higher than that of AMD both in pts on and off AMD. 3) 1 month after withdrawal, major fecal excretion of the metabolite dAMD continued, with minimal excretion of AMD. 4) There was no correlation between cumulative dose and fecal excretion. SPECULATIONS: The biliary pathway is the major route of AMD excretion. Therefore, the relatively low fecal excretion of ingested AMD(5%) suggests a much higher rate of absorption of AMD than previously reported and a major enterohepatic circulation of AMD. Thus, resin binding drugs such as cholestyramine may have a role in treating AMD side effects by enhancing fecal elimination of AMD.

ABLATION OF CANINE VENTRICULAR MYOCARDIUM WITH A CRYOGENIC CATHETER: A NEW CLOSED-CHEST ABLATIVE TECHNIQUE ? Thomas Lavergne M.D., Jacques Verdier Ph.D., Patrick Bruneval M.D., Louis Guize M.D., Dominique Von Euw, JeanYves Le Heuzey M.D., Thierry Béard M.D., Pierre Peronneau Ph.D. INSERM U 256/28 & CEA/CENG Paris, France.

Cryothermal techniques can be used to cure refractory arrhythmias, but the currently available cryoprobes imply a surgical approach. In order to achieve closed-chest cryoablation of myocardial tissue we have developed a cryogenic catheter (CC), with a 2.6 mm diameter tip electrode (E) cooled by expanding nitrous oxide. In a saline bath at 37°C, the E temperature was reduced to −30°C. The efficacy of the CC was assessed in 9 dogs. In each dog, 4 consecutive 60 sec duration cooling sequences (CS) were delivered to a single site of the right ventricle. Aortic pressure and ECG were monitored. An electrophysiologic study was performed before and after ablation. Twenty-four hour Holter recordings (H) were obtained in all dogs immediatly after ablation (H1), and in 5 dogs one day before the sacrifice (H2), 2 to 5 weeks later. The ablated site pacing threshold significantly increased after cooling (3.9 ±1.3 vs 1.1 ±0.4 mA, $p<0.001$). No hemodynamic impairment was noted. Spontaneously terminating ventricular tachycardias (VT) occurred shortly after CS in 3 dogs. Non-sustained VT were present on 8/9 H1 but none on H2. One dog died suddenly at day 4. Anatomic study identified endomyocardial lesions in 7/9 dogs, (4 transmural). The histologic lesions consisted in well circumscribed areas of fibrotic tissue with a depth of 2.9 ±1.0 mm and a diameter of 4.0 ±0.9 mm. In conclusion: transcatheter cryoablation of ventricular myocardium can induce well delineated injury. This technique has potential for being a new closed-chest ablative method. Nevertheless further experimental data are required in regard to its early and transient arrhythmogenic effects.

## Wednesday, March 22, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 9:00AM–10:00AM
## Pacific Room, Anaheim Convention Center
## Basic Regulatory Mechanisms in the Coronary Circulation

IS ATRIAL NATRIURETIC FACTOR INVOLVED IN THE MODULATION OF CORONARY TONE IN MAN ? Helmut Drexler M.D., Andreas M. Zeiher M.D., Helmut Wollschläger M.D., Thomas Münzel M.D., Jürgen Holtz M.D., Thomas Meinertz M.D., Hanjörg Just M.D., Medizinische Klinik III, University of Freiburg, F.R.G.

To test, whether atrial natriuretic factor (ANF) may be involved in the modulation of coronary vasomotor tone, we injected 1-28 ANF into the left coronary artery in 17 patients with angiographically normal coronary arteries. Measurement of epicardial diameters of the A.circumflexa (Cx) and left anterior descending (LAD) were made from biplane angiography by an automatic contour detection system. Bolus injection of ANF (0.07 µg/kg, diluted in 1 ml 0.9% NaCl, n=7) increased diameter of proximal segments of LAD (11±4%) and Cx (10±4%) ($p<0.02$ each versus control) without altering heart rate and mean arterial pressure (MAP). Intracoronary nitroglycerin (NTG, 0.3mg) increased identical LAD and Cx segments by 18±3% and 20±4% while MAP declined. Intracoronary ANF infusion (0.02 µg/kg/min over 5 min followed by 0.1 µg/kg/min, n=10) exerted dose-dependent increases in diameters of LAD and Cx (low dose: +5±2%, high dose: +13±3% versus control, $p<0.02$ each versus control). ANF-infusion increased arterial plasma ANF levels from 280±80 pg/ml during control to 894±82 pg/ml (low dose) and to 2290±228 pg/ml (high dose). Severe ischemia in patients undergoing angioplasty exerted a 4-5 fold increase in arterial ANF levels, similar to the increase elicited by low-dose infusion of ANF. Thus, ANF caused dose-dependent coronary vasodilatation in man. Although intracoronary ANF levels during infusion were estimated to exceed by far peripheral ANF levels, ventricular release of ANF (e.g during severe ischemia) may lead to comparable coronary ANF-levels thereby contributing to the modulation of coronary vasomotor tone.

## OXYGEN CONSUMPTION DURING EXERCISE IN THE PRESSURE-OVERLOADED HYPERTROPHIED HEART.

Xue-Zheng Dai, M.D., Eugene Sublett, B.A., Paul Lindstrom, Robert J. Bache, M.D., F.A.C.C. University of Minnesota, Minneapolis, Minnesota.

The chronically hypertrophied left ventricle (LV) has increased vulnerability to ischemia during exercise. This is in part related to abnormalities of myocardial perfusion, but could also result from abnormally great increases of $O_2$ demands (MVO2) secondary to exagerated increases of LV systolic wall stress during exercise. This study tested the hypothesis that exercise results in abnormally great increases of MVO2 in pressure overload LVH. Seven dogs underwent banding of the ascending aorta at 8 weeks of age and were studied at one year when left ventricular mass was 90% > 5 normal dogs. Myocardial blood flow (MBF), measured with microspheres, and the aortic-coronary sinus $O_2$ difference, were used to compute MVO2 during graded treadmill exercise.

| Speed/ Grade | HR (b/min) | | LVSP (mmHg) | | MVO2 (ml/min/100 g) | |
|---|---|---|---|---|---|---|
| (km/h,%) | CON | LVH | CON | LVH | CON | LVH |
| Rest | 128 | 154 | 126 | 230* | 18±3 | 22±1 |
| 6.4,5% | 192 | 227 | 157 | 300* | 29±3 | 43±3* |
| 6.4,20% | 241 | 264* | 188 | 358* | 44±6 | 64±3* |

HR= heart rate; LVSP=systolic pressure. *p<0.05

Animals with LVH had higher heart rates and higher left ventricular systolic pressures at each workload, with significantly greater MVO2. Thus, increased vulnerability to ischemia in left ventricular hypertrophy may be related in part to abnormally great increases of MVO2 during exercise.

## REDUCED MYOCARDIAL BLOOD FLOW WITH PERSISTENT VASODILATOR RESERVE: ROLE OF ADRENERGIC ACTIVATION

Barry Sharaf, M.D., Frank A. Fedele, M.D., Albert S. Most, M.D., FACC, Henry Gewirtz, M.D., RI Hospital, Providence, RI

This study tested the hypothesis that alpha adrenergic tone contributes to reduced myocardial blood flow in the face of persistent vasodilator reserve. Seven closed chest, domestic swine were instrumented with an artifical coronary arterial stenosis (CAS) which reduced luminal diameter 80%. Measurements of hemodynamics and regional myocardial blood flow were made at; 1) Control (C); 2) 5 min after completion of regional alpha receptor blockade with phenoxybenzamine (PBX) (0.25 mg/Kg distal to the CAS); 3) after 10 min of adenosine infusion (800 µg/min) distal to the CAS and; 4) late PBX, 1 hour post drug. At C distal endocardial (EN) flow (0.94±0.16 ml/min/g; mean ± SD) was reduced vs circumflex (CX) zone EN flow (1.69±0.39, p<.01). Five min after PBX, distal zone EN and epicardial (EP) flow (1.23±0.27) were unchanged vs C. Infusion of adenosine reduced distal EP and EN resistance (51±11 to 23±7 mmHg/ml/ming/g; and 49±16 to 39±11; EP and EN, respectively; both p <.05 vs C) and increased (p<.05) distal zone EP flow (1.23±0.27 to 1.86±0.45, ml/min/g). Distal zone EN flow did not change significantly vs C during adenosine (0.94±0.16 to 0.77±0.15). Distal zone EP flow (1.39±0.29) increased and resistance decreased (41±11) late after PBX (both p<.05 vs C) without change in EN flow or in the EN:EP flow ratio. EN resistance (41±13) also declined vs C in 5/7 animals (0.05<p< 0.10). PBX (late) reduced distal EN resistance to a similar extent vis-a-vis adenosine (49±11 at C to 41±13 with PBX vs 39±11with adenosine). In contrast, the decline in distal EP resistance induced by PBX (late) was only a third that caused by adenosine (51±11 at C to 41±11with PBX vs 23±7 with adenosine). Thus, the data confirm the presence of residual EN vasodilator reserve despite reduced resting blood flow in the setting of a severe CAS. Alpha adrenergic tone accounts for much of the available EN reserve but only 1/3 of EP reserve.

## EFFECTS OF SHORT- AND LONG-TERM HYPERTENSIVE CARDIAC HYPERTROPHY ON THE STRUCTURAL PROPERTIES OF THE CORONARY RESISTANCE VESSELS.

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Depression of coronary reserve in hypertensive cardiac hypertrophy is in part due to structural alterations of coronary arteries. But, it has been suggested that long term hypertrophy is associated with arterial vascular expansion and an improvement in coronary reserve. There are no studies however that have systematically examined the arterial vasculature both in short- and long-term hypertensive cardiac hypertrophy in the same model. We therefore determined the structural characteristics of the coronary arteriolar bed relevant to flow resistance: arteriolar density (AD) and wall thickness to lumen ratio (WLR) in a total of 43 hypertensive (SHR) and normotensive (WKY) rats of 1.5, 4, 11, 16 and 22 months of age. Using standard histometric techniques, a total of 8521 arterioles (WKY: n=4914; SHR: n=3607) were sampled from the LV and read blindly. The WLR was not significantly affected by the strain or duration of hypertrophy (WKY: .14 to .19, SHR: .12 to .17 $\mu/\mu$, p=ns), but AD was significantly lower by 6% to 27% in SHR at all ages (4.41 to 5.9 in WKY, 3.3 to 5.1 art/mm$^2$ in SHR, p<.05 by 2 WAY-ANOVA).

The data show that arteriolar growth lags behind cardiac growth during all phases of development of hypertensive cardiac hypertrophy. Since no significant arteriolar growth occurs during long-term hypertrophy in SHR, these abnormalities may contribute to the decrement in coronary reserve observed in this model of genetic hypertension.

## IMPLANTATION OF THE INTERNAL MAMMARY ARTERY AS A MEANS OF MYOCARDIAL REVASCULARIZATION IN A CANINE MODEL OF MYOCARDIAL ISCHEMIA: A REASSESSMENT

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It has been demonstrated that myocardial angiogenesis can occur between an implanted internal mammary artery (IMA) and the coronary circulation; however, these implants afford limited flow to ischemic myocardium. The purpose of this study was to attempt to enhance this flow by infusing heparin and basic fibroblast growth factor directly into the implant, and to assess the functional importance of the collateral flow provided by the IMA. Ameroids were placed on the proximal left anterior descending coronary artery (LAD) of 23 dogs. The IMA was implanted in the LAD zone. After 8 weeks, regional myocardial blood flow was assessed in the conscious state with microspheres during chromonar induced vasodilatation, and regional LV function was assessed with ultrasonic crystals. Regional flow (ml/min/g ± SEM) and segmental shortening (%Δlength of control ± SEM) were determined with the IMA and circumflex patent (CONTROL), the IMA occluded (IMA), the circumflex occluded (CIRCUMFLEX), and both occluded (BOTH).

| | CONTROL | IMA | CIRCUMFLEX | BOTH |
|---|---|---|---|---|
| FLOW | 2.42±0.21 | *1.94±0.11 | 1.71±0.23 | **1.11±0.19 |
| %ΔLENGTH | 100±0% | 98±2% | 105±7% | **90±7% |

*p<0.01, CONTROL vs. IMA; **p<0.01 CIRCUMFLEX vs. BOTH

Thus IMA occlusion alone decreased maximal LAD zone flow by 20%, without affecting regional function. Occlusion of the IMA during circumflex occlusion decreased LAD territory flow by an additional 35% and caused systolic dysfunction. We conclude that the implanted IMA is capable of providing nutritive perfusion to ischemic myocardium, and this flow has significant functional import.

HYPERSENSITIVITY OF CORONARY ARTERIES TO INTRACORONARY ERGONOVINE FOLLOWING ORTHOTOPIC CARDIAC TRANSPLANTATION.

Sudhir Kushwaha MRCP, David Lythall MRCP, Attilio Maseri MRCP, Andrew Mitchell MRCP, Magdi Yacoub FRCS, FACC., Harefield Hospital, Middlesex, England.

The in vivo behaviour of coronary arteries in denervated transplanted hearts is not known. Having documented severe coronary spasm in 4 such patients (pts) we studied the response of the coronary arteries to intracoronary ergonovine maleate (EM) in 10 other patients who had undergone orthotopic cardiac transplantation and shown to have normal coronary arteries at angiography. EM in doses of 1, 5 and 10μg was injected into the left coronary artery followed by 2 mgs. of isosorbide dinitrate (IDN). The proximal left anterior descending (LAD), mid LAD and mid circumflex arteries showed a decrease in measured diameter in response to 1μg of EM (mean ± SE, 12.3 ± 3.4, 10.3 ± 6.1, 4.9 ± 6.8 respectively). Further increments produced no significant response and contraction was reversed by IDN in all vessels. The dose response curve of EM was displaced to the left by nearly a log cycle compared with previous studies on normal vessels, indicating hypersensitivity to the drug. However, the magnitude of the reduction in diameter was similar to that of normal vessels rather than that described previously in patients with variant angina. This suggests that denervated coronary arteries are hypersensitive to EM.

COMPARISON OF REGIONAL CORONARY VASODILATORY RESERVE BETWEEN NORMAL AND POST ANGIOPLASTY ARTERIES IN THE SAME PATIENT

Chalapathirao Gudipati, M.D., Ubeydullah Deligonul, M.D.,Morton Kern, M.D., F.A.C.C., Frank Aguirre, M.D., Harvey Serota, M.D., Brian Lew, M.D., Michel Vandormael, M.D., F.A.C.C., St. Louis University, St. Louis, Missouri

The importance of regional differences in coronary vasodilatory reserve (CVR) in the same human subject is not well known. We assessed CVR by intracoronary Doppler flowmetry in anterior descending (LAD) and circumflex (CX) coronary arteries of 10 pts without LV hypertrophy or myocardial infarction. Mean flow velocity (mVel) was measured at rest and after peak hyperemia induced by intracoronary injection of 10 mg. of papaverine. CVR = mVel at hyperemia/mVel at rest. 5/10 pts (Group I) had successful single vessel LAD dilation with decrease in stenosis from 82±5% to 16±3% as measured by electronic calipers. All 5 had angiographically normal CX arteries. In the remaining 5 pts (Group II), LAD and CX were angiographically normal. The results were: Mean ± SEM.

| | Group I | | | Group II | |
|---|---|---|---|---|---|
| | Pre PTCA | Post PTCA | CX | LAD | CX |
| CVR | 2.2±0.8 | 2.65±0.5 | 2.91±0.5 | 3.9±0.5* | 3.3±0.6 |
| LAD/CX | 0.75±0.2 | 0.94±0.2 | | 1.3±0.3* | |

*p<.05 Group I LAD pre PTCA vs. Group II LAD

Conclusions: 1) CVR in dilated and nonstenotic neighboring arteries of Group I pts appear to be lower than normal (Group II).
2) After successful coronary angioplasty, LAD CVR is improved and approaches that of normal CX in the same subject.
3) The measurement of CVR in nondilated, nonstenotic neighboring artery may provide a reference for assessing the success of coronary angioplasty in individual pts.

## Wednesday, March 22, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 10:00AM–11:00AM
## Pacific Room, Anaheim Convention Center
## Technical Considerations of Electrocardiography

LATE POTENTIAL AND NOISE LEVEL VARIABILITY CAUSED BY BANDPASS VERSUS HIGH-PASS FILTERING, AND TYPE OF SIGNAL-AVERAGING EQUIPMENT.

James Vacek, M.D., F.A.C.C., Scott Smith, M.D., Tim Boyer, M.D., Marvin Dunn, M.D., F.A.C.C., University of Kansas Medical Center, Kansas City, Kansas.

Late potentials (LP) detected by signal-averaged electrocardiography (SAECG) are predictive of ventricular arrhythmia induction and sudden death. Prior studies have used a variety of equipment and filtering parameters. The correlation between data from two commercially available SAECG units and the effects of bandpass (BP) opposed to high-pass (HP) filtering was studied in 18 hospitalized patients.

| | C40Hz HP | | C40-250Hz BP | | A40-250Hz BP |
|---|---|---|---|---|---|
| QRS | 109 ± 15 | (0.141) | 107 ± 15 | (0.003) | 102 ± 14 |
| RMS | 32 ± 26 | (0.023) | 31 ± 25 | (0.021) | 36 ± 25 |
| LAS | 34 ± 14 | (0.135) | 35 ± 14 | (0.287) | 33 ± 11 |

Values are mean ± SD. A = ART 1200 EPX, C= Corazonic Predictor, LAS = duration of LP < 40 uV, QRS = filtered QRS duration, RMS = root mean square amplitude of last 40 ms of QRS. () = p values. Final noise levels were lower for A (0.28 ± 0.06) than for C (0.33 ± 0.07) ($p < 0.05$) in spite of fewer beats averaged (123 ± 50 for A, 300 ± 114 for C, $p < 0.001$). We conclude: (1) BP filtering does not effect time domain LP variables in a clinically relevant fashion. Requiring two of three parameters to be abnormal for an abnormal study, no patient was miscatagorized by HP versus BP filtering. (2) Significant data differences between the two machines existed, causing miscatagorization of three of 18 patients. (3) Significant differences in noise levels and cycle aquisition number exist between units powered by AC line (C) versus batteries (A).

A MICROPROCESSOR BASED ECG ANALYZER AND TONE GENERATOR WHICH PERMITS IMMEDIATE RECOGNITION AND CATEGORIZATION OF ECTOPIC RHYTHMS BY SOUND

Lloyd Marks M.D., F.A.C.C., Scott Smith, Timothy Brophy, Robert Grane, Thomas Moore Ph.D., Temple University Department of Pediatrics, St. Christopher's Hospital for Children, Phila., PA

A conventional ECG monitor produces identical short, high pitched tones with each QRS complex. As these tones do not vary with QRS morphology, the ECG trace must be visually inspected to determine the specific nature of the cardiac rhythm. When performing certain tasks, it would be advantageous if ectopic rhythms could be recognized and categorized with purely auditory information as it is impractical or impossible to inspect the ECG trace continuously. Such tasks include cardiac catheterization, transtelephonic evaluation of cardiac rhythms, and monitoring patients during surgery. We have developed and evaluated a new cardiac monitor which allows the physician to recognize and categorize ectopic rhythms with purely auditory information.

The ECG and its first derivative are input to a dedicated microprocessor system. Tones are generated with each QRS complex such that narrow QRS complexes produce short, clipped, high pitched tones and wide QRS complexes produce long, low pitched tones. Wide QRS complexes which are different from one another produce different long, low pitched tones.

The system was evaluated by playing the tones generated from 7 different cardiac rhythms (normal sinus, sinus tachycardia, isolated uniform premature ventricular beats, uniform bigeminy, uniform couplets, multiform triplets, and runs of uniform ventricular tachycardia) each for 15-20 seconds to a group of 14 physicians (5 staff cardiologists, 2 cardiology fellows, 3 cardiothoracic surgeons, 3 residents, 1 anesthesiologist) after presenting them with a brief written description of the system and a 30 second videotape demonstration. Thus, there were a total of 7 x 14 = 98 trials. None of the teaching material was used during the trials. The rhythms were correctly identified in 47/49 trials (96%) by the 7 cardiologists and in 45/49 (92%) by the other 7 physicians. The difficulties in identification resulting in the few errors appeared to be remediable with minimal additional teaching.

We conclude that this device provides audio information which allows physicians to identify and categorize a wide variety of ectopic rhythms with purely auditory cues. This may be useful when a physician can not continuously inspect an ECG tracing.

## DOES THREE CHANNEL AMBULATORY ELECTROCARDIOGRAPHIC MONITORING INCREASE DETECTION OF ISCHEMIA?

Bijoy Khandheria, M.D., Stephen Hammill, M.D., F.A.C.C., Carolyn O'Connor, Addie Muri, R.N., and Gerald Gau, M.D., F.A.C.C., Mayo Clinic, Rochester, MN

Silent ischemia (SI) is a relevant clinical problem that is being intensively investigated. One of the commonly utilized methods for diagnosis of SI is ST segment analysis on 2 channel ambulatory electrocardiographic monitoring (AECG). However, analysis of 2 channels alone may not be adequate for detection of SI. We evaluated the usefulness of 3 channel AECG versus 2 channel AECG using a newly developed 3 channel AECG monitoring device (Clinical Data, Boston) in 47 consecutive Pt undergoing treadmill exercise testing (TMET). There were 36 males, 11 females, mean age 51 yrs (range 25-67 yrs) who had simultaneous AECG with leads piggybacked to 12 lead electrocardiogram. Leads utilized for AECG were aVF, $V_3$ and $V_5$. All Pt exercised to stage II or more of the Bruce protocol. TMET was positive in 18 Pt, while AECG was positive in 17 Pt. Results:

| | TMET | AECG |
|---|---|---|
| only AVF | 4 | 3 |
| only $V_5$ | 2 | 2 |
| only $V_3$ | 1 | 1 |
| combination (2 channel) | 11 | 11 |

The sensitivity of AECG for detection of ischemia was 94%, while the specificity was 100%. Analysis of 2 leads improved detection of ischemia than 1 lead in 33% (6/18) Pt with positive TMET. Addition of a third lead (aVF) improved ischemia detection in 17% (3/18) Pt. Conclusion: Three channel AECG monitoring improved detection of ischemia in 17% more Pt in comparison to 2 channel AECG.

## SIGNAL-AVERAGED ELECTROCARDIOGRAPHIC DIFFERENCES BETWEEN PATIENTS WITH NON-MYOPATHIC LEFT VENTRICULAR HYPERTROPHY AND PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY.

Lameh Fananapazir, M.D., Anne Danforth, B.S.N., Judith B. Winkler, B.S., NHLBI., Bethesda, Maryland.

Differentiation of hypertrophic cardiomyopathy from other causes of left ventricular hypertrophy (LVH) has therapeutic and prognostic implications. This study compares signal-averaged ECG results in 3 groups of Pts - A: 37 Pts with hypertrophic cardiomyopathy (20 Pts with and 17 Pts without inducible ventricular tachycardias at programmed electrical stimulation), B: 15 Pts with ECG and echo evidence of LVH -13 Pts with AO valve disease, 2 Pts with hypertension and C:16 normal subjects. All Pts had normal coronaries. The total, initial and terminal 40ms of the QRS were evaluated:

| Parameter | Normal | LVH | Hypertrophic Cardiomyopathy Non-Inducible | Inducible |
|---|---|---|---|---|
| QRS width >112 ms | 0 | 4 | 9 | 9 |
| **(Terminal 40 ms)** | | | | |
| RMS <20μV | 1 | 1 | 1 | 6 |
| LAS >35ms | 1 | 2 | 0 | 6· |
| **(Total QRS)** | | | | |
| RMS >300μV | 0*** | 6 | 0*** | 0*** |
| Vector Integral >15 | 2 | 4 | 2 | 0** |
| **(Initial 40 ms)** | | | | |
| RMS-i μV | 119±57 | 168±180 | 98±70 | 109±95 |
| Ratio of RMS-i to RMS Total <0.31 | 0 | 2 | 8* | 4 |

RMS=root mean square; RMS-i=RMS of initial 40ms; LAS=low amplitude signal; *p=0.05,**=p<0.025,***=p<0.005, compared to LVH Pts;·=p<0.02 compared to non-inducible Pts. **Conclusion** 1) high total QRS RMS values, or a low ratio of RMS (initial 40ms):total QRS RMS, suggests that the etiology of the LVH is hypertrophic cardiomyopathy and 2) finding of abnormal QRS (>112ms), terminal RMS (<20μV) and LAS (>35ms) indicates an arrhythmogenic LV in these Pts.

## ST Analysis: Intragroup Versus Intrapatient Variability of Holter Results

Peter Nikutta, Dirk Hausmann, Paul Wenzlaff, Hannover Medical School, Hannover, FRG.

The evaluation of the efficacy of antiischemic interventions by Holter ECG causes difficulties due to the variability (VAR) of ischemic activity during daily life. We compared intragroup and intrapatient VAR in 38 patients (PTS) with proven CAD (stenoses > 70%) and 417 ischemic episodes (IE) during Holter monitoring on 3 consecutive days. Mean values of the total study group for day 1, 2 and 3 as well as the mean intrapatient VAR from day to day were analyzed for incidence (INC) of IE, mean duration (D), total duration per day (D/d), max. ST-depression (max. STD) and max. heart rate (HR) of IE:

| | day 1 | day 2 | day 3 | p | VAR(%) |
|---|---|---|---|---|---|
| INC | 3.8 | 3.8 | 3.4 | n.s. | 52.3 |
| D (min) | 11.8 | 13.5 | 12.6 | n.s. | 113.3 |
| D/d (min) | 54.1 | 54.9 | 48.0 | n.s | 186.6 |
| max. STD (mV) | 0.20 | 0.21 | 0.21 | n.s. | 20.6 |
| max. HR (b/min) | 111.5 | 109.6 | 110.1 | n.s. | 11.7 |

The peek INC resp. peek D/d, observed during any of the 3 days recorded, occured during the first 2 days of monitoring in 86.9% resp. 84.2% of PTS. Conclusion: The intragroup VAR shows no significant differences at 3 consecutive days in 38 PTS; in contrast, a marked intrapatient VAR of INC, D and D/d from day to day is present. I. e., for the evaluation of group effects to interventions 24 hour Holter ECG is sufficient. The classification of each PT as responder or non-responder requires a prolonged recording.

## HOLTER MONITORING IN THE DIAGNOSIS OF SLEEP APNEA SYNDROME

Jean-Yves Le Heuzey M.D., Philippe Romejko M.D., Bernard Fleury M.D., Pierre-Jean Scala M.D., Jean-Philippe Derenne M.D., Louis Guize M.D., Thomas Lavergne M.D. and Jean Valty M.D. Departments of Cardiology and Pneumology, Saint Antoine and Broussais Hospitals, Paris, France.

In order to assess the ability of Holter monitoring (HM) to contribute to the diagnosis of sleep apnea syndrome (SAS), we studied 39 patients (pts) clinically suspected of SAS. Polygraphic recordings during sleep and 24 hour HM were performed in all pts. Polygraphic recordings comprised electrocardiogram, electroencephalogram, electrooculogram, electromyogram of the chin muscles, measurement of naso-buccal airflow, measurement of thoracic and abdominal movements and oxymetry. It were positive (> 10 episodes of apnea/h, duration > 10 sec) in 32 pts, negative in 7. The analysis of HM showed, in SAS (+) pts, the occurrence during the nocturnal period (midnight to 5 AM) of sino-atrial blocks (n=6) and/or RR interval pauses > 2.5 sec (n=10). Such abnormalities did not occur in SAS (-) pts. The mean number of supraventricular and ventricular premature beats, during this nocturnal period, was higher in SAS (+) pts : 89.9 ± 28.6 and 34.1 ± 14.1 versus 9.6 ± 5.2 and 2.8 ± 0.8, respectively. The analysis of nocturnal heart rate showed, in SAS (+) pts, a significantly higher discrepancy between minimal and maximal heart rate (63.1 ± 3.6 versus 45.4 ± 3.9 beats/mn, p <.05), due to successive episodes of apneas inducing bradycardia and ventilatory resumptions inducing tachycardia.

In conclusion, this discrepancy between maximal and minimal heart rate being a discriminant parameter, HM can contribute to the diagnosis of SAS and is easier to perform in routine than polygraphic recordings.

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## Wednesday, March 22, 1989
## Poster Displayed: 9:00AM–12:00NOON
## Author Present: 11:00AM–12:00NOON
## Pacific Room, Anaheim Convention Center
## The Signal Averaged ECG

COMPLEMENTARY ROLE OF SIGNAL-AVERAGED ECG AND EXERCISE TESTING IN PREDICTING CARDIAC EVENTS AFTER MYOCARDIAL INFARCTION.

D Kuchar MD , J Freund MB, M Yeates MB, C Thorburn MB, N Sammel MB FACC. St Vincent's Hospital, Sydney, Australia.

Recent studies have shown that serious cardiac events occurring after myocardial infarction (MI) can be predicted by results of exercise testing and by identification of late potentials on the signal-averaged electrocardiogram (SAECG). In order to assess the interrelationship of these tests in predicting these events, we performed SAECG and submaximal exercise testing in 150 consecutive patients (pts) who were able to exercise after recovery from MI, prior to hospital discharge. SAECG was performed with a commercially-available instrument, and was defined as abnormal if QRS duration >120ms or terminal voltage <20uV using a 40 Hz filter. Exercise testing was performed using radionuclide ventriculography and was abnormal if there were ECG or hemodynamic changes, or a fall in ejection fraction or new wall motion abnormality. SAECG was abnormal in 62 pts (41%) and exercise testing was abnormal in 81 pts (54%). During a median follow-up of 14 months, there were 20 events: 12 pts had recurrent MI, 5 had symptomatic ventricular tachycardia (VT) and 3 died suddenly. An abnormal SAECG was recorded in 33/81 pts with an abnormal exercise test ($X^2$=0,p=NS). SAECG was abnormal in 3/12 pts with MI, 5/5 pts with VT, and in 2/3 pts with sudden death. Exercise testing was abnormal in 9/12 pts with MI, 3/5 pts with VT and in 2/3 sudden deaths. An abnormality of either test predicted 17/20 (85%) of all events. Conclusions: SAECG and exercise testing are independent predictors and probably identify different pathophysiologic substrates. Evaluation of both parameters enhances detection of patients prone to life-threatening events after recovery from MI.

THE SIGNAL-AVERAGED ELECTROCARDIOGRAM PREDICTS ARRYTHMIC EVENTS IN PATIENTS WITH LEFT BUNDLE BRANCH BLOCK.

Pierce Vatterott, M.D.; Stephen Hammill, M.D., F.A.C.C.; Kent Bailey, Ph.D. Mayo Clinic, Rochester, MN.

The signal-averaged ECG is believed to be less predictive of sustained monomorphic ventricular tachycardia (SMVT) at electrophysiologic testing or spontaneous SMVT in patients with left bundle branch block. We evaluated if signal-averaging can predict arrythmic events (AE) (AE=sudden death or clinical SMVT or SMVT at electrophysiologic testing) in 41 left bundle branch block patients with complex ectopy (13), syncope (14), clinical SMVT (5) and other (9) prior to electrophysiology testing. Patients were followed for a median of 11.3 months during which 18 AE (12 sudden deaths, 6 SMVT) occurred. Seven additional patients had SMVT only at electrophysiology testing. The parameters of QRS duration, root mean square voltage of the QRS terminal 40 msec (RMSV), and duration of low-amplitude signal at the terminal QRS <40 uV after 25, 40, and 80 Hz filtering and 5 clinical variables were subjected to stepwise logistic regression to create a model for predicting AE. This model consisted of 4 variables: ejection fraction, 25 Hz and 80 Hz RMSV and 40 Hz low-amplitude signal. Results of selected standard late potential criteria and the model were:

| Standard Criteria | | | Sensitivity % | Specificity % |
|---|---|---|---|---|
| 25 Hz | RMSV | <25 uV | 68 (17/25) | 75 (12/16) |
| 40 Hz | RMSV | <20 uV or low amplitude signal >38 msec | 84 (21/25) | 38 (6/16) |
| Model | | | 96 (24/25) | 62 (10/16) |

CONCLUSIONS: Signal averaging predicts arrythmic events in left bundle branch block patients. The described model should improve the clinician's ability to predict arrythmic events in this patient group.

REPRODUCIBILITY OF THE SIGNAL-AVERAGED ECG IN THE ACUTE PHASE OF MYOCARDIAL INFARCTION AND AT LONG TERM FOLLOW-UP.

Ma Hong, MD, Eli S. Gang, MD, FACC, Fang Z. Wang, MD, Carol Siebert, RN, Yu Xiu Xu, MD, Thomas Peter, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, California.

We assessed the variability of sequential recordings of the signal-averaged ECG (SAECG) in 283 consecutive patients (pts) with acute myocardial infarction (AMI). During the in-hospital phase, each pt had 4±1 recordings (at 2-3 day intervals). Follow-up SAECG recordings were obtained at 3 months (146 pts), at 6 months (113 pts), and at 1 year (103 pts). Abnormal (Abnl) results were defined as terminal voltage ≤25 uV and a filtered QRS duration ≥110 msec. Pts with bundle-branch block were excluded. Results: (a) During hospitalization, 89% of pts retained their initial SAECG pattern, i.e., remained normal (Nl) or Abnl. Specifically, 226 of 249 (91%) initially Nl remained Nl, while 25 of 34 (74%) of Abnl retained this pattern. (b) At 3 months, 98% of Nls remained Nl; in contrast, 67% (20 of 30) Abnls changed to Nl. (c) At 6 months, 100% concordance with the 3 months tracings was found. (d) At 1 year, a 98% concordance with the 6 months' tracings was seen; the 2% discordance being due to Abnl tracings changing to Nl.
Conclusion: The initially Nl SAECG rarely becomes Abnl during AMI and at long term follow-up. In contrast, a sizable number of Abnl tracings normalize within the first 3 months. These changes may reflect infarct healing and parallel the well-known decreasing risk for sudden cardiac death following AMI.

SIGNAL-AVERAGED ELECTROCARDIOGRAPHIC ABNORMALITIES IN NON-AFFECTED FIRST DEGREE RELATIVES OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY.

Deborah J. Barbour, M.D., Judith B. Winkler, B.S., Barry Maron, M.D., F.A.C.C., Lameh Fananapazir, M.D., NHLBI, Bethesda, Maryland.

Signal-averaged ECG detection of late potentials is an indicator of arrhythmogenic LV in Pts with hypertrophic cardiomyopathy (HCM). We compared the incidence of late potentials in 3 groups of subjects:1) 15 Pts with echocardiographically proven HCM, 2) 31 first degree relatives of these Pts with normal echocardiograms and 3) 16 normals. Signal-averaged ECG was performed with a 40 Hz bidirectional filter, to a noise level of <0.3uV. Late potential indices studied were: 1) QRS duration, 2) Root Mean Square (RMS) in terminal 40ms of QRS, and 3) Low amplitude signal (LAS). The results were:

| | Abnormal | Abnormal Signal-Averaged ECG | | |
|---|---|---|---|---|
| Subjects | 12-lead ECG | QRS>112ms | RMS<20ms | LAS>35ms |
| Normals | 0 | 0 | 1 (6%) | 1 (6%) |
| HCM Pts | 12 (75%) | 2 (13%) | 3 (20%) | 5 (33%) |
| Relatives | 8 (26%)*° | 1 (3%) | 4 (13%) | 10 (32%)** |

*=p<0.05, **=p<0.005, compared with normals; °=p<0.005 compared with HCM Pts.
Conclusion: The finding of abnormal 12-lead ECG and SA ECG in first degree relatives of HCM Pts suggests that a significant number of these individuals have electrically abnormal hearts despite the negative echocardiographic appearances. The prognostic significance of this observation requires further study.

EFFECT OF ANTIARRHYTHMIC DRUGS ON FREQUENCY-DOMAIN PARAMETERS OF SIGNAL-AVERAGED ECG Roger A. Freedman MD FACC, Marc S. Fuller PhD, Jonathan S. Steinberg MD, for the ESVEM investigators. University of Utah Medical Center, Salt Lake City, UT.

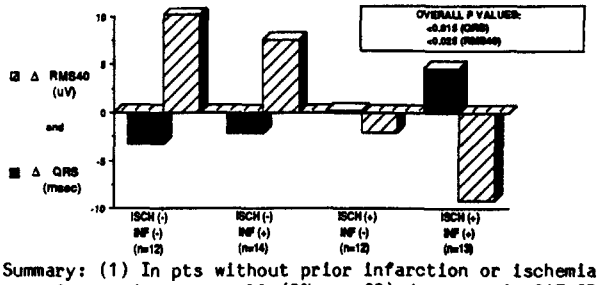
Frequency-domain analysis of signal-averaged ECG (SAECG) can identify pts with sustained VT. The effect of antiarrhythmic drugs on frequency-domain parameters was examined in 26 pts with spontaneous and inducible VT undergoing total of 60 drug trials (7 quinidine, 8 procainamide, 11 imipramine, 10 mexiletine, 8 propafenone, 16 sotalol). FFT area ratio (0-25Hz)/(25-50Hz) was computed for 100 msec segments of SAECG QRS-ST, multiplied by Blackman-Harris window, starting 40 msec (AR40) and 100 msec (AR100) after QRS onset. High-frequency (>40 Hz) QRS duration (fQRS) was derived from time-domain analysis. Results:

| | ---------AR40--------- | | | --------AR100-------- | | |
|---|---|---|---|---|---|---|
| Drug | Baseline | Drug | p | Baseline | Drug | p |
| all | 13.9±7.7 | 16.1±8.8 | .004 | 213±223 | 104±106 | .0002 |
| quin | 13.7±9.5 | 13.9±6.5 | NS | 207±142 | 128±136 | .14 |
| proc | 13.0±8.5 | 17.0±8.0 | .02 | 276±261 | 130±122 | .16 |
| imip | 14.1±8.4 | 14.9±7.0 | NS | 230±262 | 102±122 | .14 |
| mexil | 12.5±6.1 | 14.8±7.2 | NS | 120±86 | 113±103 | NS |
| propaf | 14.2±7.8 | 21.5±14 | .06 | 258±306 | 47±23 | .08 |
| sotal | 15.0±7.8 | 15.7±8.9 | NS | 208±229 | 108±103 | .06 |

Drug effect on AR100, but not AR40, showed significant correlation with drug effect on fQRS ($r=-0.48$; $p<0.001$). Conclusions: (1) Drugs decrease high-frequency relative to low-frequency signal in mid-QRS, reflected in ↑AR40. (2) Drugs increase high-frequency relative to low-frequency signal in late QRS-ST, reflected in ↓AR100, and this correlates with ↑fQRS. (3) These effects are caused by wide range of drugs, with propafenone showing greatest effect. (4) Studies are warranted to examine relation between these effects and drug efficacy.

EFFECTS OF EXERCISE INDUCED ISCHEMIA ON THE SIGNAL AVERAGED ELECTROCARDIOGRAM.
Charles Gottlieb M.D., Nancy Britton R.N., Howard Eisen M.D., Mark Rosenthal, M.D., F.A.C.C., John Miller, M.D., F.A.C.C., Michael Lesh, M.D., Mark E. Josephson M.D., F.A.C.C., Michael Simson M.D., F.A.C.C.

To determine the effect of exercise-induced ischemia on the signal averaged electrocardiogram (SAE), 51 pts had SAE prior to and immediately after thallium stress testing. Four subgroups were defined based on thallium scintigraphy by the presence (+) or absence (-) of ischemia (ISCH) or infarction (INF). The change in SAE QRS duration and root mean square voltage in the last 40 ms (RMS 40) with exercise was evaluated.




Summary: (1) In pts without prior infarction or ischemia, exercise produces a small (3%, p=.03) decrease in SAE QRS duration and a modest (16%, p=.07) increase in RMS 40. (2) Ischemia is associated with SAE QRS prolongation and a decrease in RMS 40 voltage. The change in RMS 40 with ischemia was more marked in pts with prior infarctions, 3% vs 15%. (3) In some pts with prior infarction, ischemia may complete the substrate for ventricular arrhythmias since the changes in SAE are similar to those seen in pts with chronic ventricular arrhythmias.

PERIODICITY OF TRANSMURAL AND EPICARDIAL ELECTROGRAMS DURING SINUS RHYTHM IN PATIENTS WITH VENTRICULAR TACHYCARDIA.
Nancy A. Branyas M.D., Dennis M. Cassidy M.D., F.A.C.C., Michael E. Cain M.D., F.A.C.C., Washington University, St. Louis, Missouri.

Despite widespread reliance on signal-averaged ECGs for detecting patients prone to sustained ventricular tachycardia (VT), the periodicity of global ventricular activation during sinus rhythm has not been defined. Accordingly, transmural and epicardial ventricular electrograms during 6 consecutive sinus beats were evaluated in 10 patients with abnormal signal-averaged ECGs undergoing surgery for sustained VT. For each patient, bipolar electrograms were recorded simultaneously using sock and needle electrodes from up to 96 epicardial and 160 transmural sites. Electrogram morphology, duration, and activation were compared on a beat-by-beat basis. A total of 9816 electrograms were analyzed. Mean durations of epicardial and transmural electrograms were 33+16 msec (range 6-199 msec) and 23+10 msec (range 6-72 msec) respectively, with beat-to-beat variation of 1.9+1.4 msec per site. Similarly, local activation times did not vary significantly during the 6 cardiac cycles (mean variation 1.7+2.0 msec). Local conduction failure was not observed. Although electrograms during the terminal 40 msec of the QRS were significantly longer (36+20 msec vs 26+12 msec, $p<0.001$) when compared to those occurring earlier, beat-to-beat variation in duration (2.1+1.6 msec) and activation (1.7+2.3 msec) were not significant. Results demonstrate that epicardial and transmural electrograms during sinus rhythm from patients with sustained VT are periodic signals and thus establish a physiologic basis for signal-averaging ECG waveforms in these patients.

## Wednesday, March 22, 1989
## 2:00PM–3:30PM, Anaheim Room
## Anaheim Convention Center
## Thrombolytic Therapy in Acute Myocardial Infarction II

TISSUE PLASMINOGEN ACTIVATOR FOR UNSTABLE ANGINA PECTORIS: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL.
EJ Topol MD, FACC, NS Kleiman MD, JM Joelson MD, SG Ellis MD, FACC, T Wahl MD, RM Califf MD, FACC, M O'Brien, A Hopkins, R Roberts MD, FACC, DO Williams MD, FACC, University of Michigan, Ann Arbor, Michigan.

To determine the role and appropriate dose regimen of thrombolytic therapy for unstable angina, 66 pts were enrolled in a 4 center randomized, double-blind, placebo-controlled trial. Pts with chest pain at rest and a culprit vessel stenosis >70% were randomized to high dose iv t-PA (100 mg/6 hrs), low dose t-PA (60 mg/1 hr) or placebo. All pts received aspirin 325 mg/d, i.v. heparin 1,000 U/hr, and underwent baseline and repeat coronary angiography at 12-48 hrs. The primary endpoint was change in % diameter stenosis established by computer edge detection in a blinded fashion at a core lab. The 3 groups were similar with respect to age, sex, weight, duration of symptoms, and presence of intraluminal thrombus at baseline. Negative outcomes were defined as MI or emergency need for PTCA or CABG. No deaths occurred in the study.

| | | t-PA | |
|---|---|---|---|
| Endpoint | Placebo n=22 | Low Dose n=22 | High Dose n=22 |
| % Diameter stenosis pre | 76±13* | 75±16** | 82±11*** |
| % Diameter stenosis 24° | 72±14* | 71±18** | 77±17*** |
| Negative outcomes (type) | 1 (MI) | 1 (PTCA) | 3 (MI) |
| Thrombus dissolved (pts) | 5 | 2 | 3 |
| | *p=0.07 | **p=0.03 | ***p=0.19 |

In conclusion, these results indicate that using a quantitative angiographic endpoint, heparin and aspirin therapy for unstable angina is equally effective as low or high dose t-PA.

PREDICTION AND PREVENTION OF MYOCARDIAL INFARCTION DURING THE ACUTE PHASE OF UNSTABLE ANGINA.

Pierre Théroux, M.D., F.A.C.C., Hélène Ouimet, M.D., Jean-Gilles Latour, Ph.D., John McCans, M.D., F.A.C.C., Guy B. Pelletier, M.D., F.A.C.C., Martin Juneau, M.D., David Waters, M.D., F.A.C.C., Montreal Heart Institute, Montreal, Canada.

Myocardial infarction (MI) occurred in 21 of 479 pts enrolled in a double-blind, placebo-controlled, randomized, factorial-design trial testing aspirin (A), heparin (H), and both (A+H) during the acute hospitalization phase of unstable angina. MI occurred in 12% of the 118 placebo pts, significantly more frequently than in A (3.3% of 121 pts, p=.01), H (0.8% of 118, p<.001) and A+H (1.6% of 122, p=.001). New Q waves developed in 12 of the 14 placebo MI's (86%) compared to 2 of the 7 MI's (29%) in the active treatment groups (p<.01); peak CK elevations were 2639±1932 IU and 1555±2275 IU respectively (p=NS). No mortality occurred except for 2 deaths in the placebo group.

In addition to treatment, other predictors of MI were age (63±7 vs 58±10 years, p=.02), recurrent angina during hospitalization (81% of MI pts vs 32% of others, p<.001), number (0.8±1.2 vs 0.2±0.6 per pt, p=.002) and duration (17±32 vs 2.6±9.5 min, p<.001) of chest pain episodes during the first 24 hours. The clinical presentation of unstable angina, the presence of risk factors, concomitant medications and involvement of the left anterior descending coronary artery were not predictive of MI.

Thus, aspirin and heparin protect against MI in the acute phase of unstable angina. MI's that do occur on these drugs are more likely to be non-Q than in untreated pts. Persistent ischemia early during hospitalization warrant aggressive intervention.

IS DELIVERY OF rt-PA BY HELICOPTER TRANSPORT TEAMS SAFE AND TIME-EFFECTIVE?

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In order to assess the safety and feasibility of rt-PA delivery by specially trained physician/nurse helicopter transport teams to rural community hospitals and the subsequent transport of patients to tertiary care facilities, we recorded transport and treatment times and complications frequencies in 193 patients (pts) treated with rt-PA within 4 hr onset AMI (myocardial infarction) symptoms in the TIMI II protocol at Birmingham, AL, and Worcester, MA. Of the 193 pts, 84 were treated post-flight, whereas 109 were treated pre- and during flight by the transport team. Time from onset of AMI symptoms to rt-PA bolus was 201±34 min in post-flight treated pts vs 165±38 min in pre-flight treated pts (p=.0001). Pts treated pre-flight received rt-PA 28±9 min after team arrival, whereas pts transported without rt-PA to tertiary care facilities received rt-PA 41±18 min after arrival there (p=.0001). There were no in-flight deaths or CPR in either group. Frequency of in-flight arrhythmias was similar between groups and, overall, averaged: V fib 0.7%, V tach 3.6%, 3rd degree AV block 1.5%, bradycardia <60/min 13.9%. Hypotension was significantly more common during transport in the pre-flight treated group (19.2% vs 3.1%, p=.004), and this group also received atropine in-flight more frequently for symptomatic bradycardia (6.5% vs 0, p=.025). Hemorrhagic complications over the first 24 hr after starting rt-PA were lower in the pre-flight treated pts (42% vs 60%, p=.046). MI was confirmed prior to hospital discharge in all patients.

Thus, skilled helicopter transport teams can appropriately evaluate AMI pts and, on arrival, can administer rt-PA more rapidly than tertiary hospital emergency staff. Symptomatic bradycardia and hypotension are the most frequent in-flight complications of rt-PA therapy and can be managed effectively.

FATE OF ACUTE MYOCARDIAL INFARCTION PATIENTS WITH SUCCESSFUL MECHANICAL (RESCUE) VS. CHEMICAL PATENCY OF THE INFARCT VESSEL AT EMERGENCY CATHETERIZATION.

Charles W. Abbottsmith, M.D.C.M., F.A.C.C., Eric J. Topol, M.D., F.A.C.C., Dean J. Kereiakes, M.D., F.A.C.C., Barry S. George, M.D., Linda Martin, R.N., Linda Anderson, R.N., Lynn Harrelson, Richard Candela, M.D., F.A.C.C., Richard S. Stack, M.D., Robert M. Califf, M.D., and the Thrombolysis in Acute Myocardial Infarction (TAMI) Study Group.

Rescue percutaneous coronary angioplasty (PTCA) after failed thrombolytic therapy has not been associated with a uniformly good outcome. We analyzed the data of 773 patients with patent infarct vessels at the end of emergency catheterization studied in the course of five TAMI trials. All 773 patients received emergency catheterization and 199 patients with occluded vessels at 90 minutes had rescue PTCA (success in 168, 88%). Baseline demographics were similar with respect to age, sex, infarct vessel, and multivessel disease.

| | Chemical | Rescue | P |
|---|---|---|---|
| No. Patients with Patency | 605 | 168 | |
| Baseline Ejection Fraction | 51.4% | 48.3% | .003 |
| Reocclusion | 67(11%) | 37(22%) | <.001 |
| 7-Day Δ Ejection Fraction | 1.0 | -.02 | .008 |
| 7-Day Δ in Regional Function (SD/Chord) | +.45 | +.2 | .001 |
| Deaths (in-hospital) | 28(5%) | 10(6%) | .36 |

Conclusion: Chemical patency is preferrable with better baseline ejection fraction, ventricular functional recovery, and less reocclusion. Despite this, the low in-hospital mortality is the same in both groups, suggesting the pivotal importance of an open infarct vessel acutely, no matter how it is achieved.

DEMONSTRATION OF VIABLE MYOCARDIUM AFTER AN ACUTE INFARCTION SUBMITTED TO THROMBOLYSIS : COMPARISON BETWEEN POSITRON EMISSION TOMOGRAPHY AND DOBUTAMINE ECHOCARDIOGRAPHY

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To identify myocardial viability in acute anterior myocardial infarction (AMI) treated within 3 hours by intravenous streptokinase, 17 patients (pts) underwent echocardiography (Echo) at rest and during dobutamine (Dobu) infusion at 10 µg/kg/min, 7 ± 4 days after AMI. They were studied with positron emission tomography (PET), 9 ± 5 days after AMI. Coronary anatomy was defined in all pts. Follow-up echo and PET were performed 9 ± 7 months later. Six segments, specific of the territory of the left anterior descending artery were analysed with both techniques. An echo score index was calculated, based on the 6 segments. Segmental perfusion (P) (with N-13 ammonia or K38) and glucose uptake (G) (with 2-F-18-2 deoxyglucose) were measured and a ratio of G over P was calculated in each segment. Myocardial viability was detected with PET in 11 pts : 5 had normal P in the area at risk (group 1A) and 6 had a high G/P ratio (group 1B). No viability was detected in 6 pts (group 2).

| Echo score index | Rest | *** | Dobu | Follow-up |
|---|---|---|---|---|
| Group 1A | 12 ±2 | *** | 7.8 ±1.3 | 7.4± 1.7 |
| Group 1B | 14.8 ±2.2 | * | 12 ± 2.1 | ** 16 ± 1.7 |
| Group 2 | 14.6 ±1.4 | | 14.1± 1.6 | ** 15.3±1.1 |
| p * = 0.05 | ** < 0.05 | | *** < 0.005 | |

Concordant interpretation with the 2 techniques was found in 79 % of affected segments for both acute and follow-up studies. Thus, dobu echo is a promising method to unmask viable, stunned myocardium in AMI. Normal P of the area at risk is associated with good functional outcome, whereas high G/P ratio indicates jeopardized myocardium which frequently loses viability.

CORONARY THROMBOLYSIS WITH UROKINASE PREACTIVATED INTRAVENOUS PRO-UROKINASE

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In two consecutive dose finding studies (A: non randomized; B: randomized) a total of 78 patients (pts) with acute Q-wave myocardial infarctions were treated with a combination of 250 000 IU of urokinase (UK) as an iv bolus (for preactivation) and 4.5 or 6.5 mega U of natural pro-urokinase (nPUK). All pts concomitantly received a 5000 IU iv heparin (hep) bolus and a continuous hep infusion (1250 IU/h). The patency rate (PR) was assessed at 60 min after onset of thrombolytic therapy by angiography.
Results:

| group | n | U nPUK | PR | sign. | fib | PLG | AP |
|---|---|---|---|---|---|---|---|
| A1 | 15 | 4.5 mega | 33% | | - 9% | -29% | -59% |
| A2 | 16 | 6.5 mega | 75% | p< 0.05 | -13% | -34% | -63% |
| B1 | 23 | 4.5 mega | 30% | | + 7% | -31% | -63% |
| B2 | 24 | 6.5 mega | 71% | p< 0.01 | -18% | -38% | -73% |

fib: fibrinogen; PLG: plasminogen; AP: α-2-antiplasmin

Bleeding complications were mainly related to arterial puncture sites (30% hematomas). No other major haemorrhage was observed. We conclude that thrombolysis with low dose UK preactivated nPUK is highly effective and almost completely fibrin specific. For further studies the combination of 250 000 IU UK and 6.5 mega U nPUK should be used.

## Wednesday, March 22, 1989
## 4:00PM–5:00PM, Anaheim Room
## Anaheim Convention Center
## Coronary Angioplasty in Acute Myocardial Infarction

EARLY HISTOPATHOLOGY OF REPERFUSION THERAPY FOR MYOCARDIAL ISCHEMIA: STUDY OF 29 AUTOPSIED CASES.

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The purpose of this study was to describe early pathologic lesions associated with percutaneous transluminal coronary angioplasty (PTCA) or thrombolysis for the treatment of myocardial ischemia. Of 2,235 Pts undergoing coronary reperfusion therapy (RT) at our institution between January 1982 and July 1988, 138 have died. Hearts were available from 29 (ages 28-88 years; mean, 62 years; 18 were men) who died within 3 weeks of RT; 32 treated and 58 nontreated epicardial coronary arteries and myocardium were studied systematically. For each Pt, clinical and angiographic data were reviewed and recorded; 27 were treated for acute ischemia. Treatment groups included PTCA alone (17), thrombolysis alone (5), and PTCA and thrombolysis (7). At autopsy, intimal fissures were observed in 28 treated arteries and extended into the media in 2. Dissection was observed in 15 arteries, all treated by PTCA. One coronary artery treated by PTCA and thrombolysis ruptured. Plaque extrusion was observed in 14 treated arteries (13 by PTCA) and was associated with atheroembolization in 2. Occlusive or nearly occlusive thrombi were seen in 15 treated arteries. In nontreated arteries, intimal fissures were seen in 11, plaque extrusion in 4, occlusive thrombi in 7, and dissection in none. Hemorrhagic infarction was observed in 18 of the 29 Pts and was moderate or severe in 10. Cardiac rupture occurred in 5 Pts (3 with hemorrhage). Clinical failure of RT with death may have diverse causes including coronary and myocardial rupture, hemorrhagic infarction, and coronary occlusion due to thrombosis, dissection, or embolization.

TWO-YEAR POST-DISCHARGE SURVIVAL AFTER EMERGENCY CORONARY ANGIOPLASTY FOR MYOCARDIAL INFARCTION: IMPORTANCE OF THE TIMING AND SUCCESS OF ANGIOPLASTY.

NH Kander, WW O'Neill, R Mileski, EJ Topol, SG Ellis. University of Michigan Hospital, Ann Arbor, MI.

Long term follow-up of large numbers of patients with acute myocardial infarction (AMI) treated with angioplasty (PTCA) is limited. Therefore, we analyzed 336 consecutive patients who underwent PTCA for AMI. Two-hundred ninety-nine patients survived hospitalization, of whom, 293 (98%) were followed a median of 24 months. In this group, mean age = 55±11 years, 49% had adjunctive thrombolytic therapy, 53% had multivessel disease, baseline ejection fraction (LVEF) = 48±10% and median time to PTCA = 4.5 hours. Actuarial survival was 96.1% at one year and 93.6% at 2 years. Survival was independently predicted (logrank analysis) by no prior AMI (96.9% vs. 87.3% 2 year survival; p<.001), predischarge ejection fraction ≥ 40% (98.1% vs 85.8% 2 year survival; p=.01), infarct artery patency at hospital discharge (97.4% vs. 93.4% 1 year survival but 94.2% vs. 93.4% 2 year survival; overall p=.02), and successful PTCA ≤ 4 hours after AMI onset (97.1% vs. 91.7% 2 year survival; p=.04). Survival was not dependent on prior thrombolytic therapy or 14 other variables.

Conclusions: 1) overall post-discharge survival after treatment of AMI with PTCA was 93% at 2 years, 2) 2 year survival of 97% was achieved in patients with successful PTCA ≤ 4 hours from symptom onset, or without prior infarction, or with pre-discharge LVEF > 40, 3) the improved post-discharge survival with early treatment that has not been noted after thrombolytic therapy alone suggests a long-term benefit from early complete revascularization of the infarct artery.

"RESCUE" PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY AFTER FAILED THROMBOLYTIC THERAPY--4 YEAR FOLLOW-UP

David R. Holmes Jr. M.D., F.A.C.C., Bernard J. Gersh M.D., F.A.C.C., Kent R. Bailey Ph.D., Guy S. Reeder M.D., F.A.C.C., John F. Bresnahan M.D., F.A.C.C., Dennis R. Bresnahan M.D., F.A.C.C., Ronald E. Vlietstra M.D., F.A.C.C., Mayo Clinic, Rochester, Minnesota.

Four year (yr) outcome in 34 pts undergoing "rescue" coronary angioplasty (PTCA) after failed lytic therapy for treatment of persistent occlusion for acute infarction (Group 1) (Gr 1) was compared to 29 pts undergoing PTCA for residual subtotal stenosis after successful lytic therapy (Group 2) (Gr 2). After PTCA, patency was present in 71% Gr 1 and 90% Gr 2. There was single vessel disease in 56% Gr 1 and 52% Gr 2 of pts. Initial and final infarct artery stenosis (IRA-S) and left ventricular function (EF) were:

| | Initial Mean IRA-S | Final Mean IRA-S | Initial EF | Dismissal EF |
|---|---|---|---|---|
| Gr 1 | 100% | 61% | 47% | 36% |
| Gr 2 | 98% | 54% | 58% | 50% |

In-hospital mortality was 3% in Gr 1 and 0% in Gr 2; in-hospital CABG was 29% in Gr 1 and 14% in Gr 2. After discharge at mean follow-up of 4 yrs, survival free of events was as follows:

| | Death | Death/MI | Death/MI/CABG |
|---|---|---|---|
| Gr 1 | 89% | 81% | 75% |
| Gr 2 | 97% | 93% | 90% |

Pts with rescue PTCA have lower EF at dismissal as well as increased late mortality/morbidity. Late survival was less in Gr 1 than in Gr 2 but the relatively good overall survival of 89% in pts with significantly decreased EF (36%) at the time of discharge is encouraging and raises the issue whether reperfusion could improve mortality by mechanisms other than myocardial salvage.

**THE TIMI II A STUDY OF PTCA TIMING AFTER RT-PA THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION (AMI)**

Donald S. Baim MD FACC, William J. Rogers MD FACC, Joel M. Gore MD, Genell L. Knatterud PhD, Eugene Passamani MD FACC, and the TIMI II A Investigators. Beth Israel Hospital and Harvard Medical School, Boston, MA.

Seven clinical centers in TIMI II A randomized 586 pts with AMI (symptom duration < 4 hrs, mean 2.9 hrs) to one of three treatments following rt-PA thrombolysis: 1) acute (2 hr) cath, and PTCA if possible, 2) delayed (18-48 hr) cath and PTCA if possible or 3) no cath/PTCA unless prompted by clinical ischemia. Findings at discharge cath (*) and 6 week follow-up (**) included the following:

| | 2 HR PTCA | 18-48 HR PTCA | NO PTCA |
|---|---|---|---|
| N | 195 | 194 | 197 |
| Revascularization | 158 (81%) | 121 (62%) | 55 (28%) |
| PTCA | 141 (72%) | 107 (55%) | 35 (17%) |
| CABG after PTCA | 15 (8%) | 5 (3%) | 5 (3%) |
| CABG without PTCA | 17 (10%) | 14 (7%) | 20 (10%) |
| Death** | 15 (8%) | 11 (6%) | 17 (9%) |
| Re-infarction** | 13 (7%) | 8 (4%) | 12 (6%) |
| LVEF (rest/ex)** | 49/52 | 48/53 | 50/52 |
| Arterial patency* | 119/152(78%) | 121/151(80%) | 142/168(85%) |
| Transfusion (>1U, $\bar{5}$ CABG) | 27 (14%) | 6 (3%) | 4 (2%) |

**In conclusion,** 1) Despite significantly less ($p<.001$), utilization of mechanical revascularization,the strategy of NO PTCA unless ischemia had a comparable outcome to routine cath and PTCA, and 2) Of the two routine PTCA strategies, 2 HR PTCA after rt-PA offered no additional benefit, and carried a greater risk of complications (transfusion [$p<.001$], CABG after PTCA [$p<.01$]) than either the 18-48 HR PTCA or NO PTCA strategies.

MEDIA THINNING OF SEVERELY DISEASED CORONARY ARTERIES: GUIDELINES FOR NEW INTERVENTIONAL PROCEDURES

Yaron Almagor M.D., Martin B. Leon M. D., F.A.C.C., Antonio L. Bartorelli M.D., Steven D. Lenhard, Michael W. Perlman B.A., Dean A. Follmann Ph.D., William C. Roberts M.D., F.A.C.C., Robert F. Bonner Ph.D. NHLBI, Bethesda, MD.

Since many new catheter-based laser and mechanical devices have been designed for definitive atheroma removal, safe and successful clinical procedures in small, tortuous coronary arteries (CA) may be critically dependent on the strength and integrity of the underlying media (M). To examine M dimensions of diseased CA, we studied 287 transverse histologic sections from 21 patients (66±10 yrs) dying after myocardial infarction, and measured 1) cross sectional areas of lumen, plaque, and media and 2) M thickness at 36 circumferential points. From these data, we calculated average thickeness of the media (ATM), % lumen cross-sectional narrowing (CSN), and % M points >100 μm.

| | LAD(n=95) | LCX(n=52) | RCA(n=131) | LM(n=9) |
|---|---|---|---|---|
| ATM±SD(μm) | 123±38 | 133±38 | 167±48 | 247±49 |
| %>100 | 63 | 72 | 85 | 99.4 |
| CSN±SD (%) | 66±21 | 67±20 | 68±21 | 59±13 |

Compared to normal patients without antemortem cardiac illness (n=103 sites), the ATM was 27% thinner in diseased CA (195±63 vs 147±49 μm, $p<.001$). Both ATM and % M points >100 μm decreased significantly ($p<.001$) with increasing stenosis (%CSN). Furthermore, for diseased CA sections, plaques were significantly thicker where the media was thinnest ($p<.001$). Thus, in diseased CA: 1) ATM is thinnner than in normal pts and M is thinnest in regions of greatest plaque accumulation, and 2) ATM and % M points >100 μm decrease with increasing stenosis. These data suggest that preservation of M integrity will require precise ablative techniques and that complete atheroma removal ("debulking") without transmural perforation may be an unrealistic goal in some patients.

## Wednesday, March 22, 1989
## 2:00PM–3:30PM, Marriott Hall North
## Anaheim Marriott Hotel
## Coronary Angioplasty: Experimental and Pathologic Observations

CORONARY SPASM INDUCED BY STENT IMPLANTATION

George Rodgers MD, Albert Raizner MD FACC, Douglas Cromeens DVM, Kenneth Wright PhD, Clifton Stevens DVM, Gary Roubin MD FACC, Steven Minor MD. Baylor College of Medicine, Houston, Texas

A feature of the swine model which is shared with humans is their propensity for coronary artery spasm. We implanted the Gianturco-Roubin balloon expandable stent in the left anterior descending or circumflex coronary artery of 28 6-month old Hanford miniature swine (25-35kg). Atherosclerosis had been induced in 9 of these animals. All were treated with diltiazem 2-4mg/kg 3 times daily for 3 days prior to stenting. All received intracoronary nitroglycerin (NTG) 200-300mcg and all received nifedipine 10mg buccally prior to stent implantation. Stents were selected such that they were 20% greater than or equal to the vessel diameter. Coronary arteriograms were performed immediately following and 15 minutes after stenting. Coronary spasm (a transient focal narrowing) distal to the stent was observed in 15 animals (53%); 7/9 (78%) atherosclerotic pigs developed spasm and 8/19 (42%) of the normal pigs. In all but 1 case spasm was relieved by additional doses of intracoronary NTG and/or buccal nifedipine 10mg. One animal died of intractable coronary spasm during the stenting procedure. Two other pigs who had transient coronary spasm after stenting died approximately 8 hours later. At necropsy both had patent stents, but 1 had thrombus distal to the stent at the site of the previously observed spasm. We conclude: 1) Swine appear to be a sensitive model for coronary artery spasm; 2) Stent induced spasm is a major problem in this experimental model and may have similar importance in man.

IMPEDANCE MEASUREMENT OF ABSOLUTE BLOOD FLOW USING AN ANGIOPLASTY GUIDEWIRE.

Lisa W. Martin, M.D., F.A.C.C., Robert A. Vogel M.D., F.A.C.C., Rodney A. Johnson, M.D., F.A.C.C., Mark Englehardt M.D., Helen Scott M.T., University of Maryland, Baltimore, Maryland.

The impact of a coronary stenosis on blood flow has been difficult to assess, particularly during angioplasty. We have previously developed an impedance angioplasty catheter able to measure absolute blood flow. Impedance changes induced by a 5% dextrose indicator solution ($D_5W$) and indicator dilution techniques are used. One half ml of $D_5W$ is infused upstream over five seconds through a side port located just proximal to the angioplasty balloon. Blood impedance is measured downstream at the catheter tip at a frequency of 50 kHz, using two electrode sets spaced 2 mm apart. (Small currents (10 uA) are used to eliminate cardiac stimulation.) Flow is calculated using the area under the first pass transit curve. In order to reduce the size of the impedance instrument and thus prevent interference with intrinsic blood flow, the electrodes are now on a .016 inch standard guidewire. The angioplasty catheter containing the guidewire may now be positioned proximal to the stenosis for injection of the indicator, with the electrode system distal to the stenosis. A 2 mm teflon electrode gap is located on the guidewire 3 cm from the tip to allow a bipolar electrode system. We have validated this guidewire system in plastic arterial phantoms with 2 to 4 mm diameter using one half normal saline (with impedance similar to blood) injected at known flow rates. An excellent correlation was found over a flow range of 10 to 300 ml/minute ($Y = .95X + 10.8$, $R = .98$, $N = 24$) between calculated and known flow rates. These results suggest that it may be feasible to measure absolute blood flow in arteries with stenoses using an angioplasty guidewire system.

In Vivo Recanalization of Total Atherosclerotic Arterial Occlusions: Combined Use of an Ultrasonic Probe and Balloon Angioplasty System

Robert J. Siegel M.D., FACC, T. Anthony DonMichael, M.D., FACC Eugene DeCastro A.A.S., Michael C. Fishbein, M.D., FACC, Zia Hashemi M.D., Louis Adler M.D., Joseph Bookstein M.D. James S. Forrester M.D., FACC Cedars-Sinai Medical Center, Los Angeles, California

Arterial recanalization using a prototype ultrasound probe with subsequent balloon angioplasty was studied. Totally occluded human atherosclerotic arterial xenografts (n=7) were surgically implanted in canine aorta or iliac arteries. Arterial occlusions were 2 to 5 cm in length and 6 vessels were calcified. Attempts at passage of conventional guide wires failed to open a channel in the occluded vessels. Ultrasonic energy was applied (47 watts/cm$^2$ at a frequency of 20 kHz) with a 0.020 inch wire probe in a 7-9 Fr catheter. After 15 sec to 2 min of ultrasound, a lumen was generated permitting passage of a guide wire and balloon angioplasty system. Subsequent balloon angioplasty was readily accomplished in all vessels. The angiographic residual stenosis was 24±10%. Angioscopy after ultrasound ablation and balloon dilatation revealed an endothelial surface comparable to that produced by balloon angioplasty alone. Perforation occurred in 1 vessel at the sutured anastomosis site. Histologic sections of the arteries demonstrated findings similar to those of balloon angioplasty alone, cracking of calcific and fibrotic plaques and focal separation of intimal plaques from underlying media. Potential limitations of the prototype system include arterial perforation due to the stiffness of the ultrasonic wire probe as well as the generation of embolic debris. Combined use of this ultrasonic probe and balloon angioplasty permit in vivo recanalization and dilatation of atherosclerotic arteries, with calcfied, long, complete occlusions.

INTRACORONARY DILTIAZEM LIMITS INFARCT SIZE DURING PROLONGED ANGIOPLASTY BALLOON INFLATION

G.C. Rose, M.D., J.C. Jordan, and S.R. Jolly, Ph.D., East Carolina University School of Medicine, Greenville, NC

The effect of intracoronary diltiazem (D) through a balloon catheter lumen was examined on regional ischemia and degree of necrosis during prolonged balloon inflation followed by reperfusion. Ischemia (I) was produced in closed -chest, pentobarbital anesthetized, male mongrel dogs by inflation of 2.5-3.0 mm diameter balloons introduced under fluoroscopy into the left anterior descending or left circumflex coronary arteries. Animals were randomly assigned to control (C) or D, administered at the time of balloon inflation. D was titrated to obtain significant systemic hemodynamic effects: 27±6 mm Hg reduction in mean arterial pressure achieved with a median dose of 900 ug/kg. An equivalent volume of saline was without effects. After 50 min of I, a left thoracotomy was performed and the left atrium was cannulated for injection of radiolabelled microspheres at 70 mins. The animal was then reperfused by deflating and removing the balloon. At 4 hr, animals were sacrificed and the heart removed for measurement of area at risk (AR) and infarct size (IS), using a dual staining technique. Regional subendocardial blood flow did not differ in the I area between groups: 12.0±2.6 vrs 13.8±2.8 ml/min/100 g in C and D respectively. AR did not differ between groups 38±4 vrs 39±3 percent of left ventricle. IS was significantly reduced as percent of AR: 22 ± 5 vrs 9 ± 2 in C and D respectively. Therefore, intracoronary D produced significant reduction in myocardial injury attributable to reduction of $O_2$ demand plus potential direct effects on the myocardium. This intervention may be useful to delay cell death in the setting of failed coronary angioplasty.

PERSISTENT ENDOTHELIAL DYSFUNCTION FOLLOWING EXPERIMENTAL ANGIOPLASTY.

Franz Weidinger, MD, James McLenachan, MB, Peter Ganz, MD, FACC, John Cooke, MD, PhD, FACC, Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Endothelium (E) can inhibit vascular smooth muscle tone and growth. To examine the late effects of vascular injury on E vasodilator function, angioplasty was performed in the left iliac artery (inj) of 3 groups of New Zealand rabbits, the right iliac serving as control (ctl). A moderate and a severe injury were compared (2.5 and 3.0mm balloons, respectively); both resulted in complete E denudation, but only the latter caused substantial intimal proliferation of smooth muscle. Vascular reactivity was studied at 2 and 4 weeks after injury in arterial rings in organ chambers. E-dependent relaxations were tested to acetylcholine (ACH) ($10^{-9}$ to $10^{-5}$ M) and calcium ionophore A23187 ($10^{-8}$ to $10^{-6}$ M) and E-independent relaxation to nitroprusside (NP)($10^{-9}$ to $10^{-4}$ M) after preconstriction with norepinephrine.

Results (relaxation expressed as % of maximum; all values mean±SEM; *p<0.05; **p<0.01; ***p<0.001 vs control):

| | ACH | | A23187 | | NP | |
|---|---|---|---|---|---|---|
| | ctl | inj | ctl | inj | ctl | inj |
| 2wk moderate (n=6) | 99±1 | 69±15 | 98±2 | 66±17 | 100 | 98±2 |
| 2wk severe (n=6) | 95±5 | 61±9** | 95±4 | 42±14** | 100 | 100 |
| 4wk severe (n=6) | 94±4 | 36±10*** | 91±5 | 45±14* | 97±3 | 100 |

E regrowth was confirmed histologically. There was a good correlation (r=-.65, p<0.005) between the impairment of E-dependent relaxation and the degree of intimal proliferation. Thus, following angioplasty, there is progressive impairment of endothelial vasodilator function despite endothelial regeneration. Persistent dysfunction of endothelium could contribute to altered vasomotor tone after angioplasty, and if generalized, could be a cause of restenosis.

## Wednesday, March 22, 1989
## 4:00PM–5:00PM, Marriott Hall North
## Anaheim Marriott Hotel
## Modification and Delineation of Coronary Atherosclerosis: New Aspects

**DIETARY SUPPLEMENTATION WITH FISH OIL PREVENTS CORONARY OCCLUSION BY THROMBUS FORMATION.**

Claude Benedict MD, FACC, Wen L Sheng MS, Gerald E Todd, University of Texas Medical Branch, Galveston, Texas.

In Eskimos, intake of fish oils is associated with low incidence of coronary artery disease. Whether dietary supplementation with fish oil leads to a decreased incidence of coronary occlusion by thrombus formation was investigated in a chronically instrumented dog model of coronary thrombosis. In this model in vivo platelet aggregation (PA) correlates with elevated coronary sinus serotonin (5HT) levels measured by a radioenzymatic method. 16 dogs fed on a diet supplemented with menhaden fish oil (total omega-3 fatty acid intake 400mg/kg/day) for 12wks were subjected to thrombus formation. Thrombosis is initiated by applying 150μA of current to the circumflex coronary artery until a 50% decrease in cross-sectional area (stenosis) develops. At this point current is stopped and occlusion develops spontaneously due to ongoing thrombus formation. Vessel closure was determined by absence of flow (doppler) and impairment in myocardial contractility. Vasoconstriction was monitered by dimension crystals sewn to the arterial wall.

| | Controls | Fish Oil |
|---|---|---|
| Number | 10 | 16 |
| Time for occlusion (min) | 85.0±16.0 | >180* |
| Episodes of vasospasm (per hr) | 6.0± 2.3 | < 1 * |
| Peak 5HT levels (ng/ml) | 45.0±17.0 | 3.2+1.7* |

Values are mean ± 1SD; *p < 0.01 compared to controls. The data shows a marked attenuation of in vivo PA and vasospasm in fish oil supplimented dogs. This suggests that inhibition in vivo PA and attenuation of coronary vasospasm are some of the mechanisms by which omega-3 fatty acids may prevent coronary occlusion by thrombus formation.

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REGRESSION OF ATHEROSCLEROSIS IN CHOLESTEROL FED RABBITS: EFFECTS OF FISH OIL AND VERAPAMIL

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We have previously shown that either fish oil or verapamil could attenuate the development of atherosclerosis in the lipid fed rabbit. The present study was designed to evaluate the individual and combined effects of these two interventions on regression. 50 New Zealand rabbits (5 groups) were fed a .3% cholesterol diet for 10 weeks. Group C10 was then sacrificed. Group C20 was fed a .3% cholesterol diet and the other groups were fed a normal diet for an additional 10 weeks. Group F received 2ml/day of fish oil (EPA 180mg + DHA 120 mg/ml). Group V received 2g/1000ml-water of verapamil and group FV received both fish oil and verapamil. Serum cholesterol at 10 weeks was similar in all groups (average 1033 mg/dl). After converting to a normal diet the serum cholesterol in group F was lower than levels in other groups ($P < .01$).

| | Groups | | | | |
|---|---|---|---|---|---|
| %Lesions | C10 | C20 | F | V | FV |
| Aorta | 40±15 | 57±22 | 15±17* | 16±12* | 26±24* |
| Pul. Art. | 20±7 | 37±11 | 11±9* | 12±9* | 17±14* |

*Significantly different from control groups.

Our previous study showed that a normal diet was ineffective in causing regression of atherosclerosis over a second 10 weeks. Thus, along with diet, fish oil or verapamil significantly reduced lesions in the aorta and pulmonary artery. These data demonstrate that either fish oil or verapamil can regress atherosclerosis in cholesterol-fed rabbits put on a normal diet. However, there was no additive effect of fish oil and verapamil. Although not statistically significant, there was a suggestive antagonistic effect between these two.

COMPENSATORY CORONARY DILATATION AND MEDIA THINNING: ADAPTIVE RESPONSES TO PROGRESSIVE ATHEROSCLEROSIS

Yaron Almagor M.D., Martin B. Leon M.D., F.A.C.C., Antonio L. Bartorelli M.D., Steven D. Lenhard, Michael W. Perlman B.A., Dean A. Follmann Ph.D., Robert F. Bonner Ph.D. NHLBI, Bethesda, MD

Since clinical manifestations of myocardial ischemia are dependent on coronary lumen area (A), pathophysiologic responses to maintain lumen A during progressive atherosclerotic plaque deposition are critically important. Using computerized video planimetry of transverse histologic sections, we compared the coronary architecture from 21 patients (313 sections) with severe atherosclerosis dying after myocardial infarction (Group I) to 9 control patients (103 sections) with minimal atherosclerosis and no cardiac symptoms (Group II). After measuring 1) cross-sectional (CS) A of lumen, plaque, and media and 2) thickness of the media (TM) at 36 circumferential points in each section, we compared (mean±SD) average TM, lumen A, plaque A, media A, CSA, and % CS narrowing for both groups.

| | Average TM(μm) | Media A($mm^2$) | Plaque A($mm^2$) | Lumen A($mm^2$) | CSA ($mm^2$) | %CS Narrowing |
|---|---|---|---|---|---|---|
| I | 147±49 | 1.6±.8 | 3.9±2.5 | 1.9±1.7 | 5.8±3.6 | 67±20 |
| II | 195±63 | 1.7±.7 | 1.1±0.6 | 2.1±0.9 | 3.1±1.4 | 33±11 |
| | p<.0001 | N.S. | p<.0001 | N.S. | p<.0001 | p<.0001 |

Although Group I patients had 4X greater plaque A than Group II controls, compensatory dilatation (↑CSA) maintained normal lumen A. Group I vessel enlargement was associated with significant thinning of the media (p<.0001) without reduction in media mass. Moreover, for individual vessels, plaque was thickest over regions of thinnest media (p<.0003). These findings suggest that the mechanism of compensatory coronary enlargement during progressive plaque accumulation is local vasodilation (and thinning) of the underlying media. Thus, in patients with coronary disease, adaptive media responses to enlarge CSA preserve the lumen A which may delay the onset of clinical ischemia.

THE IMPACT OF COMPENSATORY ENLARGEMENT OF ATHEROSCLEROTIC CORONARY ARTERIES ON THE ANGIOGRAPHIC ASSESSMENT OF CORONARY ARTERY DISEASE

Georg M. Stiel, MSc, BM, Ludmilla S.G. Stiel, MA, BM, Jochen Schofer, MD, Detlef G. Mathey, MD. Department of Cardiology, University Hospital Eppendorf, Hamburg, West Germany.

To determine whether compensatory enlargement of atherosclerotic coronary arteries occurs and to what degree it affects the angiographic assessment of coronary artery disease, we performed postmortem coronary angiography in 30 human hearts and morphometric measurements of 50 diseased arterial segments of these hearts. For this purpose, the coronary arteries were filled at a pressure of 100 mm Hg with an acrylic radiopaque resin and closely embedded in acrylic resin by the use of which shrinkage and mechanical artifacts could be avoided. The angiographic and corresponding morphometric degree of stenosis was assessed. The area circumscribed by the internal elastic lamina (IEL Area) was taken as a measure of the area of the arterial lumen if no plaque had been present. The correlation between the IEL Area and the area of the plaque (Lesion Area) is highly significant ($r=0.85$, $p \leq 0.0001$), suggesting that coronary arteries enlarge as Lesion Area increases. With an increase of the morphometric degree of stenosis, the normal anatomical diminution of the coronary artery (expressed as ratio of IEL Area distal to IEL Area proximal) was increasingly abolished due to the compensatory enlargement in atherosclerotic segment ($r=0.79$, $p \leq 0.0001$). The angiographically assessed degree of stenosis was underestimated. Compensatory coronary enlargement was the main factor of angiographic underestimation which was 3.50-1.37 fold up to an angiographic degree of 50% area and 30% diameter stenosis, resp. At higher degrees of stenosis, angiographic underestimation resulted mainly from disease with compensatory enlargement in the prestenotic reference segment, with an underestimation factor of 1.37.

Conclusions: 1, Compensatory enlargement in stenotic coronary artery segments occurs and 2, results in a significant angiographic underestimation of coronary atherosclerosis during the early stage of coronary artery disease.

## Wednesday, March 22, 1989
## 2:00PM–3:30PM, California Room D
## Anaheim Convention Center
## Echocardiography: Assessment of Diastolic Function

DIFFERENTIAL EFFECTS OF RIGHT VENTRICULAR PRESSURE AND VOLUME LOADING ON LEFT VENTRICULAR FILLING ASSESSED BY DOPPLER ECHOCARDIOGRAPHY

Eric Louie, M.D., F.A.C.C., Stuart Rich, M.D., F.A.C.C., Sidney Levitsky, M.D., F.A.C.C., Bruce Brundage, M.D, F.A.C.C., Loyola U., Maywood IL & U of IL, Chicago IL.

The effects of severe RV pressure overload (RVPO) and severe RV volume overload (RVVO) were studied in 11 pts with primary pulmonary hypertension (PA pressure 53±14 mmHg, RA pressure 5±5 mmHg) who had minimal or no TR by Doppler and 11 age matched pts who had undergone tricuspid valvulectomy for endocarditis (RA pressure 14±4 mmHg) who had severe TR but no pulmonary hypertension (peak TR velocities < 2m/s). LV eccentricity (E-minor axis parallel to the ventricular septum/axis perpendicular to septum = 1.0 normally in the absence of leftward septal shift) was measured by 2D echo and transmitral filling fraction was measured by PW Doppler. In RVPO leftward ventricular septal shift was most marked at end-systole (E=1.64±.48) and improved at mid-diastole (E=1.32±.22) and end-diastole (E=1.33±.33 p < .01 v. end systole). By contrast in RVVO E was relatively normal at end-systole (1.07±.09) and increased at mid-diastole (E=1.30±.22) and end diastole (E=1.35±.13 p < .001 v. end systole) as the ventricular septum shifted leftward. The transmitral late diastolic filling fraction in RVPO (0.48±0.16) was significantly greater than in RVVO (0.22±0.11, p < .001) and the transmitral early filling fraction in RVPO (.52±.16) was significantly less that in RVVO (.78±.11 p < .001). RVPO results in maximal geometric distortion of the LV in early diastole resulting in preferential late LV diastolic filling whereas RVVO results in maximal leftward ventricular shift in late diastole resulting in preferential early LV diastolic filling.

**STUNNED MYOCARDIUM: EVIDENCE THAT DIASTOLIC VENTRICULAR DYSFUNCTION PERSISTS EVEN AFTER RESOLUTION OF SYSTOLIC DYSFUNCTION - EXPERIMENTAL DOPPLER ECHOCARDIOGRAPHIC STUDIES.**

Shan Shen Wang, MD, Steven Schwartz, MD, Natesa Pandian, MD, FACC. Tufts-New England Medical Center, Boston, Massachusetts.

While systolic abnormalities in stunned myocardium have been well characterized, knowledge on changes in diastolic function is limited. We used Doppler analysis of mitral flow to study diastolic LV function in stunned myocardium. In 7 dogs a state of stunned myocardium was created by multiple brief occlusions of LAD coronary artery. With 2D echo we analysed regional systolic LV function. From mitral flow velocity recordings, we measured the isovolumic relaxation time (time from the end of aortic flow to the onset of mitral flow, IRT) and also early diastolic (E), and late diastolic velocity (A). Data were obtained in the control state, 15 min after reperfusion following cessation of multiple brief occlusions, and hourly thereafter. Results (mean±SD): In all dogs there was dysynergy of the anterior LV wall at 15 min after reperfusion. The dysynergy remained abnormal at 1 hour but resolved at 2 hours onwards. (%Systolic wall thickening was 40% in control, 8% at 15 min, 24% at 1 hr. ($p<0.01$); At 2 hrs %SWT was 37% (p=NS). While systolic function returned to normal range 2 hrs onwards, prolongation of IRT and diminution of E velocity were abnormal not only at 15 min but remained abnormal for 4 more hours. IRT (millisec) was 90 in control, and after reperfusion, it was 146 at 15 min, 149 at 1 hr, 147 at 2 hrs, 147 at 3 hrs, 140 at 4 hrs (All $p<0.05$ vs control). Although E/A ratio was not significantly altered, E velocity showed significant and persistent decrease. E velocity (cm/s) was 44 in control; After reperfusion, it was 27 at 15 min, 20 at 1 hr, 23 at 2 hrs, 25 at 3 hrs, 23 at 4 hrs (all $p<0.05$ vs control). These data indicate that diastolic ventricular dysfunction persists longer than systolic dysfunction in the post-ischemic period.

**REDUCTION OF LEFT VENTRICULAR PRELOAD PRODUCED BY LOWER BODY NEGATIVE PRESSURE ALTERS DOPPLER TRANSMITRAL FILLING PATTERNS**

Martin R Berk, MD, Patrick McGinnis, MD, Paula Taylor, RN, Charles Knapp, PhD, Joyce Evans, MS, Theodore Kotchen, MD, Anthony N DeMaria, MD, FACC, University of Kentucky, Lexington, Kentucky.

Although transmitral filling velocities have been used to assess LV diastolic function, few data are available regarding the influence of changes in preload upon mitral filling patterns. Therefore, we studied the effect of variable preload induced by lower body negative pressure (LBNP) upon transmitral flow velocities: eight normal males (age 30-32) had graded LBNP applied (0, -20, & -50 mm Hg). Pulsed wave Doppler was obtained with the sample volume at tips and annulus of the mitral valve. LV dimensions were measured with 2-D guided M-mode.

RESULTS(annulus): statistics indicate overall LBNP effect

| LBNP (mm Hg) | HR (bpm) | $E_{vel}$ (cm/s) | $A_{vel}$ (cm/s) | E/A ratio | DVI (cm) | $P_{\frac{1}{2}t}$ (sec) | LVDD (cm) |
|---|---|---|---|---|---|---|---|
| Rest | 62 | 60 | 39 | 1.56 | 12.9 | .063 | 5.0 |
| -20 | 67 | 48 | 35 | 1.45 | 11.9 | .079 | 4.6 |
| -50 | 80 | 38 | 37 | 1.05 | 10.5 | .094 | 4.3 |
| | p<.01 | p<.01 | NS | p<.02 | p<.03 | p<.03 | p<.01 |

Thus, LBNP produced graded reductions in preload (↓LVDD) and in stroke volume (↓DVI). The decreased transmitral flow induced by the lowered preload was confined to early passive filling ($\downarrow E_{vel}$), while late active atrial filling ($A_{vel}$) was maintained. The net effect was a decreased E, increased pressure halftime ($P_{\frac{1}{2}t}$), and unchanged A, a pattern similar to that previously associated with impaired diastolic properties. Thus, reduction of preload may profoundly affect transmitral filling patterns, compromising early passive filling but not active atrial flow, and must be considered when interpreting Doppler studies.

DOPPLER LEFT VENTRICULAR FILLING PATTERN IS CLOSELY RELATED TO VENTRICULAR RELAXATION ABNORMALITIES.

William R. Davidson, Jr. M.D., FACC, Michael J. Pasquale M.D., Robert D. Aronoff M.D., Pennsylvania State University College of Medicine, Hershey, Pennsylvania.

Alterations in Doppler-measured left ventricular filling (LVF) are commonly observed in coronary disease (CAD). To determine the importance of abnormal ventricular relaxation in producing these patterns 12 pts with suspected CAD (7M, 5F; age 56±7 years, mean±SD) were studied simultaneously with Doppler/Echo and a micromanometer-tipped LV catheter before and after left ventriculography (LVgram). Doppler LV isovolumic relaxation time (IVRT), peak early LVF velocity (E) and the ratio of early to late LVF (E/A ratio) were compared to pulmonary wedge pressure (PWP) and the time constant of ventricular relaxation (Tau).

Results: In all pts ejection fraction was >40% (63±8%) and normalized chamber stiffness was normal (3±0.8). At baseline PWP was 10±3 mm Hg, LVEDP 16±5 mm Hg, and LVEDV 129±35 cc rising to 15±3 mm Hg**, 23±5 mm Hg** and 143±30 cc* respectively after LVgram. E/A rose from .94±.50 to 1.04±.41 (P=0.06) and E from 44±12 to 53±12 cm/s**. Tau shortened from 50±20 to 43±16 msec*, and IVRT fell from 94±26 to 82±22msec** (*$p<0.05$, **$p<0.001$). IVRT was closely correlated with Tau (r.95, $P<0.001$) but not PWP (r=.22, p=0.11). E and E/A were moderately associated with Tau (r.73 and .64, both $p<0.001$). E, but not E/A, correlated modestly with PWP (r.45, $p<0.05$).

Conclusions: In CAD patients with near normal LV systolic function, Doppler LV filling pattern (IVRT and E/A ratio) is closely related to ventricular relaxation rate and less so to preload. In defined subgroups of patients, Doppler techniques should be useful in predicting abnormalities of ventricular relaxation.

ARE DOPPLER INDICES MORE LOAD SENSITIVE THAN OTHER MEASURES OF DIASTOLIC LEFT VENTRICULAR FUNCTION?

Pamela S. Douglas, MD, FACC, Barbara A. Berko, MD, FACC, Cynthia Parr, Alfred Ioli, Nathaniel Reichek, MD, FACC. University of Pennsylvania, Philadelphia, Pennsylvania.

Doppler indices of left ventricular filling are sensitive to changes in loading conditions, but comparison of this sensitivity with that of hemodynamic and dimensional indices of diastolic function has not been performed. Therefore, we studied 12 open-chest normal dogs during paired baseline (B), nitroprusside (N; 10 mcg/kg/min) and phenylephrine (P; 4mcg/kg/min) interventions. Data included Doppler early (E; cm/s), atrial (A) LV inflow velocities, their ratio (E/A) and atrial filling fraction (AFF); sonomicrometry derived normalized peak rates of LV filling (dV; $cm/s^2$) and wall thinning (-dh), micromanometer LV pressure decay (-dP/dt, Tau) and LA-LV pressure crossover (PCO, mmHg). Results were (*$p<.05$ vs paired B):

| | HR | LVP | -dP/dt | Tau | PCO | dV | -dh | E | A | E/A | AFF |
|---|---|---|---|---|---|---|---|---|---|---|---|
| B-N | 112 | 116 | -2289 | 32 | 15 | 9.0 | -2.7 | 46 | 30 | 1.67 | 31 |
| N | 121* | 103* | -2019* | 30 | 15 | 9.2 | -2.4 | 56* | 33 | 1.84 | 29 |
| B-P | 115 | 105 | -2186 | 28 | 15 | 9.2 | -2.4 | 49 | 31 | 1.63 | 30 |
| P | 117 | 155* | -2587 | 33 | 15 | 5.2* | -2.0 | 39* | 35 | 1.28 | 43* |

Changes in E (ΔE) correlated with changes in ΔdV (r=-.51, $p<.03$), while changes in E/A did not correlate closely with other variables.

Thus, Doppler indices appear more sensitive to loading conditions than were hemodynamics or wall thinning. This sensitivity may limit the clinical usefulness of Doppler measurements.

**NET LEFT ATRIAL AND VENTRICULAR COMPLIANCE CAN BE DERIVED FROM TRANSMITRAL VELOCITY CURVES: A HYDRODYNAMIC *IN VITRO* STUDY**

James D. Thomas, MD, Frank A. Flachskampf, MD, J. Luis Guerrero, John P. O'Shea, MB BS, Arthur E. Weyman, MD, FACC. Massachusetts General Hospital, Boston, MA.

The direct assessment of left atrial and ventricular compliance by Doppler echocardiography remains an important goal. Using a previously described mathematical model of left ventricular filling, we predict that, for flow restricted by the mitral valve (mitral stenosis), net atrioventricular compliance will be inversely proportional to the observed rate of change in transmitral velocity (*i.e.*, the slope of the Doppler velocity curve):

$$C_n = \frac{-MVA}{\rho dv/dt},$$

where MVA is effective mitral valve area, v is transmitral velocity, $\rho$ is blood density, and $C_n$ is net compliance, combining atrial ($C_a$) and ventricular ($C_v$) compliance as $(1/C_a + 1/C_v)^{-1}$. This relationship is valid both for constant and continuously variable compliance. We tested this hypothesis in an *in vitro* model of mitral flow where net compliance could be independently and continuously varied between 8 and 28 $cm^3/mmHg$ throughout "diastole". **RESULTS:** Distinctive Doppler velocity curves were observed: concave upward when compliance increased during diastole, concave downward when compliance decreased, and linear when compliance was constant. The above equation correctly predicted net compliance throughout ventricular filling for rising, falling, and constant compliance: $r = 0.96$, $p<0.001$. **CONCLUSION:** Using the readily obtainable noninvasive parameters of planimetered mitral valve area and transmitral velocity curve, it appears possible to derive atrioventricular compliance throughout diastole.

**HEPARIN POTENTIATES THE THROMBOLYTIC EFFICACY OF NATURAL PRO-UROKINASE**

Dietrich C. Gulba, M.D., M.Sc.; Klaus Fischer, M.D.; Gert-H. Reil, M.D.; Werner G. Daniel, M.D.; Stefan Jost, M.D.; Ingrid Wagenbreth, M.D.; Reinhold Frombach, M.D.; Paul R. Lichtlen, M.D., F.A.C.C. Hannover Medical School, Hannover, FRG

Natural Pro-Urokinase (nPUK) is inactivated by thrombin. If this effect is of importance for thrombolysis (T) in vivo, heparin (hep) should overcome this problem. In a non randomized study, we treated 18 patients (pts) with acute myocardial infarctions with a 250 000 IU urokinase bolus and a 4.5 Mio U nPUK infusion given within 40 min i.v.. Nine pts (group I) were treated without hep while 9 pts (group II) received a 5000 IU hep bolus and a 1250 IU/h continuous hep infusion starting before T. Angiograms were recorded at 60 min after onset of T. In group I, only one pt (11%) demonstrated an open infarct vessel; however, after a 5000 IU hep bolus reperfusion was achieved by a second 4.5 Mio U nPUK infusion in 7 of the 8 remaining pts (87,5%). In contrast, in 7 out of 9 group II pts (77,8%) primary patency was demonstrated by the first angiogram. The difference between both groups is highly significant ($p<0.01$). We conclude: 1) Thrombin related nPUK inactivation is of significant importance for T in vivo. 2) Hep can overcome this effect. 3) There is synergism between hep and nPUK. 4) nPUK should only be given together with high dose hep.

## Wednesday, March 22, 1989
## 4:00PM–5:00PM, California Room D
## Anaheim Convention Center
## Thrombolysis: Clinical Studies of Efficacy

DOSE RESPONSE RELATIONSHIP OF RT-PA INFUSION TO INDUCTION OF SYSTEMIC FIBRIN(OGEN)OLYSIS IN THE NHLBI THROMBOLYSIS IN MYOCARDIAL INFARCTION (TIMI-II) TRIAL.

E. Bovill, D. Stump, R. Tracy, D. Collen, T. Robertson, M. Terrin, J. Cheseboro, F. Feit, C. Lambrew, K. Mann for the TIMI investigators, University of Vermont, Burlington, VT.

Patients presenting with early acute myocardial infarction were treated with a 5,000 IU IV bolus heparin and a 6 hour intravenous infusion of rt-PA at either a 150 mg or 100 mg total dose. Plasma fibrinogen, fibrin(ogen) degradation products (FDP) and rt-PA levels were monitored in samples collected in sodium citrate (0.01 M) and the protease inhibitor phenylalanyl-1-prolyl-arginine chloromethylketone-2-HCL (PPACK; 20 $\mu$M).

| | Time | 100 mg | | 150 mg | |
|---|---|---|---|---|---|
| Assay | (min) | mean | (n) | mean | (n) |
| Fibrinogen | 0 | 312 | (1389) | 324 | (85) |
| (clotting | 50 | 257 | (1353) | 159 | (88) |
| rate) | 300 | 196 | (1468) | 87 | (91) |
| mg/dl | 480 | 192 | (1358) | 85 | (91) |

Peak rt-PA and FDP levels at the 100 mg dose were lower by about half in comparison with the 150 mg dose. Coronary artery patency rates observed at 2 hours were 75% after 100 mg rt-PA vs. 76% on 150 mg rt-PA, and at 18-48 hours were 85% after 100 mg rt-PA vs. 86% after 150 mg rt-PA. Clinic reported intracranial hemorrhage occurred among 1.6% of patients treated with 150 mg rt-PA vs. 0.6% of patients treated with 100 mg (JACC, 10:970). These data suggest that fibrin(ogen)olysis is frequent and dose related. Furthermore, although 150 and 100 mg rt-PA doses are associated with similar infarct-related artery patency at both 2 and 18-48 hours, 150 mg rt-PA is associated with greater frequency of hemorrhage.

OVERVIEW OF BLEEDING RISK FROM THE TAMI TRIALS: TWO AGENTS ARE BETTER THAN ONE

RM Califf, M.D., FACC, D Stump, M.D., EJ Topol, M.D., FACC, TC Wall, M.D., E Kline, DJ Kereiakes, M.D., FACC, B George, M.D., S Mantell, K Sigmon, RS Stack, M.D., FACC, Duke University Medical Center, Durham, North Carolina

In order to evaluate factors associated with bleeding during thrombolytic therapy of acute myocardial infarction (MI) 810 consecutive patients (pts) with acute myocardial infarction entered into the TAMI trials were evaluated. Pts were treated with t-PA at doses of 100-150 mg (561 pts), urokinase (UK) at a dose of 3 million units (102 pts) or the combination at doses of 1 mg/kg of t-PA and 0.5-2 million units of UK (147 pts). All pts underwent immediate angiography shortly after initiation of therapy; adjunctive therapy included heparin and aspirin in all pts. The majority of bleeding occurred in peri-access sites, although gastrointestinal bleeding occurred in 15% and intracranial bleeding in 0.7%. The median drop in hematocrit from admission to nadir value in nonsurgical pts was 10.5% with t-PA, 11% with UK and 9.2% with the combination. When clinical factors associated with bleeding were examined, the same factors were important regardless of thrombolytic regimen. Coronary bypass surgery was most important ($p<.01$). In pts treated without bypass surgery use of intraaortic balloon pumping ($p=.0001$), older age ($p<.01$), female sex ($p=.03$), lighter weight ($p<.01$) and history of prior cerebrovascular disease ($p<.01$) were the most important factors related to bleeding risk. When the thrombolytic regimens were evaluated, combination therapy was associated with significantly less bleeding ($p=.004$), even when the other important factors were taken into account. Thus, in pts treated with thrombolytic therapy and aggressive pharmacologic and mechanical methods to maintain patency, invasive procedures and demographic factors are more important than the thrombolytic regimen used in predicting bleeding complications. A brief (60 min) combination thrombolytic regimen was, however, associated with the least bleeding risk.

EFFECT OF LOW DOSE-ASPIRIN ON THE INCIDENCE AND HEMATOLOGICAL ACTIVITY OF LEFT VENTRICULAR THROMBOSIS IN PATIENTS WITH ANTERIOR MYOCARDIAL INFARCTION

Albert J. Funke Küpper M.D., Freek W.A. Verheugt M.D., F.A.C.C. Free University Hospital, Amsterdam, The Netherlands.

Serial echocardiography (2DE) was used to identify left ventricular thrombosis (LVT) in 100 consecutive pts with first acute anterior myocardial infarction (MI). Pts were randomised to aspirin (ASA) 100 mg qd or placebo (P) < 12 hours after onset of symptoms. Heparin s.c. 50 mg b.i.d. was given 3-4 days. 2DE was done: < 24 hours, 48-72 hours, 1,2, and 12 weeks after MI. In pts with LVT at the second week 2DE indium-111 platelet scintigraphy (IND) was performed.
LVT was detected by 2DE in 30 of the 92 evaluable pts (15 ASA, 15 P). IND performed in 17 pts was positive in 9 pts (4 ASA, 5 P) and negative in 8 pts (3 ASA, 5 P). Of the 30 pts with LVT, 6 pts died, one pt was lost for follow up and in one pt LVT was found only at 12 weeks. The remaining 22 pts showed LVT before or at the 2nd week 2DE and were follwoed for 12 weeks. Oral anticoagulants started in week 3 in 15/22 LVT pts resulted in LVT resolution in 8/15 pts, similar to the non-anticoagulated pts: 4/7. Thrombus resolution was noted in 3/9 IND positive and in 5/8 IND negative pts (p=ns) and in 7/10 of the ASA treated pts and 5/12 of the placebo treated pts (p=ns). Arterial embolism occurred in 2 pts with LVT both on ASA.
Thus, low dose ASA had no effect on the incidence, hematological activity and embolic potential of LVT in acute anterior MI.

**$^{31}$P-Magnetic Resonance Spectroscopy and Cine $^{1}$H Magnetic Resonance Imaging of Dilated Cardiomyopathy in Humans**

Wolfgang Auffermann, MD, William M Chew, PhD, Nuno J Tavares, MD, Thomas Donnelly, MD, William W Parmley, MD, Kanu Chatterjee, MD, Christopher Wolfe, MD, Charles B Higgins, MD. University of California, San Francisco, California

Comprehensive evaluation of cardiac structure, function and metabolism was achieved by combining $^{31}$P-magnetic resonance spectroscopy (MRS) and cine $^{1}$H-magnetic resonance imaging (MRI) at 1.5 Tesla. Five patients with dilated cardiomyopathy and 7 normal volunteers were studied using a one dimensional spectroscopic imaging sequence and a gradient refocussed echo sequence in a cinematographic mode. A homebuilt 9 cm circular double-tuned ($^{1}$H-$^{31}$P) surface coil was used to both transmit and recieve radiofrequency signals. Cardiac volumes, contractility patterns, muscle mass and wall stress were determined by cine MRI. The peaks of adenosinetriphosphate (ATP), phosphocreatine (PCr), phosphodiesters (PDE) and peaks attributable to 2,3 diphosphoglycerate, inorganic phosphate and phosphomonoesters were identified and the areas under each peak numerically integrated after baseline correction of the spectra.

Prominent peaks in the phosphodiester and phosphomonoester regions were observed in cardiomyopathic patients. PCr/ß-ATP was not significantly lower (1.49±0.08 vs 1.53±0.04), but PDE/PCr (1.1±0.02 vs 0.6±0.08) (p≤0.01) and PDE/ß-ATP (1.50±0.04 vs 0.96±0.15) (p≤0.05) were significantly higher in patients with dilated cardiomyopathy (EF: 24±4%) compared to normal volunteers (EF: 62±3%).

Thus, localized, gated $^{31}$P-MRS combined with cine $^{1}$H-MRI identifies abnormal myocardial phosphate metabolism related to abnormal contractility which might be useful in characterizing patients with dilated cardiomyopathy.

## Wednesday, March 22, 1989
## 2:00PM–3:30PM, Garden Grove Room
## Anaheim Convention Center
## Magnetic Resonance Spectroscopy: Characterization of Ischemia

IN VIVO $^{31}$P SPECTROSCOPY FROM TURTLE HEART DURING ANOXIA AND RECOVERY.

Yoseph Rozenman M.D., Xueming Zou, Jeremy Wasser Ph.D., Timothy R. Wu M.D., Bernard Hitzig Ph.D.,Howard L. Kantor M.D.,Ph.D.,F.A.C.C, Mass. General Hosp., Boston ,MA.

The turtle can survive during extended periods of anoxia, and therefore provides an opportunity to examine physiological adaptations to anoxia. This study is an NMR $^{31}$P in vivo examination at 4.7T of 5 turtle hearts during control(C), 2h of anoxia(A), and 1h of recovery(R). Spectra were obtained at room temperature using a surface coil within the shell below the heart. For each spectrum 400 aquisitions were obtained with a relaxation delay of 1 sec. Control resonances observed were: sugar phosphate, inorganic phosphate(Pi), creatine phosphate(PCr), adenosine triphosphate(ATP), and a peak at 2.7 ppm which is currently unidentified(Px). The control values of PCr/Pi, PCr/ATP, PCr/Px from fully relaxed spectra were 1.47±0.07, 1.62±0.21, and 1.32±0.31 respectively. PH values were estimated from Pi chemical shift(C-PH was 7.68±0.22). Results are presented as percentages of C concentrations.

| TIME(h) | PCr | Pi | ATP | Px | PH |
|---|---|---|---|---|---|
| 0.5A | 70.6±3.8* | 142.4±19.8 | 82.8±4.6# | 92.7± 3.1# | 7.44±.05 |
| 1.0A | 55.3±7.5* | 141.6±24.5 | 77.5±4.2$ | 80.6±11.6# | 7.16±.02# |
| 1.5A | 40.5±6.0* | 138.6±14.9# | 69.6±3.5$ | 76.3± 4.7$ | 7.05±.02* |
| 2.0A | 43.7±8.0* | 144.7±19.6# | 75.0±6.8$ | 82.8±11.5# | 6.98±.03# |
| 0.5R | 79.6±6.9$ | 128.6±13.5 | 87.2±4.0 | 97.9±10.6 | 7.56±.16 |
| 1.0R | 91.4±6.9 | 112.7±20.6 | 98.3±7.0 | 101.1±13.7 | 7.54±.04 |

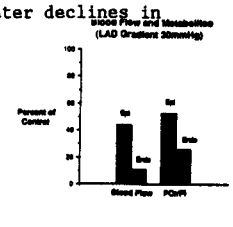
#-p<0.05, $-p<0.01, *-p<0.001

PCr evolution was fit with an exponential, with half life of 38.4±10.6 min (p<0.005) and 10.7±3.9 min (p<0.05) for A and R respectively, and an asymptote at 26.4±9.9% (p<0.05).
**Conclusions**: 1. Myocardial turtle spectra are similar to those obtained from mammals with an additional peak at 2.7 ppm. 2.The response to anoxia is slow, and stabilizes for the final 0.5h of a 2h period of anoxia.

TRANSMURALLY LOCALIZED 31P MRS: METABOLIC HETEROGENEITY DURING REGIONAL ISCHEMIA.

Barry Massie MD, FACC, Joel Gober PhD, Saul Schaefer MD, S. Albert Camacho MD, Eli Botvinick MD, FACC, Michael Weiner MD VAMC and Univ. of CA, San Francisco, CA.

Myocardial blood flow is often heterogeneous across the LV wall, but corresponding metabolic differences have not been sought under steady-state conditions. 31P-MRS can provide serial assessments of myocardial metabolism, with the potential for transmural localization. Therefore, we attempted to obtain spectra predominantly localized to the subepicardium (EPI) and subendocardium ENDO). Initial experiments with a 3 compartment bar phantom demonstrated >95% pure signal from each chamber. Using a plane phantom, uncontaminated spectra could be obtained from the EPI chamber, and although some contamination was present in the ENDO spectrum, improvement compared to non-localized techniques was substantial. Studies were then conducted on open-chest swine during partial coronary stenosis with the coil overlying the ischemic zone. 12 min spectra were derived from the ENDO and EPI. The PCr/Pi ratio was related to microsphere measurements of ENDO and EPI blood flow. In 3 animals, pre-stenosis ENDO and EPI spectra were similar. With partial stenosis, a greater decline in ENDO blood flow was noted, and this was associated with significantly greater declines in PCr/Pi in the ENDO layer (see figure). Thus, transmurally localized 31P spectra can be obtained in vivo, and these reveal metabolic heterogeneity consistent with transmural differences in myocardial blood flow during ischemia.



NMR LIPID IMAGING: A NEW STRATEGY FOR ASSESSING THE MYOCARDIAL ISCHEMIC INSULT

Alain Bouchard, M.D., F.A.C.C., Randall Wilson, M.D., Mark Doyle, Ph.D., Russell C. Reeves, M.D., F.A.C.C., Sanford P. Bishop, D.V.M., Ph.D., Gerald M. Pohost, M.D., F.A.C.C. University of Alabama, Birmingham, Al.

Proton NMR methods can monitor changes in mobile lipids (e.g.,triglycerides) in myocardium. In a canine model of myocardial infarction (MI), $^1$H NMR spectroscopy has demonstrated increases in lipid resonances in zones of decreased myocardial blood flow (MBF), 24hrs after coronary occlusion (Occl). To evaluate $^1$H NMR imaging of lipid accumulation in MI and periinfarct (PI) regions, we studied 10 dogs, 24 hrs after Occl.(LAD = 6, Cx = 4) using ex vivo lipid imaging and compared the findings to MBF, gross infarct location and Oil Red O histology. At 24 hr post Occl., microspheres were given and the heart excised. Lipid imaging was done using a Philips 1.5T imager and the Dixon technique (repetition time = 1 sec, echo time = 30 msec, slice thickness = 10 mm, field of view =20 cm, matrix =128 x 128). The lipid image revealed enhanced signal (12-70%, mean =45%) in regions corresponding to the post mortem identified PI zone. Histologically, a sharp border between necrotic and viable tissue in the subepicardial region corresponded to a MBF reduction of 74% (60-89%) in the peripheral MI and 48 % (30-60%) in the PI viable tissue. Viable PI myocardium stained intensely with Oil Red O, while MI tissue stained minimally.

Thus, $^1$H NMR lipid imaging identified viable tissue with moderately reduced MBF in the periinfarct region.

**MYOCARDIAL PROTECTION WITH VERAPAMIL DURING ISCHEMIA AND REPERFUSION: ASSESSMENT BY MAGNETIC RESONANCE SPECTROSCOPY**

Christopher L. Wolfe, MD, FACC. Thomas Donnelly, MD, Richard Sievers, BS, William Parmley. MD, FACC Univ.of California, S.F.

To test the hypothesis that verapamil is protective during myocardial ischemia and reperfusion, in vivo $^{31}$P magnetic resonance spectroscopy was performed on rats pretreated with verapamil (5mg/kg, n=11) and controls (n=11) during 45 min of LAD occlusion and 60 min reflow. Myocardial phosphocreatine (PCr) and adenosine triphosphate (ATP) were reduced in both verapamil and control animals by similar amounts after 45 min ischemia (57.4±3.7% vs 64.9±2.4%; 67.6±2.4% vs 70.5±3.4%; mean±SE; % of baseline value) After 60 min reflow, there was significant recovery of PCr (91.1 ±.4.2%; P<0.05; % of baseline value) in the verapamil group but no significant PCr recovery in controls. Infarct size was significantly reduced in the verapamil group compared to controls (7.6±2.4%, n=9, vs 29.6±5.4%, n=10; infarct % of LV mass). The LV systolic pressure, HR, RPP, and LV dP/dT were similar prior to ischemia, and during ischemia in both groups (Verapamil/Control, n=14 in each group, p=NS):

| | Baseline | 40' Ischemia |
|---|---|---|
| HR | 363±18/391±17 | 291±22/328±15 |
| Syst BP | 100±9/121±12 | 85±7/94±6 |
| RPPx10$^3$ | 37.3±4.3/49.0±6.0 | 26.4±3.8/31.1±2.9 |
| dP/dTx10$^3$ | 5.1±.6/5.6±.6 | 3.6±.5/4.1±.4 |

Thus, pretreatment with verapamil extends the time of myocardial ischemia after which reperfusion results in myocardial salvage. This resulted in reduced infarct size and enhanced high energy phosphate recovery in this model of ischemia/reperfusion. This protective effect appears to be independent of factors that determine myocardial oxygen demand during the ischemic period.

**SIMULTANEOUS CARDIAC MECHANICS AND MYOCARDIAL PHOSPHORUS-31 NMR ENERGETICS DURING GLOBAL ISCHEMIA & REPERFUSION IN THE CLOSED-CHEST CONSCIOUS DOG.**

D. Douglas Miller, MD, FACC, Felix Salinas III,BS, Mark Canales,MD, Danny Escobedo, Richard Walsh,MD, FACC. U. of Texas HSC, San Antonio, TX.

To investigate the cardiac mechanical correlates of myocardial high-energy phosphate metabolism during onset and recovery from global ischemia in the conscious state, 7 pre-instrumented dogs had phosphorus P-31 NMR spectroscopy(NMR-S) during 5min. of bilateral coronary occlusion± pacing(O) and reperfusion(R). ECG-gated spectra acquired q5min. at 2Tesla[128 averages,TR=2000ms,pulse width=65μs] with a 6cm. 2-turn RF surface coil had signal(βATP):noise =10:1. Myocardial phosphocreatine(PCr), inorganic P(Pi), adenosine triP(ATP) and pH were correlated with continuous micromanometer LV dP/dtmax, LVEDP and on-line sonomicrometer derived ejection fraction(EF);[*=p<0.05]:

| | +dP/dt(mmHg/s) | LVEDP(mmHg) | LVEF(%) | PCr/Pi |
|---|---|---|---|---|
| Control | 2396±578 | 8.5±4 | .32±.07 | 2.8±.8 |
| O | 2051±906 * | 19.3±14 * | .10±.14 * | 1.8±.5 * |
| R 15min. | 2185±478 | 9.2±6 | .08±.06 * | 2.1±.5 * |
| R 30min. | 2462±467 | 8.7±5 | .26±.09 | 2.2±.5 |

Myocardial pH remained depressed(-0.22±.23units;p<0.05) until R 30min. Myocardial ATP content was unchanged. PCr/Pi and dP/dtmax were significantly correlated at control(y=558x +862;r=0.75;p<0.01), with an insignificant trend in R(p=0.07).

We conclude that: 1)simultaneous hemodynamic measurements are feasible during NMR-S without degrading P-31 data 2) the extent and time course of functional and P-31 metabolic changes during global ischemia and recovery are significantly correlated, and 3) post-ischemic LV dysfunction is associated with profound hydrogen ion accumulation and PCr depletion in the intact conscious dog.

## Wednesday, March 22, 1989
## 4:00PM–5:00PM, Garden Grove Room
## Anaheim Convention Center
## Magnetic Resonance Imaging

MAGNETIC RESONANCE IMAGING IN ISCHEMIC INJURY FOLLOWING CARDIAC TRANSPLANT IN RATS

Marvin A Konstam MD FACC, Mark J Aronovitz, Val M Runge MD, Dean M Kaufman, Arthur R Dresdale MD, James T Diehl MD, Nicholas A Katzen MD, Elliot Kaplan MD, Douglas D Payne MD FACC, Richard J Cleveland MD FACC, Tufts University-New England Medical Center, Boston, MA.

Magnetic resonance imaging (MRI) with and without gadolinium (Gd)-DTPA has been shown to detect a) coronary occlusive ischemic injury and b) cardiac transplant (CT) rejection. To examine the ability of MRI to detect ischemic injury post-CT in the absence of rejection, we performed MRI in 18 rats with isogeneic [Lewis graft; Lewis host] heterotopic CT. Rats underwent MRI (1 Tesla) followed by sacrifice 1-90 days post-CT. Ischemic injury, characterized histologically by cellular infiltration and/or necrosis, was present in 5/5 rats sacrificed at 1-2 days, 3/4 rats at 12-14 days, and 0/9 rats at 30-90 days. On MRI, rats with histologic ischemic injury had increased T2-weighted image intensity (TR 2.3s; TE 90ms) and focal areas of intense enhancement post Gd-DTPA (0.5 mmol/kg) on T1-weighted images (TR 0.5s; TE 25ms) (*:p<0.05):

| Histology | T2 intensity (mean ± SE) | % of animals with Gd-DTPA enhancement |
|---|---|---|
| Ischemia absent | 104 ± 17 | 10 % |
| Ischemia present | 173 ± 27 * | 75 % * |

Conclusions: Post-CT ischemia causes increased T2 and Gd-DTPA-induced T1 enhancement, findings similar to those described in coronary occlusive ischemia and in CT rejection. MRI abnormalities in the first 2 weeks post-CT may represent ischemic injury rather than rejection.

MAGNETIC RESONANCE IMAGING WITH GADOLINIUM-DTPA IN MAN FOR DETECTION OF ACUTE MYOCARDIAL INFARCTION WITH OCCLUDED AND REPERFUSED VESSELS.

Albert C. van Rossum M.D., Frans C. Visser M.D., Jaap Valk M.D., Jan P. Roos M.D., Free University Hospital, Amsterdam, The Netherlands.

Canine studies have shown enhanced contrast between infarcted (I) and normal (N) myocardium by magnetic resonance imaging (MRI) using Gadolinium-DTPA (Gd). This was more distinct in reperfused compared to nonreperfused hearts. In this study we evaluated the use of Gd in 18 pts with acute myocardial infarction treated with intravenous streptokinase. Catheterization was performed at 35 ± 24 hrs after infarction. Four pts had occluded infarct related vessels without collaterals. Cardiac gated Tl-weighted spin echo MRI was obtained at 58 ± 9 hrs after infarction. Based on the ECG and ventriculogram the imaging plane was selected as to encomprise I and N myocardium. Imaging was performed before and serially up to 35 minutes after injection of 0.1 mmol/kg Gd. Two healthy volunteers underwent the same protocol, assigning half of their myocardium as pseudo-infarct. Images were analyzed using a circumferential signal profile. In this profile I myocardium could be identified by its increased signal intensity (SI). Results are expressed as SI ratios.

| | *pts* | | *controls* |
|---|---|---|---|
| 1. I/N pre Gd | 1.06 ± 0.16 | NS | 0.96 ± 0.06 |
| post Gd | 1.39 ± 0.13 | p<0.001 | 1.03 ± 0.08 |
| 2. N post Gd/N pre Gd | 1.28 ± 0.10 | NS | 1.23 ± 0.12 |
| 3. I post Gd/I pre Gd | 1.56 ± 0.21 | p=0.08 | 1.29 ± 0.09 |

4. I/N occlusion vs reperfusion: 1.37±0.09 vs 1.39±0.14

Conclusion: 1. Gd-DTPA improves MRI detection of acute myocardial infarction in man. 2. No difference was noted for myocardium supplied by occluded and reperfused vessels.

T2 RELAXATION TIME AS A PREDICTOR OF CARDIAC TRANSPLANT REJECTION IN HUMANS.

Tereasa Simonson, B.A., David W. Hunter, M.D., Elizabeth Braunlin, M.D., F.A.C.C., Maria Teresa Olivari, M.D., University of Minnesota Hospital and Clinic, Minneapolis, Minnesota

Magnetic resonance (MR) is a non-invasive imaging modality which can characterize tissue water content through measurement of T2 relaxation time measurements. Cardiac rejection has been shown to be associated with a significant increase in tissue water content, suggesting MR as a possible method for evaluating transplant rejection. To assess the diagnostic potential of MR in detecting cardiac allograft rejection, 99 myocardial T2 relaxation measurements were performed on 27 transplant patients aged 6 months to 64 years who had undergone cardiac transplantation and correlated with concomitant myocardial biopsy specimens. Patients underwent imaging at variable times between one to 150 weeks post transplant for an average total of 3.7 times per patient. Endomyocardial biopsies were obtained within 24 hours of imaging in most cases. However, three of the 18 rejecting biopsies were obtained within 72 hours of imaging and 14 of the 81 negative biopsies were obtained within one week of imaging in stable, non-rejecting patients. Eighteen MR observations with biopsy confirmed rejection had a mean myocardial T2 of 51 ± 10 ms, which was significantly higher than the 43 ± 7 ms found in the 81 MR observations which were biopsy negative for rejection. Using the criterion of T2 mean greater than or equal to 50 in at least one area of one axial slice of the left ventricle as evidence of rejection, sensitivity was calculated to be 78% and specificity 70%. A negative predictive value of 93% suggests MR T2 relaxation measurements may be an effective screening test to rule out rejection.

EVALUATION OF AORTIC REGURGITATION BY CINE MAGNETIC RESONANCE IMAGING COMPARING CINEANGIOGRAPHY.

Fumiaki Nishimura M.D., Yasushi Yoshino M.D., Junji Mihara M.D., Hideki Kamiya M.D., Toshihiro Oouchi M.D., Masahiro Umeda, Kameda General Hospital, Kamogawa, Japan.

It is well known that regurgitant blood flow of valvular disease shows signal loss (SL) in cine magnetic resonance imaging (cMRI). The purpose of this study is to define the significance of cMRI in evaluating aortic regurgitation (AR). Oblique cMRI showing the true long axis slice of the LV was performed in 32 patients assessed AR by cine-angiography (ANGIO). They did not have mitral stenosis or severe mitral regurgitation, because they also induced SL similar to that of AR. Each ANGIO was graded as none (8 cases), mild (9 cases), moderate (9 cases) or severe (7 cases). RESULTS: All of 25 cases with AR showed their AR as diastolic SL extending from the aortic valve into LV. On the other hand none of 8 cases without AR had SL. Shape of SL was jet like in all of the mild and moderate cases, but in all of the severe cases it was diffuse within LV. Length of SL (SLL) and area of SL (SLA) of AR planimetered in any view with the largest area, and the ratio to length of LV (LVL) and area of LV (LVA) of the same view calculated. Each index of SL excluding SLL moderate to severe was significantly high ($p<0.005$) according to the degree of AR by ANGIO. By comparing the ratio SLA/LVA (%) of cMRI to grading of ANGIO, with SLA/LVA 0~25% as mild, 26~50% moderate, 51~100% severe AR, cMRI classification was identical to severity of ANGIO in 24/25.

| | SLL (cm) | SLA ($cm^2$) | SLL/LVL(%) | SLA/LVA (%) |
|---|---|---|---|---|
| Mild : | 4.2±1.2 ]* | 3.7±2.0 ]* | 49±13 ]* | 12 ± 7 ]* |
| Moderate: | 7.8±1.2 ]NS | 17.4±5.1 ]* | 78 ± 4 ]* | 37 ± 6 ]* |
| Severe : | 8.8±1.3 ] | 29.8±6.3 ] | 94 ± 8 ] | 70±11 ] |

(mean ± 1 SD, *p<0.005)

We conclude that cMRI is a clinically useful method for documentating and grading AR by analysis of SL.

## Wednesday, March 22, 1989
## 4:00PM–5:00PM, California Room C
## Anaheim Convention Center
## Myocardial Ischemia with Normal Arteries

EFFECTS OF NITRATES ON CORONARY HEMODYNAMICS AND ANGINAL THRESHOLD IN SYNDROME X.

Raffaele Bugiardini M.D. F.A.C.C., Andrea Pozzati M.D., Filippo Ottani M.D., GianLuigi Morgagni M.D., Paolo Puddu M.D. Institute of Patologia Medica and C.C.U., University of Bologna, Italy.

Patients (pts) with angina pectoris, found to have angiographically normal coronary arteries and no evidence of coronary spasm or ventricular hypertrophy (syndrome X), offer a management dilemma to the clinician. This study was undertaken to investigate the hemodynamic effects of s.l. isosorbide dinitrate (10 mg; ID) in 10 pts presenting with the above set of findings as well as spontaneous episodes of transient myocardial ischemia (anginal pain and ≥ 0.15 mV ST↓). In these pts, we measured great cardiac vein blood flow (GCVBF; ml/min) and mean aortic pressure (AoP; mmHg) at rest and peak pacing (10 bpm increments every 2 min), both off drugs and 5 min following ID. In all pts GCVBF increased by less than 50% or even decreased during pacing. This occurred both off drugs and with ID. Administration of ID caused a significant reduction (paired t-test: $p < .05$) in AoP (x±SD: 94±16 vs 104±15 at rest, and 95±18 vs 105±20 at peak pacing) and GCVBF (94±54 vs 116±60 at rest, and 83±33 vs 121±52 at peak pacing). Angina and significant ST↓ (≥ 0.1 mV) during pacing occurred after 582±110 sec off drugs and 492±93 sec ($p < .02$) following ID. We conclude that: (1) pts with syndrome X exhibit a reduced coronary flow response to pacing; (2) in such pts, ID may further reduce blood flow, thus increasing discrepancy between myocardial $O_2$ demand and supply; (3) a failure of the autoregulatory mechanisms to adequately maintain coronary blood flow during decreased AoP is suggested.

EXERCISE CAPACITY AFTER ACUTE AMINOPHYLLINE ADMINISTRATION IN PATIENTS WITH SYNDROME X.

Michele Emdin M.D., Eugenio Picano M.D., Fabio Lattanzi M.D., Antonio L' Abbate M.D. F.A.C.C., C.N.R. Clinical Physiology Institute, University of Pisa, Pisa, Italy.

It has been shown that aminophylline (A) infusion increases exercise capacity in anginal pts with coronary artery disease, possibly through adenosine receptors blockade which prevents transmural steal phenomena due to excessive arteriolar dilation during exercise. As a mechanism of myocardial ischemia, a transmural steal has also been hypothesized in pts with syndrome X, in whom there is a coronary flow reserve reduction attributed to increased resistance at the site of small coronary arteries. In this work the effect of the adenosine receptor blocker A on effort ischemia in pts with syndrome X has been tested. Seven pts were selected on the basis of: chest pain on effort; electrocardiographically positive (>.1 mV ST-segment depression) exercise stress test and dipyridamole stress test; normal coronary arteriography and LV function; negative ergonovine test. Following double blind, randomized intravenous infusion of A (6 mg/Kg over 15') or placebo (P), the pts underwent upright bicycle exercise stress test on 2 consecutive days. With A, there was an increase in work tolerance (A: 8±.8 min of exercise vs P: 5.7±.9, p<.01) paralleled by an increase of the ischemic threshold, evaluated through the Rate Pressure Product (mm Hg x beats/ min x 1/100) at .1 mV of ST-segment depression or at peak exercise, when negative (A: 289±47 vs P:230±21, p<.01). Thus, at dosage which should effectively inhibit adenosine receptors, aminophylline infusion exerts beneficial effects on exercise induced ischemia in syndrome X, possibly through the prevention of flow maldistribution elicited by inappropriate adenosine release during effort.

**SYNDROME X: A PRIMARY METABOLIC DISEASE ?**

Paolo Camici M.D. F.A.C.C., Paolo Marraccini M.D., Roberto Lorenzoni M.D., Giuseppe Buzzigoli, Armando Perissinotto, Eleuterio Ferrannini M.D., Antonio L'Abbate M.D ,F.A.C.C., Mario Marzilli M.D
C.N.R. Institute of Clinical Physiology, University of Pisa, Italy.

Syndrome X ( angina pectoris associated with positive exercise stress test , angiographically normal coronary arteries and no evidence of spasm) is a challenging pathophysiological model. In this study we investigated, at rest in the postabsorptive state, coronary hemodynamics and myocardial metabolism, by simultaneous arterial (art) and great cardiac vein (GCV) catheterization, in 6 Pts with Syndrome X (PX) and in 6 Pts with a chest pain syndrome, no evidence of ischemia and normal coronary arteries (PN). GCV flow (thermodilution) and coronary resistance were similar in PN and PX (52±9 vs 49±5 ml/min; 1.9±.2 vs 2.1±.2 mmHg/ml/min; p=N.S.). PN and PX had comparable arterial levels (6.4±.2 vs 5.9±.2 mM; p=N.S), myocardial extraction fraction (art-GCV/art) (1.4±1.6% vs 2.3±1.1%; p=N.S.) and myocardial uptake [(art-GCV)GCVflow] (1.6±5.8 vs 4.6±2.1µmol/min; p=N.S.) of glucose. Free fatty acids arterial levels, myocardial extraction and uptake were also comparable in PN and PX (1.1±.3 vs .9±.9 mM; 30.4±4.8% vs 25.6±3.4%; 10.0±2.5 vs 6.9±.8 µmol/min; p=N.S.). By contrast arterial lactate (.64±.69 vs 1.21±.15 mM; p<.01) and myocardial lactate uptake (6.8±1.2 vs 19.0±5.0 µmol/min; p<.05) were lower in PX than in PN whilst the extraction fraction was similar (31±6% vs 36±5%; p=N.S.). Pyruvate arterial content (46±4 vs 87±11 mM; p<.05), myocardial extraction (11±14% vs 49±4%; p<.05) and uptake (.2±.2 vs 1.86±.54 µmol/min; p<.05) were also lower in PX than in PN. A positive uptake of alanine was found in PX whilst the substrate was released in PN (.8±.7 vs -1.2±.5 µmol/min, p<.05). In conclusion, Pts with Syndrome X show multiple metabolic abnormalities at rest (reduced lactate and pyruvate and increased alanine myocardial utilization) in the absence of any evidence of myocardial ischemia. This suggests that a primary metabolic alteration might play a role in the pathogenesis of this disease.

**ENDOTHELIAL FUNCTION INFLUENCES THE CORONARY VASOMOTOR RESPONSE TO SYMPATHETIC STIMULATION IN MAN**

Andreas M. Zeiher, MD, Helmut Wollschläger, MD, Helmut Drexler, MD, Bernward Saurbier, MSc, Hanjörg Just, MD.
Medical Clinic, University of Freiburg, F.R.G.

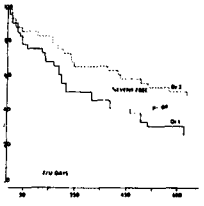
Sympathetic stimulation by cold pressor test(CPT)has been shown to dilate normal, but paradoxically constrict atherosclerotic coronary arteries(CA)in man.To test the hypothesis that endothelium-dependent dilation plays a role in this response, we compared the effects of CPT and the endothelium-dependent dilator acetylcholine(ACh) in 9 normal subjects and in 10 patients with coronary atherosclerosis (minimal disease with lesions < 30%, CAD). Blood flow velocity within the LAD was continuously assessed by intracoronary Doppler catheter, LAD diameters were measured by automated quantitation of digitized cine-frames. ACh($10^{-8}$M, $10^{-7}$M,$10^{-6}$M) was infused into the LAD via the Doppler catheter.
Results (mean % change from baseline ± 1SD): In all normal subjects, CPT increased LAD blood flow velocity by 38.3±8.5% and LAD diameter by 7.5±3.1%. Similarly, there was a dose-dependent increase in LAD blood flow velocity (+94.2±19.1%) and LAD diameter (+9.8±3.6%) at ACh concentration of $10^{-6}$M in all normal subjects. In contrast, in all patients with CAD, CPT increased LAD blood flow velocity by 44.1±26.5%, but decreased LAD diameter by -8.6±3.9%. Identically, there was a dose-dependent increase in LAD blood flow velocity by 121.7±54.6%, but a decrease in LAD diameter by -17.2±5.9% at ACh concentration of $10^{-6}$M in all patients with CAD. There was complete agreement in the direction of the response to CPT and ACh. Intracoronary nitroglycerin (endothelium-independent) caused LAD dilation by 17.1±4.5% in all subjects.
Thus, the dilation of normal CA and the constriction of atherosclerotic CA with CPT exactly mirror the response to the endothelium-dependent dilator ACh. These results suggest that endothelial function may play an important role in the coronary vasomotor response to sympathetic stimulation by CPT in man.

## Wednesday, March 22, 1989
## 4:00PM–5:00PM, Santa Ana Room 1
## Anaheim Convention Center
## Ischemia and The Ambulatory Electrocardiogram

**SILENT ISCHEMIA ON AMBULATORY ECG MONITORING PROVIDES ADDITIONAL PROGNOSTIC INFORMATION IN PATIENTS WITH STABLE ANGINA AND A POSITIVE EXERCISE TREADMILL TEST**

Prakash Deedwania, M.D., F.A.C.C., John Nelson, M.D., Enrique Carbajal, M.D., VAMC/UCSF, Fresno, California

Patients (pts) with chronic stable angina (CSA) and diagnostic ST depression (ST↓) on exercise testing (ET) have frequent silent ischemic events (SIEs) during ambulatory ECG monitoring (AEM). However, it is unknown whether SIE on AEM provides prognostic stratification in addition to that of ET in pts with CSA. In this study, we prospectively evaluated 76 consecutive male pts with CSA, proved CAD, ST↓ on ET who underwent 24 hr AEM with a FM system. All pts were followed every 3-4 months and continued their antianginal drugs. Clinicians were blinded to the AEM data. A SIE on AEM was defined as ST↓ ≥ 1mm (80 msec from J), lasting ≥ 1min, and without symptoms in the diary. Based on AEM and ET data, the pts were divided into 2 groups (Gr); Gr-1, 31 pts with >40 min/d of SIE and time to 1mm ST↓ on ET of ≤6min (6minET) and Gr-2, 45 pts with ≤40min/d of SIE and ≤6minET. During the mean follow-up period of 23±8 mos, Kaplan-Meier actuarial analysis was performed for the time-dependent probability of cardiac events including death, MI and unstable angina. As shown in Fig, the Gr1 pts had significantly (P=0.036) worse prognosis. The stepwise Cox hazard analysis of 9 variables including ET data revealed presence of SIE on AEM as the most powerful predictor of mortality (p=0.007). Thus, SIE on AEM is an independent marker of poor prognosis in pts with CSA and a positive ET.



SIGNIFICANCE OF EXERCISE-INDUCED ST-SEGMENT ELEVATION IN PATIENTS WITH Q WAVE ANTERIOR MYOCARDIAL INFARCTION: EVALUATION BY POSITRON EMISSION TOMOGRAPHY.

Tetsuro Fudo M.D., Hirofumi Kambara M.D., F.A.C.C., Masataka Hayashi M.D., Tetsuo Hashimoto M.D., Ryuji Nohara M.D., Nagara Tamaki M.D., Keiji Yamashita M.D., Junji Konishi M.D., Chuichi Kawai M.D., F.A.C.C. Kyoto University, Kyoto, Japan.

To evaluate the significance of exercise-induced ST-segment elevation, we utilized positron emission tomography (PET) with F-18 deoxyglucose (FDG) and N-13 ammonia to characterize regional myocardial blood flow and glucose metabolism in 27 patients with Q wave anterior myocardial infarction. PET was performed with N-13 ammonia at rest and after ergometer exercise, and with FDG at rest with fasting. Thirteen patients developed ST-segment elevation during exercise, and the remaining 14 did not. The results were as follows;

| | LVEF (%) | Regional EF (%) | Asynergy | Exercise -Induced Ischemia | Increased FDG Uptake |
|---|---|---|---|---|---|
| ST elevation (+) (n=13) | 42±8 | 11±10 * | 12/13 | 10/13 | 10/13 * |
| ST elevation (-) (n=14) | 45±11 | 21±11 * | 10/14 | 6/14 | 4/14 * |

*p<.05

These data indicate that (1) maintained glucose activity despite the presence of severe left ventricular asynergy may contribute to exercise-induced ST elevation, and (2) exercise-induced ischemia detected by N-13 ammonia PET may or may not cause ST elevation.

THE IMPORTANCE OF ASSESSING ST ELEVATION BY HOLTER MONITORING IN UNSTABLE ANGINA.

Anatoly Langer M.D., Michael R. Freeman M.D., FACC, Paul W. Armstrong M.D., FACC. Toronto, Canada.

The clinical significance of ST elevation (ST-E) on Holter monitoring (HM) in pts with unstable angina is uncertain since previous studies have grouped ST-E together with ST depression (ST-D) in assessing prognosis. We studied 135 pts with 24 hr HM and continuous intra-arterial BP monitoring on admission to CCU. Coronary angiography (CA) was performed at 4.2±2.6 days.

There was ST shift in 89 pts: 20% had ST-E (≥1 mm at J), 62% had ST-D (≥1 mm, 80 msec after J), and 18% had both. Pts with ST-E were similar to those with ST-D or both with respect to clinical characteristics, previous infarction (MI), frequency of symptoms with ST shift, and severity of coronary artery disease (CAD). The incidence of cardiac events (death, MI, urgent revascularization) was also similar: ST-E 50%, ST-D 46%, and both 62%. Compared to pts without ST shift, pts with ST-E had more vessels with ≥50% stenosis (2.3±.9 vs 1.6±1.2, p<.05) and more in-hospital cardiac events (50% vs 22%, p<.05). A total of 593 episodes of ST shift were detected, of which 33% were ST-E and 67% ST-D; there was no difference in duration of ST shift (16±30 vs 18±30 min) or rate-pressure product associated with ST shift (9.0± 2.7 vs 9.4±2.8 $BPxHRx10^{3}$) but the magnitude of ST shift was slightly greater with ST-E (1.5±.9 vs 1.3±.5 mm, p<.01).

We conclude that patients with unstable angina and ST-E on Holter monitor have more severe CAD and more frequent cardiac events than pts without ST shift. Even though ST-E is less frequent than ST-D, it implies a similarly poor outcome and, therefore, should be considered together with ST-D for prognostic stratification.

LEFT VENTRICULAR FUNCTION AT REST AND THE PREVALENCE OF AMBULATORY SILENT ISCHEMIA IN CORONARY ARTERY DISEASE

Arshed A. Quyyumi, M.D., Julio A. Panza, M.D., Kevin E. McCarthy, M.D., Timothy S. Callahan, Robert O. Bonow, M.D., FACC., Stephen E. Epstein, M.D., FACC, NHLBI, Bethesda, MD

LV function at rest and during exercise (ex) have important prognostic implications in coronary disease (CAD). The relation between LV function and the prevalence and frequency of silent ischemia during daily activities is unknown. We studied 80 CAD pts free of cardiac drugs with ex radionuclide angiography and 48 hr ambulatory ST monitoring. The incidence and duration (min/48hr) of ambulatory ischemic episodes (IE) in 51 pts with normal resting ejection fraction (EF) (≥45%) and in 29 pts with subnormal resting EF (<45%) was evaluated. IE in the subgroups of pts manifesting an ischemic response to exercise (≤2% increase or a decrease in ex EF) was also evaluated:

| All pts | Subnormal EF | Normal EF |
|---|---|---|
| Pts with IE | 41% | 71%** |
| Duration (m) | 70±29 | 103±18 |
| % of silent IE | 81% | 89% |
| Q Wave MI | 45% | 12%** |
| Pts with ex EF↓ | 17 | 40 |
| Pts with IE | 47% | 78%* |
| Duration (m) | 81±39 | 120±23 |

*= p<.05, **= p<.01 mean ± SE

Pts with subnormal rest EF had lower prevalence of IE. Once IE occured, the duration of silent or painful IE was similar in both groups. Thus, IE are less frequent in pts with resting LV dysfunction even in the subgroup developing more severe dysfunction with ex, compatible with ex-induced ischemia. Ambulatory ST segment electrocardiography may not be a sensitive indicator of silent ischemia in pts with resting LV dysfunction.

## Wednesday, March 22, 1989
## 2:00PM–3:30PM, Santa Ana Room 2
## Anaheim Convention Center
## Clinical Electrophysiology: Wolff-Parkinson-White Syndrome

THE MECHANISM OF THE ONSET OF ATRIAL FIBRILLATION IN THE WOLFF-PARKINSON-WHITE SYNDROME: HOW IMPORTANT IS THE ACCESSORY PATHWAY?

Osamu Fujimura M.D., George Klein M.D., F.A.C.C., Arjun Sharma M.D., F.A.C.C., Raymond Yee M.D., F.A.C.C., University Hospital, London, Ontario, Canada.

It has been suggested that reentry in branching networks of accessory pathways (AP) may be implicated in the high incidence of atrial fibrillation (AF) observed in the Wolff-Parkinson-White (WPW) syndrome. To evaluate this, we studied the mode of onset of 98 episodes of AF lasting at least 30 seconds in 78 patients during diagnostic electrophysiolgical study. No patient had organic heart disease and 31 had clinical AF prior to study. AF occurred during routine pacing and extrastimulus testing for 71 episodes and occurred in the absence of stimulation in 27. Electrograms were recorded from the high right atrium, His bundle position and coronary sinus (LA). AF patients were then compared to a control group of 53 WPW patients in whom atrial fibrillation could only be sustained with rapid atrial pacing.

Ninety-two of 98 episodes were technically suitable for analysis. AF invariably began with a rapid atrial tachycardia which became progressively disorganized within 10 to 20 cycles. It was initiated during RA stimulation (n=57), RV stimulation (n=11), during reciprocating tachycardia (n=22) and apparently spontaneously during sinus rhythm (n=2). Earliest atrial activation during the initiating rapid tachycardia occurred at a right atrial site in 73 episodes and at a LA site in 19 episodes. Most episodes started at a high right atrial site regardless of AP location with only 20% of episodes starting at the electrode closest to the AP. However, AF started at the AP site in 12 of 22 episodes occurring spontaneously during reciprocating tachycardia. Patients with AF had longer PA intervals (54 ± 14 vs 42±12, p<0.001) shorter atrial functional refractory period (226 ± 38 vs 240±30, p=0.49) and shorter effective refractory period of the AP (279 ± 26 vs 304 ± 75 msec , p=0.03).

These data suggest that multiple factors may explain the high incidence of AF in WPW with intrinsic atrial factors and accessory pathway factors probably both playing a role. Onset of AF close to the AP site supports the theory of AP involvement in the genesis of AF in some patients.

## THE RELIABILITY OF PROCAINAMIDE IN PREDICTING THE SHORTEST PREEXCITED R-R INTERVAL DURING ATRIAL FIBRILLATION IS DOSE DEPENDENT

K. Atta Boahene M.D., George J.Klein M.D., F.A.C.C., Arjun D.Sharma M.D., F.A.C.C., Raymond Yee M.D., F.A.C.C., Osamu Fujimura M.D., University Hospital, London, Ontario, Canada.

A shortest R-R interval (SRR) during atrial fibrillation (AF) ≤ 250 msec identifies patients (pts) with preexcitation potentially at risk for ventricular fibrillation. Loss of preexcitation with procainamide infusion during sinus rhythm has been suggested as a means to identify pts with long effective refractory periods (ERP) and hence low risk during AF. These findings have been questioned. We hypothesized that the conflicting results are related to different methodologies and dosages, and proceeded to test procainamide, in a rigidly, standardized fashion, with the goal of predicting SRR ≤ 250 by loss of preexcitation ("true positive"). Thirty-two consecutive pts with preexcitation referred for electrophysiologic testing were studied. After control data were obtained, AF was induced by rapid atrial pacing and SRR during AF was determined. After termination of AF, we gave procainamide in incremental doses of 50, 100, 200, 400 and 250 mg every 10 minutes up to a cumulative dose of 1 gm or to loss of preexcitation. These doses were given over 1-2 minutes in the supine position, except for the 400 mg dose given over 3-4 minutes. During the control period and after each dose, accessory pathway ERP, blood pressure, heart rate and blood level of the drug were determined.

RESULTS:

| CUMULATIVE DOSE | SENSITIVITY | SPECIFICITY | +PREDICTIVE VALUE | -PREDICTIVE VALUE |
|---|---|---|---|---|
| 50 | 0 | 100 | 0 | 32 |
| 150 | 16 | 100 | 100 | 36 |
| 350 | 42 | 89 | 89 | 42 |
| 550 | 63 | 89 | 92 | 53 |
| 750 | 72 | 55 | 68 | 45 |
| 1000 | 74 | 40 | 74 | 44 |

We conclude that the ability of procainamide to predict SRR ≤ 250 by loss of preexcitation in sinus rhythm is dose dependent. Specificity declines markedly after cumulative doses >550 mg.

## SUSTAINED PREEXCITED TACHYCARDIA: AV NODAL RATHER THAN TRUE ANTIDROMIC REENTRY AS THE MAIN MECHANISM.

Mohammad Jazayeri M.D., Galen Van Wyhe M.D., James McKinnie M.D., Boaz Avitall M.D., Sergio Kershenovich M.D., Patrick Tchou M.D., Masood Akhtar M.D., F.A.C.C., Sinai Samaritan Medical Center, Milw. WI.

Determination of underlying mechanism of preexcited tachycardia (PRET) has important clinical implications especially when surgical ablation of accessory pathway is considered. During electrophysiologic evaluation of 94 consecutive pts with manifest ventricular (V) preexcitation, 11 pts had PRET. Pts with PRET due to atrial (A) flutter/fibrillation were excluded. Three mechanisms were identified: 1) AV nodal tachycardia (6 pts) by meeting the following criteria: a) His bundle-right bundle activation interval similar to that during narrow QRS tachycardia. b) Retrograde conduction delay in the His-Purkinje system during introduction of premature ventricular complex without affecting the corresponding A-A interval. c) Abrupt A-A interval prolongation followed by V-V interval lengthening of the same degree. In 4 pts who underwent surgery, intraoperative mapping confirmed the diagnosis. 2) Antidromic reentry utilizing 2 accessory pathways (4 pts). No pt had true antidromic reentry using normal pathway as the retrograde limb. 3) Atrial tachycardia (1 pt). Conclusion: Our data indicate that AV nodal tachycardia is not an uncommon mechanism of PRET. A thorough electrophysiologic evaluation is necessary to separate AV nodal tachycardia from other mechanisms of PRET (e.g. true antidromic reentry). This information is particularly useful for pts undergoing surgical ablation of accessory pathway, since AV nodal tachycardia is also amenable to surgical correction.

## AGE-RELATED DIFFERENCES IN THE ELECTROPHYSIOLOGIC PROPERTIES OF ACCESSORY PATHWAYS IN PATIENTS WITH THE WOLFF-PARKINSON-WHITE SYNDROME.

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In order to assess the relationship between age and electrophysiologic characteristics of accessory pathways, 102 pts under 16 years of age (mean age 13 ± 4 yrs) (PEDS) and 503 pts older than 16 yrs (mean age 36 ± 14 years) were studied. The prevalence of other heart disease and sudden death were similar in both groups. Right freewall and multiple accessory pathways were significantly more common in PEDS than adults (28% vs. 18% and 25% vs. 15%). The accessory pathway anterograde effective refractory period (APERP), the shortest RR interval between 2 preexcited complexes and average RR intervals during atrial fibrillation, and the reciprocating tachycardia cycle length (RTCL) were compared as shown:

| | APERP | Shortest RR | Average RR | RTCL |
|---|---|---|---|---|
| Peds | 257 ± 56 | 213 ± 50 | 300 ± 71 | 283 ± 45 |
| Adult | 284 ± 91 | 240 ± 66 | 346 ± 81 | 323 ± 51 |
| p= | .025 | .0014 | .0001 | .0001 |

The APERP and shortest and average RR intervals were significantly shorter in PEDS than adults. The RTCL difference was due to a shorter A-H interval in the former group (113 ± 43 vs. 133 ± 52/p=.0065), with no difference in the ventriculo-atrial interval (113 ± 39 vs. 115 ± 37) despite expected differences in cardiac size. These data indicate an increased prevalence of right and multiple pathways in symptomatic PEDS, more rapid atrial fibrillation and RT rates in younger pts, and suggest that the change in RTCL with age is due to AH and not VA interval prolongation.

## SAFETY AND EFFICACY OF ORAL FLECAINIDE THERAPY IN PATIENTS WITH THE WOLFF-PARKINSON-WHITE SYNDROME

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A total of 59 pts with the Wolff-Parkinson-White (WPW) syndrome underwent electrophysiologic studies (EPS) before and after oral flecainide (F) therapy. Flecainide therapy prevented induction of sustained supraventricular tachycardia (SVT) in 41 pts (69%) and these pts were treated chronically with F. Of the remaining 18 pts, the drug was discontinued in 5 during in-hospital monitoring (spontaneous life-threatening atrial fibrillation -2 pts, breakthrough paroxysmal supraventricular tachycardia (PSVT) -1, and incessant SVT -2), and 13 (22%) had F discontinued after repeat EPS (inducible sustained SVT -11, new atrial arrhythmias -1, and severe suppression of sinus node function -1). Over a follow-up of 18±10 months (range, 3-31), 32 of the 41 pts (78%) treated with F have continued to do well with no significant symptoms or adverse reactions. F was discontinued in 9 (22%) because of sudden death (1), central nervous system side effects (3), recurrent PSVT (3) or pt preference for surgery (2). Six of the 59 pts had significant proarrhythmic effects, including sudden death, incessant SVT, new atrial arrhythmias or prolonged sinus pauses. These pts had more organic heart disease (4 0f 6 had OHD, vs 0/53 pts without proarrhytmic effects), and were older (45±17, range 22-82 vs 36±12, range 9-73). Conclusion: (1) Flecainide constitutes effective long-term therapy for the majority of pts with WPW. (2) Pre-discharge EPS and in-hospital monitoring detected most pts with serious proarrhythmic effects. (3) Proarrhythmic effects occurred predominately in older subjects with organic cardiac disease.

EFFECTS OF UPRIGHT POSTURE ON ATRIOVENTRICULAR ACCESSORY PATHWAY CONDUCTION

David E. Mann, M.D., F.A.C.C. and Michael J. Reiter, M.D., Ph.D., F.A.C.C. University of Colorado Health Sciences Center, Denver, Colorado.

Electrophysiologic testing of patients with atrioventricular (AV) accessory pathways (AP) is usually performed in the supine position. To study the effects of upright posture (UP) we measured anterograde (ante) and retrograde (retro) AP block (B) cycle length (CL) and effective refractory periods (ERP) in 19 patients (mean age 28 years) while supine and with 45° UP. UP enhanced ante and retro AP conduction:

| | supine (ms) | UP (ms) | p |
|---|---|---|---|
| ante AP BCL | 374 ± 52 | 303 ± 33 | <.05 |
| ante AP ERP | 286 ± 17 | 249 ± 10 | <.01 |
| retro AP BCL | 320 ± 33 | 285 ± 31 | <.05 |
| retro AP ERP | 312 ± 26 | 274 ± 15 | .06 |

During induced atrial fibrillation (AFB) the mean RR interval shortened with UP (377 ± 13 to 325 ± 11 ms, p <.01) and the shortest RR shortened, but not significantly (259 ± 16 to 234 ± 14 ms, p NS). The percentage of preexcited beats during AFB did not change (70 ± 14% supine, 61 ± 15% during UP, p NS). Sustained orthodromic reciprocating tachycardia (RT) was induced in 11 patients. RT CL shortened with UP (357 ± 26 to 304 ± 21 ms, p <.01), primarily due to a decrease in ante AV nodal conduction time (198 ± 25 to 162 ± 14 ms, p <.05). Retrograde AP conduction time during RT shortened slightly (130 ± 17 to 123 ± 16 ms, p < .05). In patients with RT or AFB, both supine and UP testing overestimated the spontaneous tachycardia CL, but UP testing did so to a lesser degree (24 ± 25 ms overestimation with UP vs 69 ± 25 ms supine, p <.05). Thus UP 1) enhances ante and retro AP conduction, 2) shortens the mean RR interval during AFB, 3) shortens RT CL, 4) more closely reproduces the CL of spontaneous RT and AFB, and 5) may be useful in the assessment of patients with AP.

## Wednesday, March 22, 1989
## 4:00PM–5:00PM, California Room B
## Anaheim Convention Center
## Pediatric Cardiac Imaging

**RESPIRATORY INFLUENCE ON RV AND LV DIASTOLIC FILLING IN NORMAL CHILDREN.**

Thomas W. Riggs, M.D., F.A.C.C. and A. Rebecca Snider, M.D., F.A.C.C., Wm. Beaumont Hosp. and C.S. Mott Hosp., Royal Oak and Ann Arbor, MI.

Our objective was to examine the effects of respiration on RV and LV diastolic filling in normal children. Twenty children (ages 1-11) had Doppler examinations of the RV and LV inflow, recorded with respiration and ECG. We measured the peak E and A velocities (cm/sec) and the E and A areas, and then computed the ratios: peak E/A velocity , E/A area, and the 1/3 area fraction. **Inspiration** significantly augmented both the **early** and the **late** phases of RV filling in a similar fashion; thus the peak E/A, E/A area and 1/3 area were unaffected by respiration. **Inspiration** selectively lowered **early** LV filling; thus the peak E, peak E/A, E/A area and 1/3 area were each decreased.

| | Inspiration | Expiration | p-value |
|---|---|---|---|
| **RV peak E** | 62.1 ± 12.8 | 49.3 ± 12.0 | < 0.0001 |
| **RV peak E/A** | 1.61 ± 0.51 | 1.48 ± 0.46 | NS |
| **RV E/A area** | 2.56 ± 1.29 | 2.48 ± 1.34 | NS |
| **RV 1/3 area** | 0.40 ± 0.06 | 0.41 ± 0.07 | NS |
| **RV peak A** | 41.7 ± 11.5 | 35.2 ± 9.3 | < 0.0001 |
| **LV peak E** | 84.8 ± 11.0 | 92.1 ± 14.1 | < 0.0001 |
| **LV peak E/A** | 1.72 ± 0.42 | 2.00 ± 0.64 | < 0.005 |
| **LV E/A area** | 2.72 ± 1.04 | 3.09 ± 1.34 | < 0.001 |
| **LV 1/3 area** | 0.44 ± 0.09 | 0.50 ± 0.09 | < 0.001 |
| **LV peak A** | 52.1 ± 12.1 | 50.0 ± 13.1 | NS |

**Conclusion:** Inspiration enhances RV venous return, while the LV response to inspiration is a complex interplay among LV preload, LV afterload and ventricular interdependence. Respiration significantly alters variables of RV and LV diastolic filling. Any pediatric assessment of RV or LV diastolic function should be standardized for respiration.

THE POOR PROGNOSIS FOR FETUSES WITH PRENATALLY DIAGNOSED TRICUSPID VALVE ABNORMALITIES.

Lisa K. Hornberger, B.A., David J. Sahn, M.D., FACC, Charles Kleinman, M.D., FACC Kathryn Reed, M.D., Univ Calif, San Diego, CA and Univ Ariz, Tucson, AZ and Yale University.

Tricuspid valve disease (TVD) in newborns and children is often well tolerated, but studies suggest a worse prognosis for TVD detected in-utero. We reviewed 27 fetuses with TVD and significant tricuspid insufficiency (TI) diagnosed in utero (19-35 wks gestation), after referral because their obstetrical ultrasounds showed an abnormal atrioventricular valve or an asymmetric four-chamber view. One fetus had Trisomy 13. None of the others had any non-cardiac defects. Seventeen fetuses had Ebstein's malformation, 7 had TV dysplasia with poorly developed, normally inserting leaflets, and 3 had an unguarded orifice without significant TV tissue and low velocity, non-turbulent Doppler TI. Four fetuses initially had normal forward PA flow but on subsequent studies had retrograde ductal PA flow in association with the development of critical pulmonary stenosis (PS) [1] or pulmonary atresia (ATR) [3]. Four other fetuses had PS and 3 had ATR on their initial exam. Serially studied fetuses had progressive right-sided cardiomegaly including 3 fetuses who had normal RV size when initially referred. Twelve fetuses died in utero and 11/15 who were liveborn died despite vigorous medical and, when indicated, surgical management. Confirmation of anatomic diagnosis was obtained by autopsy for 19 fetuses and by cath or at surgery in all but 3 of the others. Ten autopsies documented pulmonary hypoplasia, total lung weight < ½ of expected. The prognosis for fetuses with in-utero diagnosed TVD is extremely poor and their prenatal course includes progressive right heart dilatation, lung hypoplasia and in some, development of pulmonary stenosis or pulmonary ATR.

A NEW METHOD FOR NONINVASIVE ESTIMATION OF VENTRICULAR SEPTAL DEFECT (VSD) SHUNT FLOW BY COLOR DOPPLER: IMAGING OF THE LAMINAR FLOW CONVERGENCE REGION ON THE LEFT SEPTAL SURFACE.

Valdir A. Moises, M.D., Lisa Hornberger, Benedito Maciel, M.D., Azucena Murillo, M.D., David J. Sahn, M.D., FACC, Univ Calif, San Diego, CA.

Flow convergence (FC) on the left septal side of a VSD is commonly imaged by color flow Doppler (CFD) as a region of aliased velocities going into the VSD orifice. If the first aliasing region represents a hemispherical isovelocity boundary of FC going into the VSD, volume flow can be estimated using the radius (R) of the first alias from the VSD orifice and the Nyquist limit (NL) velocity. R should increase as a function both of VSD size and trans-VSD flow velocity. We measured R (normalized for body surface area [BSA]) and calculated R x NL, the BSA normalized planimetered area (A) inside R (x NL), the hemisphere volume (HV) of radius R ($2/3\ \pi\ R^3$), and the hemisphere surface (HS) area ($2\ \pi\ R^2$) as estimates of VSD flow from CFD studies in 18 children aged 2 to 84 months with single perimembranous VSD using a Toshiba SSH 65A, 3.75 MHz 4 kHz. These measurements were compared to catheterization determined shunt flow through the VSD (Qp-Qs) and pulmonary/systemic flow ratio (Qp/Qs). For simple indices, R (r=0.80), R x NL (r=0.84) A (r=0.97) and A x NL (r=0.94) had the closest correlation with Qp-Qs for the 10 Pts who showed good FC in four-chamber views and A (r=0.90) and A x NL (r=0.92) correlated well with Qp/Qs. For FC on long-axis images of 15 Pts, A (r=0.85) HV (r=0.80) HV x NL (r=0.89) and HS x NL (r=0.88) showed good correlation to Qp-Qs, and A x NL (r=0.79) HV x NL (r=0.80) and HS x NL (r=0.82) correlated well with Qp/Qs. Indices derived from the FCR proximal to a VSD allow calculation of trans-VSD shunt flow and may serve as simple and clinically useful estimates of VSD shunting.

**DOES COLOR DOPPLER ECHOCARDIOGRAPHY DETECT ADDITIONAL SMALL MUSCULAR DEFECTS IN INFANTS WITH A LARGE VENTRICULAR SEPTAL DEFECT?**

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Although color Doppler (CD) can clearly detect one or more small ventricular septal defects (VSD's), whether it can do so in the setting of a known large (non-restrictive) VSD is unknown. In the presence of a large (low-resistance) pathway through the septum, the amount and velocity of blood shunting through additional small muscular VSD's (ASM VSD's) may be low. In the face of the trend toward neonatal reparative surgery of many congenital heart malformations, one of the only mitigating factors is the identification of ASM VSD's; for example, a neonate with transposition, a large malalignment-type VSD, and ASM VSD's might more easily undergo arterial switch repair 3 months later when the ASM VSD's may have closed spontaneously.

We evaluated with CD and angiography (angio) 129 pts under 2 years who subsequently underwent surgical closure of a large VSD: tetralogy of Fallot 49, transposition 11, perimembranous VSD with normal great arteries (NL GA's) 27, aortic arch anomaly 13, atrioventricular canal 15, other lesions 14. Only 4 had ASM VSD's at repair. The ASM VSD's were detected by both angio and CD in 2, by angio only in 1, and were missed by both techniques in 1. The negative predictive values of CD and angio in the detection of ASM VSD's is 0.98 and 0.99, respectively. Of those 67 pts who were over 6 mos old, only 1 had an ASM VSD.

Conclusions: 1) CD does not appear to completely eliminate, false-negative diagnosis of ASM VSD's in the presence of known large VSD; 2) The prevalence of ASM VSD's, estimated by previous reports to be as high as 15% in infants less than 12 mos, falls to 1.5% by age 6 mos; 3) The vast majority of ASM VSD's close in the first few mos.

**CHANGES IN LEFT ATRIAL SIZE DUE TO CHRONIC ATRIAL FIBRILLATION.** Guillermo Sosa-Suarez, Steven Lampert, Thomas B. Graboys, Shmuel Ravid, Bernard Lown, Brigham and Women's Hospital and Harvard School of Public Health, Boston, MA 02115

Unsettled is the question of whether left atrial (LA) enlargement (E) in patients with atrial fibrillation (AF) is a consequence of left ventricular (LV) function or whether the AF alone causes LAE. We reviewed 436 patients (PTs) with AF and selected 22 with lone AF who were free of any structural heart disease based on the normal physical exam and doppler-echocardiography study. AF was chronic (CAF) in 10 PTs (age: 64 yrs.) and paroxysmal (PAF) in 12 PTs (age: 63 yrs). All PTs were followed for an average of 6.2 yrs (1.1 - 13 yrs); there was no difference in average follow-up in the 2 groups. Baseline measurements of LA size, LV size, fractional shortening (FS) and heart rate (HR) were similar in the CAF and PAF groups. LA size increased an average of .6 cm (-0.1-1.5) in all patients. In CAF PTs it increased .81 cm compared to .38 cm in PAF PTs ($p = .05$). LV dimensions and FS did not change significantly during the observation period. HR tended to increase in the CAF group (11 $\pm$ 27 bpm) and decreased slightly in the PAF group (-4 $\pm$ 17 bpm) (NS). The change in LA size was most closely related to duration of follow-up and whether AF was chronic or paroxysmal. The LA increases 0.12 cm/yr in patients with CAF. LAE did not correlate with either baseline measurements of LV function or with changes in LV size or function. We conclude that the LA can increase in size as a consequence of CAF alone, independent of any changes in LV size or function. The mechanism for this effect needs to be explored.

## Wednesday, March 22, 1989
## 2:00PM–3:30PM, California Room A
## Anaheim Convention Center
## Left Atrium/Atrial Fibrillation/Pericardium

**LEFT ATRIAL ENLARGEMENT AS A CONSEQUENCE OF ATRIAL FIBRILLATION: A PROSPECTIVE ECHOCARDIOGRAPHIC STUDY.**
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Massachusetts General Hospital, Boston.

Left atrial enlargement (LAE) is commonly observed in patients presenting with atrial fibrillation (AF). It is not clear, however, whether the LAE is the cause or consequence of the AF. This issue is of clinical importance since LAE is known to increase risk for thrombus formation and embolization. Its potential prevention by correction of the AF would support aggressive treatment of the arrhythmia in even asymptomatic patients.

To address this question, 14 pts (age 48-78 yrs, mean =68.3 yrs) with non-rheumatic AF prospectively underwent serial echocardiographic (echo) studies separated by 11-28 mos (mean=20.4 mos). The patients were selected on the basis of the following findings at their inital echo: 1) no significant mitral valve or LV pathology, 2) no or minimal mitral regurgitation (MR), 3) normal or only mildly increased LA size. LA measurements were carried out in the antero-posterior (AP), medio-lateral (ML) and supero-inferior (SI) dimensions. Volume (VOL) was calculated using an ellipsoid formula.

**RESULTS:** (all values given $\pm$ standard deviations)

| | AP (mm) | ML (mm) | SI (mm) | LA VOL ($cm^3$) |
|---|---|---|---|---|
| Study #1 | 38.6 $\pm$ 4.9 | 40.6 $\pm$ 3.7 | 54.6 $\pm$ 7.8 | 45.2 $\pm$ 11.0 |
| Study #2 | 42.4 $\pm$ 4.6 | 46.1 $\pm$ 5.2 | 62.4 $\pm$ 6.2 | 64.1 $\pm$ 13.5 |
| p value | <0.008 | <0.005 | <0.002 | <0.0001 |

**CONCLUSIONS:** LA size increases in patients with AF even in the absence of significant MR, mitral valve pathology, or LV disease. Thus, AF appears to induce LAE. Correction of the AF may therefore prevent LAE and potentially reduce risk for thrombus formation and stroke.

THE EFFECT OF ATRIAL CONTRACTION AND SYNCHRONEITY OF CARDIAC CONTRACTION ON VENTRICULO-ARTERIAL COUPLING.
Kazuhiro Yamamoto M.D., Kazuhisa Kodama M.D., Atsushi Hirayama M.D., Tomoki Ohara M.D., Masaaki Uematsu M.D., Akira Kitabatake M.D., Takenobu Kamada M.D., Cardiovascular Div., Osaka Police Hospital, Osaka, Japan

We investigated the effect of the atrial contraction and synchroneity of cardiac contraction on ventriculo-arterial coupling in 6 patients with sick sinus syndrome. Pacing leads were placed in right atrium (A) and right ventricle (V), then we obtained left ventricular pressure-volume data by conductance catheter inserted into left ventricle during A pacing, AV sequential pacing, and V pacing. In V pacing, VA sequential pacing was performed to neglect atrial contraction. In AV sequential pacing, Atrioventricular delay was kept at 150 msec. The slope of the end-systolic pressure-volume relationship (Ees) was determined by inferior vena caval occlusion. The effective arterial elastance (Ea) was expressed by the ratio of end-systolic pressure to stroke volume. Because heart rate was controlled at a constant rate (90bpm), we used Ea as an index of afterload. The mechanical energy efficiency (Eff) was determined by the ratio of external work to pressure volume area. In AV sequential pacing, compared with A pacing, Ees and Eff were reduced, (-15$\pm$12%, -8$\pm$6%, $p<0.05$), but Ea didn't change significantly. In V pacing, compared with AV sequential pacing, Ees, Eff, and Ea altered significantly (-24$\pm$11%, -16$\pm$14%, +16$\pm$15%, $p<0.05$). Conclusions: 1), Synchroneity of cardiac contraction enhances contractility of left ventricle; 2), Atrial contraction enhances contractility of left ventricle, and reduces afterload; 3), Atrial contraction and synchroneity of cardiac contraction are important factors on ventriculo-arterial coupling.

LEFT VENTRICULAR FUNCTION IN ATRIAL FIBRILLATION: A COMPARISON BEFORE AND AFTER CARDIOVERSION.

Harry Crijns M.D., Isabel van Gelder M.D.,Paul Blanksma MD Nico Knop, Kong Lie M.D., Dept.of Cardiology, Thoraxcenter University Hospital Groningen, The Netherlands.

LV function is difficult to establish in atrial fibrillation(AF) because of the variable preload.To compare it before and after electrical cardioversion(CV) we developed a computerized system for on line beat-to beat measurement of RR-interval, filling time, filling volume and ejection fraction(EF). For EF and filling volume measurement we used a nuclear probe(Nuclear Stethoscope) connected to a microcomputer via an A/D converter. With the help of this system we looked after the influence of the duration of the preceding RR intervals on diastolic and systolic LV function. In 10 pts with AF we found a linear relationship between filling time and RR-interval. The regression line crossed the RR-axis at 369±13 ms. This may be considered as the minimal duration of the electromechanical systole. Filling time was relatively increased when the preceding RR-interval was less then 500 ms.This curvilinear relation ship may be considered as a measure of diastolic function. EF was dependent on at least two preceding RR-intervals in a curvilinear relationship.Mean EF during AF was 37±10%, found at a mean RR of 647±40 ms.EF during AF,using only the RR-intervals with the duration found after CV, was 41±11% ±8p 0.05),whereas EF after CV(sinus rhythm with a mean RR-interval of 853±83 ms) was 40±11% (N.S.,compared to EF before cardioversion). Conclusions:1. LV function in AF is influenced by at least the two preceding RR-intervals.2. After CV EF can be predicted from the obtained relationship of EF and RR-interval during AF. 3. EF does not change after CV.

INFLUENCE OF THE PERICARDIUM ON DYNAMIC RIGHT AND LEFT VENTRICULAR FILLING

Brian D. Hoit, M.D., F.A.C.C., Valmik Bhargava, Ph.D., Nancy Dalton, R.D.M.S., Ralph Shabetai, M.D., F.A.C.C. University of Cincinnati, Cincinnati, OH

To evaluate pericardial restraint of ventricular filling, we performed Doppler echo of right (RV) and left (LV) ventricular inflow in 10 open chest dogs at three levels of LV end-diastolic pressure (EDP) before and immediately after pericardiectomy (P). Dextran infusion and P caused a significant increase in the transmitral early filling velocity (Em) and tended to increase the ratio of early to late filling velocity (Em/Am, p=.079). For RV inflow, increasing preload with the pericardium intact resulted in significant increases in early (Et) and late transtricuspid velocity (At), but no change in Et/At. In contrast, P greatly increased At, but not Et, causing a significant decrease in Et/At:

| EDP (mmHg) | 7±2 | | 13±2 | | 21±4 | |
|---|---|---|---|---|---|---|
| | beforeP | afterP | beforeP | afterP | beforeP | afterP |
| Em | 43±6 | 60±10[a] | 63±11[b] | 73±12[a] | 71±13[b] | *91±13[a] |
| Am | 30±9 | 34±10 | 32±9 | 39±21 | 40±16 | 42±17 |
| Em/Am | 1.4±.4 | 1.9±.5 | 2±.7 | 2.1±.8 | 1.3±.5 | 2.5±1.1[a*] |
| Et | 27±8 | 27±12 | 29±8 | 31±7 | 39± 6[b,c] | 36± 8 |
| At | 24±8 | 40±10[a] | 29±13 | 43±11[a] | 31±12[b] | 51±15[a] |
| Et/At | 1.2±.4 | .8±.3 | 1.3±.9 | .8±.2[a] | 1.5±.6 | .8±.2[a] |

a=before vs. after P, b=compared to EDP 6, c=compared to EDP 12. P < 0.05 *P=0.058

We conclude that filling of the two ventricles is strongly affected by the pericardium over a wide range of volumes and pressures, and that there are important differences in pericardial influences on RV vs. LV filling. The effect of the pericardium on inflow velocities must be considered when assessing interventions that alter pericardial restraint.

SHIFT OF THE LEFT VENTRICULAR DIASTOLIC PRESSURE-VOLUME CURVE WITH ISCHEMIA: IMPORTANCE OF VOLUME AND THE PERICARDIUM

Robert J. Applegate, M.D., Jakob Vinten-Johansen, Ph.D., William E. Johnston, M.D., William C. Little, M.D., F.A.C.C. Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, N.C.

Acute coronary artery occlusion has been variably reported to produce upward or rightward shifts of the left ventricular (LV) end-diastolic (D) pressure (P)-volume (V) relation. These variable responses may be due to several factors including the effect of the initial LV V and a pericardial effect. The purpose of this study was to evaluate the effect of LV size and the pericardium (PER) on the LVDPV relation during coronary occlusion. LV end-diastolic pressure (EDP) and LVV (impedance catheter) were monitored during intraluminal balloon occlusion of the left circumflex coronary artery in 7 anesthetized closed chested mongrel dogs. Balloon occlusion was evaluated at 2 different LV V before and after removal of the PER. From the initial baseline LVEDP (5±4mmHg) and low LVV (64±16ml) in the presence of an intact PER, the LVDPV curve shifted to the right during coronary occlusion. This shift was unchanged by removal of the pericardium. After volume loading (LVEDP 23±8mmHg, LVEDV 95±22ml), the LVDPV curve shifted upwards in the presence of the pericardium. Following removal of the pericardium similar coronary occlusion produced a rightward shift.

**Conclusions:** Coronary occlusion at low LVV causes a rightward shift of the left ventricular diastolic pressure-volume curve which is independent of the presence of the pericardium. At high LVV during coronary occlusion, the curve shifts to the right in the absence of the pericardium, but shifts upwards when it is present. Thus, the response of the LVDPV curve during coronary occlusion is modulated by the initial LVV and the pericardium.

## Wednesday, March 22, 1989
## 4:00PM–5:00PM, California Room A
## Anaheim Convention Center
## Cardiac Function: Basic Cellular and Molecular Studies

Reversible Cardiac Depression Caused by The Supernatant of Lymphocytes Cultured with Interleukin-2.

P. A. Sobotka, J. McMannis, R. I. Fisher, S. W. Orlow, J. X. Thomas, Jr. Loyola Univ. Medical Center, Maywood, IL

Lymphocytes in acute cardiac allograft rejection and acute myocarditis have been suggested to participate in the heart failure seen in these conditions. Also cancer immunotherapy protocols including recombinant interleukin-2 (rIL-2), a potent activator of lymphocytes has been associated with severe cardiovascular depression. To investigate the relationship between lymphocytes, rIL-2 and cardiac function we evaluated the direct effect of rIL-2, and the supernatant from either cultured lymphocytes (LYM) or lymphocytes cultured with rIL-2 (Lymphocyte Activated Killer Cells; LAK) on cardiac output in the isolated, perfused working rat heart. The cardiac outputs (ml/min/gm wet wt) as measured after 60 min with perfusion with rIL-2 (n=11), LYM (n=8), and LAK (n=9) were (mean ± SEM):

| | 0 min | 20 min | 40 min | 60 min |
|---|---|---|---|---|
| rIL-2 | 70±3 | 66±4 | 64±4 | 62±4 |
| LYM | 70±4 | 70±4 | 68±3 | 65±3 |
| LAK | 62±2 | 42±2†‡ | 35±3†‡ | 29±3†‡ |

† p<0.001 with 0 min; ‡ p<0.001 with rIL-2 & LYM

Another group (n=6) perfused with LAK for 20 min followed by washout, indicated that LAK induced myocardial depression was reversible. The depression was not associated with a decrease in coronary flow. Thus, LAK produced soluble factor(s) that caused a reversible depression of cardiac function. The depression of cardiac function seen in acute allograft rejection or myocarditis could conceivably be a consequence of a soluble product(s) of lymphocytes. Similarly, immunotherapy with rIL-2/LAK can be associated with a direct depression of myocardial performance due to this product.

PRELIMINARY BIOCHEMICAL CHARACTERIZATION OF THE CANINE CARDIAC SODIUM CHANNEL.

Sidney A. Cohen, MD, PhD and Robert L. Barchi, MD, PhD, Hospital of the University of Pennsylvania, Phila., PA.

Electrophysiologic studies have indicated that two subtypes of sodium channel exist in the heart, a toxin insensitive form responsible for the upstroke of the action potential and a toxin sensitive form which may contribute to action potential duration. In these studies, tritiated saxitoxin ($^3$H-STX) was used in binding studies to identify the two subtypes in dog heart ventricular membranes. Under conditions of 100 mM choline chloride, 50 mM $KHPO_4$, and pH 7.4 at 0°C., $K_d$'s of 11.5 and 1.0 and $B_{max}$'s of 151 and 45 fmoles/mg were obtained for the toxin insensitive and toxin sensitive forms, respectively. These values were confirmed by kinetic determination of on and off rates. Unlabeled STX and tetrodotoxin were equally able to displace $^3$H-STX from both channel subtypes. Channel protein could be solubilized by several non-ionic detergents (including Tween-20 and Nonidet P-40) in a form which maintained toxin binding ability. The channel was demonstrated to be an anionic glycoprotein as evidenced by specific binding to lectin affinity and ion exchange columns. Further biochemical manipulation caused the loss of toxin binding ability; therefore, alternate probes for the solubilized channel were sought. Several anti-skeletal muscle monoclonal antibodies and eel-sequence specific polyclonal antibodies were able to identify partially purified channel protein in dot-blot assays. Iodinated Tityus gamma toxin also bound to the channel protein in binding assays. Conclusions: 1, Two subtypes of cardiac sodium channels have been identified in binding assays using $^3$H-STX; 2, canine ventricular muscle sodium channels share biochemical and biophysical characteristics with sodium channels in other tissues.

ALTERATIONS IN COLLAGEN CROSS-LINKING IMPAIR MYOCARDIAL CONTRACTILITY IN VITRO OF THE *Movbr* MOUSE HEART

Joseph M. Capasso Ph.D., Emily Puntillo, Giorgio Olivetti M.D., Giancarlo Guideri Ph.D., Piero Anversa M.D. New York Medical College, Valhalla, NY

A number of genetic disorders in humans are associated with defects in the synthesis and metabolism of collagen which are accompanied by multiple cardiovascular disease processes. To determine whether genetically determined cross-linking abnormalities of collagen may alter cardiac function, left ventricular papillary muscles of *Movbr* mice were studied in vitro. With respect to controls (N: NIH[S]), increases in time to peak tension, from 102 ± 1.4 to 125 ± 5.4 ms ($p<0.001$), and time to one half relaxation, from 76 ± 5 to 98 ± 9 ms ($p<0.05$) were measured. Moreover, resting tension was elevated, from 11.1 ± 1.7 to 19.3 ± 1.1 mN/mm2 ($p<0.001$), while developed tension, peak rate of tension rise and decay, and time to peak rate of tension rise and fall remained substantially constant. Alterations of the isotonic phase of contraction consisted of a decrease in the magnitude of peak shortening, from 4 ± 0.5 to 2 ± 0.2 % ($p<0.04$), and a reduced muscle length at which peak isotonic shortening occurred, from 1.8 ± 0.2 to 1.0 ± 0.1 % ($p<0.02$). In conclusion, the inability to cross-link collagen increases muscle stiffness and alters cardiac mechanics in a manner similar to that found in pressure overload hypertrophy.

A MODEL FOR CONGESTIVE HEART FAILURE: SELENIUM AND VITAMIN E DEFICIENT MINI PIGS

Karl H. Konz MD, Michael Haap SRA, Kristina E. Hill PHD, Raymond F. Burk MD, Richard A. Walsh MD*, Dept. of Med., V U, Nashville, TN 37232 and *UTHSC, San Antonio TX 78284.

Selenium deficiency has been thought to cause Keshan disease. Glutathione peroxidase (GSH-Px) a selenoenzyme, detoxifies peroxides. Vitamin E is known to prevent lipid peroxidation. The effect of these nutrients was studied using doubly-deficient (OSE OE) and control pigs. OSe OE pigs were devided into those that died and those that survived. Biplane cineangiography and high fidelity micromanometery were done. At necropsy, tissue samples were taken for GSH-Px and total glutathione (GSH).Heart rate LV pressure, and $dp/dt_{max}$ were similar in all groups. LV diastolic function however was diminished as shown by impaired relaxation (Tau as time constant of isovolumic relaxation $P=P_0 \cdot e^{-t/\tau}$) and substantial elevation of LV end-diastolic pressure in OSe OE animals that died. LV mass was increased 20% in OSe OE. Relative organ weihts (organ/bw) indicate left and right sided heart failure. Heart GSH-Px activity was 30% of control (5.3±3.8 vs 18.1±9.6 U/g)*. GSH was not affected.

| | LVEDP (mm Hg) | Tau (ms) | LV/bw | Lung/bw (g/kg) | Liver/bw |
|---|---|---|---|---|---|
| OSe OE (died,n=13) | 36±29 | 74±28 | 3.3±.2 | 19.7±9.7 | 45±5 |
| OSe OE (survived,n=7) | 16±7* | 43±10* | 3.2±.3 | 11.3±3* | 33±6* |
| Control (n=6) | 14±6* | 49±18* | 2.7±.8* | 10.5±2* | 35±13* |

*p<0.05 OSE OE (died) vs control or OSe OE (surv.)

We conclude that OSe OE mini pigs develop LV hypertrophy, impaired LV diastolic function and biventricular congestive heart failure.

## Wednesday, March 22, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 2:00PM–3:00PM
## Pacific Room, Anaheim Convention Center
## Coronary Angioplasty Technique II

THE EFFECT OF LARGER BALLOON SIZE ON RECURRENCE AFTER REPEAT CORONARY ANGIOPLASTY DUE TO RESTENOSIS.

Brian Lew, M.D., Morton Kern, M.D., F.A.C.C., Ubeydullah Deligonul, M.D., Michel Vandormael, M.D., F.A.C.C., St. Louis University Hospital, St. Louis, MO.

The use of a larger balloon during repeat percutaneous transluminal coronary angioplasty(PTCA) for restenosis is controversial. To assess whether a larger balloon during repeat PTCA influences recurrence, a retrospective analysis of 58 single vessel lesions requiring repeat PTCA for restenosis after initial successful PTCA was performed. Recurrence was determined by restenosis on repeat angiograms defined as >=50% average diameter stenosis at the previous dilatation site (8 restenosis out of 10) and/or recurrence of severe anginal symptoms within 6 months after repeat PTCA. Angiographic balloon and artery diameters were measured by digital calipers. Analysis was performed according to whether the measured balloon size used during the repeat PTCA was (B1) or was not (B0) 0.5mm greater than that used during the initial PTCA. There was no significant differences between the groups with respect to sex, tobacco use, hypercholesterolemia, or diabetes. Values listed are for the second PTCA, mean (S.D.). (VES = Vessel, BAL = Balloon).

| | N | % Stenosis pre | % Stenosis post | VES SIZE | BAL SIZE | Percent Recurrence at 6 months |
|---|---|---|---|---|---|---|
| B0 | 40 | 83 (13) | 21 (11) | 3.0 (0.3) | 2.9 (0.4) | 28 P=NS |
| B1 | 18 | 78 (11) | 25 (16) | 3.2 (0.6) | 3.3 (0.3) | 33 |

It is therefore concluded that use of a larger balloon for repeat PTCA for restenosis does not influence recurrence.

## Wednesday, March 22, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 3:00PM–4:00PM
## Pacific Room, Anaheim Convention Center
## Echo Doppler: General V

### EVALUATION OF VENTRICULAR SEPTAL DEFECT COMPLICATING ACUTE MYOCARDIAL INFARCTION: IDENTIFICATION, LOCALIZATION AND DIFFERENTIATION FROM MITRAL REGURGITATION BY COLOR DOPPLER FLOW IMAGING

Michael R Harrison, MD, FACC, Edward A Harlamert, MD, John C Gurley, MD, Blair MacPhail, MD, Mikel D Smith, MD, FACC, Anthony N DeMaria, MD, FACC. University of Kentucky Medical Center, Lexington, Kentucky.

Although color Doppler flow imaging (CFI) has been demonstrated to be useful in assessing congenital ventricular septal defects (VSD), few data exist regarding the accuracy of CFI in evaluating VSD's complicating acute myocardial infarction (MI). Similarly, the ability of CFI to differentiate VSD from acute mitral regurgitation (MR) is uknown. Thus, we analyzed the results of CFI, cardiac catheterization and surgery in 15 patients (mean age 71.6) with MI referred for evaluation of hemodynamic instability associated with a new systolic murmur. CFI was performed using standard echocardiographic windows and VSD was identified as systolic turbulence traversing the interventricular septum. For purposes of VSD localization, the interventricular septum was divided into anterior, posterior, and apical regions. Results: CFI correctly identified 8 of 8 ventriculoseptal defects. The remaining 7 patients had acute MR as demonstrated by large areas of turbulent systolic flow in the left atrium by both CFI and cineventriculography. CFI located the VSD as anterior (3), posterior (3), or apical (2), and was 100% concordant for location compared to cine and surgery. In this series, CFI was accurate in identifying the presence and location of acute VSD complicating MI, and accurately differentiated VSD from MR. CFI provides easy, safe and rapid diagnosis of acute VSD complicating MI, and may alleviate the need for preoperative cineventriculography.

### ARE DOPPLER INDICES OF DIASTOLIC FILLING AFFECTED BY LEFT VENTRICULAR HYPERTROPHY?

John W. Cooper, Mahmoud M. Awad M.D., Vinod K. Shah M.D., Hirday K. Chopra, M.D., Dinyar Daruwala M.D., Navin C. Nanda M.D. F.A.C.C., Albert Oberman M.D., Neal Zimbaldi, University of Alabama at Birmingham, AL.

Doppler studies were performed on 373 mildly hypertensive (HTN) Pts (diastolic blood pressure (BP) 90-100 mmHg, $\overline{age}$=54). The ratio of atrial systolic velocity (A), to mitral inflow velocity (E), ratio of time-velocity integrals, and A velocity correlated well with age (in quintiles) and fairly well with baseline systolic and BP (r=.74,r=.71). A velocity increased by 3.8 cm/sec/quintile (r= .97, p<.05) and A/E by 8.2%/quintile (r=.94, p<0.5). In the two oldest quintiles (50-65 yr), A>E in 69% of subjects, while A>E frequency in the remaining quintiles was 28%. Of 26 Pts with heart rates (HR) ≥ 90, 24 (92.4%) showed increased A and A/E, and decreased E-F slope (r=.99, p=<.01). In subjects with A>E (43%), E velocity varied inversely with LV mass septile (-2.5 cm/sec/septile, r=.91, p<.05). This was not seen in subjects with E>A. No significant differences were seen with sex, race, or previous medication. Calculated LV mass (M) by echo in septiles ($\overline{LVM}$=222±58 gm), and LVM corrected for body surface area, height, weight, and LV cavity volume did not correlate with any Doppler parameter (range r=.09-.46). A separate group of 25 Pts with hypertrophic cardiomyopathy (HCM) ($\overline{age}$=52, $\overline{LVM}$=390±157gm) was studied similarly, and showed poor correlation of LVM with Doppler indices (range r=.04-.43). Our study suggests that unlike age, BP, and HR, calculated LV mass in Pts with mild HTN or HCM has no relation to Doppler diastolic filling parameters.

### PULSED DOPPLER ECHOCARDIOGRAPHIC MITRAL VALVE FLOW PATTERNS AND LEFT VENTRICULAR CHAMBER PROPERTIES IN PATIENTS WITH PREVIOUS MYOCARDIAL INFARCTION

Shinji Miki M.D., Tomoyuki Murakami M.D., Tomoyuki Iwase M.D., Yukizono Suzuki M.D., Chuichi Kawai M.D.,F.A.C.C. Kyoto University Hospital, Kyoto, Japan

Using pulsed Doppler echocardiography and frame-by-frame biplane cineangiocardiography with simultaneous micromamonetry, left ventricular(LV) filling patterns were assessed in 25 patients(pts) with previous myocardial infarction(MI): 5 with normal ejection fraction(EF≥55%) and end-diastolic pressure(EDP≤14 mmHg)(MI1); 10 with an EF <55% and EDP≤14 mmHg(MI2); and 10 with an EF <55% and EDP>14mmHg(MI3). Peak E and A waves(E,A;cm/s), the ratio of A to E wave(A/E), end-systolic volume (ESV; $ml/m^2$), the time constant of LVP decay(T;ms), mitral valve opening pressure(MVOP;mmHg) defined as the LVP at the beginning of E wave, and the constant of LV chamber stiffness(b;$1/ml/m^2$) from $P = ae^{bV}+C$ were determined. (*;p<0.05 vs MI1, #;p<0.05 vs MI2 ;ANOVA)

| | EF | EDP | ESV | T | MVOP | b | E | A | A/E |
|---|---|---|---|---|---|---|---|---|---|
| MI1 | 59 | 12 | 43 | 56 | 12 | .045 | 41 | 49 | 1.27 |
| MI2 | 45* | 11 | 76* | 63 | 13 | .048 | 35 | 52 | 1.50 |
| MI3 | 42* | 21*# | 78* | 78* | 21*# | .085* | 54*# | 47 | 0.89# |

The A/E ratio of ≤1 was observed in 1/5, 0/10 and 7/10 pts in the MI1,MI2 and MI3 groups, respectively.

**CONCLUSIONS:** Decreased E wave along with increased A/E ratio indicates an impairment of early diastolic filling in pts with MI and normal EDP (compliant LV). In contrast, elevated atrial driving P (MVOP↑) may increase E wave and reduce A/E ratio in pts with MI and high EDP(reduced LV compliance). Thus, in pts with prior MI, Doppler echocardiographic A/E ratio of ≤1 is a sensitive indicator of reduced LV compliance (EDP↑) associated with depressed systolic function (EF↓).

### ACCURACY OF MODIFIED PRESSURE-HALF-TIME METHOD FOR EVALUATION OF STENOTIC MITRAL VALVE AREA

Rainer Jacksch M.D.,Beate Einsele,Wolfram Völker M.D., Karl-R. Karsch M.D.,Ludger Seipel M.D., Department of Cardiology, University of Tübingen, West-Germany

In previous studies the Doppler velocity profile of mitral stenosis was defined as a linear curve during diastole. The problems to quantify an exponential curve of the velocity profile has yet not been addressed, although in a considerable number of patients with mitral stenosis this downslope appeared non linear. Aim of this study was to investigate the frequency of an exponential slope and to develope a method for quantification. In 23 of 60 patients with isolated mitral valve stenosis the CW-Dopplerspectrum was characterized by an exponential slope. The quantitative analysis of this downslope was performed according to 3 different methods. A sufficient correlation between the pressure-half-time method (PHT) and mitral valve area (MVA) evaluated by 2-dimensional echocardiography (2d) and Gorlin-method (Go) was found when using the PHT after definition of a meso-to enddiastolic tangent ($PHT_{ED}$). The best correlation was found by quantitative analysis of the slope using an exponential function (PHTe). These both methods were superior to a two point (2P) method (early to enddiastolic linear slope).

$MVA(PHT_{2P}) = 0,65 \cdot MVA_{2d} + 0,48$ ; r=0,70, p<0,001
$MVA(PHT_{ED}) = 0,83 \cdot MVA_{2d} + 0,21$ ; r=0,87, p<0,001
$MVA(PHTe) = 1,2 \cdot MVA_{2d} + 0,01$ ; r=0,92, p<0,001
$MVA(PHTe) = 1,41 \cdot MVA_{Go} + 0,09$ ; r=0,84, p<0,001

The invasive and noninvasive study was performed simultaneously. Conclusion: In 30% of pat. with mitral stenosis CW-Dopplerspectrum shows an exponential slope. In these patients the MVA can be determined with high accuracy by a quantitative analysis of the exponential slope.

VALUE AND LIMITATIONS OF TRANSESOPHAGEAL COLOR DOPPLER ECHOCARDIOGRAPHY FOR THE RECOGNITION OF TRANSVALVULAR REGURGITATION IN THE NORMALLY FUNCTIONING ST. JUDE VALVE
Helmut W. Lange MD, Jeanne Olson RDMS, Maureen Kane MD, James A. Daniel MD, FACC, Irvin F. Goldenberg MD, FACC. Minneapolis Heart Institute, Minneapolis, MN
The distinction between normal transvalvular and abnormal paravalvular regurgitation (regurg) in the bileaflet St. Jude valve by transthoracic color Doppler echocardiography (TTE) is difficult. To assess whether transesophageal echocardiography (TEE) offers greater accuracy in imaging transvalvular regurg, we studied 30 St. Jude valves (15 aortic valves [AV], 15 mitral valves [MV]) in 28 pts without clinical evidence of valvular dysfunction. Results: Among 15 pts with AV prosthesis, TTE identified aortic regurgitation (AR) in 11 pts (73%). By TEE, AR was present in all 15 pts (100%). The total number of AR jets was 15 by TTE and 25 by TEE ($p < .05$). A transvalvular jet origin was seen in only 3 of 15 AR jets (20%) by TTE, and 4 of 25 jets (16%) by TEE. Among 15 pts with MV prosthesis, TTE identified mitral regurg (MR) in 3 pts, of whom all had only 1 jet. By TEE, MR was present in all 15 pts (total number of jets = 52). By TTE, the origin of the 3 MR jets could not be seen. By contrast, in 48 of 52 MR jets (92%) by TEE, the jet origin was clearly identified as being the central orifice (27 jets) or the side orifice (21 jets). TEE M-mode color Doppler identified all 4 MR jets of undetermined origin as transvalvular by showing early systolic closure back flow and holosystolic leakage back flow. Conclusions: TEE identifies transvalvular AR with higher sensitivity than TTE. However, due to the perpendicular imaging angle of TEE, both techniques have similar limitations in localizing the origin of AR jets. TEE is clearly superior to TTE in identifying the presence and jet origin of transvalvular MR.

ATTENUATION OF EARLY MITRAL FLOW VELOCITY BY ACUTE AORTIC INSUFFICIENCY.
Peter S. Rahko, M.D., F.A.C.C., Larry F. Whitesell, B.S., Stephen H. Nellis, Ph.D., University of Wisconsin, Madison, WI.
The purpose of this study was to evaluate changes in mitral flow patterns produced by graded levels of acute aortic insufficiency (AI). In 13, open-chested, mongrel dogs who were continuously paced from the RA, acute AI was created at graded levels of severity with a basket catheter. Measurements made were: LV end diastolic pressure (LVEDP) and mean LA pressure (LAP) by micromanometer catheters; aortic valve stroke volume (AVSV), regurgitant volume (RV) and regurgitant fraction (RV/AVSV) by aortic flow probe; peak early mitral flow velocity (E), peak atrial flow velocity (A), E/A ratio, early (EVI) and atrial (AVI) velocity integrals and the early filling fraction (EFF) EVI/(EVI + AVI) by pulsed Doppler. Results: (mean ± standard error, *=p <0.05 by analysis of variance)

| RV/AVSV | 0% | 1-20% | 21-40% | 40% |
|---|---|---|---|---|
| n | 13 | 9 | 9 | 8 |
| *E (cm/s) | 39±3 | 32±2 | 33±3 | 27±2 |
| A (cm/s) | 31±2 | 30±1 | 28±3 | 31±2 |
| *E/A | 1.3±0.1 | 1.1±0.1 | 1.3±0.2 | 0.9±0.1 |
| EFF (%) | 66±2 | 68±2 | 65±4 | 56±5 |
| *RV (ml) | 0 | 13±3 | 25±4 | 32±11 |
| LVEDP (mm Hg) | 4±1 | 7±1 | 7±1 | 6±1 |
| LAP (mm Hg) | 10±1 | 10±1 | 11±2 | 14±1 |

Conclusions: In normal dogs, acute progressive levels of AI attenuates peak early mitral flow velocity but does not change peak atrial filling velocity. This causes a significant decline in E/A but not EFF. These changes are not due to changes in filling pressures but are probably a consequence of progressively greater competitive filling of the LV by AI.

LOAD DEPENDENCE OF REDUCED EARLY DIASTOLIC FILLING IN LEFT VENTRICULAR HYPERTROPHY.
Thomas R. Downes, MD, Abdel-Mohsen Nomeir, MD, William C. Little, MD, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC.
Patients with left ventricular hypertrophy (LVH) frequently have Doppler evidence of decreased early diastolic mitral flow thought to indicate diastolic LV dysfunction. We hypothesized that changes in loading conditions might further alter the pattern of early diastolic filling in patients with LVH. Accordingly, we evaluated 9 patients with concentric LVH (LV wall thickness > 12 mm) and decreased early diastolic mitral flow (ratio of peak early (E) to late (A) diastolic flow velocity < 1.1). Doppler mitral flow velocities were measured at rest (supine) and immediately following tilt to the upright and head down positions. Mitral flow velocities were determined prior to a change in heart rate with each maneuver. Early diastolic flow velocity integral ($E_I$) total diastolic flow velocity integral ($T_I$), and the ratio $E_I/T_I$ were also measured.

| | HR | E | A | E/A | $E_I/T_I$ |
|---|---|---|---|---|---|
| Control | 70±11 | 67±18 | 88±18 | 0.76±0.15 | 0.15±.06 |
| Upright | 72±11 | 54±14* | 81±19 | 0.68±0.16* | 0.45±.09* |
| Head Down | 70±13 | 84±24* | 87±23 | 0.98±0.24* | 0.58±.07* |

mean±SD, *=<0.05 vs control

Conclusion: In patients with LVH, upright tilt further decreases early diastolic filling, while head down tilt augments early filling without altering late diastolic filling. Thus, the Doppler pattern of LV diastolic filling in patients with LVH is load dependent. An increase in LV preload may mask Doppler evidence of diastolic dysfunction while diminished preload may result in overestimation of filling abnormalities.

## Wednesday, March 22, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 4:00PM–5:00PM
## Pacific Room, Anaheim Convention Center
## Cardiac Surgery I

TREATMENT OF CARDIAC ALLOGRAFT REJECTION WITH PULSED STEROIDS: A THREE YEAR EXPERIENCE
Leslie W. Miller, M.D., F.A.C.C., Lawrence R. McBride, M.D., D. Glenn Pennington, M.D., St. Louis University, St. Louis, Missouri
Between January, 1985 and December, 1987, 42 pts underwent cardiac transplantation (CTx) and survived > 6 months. Thirty-seven pts were managed with Cyclosporine (CyA), Azathioprine (AZ) and Prednisone (P) alone and 5 received CyA + P alone. Antilymphocyte sera was not given except for refractory rejection (n=4). Pts were biopsied at a predetermined frequency and graded 0-4. Only grade ≥ 2.0 was treated. Rejection treatment consisted of Solumedrol (SOL) (1 gm IV/dX3 d). There were a total of 38 rejections during the 620 months of pt follow-up (0.06/pt month). There were 25 (66%) rejections graded as mild, 10 (26%) moderate and 3 (8%) severe. Seventeen pts (44%) have had no rejection. Twenty-eight (74%) responded to the single course of SOL, 6 (15%) were treated with a second course of SOL within 2 weeks of the initial course for unresolved rejection and 4 (11%) required the use of antilymphoblast globulin (ALG). There were no infections during or within 2 weeks of the rejection therapy with steroids, and only 1 with ALG therapy. Eight of 11 pts with a biopsy rejection grade ≥ 2.5 required either a second course of steroids or ALG for resolution. Most mild rejections can be successfully treated with SOL, but pts with more than mild rejection should be treated with antilymphocyte globulin for optimal control of rejection.

## VENTRICULAR ARRHYTHMIAS FOLLOWING ORTHOTOPIC CARDIAC TRANSPLANTATION: RELATIONSHIP TO ACUTE REJECTION AND SUDDEN DEATH

Randall E. Little MD, G. Neal Kay MD, Robert C. Bourge MD FACC, Vance J. Plumb MD FACC, James K. Kirklin MD FACC, Andrew E. Epstein MD FACC. University of Alabama, Birmingham, AL

The relationship of ventricular arrhythmias (VA) to acute rejection (AR) or sudden death (SD) after cardiac transplantation is unknown. We analyzed telemetry data from 2311 monitored days (November 1981 to July 1987) in 33 cardiac transplants (TX) in 29 consecutive pts to determine if premature ventricular complexes (PVCs), accelerated idioventricular rhythm (AIVR), ventricular tachycardia (VT), VT duration, VT rate, or Lown Class were markers for AR or SD. Hypokalemia and/or catecholamine therapy were exclusion criteria. PVCs were recorded during 359 days in 26 of 33 TX (79%) and were Lown Class I(60%), II(9%), III(2%), and IV(29%). AIVR (25 episodes) occurred in 9 of 33 TX (27%). VT (76 episodes) occurred in 18 of 33 TX (54%) with a mean duration of 6 beats (range 3-41) and a mean rate of 158 beats per minute (range 100-250). The presence of PVCs, AIVR, VT, VT duration, VT rate, and Lown Class did not predict AR (36 episodes in 22 TX) before or after controlling for differences in immunosuppressive therapy (p=NS). 4 pts died suddenly, 2 with no prior VA and 2 with prior VA (monitoring at the time of SD in the latter 2 pts revealed acute sinus bradycardia leading to asystole). Inferences: after orthotopic cardiac transplantation, high grade VA are common, do not predict acute rejection, and are not a marker for sudden death from ventricular arrhythmias.

## IS LUNG TRANSPLANTATION FEASIBLE IN PATIENTS WITH PULMONARY HYPERTENSION ?

Gregory J. Mishkel MD., Chia-Ming Hsieh, G. Alexander Patterson M.D., Joel Cooper M.D., Stephen C. Dunn M.D., Cris Gresser, Jagdish Butany M.D., Richard D. Weisel M.D., Harry Rakowski M.D. Toronto General Hospital, Toronto, Canada.

To assess the role of lung transplantation alone as a treatment for pulmonary hypertension we developed a canine model of chronic reversible RV pressure overload and right heart failure (RHF). PA banding was performed in 23 dogs to produce RHF (156 +- 72 days). Dogs were then randomized to immediate unbanding (UNB, n=11) or maintained (MRHF) in RHF for a further 3 months (n=12). Clinical, hemodynamic, and echo-doppler studies were done at control (C), onset RHF (ORHF), MRHF, and 1 (UNB1) and 4 months (UNB4) post-UNB. Pathology was obtained at ORHF, post-UNB, and in 6 additional controls.

| | C | P<.05 | ORHF | MRHF | UNB1 | UNB4 |
|---|---|---|---|---|---|---|
| RVSP | 24 | * | 93 | 108 | 46 | 40 |
| RVEDA | 5.4 | * | 13.4 | 14.1 | 8.5 | 6.5 |
| %FS | 43 | * | 21 | 24 | 26 | 38 |
| TR(1-4) | 0 | * | 2.6 | 2.5 | 0.2 | 0.1 |
| RV(gm) | 30 | * | 71 | 70 | 55 | 56 |

With onset of RHF there was a marked increase in RV systolic pressure (RVSP), tricuspid regurgitation (TR), RV end-diastolic area (RVEDA), and RV weight (gm), and a decrease in RV fractional shortening area (%FS). No worsening occurred with maintaining RHF. At 4 months post UNB values normalized except for RV weight.

In patients with pulmonary hypertension, removal of pressure overload by lung transplantation alone might lead to dramatic improvements in RV size and function.

## EFFECTS OF CORONARY REVASCULARIZATION ON REGIONAL WALL MOTION: AN INTRAOPERATIVE ECHO STUDY

Harold L. Lazar, M.D., FACC, Jonathan Plehn, M.D., Edgar Schick, M.D., Dusan Dobnick, M.D., Richard J. Shemin, M.D., FACC, Boston University Medical Center, Boston, MA.

Although Coronary Artery Bypass Grafting (CABG) effectively reduces the symptoms of myocardial ischemia, its immediate effect on regional wall motion is not well defined. This intraoperative echo study was undertaken to determine whether CABG improves regional wall motion in areas of preoperative ischemic dysfunction. In 17 patients undergoing CABG, short axis open-chested echocardiograms where obtained 30 minutes prior to and following cardiopulmonary bypass. Quantitative regional wall motion (RWM) was calculated as the % increase in segmental wall thickening during systole where $\leq$ 40% thickening was defined as ischemic dysfunction. Qualitative RWM was evaluated by visual changes in endocardial wall motion using a graded score (0=normal to 4=dyskinesis). In the 136 segments studied, 44 (32%) had evidence of pre-CABG ischemic dysfunction. When post-CABG RWM was analyzed in all 136 segments, there was no significant change in either quantitative RWM (62 $\pm$ 7 pre-CABG vs 58 $\pm$ 6% post-CABG) or qualitative RWM (.19 $\pm$ .06 vs .17 $\pm$ .06). However, in those segments with ischemic dysfunction pre-CABG, there was a significant increase in quantitative RWM post-CABG (24 $\pm$ 2 vs 50 $\pm$ 5% P< .02); while qualitative indices of RWM failed to show any significant improvement (1.3 $\pm$.1 vs 1.05 $\pm$.2). We conclude that CABG results in an immediate improvement in systolic thickening in those segments with pre-existing ischemic dysfunction. These changes can be difficult to detect with visual qualitative methods and are best analyzed by computer derived indices of quantitative regional wall thickening.

## REPAIR OF COMPLEX CONGENITAL HEART DISEASE WITH THE USE OF THE VALVED CONDUIT.

Jeffrey Pearl, M.D., Hillel Laks, M.D., Davis Drinkwater, M.D., Barbara George, M.D., Thomas Santulli, M.D., Roberta Williams, M.D., UCLA Medical Center, Los Angeles, CA.

Repair of complex cardiac lesions has been facilitated by the availability of valved conduits to reestablish right ventricular to pulmonary artery continuity. From 1977 to 1988, 88 patients underwent repair with insertion of a conduit for transposition (TGA) with ventricular septal defect (VSD) in 46, pulmonary atresia (PAtr) with VSD in 22, truncus arteriosus is 16, PAtr with intact ventricular septum in 3, and atrio-ventricular canal with PAtr in one. The mean age was 6.8 years (11 days to 45 years). Dacron porcine valved conduits were used in 37, homografts in 47, and non-valved conduits in 4. There were 10 early deaths overall (11%); 8 received dacron grafts (22%) and 2 received homografts (4%). Among dacron grafts there was one late death (3.7%) in 27 pts. followed for a mean of 4.9 years, and six patients have required reoperation for conduit obstruction. In 40 homograft recipients there was one late death (2.5%). No homografts have required replacement for stenosis during a mean follow-up of 19 months. The use of a valved homograft has been associated with a reduced early mortality and excellent long-term results for repair of complex right heart lesions.

## Wednesday, March 22, 1989
## Poster Displayed: 2:00PM–5:00PM
## Author Present: 2:00PM–3:00PM
## Pacific Room, Anaheim Convention Center
## Cardiac Surgery II

FATAL AND NON FATAL RECURRENCES AFTER ENDOCARDIAL RESECTION: ROLE OF THE UNDERLYING ETIOLOGY

Hans-Joachim Trappe M.D., Helmut Klein M.D., Guenter Frank M.D., Paul Wenzlaff Ph.D., Paul Lichtlen M.D., F.A.C.C., University Hospital Hannover, West Germany

We studied the follow up of 108 patients (pts) who underwent mapping guided surgery (MGS) due to drug refractory sustained monomorphic ventricular tachycardia (VT). There were 97 pts with an old myocardial infarction (MI)(Group G I) and 11 pts with arrhythmogenic right or left ventricular dysplasia (Group G II). Mean follow up was 28±27 months in G I and 35±27 months in G II. Results: There were no significant differences in total mortality (TM), incidence of sudden (SD) or cardiac death (CD) between G I and G II. However, non fatal recurrences (REC) occurred more frequently in G II than in G I (p<.01):

| | G I (97) | G II (11) | p |
|---|---|---|---|
| TM | 29 (30%) | 2 (18%) | ns |
| SD | 7 ( 7%) | 1 ( 9%) | ns |
| CD | 20 (21%) | 1 ( 9%) | ns |
| REC | 7 ( 7%) | 5 (45%) | <.01 |

Conclusions: The risk of fatal (SD) or non fatal REC is rather low in pts with an old MI (7%) after MGS. Although the incidence of non fatal REC is high in pts with non MI (G II), there is a low risk for subsequent sudden cardiac death.

PREDNISONE WITHDRAWAL IN "HIGH RISK" CARDIAC TRANSPLANT RECIPIENTS.

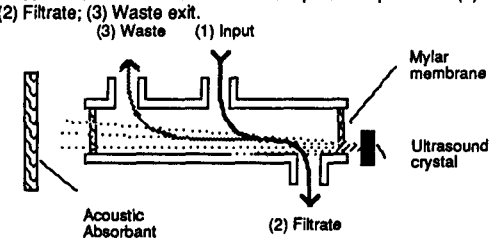
David O. Taylor M.D., James A. Thompson M.D., Sheelah Rider Katz R.N., Barbara McClung RN, Glenn Barnhart M.D., Andrea Hastillo M.D. F.A.C.C., Richard R. Lower M.D., and Michael Hess M.D. F.A.C.C. Medical College of Virginia, Richmond, Virginia 23298.

Prednisone has long been a significant part of immunosuppressive protocols for clinical cardiac transplantation. We have shown transplantation without maintenance steroids is both feasible and safe for many patients. We hypothesized that most patients, including "high risk" ones (those with 3 or more treated rejections requiring maintenance prednisone) could be eventually weaned from prednisone with careful surveillance. Thus we attempted to wean prednisone from 15 "high risk" patients and 12 "low risk" patients (2 or less treated rejections) who required prednisone for reasons other than rejection. Prednisone tapering schedules were dictated by ease of follow up, biopsy results, duration of prednisone usage, and adrenal function as evidenced by ACTH stimulation tests. Eleven of 15 "high risk" patients and five of twelve "low risk" patients were successfully weaned from prednisone, p=ns. Acute rejection occurred during or after prednisone withdrawl in 3 "high risk" patients and 2 "low risk" patients, p=ns. Five of 12 patients weaned in less than 12 months had acute rejection compared to none of the 9 patients weaned over 12 or more months. There were no signficant differences between the 5 patients who acutely rejected and those who did not in terms of cyclosporine doses or levels, serum creatinines, WBC, or number of rejections prior to prednisone tapering. We conclude that 1) predisone can be safely weaned from many patients, including "high risk" and long-term users, but only with frequent surveillance biopsies and close follow up, and 2) longer tapering schedules appear superior in this patient population.

ACOUSTIC FILTRATION OF GAS MICROEMBOLI IN BLOOD.

Karl Q Schwarz, MD, Charles C Church, PhD, Richard S Meltzer, MD, PhD, FACC. University of Rochester, Rochester, NY.

Post-cardiopulmonary bypass encephalopathy is thought to be due in large part to continuous microembolization of the brain with gaseous microbubbles (MBs: size <40 microns) while on pump. Current mechanical filter technology cannot effectively remove MBs below 40 microns in "fragile" fluids such as blood. We developed a non-mechanical ultrasound based fluid filtration system (acoustic filter-AF) capable of filtering small MBs (<40 microns) from fluid using acoustic radiation force. Traveling ultrasonic waves, directed along the length of an acrylic tube, "sweep" the fluid clean as it enters the filtrate exit port. A sheet of mylar seals the tube at both ends, allowing for water-tight integrity and transparent passage of the ultrasound without reflection. Three fluid ports are provided: (1) Fluid entry; (2) Filtrate; (3) Waste exit.




A turbid concentrate of stable albumin MBs in the size range 4-32 microns (suspended in albumin) were used to test the filtration efficiency (FE). 2.5 MHz CW Doppler was used as a bubble detector (CW). Bubbles passing through the CW targeting area produce a characteristic sound and a sharp spike on the visual display. By monitoring the pre- and post- AF CW, an assessment of FE was made. Inactivated, the AF had no effect on the FE (at baseline, or after albumin MB injection). Activated, the AF provided total or near total clearing of the post-AF CW signals. When the albumin MBs were introduced into the pre-AF input line, the pre-AF CW was immediately saturated, whereas the post-AF CW signal remained clear, indicating effective filtration. The effect was the same in water or blood. CONCLUSION: The AF may provide more effective arterial filtration of small gas MBs than currenly available mechanical bypass filters.

SERIAL EVALUATION OF CARDIAC TRANSPLANT FUNCTION: RELATIONSHIP TO DONOR HEART ISCHEMIC TIME, DONOR HEART AGE AND SEVERE REJECTION EPISODES.

Peter S. Rahko, M.D., F.A.C.C., Barry L. Fields, M.D., Herbert A. Berkoff, M.D., David C. Wilson, R.N. University of Wisconsin, Madison, WI.

Using echocardiography, we evaluated serial changes in LV size, mass and systolic function for 28 pts during the first yeart following cardiac transplantation. Parameters measured were: % fractional shortening (%FS); mean velocity of circumferential fiber shortening (mVcf); LV end diastolic dimension (LVEDD) and LV mass (LVM). Results: (mean±standard deviation, p values for analysis of variance).

| Week post Transplant | %FS | mVcf (circ/s) | LVEDD (cm) | LVM (g) |
|---|---|---|---|---|
| 1 | 41±7 | 1.71±0.25 | 4.8±0.5 | 197±30 |
| 4 | 40±6 | 1.62±0.31 | 4.8±0.4 | 207±43 |
| 13 | 38±6 | 1.52±0.23 | 5.0±0.4 | 183±44 |
| 26 | 36±5 | 1.52±0.23 | 4.9±0.5 | 180±42 |
| 52 (n=22) | 35±8 | 1.39±0.31 | 4.9±0.6 | 164±35 |
| p | 0.004 | 0.001 | NS | 0.002 |

Correlations between donor heart ischemic time (mean 154, range 61-257 minutes) and donor age (mean 25, range 15-41 years) were determined. Neither ischemic time nor donor age correlated with %FS, mVcf, LVEDD or LVM. At 52 weeks post transplant, 12 pts had experienced 1 or more grade 3 rejection episodes, 10 pts had none. Comparing those having rejection to those not having rejection there was no significant difference in %FS (36±7 vs 34±9), mVcf (1.47±0.26 vs 1.34±0.34 circ/s), LVEDD (4.8±0.5 vs 5.0±0.6 cm) or LV mass (158±39 vs 169±34 g). Conclusions: There is a mild but significant decline in LV function and LV mass over the first year following cardiac transplantation. This is not related to donor heart ischemic time, age or episodes of severe rejection.

## CARDIAC TRANSPLANTATION FOR PERIPARTUM CARDIOMYOPATHY.

Dan Aravot MD, Asghar Khaghani FRCS, Nicholas Banner MRCP, Melissa Fitzgerald MB, BS, Andrew Mitchell MRCP, Magdi Yacoub FRCS, FACC.
Harefield Hospital, Middlesex, England.

Peripartum cardiomyopathy is a relatively uncommon form of heart failure affecting woman in their last month of pregnancy or the first six months after delivery. The etiology is inknown and could involve different mechaniems when compared to other forms of congestive cardiomyopathy. Since 1983, 6 women aged 21 to 35 years (mean 30) have undergone cardiac transplantation (CTx) for peripartum cardiomyopathy. Possible risk factors included age (4 above 30 years), hypertension associated with pregnancy in 2 of whom 1 also had Raynaud's syndrome and the other had steroid dependant asthma. Presenting symptoms were dyspnoea, lethargy and ankle oedema in all, palpitation in 3, pneumonia in 2 and pulmonary infarct in 2. All delivered normal babies. Two required early induction of labour due to severe cardiac decompensation. The time interval between onset of symptoms and CTx ranged between 2 weeks to 2 years (median-2 months). Four CTx were performed on emergency basis; 1 patient required intra-aortic balloon pumping prior to CTx and 1 was put on emergency cardiopulmonary bypass for 1 hour while awaiting the donor heart. One patient had cytotoxic antibodies and strongly positive lymphocyte cross-match. There were 2 early deaths, 1 from hyperacute rejection and 1 from streptococcal septicaemia 2 and 18 days following CTx. Four pts are currently alive 15 months to 5 years following CTx.
It is concluded that peripartum cardiomyopathy can result in a very rapid deterioration requiring urgent CTx which gives acceptable results. Preformed antibodies resulting in hyperacute rejection can occur.

## THE ROLE OF RADIONUCLIDE ANGIOGRAPHY IN SELECTING PATIENTS FOR CORONARY BYPASS SURGERY

Kerry L Lee, PhD, Karen S Pieper, MS, Frank E Harrell Jr, PhD, Robert M Califf, MD, FACC, Daniel B Mark, MD, Mark A Hlatky, MD, FACC, R Edward Coleman, MD, Frederick R Cobb, MD, David B Pryor, MD, FACC, Robert H Jones, MD, FACC, Duke University Medical Center, Durham, NC

To determine the usefulness of exercise radionuclide angiography (RNA) in selecting patients for coronary artery bypass surgery (SURG), we studied 873 pts with significant coronary artery disease (CAD) (≥75% stenosis who had rest and exercise RNA within three months of cardiac catheterization (Cath). Pts with significant left main disease and severe mitral regurgitation were excluded. 342 pts underwent SURG within 6 months following Cath and RNA, while 531 were medically treated (MED). Median followup was 6 years. To date 87 medical pts and 44 CABG pts have died from cardiovascular causes. At 5 years, Kaplan-Meier survival rates were 93% for SURG and 87% for MED. Using the Cox proportional hazards model, exercise ejection fraction (EF) was the most prognostic RNA variable. It contributed significant independent information ($p<.0001$) in both treatment groups to established clinical and Cath prognostic factors. The relative benefit of surgery did not change ($p>.50$) for different levels of exercise EF, rest EF, or the change from rest to exercise ($\Delta$EF). However, the absolute difference in survival between SURG and MED was greatest in pts with he lowest exercise EF (5 yr. survival 62% MED, 78% SURG where exercise EF <35) and least in pts with high exercise EF (5 yr. survival 95% MED, 97% SURG where exercise EF ≥50)

Exercise EF may be useful in selecting pts for SURG, and defines treatment benefit more clearly than $\Delta$EF.

## CYTOMEGALOVIRUS INFECTION IN CARDIAC TRANSPLANT RECIPIENTS PREDICTS THE INCIDENCE OF ALLOGRAFT ATHEROSCLEROSIS

Ken McDonald, M.R.C.P.I., Thomas Rector, Ph.D., Elizabeth Braunlin, M.D., Maria Teresa Olivari, M.D., University of Minnesota, Minneapolis

Allograft atherosclerosis now represents the major limitation to long term survival after heart transplant (Tx). Its etiology remains obscure. The possible role of viral infection in the genesis of coronary artery disease (C.A.D.) stimulated the review of 102 heart Tx performed since the introduction of triple drug immunosuppression (cyclosporine, azathioprine, corticosteroids) to assess the relevance of post Tx. cytomegalovirus (C.M.V.) infection to C.A.D. C.M.V. infection was defined as a 4-fold increase in immunoglobulin G titre (complement fixation) occurring in association with a positive culture. C.A.D. occurred in 16 Pts. (15.6%) with 11 Pts. having C.A.D. at one year after Tx. Recipient age, sex, pre-Tx diagnosis, frequency of acute rejection episodes, cyclosporine, triglyceride or cholesterol levels did not differ between those with or without C.A.D. Pts. with C.A.D. received hearts from older donors (31±8 yrs. vs. 26±9 yrs.) but this difference did not attain statistical significance ($p = 0.067$). C.M.V. infection, occurring in 62% of Pts. with C.A.D. and in only 25% of those without C.A.D., did independently predict the occurrence of C.A.D. ($p = 0.007$). This data supports the existence of a strong relationship between post Tx C.M.V. infection and allograft atherosclerosis. It is possible that the virus contributes to the initial injury to the coronary endothelium.

## AUGMENTATION OF MYOCARDIAL FUNCTION WITH DYNAMIC CARDIOMYOPLASTY IN A CHRONIC CANINE MODEL.

Mark Soberman M.D., Alexander Justicz M.D., Naomi Alazraki M.D., Garth Austin M.D., Ph.D., John Coleman III M.D., Charles Hatcher, Jr. M.D., F.A.C.C., James Sink M.D., F.A.C.C., Emory University and V.A. Medical Center, Atlanta, Georgia.

This study was undertaken to determine the ability of the latissimus dorsi muscle (LDM) to function as a partial myocardial replacement. In 5 hounds, a full thickness RV cardiomyplasty was successfully performed. A defect was created in the RV and repaired with a right LDM flap sutured over a pericardial patch. A Medtronic Cardiomyostimulator was used to provide stimulation. After training, LDM pacing eventually utilized 30 Hz bursts with each native R-wave. 14 weeks after cardiomyoplasty, ECG, RV pressure and dP/dt were recorded. MUGA ejection fractions (RVEF) were determined in 2 dogs.

| | Unstimulated | Stimulated |
|---|---|---|
| RV | 23.2 ± 0.95 | 25.1 ± 1.5* |
| dP/dt | 225.7 ± 13.0 | 308.9 ± 12.1* |
| RVEF | 51.5 ± 13.5 | 66.5 ± 14.5* |

(RV=RV peak systolic pressure in mm Hg; dP/dt=RV dP/dt in mm Hg/sec; Stimulated 7.5V, 30 Hz, 185msec; * denotes $p\leq0.05$).
These data indicate for the first time that cardiomyoplasty augments ventricular function in a chronic canine model, and suggest that cardiomyoplasty may be a suitable technique for repair of ventricular aneurysm.

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## HIGH FREQUENCY (ULTRASONIC) MECHANICAL DEBRIDEMENT IN THE TREATMENT OF CALCIFIC AORTIC STENOSIS: AN ECHOCARDIOGRAPHIC STUDY

Matthew Schwinger, M.D., Stephen Colvin, M.D., Susan Harty, R.N., Itzhak Kronzon, M.D., F.A.C.C. New York University Medical Center, NY, NY.

Repair of aortic stenosis may lead to hemodynamic and clinical improvement without the problems inherent to prosthetic valves. The use of a high frequency (ultrasonic) device (Cavitron) for the debridement of calcium from the aortic valve is currently undergoing evaluation as an adjunct to standard mechanical debridement. Nine pts ( 5 female, 4 male; ages 63 - 83) were studied by m-mode, two-dimensional, and Doppler echocardiography before and an average of 28 days after this procedure. The degree of calcification of the valve cusps was markedly reduced. The maximal cusp excursion increased from 0.7 ± 0.1 cm. pre-op to 1.5 ± 0.4 cm post-op (p=0.006). The peak aortic gradient fell from 80 ± 39 mmHg to 27 ± 10 mmHg (p=0.002). The mean aortic gradient fell from 52 ± 22 mmHg to 16 ± 5 mmHg (p=0.0001). Aortic valve area calculated by the continuity equation increased from 0.6 ± 0.2 cm2 to 1.4 ± 0.4 cm2 (p=0.0008). The degree of aortic insufficiency detected by color decreased in 1 pt, remained the same in 4 pts and increased in 4 pts.

Conclusion: High frequency mechanical debridement of the aortic valve results in a significant increase in the mobility of the valve cusps with a decrease in the amount of calcium. There is a marked increase of the aortic valve area with a concomitant reduction of the aortic valve gradient. However, aortic insufficiency may worsen after the procedure.

## AN IMPLANTABLE AND EXTRACTABLE SENSOR FOR INTRA AND POSTOPERATIVE MONITORING OF BLOOD FLOW IN MAN.

Raphael S. Rabinovitz Ph.D., Craig J. Hartley Ph.D., Lloyd H. Michael Ph.D., Peggy L. Jackson, Gary L. Liedtke, Gerald W. Parker D.V.M., George P. Noon M.D., F.A.C.C., Baylor College of Medicine, Houston, Texas.

Continuous monitoring of blood flow during and after vascular reconstructive operations can provide immediate information about heart function, vascular patency, and effectiveness of drug administration. To do this, we have developed a miniature implantable 10 or 20 MHz pulsed ultrasonic Doppler blood flow sensor. The sensor is made from silicone rubber and during surgery can be wrapped around a blood vessel and secured in place with a releasable tie. No tissue puncturing techniques are required. The wire leads and a release cable are sheathed in 2mm diameter silicone rubber tubing and are exteriorized through the skin. Two to six days postoperatively when monitoring is no longer needed, the tie is externally released by pulling the release cable, and the sensor is extracted from the closed patient by pulling on the tubing. We have tested 29 sensors on 6 carotid and 13 coronary arteries (2.5-4mm diameter) and 10 ascending aortas (16-25mm diameter) in 16 chronically instrumented dogs for up to 12 days. Each sensor was extracted from the awake dogs with no visible behavioral reaction. Postmortem exams showed that none of the vessels were damaged or thrombosed. *In-vivo* and *in-vitro* calibrations showed high linear correlations (r>0.88) with electromagnetic flowmeters and timed blood collections. Three sensors have been successfully applied to and released from coronary grafts of patients during surgery. The measured flow velocity signals were similar to simultaneous electromagnetic flowmeter tracings. Thus, the new sensor is a promising method for continuous monitoring of blood flow in vessels 2.5-25mm diameter during surgery and the early postoperative period.

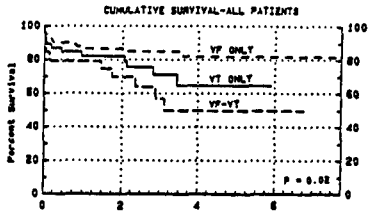
## DIFFERENCES IN SURGICAL OUTCOME FOR VENTRICULAR TACHYCARDIA AND FIBRILLATION.

Jeanne E. Poole, M.D., Melinda L. Marks, M.D., Judy L. Powell, R.N., Charles Maynard, Ph.D., Alexandra P. Kruse, R.N., Gust H. Bardy, M.D., F.A.C.C., Tom D. Ivey, M.D., F.A.C.C., H. Leon Greene, M.D., F.A.C.C., University of Washington, Seattle, Washington.

We evaluated 182 pts with a history of primary ventricular fibrillation (VF), sustained ventricular tachycardia (VT) or both (VT/VF) who underwent cardiac arrhythmia surgery. There were no differences in age, presence of coronary artery disease or remote myocardial infarction among these 3 groups.

| | VF | VT | VT/VF | p |
|---|---|---|---|---|
| Number of Pts | 99 | 45 | 38 | |
| Ejection Fraction | 0.45 | 0.40 | 0.38 | 0.03 |
| >1 Surgical Procedure | 37% | 73% | 53% | <0.01 |
| Operative Mortality | 5% | 13% | 19% | 0.04 |
| VT/VF Recurrence | 14% | 15% | 32% | <0.01 |
| Two year survival | 86% | 82% | 70% | 0.02 |

Conclusions: 1. Operative and long-term mortality is lowest in pts with VF only. 2. VT/VF pts are at greatest risk for recurrent arrhythmia and death. 3. Poor outcome in VT/VF pts may reflect impaired cardiac function and more extensive surgical procedures.




## EVIDENCE OF LATISSIMUS DORSI MUSCLE ADAPTATION BEFORE CARDIOMYOPLASTY.

Frederik van der Veen Ph.D, Miek Havenith M.D., Pierre Grandjean PhD, Caroline Lucas M.D., Willem Dassen Ph.D., Olaf Penn M.D. and Hein Wellens M.D., Department of Cardiology, University of Limburg, Maastricht, The Netherlands.

Continuous electrical stimulation of the latissimus dorsi (LD) muscle to obtain a fatigue resistant skeletal muscle is required for clinical use of cardiomyoplasty. The effect of burst stimulation on both LD muscle enzyme activity and muscle fusion frequency was studied during 3 months of training. In dogs, the left LD was stimulated 24 hours a day with bursts of stimuli (30 Hz) during 0.25 seconds. The time interval between two bursts was decreased every two weeks resulting initially 30 and at the end 80 contractions per minute. Biopsies (n=6) were obtained from the stimulated and contralateral muscle every 4 weeks. Similar to the fiber type change within 2 months from 35% to more than 70% type I fibers, the LDH-isoenzymes changed from predominantly $LDH_5$ to $LDH_1$, $LDH_2$ and $LDH_3$. The increase in total mitochondrial volume was not reflected in changes in ASAT isoenzymes (54 ± 6% m-ASAT after 3 months). Muscle fusion frequency (n=4) was measured in vivo with a force displacement transducer (2 up to 256 Hz). At 10 Hz the ripple decreased gradually from 100% (unstimulated) to 0% (3 months), indicating adaptation to a predominant slow fiber type. The fatigue test (100 contractions/min; 85 Hz) was significantly better tolerated after 8 weeks of training. In conclusion muscle fusion frequency, muscle fatigue-test, and LDH-isoenzyme activity appear to be reliable measures of muscle adaptation.

# Wednesday, March 22, 1989
# Poster Displayed: 2:00PM–5:00PM
# Author Present: 3:00PM–4:00PM
# Pacific Room, Anaheim Convention Center
# Cardiac Pacing and Defibrillation

IMPAIRED ACTIVITY RATE RESPONSIVENESS OF ATRIAL ACTIVITRAX II PACEMAKERS.

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The physiological benefit of rate-response (RR) during single chamber cardiac pacing is well documented. Post-implantation testing is important to ensure adequate activity-mediated RR. We studied the activity response of 7 (3 bipolar) atrially placed Activitrax II pacemakers. Six were noted to have inadequate RR with maximal pacing rates of 85 to 101 bpm, despite maximally sensitive activity settings, and upper rate limit (URL) of 150. Marker channel analysis revealed that the URL was reset by far-field R-wave sensing, even when sensed in the atrial refractory period. These 7, and 2 pacemakers with identical sensing circuits (Pasys) were tested by P-wave sensitivity adjustment for ability to exclude far-R sensing while preserving P-wave sensing. Implantation data were then examined for predictors of differential R and P sensing. Results; differential sensing occurred in 5/9 (4/5 bipolar; 4/9 unipolar). An index of unipolar peak P amplitude x P slew rate divided by peak R amplitude x R slew rate rest indicated future differential P and R sensing. A value of > 8 discriminated outcomes for 8/9 pacemakers ($p<.02$).

Conclusions: 1, The RR of atrial Activitrax II pacemakers is limited by far-field R-wave sensing even during atrial refractoriness; 2, reprogramming atrial sensitivity to differentially sense P and R-waves may restore appropriate RR in some unipolar and many bipolar units; 3, although an implant discriminant index correctly identifies future RR in most cases, the atrial application of the Activitrax II pacemaker is cautioned until further validation is forthcoming.

DIRECT EXCITATION OF RELATIVELY REFRACTORY TISSUE BY MONOPHASIC AND BIPHASIC SHOCKS

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The mechanism for the greater efficacy of biphasic over monophasic defibrillation shocks is unknown, but could be due to differing effects on relatively refractory tissue, which is thought to be present during fibrillation. Using a 117 electrode epicardial recording grid over a 32x30 mm region of RV, we studied the response of partially refractory tissue to 3 ms monophasic and 2-1 ms biphasic shocks in 6 dogs. S1 pacing and S2 shocks were both delivered from electrodes along the same side of the grid to create parallel S1 activation fronts and S2 isogradient lines. The parallel S1 activation sequence resulted in nearly parallel isorefractory lines with refractoriness increasing away from the S1 and S2 electrodes. Premature S2 shocks ranging from 40V to 110V generated potential gradients that progressively decreased with distance away from the S1 and S2 electrodes. At long S1-S2 coupling intervals the S2 shock directly excited (DE) tissue under the grid extending away from the S1 and S2 electrodes. The DE region was always smaller for biphasic than monophasic shocks of equal leading edge voltage and timing. After the shock for both biphasic and monophasic waveforms, conduction propagated away from the border of the DE region at long S1-S2 intervals. At shorter coupling intervals for both biphasic and monophasic shocks, the tissue was more refractory so that the border of the DE region occurred in regions of greater refractoriness nearer the S2 electrode; where the gradient was more than 2.5 to 6 V/cm, conduction block occurred at the border of the DE region. *Conclusions:* For monophasic and biphasic shocks of equal leading edge voltage, duration and coupling interval, similar responses of either conduction or block occur at the DE border of relatively refractory tissue, but the DE region is smaller for biphasic than monophasic shocks. This suggests that additional factors besides excitation are important for defibrillation, such as reinitiation of fibrillation by stimulation of relatively refractory myocardium.

CLINICAL EVALUATION OF AN IMPLANTABLE CARDIOVERTER/ DEFIBRILLATOR WITH NONEPICARDIAL LEADS IN PATIENTS WITH REFRACTORY VENTRICULAR TACHYARRHYTHMIAS.

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We evaluated an implantable cardioverter/defibrillator (CD) with a nonepicardial lead system in pts with refractory ventricular tachycardia/ fibrillation (VT/VF). 7 pts, mean age 67 yrs, mean LV ejection fraction 32%, refractory to 5±2 drugs having prior cardiac surgery (4 pts), severe lung disease (2 pts), and renal failure (1 pt) were studied. A tripolar electrode catheter with 1 sensing electrode and 2 defibrillating electrodes was placed in the RV apex and a submuscular patch (SP) electrode was used in an epicostal location. Defibrillation threshold (DFT) was determined using 2 to 4 dual or triple electrode configurations. Optimal SP location was determined after temporary use of cutaneous R2 patch prior to CD implant. Electrophysiologic studies (EPS) were performed predischarge and after 3 mos.

RESULTS: Percutaneous insertion and placement of the electrode catheter were achieved in all pts. DFT testing was done using 1 to 4 (mean 2.4) electrode configurations and required 6 to 21 (mean 12) VF inductions and 8 to 56 (mean 20) shocks per patient. In all pts, lowest reliable DFT was obtained with a triple electrode configuration and bidirectional shocks (mean DFT = 16±6J). Cutaneous patch "mapping" preceding SP implant could be performed in 6 pts and all 6 pts had CD implant. CD implanted had sensing rates of 142 to 158 bpm, with (4 pts) or without (2 pts) morphology sensing, and initial shock energy of 28 to 32J. VF termination with the first CD shock was documented in all pts. Device charge times ranged from 5.3 to 6.7 and total time to defibrillation was 10.5 to 17.1 sec. There was no mortality in CD implanted pts. Postop EPS predischarge (6 pts) and at 3 mos (2 pts) continued to demonstrate successful defibrillation by first CD shock. During followup (2 to 6 mos) there was no sudden or cardiac death and spontaneous CD discharges occurred in 3 pts. Successful VT/VF termination occurred in 2 pts and 1 pt had a lead fracture with inappropriate shocks requiring lead replacement. Antiarrhythmic drug therapy could be withdrawn in 4 pts and reduced in 2 pts.

CONCLUSIONS: 1) CD can be used clinically with nonepicardial lead systems. 2) Optimal DFT determination requires use of temporary patch electrode mapping and evaluation of bidirectional shocks. 3) DFT with this lead system are acceptable for use with the current CD in most pts. 4) Nonepicardial lead systems should be initially considered for CD implants.

RESPONSE OF RATE-ADAPTIVE PACEMAKERS TO PHYSIOLOGICAL STIMULI OTHER THAN ISOTONIC EXERCISE: COMPARISON OF SIX DIFFERENT SENSORS.

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An ideal rate-adaptive pacemaker is one that responds to all stimuli in a physiological manner. Most comparative studies have evaluated rate response to isotonic exercise We assessed the response of 20 patients with rate-adaptive pacemakers to the following stimuli: head-up tilt from the supine position, isometric exercise (one third maximum hand grip), standardised mental activity test and mild emotional stress. 5 patients had pacemakers using activity as the sensor (3 Activitrax, 2 Sensolog), 5 using minute ventilation (Meta MV), 4 using stimulus-T wave interval (Vitatron 919), 4 using the integral of the paced evoked depolarisation (Prism), one using right ventricular temperature (Nova MR) and one using dP/dT (Deltatrax). No response was seen in the patients with activity-sensing pacemakers to any of the manoeuvres. One patient with a Meta MV had a 10% increase in rate with isometric exercise. All patients with Vitatron 919 pacemakers had an increase in rate (mean 19%±3.4) to all of the manoeuvres. All patients with Prism pacemakers and the patient with the Deltatrax had an increase in rate (mean 15%±2.8 and 19% respectively) to isometric exercise, mental activity and emotional stress but none had any increase in rate in response to tilt.
The patient with the Nova MR showed a 7% increase to isometric exercise and a 6% response to tilt.
Conclusion: Pts with pacemakers using stimulus-T wave measurement were the only group to increase their pacing rate to all the stimuli tested and therefore most closely mimic the physiological response of the normal heart.

RELATIONSHIP OF INTERPULSE SEPARATION AND DEFIBRILLATION EFFICACY FOR BIPHASIC WAVEFORMS.

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Biphasic pulse (B) defibrillation has been shown to be superior to monophasic (M) defibrillation. The optimal P1-P2 separation for B defibrillation over a single pathway has not been defined. Five pentobarbital anesthetized mongrel dogs (19.3 ± 1.3 Kg) underwent placement of 4 cm2 right ventricular catheter electrode (cathode) and an apical subcutaneous patch electrode (13.9 cm2, anode). Variable tilt B pulses with a 5 msec positive phase (P1) and a 5 msec trailing negative phase (P2) were studied at P1-P2 separations of 0, 1, 3, 5, 7, and 10 msec. Capacitance was 150 μF. Leading edge voltages for P1 were 200, 300, 400, 500, and 600 volts and for P2=0.5 x P1. Four trials were conducted at each voltage level for each P1-P2 separation and defibrillation efficacy curves constructed using logistic regression. Energies associated with 80% successful defibrillation (E80) were compared:

| | P1 - P2 SEPARATION | | | | | |
|---|---|---|---|---|---|---|
| | 0 msec | 1 msec | 3 msec | 5 msec | 7 msec | 10 msec |
| E80 | 18.1 J | 17.8 J | 19.7 J | 23.8 J | 23.9 J | 27.1 J |

p<0.01

Conclusion: For a 10 msec biphasic single-capacitor shock delivered over a single pathway, P1-P2 separations of 0-3 msec are superior to P1-P2 separations of 5-10 msec.

VENTRICULAR FIBRILLATION WAVEFORM CHARACTERISTICS ASSOCIATED WITH SUCCESSFUL DEFIBRILLATION USING FIXED LOW ENERGY DC SHOCK

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Low energy DC shocks (DCS) are often observed to successfully defibrillate at one attempt but not at another, even when energy, hardware, and duration of ventricular fibrillation (VF) are kept constant.

Methods: In order to identify factors associated with VF waveform which may determine success or failure, a fixed capacitor discharge (successful at the approximate 50% level) was used in a canine VF model. In addition, patch size and location, energy and duration of VF were kept rigidly constant. VF waveform was digitized at 500 Hz sampling rate and following parameters were examined for each successful (N=46) as well as unsuccessful (N=70) DCS. 1) Instantaneous transmyocardial resistance (TMR), 2) delivered energy , 3) degree of concordance of polarity (COP) of DCS pulse with VF waveform 2 msec prior to DCS (max COP score = 3) and 4) absolute VF waveform voltage (V) 2 msec prior to DCS.

| Results (± SD) | TMR ohms | Energy joules | COP | VFV |
|---|---|---|---|---|
| Successful DCS | 73.4±8.2 | 7.8±6.6 | 2.3±0.5 | 0.4±0.2 |
| Unsuccessful DCS | 72.9±8.4 | 7.9±6.7 | 1.8±0.3 | 0.3±0.1 |
| P value | NS | NS | <.01 | <.01 |

Conclusions: Successful defibrillation appears to be associated with both degree of concordance of VF waveform with DCS pulse as well as absolute VF voltage at time of DCS. TMR and delivered energy are the same for successful and unsuccessful DCS. These findings may explain why a fixed energy DC shock is successful at certain times but not at others.

OPTIMAL CATHETER ELECTRODE DIMENSIONS FOR NON-THORACOTOMY CARDIOVERSION/DEFIBRILLATION LEAD SYSTEMS.

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We evaluated the efficacy of 2 different nonepicardial electrode systems for cardioversion of polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF) in 23 pts, mean age 65±8 yrs, mean LV ejection fraction 35±15%, undergoing electrophysiologic study (EPS). 2 different tripolar transvenous cardioversion-defibrillation electrode catheters (CDC) were used in conjunction with a cutaneous R2 patch electrode (surace area = 50 $cm^2$) on the anterior left thorax. The distal defibrillation electrode was located in the RV apex and the proximal electrode at the SVC/RA junction for both systems. Defibrillation catheter electrode surface area was different for each catheter system (CDC 1- distal = 125 $mm^2$ & proximal = 125 $mm^2$; CDC 2- distal = 400 $mm^2$ & proximal = 800 $mm^2$). Sustained VT or VF was induced at EPS. 1 asynchronous 25J bidirectional shock was delivered using an RV catheter electrode as a common cathode and SVC catheter and cutaneous patch electrodes as dual anodes.

RESULTS: 29 polymorphic VT/VF episodes were analyzed. CDC 1 (11 pts) and CDC 2 (12 pts) were comparable for mean LV ejection fraction (CDC 1- 38%; CDC 2- 34%; p >.4) and concomitant antiarrhythmic drug therapy (CDC 1- 53%; CDC 2- 33%; p >.2).

| | CDC 1 | CDC 2 | p (CDC 1 vs CDC 2) |
|---|---|---|---|
| Polymorphic VT (n=9) | | | |
| Efficacy | 67% | 100% | >.6 |
| VF (n=20) | | | |
| Efficacy | 33% | 91% | <.03 |
| Total (n=29) | | | |
| Efficacy | 47% | 93% | <.03 |

In Group 1, a second 25J bidirectional shock terminated all remaining polymorphic VT episodes but did not defibrillate VF.

CONCLUSIONS: 1) 25J bidirectional shocks can cardiovert polymorphic VT and VF with a triple nonepicardial lead system. 2) Large surface area catheter electrodes are more effective for VF defibrillation for this triple nonepicardial electrode configuration.

SEQUENTIAL PULSE DEFIBRILLATION IN MAN: EFFECTS OF LIDOCAINE AND VERAPAMIL.

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Patients with automatic defibrillators frequently require antiarrhythmic drug therapy or receive acute therapy with the onset of symptoms. Many of these drugs have not been evaluated for their effects on defibrillation. We examined the effects of lidocaine and verapamil on sequential pulse defibrillation in 19 patients during corrective arrhythmia surgery. The minimum energy requirements for ventricular defibrillation before and 5 min after the intravenous administration of 150 mg of lidocaine (n=8) or 10 min after 10 mg of verapamil (n=11) were determined. Patients were studied intraoperatively after routine epicardial mapping. Three mesh coil defibrillating electrodes (Medtronic 6891, 6892) were attached to the epicardium of the right and left ventricles. Each patient was assigned to receive either verapamil or lidocaine. Ventricular fibrillation was induced using AC current and after a minimum of 10 sec of fibrillation the minimum energy for defibrillation was established. The drug was then infused and a 5 or 10 min circulation time was allowed. Lidocaine did not alter the minimum energy for defibrillation (3.0 ± 1.4 J vs 3.0 ± 1.8 J, mean ± SD), despite levels averaging 13.2 ± 1.9 μM/L. However, verapamil significantly increased (3.9 ± 2.2 J vs 6.5 ± 2.9 J) the energy necessary for defibrillation. These data indicate the necessity for determining the efficacy of defibrillation before medication changes are instituted in patients. They also point out the desirability for programmability of delivered energy in automatic devices. Further they indicate the need for caution in the use of verapamil in patients with automatic defibrillators and marginal defibrillation thresholds.

AUTOMATIC IMPLANTABLE CARDIOVERTER DEFIBRILLATOR IMPLANTATION BY A NON-THORACOTOMY APPROACH

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Implantation of the VENTAK AICD implantable cardioverter defibrillator (device) by a non-thoracotomy (NT) approach is desirable. Nine men had defibrillation threshold (DFT) assessment for device implantation. Implant indications were sudden cardiac death (3) and drug refractory ventricular tachycardia (6). Mean ejection fraction was 25±10%. The implanted device comprises an endocardial lead with proximal and distal springs, a subcutaneous patch lead, and pulse generator. DFTs were assessed using different lead configurations. The implanted configurations were: A) distal spring as cathode with proximal spring and patch as anodes; B) proximal and distal springs as cathodes nd patch as anode.

| | Configuration A | Configuration B |
|---|---|---|
| DFTs | ≥10 ≤ 15 joules(2pts) | ≤30 joules(1pt) |
| | >15 ≤ 20 joules (2pts) | >20 ≤ 25 joules(1pt) |
| | ≤10 joules (1pt) | >15 ≤ 20 joules(1pt) |

One system was not implanted due to DFT ≥40J at NT implant and at thoracotomy. Days in hospital post implant were a mean 6±2 days excluding 1 pt (36 days urosepsis). No implant or post operative complications occurred. During pre-discharge device assessment all episodes of induced ventricular fibrillation were terminated with 1-2 shocks.

CONCLUSION: VENTAK AICD implantation using a NT approach shortens post-operative hospital stay, has a low complication rate, and has acceptable DFTs.

PROHORMONE ATRIAL NATRIURETIC PEPTIDES 1-30, 31-67, AND 99-126 INCREASE IN PROPORTION TO RIGHT VENTRICULAR PACING RATE.

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To determine if heart rate influences the release of three new cardiac peptides (amino acids 1-30, 31-67, and 99-126 of the 126 amino acid prohormone of atrial natriuretic factor) their circulating concentrations were measured by radioimmunoassays in 6 dogs before and after pacing. Right atrial blood samples were obtained immediately prior and just after pacing at 100, 125, 150, and 180 beats/min (bpm) and every 30 min for 2 hours post-pacing. At pacing rates of 125 bpm and above, proANFs 1-30, 31-67 and ANF plasma concentrations increased two to threefold from their pre-paced levels of 885±118 pg/ml, 857±118 pg/ml, and 59±3 pg/ml respectively ($p<.002$). Mean atrial pressure decreased significantly with pacing at 150 and 180 bpm while mean systemic blood pressure decreased when paced at 180 bpm. The plasma levels of these three peptides correlated better with heart rate ($r=0.68$; $p<0.001$) than with mean right atrial pressure ($r=0.48$; $p<0.001$). Within 30 min of pacing cessation ANF's concentration returned to its pre-pacing level while proANFs 1-30 and 31-67 remained elevated for 2 hours. Conclusions: 1. All 3 of these peptides hormones are simultaneously released from the heart at heart rates of 125 bpm and above. 2. ProANFs 1-30 and 31-67 remained elevated for at least 2 hours post-pacing which may help explain the prolonged diuresis observed after rapid pacing or tachycardia.

THE EFFECT OF CARDIAC PACING MODE ON THE LONG-TERM DEVELOPMENT OF ATRIAL FIBRILLATION.

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The maintenance of sinus rhythm (SR) is important to ensure optimal cardiac performance and reduce potential for systemic thromboembolism. In patients with cardiac pacemakers, the mode of pacing determines atrioventricular synchrony, and might impact on the future development of atrial fibrillation (AF). To test this hypothesis, we compared the most current rhythm of 110 consecutive patients in the VVI mode, F/U 47.6 months ±34, to that of 110 patients in DDD mode, F/U 40.2 months ±20 (p=NS). All patients were in SR at implant. In the VVI group, 20 patients (18%) developed AF versus 9 (8%) in the DDD group ($p<.05$). In those with sick sinus syndrome (SSS), 15/61 in VVI versus 8/70 in DDD developed AF (p=NS). When these results were pooled and compared to patients with atrioventricular block, AF occurred more frequently in SSS ($p<.02$). Examination of pre-implantation characteristics demonstrated that only paroxysmal atrial tachyarrhythmias (PATA) on electrocardiogram or Holter monitor predicted AF in VVI (16/33, $p<.0001$), but not in DDD mode (4/38, p=NS). There were significant intermodal differences ($p<.002$).

Conclusions: 1, the incidence of AF is significantly higher in those patients with VVI versus DDD pacemakers; 2, the development of AF predominates in SSS; 3, pre-implantation PATA is strongly associated with future AF in the VVI group only, suggesting that DDD pacing, in comparison to VVI, may reduce the incidence of AF in the subgroup with PATA.

EFFECTS OF DIFFERENT PACING MODES ON RIGHT ATRIAL PRESSURE AND ATRIAL NATRIURETIC PEPTIDE IN PATIENTS WITH ATRIOVENTRICULAR BLOCK.

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We examined mean right atrial pressure (RAP) and atrial natriuretic peptide (ANP) in plasma from the femoral artery in 9 patients with high-degree atrioventricular (AV) block prior to pacemaker implantation. Pacing was performed for 10 minute periods in random order with (1)AV pacing to simulate normal sinus rhythm, (2) ventriculoatrial (VA) pacing to simulate spontaneous VA conduction or (3) ventricular (VVI) pacing. Each study period was preceded by 15 minutes of VVI pacing. The stimulation rate was 80 beats/minute during all three pacing modes, and the delay between stimulation of the atria and ventricles was +175 ms and -175 ms during AV and VA pacing, respectively. RAP was recorded and blood samples were drawn just before and at the end of the 10 minute periods of investigation. Differences between ANP (Δ ANP) and RAP (Δ RAP) after the 10 minute pacing period and the end of the preceding VVI period were (mean ± sem):

| | VVI | AV | VA |
|---|---|---|---|
| Δ ANP (pmol/l): | -8.5 ± 3.0* | -57.8 ± 3.9** | +40.3 ± 2.4† |
| Δ RAP (mmHg): | 0.1 ± 0.03* | -2.6 ± 0.1† | +1.5 ± 0.1† |

*- p = ns; ** - p < .002; † - p < .001

The 10 minute period of VVI pacing did not alter RAP or ANP compared to the initial 15 minute period of VVI pacing. During the 10 minutes of the AV pacing period, RAP and ANP *decreased* significantly compared to the preceding VVI stimulation period while the VA pacing period induced an *increase* in both RAP and ANP. The more physiological findings with AV pacing (substantial reduction of ANP and RAP) suggest that this mode offers the most favorable hemodynamic response of the three modes evaluated.

TRIPHASIC WAVEFORMS INCREASE DEFIBRILLATION EFFICACY OVER BIPHASIC WAVEFORMS WITH CATHETER/SUBCUTANEOUS PATCH ELECTRODES

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To determine whether triphasic waveforms (T) improve defibrillation efficacy, compared to biphasic waveforms (B), percent success was determined for bi- and triphasic shocks in a paired study with a total of 232 episodes in 5 dogs (3 acute and 2 chronic) using a right ventricular catheter/subcutaneous patch electrode system. Initial shocks followed 15s fibrillation and backup shocks 30s fibrillation. B had 60% undershoot and T was similar to B but with a third pulse having overshoots of 20-40%. Percent tilt was 50-80%. Dogs with thresholds <600V showed no significant difference in $V_{50}$; however, T decreased curve width making the $V_{90}$ better for T than B. For dogs with threshold >600V, T decreased $V_{50}$ by 70V. B and T pairs delivered at each voltage showed 20 episodes where B only and 38 episodes where T only defibrillated ($p<0.02$). Results were subdivided into high and low voltage groups. For V=300-500, B only episodes=10 and T only=13 (NS); for v=500-700, B only episodes=10 and T only=25 ($p<0.02$). These results suggest that specifically shaped triphasic waveforms increase the probability for success especially when the defibrillation threshold is high.

INCREMENTAL CRITICAL CORONARY STENOSIS CONTRACTS RATHER THAN EXPANDS MYOCARDIAL VASCULAR VOLUME

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Pressure gradient-flow dependent coronary stenosis (PG-FDCS) may abolish vasodilator reserve (VDR). This is thought to be secondary to near maximal dilatation of the distal coronary vasculature (i.e. exhausted reserve). We evaluated the relationship between changes in myocardial vascular volume (V) as a function of decremental changes in coronary blood flow (F) using a previously validated method for determining V. Four dogs were instrumented with carotid to LAD shunts, and in-line flow probes. Myocardial vascular transit times (T) were measured using a multicrystal camera after intrashunt injection of 0.1ml. 99m Technetium-DTPA (3mCi). Mean distal coronary pressure (P) was varied from 90-30 mm Hg by screw clamp yielding flows between 60-2 ml/min. (N=45). Since V=FT, and F and T are measured, V can be determined.

Results: For each animal the inverse of T varied linearly with F (range r=0.96-0.99). As expected, P vs F was linear (range r=0.94-0.97). However, V decreased as a linear function of P (range r= 0.91-0.98). When P was between 30 and 50 mm Hg, the mean value for V decreased by 39±10% of the resting V ($P \leq .05$).

Conclusion: Previously we have shown that a normal 5-fold VDR is associated with a 2- fold increase in V. Contrary to previous beliefs, progressive PG-FDS engenders a linearly dependent reduction in V from resting values and not a "compensatory" increase in V. These findings seriously question the concept that PG-FDCS yields maximal downstream vasodilatation as a result of ischemia.

## Wednesday, March 22, 1989
## 4:00PM–5:00PM, Pacific Room
## Anaheim Convention Center
## Left Ventricular Function—Basic

NORMALIZATION OF CORONARY FLOW RESERVE AFTER SUCCESSFUL ANGIOPLASTY ASSESSED WITH POSITRON EMISSION TOMOGRAPHY AND $H_2{}^{15}O$

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We have previously demonstrated that myocardial blood flow (MBF) and coronary flow reserve (CFR) can be measured quantitatively by positron emission tomography (PET) with $H_2{}^{15}O$. To assess changes in MBF and CFR in absolute terms in patients undergoing percutaneous transluminal coronary angioplasty (PTCA), we characterized MBF at rest and after dipyridamole induced hyperemia (0.14 mg/kg/min for 4 min) in 7 patients before and after angiographically successful PTCA. Minimum luminal area, assessed by quantitative angiography prior to PTCA was 0.8 ± 0.7 $mm^3$ and increased to 3.56 ± 1.16 $mm^3$ after angioplasty ($p < 0.01$). Prior to angioplasty, MBF at rest was not different between regions distal to stenoses (1.54 ± 0.5 ml/g/min) compared with regions supplied by arteries without significant stenoses (1.46 ± 0.42 ml/g/min). In contrast, after dipyridamole, regions distal to stenoses had flow of only 64 ± 15% of normal (1.98 ± 1.05 compared with 3.24 ± 2.07 ml/g/min, $p < 0.025$). After PTCA, hyperemic flow distal to the stenosis site increased to 115 ± 59% of flow in normal regions and averaged 104 ± 23% at a follow-up PET study > 4 months after PTCA (absolute flows after dipyridamole of 3.07 ± 1.05 ml/g/min in regions supplied by the angioplasty vessel compared with 3.04 ± 1.12 ml/g/min in normal regions). Thus, PET and $H_2{}^{15}O$ document noninvasively augmentation of CFR after successful PTCA and should permit objective comparison of therapies designed to augment flow.

IN VIVO MEASUREMENT OF SEGMENTAL ARTERIAL WALL STIFFNESS IN PIGS USING A REAL-TIME ULTRASONIC SECTOR IMAGING CATHETER

David T. Linker, M.D., Erling Johansen, M.S., Stig Sloerdal, M.D., Paul G. Yock, M.D., F.A.C.C., Aage Groenningsaeter, M.S., Hroar Piene, M.D., Ph.D., Bjoern A.J. Angelsen, Dr. Techn., University of Trondheim, Trondheim, Norway

The local elastic properties of the arterial wall influence the complex impedance, and thereby the propagation of the pressure wave and the systolic load on the ventricle. In order to measure these local properties, we used an ultrasound system consisting of a custom, highly flexible, 8 french intra-arterial catheter probe with a 20 MHz transducer, and a custom ultrasound instrument, capable of generating 360 degree sector images in a plane perpendicular to the catheter. Three anesthetized pigs were studies by passing the ultrasound catheter into the aorta through an arteriotomy in the carotid or femoral artery, and a pressure catheter to the same position through a separate arteriotomy. Each measurement consisted of twenty nine frames of digital image data which were collected in real time at 30 frames per second and transferred to a computer for further analysis. Blood pressure was digitized and stored with the corresponding image data. The collected data was analyzed by manually identifying the borders on each frame, and calculating an equivalent radius (ER) from the area, circumferential wall stress (WS) based on pressure and equivalent radius, and wall stiffness (Ep, in dynes/$cm^2$ x $10^6$) based on the slope of the linear regression line of WS as a function of ER. A total of fifteen measurements were performed at different sites in the aorta. The values of Ep ranged from 0.47 to 2.04, with a mean of 0.89±0.49. The graphs of WS versus ER also demonstrated the known hysteresis of the stress-strain relationship of the arterial wall. We conclude that the ultrasonic intra-arterial imaging catheter provides a new method for measuring segmental arterial wall stiffness in vivo.

**TIME-AVERAGED PHOSPHORUS-31 NMR SPECTROSCOPY OF THE METABOLIC RESPONSE TO HEMODYNAMICALLY EQUIVALENT PACING-INDUCED AND FLOW-LIMITED ISCHEMIA IN THE CONSCIOUS DOG.**

D. Douglas Miller,MD, FACC, Mark Canales,MD, Felix Salinas, BS, Danny Escobedo, Richard A. Walsh,MD, FACC.
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To compare the myocardial high-energy phosphate metabolic response to equivalently severe pacing-induced(demand) and flow-limited(supply) ischemia in the conscious dog, serial phosphorus P-31 NMR spectra(NMR-S) were acquired at 2Tesla using an RF surface coil during and after partial coronary occlusion+pacing(220/min.) x5min.[n=5] or bilat. total occlusion x1min.[n=5]. Comparability of demand and supply ischemia was confirmed by continuous on-line record of micromanometer LV dP/dtmax(2124±1132 vs 1978±745mmHg/s), LVEDP(12±13 vs 18±10mmHg) and sonomicrometer-derived ejection fraction[EF](.10±.15 vs .11±.16); all p=NS. Myocardial P-31 NMR-S phosphocreatine(PCr), inorganic P(Pi), β peak adenosine triP(β-ATP) and pH were measured at control, peak ischemia and recovery[*=p<0.05;#=p<0.05 between groups]:

| | PCr/Pi Ratio | | β -ATP | |
|---|---|---|---|---|
| | Demand | Supply | Demand | Supply |
| Control | 2.6±.7 | 2.9±.7 | 12.9±2.2 | 14.3±2.1 |
| Ischemia | 1.7±.4 * | 1.8±.5 * | 13.4±2.1 # | 11.2±1.4 * |
| Recovery 15' | 2.1±.6 * | 2.0±.5 * | 14.2±2.6 | 13.7±1.4 * |
| Recovery 30' | 2.2±.5 | 2.1±.5 | 13.7±1.9 | 15.0±2.6 |

Ischemic myocardial pH(7.06±.14 vs 7.14±.20units;p=NS) and all hemodynamic parameters normalized by 30 min. of recovery, except LVEF which remained depressed in the 'supply' ischemia group(.23±.06 vs .33±.04;p<.05 vs control).

We conclude that: 1)P-31 NMR-S demonstrates significant discordance in the metabolic response to equivalent demand vs supply ischemia, and 2)prolonged depression of global LV function is associated with profound ATP depletion in the conscious dog.

PERCENT WALL THICKENING IS PRELOAD DEPENDENT AT LOW BUT NOT AT HIGH LEVELS OF AFTERLOAD. Joao A. C. Lima, Thomas Aversano, David Kass, W. Lowell Maughan. Johns Hopkins Hospital, Baltimore, Md.

Percent systolic thickening (%ST) is often used as an index of regional myocardial function. Although its dependence on loading conditions is recognized, the precise magnitude of its preload and afterload dependencies, as well as the extent of their interaction have not been well characterized. In order to define %ST preload dependence at different levels of afterload and vice-versa, 6 isolated cross-perfused canine left ventricles were instrumented with sonomicrometers and made to eject into a simulated arterial system. %ST was measured at 4 levels of preload (EDP1 = 1 ± 1, EDP2 = 6 ± 1, EDP3 = 13 ± 2, EDP4 = 25 ± 2 mmHg) for each of 3 levels of afterload resistance (AR = 1.5, 3 and 6 mmHg.sec/ml).

%ST at increasing EDP's for each level of AR

| | EDP1 | EDP2 | EDP3 | EDP4 | ANOVA |
|---|---|---|---|---|---|
| AR (1.5) | 15 ± 3 | 16 ± 4 | 19 ± 4 | 21 ± 4 | < 0.01 |
| AR (3.0) | 13 ± 4 | 13 ± 4 | 14 ± 4 | 15 ± 4 | NS |
| AR (6.0) | 9 ± 4 | 7 ± 4 | 8 ± 4 | 9 ± 3 | NS |
| ANOVA | < 0.001 | < 0.001 | < 0.001 | < 0.001 | |

Repeated measures ANOVA showed that only at the lowest level of AR %ST increased with increasing preload, while at all four preload levels it decreased with increasing AR's. Preload versus afterload interaction was statistically significant by ANOVA (p < 0.02). In conclusion, %ST is altered by preload at low but not at high levels of afterload. This load interdependence may be important in interpreting thickening changes in patients with varying arterial resistance.

REGIONAL DEFORMATION OF THE PERICARDIUM DURING THE CARDIAC CYCLE.

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We hypothesized that contact forces between the pericardium and the heart cause regional variation in pericardial deformation during the cardiac cycle, reflecting changes in volume of the individual chambers. To test this, we measured regional pericardial area (PA) over the right atrium (RA) and ventricle (RV) with orthogonal pairs of sonomicrometers in 6 open-chest dogs. At left ventricular end-diastolic pressure (LVEDP) of 5 mmHg, RV PA paralleled RV volume, i.e., shrinkage during ejection ($S_{ej}$) by 8±8(SD)% and expansion during filling. RA PA was reciprocally related to RV PA, with average expansion during ventricular ejection of 3±4%, thus paralleling RA volume during RV ejection. With volume loading (LVEDP 11 mmHg), RV $S_{ej}$ increased to 14±6%, but RA PA no longer was reciprocal (0±3% change during RV ejection). Elimination of contact forces by cardiac tamponade resulted in both marked attenuation of RV PA changes and synchronization of the RV and RA PA pattern, i.e., both shrank during RV ejection (RV by 3±2%, RA by 1±1%). In 2 additional dogs, measurement of PA over LV and left atrium showed similar results. We conclude that dynamic pericardial contact forces cause regional variation in pericardial deformation which reflects volume changes of the underlying chambers. These findings imply that the influence of the pericardium on filling is more complex than previously recognized, varying both by chamber and dynamically over the course of the cardiac cycle.

**DOES ACUTE PHARMACOLOGIC STIMULATION OF STUNNED MYOCARDIUM HAVE CHRONIC DELETERIOUS EFFECTS?**

Karin Przyklenk PhD, Sharon L. Hale BS, and Robert A. Kloner MD PhD FACC, Harper Hospital/Wayne State University, Detroit MI & Hospital of the Good Samaritan, Los Angeles CA.

Pharmacologic agents can 'force' stunned myocardium to contract, but this acute inotropic recruitment may have deleterious effects on adenosine triphosphate (ATP) stores and later recovery of contractile function. To study this issue, 12 dogs underwent 15 min of coronary occlusion (CO) and 30 hours of reperfusion (R). At 30 min postR (i.e. when stunned), 6 dogs were randomized to receive a bolus of hydralazine (0.57 mg/kg), while 6 received saline. % Wall thickening (WT) in the center of the ischemic region and % change in LV cavity area (%ΔA) were measured from short axis 2-D echocardiograms obtained at frequent intervals throughout the protocol:

| | | During | Stunned: | Posttreat: | |
|---|---|---|---|---|---|
| | PreCO | CO: | 25'postR | 2 h | 30 h |
| %WT: Saline | 33±4% | -1±4% | 1±5% | 7±7% | 15±11% |
| %WT: Hydralazine | 40±5% | -8±3% | 6±5% | 54±7%** | 7±5% |
| %ΔA: Saline | 41±6% | 26±5% | 35±6% | 36±4% | 41±7% |
| %ΔA: Hydralazine | 48±3% | 19±5% | 34±4% | 71±3%** | 44±2% |

In addition, myocardial biopsies were obtained at 2 hours and 30 hours posttreatment. Mean ATP content in the previously ischemic epicardium (expressed as a % of nonischemic values) was:

| | | |
|---|---|---|
| ATP: Saline | 93±6% | 83±1% |
| ATP: Hydralazine | 78±4%* | 85±6% |

Hydralazine acutely enhanced contractile function (**p<0.001 vs. saline) and reduced epicardial ATP levels (*p<0.05 vs. saline) at 2 hours posttreat. However, by 30 hours posttreat, %WT, %ΔA and epicardial ATP values did not differ between the hydralazine-treated and saline control groups. Thus, acute inotropic stimulation of stunned myocardium with hydralazine did not impair later recovery of contractile function or ATP stores in this canine model.

CARDIAC RESUSCITATION BY EXTRACORPOREAL PUMP OXYGENATOR (ECPO) AFTER FAILURE OF PRECORDIAL COMPRESSION.

Raul J. Gazmuri M.D., Max Harry Weil M.D. Ph.D., Martin von Planta M.D., Joe Bisera MSEE, Sandra Erickson RN, Eric C. Rackow M.D., Division of Cardiology, UHS/The Chicago Medical School, North Chicago, Illinois.

After cardiac arrest, cardiac resuscitability is contingent on prompt restoration of effective myocardial perfusion. We investigated ECPO, utilizing jugular vein and femoral artery access for rapid restoration of coronary blood flow. Ventricular fibrillation was electrically induced in 26 pigs with the aid of an electrode catheter impinged on the endocardium of the right ventricle. After 10 minutes, two maximal DC countershocks failed to restore viable rhythm. After an additional 5 min of precordial compression, ventricular fibrillations unresponsive to countershock (n=13) or electromechanical dissociation (n=13) were observed. Of 5 control animals (sham ECPO), continued precordial compression and maximal doses of epinephrine failed to increase coronary perfusion pressure to more than 12 mmHg and none of these animals were resuscitated. ECPO, however, increased coronary perfusion pressure to 22 mm Hg or greater in each instance. This exceeds the threshold value previously identified as predictive of successful resuscitation. ECPO restored spontaneous circulation in 19/21 pigs and 12/21 animals survived for 24 hours or more. With concurrent administration of epinephrine (3ug/kg/min) in the last 13 animals, all maintained spontaneous circulation after only 17 $\pm$ 13 min of ECPO. Of 4 animals observed for $\geq$ 48 hr, 3 were fully responsive and fed themselves. ECPO is therefore a strikingly effective intervention after 15 min of "clinical death" and failure of conventional CPR.

## Wednesday, March 22, 1989
## 2:00PM–3:00PM, Pacific Room
## Anaheim Convention Center
## Outcome of Coronary Angioplasty

Histopathologic phenomena at the site of percutaneous transluminal coronary angioplasty. Michael B. Gravanis, M.D., Gary S. Roubin, M.D., PhD., Atlanta, Georgia.

Eighteen post-angioplasty cases were morphologically studied at postmortem. Eight out of nine early cases (few hours post-PTCA) exhibited intimal disruptions, which with the exception of two were superficial and of limited extent. All intimal cracks, in eccentric plaques, occurred at the junction of the atheromatous plaque with the atheroma-free segment of the arterial wall. All early cases showed an aneurysmal dilatation of the plaque-free segment of the arterial wall, in eccentric plaques. This was interpreted as the result of uneven distribution of the dilating force (circumferential stress) on the arterial wall, apparently contributing in the primary success of this procedure. Late cases (survival over one month post-PTCA) revealed characteristic medial and intimal lesions of the atheroma-free segment of the wall indicative of dilatation injury. Those lesions (media destruction with myofibroblastic replacement and intimal thickening) were present regardless of the degree of luminal stenosis. It is hypothesized that intrinsic arterial wall changes (media disruption) at the plaque-free segment and the resulting altered arterial geometry have significant effect on the vascular conduit and may enhance and sustain the myoproliferative intimal response resulting in restenosis.

INSIGNIFICANCE OF "LOAD DEPENDENCE" ON LEFT VENTRICULAR RELAXATION AND FILLING.

Srdjan Nikolic M.S., Steven Solomon B.S., Guangfu Gong M.D., Robert W.M. Frater M.D., F.A.C.C., Edward L. Yellin Ph.D.
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To investigate the effects of systolic loading on LV relaxation and filling, we instrumented six anesthetized dogs to measure LVP, LAP, mitral (Mi) and aortic (Ao) flows. A computer driven mitral valve occluder and aortic clamp accurately controlled the timing of aortic and mitral occlusions (AoOc, MiOc) during a single cycle. We performed perturbations of outflow and the subsequent inflow to create: 1) AoOc and MiOc, i.e., completely isovolumic cycles (IV); 2) AoOc, i.e., isovolumic contractions, with normal filling (IVC-NF); 3) AoOc close to end-systole and MiOc to give complete relaxation, (AoOc-CR); and 4) AoOc with normal filling (AoOc-NF). Results (at constant HR): in AoOc-CR and AoOc-NF vs IV, time of the onset of relaxation (time of peak LVP in isovolumetric contraction) increased ($p<.01$); in AoOc-CR vs IV the time to end relaxation (minimum LVP in MiOc) increased ($p<.01$); filling volume in IVC-NF vs control decreased ($p<.001$) due to decrease in filling time ($p<.01$). In AoOc-NF vs. control: rate of relaxation increased ($p<.01$); time to LVP minimum in early diastole, LVPmin, LVEDP and filling volume were unchanged. In summary, the computer controlled aortic and mitral occluders allowed us to precisely control ventricular ejection and filling, and to distinguish the individual effects of passive and active properties, thereby revealing the complete time course of myocardial relaxation in the intact ventricle. We conclude: in the intact LV, the "load dependence" of ventricular relaxation has an insignificant effect on diastolic filling.

EARLY AND LATE CLINICAL OUTCOME FOLLOWING SUCCESSFUL CORONARY ANGIOPLASTY OF TOTAL CORONARY OCCLUSIONS.

Edward S. Thomas, M.D., David O. Williams, M.D., F.A.C.C., Robert J. Mich, M.D., Albert S. Most, M.D., F.A.C.C., Rhode Island Hospital, Brown University, Providence, RI.

To assess the long-term efficacy of coronary angioplasty (PTCA) for total coronary occlusion (TCO), we reviewed the outcome of 94 consecutive non-acute myocardial infarction patients (pts) with TCO in whom PTCA was attempted and follow-up was obtained. In addition, outcome was compared to a group of patients without TCO in whom PTCA was successful with single vessel disease (1VD, n=189) or multivessel disease (MVD, n=92). PTCA was successful (suc) in 62 and unsuccessful (unsuc) in 32 TCO pts. Prior to PTCA, each pt. had disabling angina pectoris. Follow-up exercise treadmill tests were performed at a mean of 2.8 $\pm$ 4.5 mos. in 56/62 (90%) suc pts. The incidence of ischemia and/or angina during exercise testing was more common in suc TCO pts than in 1VD pts (27% vs. 13%, $p<.01$) but similar to MVD pts (33%, $p>.05$). After a mean follow-up of 21 $\pm$ 11 mos, more suc pts. noted clinical improvement (89% vs. 69%, $p<.04$) than unsuc pts. Furthermore, fewer suc TCO pts had subsequent hospitalization for chest pain (21% vs. 50%, $p<.01$) or coronary bypass surgery (3% vs. 28%, $p<.001$) than unsuc. Repeat PTCA (16%), non-fatal MI (2%) and death (0%) occurred infrequently in suc TCO pts. TCO pts were more likely to experience late recurrent angina pectoris or have repeat PTCA or CABG than 1VD pts. Thus, successful PTCA in symptomatic patients with TCO results in both acute and late clinical improvement but not to the degree achieved by pts with subtotal 1VD.

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY OF INTERNAL MAMMARY ARTERY BYPASS GRAFTS

David M. Hill, M.D., Bruce J. McAuley, M.D., F.A.C.C., Dennis J. Sheehan, M.D., John B. Simpson, M.D., F.A.C.C., Matthew R. Selmon, M.D., Edward T. Anderson, M.D., F.A.C.C., Sequoia Hospital, Redwood City, California

Internal mammary artery (IMA) bypass grafts offer superior patency rates when compared to saphenous vein grafts; however, stenosis of the IMA graft may occur in the early post-operative period. We reviewed our experience with PTCA in 11 patients who underwent IMA bypass graft dilatation.

Eight of the 11 patients had left IMA grafts placed to the LAD. Three patients had right IMA grafts—one to the LAD and two to the RCA. All patients developed recurrent angina within 4 months of coronary bypass surgery. In 10 of 11 patients, there was severe stenosis of the IMA at the distal anastomosis. In one patient there was stenosis of the proximal IMA.

Nine of 11 patients had successful PTCA of the IMA graft without complication. Extreme angulation of the anastomosis with the LAD prevented passage of a guidewire in one patient. Failure secondary to imcomplete balloon expansion was encountered in one patient. At re-operation, a marked fibrotic reaction of the IMA pedicle with extrinsic compression was found.

At a mean follow-up of 13 months post-PTCA, 8 of 9 patients successfully dilated were asymptomatic. Two patients developed restenosis and were successfully dilated.

CONCLUSION: PTCA can be successfully performed in IMA bypass grafts with a high success rate and a low restenosis rate. Significant stenosis at the distal IMA anastomotic site occurs early post-CABG and in one case was secondary to fibrosis with extrinsic compression.

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY OF LEFT INTERNAL MAMMARY ARTERY GRAFTS USING A FEMORAL APPROACH.

Malcolm R. Bell, M.B.,B.S., Ronald E. Vlietstra, M.B., Ch.B., F.A.C.C., Dennis R. Bresnahan, M.D., F.A.C.C., David R. Holmes, Jr., M.D., F.A.C.C., Mayo Clinic, Rochester, MN.

Use of the internal mammary artery (IMA) as a conduit for coronary artery bypass grafting is increasing. Despite excellent long term patency rates, stenosis of the IMA graft and the distal native vessel can occur. Experience with percutaneous transluminal angioplasty (PTA) in treating these stenoses has been limited and there have been technical concerns regarding the use of a femoral approach.

We have performed PTA through IMA grafts on 11 pts, mean age 58 ± 11 yrs. Standard PTA techniques were used employing low-profile balloons with a standard IMA guide catheter positioned via the femoral artery. There were 7 stenoses at the distal anastomotic site and 4 in the distal native coronary artery. The median interval from surgery to PTA was 6 mos (range 5 days to 6 yrs). PTA was successful (>40% improvement in stenosis) in 10 pts (91%), including 1 pt with a totally occluded distal graft and 1 pt treated at the time of an acute myocardial infarction. There were no major complications related to PTA although 1 pt had a transient occlusion at the site of PTA. Clinical improvement was noted in 10 pts during follow-up of 10 ± 8 mos; 1 late death occurred in a pt with a history of "sudden death". No clinical or angiographic restenoses have occurred.

These results suggest that PTA via the femoral artery is both safe and effective for IMA graft and distal coronary artery stenoses. This has important therapeutic implications for the expected increase in the number of pts presenting with IMA graft stenoses.

INTERNAL MAMMARY ARTERY GRAFT ANGIOPLASTY: CLINICAL AND ANGIOGRAPHIC FOLLOW-UP

Michael H. Sketch Jr. MD, Jose A. Perez MD, Peter J. Quigley MD, James Herndon Ph.D, Christopher M. O'Connor MD, James E. Tcheng MD, Joseph B. Muhlestein MD, Richard S. Stack MD, FACC. Duke Medical Center. Durham, NC

With improved graft patency rates of internal mammary artery (IMA) conduits, little data has accumulated regarding outcome following PTCA of IMA stenoses. Over a 48 month period, 13 consecutive pts (11 males) with a mean age of 57.9 yrs underwent PTCA of IMA stenoses. The lesion sites were 11 distal, 1 proximal and 1 body, with a mean graft age of 7.4 months. The procedural success rate was 92% (12 of 13 grafts) with a reduction in the mean IMA luminal narrowing from 88% to 18%. The one acute failure was due to the inability to cross the lesion (100% stenosis pre-PTCA). No in-hospital reocclusions occurred.

Of the 12 initially successful angioplasties, there was 92% angiographic and 100% clinical follow-up (mean = 7.5 months). Angiographic restenosis (> 50% occlusion) occurred in one patient (9%).

In comparing these results to 84 saphenous vein (SV) graft angioplasties performed during the same time period, initial success and in-hospital reocclusions rates were similar. However, the restenosis rate was 38% for SV grafts vs. the 9% for IMA grafts (p=0.08).

In conclusion, PTCA of IMA grafts appears to be both safe and effective with an excellent short and long-term outcome.

CORONARY ANGIOPLASTY DISSECTION: IN-HOSPITAL OUTCOME.

James D. Madison MD, FACC, Jodi Fishman Mooney RN MS, Michael R. Mooney MD, Irvin F. Goldenberg MD, FACC. Minneapolis Heart Institute, Minneapolis, MN.

To determine the effect of the type of coronary angioplasty (CA)-associated dissection upon in-hospital cardiac events and success rates at hospital discharge, we reviewed our last 104 NHLBI type B-F dissection cases. The type of dissection was defined angiographically. Type B appears as a radiodense intraluminal parallel tract during contrast injection, without contrast persistence, C as the persistence of contrast outside the lumen following injection, D as a spiral defect without delay in antegrade flow, E as a new, persistent filling defect during injection, and F as a total coronary occlusion. The 104 cases were evaluated for incidence of each dissection type, for in-hospital complications by dissection type, and for angiographic and clinical success at the time of discharge. In-hospital complications evaluated included acute closure, emergent bypass surgery (Em-S), myocardial infarction, elective bypass surgery (El-S), and repeat CA during the same hospitalization. There were no deaths in the series.

| Type | Successful CA % | Acute Closure % | Em-S % | Myocardial Infarction % | El-S % | Repeat CA % |
|---|---|---|---|---|---|---|
| B (N=75) | 92 | 1 | 0 | 0 | 7 | 3 |
| C-F (N=29) | 41 | 28 | 41 | 14 | 10 | 3 |
| P Value | <.001 | <.001 | <.001 | <.005 | (NS) | (NS) |

Thus, pts with type B dissection have an excellent in-hospital outcome. In contrast, pts with type C-F dissections commonly have adverse in-hospital events. These data suggest that new interventional devices may play a role in the future treatment of pts with Type C-F dissections.

CORONARY ANGIOPLASTY IN PATIENTS WITH SEVERE DEPRESSION OF LEFT VENTRICULAR FUNCTION

RS Kohli, M D, GW Vetrovec, MD, FACC, G DiSciascio, MD., FACC, SA Lewis, MD, FACC, A Nath, M D, MJ Cowley, MD, FACC, Medical College of Virginia, Richmond, Va.

High risk salvage coronary angioplasty (CA) frequently includes patients (pts) with severe left ventricular dysfunction. We report here the acute and chronic outcome of CA in 63 pts with left ventricular ejection fraction (LVEF) $\leq$ 35%, who underwent CA between 1985 and 1987 because they were deemed high risk or poor candidates for bypass surgery as a primary treatment. There were 49 males (M) and 14 females (F) with a mean age of 59 $\pm$ 15 (SD) years. Mean LVEF was 28 $\pm$ 7% (SD). (Range 9-35%). One had an acute myocardial infarction (MI), 13 had previous MI and 24 had recent MI (<15 days) while 42 had unstable angina. Twelve pts had previous bypass surgery. Single vessel CA was performed in 45 pts and multiple vessels in 18. Successful CA was performed in 116 of 123 lesions (94%). Clinical improvement was seen in 56 (90%) pts. Major complications (MI, death, urgent bypass surgery) were seen in 8 (12.5%) pts. Two (3%) pts died during the procedure, both were M with LVEF of 15% and 23%. One pt was sent for emergency revascularization. Five (7%) pts developed MI during CA (including a non-Q wave MI). All pts had follow-up for greater than 6 months; 45 (71%) remained clinically improved. Nine (14%) had restenosis, 2 (3%) had new disease and 7 (11%) pts died. This data indicates that CA is an acceptable method of coronary revascularization in selected, potentially high risk surgical pts, although complications are higher compared to CA in pts with normal cardiac function. Furthermore, such pts require close follow-up in order to detect early clinical recurrence which may have an impact on the higher incidence of late morbid events.

## Wednesday, March 22, 1989
## 3:00PM–4:00PM, Pacific Room
## Anaheim Convention Center
## Coronary Atherectomy and Imaging Catheters

**INTRAVASCULAR ULTRASOUND VISUALIZATION OF ATHEROMA PLAQUE REMOVAL BY ATHERECTOMY**

Jonathan M. Tobis, M.D., FACC; John A. Mallery, M.D.; Don Mahon, M.D.; James Griffith, Ph.D.; James Gessert; Lachlan Macleay, M.D.; Michael Mcrae, M.D.; Matthew Bessen, M.D.; Walter L. Henry, M.D., FACC;
University of California, Irvine, CA

Although atherectomy methods are designed to remove atheroma mass, present angiographic methods do not permit an adequate analysis of either the amount of mass removed or the residual wall thickness. Because it may be important to assess these parameters, a technique to visualize the atheroma mass and arterial wall in cross section during interventional procedures could have significant benefit. Toward this purpose, a 1.2 mm diameter 20 MHz intravascular ultrasound imaging catheter was used to obtain cross-sectional arterial images in vitro in 12 atherosclerotic human peripheral and coronary artery segments. Each arterial segment was imaged with the intraluminal ultrasound probe at 1 mm increments. Lumen dimensions were measured on multiple cross-sectional ultrasound images before and after a portion of the atheroma was removed with a Simpson atherectomy catheter. In each arterial segment, the cross-sectional ultrasound images demonstrated a significant decrease in fibrocalcific plaque. The mean values of the lumen before and after atherectomy were:

| | Diameter (mm) | Area ($mm^2$) | Perimeter (mm) |
|---|---|---|---|
| Pre: | 2.7x3.2 | 6.6$\pm$4.2 | 9.7$\pm$5.3 |
| Post: | 4.2x4.8 | 16.1$\pm$7.4 | 14.3$\pm$6.1 |

This preliminary experience in vitro suggests that an intravascular ultrasound imaging catheter may provide information of considerable value to the interventional cardiologist.

**UTILITY OF AN INTRAVASCULAR ULTRASOUND IMAGING DEVICE FOR ARTERIAL WALL DEFINITION AND ATHERECTOMY GUIDANCE.**

Susan P. Graham M.D., David Brands, Adam Savakus M.S., John McB. Hodgson M.D., F.A.C.C., McGuire VAMC and Medical College of Virginia, Richmond, VA.

We have used a percutaneous 5.5F, phased array 20 MHz ultrasound imaging catheter to examine arterial wall characteristics before and after atherectomy in isolated human ileofemoral arteries (ART) and in intact anesthetized dogs. The catheter produces 2-D cross-sectional images in ART up to 16mm in diameter. Ultrasound images were compared to histologic sections. Normal ART walls appear as a single layer < 1.0mm thick. Diseased ART have wall thickness proportionate to the medial thickening and subintimal plaque seen on histology. Diseased ART also have 3 distinct layers. With increasing disease and especially with calcium, the separation of layers may be lost. Penetration of the innermost layer (plaque) by atherectomy is easily visualized. Progression through the echo-lucent media cannot be exactly determined. The outer border echos remain visible until the adventitia is completely penetrated (in vitro). Potential limitations included the need to position the catheter coaxially, lateral spread of the echo beam and "shadowing" effects from calcified regions.

Conclusion: Intravascular ultrasound imaging allows differentiation of normal from abnormal ART walls. Plaque removal by atherectomy can can be easily assessed using this catheter.

COMPLICATIONS: EARLY EXPERIENCES OF PERCUTANEOUS CORONARY ATHERECTOMY

Gregory Robertson, MD; Tomoaki Hinohara, MD, FACC; Matthew Selmon, MD; Michael Rowe, MD; Neil White, MD; John Simpson, MD, FACC; Sequoia Hospital, Redwood City, CA.

Percutaneous Coronary Atherectomy (PCA) was developed to achieve predictable removal of coronary atheroma with low complications. Since October 1986, PCA was attempted in 93 lesions in 83 patients (pt) at Sequoia Hospital. Overall success rate (<50% residual stenosis) was 72%. Complications during the procedure and hospitalization were as follows.

| | |
|---|---|
| Major Complications | n=3 (4%) |
| Coronary occlusion requiring surgery | 1 |
| Transient coronary occlusion requiring PTCA | 1 |
| Distal embolization | 1 |
| Q Wave infarct | 1 |
| Death | 0 |
| Late coronary occlusion | 0 |
| Major dissection not requiring surgery | 0 |
| Vessel perforation | 0 |
| Minor Complications | n=6 (7%) |
| Small side branch occlusion | 2 |
| Air embolization without sequlae | 1 |
| Non- Q Wave Infarct | 1 |
| Surgical repair of access site | 2 |
| Transient thrombus formation | 1 |

Distal embolization occured during PCA of a 12 year old bypass graft resulting in a Q wave infarct and 1 pt with small side branch occlusion had a non-Q wave infarct. In conclusion, our preliminary experience suggests that significant complications are infrequent and PCA is a relatively safe procedure with experienced operators using current equipment.

ANGIOGRAPHIC APPEARANCES FOLLOWING PERCUTANEOUS CORONARY ATHERECTOMY

Tomoaki Hinohara, MD, FACC; Matthew Selmon, MD; Gregory Robertson, MD; Neil White, MD; Michael Rowe, MD; John Simpson, MD, FACC; Sequoia Hospital, Redwood City, CA.

Percutaneous coronary atherectomy (PCA) was developed to achieve a wider lumen and smoother surface removing tissue from the coronary artery. The purpose of this study was to analyze angiographic appearances following successful PCA. Between April and August 1988, PCA was attempted in 62 lesions in 54 patients. Seventy-nine % of these lesions were in native coronary arteries and 21 % in vein grafts. Fifty lesions were successfully treated with PCA alone with reduction of stenosis from median of 90% to 10%. Adjunctive coronary angioplasty (PTCA) was performed in remaining 12 lesions because of failure to place the PCA catheter (9 lesions) or significant residual stenosis following PCA (3 lesions). Angiographic appearance following failed PCA prior to adjunctive PTCA did not show new dissection, intimal flap or thrombosis. Angiographic appearances of post successful PCA site (n=50) were as follows: irregular rough appearance 6%; filling defect suggestive of thrombus 2%; intraluminal linear radioluceny 8%; minor dissection 6%; major dissection 0%; hazy appearance 4%. In conclusion, our study demonstrates that PCA typically creates a smooth angiographic surface without the major dissections commonly seen after PTCA.

BARD ROTARY ATHERECTOMY SYSTEM (BRAS) IN NORMAL CANINE CORONARY ARTERIES

Alexander Battler, M.D., F.A.C.C., Mickey Scheinowitz, M.Sc., Samuel Rath, M.D., Gary Boseck, Ph.D., Michael Eldar, M.D., Research Laboratory for Laser Application in Cardiology, Sheba Medical Ctr, Tel Aviv University, Tel Hashomer, Israel.

A new mechanical atherectomy device, the BRAS system, was evaluated in 10 coronary arteries of 5 normal dogs. The device comprises a non rotating guidewire with a spiral shaped distal end and a 5F rotary catheter equipped with a hollow blade. This system is designed to remove and collect atherosclerotic occlusive material using conventional coronary catheterization techniques. The BRAS was advanced into the distal coronary vessel through a 8F guiding catheter over .014" exchangeable guidewire using the percutaneous femoral approach. This procedure was performed twice in each dog, initially in either the left anterior descending or circumflex coronary artery and 1-3 days later in the other coronary artery. The dogs were maintained on aspirin 250mg/day and were sacrificed after the second procedure and the endarterectomy sites underwent pathological and histological examination. Angiography performed immediately after endarterectomy and 1-3 days later demonstrated patent coronary vessels without perforation or thrombosis in all cases. Macroscopic examination of the excised hearts, demonstrated the presence of minimal perivascular hemorrhage in 5 of the arteries, irrespective of the time and site of endarterectomy. It is concluded that percutaneous coronary endarterectomy with the BRAS system is feasible without acute or chronic angiographic evidence for perforation or thrombosis.

INITIAL EXPERIENCE WITH A FLEXIBLE ROTATIONAL ATHRECTOMY SYSTEM DESIGNED FOR REMOVAL OF CORONARY AND SMALL PERIPHERAL ARTERY ATHEROMAS.

Richard W. Smalling, M.D., Ph.D., F.A.C.C.,David B. Cassidy, M.D., Waldemar A. Schmidt, M.D., Ph.D., Glenda M. Wise, M.S., Patricia R.Felli, B.S., Robert L. Barrett, M.D. and Gary L. Boseck, Ph.D., University of Texas Medical School at Houston, Houston, Texas.

A 4.5 French flexible rotational athrectomy system (RAS) capable of being introduced through a guiding catheter over a standard coronary angioplasty guide wire has been developed by BARD. The RAS uses an auger device which is placed into atheroma and effectively captures debris as the flexible cutting shaft is advanced over it. After initial studies in canine peripheral, renal and coronary arteries demonstrated its ability to negotiate tortuous vessels it was used to remove atheromas in 4 human below knee amputation specimens. Quantitative arteriography of diseased segments before and after athrectomy demonstrated improvement in lumen diameter from .49-.83 to 1.17-1.31 mm. Histologic examination of normal arteries showed no structural abnormalities after treatment with the RAS. The RAS seemed to preferentially track the "true" lumen in diseased vessels removing atheromatous material while leaving a smooth border and sparing the muscularis. The RAS successfully recanalized long segments of totally occluded vessel without perforation. Conclusion: The RAS is capable of removing atheromatous lesions in severely diseased, tortuous vessels using co-axial, wire-guided techniques.

EVALUATION OF AORTIC IMPLANTATION AND REDILATION OF BALLOON EXPANDABLE INTRAVASCULAR STENTS IN JUVENILE MINIPIGS.

G.Wesley Vick, III MD, Martin O'Laughlin MD, Tim Myers RRT, Takeshi Nakatani MD, Julio Palmaz MD, Richard Schatz MD FACC, W. Robert Morrow MD, Charles Mullins MD FACC. The Lillie Frank Abercrombie Section of Cardiology, Department of Pediatrics, Baylor College of Medicine, Houston, TX

Balloon expandable intravascular stents (BEIS) are potentially an efficacious catheter treatment for pediatric patients with congenital and acquired vascular stenoses. More information is needed, however, regarding the feasibility of redilation of BEIS and implantation of BEIS in series as a possible treatment for long segment stenoses. Nine BEIS were placed in the abdominal aortas of 6 juvenile minipigs (weight 14.7 ± 1.2 kg, age 90 ± 12 d) under general anesthesia. In three cases, stents were implanted in series (ie, overlapping each other). Initial implantation of stents was successful in 8 of 9 instances. Series implantation of BEIS was successful in each of 3 attempts. Five animals were evaluated by repeat catheterization and aortography at 196 d ± 17 d after placement. Weight at redilation was 43.5 ± 2.1 kgs. Stents were patent in each instance, but mild constriction with growth relative to the normal proximal aortic diameter was noted. There were no pressure gradients at the site of the stents at the subsequent examination, however. Redilation was successful in 4 of 4 attempts (1 after series implantation), and the mild constriction of the aorta at the BEIS site was relieved. Redilation increased the diameter of the aorta at the BEIS site by an average of 35%. One animal died due to unexplained ventricular fibrillation at the follow-up catheterization before redilation could be attempted. No evidence of perforation or other technical problems were noted at autopsy. Pathological examination of the BEIS taken from this animal and the aorta at the stent site revealed no evidence of thrombosis. The BEIS was covered with a thin layer of neointima. We conclude: 1) stents do not interfere with normal growth in animals, 2) implantation of stents in series is feasible, and 3) redilation of stents is possible subsequent to growth.

ADDITIONAL IMPROVEMENT IN VESSEL LUMEN IN THE FIRST 24 HOURS AFTER STENT IMPLANTATION DUE TO RADIAL DILATING FORCE

Kevin J. Beatt, M.R.C.P., Michel Bertrand M.D., Jaques Puel M.D., Tony Rickards M.D., F.A.C.C., Patrick W. Serruys M.D., F.A.C.C., and Ulrich Sigwart M.D., F.A.C.C.
Core laboratory for quantitative angiography: on behalf of the working group for endoluminal coronary artery prostheses.
Thoraxcentre, Erasmus University Rotterdam, The Netherlands.

Quantitative coronary angiography was performed in 18 patients pre-PTCA, post-PTCA, post-stent implantation, and at 24 hours following implantation. The minimal lumen diameter (MLD), the reference diameter (RD) of the stented coronary artery segments, the percentage diameter stenosis (DS) and the mean diameter of the stented segment (STN MD) were determined.

Results:

| | MLD | RD | DS | STN MD |
|---|---|---|---|---|
| Pre-PTCA | 1.31±0.56 | 2.97±0.65 | 52±16 | |
| Post-PTCA | 1.84±0.47 * | 2.91±0.68 ** | 36±15 * | |
| Post-stent | 2.38±0.38 * | 3.09±0.55 ** | 22± 9 * | 2.82±0.51 ** |
| 24 hour F\U | 2.79±0.51 | 3.39±0.78 | 17± 9 | 3.08±0.59 |

* p<0.001. ** p<0.02.

Immediately following stent implantation there was a significant improvement in the MLD, the DS and the STN MD with a further significant increase over the next 24 hours. The radial force of the self expanding prosthesis has the effect of improving the caliber of the entire stented segment, creating an optimal hemodynamic profile, and this effect continues for at least the first 24 hours. The effect will tend to reduce the significance of any subsequent intimal hyperplasia, and may be important in determining the long term outcome of this device.

## Wednesday, March 22, 1989
## 4:00PM–5:00PM, Pacific Room
## Anaheim Convention Center
## Echo Doppler I

ECHOCARDIOGRAPHIC COMPUTED TOMOGRAPHY OF THE HEART: PRELIMINARY RESULTS. Riccardo Pini, M.D., Elisabetta Monnini, D.El.Eng., Leonardo Masotti, D.El.Eng., Barbara Greppi, M.D., Marino Cerofolini, M.D., Richard B. Devereux, M.D., FACC. Cornell Medical College, New York, N.Y.

To perform three-dimensional reconstruction of the heart by ultrasound, we developed a new echocardiographic transducer that allowed acquisition of 60 standard fan shaped two-dimensional (2-D) views at 3 degree increments of rotation about its central axis from any acoustical window, terminating at 180° with a mirror image of the starting echocardiographic view. Acquisition time is 72 to 120 seconds in sinus rhythm. Comparing the 0 to 180 degree images provides an immediate check of stability of the axis of rotation during the recording. A PDP 11/44 digital computer with a 512 x 512 pixel x 256 grey level frame grabber digitized the 60 videotaped images with electrocardiographic gating and converted the original 2-D images acquired in cylindrical coordinates to reconstruct a three-dimensional cone of information including the heart, with enhancement by a scan converter, from which 2-D images in any plane at specified times or throughout the cardiac cycle can be derived. Tubes and wires in a standard ultrasound phantom were accurately reconstructed, as were planes visualizing the aortic valve cusps and proximal left coronary artery when the transducer's axis of rotation was at mitral tip level in clinical studies. In conclusion: 1) a novel rotating echocardiographic transducer images a solid cone encompassing the heart from the chest surface; 2) short imaging time (≤120 seconds) does not prolong the echocardiographic examination and allows stability of the axis of rotation; and 3) this system permits computed tomography of the heart without cumbersome external reference systems, expensive immobile equipment, or radiation exposure.

PATHOLOGIC FINDINGS AFTER IN VIVO PLACEMENT OF PERCUTANEOUS BALLOON EXPANDABLE TANTALUM STENTS.

Christopher White, M.D., F.A.C.C., Saurabh K. Chokshi, M.D., Jeffrey M. Isner, M.D., F.A.C.C., Ochsner Clinic, New Orleans, LA, and St. Elizabeth's Hospital, Tufts University School of Medicine, Boston, MA

Balloon expandable endovascular stents represent a potential solution to certain complications of balloon angioplasty, namely restenosis and abrupt closure. We examined pathologic findings evaluating tissue reaction and biocompatibility of balloon mounted Wiktor stents placed percutaneously in peripheral and coronary arteries of normal Yucatan swine. These stents are constructed of tantalum designed to enhance radiographic visualization. A total of 20 stents, 15 mm in length, were placed in 12 external iliac, 1 internal iliac, 1 caudal, 1 left circumflex coronary and 5 left anterior descending coronary arteries. No chronic antiplatelet agents or anticoagulants were employed. Sequential angiography performed at 1 day in 6 arteries, 1 wk in 2 arteries, 2 wks in 2 arteries, 4 wks in 6 arteries and 6 wks in 4 arteries, showed 100% patency of stented segments. Light microscopy of the stents at 1 day post-placement revealed an irregular intimal surface with thrombus covering the struts of the stent. Over the next 3 wks, complete covering of the stent wire with neointima resulted in "smoothing" of the intimal surface. The neointimal growth was asymmetric; foci of maximal thickness were observed adjacent to the stent "struts". The thickness of the neointima varied from 108-436 um; peak neointimal growth developed at 4 wks post-implantation; by 6 wks, maximum neointimal thickness measured ≤248 um. In all segments examined at 4 wks or more post-stent-implantation, the media underlying the stent was severely attenuated. These findings document the biocompatibility of a tantalum stent, designed to enhance radiographic visualization, which in this animal model was associated with 100% patency.

DETECTION OF PULMONARY ARTERY THROMBI BY TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN PATIENTS WITH SUSPECTED PULMONARY EMBOLISM

Norbert Wittlich M.D., Raimund Erbel M.D., F.A.C.C., Michael Todt M.D., Susanne Mohr-Kahaly M.D., Michael Drexler M.D., Jürgen Meyer M.D.
II. Medical Clinic, University of Mainz, FRG

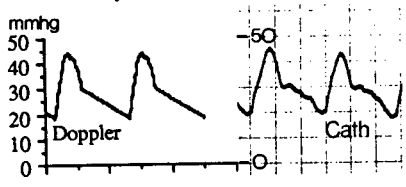
Transesophageal echocardiography (TEE) allows a visualization of the pulmonary artery (PA). Especially the right PA (RPA) can be depicted at a length of 3-6 cm. We examined 23 patients (pts) with suspected pulmonary embolism (PE) by TEE in order to evaluate the capability of this approach to detect pulmonary artery thrombi (PAT). In 7 pts with the age of 52.29 ± 18.07 years, 4 female, 3 male, we observed thrombi in the RPA, filling more than half of the lumen of the vessel, in two cases nearly occluding. These 2 pts went to surgery after confirmation of the TEE findings by angiography (ANG). The emboli were removed. In another pt the thrombus was not seen by ANG but could be visualized by computed tomography. In 2 other pts the TEE findings were confirmed by ANG. In all pts PA pressure was elevated: systolic 73±27.68 mmHg, diastolic 32.4±9.34 mmHg, mean 48,4±15,77 mmHg. With the exception of one pt (surgery case) all pts had repeated PE; in all venous thrombosis was detected as source of embolism.
Conclusion: The detection of PAT in pts with PE is possible by TEE. The clinical value of this tool, its sensitivity and specificity is still to be evaluated.

## NON-INVASIVE COMPUTER RECONSTRUCTION OF THE PULMONARY ARTERY PRESSURE WAVEFORM USING DOPPLER ECHOCARDIOGRAPHY

Karl Isaaz M.D., S. Albert Camacho M.D., John Webb, M.D., Kanu Chatterjee M.D., FACC, Nelson B. Schiller M.D., FACC. University of California, San Francisco, CA.

We developed a method for non-invasive reconstruction of the PA pressure waveform using continuous wave Doppler. RV systolic pressure waveform was digitized from tricuspid regurgitant jet velocity using the modified Bernoulli equation and estimation of RA pressure from inferior vena cava dynamics. The systolic portion of the PA pressure waveform was derived from the RV pressure curve between the opening and the closing of the pulmonary valve (PV). The diastolic portion of the the PA pressure waveform was derived from a straight line interpolation between the RV pressure at the time of PV closing and PV opening. The time of PV opening and closing was measured from doppler at the right ventricular outflow tract. The timing of tricuspid regurgitation and RV outflow signals were referenced to the onset of the QRS to allow determination of the RV pressure at the time of PV opening and closing. We compared simultaneous doppler and catheter PA pressure measurements in 12 CCU patients.

| (y=doppler; x=catheter) | | R | SEE | p |
|---|---|---|---|---|
| systole | y=0.74x+12 | 0.84 | 5 | 0.0006 |
| diastole | y=0.99x+ 0.6 | 0.87 | 4 | 0.0003 |
| mean | y=0.87x+4 | 0.83 | 4 | 0.0008 |




We conclude that both PA pressures and the PA pressure waveform can be computer generated from noninvasive Doppler tracings.

## SAFETY OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN AWAKE PATIENTS: EXPERIENCE WITH 400 PROCEDURES.

Bijoy Khandheria, M.D., James Seward, M.D., F.A.C.C., Jae Oh, M.D., F.A.C.C., William Freeman, M.D., L. J. Sinak, M.D., Barbara Nichols, R.N., and A. Jamil Tajik, M.D., F.A.C.C., Mayo Clinic, Rochester, MN

Transesophageal echocardiography (TEE) is being used with increasing frequency in the awake Pt. We report our initial experience with 400 procedures in 387 Pt, 207 males; age range 12-88 yrs (mean=61 yrs). TEE studies represented 2.7% of all transthoracic echo examinations (14,881). Indications included: suspected malfunctioning prosthesis (90) or native valve (55), thromboembolic event (56), endocarditis (47), aortic pathology (40), critically ill (40), congenital heart disease (20), and miscellaneous (39). An echoscope was introduced following left lateral positioning (90%), pharyngeal anesthetic (100%), intravenous drying agent [0.2 mg glycopyrollate] (100%), and Midazolam sedation (73%) [mean dose 3.5 mg, range 1-7 mg]. There were 29 critically ill patients studied with endotracheal tube in place. TEE was unsuccessful in 2/400 (0.5%) [cervical spondylosis (1), uncooperative (1)], aborted 1/400 procedures (0.25%). Examination time ranged 5-45 minutes (mean=16 minutes). Minor complications occurred in 2/400 procedures (0.5%) [supraventricular tachycardia (2)]. Minor sore throat was reported in 71% Pt. In response to a questionnaire, 99% Pt reported they would undergo a repeat examination if indicated. Superior TEE information was found in Pt with mitral prosthesis, aortic dissection, thromboembolic episodes, endocarditis, cardiac masses, and critically ill Pt. Conclusion: TEE is a feasible examination in the awake Pt and can be performed safely and expediently, and provides high resolution diagnostic images.

## TIME COURSE OF PULMONARY ARTERIAL PRESSURE CHANGE IN THE EARLY POSTNATAL PERIOD - NONINVASIVE COLOR DOPPLER AND CONTINUOUS WAVE DOPPLER ECHOCARDIOGRAPHIC STUDY

Kai-Sheng Hsieh M.D., Be-Tau Hwang M.D., Kwan-Shan Yeh M.D., Laura Meng M.D., Veterans General Hospital and National Defense Medical Center, Taipei, Taiwan.

It is well known that pulmonary arterial pressure drops after birth. However, the exact time course of this change ramains unclear. We prospectively studied the blood flow characteristics across the patent ductus arteriosus (PDA) among 42 full term newborns using non-invasive color Doppler flow mapping (CDF) and CDF-guided continuous wave Doppler echocardiography. The closure rate of PDA was 2.4%, 53.2%, 78.6%, 88.1%, 92.9%, 95.2% and 97.7% from day 1 through day 7. CDF revealed bidirectional shunt, with systolic right to left and diastolic left to right shunt ocurred in 45.2% of the neonates during the first 12 hours of life. At 24 hour of life, only 2.4% showed bidirectional shunt. Pure left to right shunt prevails over the days afterwards. The maximal pressure difference between the pulmonary artery and descending aorta was 14.4±0.5, 31.4±1.5, 29.2±0.4 and 33.6±1.0 mmHg at 12, 36 and 60 hours of life. Our data suggest that the pulmonary arterial pressure drop occurs majorly within 24 hours of life. By the age of 36 hours most of the newborns (34/42) had stable pulmonary artery pressure without further change of the pressure difference between the 2 great arteries. We conclude that the pulmonary arterial pressure drop occurs substantially over the first 12-24 hours of life instead of abrupt change immediately after establishment of spontaneous aspiration. Right to left ductal shunt ( a variant form of fetal circulation ) is common during the first 12-24 hours of life.

## DOPPLER COLOR FLOW MAPPING OF THE "PROXIMAL ISOVELOCITY SURFACE AREA": A NEW METHOD FOR MEASURING VOLUME BLOOD FLOW ACROSS AN ORIFICE.

Toshinori Utsunomiya, MD; Toshio Ogawa, Hoang A. Tang, Walter L. Henry, MD, FACC; Julius M. Gardin, MD, FACC; University of California, Irvine, CA.

Flow through a narrowing is characterized by the convergence of radial streamlines proximal to the orifice. If a proximal isovelocity surface area (PISA) can be identified and quantified, then volume flow rate can be calculated as PISA X isovelocity (V). Using Doppler color flow mapping, it might be possible to visualize an isovelocity region as a red-blue interface proximal to the orifice. Because the aliasing V is known, volume flow can be calculated. To evaluate this possibility, we used a Hitachi-Biosound CVC 151 color flow mapping (CFM) machine to attempt to visualize a PISA proximal to circular orifices in both constant and pulsatile flow models in vitro. Over a range of orifice diameters from 3 to 16 mm, and flow rates of 0.5 to 18 L/min, a PISA could be visualized and was best described by an elliptical model with two different radii measured from long axis and short axis views. Actual volume flow was measured simultaneously using a cylinder and stopwatch. In the constant flow model, volume flow calculated from Doppler PISA correlated well with actual flow ($r=0.997$, $P<0.001$, SEE=0.42 L/min). In the pulsatile flow model, with jet velocities ranging from 2.5 to 7.6 m/sec, calculated volume flow also demonstrated an excellent correlation with actual flow ($r=0.986$, $P<0.001$, SEE=0.33 L/min). In conclusion, color flow mapping identification of the proximal isovelocity surface area appears to be a promising technique for estimating volume flow across an orifice.

## CLINICAL APPLICATION OF ULTRASONIC BACKSCATTER IN TRANSESOPHAGEAL ECHO TO DETECT ISCHEMIC MYOCARDIUM.

Annie Karpati MS, Stephen Corday MD, FACC, Michael Jaffe MS, Gustavo Velasquez MD, Julian Gold MD, Joe Areeda, Cedars-Sinai Medical Center, Los Angeles ,CA.

We utilized the cyclic variation in ultrasonic backscatter to detect ischemia in patients undergoing surgical procedures who were monitored by transesophageal two-dimensional echocardiography. Ten patients, who were judged by an independent anesthesiologist to become ischemic by wall motion criteria during the surgical procedure, were selected.

In each patient, a baseline(base) image and an image at time of greatest ischemia(hypo) were identified by an independent observer.

We measured over the same area of myocardium the cyclic changes in backscattered power , skewness and kurtosis between end-diastolic and end-systolic myocardium as shown below ( * p<0.001):

| | Cyclic Changes | | |
|---|---|---|---|
| | Mean Gray | Skewness | Kurtosis |
| Base | 21.16±9.56* | -.204±2.28 | -2.96±3.64 |
| Hypo | 6.32±5.72* | -2.45±5.80 | -.624±2.64 |

Conclusion: We conclude that tissue characterization techniques are easily applied to transesophageal 2D echocardiograms due to their superior image quality. These measurements allow us to clearly separate ischemic from nonischemic myocardial segments by changes in cyclic backscatter. This technique shows great promise for future clinical applications to allow objective detection of ischemic myocardium.

## DO DOPPLER FLOW ALGORITHMS FOR MAPPING DISTURBED FLOW MAKE SENSE?

Julius M. Gardin, MD; Slawomir Lobodzinski, Ph.D; University of California, Irvine, CA

It has been suggested that a major advantage of Doppler color flow mapping (CFM) is its ability to localize areas of disturbed flow--e.g., in stenosis, regurgitation, or shunts. To investigate the ability of CFM to display disturbed flow, we employed custom programs to evaluate the CFM algorithms of 7 commercially available ultrasound machines. In these algorithms, green is reportedly used to map disturbed flow areas. We calculated the % green added to each pixel along the red and blue portions of the velocity reference color bar for each machine. Velocities (V) ranged from ±46 to ±64 cm/sec, depending on the Nyquist limit. The Table shows mean % green added to the red color bar at a mean V of 25cm/sec. This V is below velocity threshold at which turbulence is expected (Reynolds # <2000) in an adult aorta.

| Machine # | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Mean % green | 25% | 38% | 38% | 31% | 12% | 18% |

In Machine 7, the reference color bar did not correspond to colors in the images because green is not blended with red and blue; rather, its intensity is a direct marker of degree of disturbed flow defined as turbulence, noise or aliasing. Although most machines displayed increased % green with increasing +/- V, two demonstrated different gradients for adding green to the primary colors. At 25 cm/sec on the blue scale, Machine 6 displayed green varying from 12 to 89%. We conclude that CFM machines add green according to markedly different algorithms and at velocities not producing turbulence. If color flow mapping is to be useful quantitatively, detailed information regarding mapping algorithms must be provided.

## CYCLIC VARIATION OF ULTRASOUND BACKSCATTER IN NORMAL MYOCARDIUM IS VIEW DEPENDENT: CLINICAL STUDIES USING A REAL-TIME BACKSCATTER IMAGING SYSTEM

Byron F. Vandenberg, M.D., F.A.C.C., Linda Rath, Thomas A. Shoup, Ph.D., Richard E. Kerber, M.D.,F.A.C.C., Steve M. Collins, Ph.D., David J. Skorton, M.D., F.A.C.C., University of Iowa, Iowa City, Iowa

Open chest animal experiments suggest that the cyclic variation in integrated backscatter noted in normal myocardium may be independent of the angle between the ultrasound interrogation beam and myocardial fiber orientation. Such angle independence is very desirable in the clinical setting. A new 2D real-time backscatter imaging system allows transthoracic clinical evaluation of cyclic backscatter variation, but has only been tested in limited regions of the normal human left ventricle imaged from a single view. We evaluated possible angle dependence of cyclic variation in backscatter in the clinical setting by imaging multiple regions of the left ventricle from four standard echo views. Parasternal long (PSLAX) and short (PSSAX) axis views, and apical (2 and 4 chamber) views were obtained in 20 normal male subjects (mean age=28±5 [SD]).

Results (cyclic change in backscatter [dB, mean±SD]):

| View | Septum | n | Posterior | n | Lateral | n |
|---|---|---|---|---|---|---|
| PSLAX | 2.7±3.1* | 20 | 4.6±1.6* | 19 | -- | -- |
| PSSAX | 1.2±2.6 | 18 | 2.8±2.2* | 17 | -1.1±1.4 | 9 |
| Apical | -1.6±1.8 | 19 | -0.2±2.5 | 11 | 0.1±1.3 | 6 |

*p<0.01, diastole vs. systole.

Conclusion: (1) 2D real-time integrated backscatter imaging demonstrates that cyclic variation of backscatter is view dependent in normal posterior and septal myocardium. (2) View dependence of cyclic variation in backscatter may be related to the attenuation of ultrasound by intervening chest wall or myocardium, or to the orientation of myocardial fibers to the ultrasound beam.

## TWO TO FIVE YEAR ECHOCARDIOGRAPHIC FOLLOW-UP OF PATIENTS WITH MITRAL VALVE PROLAPSE: IS APICAL FOUR-CHAMBER VIEW DISPLACEMENT A PRECURSOR OF ABNORMALITY?

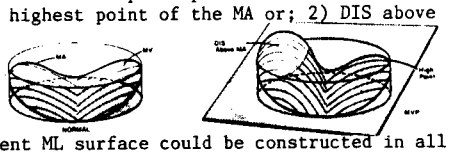
Anthony J Sanfilippo MD, Aleksandar D Popovic MD, Pamela Harrigan RDMS, Mark D Handschumacher BA, Arthur E Weyman MD FACC, Robert A Levine MD FACC. Massachusetts General Hospital, Boston MA.

Recent studies in over 400 patients from this laboratory have suggested that superior mitral leaflet displacement (MLD) limited to the 2D echocardiographic (2DE) apical four-chamber (A4C) view is within the normal range because it is not associated with independent markers of mitral valve (MV) disease. However, the question has been raised as to whether A4C view MLD might be a precursor of subsequent abnormality, such as progressive MLD or the development of MLD in the parasternal long-axis view (PLA). In order to explore this possibility, we reviewed our echo database to select patients having two 2DE examinations separated by at least 2 years, with superior systolic MLD noted on the initial study. Pts with intrinsic MV disease other than MVP were excluded. We studied 53 consecutive pts satisfying these criteria (mean follow-up 41 mos). MLD was initially limited to the A4C view in 28. The PLA was also involved in 25. **RESULTS:** 1) Of the 28 pts who had MLD limited to the A4C view initially none showed evidence of progression while in 8 the MLD was no longer evident, 2) 25 pts had MLD in the PLA and A4C views initially; of these 24 continued to have these findings in follow-up. In 1 pt. the PLA MLD resolved in association with new severe LV dysfunction. **CONCLUSIONS:** Patients with MLD limited to the A4C view did not show evidence of progression in a follow-up period of up to 5 years. These results support the normality of MLD limited to the A4C view.

A NEW THREE-DIMENSIONAL ECHOCARDIOGRAPHIC METHOD FOR QUANTITATING MITRAL VALVE PROLAPSE

Mark D Handschumacher, BS, Anthony J Sanfilippo, MD, Pamela Harrigan RDMS, Arthur E Weyman, MD, FACC, Robert A. Levine, MD, FACC, Massachusetts General Hospital, Boston, Massachusetts

Mitral valve prolapse (MVP) represents systolic leaflet displacement (ML DIS) above the mitral annulus (MA). We have previously shown that the MA is nonplanar in systole, so that no 2-dimensional echo (2DE) view fully reflects the degree of DIS and a 3D measure of volumetric (VOL) DIS is required. We therefore developed a technique for non-invasive 3D reconstruction of the MLs and MA from intersecting systolic 2DE scans localized by spark gaps. This method has been applied to 10 normal subjects and 5 pts with MVP, providing for each: 1) a topographic ML surface; 2) a 3D annulus, and 3) a least squares plane of fit (LSP) to the MA to provide a frame of reference. VOL ML DIS was measured as: 1) DIS above a plane parallel to the LSP at the level of the highest point of the MA or; 2) DIS above the LSP.



RESULTS: A coherent ML surface could be constructed in all cases. VOL DIS was:

| | DIS above MA | DIS above LSP |
|---|---|---|
| NORMALS (n=10) | 0 | 0.5 ± .3cm$^3$ |
| MVP (n= 5) | 1.1 ± .5cm$^3$ | 1.6 ± .7cm$^3$ |

CONCLUSIONS: 1) We have developed a technique to reconstruct a topographic ML surface and measure its 3D volumetric DIS above the MA. 2) Measures of VOL DIS can be derived and their normal range established. This can be used to relate VOL DIS to DIS in routine 2DE views and to clinical and echo measures of MV disease.

ESTIMATION OF EFFECTIVE MITRAL TISSUE PROSTHETIC AREA USING THE CONTINUITY EQUATION.

Kanwal K. Kapur M.D., PoHoey Fan M.D., Hirday K. Chopra M.D., Raj Ballal M.D., Navin C. Nanda M.D. F.A.C.C. University of Alabama at Birmingham, Alabama.

We evaluated the use of the continuity equation (CE) at the mitral orifice, in the estimation of effective mitral tissue prosthetic area (EA) in 9 Pts with no or Grade I mitral regurgitation who were catheterized within 0-14 days (mean 3.7 days) of the color Doppler study. The previously validated method of color pixel intensity was used to estimate maximal proximal velocity in LA close to the prosthesis. The inner diameter of the prosthetic annulus was measured using the prosthetic stents (apical view) and crossectional area (CSA) estimated assuming a circular configuration of the prosthetic annulus. Peak velocity across mitral prosthesis was estimated by aligning the continuous wave cursor parallel to the antegrade mitral flow signals using the apical plane. The EA was computed using CE.

$$EA = \frac{\text{CSA prosthetic annulus X proximal velocity}}{\text{Peak mitral velocity}}$$

The EA by CE (0.6-2.01 cm$^2$ mean 1.18±0.52cm$^2$) correlated very well with Gorlin's EA at cath. (0.5-2.6 cm$^2$ mean 1.32±0.74 cm$^2$) r=0.92. In 5 Pts with EA by CE of 0.6-1.03 cm$^2$ (mean 0.79 cm$^2$) prosthetic obstruction (thickened immobile leaflets) was noted at surgery, while in the remaining 4 with clinically normal prostheses the EA was 1.3-2.01 cm$^2$ (mean 1.67 cm$^2$, p=.002). Thus CE at mitral orifice provides another method by Doppler for the estimation of prosthetic mitral EA.

# Thursday, March 23, 1989
# 8:30AM–10:00AM, Anaheim Room
# Anaheim Convention Center
# New Devices for Intraarterial Angioplasty and Imaging

TREATMENT OF PERIPHERAL VASCULAR DISEASE WITH THE TRANSLUMINAL EXTRACTION CATHETER: RESULTS OF A MULTICENTER STUDY

Richard S. Stack MD, FACC, Jose A. Perez MD, Glenn E. Newman MD, Richard L. McCann MD, Mark H. Wholey MD, Frank E. Cummins MD, Joseph T. Galichia MD, Patricia U. Hoffman, James E. Tcheng MD, Michael H. Sketch Jr. MD, Myoung M. Lee MD, Harry R. Phillips MD, FACC. Duke Medical Center. Durham NC

The transluminal extraction catheter (TEC) is a new rotary cutting device that is advanced over an .014 inch PTCA guidewire. When the conical cutting head enters a lesion, rotation begins (750 RPM) and material is continuously extracted from the vessel via suction.

Seventy-one atherosclerotic lesions were treated during 41 procedures in 41 extremities of 36 patients (mean age = 62; 72% males) at 4 medical centers. TEC was used exclusively in 49 lesions and in conjunction with angioplasty in 8 lesions. In addition, 14 lesions remote from the TEC site were treated with angioplasty alone. Mean ankle/arm index went from .60 ± .12 to .72 ± .19 ($p < 0.0003$) and mean luminal diameter stenosis went from 72% ± 17% to 29% ± 16% ($p < 0.0001$). The TEC procedural success rate (≤ 50% residual stenosis in all lesions) was 98% (40/41) and the patient success rate was 97% (35/36). There was no evidence of distal embolization arteriographically or clinically and no vessel perforations. Two pts had temporary thrombotic occlusions during the hospitalization at sites where angioplasty only was used (successfully recannulated with urokinase) and 2 pts required vascular repair at the sheath insertion sites.

These results suggest that the TEC procedure is safe and effective for reducing stenosis and improving flow in patients with peripheral vascular disease.

MECHANICAL TRANSLUMINAL CORONARY ENDARTERECTOMY: INITIAL CLINICAL EXPERIENCE WITH THE AUTH MECHANICAL ROTARY CATHETER.

William W. O'Neill, M.D., Eric R. Bates, M.D., Marvin Kirsh, M.D., Joseph Bassett, M.D., Mark Sakwa, M.D., Mark Elliott, M.D., Dennis Doppke, William Beaumont Hospital, Royal Oak, Michigan.

We have performed intra-operative transluminal coronary endarterectomy with the Auth mechanical rotary catheter to assess safety and efficacy in patients prior to percutaneous usage. Nine patients have had 11 segments treated. Only lesions above the arteriotomy site were treated. Since all vessels treated also underwent bypass, a flow limiting stenosis was required to exist in the proximal vessel to avoid competitive flow. During surgery, a sizing probe was advanced to the lesion before and after transluminal coronary endarterectomy to assess efficacy. Angiography was performed one week after transluminal coronary endarterectomy to assess vessel patency and allow computerized lesion quantitation. Transluminal coronary endarectomy was initially successful in 10/11 segments, 1 vessel perforation (of an extremely angulated segment) occurred. Angiography documented sustained patency in 9/10 vessels. Stenosis diameter decreased (72±4% to 51±9%, $p < .03$) and minimal cross sectional area improved (0.7±0.1mm$^2$ to 1.4±0.2mm$^2$, $p < .02$). We conclude that intra-operative transluminal coronary endarterectomy safely and effectively ameliorates human coronary stenoses. These results allow for cautious application of mechanical rotary catheter to the catheterization laboratory setting.

HUMAN PERCUTANEOUS CORONARY ROTATIONAL ATHERECTOMY : RESULTS AND SHORT FOLLOW UP.

Jean L. Fourrier M.D., David Auth Ph.D.,Jean M. Lablanche M.D., Jean M. Brunetaud M.D., Antoine Gommeaux M.D., Michel E. Bertrand M.D. F.A.C.C.
University of Lille - FRANCE.

Percutaneous coronary rotational atherectomy (PCRA) was performed in 10 patients (pts). The device (ROTABLATOR, USA) consist of a flexible rotating shaft 120.000 rpm with an abrasive tip of various diameter (1.25 to 1.75 mm) and a central guide wire (GW). The 10 pts (mean age : 57) presented a stenosis (ST) of LAD. (3) or RCA (7). Through a 9F catheter, the GW crossed ST under fluoroscopy. The abrasive tip was slowly advanced over the GW and several passes across the ST were made after which the device was removed, and the residual ST measured. In case of residual ST>50% a balloon dilatation (PTCA) was done.
Results : The ST was significantly enlarged from 0.58 mm ± 0.35 to 1.18 mm ± 0.25.The outline of vessel appeared smooth and regular.5 pts had PCRA alone and 5 PCRA + PTCA. No acute complication occured and the pts were discharged 2.2 days after PCRA. 1 pt dead because of a mesenteric infarction unrelated to the PCRA. 9 pts were functionnally improved and 4 pts had a new angiograms 3 months after PCRA. All the arteries were patent and only 1 pt presented a restenosis.
Conclusion : PCRA is a safe and effective method of angioplasty but long term assessment requires further investigations.

VASCULAR REPAIR AND REMODELING USING RADIOFREQUENCY BALLOON ANGIOPLASTY.

Benjamin I. Lee, M.D., F.A.C.C.; Gary J. Becker, M.D.; Bruce F. Waller, M.D., F.A.C.C.; Kevin J. Barry, M.S.; Jonathan Kaplan, M.D.; Raymond J. Connolly, Ph.D.; Paul Nardella, B.S. VA and Georgetown Medical Centers, Washington, D.C.

The combination of balloon pressure and controlled thermal energy delivery may effectively repair intimal tears (IT) and remodel atherosclerotic vessels. To test the potential for radiofrequency energy (RF) fusion of IT, 5 atmospheres (atm) pressure were applied and 200 J RF delivered from block-mounted bipolar electrodes to 24 segments of postmortem human atherosclerotic aorta which had been manually separated along the intima-media and media-adventitial plane. Stronger tissue fusion resulted with pressure and RF (28.5 ± 3.3 gm) than with pressure alone (4.8 ± .26 gm; $p < .001$). To study the feasibility of RF balloon angioplasty (RFBA), a 4 mm x 2 cm bipolar RF balloon angio - plasty catheter was used to dilate segments of postmortem human atherosclerotic arteries of similar diameter. The balloon was inflated to 3 atm pressure for 1 min and vessels additionally treated with 200 J RF or with balloon pressure alone. 10/10 RF treated vessels had significant enlargement of their luminal diameter with stretching and thermal molding of the vessel walls and histological evidence of medial myocyte injury. 10/10 control vessels demonstrated recoil to their pre-dilatation geometry without histological evidence of myocyte injury. Thus, RFBA results in 1) strong tissue fusion of intima-media flaps, 2) thermal molding of atherosclerotic vessels and 3)injury to cells implicated in the fibroproliferative response. These observations may have implications for reducing acute and chronic restenosis following balloon angioplasty.

PERCUTANEOUS TRANSLUMINAL CORONARY ROTABLATION DURING HEART CATHETERIZATION

Raimund Erbel, M.D. FACC, Ulrich Dietz, M.D., David Auth, Ph.D., Michael Haude, M.D., Uwe Nixdorf, M.D.,Jürgen Meyer, M.D.
II. Medical Clinic, University Mainz, F.R.G.

After promising results in peripheral arteries, percutaneous transluminal coronary rotablation (PTCR) was used for atherectomy in coronary arteries during heart catheterization. The device consisted of a diamond-coated brass burr rotating with up to 190.000 rpm along a coaxial guide wire with a flexible tip. The burr size ranged from 1.25 - 2.0 mm. It was advanced during rotation avoiding drop of speed > 10 %. 10 patients (pts) with single vessel disease underwent PTCR instead of balloon angioplasty (PTCA) PTCR was started with small burr sizes. The final burr size measured 1.5 mm in 3 pts, 1.75 mm in 6 pts and 2.0 mm in 1. pt. PTCA was successful (increase of luminal narrowing > 20%) in 9 of 10 pts with a decrease of coronary stenosis from 75.8 ± 28.3 % to 33.3 ± 3% ($p < 0.001$). The most effective PTCR occurred in the pts with stable angina and no previous infarction. Because of residual luminal narrowing additional PTCA was necessary in3 of 9 pts decreasing the narrowing further to 14.8 ± 13.5%. Vessel perforation was not observed. With PTCR a dissection of a proximal LAD lesion occurred using a 2.0 mm burr. Bypass surgery was performed successfully.
Conclusion: PTCR seems to be an effective method for atherectomy in coronary arteries, particularly in hard lesions.

QUANTITATIVE ANALYSIS OF CORONARY ARTERY MORPHOLOGY USING INTRACORONARY HIGH FREQUENCY ULTRASOUND: VALIDATION BY HISTOLOGY AND QUANTITATIVE CORONARY ARTERIOGRAPHY.

Charles McKay MD FACC, Bruce Waller MD FACC, James Gessert BSEE, Steve Collins PhD, Michelle Catellier MD, Steven Fleagle BSEE, Melvin L. Marcus MD FACC, University of Iowa, Iowa City, Iowa.

Intracoronary high frequency (20 mHz) ultrasound (ECHO) is a new technology. Before it can be used clinically, validation studies are essential. We placed a 1.5 mm diameter probe in the coronary artery lumen and rotated it to image the arterial wall and lumen. We performed ECHO measurements on 25 pressure perfusion fixed coronary arterial segments from cadaver bovine and porcine hearts. We validated measurements of lumen area (LA, inside the internal elastic lamina), and total arterial area (area inside external elastic lamina) using histologic (HIS) sections and quantitative coronary arteriography (QCA). The HIS measurements of LA ranged from 2.4 to 28.3 $mm^2$ and of total arterial area ranged from 2.9 to 33.9 $mm^2$. Direct measurements of arterial wall diameters by ECHO were limited in some specimens due to non-circular lumen shape or eccentric ECHO probe position. Measurements by ECHO were highly correlated with HIS and QCA:

| LUMEN (n=25) | r | SEE($mm^2$) | Slope | Intercept($mm^2$) |
|---|---|---|---|---|
| AREA (HIS vs ECHO) | .96 | 1.86 | .91 | -.49 |
| AREA (QCA vs ECHO) | .94 | 2.07 | .85 | 1.31 |
| TOTAL ARTERIAL | | | | |
| AREA (HIS vs ECHO) | .97 | 2.11 | .89 | -.33 |

We conclude that coronary artery lumen area and total arterial area can be measured accurately with high frequency intracoronary ultrasound. This technique may permit evaluation of the arterial wall and lumen during cardiac catheterization.

# Thursday, March 23, 1989
# 10:30AM–12:00NOON, Anaheim Room
# Anaheim Convention Center
# Clinical Outcome of Coronary Angioplasty

DOES THE DISADVANTAGE OF INCOMPLETE REVASCULARIZATION BY CORONARY ANGIOPLASTY INCREASE WITH TIME?

David R. Holmes Jr. M.D., F.A.C.C., Ronald E. Vlietstra M.D., F.A.C.C., LaVon N. Hammes, Guy S. Reeder M.D., F.A.C.C., Michael B. Mock M.D., F.A.C.C., Mayo Clinic, Rochester, Minnesota.

The importance of achieving complete revascularization (CR) vs incomplete revascularization (IR) by percutaneous transluminal coronary angioplasty (PTCA) remains controversial. Of 1,183 pts (474 with single, 709 with multivessel disease) followed up for successful PTCA performed between 1979 and 1987, there was CR (no residual visual assessment stenosis >70%) in 718 (61%) and IR in 465 (39%). CR was achieved in 41% of multivessel and 89% of single vessel cases. During 6-97 months follow-up (mean 30 months), CR and IR event totals were as follows: death 25 (3%) and 26 (6%) (p=.09), bypass surgery 68 (9%) and 77 (17%) (p=.006), repeat PTCA 124 (17%) and 73 (16%), and myocardial infarction 24 (3%) and 31 (7%) (p=.01), respectively. At last follow-up, 80% of CR had no angina vs 73% of IR pts. The probability (standard error) of surviving free of death, bypass grafting, angina Class III or IV, or myocardial infarction was:

| | 1 Year | 2 Years | 3 Years | 5 Years |
|---|---|---|---|---|
| CR (n=718) | 0.84(.01) | 0.78(.01) | 0.72(.02) | 0.62(.03) |
| IR (n=465) | 0.70(.02) | 0.58(.03) | 0.49(.03) | 0.37(.04) |

The event-free survival probabilities for IR were significantly lower (p<0.001) at each time interval. In addition, the discrepancy in outcome between CR and IR increased with time. This progressive disparity in outcome with time underscores the need for longer-term follow-up in studies comparing different degrees of revascularization.

CONSEQUENCES OF EARLY RESTENOSIS AFTER CORONARY ANGIOPLASTY.

Ronald E. Vlietstra M.B.,Ch.B., F.A.C.C., David R. Holmes, Jr. M.D., F.A.C.C., Richard J. Rodeheffer M.D., F.A.C.C., LaVon N. Hammes, Kent R. Bailey Ph.D., Mayo Clinic, Rochester, Minnesota.

Early restenosis is an unresolved problem whose impact on long-term outcome has not been quantitated. We evaluated all 466 successful Mayo Clinic patients (1979-1987) who had reangiography at 3 to 12 months to detect the presence (P) or absence (A) of restenosis. Restenosis was defined as a loss of 50% of the initial gain or more than 30% worsening in percentage stenosis. P and A groups were similar with respect to age, sex, number of vessels diseased, ejection fraction, and prior MI or CABG; 34% of P but only 21% of A ($P < 0.005$) had >1 segment dilated initially. Their 5-year probability of events (standard error) was as follows:

| Event | Group P (n = 236) | Group A (n = 230) | RR* (95% confidence interval) |
|---|---|---|---|
| Repeat PTCA | 0.48 (0.04) | 0.23 (0.05) | 4.26 (2.80-6.51) |
| CABG alone | 0.29 (0.04) | 0.11 (0.03) | 3.68 (2.16-6.28) |
| MI | 0.11 (0.04) | 0.06 (0.02) | 1.07 (0.44-2.64) |
| Death | 0.10 (0.04) | 0.06 (0.02) | 1.07 (0.39-2.96) |

*Relative risk, from proportional hazards model.

The 5-year probability was 0.38 for P and 0.03 for A for PTCA of previously dilated segments only, 0.04 and 0.17 for new segments, and 0.06 and 0.03 for both types of segments. We conclude that the occurrence of early restenosis markedly increases the risk of revascularization events during 5-year follow-up but has little effect on infarction or mortality. Even when early restenosis is absent, there is a significant 5-year probability of further revascularization procedures, predominantly for disease at other sites.

**DETERMINANTS OF ARTERIAL DISSECTION DURING PTCA: LESION TYPE VERSUS INFLATION RATE.**

Anil Bansal, M.D., Nishit A. Choksi, M.D., Arlene Bradley Levine, M.D., V. Gangadharan, M.D., F.A.C.C., Gerald C. Timmis, M.D., F.A.C.C., William O'Neill, M.D., William Beaumont Hospital, Royal Oak, Michigan.

Gradual balloon inflation has recently been suggested to reduce the frequency of coronary dissection (DIS) post PTCA. We hypothesized that lesion characteristics may additionally affect DIS risk. We randomized 142 lesions (120 patients) to either a gradual increase to peak inflation pressure of 8 atmospheres over 30 sec or to a rapid inflation protocol (increase of pressure to 8 atmospheres in < 5 sec). Seventy-one lesions had gradual and 71 lesions rapid inflations. Lesions were classified by level of complexity as Type A (low), B (medium), and C (high) (ACC/AHA task force on PTCA; Circ 1988; 78:486). Post PTCA angiograms were assessed for DIS and lesion type.

| | Gradual | Rapid | p Value |
|---|---|---|---|
| Frequency of DIS: | 42/71 | 48/71 | NS |

| | Type of Lesion | | | |
|---|---|---|---|---|
| | A | B | C | |
| Frequency of DIS: | 8/24 | 57/91 | 26/27 | p = <0.00001 |

| | Gradual/Rapid | DIS/Gradual | DIS/Rapid | |
|---|---|---|---|---|
| Type A | 12/12 | 2/12 | 6/12 | NS |
| Type B | 45/46 | 27/45 | 30/46 | NS |
| Type C | 14/13 | 14/14 | 12/13 | NS |

Conclusion: The balloon inflation rate appears to have no significant effect on DIS risk. In contrast, DIS occurrence post PTCA is affected by lesion type and occurs most commonly with more complex lesion morphology (B and C).

**EVALUATION OF LEFT VENTRICULAR FUNCTION IMMEDIATELY AFTER SUCCESSFUL BALLOON RECANALIZATION OF CHRONIC TOTAL CORONARY OCCLUSIONS.**

Leo Finci M.D., Bernhard Meier M.D., Bernard de Bruyne M.D., Pierre-André Dorsaz Ph.D., Pierre-André Doriot Ph.D., Wilhelm Rutishauser, M.D., F.A.C.C., Cardiology Center, University Hospital, Geneva, Switzerland.

To evaluate changes in left ventricular (LV) function after successful balloon recanalization of chronic total coronary occlusions, high fidelity LV pressure measurements using tip-manometers and biplane left ventriculograms for regional wall motion analysis were performed immediately (<5 sec) after right ventricular pacing at increments of 20 beats per min every 2 min up to 160 beats per min or onset of chest pain. Ten patients were studied before and after successful balloon recanalization of 6 left anterior descending, 2 right, and 2 left circumflex coronary arteries. All pertinent territories had visible collaterals and abnormal regional wall motion at rest. In addition, synchronism of regional wall motion was analyzed by contraction-relaxation fitted curves obtained by biharmonic Fourier transformation of each of 128 shortening lines created between end-diastolic and end-systolic points of the realigned LV silhouettes. This allowed to determine the time to peak relaxation (TPR) for each shortening line. Balloon recanalization led to better LV synchronism after pacing as expressed by a reduction in the standard deviation of TPR of the 128 shortening lines It also resulted in improved RWM and LVEDP after pacing:

| | Before | After | P |
|---|---|---|---|
| Standard deviation of TPR (°) | 43±13 | 21±10 | <0.05 |
| Regional wall motion (%) | 35±10 | 43±11 | <0.05 |
| LVEDP (mmHg) | 22±3 | 16±2 | <0.05 |

Conclusions: After successful balloon recanalization of chronic total coronary occlusions, immediate improvement of LV function after pacing can be demonstrated.

CONSEQUENCES OF OCCLUSION DURING PTCA:
THE 1985-86 NHLBI PTCA REGISTRY

Katherine M. Detre, MD, DrPH, David R. Holmes Jr, MD, FACC, Richard Holubkov, MS, and Registry Investigators, University of Pittsburgh, Pittsburgh, PA

Of 1,801 pts with revascularization by PTCA, 122 (6.8%) had occlusion during PTCA or as an abrupt closure during post-PTCA hospitalization. The occlusion rate was 6.0% in pts with single-vessel and 7.5% in pts with multivessel disease. Of these 122 pts, 60 (49%) were successfully redilated by PTCA (Group 1), 43 (35%) were not redilated and had bypass surgery (CABG) (Group 2), and 19 (16%) were treated medically (Group 3). Event rates in-hospital and during one-year post-hospital follow-up are evaluated below and compared to those of the 93% of all pts without occlusion. (Pts with PTCA for acute myocardial infarction (MI) or with prior PTCA are not included in this analysis.)

| Pt Subgroup | | In-Hospital(%) | | | Post-Hospital(%) | | | |
|---|---|---|---|---|---|---|---|---|
| Occlusion | n | Death | MI | CABG | Death | MI | CABG | PTC2* |
| Group 1 | 60 | 5 | 27 | 10 | 3 | 2 | 10 | 17 |
| Group 2 | 43 | 5 | 56 | 100 | 5 | 5 | 2 | 2 |
| Group 3 | 19 | 5 | 47 | 0 | 5 | 0 | 16 | 5 |
| No Occlusion | 1679 | 1 | 2 | 3 | 2 | 3 | 8 | 19 |

(*PTC2 denotes post-hospital repeat PTCA)

Combining all untoward events by one yr, 19% of all deaths, 38% of all MIs, and 25% of all CABGs occurred in the 7% of pts with first PTCA complicated by occlusion. Pts with occlusion related to or soon after PTCA have a high in-hospital complication rate irrespective of whether PTCA or CABG is performed. However, following discharge, the course of Group 1 pts closely resembles that of pts without occlusion.

A COMPARISON OF SOCIO-ECONOMICS AND OUTCOME AFTER MULTIVESSEL CORONARY ANGIOPLASTY OR BYPASS SURGERY.

Ben D. McCallister, M.D., F.A.C.C., Robert Ligon, M.A., Martin Stack, B.S., Michael Borkon, M.D., F.A.C.C., Geoffrey O. Hartzler, M.D., F.A.C.C. Mid America Heart Institute, Kansas City, Missouri

The purpose of this study was to compare all medical costs, complications, and the effectiveness of therapy in a consecutive series of pts. undergoing PTCA or CABG during 1986 & 1987. All pts. had an angiogram and CV evaluation during the initial hospitalization. Comparing the PTCA vs CABG groups, resp.: av. age = 64 vs 65 yrs.; males = 69 vs 71%; LVEF = 58 vs 62%; class III or IV angina = 75 vs 74%; 3 vessel disease = 47 vs 88% (P =< .001); no. of lesions dilated vs no. of grafts placed = 322 vs 378; % with total revascularization = 50 vs 77% (P =< .001); length of initial hosp. stay = 8.6 vs 16.2 16.2 days (P =< .001); CVA post-op = 0 vs 3%; in hosp. death = 2 vs 5%. No PTCA pt. required emergency CABG. AT F.U. comparing the PTCA vs CABG groups, resp.; Class I or II angina = 88 vs 96%; late deaths in 1st yr. = 3 vs 1%; nonfatal MI = 3 vs 2%; total 1 yr. mortality = 5 vs 6%; late need for CABG = 5 vs 0%; late need for PTCA = 22 vs 3%; % who felt they were living a normal life = 82 vs 89%. Cost analyses including all physician and hosp. charges during the initial hosp. stay and for 1 yr. resp.: PTCA = 13,807 & 17,732, CABG = 31,075 & 33,673 (P =< .001). Conclusions: 1) The initial and total 1 yr. medical costs for PTCA were 56 & 47%, resp., less than CABG. 2) A subsequent procedure (PTCA or CABG) was required in 24% of PTCA pts. vs 3% of CABG pts. 3) Although the PTCA procedural mortality was lower in this study, the 1 yr. mortality was similar in both groups. 4) At 1 yr. fewer CABG pts. had angina, possibly reflecting more complete revascularization, but pt. life satisfaction & activity was similar in the two groups.

## Thursday, March 23, 1989
## 10:30AM–12:00NOON, Pacific Ballroom C & D
## Anaheim Hilton Hotel
## Pharmacology of Nitroglycerin

BIPHASIC RESPONSE OF CORONARY BLOOD FLOW TO INTRACORONARY NITROGLYCERIN IN NORMAL SUBJECTS.

Ignazio Simonetti, M.D., James D. Rossen, M.D., Melvin L. Marcus, M.D., FACC, Michael D. Winniford, M.D., FACC, University of Iowa, Iowa City, IA

Coronary flow (CF) responses to intracoronary nitroglycerin in patients have been reported to be extremely variable. In dogs, intracoronary (IC) nitroglycerin has a striking biphasic effect on CF (increment/decrement). To determine if nitroglycerin had a similar effect on CF in normal humans (NLS), we injected nitroglycerin IC (50 and 300 mg) in 9 NLS and compared its effect on coronary flow velocity (CFV: 3Fr IC Doppler catheter) to that of IC papaverine (PAP: 6,8,10, and 12 mg). Peak increase and duration (DUR, sec) of CFV response were evaluated. Results (mean±SE):

| | Papaverine (mg) | | | | Nitroglycerin (mcg) | |
|---|---|---|---|---|---|---|
| | 6 | 8 | 10 | 12 | 50 | 300 |
| CFR | 2.7 | 3.4@ | 3.6@ | 3.9*@ | 2.1 | 3.1 |
| SEM | 0.1 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| DUR | 77*@ | 101*@ | 115*@ | 132*@ | 26 | 42 |
| SEM | 7 | 6 | 6 | 9 | 2 | 3 |

(*=p<0.01 vs nitroglycerin 300 mcg; @=p<0.05 vs nitroglycerin 50 mcg). At 3 min after nitroglycerin 300 mcg, resting CFV was 21±3% lower (p<0.01), mean blood-pressure was 14±2% lower (p<0.01) and quantitative proximal coronary diameter (Brown/Dodge method) 15±3% larger (p<0.01) than control. Thus, the human coronary circulation exhibits a striking biphasic response to nitroglycerin - marked increase promptly followed by a mild decrease in CFV. Failure to appreciate the biphasic nature of coronary flow response to IC nitroglycerin may explain many conflicting results reported in previous studies.

METHIONINE REVERSES TOLERANCE TO TRANSDERMAL NITROGLYCERIN

Warren S. Levy, M.D., Richard J. Katz, M.D., F.A.C.C., Alan G. Wasserman, M.D., F.A.C.C. George Washington University, Washington, D.C.

Depletion of sulfhydryl groups (SH) may contribute to nitroglycerin (NTG) tolerance following chronic exposure. We studied the ability of methionine (Meth), a SH donor, to potentiate the vasodilatory effects of NTG and reverse tolerance. The equilibrium technique of forearm plethysmography was used to measure venous tone (VT) pre and post a 0.4 mg sublingual NTG bolus in 13 pts 1) at baseline (base); 2) 2 hrs post 10 mg NTG patch (NTP-2h) and 3) 74 hrs after continuous patch exposure (NTP-74h). Repeat measures were made following 5 gms IV Meth at base (M-base) and 74 hrs (M-74h). Forearm volumes were measured at 30 mm Hg above cuff zero with results expressed as VT (cc/100 cc arm; mean ± S.D.):

| | Base | M-base | NTP-2h | NTP-74h | M-74h |
|---|---|---|---|---|---|
| Pre-NTG | 2.58±.9 | 2.56±.8 | 2.80±1 | 2.58±.9 | 2.67±.9 |
| Post-NTG | 3.37± 1* | 3.45±.9* | 3.60±1* | 3.01±.9* | 3.53± 1* |
| % change | 32±13 | 37±15+ | 31±13** | 16±10 | 35±14** |

*p<.001 vs. pre-NTG, +p<.02 vs. Base, **p<.001 vs NTP-74h

Methionine alone had no intrinsic vasodilatory action. VT changes in response to NTG bolus were attenuated at 74 hrs (p<.001 vs. 2hrs). Meth potentiated the effect of NTG more so at 74 hrs than at base (17.4% vs. 5.4%, P<.001) suggesting greater sulfhydryl donor effect in the attenuated state. Plasma volume expansion was suggested at 74 hrs vs. 2hrs by a 3% fall in hematocrit (p<.01) and increase in weight (157 vs 155 lbs, p<.01).

Conclusions: 1) Meth potentiates the vasodilatory effects of NTG and reverses attenuation, following chronic transdermal NTG exposure; 2) Plasma volume expansion after prolonged NTG exposure may contribute to attenuation.

## A NEWLY DEVELOPED NITROGLYCERIN PATCH WITH 'PHASED RELEASE'

Sigmund Silber, M.D., Ph.D., F.A.C.C., Astrid C. Vogler, M.D., Margot Vogel, R.N., Karl Theisen, M.D.. University of Munich, West Germany.

As we have shown in previous studies, constant plasma levels of isosorbide dinitrate (ISDN) and its metabolites induce the development of tolerance, whereas daily three-fold fluctuations of the plasma levels circumvent it. To test the hypothesis that the same concept can be extrapolated to nitroglycerin (NTG), we studied 12 pts with proven coronary artery disease, angina pectoris and abnormal exercise test in a placebo controlled, double-blind, randomized and cross-over protocol. To establish fluctuating plasma levels, a new NTG patch containing 20 mg NTG with 'phased release' was developed. Exercise tests were performed before as well as 2 & 10 hrs after the 1st & next day (2nd) application. The decisive parameter for unbiased assessment of the anti-ischemic effect was the exercise-induced ST-segment depression at identical work loads.

Results: NTG plasma levels 2, 10 & 24 hrs after the 1st application were 544±402, 261±183 & 176±129 pg/ml and 2 & 10 hrs after the 2nd application 521±210 & 307±310 pg/ml. The corresponding exercise-induced ST-segment depression at identical work-loads the 1st day were 2.9±0.9 (baseline), 1.0±0.8*, 2.4±0.7 & 2.8±0.7 mm; 2nd day 2.0±1.3 & 2.8±1.1 mm (* = significant as compared to placebo).

Conclusions: The newly developed NTG patch with 'phased release' lost its effect within 2 days. Even the concept of three-fold fluctuations in NTG plasma levels did not prevent the development of tolerance. Perhaps a short term removal (e.g. 90 minutes) of this 'phased release' patch will be sufficient to prevent tolerance development.

## BRACHIAL ARTERY PRESSURE MEASUREMENTS UNDERESTIMATE BENEFICIAL EFFECTS OF NITROGLYCERIN ON LEFT VENTRICULAR AFTERLOAD.

Raymond Kelly M.B, Harry Gibbs M.B, John Morgan M.B, F.A.C.C, Julie Daley R.N, Kem Mang BSc, Alberto Avolio PhD, Michael O'Rourke M.D, F.A.C.C. St. Vincent's Hospital, Sydney, Australia.

In normal doses sublingual nitroglycerin (NTG) not only reduces LV preload but also dilates peripheral and coronary arteries. Arterial dilation decreases wave reflection leading to reduced ascending aortic systolic pressure. Under clinical conditions, however, a change in sphygmomanometric pressure is not consistently seen despite symptom improvement with NTG. This study examines why beneficial effects of NTG on LV afterload are not always apparent from pressure measurements in peripheral arteries. Sublingual NTG (0.3 mg) was administered to 14 pts undergoing diagnostic cardiac catheterisation. Recordings were taken in the ascending Ao and brachial artery (BA) with a Millar micromanometer catheter before and 5-8 minutes after sublingual NTG. Ao systolic pressure always fell after NTG (- 6 to - 44, av. 22.1 mm Hg). In contrast, BA pressure change was much less: + 2 to - 33, av. 11.8 mm Hg. In some patients a marked Ao fall was accompanied by little or no BA change. Integrated mean pressure fell to a variable degree in all but 2 pts (- 1 to - 25, av. 7.5 mm Hg) with no significant change in diastolic pressure. Comparison of Ao and BA pressure wave contours explains this discrepancy. The systolic pressure peak in the Ao is normally formed by a reflected wave whereas in the BA this wave occurs after the systolic peak, on the downstroke of the wave. Thus, reduction in wave reflection by NTG does not alter the systolic peak in the BA but reduces the Ao peak pressure. Conclusion: BA pressure measurements underestimate beneficial effects of NTG on central pressure levels due to transmission changes in wave contour between Ao and BA sites as a result of different timing of wave reflection.

## THE ANTITHROMBOTIC ACTION OF NITROGLYCERIN: CYCLIC GMP AS A POTENTIAL MEDIATOR.

Michael Johnstone, M.D., Jules Y.T. Lam, M.D., F.A.C.C., David Waters, M.D., F.A.C.C., Montreal Heart Institute, Montreal, Canada.

To investigate whether cyclic GMP may be involved in the antithrombotic action of nitroglycerin (NTG) we studied platelet deposition (PD, x10⁶) onto normal porcine aortic media in an ex vivo flow chamber of 1 mm diameter. Arterial blood from control and drug treated pigs was drawn by a peristaltic pump through the chamber at 20 ml/min for 5 mins. PD was quantitated using autologous $^{111}$Indium-labeled platelets injected 18-24 hrs beforehand. Baseline PD was 55.5±6.6. A NTG infusion titrated to produce a 10% fall in mean arterial pressure decreased PD to 37.7±8.5 (n=8, p<0.01). With aspirin pretreatment (1 mg/kg for 3 days), PD was low 26.2±5.3 (p<0.005) and decreased further with a NTG infusion to 17.0±4.7 (n=8, p<0.005). Methylene blue (MB, 5x10-3 M) given as a 10 ml i.v. bolus + perfusion of 3 ml/min did not change PD compared to control: 34.0±6.8 vs 25.1±5.8 (n=8, p=NS) and a subsequent perfusion of NTG caused no decrease in PD: 31.3±8.0 (p=NS). NTG given prior to the MB infusion decreased PD; this decrease was attenuated by MB and enhanced by subsequent cyclic GMP infusion (chamber conc 7.4x10-6 M).

| | N | PD (X ± SE) | p vs control |
|---|---|---|---|
| control | 5 | 117.4±18.7 | |
| NTG | 5 | 47.1±14.4 | 0.04 |
| NTG + MB | 5 | 54.6±7.0 | 0.07 } 0.02 |
| MB + cyclic GMP | 5 | 18.4±3.8 | 0.006 } |

Thus, under controlled flow conditions, cyclooxygenase inhibition with aspirin does not attenuate the antithrombotic effect of NTG. Guanylate cyclase inhibition with methylene blue abolishes the effect of NTG, but it is restored by a cyclic GMP infusion.

## EVIDENCE FOR ANTITHROMBOTIC PROPERTIES OF NITRATE-VASODILATORS IN VIVO BUT NOT IN VITRO

C. Drummer, U. Valta-Seufzer, J.-M. Helm, R. Gerzer
Med. Klinik Innenstadt, University of Munich, FRG

The $NO_2$-containing organic nitrates and the NO-containing vasodilators like sodium nitroprusside (SNP) or SIN-1 (the bioactive metabolite of molsidomine) exert their effects through activation of soluble guanylate cyclase (sGC). While NO-compounds can directly activate sGC, the nitrates need to be metabolized to release nitric oxide prior to activation of the enzyme, a mechanism that exists in vascular smooth muscle. Its exhaustion seems to be the reason of nitrate tolerance. Nitric oxide also activates sGC in platelets. We have recently shown that in vitro only NO-containing agents, but not nitrates, can stimulate sGC in platelets and potently inhibit aggregation. To investigate this difference in vivo, we conducted a double-blind study to compare the effectiveness of each a single oral dose of molsidomine (4mg), isosorbide-5-mononitrate (ISMO,20mg) or placebo on platelet function. Twelve healthy young subjects received their medications within 6 consecutive days in a randomized order. After a 30 min resting period measurements were done before and 30 and 60 min after application (days 1,3,5) as well as during the wash-out period (days 2,4,6). RESULTS: The minimal dose of platelet activating factor (PAF) required to induce irreversible aggregation was increased significantly (p≤0.005) within 30 min after application of ISMO from about 50 to 120 nM. This threshold dose was increased in a similar manner for molsidomine, whereas in the control period it was only slightly elevated from 50 to 80 nM PAF. There was also a prolongation of the bleeding time in both intervention periods (4.5 min to 6 min) that was still detectable after 24 hours. CONCLUSION: The elevated threshold doses and prolonged bleeding times indicate antithrombotic properties of organic nitrates in vivo. These results also demonstrate that in vivo, in contrast to in vitro, not only NO-compounds, but also organic nitrates inhibit platelet function.

# Thursday, March 23, 1989
# 10:30AM–12:00NOON, Marriott Hall North
# Anaheim Marriott Hotel
# Clinical Electrophysiology: Supraventricular Arrhythmias

THE EFFECT OF EPICARDIAL ACCESSORY PATHWAY ABLATION OR ENDOCARDIAL DISSECTION FOR AV NODAL REENTRANT TACHYCARDIA ON VAGAL INNERVATION TO THE AV NODE.

William M. Miles, M.D., FACC, Raymond E. Dusman, M.D., Lawrence S. Klein, M.D., FACC, James J. Heger, M.D., FACC, Yousuf Mahomed, M.D., Robert D. King, M.D., Douglas P. Zipes, M.D., FACC, Indiana Univ. Med. Ctr., Krannert Inst. of Cardiology, VAMC, Indianapolis, IN

The effect of surgery for supraventricular tachycardia on vagal innervation to the AV node in humans is unknown; our canine data suggest that posteroseptal epicardial AV dissection interrupts vagal innervation to the AV node. Therefore, we examined reflex changes in AV nodal conduction following phenylephrine (P) in 31 patients (pts) (mean age 33 yrs) after epicardial dissection and cryoablation of accessory pathways (AP) and in 5 pts (mean age 38 yrs) after endocardial dissection of the AV node for AV nodal reentrant tachycardia (AVNR) while preserving AV nodal conduction. Boluses of P (200-1000 mcg IV) were titrated 4-19 (mean 7) days after surgery to increase BP > 20 mm Hg and sinus cycle length (CL) > 50 msec. The same dose of P was then given during atrial and ventricular pacing at constant CL (400-600 ms). Of the 31 pts with APs, P prolonged both AV and VA conduction in 16 pts, AV conduction only in 8 pts, VA conduction only in 1 pt, and AV conduction in 3 pts with no VA conduction; P failed to prolong ($\leq$ 10 ms) AV or VA conduction in 3 pts (2 with right and 1 with left free wall APs). Of the 5 pts with surgery for AVNR, P prolonged either AV or VA conduction in only 2 pts; all 5 pts had preoperative evidence of vagal innervation of the AV node and no pt had recurrent AVNR postoperatively. Thus, epicardial dissection and cryoablation for WPW does not interrupt vagal innervation to the AV node in most pts, but endocardial surgical dissection for AV nodal reentry usually, but not consistently interrupts vagal innervation to the AV node.

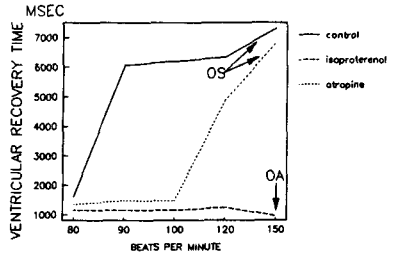
AUTONOMIC INFLUENCE ON VENTRICULAR SUBSIDIARY PACEMAKERS: A STUDY OF PATIENTS POST AV NODAL ABLATION.

Koonlawee Nademanee, M.D., F.A.C.C., H. Elizabeth Noll, M.D., William G. Stevenson, M.D., F.A.C.C., James N. Weiss, M.D., F.A.C.C., Clara M. Pruitt, R.N., VAMC, Los Angeles, California.

To study the autonomic effects on subsidiary ventricular pacemakers, we studied 8 patients (all male; 54 years) who had complete AV block post AV nodal ablation for the treatment of recalcitrant supraventricular tachyarrhythmias. The study included ventricular pacing for 30 seconds (70-180 bpm) during baseline, isoproterenol (2-3 micrograms/minute), and after 1 mg atropine infusion. The study was performed 4 to 48 hours after the ablation procedure. The basic cycle length (BCL) of the spontaneous activity and the cycle length from the last paced beat to the first spontaneous ventricular escape beat, the ventricular recovery time, were obtained in all conditions.

Results: There are two types of overdrive pacemaker responses during control: 1) overdrive suppression (OS) which occurred in the majority of patients. 2) overdrive acceleration (OA) which occurred in 2 patients. Isoproterenol significantly shortened the BCL 22% ($p < 0.01$) and abolished OS in all patients. Also, isoproterenol induced OA at a fast rate (150-180 bpm) in 6 of the 8 patients. Atropine had no effect on either the spontaneous rate or OS/OA.

Conclusions: 1) Unlike the sinus node, subsidiary ventricular pacemakers are influenced only by sympathetic activity, not by parasympathetic activity. 2) Physiologic OS occurred in the majority of patients but abnormal OA could occur during increased sympathetic activity coupled with a fast rate; these support an in vitro observation that catecolamines and a fast rate could provoke oscillation potential.




FURTHER SUPPORT OF THE ATRIO-VENTRICULAR LOCALIZATION OF SO-CALLED "MAHAIM FIBERS".

Jacob Atié, M.D., Pedro Brugada, M.D., Joep L.R.M. Smeets, M.D., Fernando E.S. Cruz, M.D., Olaf C.K.M. Penn, M.D., Hein J.J. Wellens, M.D., F.A.C.C., Depts. of Cardiology and Cardiothoracic Surgery, University of Limburg, Maastricht, The Netherlands.

To characterize the type of pathway (P) of apparently nodo-ventricular (NV) accessory (A) pathways, data of 4 Pt were retrospectively and of 2 Pt prospectively analyzed. In 5 Pt a right-sided and in one Pt left-sided NV AP was diagnosed. In 1 Pt, ventricular activation could be advanced during tachycardia (T) by a right atrial premature beat, given simultaneously with the onset of retrograde atrial activation suggesting a direct AV connection of the AP. In another Pt epicardial dissection of the right lateral AV groove interrupted anterograde preexcitation and T, thereby demonstrating a direct AV connection of the AP. In the other 4 Pt, careful analysis of the electrophysiologic studies suggested a classic NV AP. However, an AV AP with anterograde decremental conduction properties could not be excluded. In conclusion, in our 6 Pt with an electrophysiologically typical NV AP, 2 had an AV AP with decremental conduction. In the remaining 4 Pt a true AV localization of the AP could not be excluded.

THE DURATION OF SINUS NODE DEPOLARIZATION CAN INDICATE THE DEGREE OF SINUS NODE DYSFUNCTION.

James A. Reiffel, M.D., F.A.C.C., Gail Zimmerman, M.D., Columbia University, New York.

We have shown that the duration (DUR) of sinus node (SN) depolarization (D) as seen on SN electrograms is longer in patients with SN dysfunction than in normals. A reduced rate of rise and/or prolonged refractoriness of SN cells as well as delayed intranodal conduction could each prolong the SND, and might be additive. Thus, we hypothesized that the SND DUR would be longest in patients with the most extensive SN dysfunction. To test this hypothesis we determined the SND DUR in 10 patients with normal SN function and in 20 patients with 1 or more of the following SN abnormalities: prolongation of sinoatrial conduction time, prolongation of corrected SN recovery time, prolongation of peak paced cycle length (PCLp), or SN dysfunction by ECG. All results are in msec (mean/range).

| | normals | single abnormality | 2 abnormalities or more |
|---|---|---|---|
| SND DUR: | 138/95-190 | 157/120-225 | 195/140-260 |

(Carotid massage was necessary for visualization in 5 normals). SND DUR was > 150 in only 2/10 normals but in 4/8 and 9/12 with 1 or $\geq$ 2 SN abnormalities respectively. In 2 patients with all of the listed abnormalities the SND DUR was 230/200-260. We conclude the SND DUR, an easily obtained measurement, correlates with SN function. Severe SN dysfunction is unlikely if the SND DUR is < 160 msec.

CHRONIC EFFECTS OF A-V NODAL ARTERY EMBOLIZATION
Paul J. Wang, M.D., Frederick Schoen, M.D., Kathleen Reagan, M.D., Hussein Rizk, M.D., Hong Sheng Guo, M.D., Peter L. Friedman, M.D., Ph.D. Harvard Medical School, Boston, MA.

Catheter ablation of A-V conduction to treat refractory supraventricular tachycardia causes advanced A-V block and requires permanent pacemaker implantation. A new method for modifying A-V conduction (AVC) by selective A-V nodal artery catheterization and embolization (EMB) of the A-V nodal artery was tested in closed chest dogs. Autonomic blockade was first achieved by administration of atropine and propranolol. A-V nodal refractory period (AVNRP) and Wenckebach cycle length (WCL) in ms were then measured in a control state (PRE-EMB), acutely after EMB and a mean of 37 days after EMB. Results for AVNRP/WCL were:

| DOG | PRE-EMB | ACUTE EMB | CHRONIC EMB |
|---|---|---|---|
| 1 | 210/270 | 310/350 | ≤200/260 |
| 2 | ≤130/220 | 230/280 | 230/280 |
| 3 | ≤180/230 | ≤195/230 | ≤200/≤200 |
| 4 | ≤190/210 | ≤260/300 | ≤205/230 |
| 5 | ≤200/250 | ≤190/240 | ≤220/250 |
| 6 | 240/290 | 270/320 | 240/280 |

Advanced A-V block did not occur acutely after EMB, nor did it appear later after EMB. EMB acutely caused an increase in AVNRP and WCL. Subsequently, AVNRP and WCL returned to normal in all but one animal, even though all animals had histologic evidence of localized infarction within or near the A-V node and His bundle. In dogs, A-V nodal artery EMB alone does not yield long-term changes in AVC. Administration of cytotoxic ablative agents via the A-V nodal artery in addition to or instead of EMB of the A-V artery may be required to achieve clinically relevant chronic changes in AVC.

ORAL PROPAFENONE FOR PREVENTION OF RECURRENT PRIMARY ATRIAL FIBRILLATION: PREDICTIVE VALUE OF THE RESPONSE TO TRANSESOPHAGEAL ATRIAL STIMULATION.
Fulvio Bellocci M.D., Antonio Nobile M.D., Andrea Spampinato M.D., Simonetta Nava M.D., Sandro Montenero M.D., Paolo Zecchi M.D., Catholic University Sacred Heart, Rome, Italy.

We studied 34 pts(18 men,16 women,mean age 45 years)who had multiple episodes of primary paroxismal atrial fibrillation (PAF). Transesophageal atrial stimulation(TAS) was performed after all antiarrhythmic drugs had been stopped for at least 5 half-lives before testing, using a moderately aggressive protocol:single and double extrastimuli during sinus rhythm and during 600 and 400 msec cycle length pacing and 8" atrial bursts at incremental rates from 180 to 300 bpm. All pts had inducible,sustained(a>30" duration) PAF at the time of basal TAS. All pts received oral propafenone (P) in escalating dosages of 150 mg every 8 h, 300 mg every 12 h and 300 mg every 8 h. The dosage was based on pts tolerance and ECG evidence of QRS interval prolongation ≤50% from control. All pts underwent a second TAS after at least 12 days of oral P therapy. Twenty pts were considered responders(sustained PAF no more inducible) and 14 non responders(sustained PAF still inducible). There was no difference between responders and non responders in regard to age, sex,left atrial dimension,duration of PAF,electrophysiologic parameters before and after P and plasma level of P. During a follow-up of 13 ± 5 months,2 responders(10%) and 8 non responders(57%) had recurrences of sustained PAF ($p<0.05$). We conclude that oral P is effective and safe for treating pts with PAF. TAS is a rapid, simple and not expensive method in predicting the response to oral P.

## Thursday, March 23, 1989
## 8:30AM–10:00AM, California Room D
## Anaheim Convention Center
## Valvular

EVALUATION OF PROSTHETIC VALVE PERFORMANCE BY ASSESSING THE RESPONSE TO EXERCISE USING DOPPLER ECHOCARDIOGRAPHY
Hossam I. Kandil, MB BC.h., Ms.C; Claudine Moffett; Oi Ling Kwan, B.S.; Michael R. Harrison, M.D., FACC; Yahya S. Mikhael, M.D., FACC; Galal M. El-Said, M.D., FACC; Mohamed M. Ibrahim, M.D., FACC; Sherif El Tobgy, M.D.; Anthony N. DeMaria, M.D., FACC; University of Kentucky, Lexington, Kentucky

Although considerable data exist regarding the function of prosthetic heart valves(PROS) at rest, few data exist regarding the response to exercise(EX). Thus, we performed continuous wave Doppler(DOP) in 46 Pts with normal LV function (EF>55%) with 50 PROS (27 mitral (M), 23 aortic (Ao)) of varying type before and after symptom limited supine bicycle exercise. Gradient(GRAD) increased with Ex in all PROS: 4.4→8.5 mmHg for mean M, 11.5→17.8 mean Ao, and 24.2→39.0 mmHg for max Ao (all $p<.001$), and the percent increase was similar for both (51% (M) vs 64% (AO)). Linear regression failed to demonstrate a relationship between the change in gradient and indices of exercise effort including heart rate and Ex duration: ($r = 0.1$ and $r = 0.2$ respectively for all PROS). The change in GRAD with exercise was similar for tissue, tilting disc, caged, ball and bileaflet valves. No relation was observed between ΔGRAD and valve size for all PROS, or for 17 Pts with Bjork-Shiley; however an inverse relation existed for 20 Pts with St. Jude ($r= .61$). Importantly, the largest GRAD with EX was predicted by the resting GRAD: $r = 0.93$, $r = 0.79$, and $r = 0.94$, for mean GRAD of AO, M and both. Thus, Ex DOP provides a good method to assess PROS function. In asymptomatic pts with normal LV, GRAD response is not related to duration or HR. The response to EX of bileaflet valve tends to be favorable to other PROS. Of significance, the maximum GRAD produced by EX is related to and predicted by the rest GRAD.

**THE PROGRESSION OF AORTIC STENOSIS AS ASSESSED BY ECHOCARDIOGRAPHY.**
Anthony J Sanfilippo MD, Mark S Adams BS, Leonardo Rodriguez MD, Aleksandar D Popovic MD, Arthur E Weyman MD FACC. Massachusetts General Hospital, Boston MA.

Two-dimensional and Doppler echocardiography (echo) are now the major tools used in following patients with aortic stenosis (AS). Despite this, little is known about how echo-derived aortic valve areas (AVA) change with time, or how the severity of AS may effect such change. Such data would allow more rational planning of follow-up and interpretation of results. In order to clarify this we reviewed our echo database to select patients who had AS found on serial echo examinations separated by at least 2 years and in whom the examination included all data required for calculation of AVA by the continuity equation. Fifty-seven such patients have been reviewed to date (30M:27F; mean age 57.5 years). Mean follow-up (FU) was 32.7 mos.

**RESULTS:** AVA decreased from 1.45 ±.72 to 1.17 ±.51 $cm^2$. ($p<.0001$). The change in AVA (CHG) was then calculated on the basis of severity of AVA at initial study (AVA1):

| AVA1 ($cm^2$) | no. | CHG ($cm^2$) | %CHG | FU (mos) |
|---|---|---|---|---|
| ≤ 1.0 | 18 | .09±.10 | 12.5±13.6 | 34.6±11.8 |
| 1.0-2.0 | 27 | .21±.23 * | 14.2±16.3 | 31.1± 8.4 |
| > 2.0 | 11 | .74±.57 * | 26.2±16.8# | 33.6±10.6 |

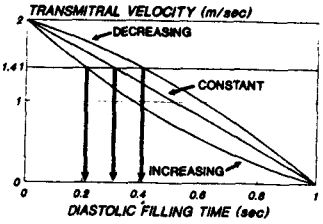
(*=p<0.03; #=p<0.05 compared with both other groups)

**CONCLUSIONS:** The change in both absolute and %AVA were greater when initial AVA was in the mild or moderate range as compared with severe AS over an average of 32.7 mos of follow-up. These results suggest that valve area decreases less rapidly as the severity of aortic stenosis increases.

## VENTRICULAR AND ATRIAL COMPLIANCE CHANGES AFFECT PRESSURE HALF TIME: EXPERIMENTAL EVIDENCE

Frank A. Flachskampf, MD, James D. Thomas, MD, J. Luis Guerrero, and Arthur E. Weyman, MD, FACC; Massachusetts General Hospital, Boston, Massachusetts

Pressure half time ($T_{\frac{1}{2}}$) from Doppler tracings is widely used to estimate valve area. We have shown previously in theory and in a flow model that it also depends on net atrial and ventricular compliance. To investigate the behavior of $T_{\frac{1}{2}}$ in the more physiologic situation where instantaneous compliance varies throughout diastole, we used an in vitro model of mitral filling where net compliance could increase or decrease up to the three-fold during diastole. **RESULTS:** 1. When compliance was constant (middle curve of figure), $T_{\frac{1}{2}}$ was 31±1.7% (mean±SD) of the diastolic filling period (DFP). 2. A steadily increasing compliance, but with the same average value, resulted in a $T_{\frac{1}{2}}$ of 22±2% of DFP (bottom). 3. A steadily decreasing compliance, average value again identical, yielded a $T_{\frac{1}{2}}$ of 41±2% of DFP (top). These changes were observed with pressure, flow, and Doppler recordings.



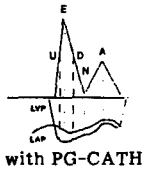

**CONCLUSION:** $T_{\frac{1}{2}}$ is affected not only by mean net compliance, but also reflects the temporal variation in compliance during diastole.

## CAN THE MODIFIED BERNOULLI EQUATION ACCURATELY ESTIMATE INSTANTANEOUS TRANSMITRAL PRESSURE GRADIENTS IN PATIENTS WITH CARDIAC PATHOLOGY?

Daniel David, M.D., F.A.C.C., Alex Neumann, B.S., Roberto M. Lang, M.D., F.A.C.C., Pinhas Sareli, M.D., Richard Marcus, M.D., Kenneth M. Borow, M.D., F.A.C.C., University of Chicago, IL

The modified Bernoulli equation (MBE) is widely used to calculate instantaneous pressure gradients (PG) from Doppler velocities. These velocities are dependent upon valve area (VA) and flow. During cath, we studied the impact of these two factors on the reliability of MBE in assessing instantaneous transmitral PG in 14 pts: 4 with mitral stenosis (MS; MVA = 1.1 ± 0.5 $cm^2$) and normal transmitral flow and 10 with dilated cardiomyopathy (CM), normal MVA and + transmitral flow (CI = 2.0 ± 0.5 $L/min/m^2$). Simultaneous PG from LA and LV microtip catheters and transmitral Doppler data using MBE were obtained at 5 points during diastole: early (E) and late (A) peak velocities, velocity nadir (N) and identical velocities on the upslope (U) and downslope (D) of early filling. Percent differences between PG-CATH and PG-MBE are shown (*p < 0.01; PG-CATH vs PG-MBE).

| TIMING | MS | | CM | |
|---|---|---|---|---|
| | % Diff | r | % Diff | r |
| U | - 2 | .98 | -71* | .30 |
| E | + 4 | .96 | -34* | .10 |
| D | -11* | .75 | -52* | .09 |
| N | -24* | .42 | -37* | .06 |
| A | -21* | .56 | -57* | .08 |

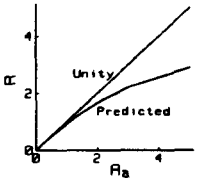



In MS pts with +MVA, PG-MBE correlated well with PG-CATH at points U and E but underestimated PG-CATH at D, N and A. This was true despite similar mean PG for MBE vs CATH (14 ± 4 vs 15 ± 2 mmHg). In CM pts with + transmitral blood flow, PG-MBE correlated poorly with PG-CATH ($r \leq 0.30$) at all measured points. Thus, the accuracy of the MBE for estimating instantaneous transmitral PG is affected by both the MVA and the magnitude of transvalvular flow.

## SYSTEMATIC ERRORS IN THE DOPPLER PRESSURE HALF-TIME FORMULA FOR MITRAL ORIFICE AREA.

Donovan M. Bakalyar Ph.D., Gerald C. Timmis M.D., F.A.C.C., Andrew M. Hauser M.D., F.A.C.C. William Beaumont Hospital, Royal Oak, Michigan

The pressure half-time ($T_{1/2}$) formula for the Doppler calculation of the mitral valve area (A), $A(cm^2)=220/T_{1/2}$, has enjoyed widespread clinical application despite the absence of theoretical justification. The potential for large systematic errors exist because in addition to the mitral valve area, $T_{1/2}$ depends strongly on muscle properties such as chamber compliance (C), the ventricular relaxation time (R), and degree of relaxation (D). We have developed a computer model employing these muscle properties and Euler's equation for fluid flow with which the Doppler curve can be reproduced by adjusting C,R,D, and A. We have used this model to produce a family of Doppler curves in which C,R, and D were held fixed while A was varied. The area $A_a$ estimated from these curves using the half-time formula was compared to the area A used in generating these curves. As is shown in the graph, $A_a$ begins to deviate strongly from A for areas larger than 1.5 $cm^2$.

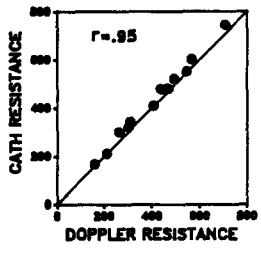



CONCLUSION: We have shown, using the principles of fluid dynamics and ventricular mechanics, that the validity of the pressure half-time formula depends on severe constraints that may often be violated in a clinical setting.

## VALVE RESISTANCE IN AORTIC STENOSIS: AN ALTERNATIVE METHOD FOR ASSESSING THE HEMODYNAMIC SIGNIFICANCE OF FLOW OBSTRUCTION.

Alex Neumann, B.S., Ted Feldman, M.D., F.A.C.C., Kenneth M. Borow, M.D., F.A.C.C., Roberto M. Lang, M.D., F.A.C.C., Lincoln E. Ford, M.D., The University of Chicago, Chicago, Illinois.

The accuracy of echo-Doppler (E-D) data for estimating valve area in patients with aortic stenosis (AS) has been well documented. These calculations are based on Gorlin's formula which relates transvalvular flow to the square root of the LV-Ao mean pressure gradient (PG). However, recent studies have suggested that flow and PG in AS vary as a linear rather than exponential function. In an attempt to develop a hemodynamic index of flow obstruction which incorporates this concept, we calculated valve resistance (VR; $d\text{-}s\text{-}cm^{-5}$) as PG/CO in 12 patients with AS and ≤ mild aortic regurgitation (AR) (valve area = 0.6 ± 0.2 $cm^2$; range 0.4-1.0 $cm^2$). During cath, PG and Fick CO were simultaneously obtained with E-D data. An excellent correlation between echo-Doppler and cath determined valve resistance was obtained (r = 0.95). In 11/12 patients, the difference between E-D and cath values were < 10%. In most cases, E-D determined LV outputs were slightly higher than Fick CO probably reflecting the failure of Fick CO measurements to include AR flow. Thus, echo-Doppler techniques are capable of accurately quantitating aortic valve resistance in AS. This capability should allow a more physiologically appropriate measure of valvular obstruction, especially when the magnitude of LV → Ao flow is altered by valvuloplasty, exercise or pharmacologic interventions.



# Thursday, March 23, 1989
# 10:30AM–12:00NOON, California Room D
# Anaheim Convention Center
# The Pericardium

LEFT VENTRICULAR PSEUDO HYPERTROPHY IN PERICARDIAL EFFUSION: A SIGN OF CARDIAC TAMPONADE.

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Reversible increase in left ventricular wall thickness (pseudo hypertrophy) resulting from cardiac tamponade has not been previously described. We reviewed the echocardiograms recorded immediately before and after pericardiocentesis in 19 Pts with cardiac tamponade. In 4 Pts the interventricular septum and the left ventricular posterior wall were thickened during tamponade, returning to normal after pericardiocentesis together with expansion of the ventricles. Interventricular septal diastolic dimension ranged between 14-17 mm in diastole before and returned to 9-11 mm after pericardiocentesis; in systole it was 16-22 mm and 10-13 mm respectively. Left ventricular posterior wall thickness decreased from 10-16 mm to 8-10 mm in diastole and from 16-21 mm to 11-13 mm in systole. Right ventricular collapse was present in one case only. Pseudo hypertrophy is a reversible phenomenon, not infrequent in cardiac tamponade. This increase in wall thickness was observed both in systole and diastole, suggesting that myocardial engorgement and congestion rather than impairment of diastolic expansion may be the underlying mechanism. Its detection is helpful in making the diagnosis of tamponade, especially in cases without right ventricular or right atrial diastolic collapse.

EFFECTIVENESS OF PERICARDIOSCOPY FOR ETIOLOGICAL DIAGNOSIS IN 18 PATIENTS WITH SUSPECTED MALIGNANT PERICARDIAL EFFUSION.

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In cases of malignancy with pericardial effusion (PE), conventional biopsy (CB) from subxyphoïd pericardial window has proved to be inadequate to assess the metastatic involvement of the pericardium (P). To improve the diagnostic yield of pericardial biopsy, we performed pericardioscopy (PCS) in 18 patients (pts) who had evidence of large PE on echocardiography. Twelve pts had an history of malignancy (neoplasm : 9 pts with radiotherapy in 5 out of 9 ; non Hodgkin lymphoma : 3 pts), 4 pts had metastases of unknown origin and 2 pts had severe biological inflammation. Performed under general anesthesia, with a rigid mediastinoscope introduced through a surgical subxyphoïd approach, PCS allowed cytological studies (C) on the fluid, CB and guided biopsies (GB) selected by direct inspection on suspect areas. No complication occured. In 6 out of 18 pts (33%) neoplastic PE was proved : with GB in 4 pts even when CB was negative in 3 out of 4 and C in 2 out of 4 ; with C in 1 pt ; in the last pt, C, CB, GB were negative in spite of metastasis on the lateral P (diagnosed with autopsy). In 12 out of 18 pts (66%) no metastasis was discovered : C, CB, and GB were negative and PCS showed alterations of the P, specific of other etiologies : post-radiation PE in 3 pts ; pyogenic PE in 2 pts ; haemopericardium in 2 pts ; idiopathic PE in 5 pts. Conclusion : without own morbidity, PCS improves the diagnosis yield of pericardial biopsy especially by allowing guided biopsies.

DIAGNOSIS OF PERICARDIAL ABNORMALITIES BY TWO-DIMENSIONAL ECHO: A PATHOLOGY-ECHO CORRELATION IN 85 PATIENTS.

Spencer W Hinds, MD, Antonio F Amico, MD, Richard S Meltzer, MD, PhD, FACC. University of Rochester, Rochester, NY.

Though pericardial thickening, nodules, and masses are often diagnosed by echocardiography, there is no series of two-dimensional echocardiography - pathology correlations in the literature. We therefore retrospectively reviewed the echocardiograms of 68 patients who died and had autopsies within six months of the echocardiogram, and 17 patientsts who had echocardiograms within six months of pericardiectomy. The echocardiograms were re-read in random order by an observer (AFA) blinded to the diagnosis and whether the echocardiogram came from the autopsy or pericardiectomy population. Pathology reports were reviewed and graded by another observer (SWH) for pericardial abnormalities (thickening or increased fibrosis, nodules, malignancy, fibrin strands or clots, and size of effusion). Pericardial abnormalities were coded separately for both echocardiographic and pathology reviews. RESULTS: There were 85 patients who met the inclusion criteria (aged 53 ± 25 years, mean ± 1 SD). The time between echocardiography and pathology was 34 ± 47 days for the autopsy group and 14 ± 17 days for the pericardiectomy group. Of the 37 patients with pathological abnormalities, 13 had echocardiographic abnormalities and 24 did not; of the 48 patients with a normal pericardium pathologically, 44 were normal by echocardiography and 4 were abnormal. In the following pathological states, echocardiographic abnormalities were noted as follows: pericardial tumors 3/6, thickening 9/12, fibrosis 8/19, postoperative adhesions 1/7, fibrin in pericardial space 6/16, late post myocardial infarction (MI) pericarditis (≥ 21 days between MI and pathology): 4/9, early post MI pericarditis (< 21 days between MI and pathology): 0/4. CONCLUSION: Two-dimensional echocardiography is fairly specific (92%) for pericardial abnormalities (exclusive of effusion) detected pathologically, but not sensitive (35%).

RIGHT VENTRICULAR INFARCTION DECREASES LEFT VENTRICULAR COMPLIANCE AND PERFORMANCE BY A PERICARDIAL MECHANISM.

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The mechanism of the impaired LV function following RV infarction (RVI) is poorly understood. We instrumented 7 dogs (sonomicrometers) to measure LV anteroposterior (Dlvap) and LV and RV septal to free wall diameters (Dlvsfw, Drvsfw). Pressures (Plv, Prv) were recorded with micromanometers and pericardial pressure with a balloon transducer. RVI was induced by right coronary ligation or Hg injection. Stroke work (SW) was calculated from the pressure-diameter loop area. Ventricular function curves were generated (venocaval occlusion/volume infusion) before and after RVI. All data were normalized to their values at Prved = 5 mmHg; data (control versus post RVI) obtained at Prved ≈ 5 and ≈ 20 mmHg were compared.

| | Prved | Plved | Plvtm | LV area% | Dlvsfw/TCD | SWlv% |
|---|---|---|---|---|---|---|
| ≈ 5 | Control | 6±1 | 1±2 | 100 | .70±.02 | 100 |
| | RVI | 4±1* | 1±1 | 95±3* | .66±.02* | 53±33* |
| ≈ 20 | Control | 23±2 | 3±1 | 106±4 | .68±.03 | 135±32 |
| | RVI | 20±2* | 1±2* | 101±4* | .64±.03* | 68±31* |

TCD = Dlvsfw + Drvsfw; * p < 0.05 versus Control;
tm = transmural = Plved - pericardial pressure

Thus, RVI caused leftward septal shift, increased pericardial pressure, reduced LV volume and SW. The increased pericardial pressure (resulting in decreased LV transmural pressure) caused the apparent decrease in LV compliance.

PERICARDITIS IN THE FACE OF THROMBOLYTIC INTERVENTION DENOTES SEVERE MYOCARDIAL DAMAGE

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To determine the significance of pericarditis (PC) in acute myocardial infarction (MI) patients treated with thrombolytic therapy, we prospectively evaluated 810 consecutive patients treated with t-PA, urokinase, or both in the TAMI Trials. Forty patients (4.8%) had clinical evidence of acute PC by clinical evaluation. There was no significant difference between patients with or without PC in regards to age, sex, weight, race, history of hypertension, diabetes mellitus, hypertension, or number of diseased vessels. Significant factors associated with PC were lower baseline ejection fraction (44.3 +/- 13.9 vs. 50.9 +/- 11.3), worse infarct zone quantitative left ventricular function (-2.96 +/- 0.91 SD/chord vs -2.53 +/- 1.09 SD/chord) and higher in-hospital mortality (15% versus 6%). Of the 6 deaths in the pts with PC, 5 were due to power failure and 1 was sudden. Patients with PC had a greater prevalence of left anterior descending as the infarct-related artery (51% versus 38%). Thrombolytic therapy resulted in TIMI Grade 3 perfusion within 90 min in 83% of pts without PC and in 74% of pts with PC. PC occurred in the majority of patients (n=23) within the first 48 hours after treatment with thrombolytic therapy. Of note pericardial tamponade did not occur.

PC in patients treated with thrombolytic therapy for acute myocardial infarction is a marker of more extensive myocardial damage and is associated with a higher in-hospital mortality rate. Despite the occurrence of PC, tamponade was not observed.

PLEURAL EFFUSION AS A CAUSE OF RIGHT VENTRICULAR DIASTOLIC COLLAPSE AND CARDIAC TAMPONADE

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Right ventricular diastolic collapse (RVDC) is a sensitive and specific marker for cardiac tamponade (CT), and is presumed to occur when intrapericardial pressure (IPP) finally exceeds right ventricular diastolic pressure (i.e. negative transmural pressure=TMP). Intrathoracic pressure is also influenced by pleural and intraesophageal pressures. To test the hypothesis that a pleural effusion in the presence of an otherwise insignificant amount of intrapericardial fluid could produce RVDC, we created CT 5 times and pleural effusion 5 times in 4 conscious dogs by intrapericardial (10 ml/min) and intrapleural (100 ml/min) infusion of warm saline, respectively. Before pleural effusion, an amount of intrapericardial saline 60±16ml was instilled equal to half of the volume required to cause the onset of RVDC in the preceding CT run. We measured aortic, intrapericardial, intrapleural, right atrial pressures (fluid-filled catheters) and short axis 2D echocardiograms (2 observers) at 2mmHg increments in IPP until the onset of RVDC. At the onset of RVDC, IPP was 7.5±0.4mmHg in CT vs. 7.7±0.2mmHg in pleural effusion (p NS). Intrapleural pressure (IPl P) tended to reflect IPP during pleural effusion only (IPl P=8.0±0.4mmHg, p NS vs. IPP). Calculated TMP at RVDC was -0.2±0.0mmHg in CT vs. -0.4±0.1mmHg in Pl E (p NS). Thus, a pleural effusion in the presence of an otherwise hemodynamically unimportant pericardial effusion may increase IPP enough to produce RVDC, perhaps leading to misdirected therapy of the intrapericardial effusion rather than the pleural effusion

## Thursday, March 23, 1989
## 8:30AM–10:00AM, Garden Grove Room
## Anaheim Convention Center
## Diagnostic and Prognostic Value of Exercise Testing

POST-EXERCISE ST SEGMENT DEPRESSION IN RELATION TO HEART RATE: IMPROVED IDENTIFICATION OF CORONARY ARTERY DISEASE BY THE RATE-RECOVERY LOOP

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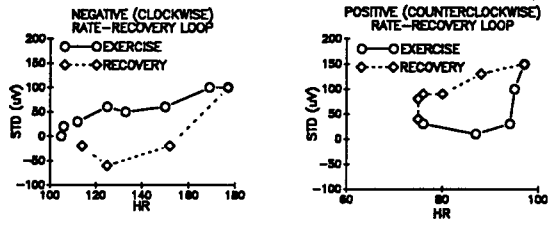
Although the time course of ST segment recovery after exercise has been related to the presence and severity of coronary artery disease (CAD), recovery phase patterns of ST segment depression (STD) with reference to changing heart rate (HR) have not been quantified. We have found distinct recovery loop patterns that separate subjects without CAD from pts with CAD when STD is examined in the HR domain. Continuous plots of STD and HR were constructed throughout treadmill exercise and recovery in 100 clinically normal subjects (Nls) and in 124 pts with catheterization proven CAD. In 95% (95/100) of Nls, STD was less at early recovery HR than at corresponding exercise HR [negative (clockwise) rate-recovery loop]. Conversely, in 93% (115/124) of pts with CAD, STD was greater at early recovery HR than at corresponding exercise HR [positive (counterclockwise) rate-recovery loop]. Standard test criteria (positive test= ≥0.1 mV horizontal or downsloping STD or ≥0.15 mV upsloping STD) were similarly specific in Nls [93% (93/100)], but had a sensitivity of only 74% (92/124, p<.001 vs the rate-recovery loop) for the detection of CAD. We conclude that the pattern of STD as a function of HR during exercise and recovery can markedly enhance the accuracy of the exercise ECG for the identification of CAD.




DETECTION OF RESTENOSIS AFTER ELECTIVE CORONARY ANGIOPLASTY USING THE EXERCISE TREADMILL TEST

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To determine the value of a 6-month treadmill test (ETT) for detecting restenosis (RST) after elective coronary angioplasty (PTCA), we studied 235 consecutive successful PTCA pts without a recent myocardial infarction and without interval cardiac events or contraindication to cath or ETT. 205 pts (87%) had both follow-up cath and ETT. RST (≥75% diameter stenosis) occurred in 51 pts (25%). Five variables were associated with a higher risk of RST: recurrent angina (p=.0002), exercise-induced angina (p=.0001), a positive ETT (p=.008), more exercise ST deviation (p=.04), and a lower maximum exercise heart rate (p=.05). However, only exercise-induced angina (p=.002), recurrent angina (p=.01), and a positive ETT (p=.04) were independent risk factors for RST. RST rates in selected subgroups were:

| | Angina At Follow-up (Restenosis / N)(%) | No Angina (Restenosis/N)(%) |
|---|---|---|
| ETT Angina | 15/26 (58%) | 6/15 (40%) |
| + ETT | 5/7 (71%) | 4/8 (50%) |
| - ETT | 10/18 (56%) | 2/7 (29%) |
| No ETT Angina | 15/48 (31%) | 15/116 (13%) |
| + ETT | 4/11 (36%) | 5/25 (20%) |
| - ETT | 9/33 (27%) | 10/89 (11%) |
| Total | 30/74 (41%) | 21/131 (16%) |

We conclude that the exercise treadmill test stratifies the risk of RST better than symptoms. Nevertheless, 20% of pts with RST had neither recurrent angina nor exercise induced ischemia. For more accurate detection of RST, the ETT must be supplemented by a more definitive test.

## ISCHEMIC THRESHOLD VARIES IN RESPONSE TO DIFFERENT TYPES OF EXERCISE IN PATIENTS WITH CHRONIC STABLE ANGINA

Giuseppe Pupita M.D., Juan C. Kaski M.D., Alfredo R. Galassi M.D., Filippo Crea M.D., Margarita Vejar J M.D., Attilio Maseri M.D. FACC. RPMS, Hammersmith Hospital, London, U.K.

It is still controversial whether ischemic threshold, in patients (pts) with chronic stable angina, can vary depending upon exercise intensity. To elucidate this, 14 pts with chronic stable angina, documented coronary artery disease and reproducible positive exercise tests were studied off antianginal therapy. Two types of exercise - carried out randomly - were compared regarding time (T) and rate-pressure product (RPP) at 1 mm ST of ST depression: a baseline exercise test on the modified Bruce protocol (MB) and a MB preceded by a warm-up period of 10 minutes at 1 mph and 0% grade (W). On a separate day all pts performed a MB before and after .5 mg of sublingual NTG. On average, ischemic ST segment changes developed at a significantly higher RPP and T during W compared to MB (20297±4782 vs 18802±4000 mmHgxbpm; 412±198 vs 301±149 secs respectively, $p<0.05$). Furthermore, the improvement of RPP with W was higher than 2000 in 7 pts (20129±4732 vs 23211±4583): all these pts showed a similar improvement with NTG (25102±5733) whereas in the remaining 7 little or no changes in RPP were seen during W (17476±2855 vs 17382±2955) and only 1 of them improved with NTG. Thus, ischemic threshold can vary in response to exercise of different intensity; the fact that these pts also had a significant improvement with nitrates suggests that a decreased coronary tone may be responsible for this phenomenon.

## WARMING UP PHENOMENON CANNOT BE EXPLAINED BY THE INCREASE IN CORONARY FLOW RESERVE

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To investigate the mechanism of warming up phenomenon, two serial identical tests of supine ergometer exercise by 15 minutes recovery period in 9 patients with stable effort angina and with angiographic evidence of left anterior descending artery (LAD) stenosis were performed. Patients with multivessel disease were excluded. Hemodynamic parameters were recorded at every one minute during exercise and coronary angiogram was performed at the onset of angina. Great cardiac vein (GCV) flow and oxygen content in aorta and in GCV were measured before and during exercise. Results: Exercise time to angina increased from 362±110sec. at the first exercise to 424±118sec. at the second exercise ($p<0.05$). Diameter of LAD at the first exercise was not significantly different from that of the second exercise. Regional myocardial oxygen consumption (MVO2: 16.4±3.4/ min) and pressure rate products (PRP: 19600±780) during the first test were not significantly different from those of the second test (MVO2: 14.6±4.0ml/min, PRP: 19100±850). We conclude that (1) significant variations in coronary blood flow do not occur and that (2) inappropriate vasoconstriction does not account for this phenomenon.

## EXERCISE-INDUCED SILENT ISCHEMIA: EFFECT OF TYPE A BEHAVIOR ON FREQUENCY AND PROGNOSIS

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Type A pts (A's) tend to ignore or underreport symptoms while performing achievement-oriented tasks such as the exercise treadmill test (ETT). To determine whether A's with coronary disease might be more likely than Type B pts (B's) to have silent ischemia on the ETT and consequently a worse prognosis, we studied 419 patients with documented coronary disease, a positive Bruce ETT and a structured interview to assess Type A behavior. A's and B's did not differ in baseline demographic and clinical characteristics, except that A's were less likely than B's to report a history of typical angina (76% vs 85%, p=.04). In addition, A's were more likely than B's to experience silent ischemia during the ETT (35% vs 24%, p=.02). However, using the Cox model, there were no significant differences in survival between A's with silent or symptomatic ischemia (4 year survival 86% vs 80%, respectively), or between B's with silent or symptomatic ischemia (4 year survival 79% vs 84%, respectively). Similar results were found for non-fatal myocardial infarction.

We conclude that A's are more likely to have silent ischemia during exercise than B's, but that they are not at uniquely increased long-term risk because of this.

## COMPARISON OF EXERCISE ELECTROCARDIOGRAHY AND RADIONUCLIDE ANGIOGRAPHY IN THE IDENTIFICATION OF SEVERE CORONARY ARTERY DISEASE

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Exercise electrocardiography (EXECG) and exercise radionuclide angiography (EXRNA) are both utilized to non-invasively identify patients with 3-vessel and left main coronary artery disease (SEVCAD). The purpose of this study was to compare these two modalities in 363 patients with a normal resting ECG who underwent supine bicycle exercise and coronary angiography within 3 months. No patient was taking digoxin. Separate logistic regression models were developed for the EXECG and EXRNA to predict SEVCAD. The EXECG model, consisting of mm ST depression, exercise heart rate-blood pressure product, patient gender, and METS of exercise, was statistically powerful ($\chi^2=92$, $p<.0001$) and could classify most patients into high-risk or low-risk groups (see below). The addition of EXRNA parameters (ejection fraction and ventricular volumes) improved the predictive power of the model slightly ($\chi^2=99$), but had little effect on its ability to classify patients (pts) into high- and low-risk groups:

| | EXECG | | EXRNA | |
|---|---|---|---|---|
| Risk Group | Pts | %SEVCAD | Pts | %SEVCAD |
| Low | 174 | 5% | 177 | 6% |
| Intermediate | 100 | 26% | 91 | 24% |
| High | 89 | 60% | 95 | 58% |

Conclusions: 1) In patients with a normal resting ECG, who are not taking digoxin, EXECG can noninvasively classify most patients with respect to their risk of SEVCAD.

2) Compared to the EXECG, EXRNA provides little additional advantage for the identification of SEVCAD in such patients.

# Thursday, March 23, 1989
# 10:30AM–12:00NOON, Garden Grove Room
# Anaheim Convention Center
# Prognostic Indicators in Unstable Angina

PREDICTING LONGTERM OUTCOME IN MEDICALLY STABILIZED UNSTABLE ANGINA: EARLY HOLTER ST SEGMENT MONITORING, PREDISCHARGE EXERCISE THALLIUM TOMOGRAPHY AND CORONARY ANGIOGRAPHY.

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The relative value of both non-invasive and invasive predictors of outcome following medically stabilized unstable angina(UA) has not been adequately assessed. Accordingly, we prospectively compared 24 hour Holter(HOL) monitoring, quantitative exercise(EX) thallium tomography ($Tl^{201}$) and cardiac catheterization in predicting 6 month outcome in 54 such pts. Unfavorable outcome(UO) was defined as recurrent UA(n=11), myocardial infarction (n=2), and death (n=1). Results(x±SD) for ST shift ≥1 mm on HOL in min during first 24 hr after admission, EX duration (DUR) in min by Bruce protocol, reversible perfusion defect by EX $Tl^{201}$ as % of total myocardium, # of vessels (VES) with ≥50% stenosis and contrast ejection fraction(EF, %, n=30) are shown in the table:

| EVENT | HOL | EXDUR | EXT$l^{201}$ | VES | EF |
|---|---|---|---|---|---|
| UO | 37±43 | 7.9±3.1 | 17±18 | 2.1±1.0 | 69±15 |
| NO UO | 52±119 | 8.0±3.6 | 6±11 | 1.1±1.2 | 70±10 |
| p | NS | NS | <0.05 | <0.05 | NS |

Age, sex, pain or presence of ST shift on EX were not associated with UO. On multiple regression analysis, exercise $Tl^{201}$(F=7.50) was of similar value as number of VES(F=6.97) in predicting UO.
These results suggest that in unstable angina after medical stabilization, exercise $Tl^{201}$ has greater value for risk stratification than early Holter ST monitoring and is as good a predictor of unfavourable 6 month outcome as extent of angiographic disease.

SERIAL URINARY FIBRINOPEPTIDE A LEVELS IN UNSTABLE ISCHEMIC HEART DISEASE

Robert L. Wilensky, MD, Jack A. Zeller, MD, Marc H. Wish, MD, Mark Tulchinsky, MD, The Krannert Institute of Cardiology, Indianapolis, IN, VA Medical Center, Washington, DC.

Since acute intracoronary thrombosis can lead to unstable angina (UA) and myocardial infarction (MI) urinary Fibrinopeptide A (uFpA) was evaluated as a non-invasive marker of thrombus. We measured spot uFpA normalized for urinary creatinine (Cr), in consecutive CCU pts with UA (n=21) and MI (n=13) 0,2,8 hrs after admission. Consecutive pts with stable angina (SA n=20) and without known CAD (n=13) had urine obtained at 0 and 2 hrs. The SA and no CAD pts had similar admission levels (3.2±1.1, 3.3±1.4 ng/mg Cr). The mean admission uFpA value of UA pts was 5.7±2.6 ng/mg Cr ($p<0.001$, $p=0.008$ compared to SA and no CAD). The mean admission value of MI pts was 8.4 ±10.0 ng/mg Cr ($p<0.001$, $p=0.005$ compared to SA and no CAD groups). There was no difference between UA and MI admission levels. UA peak values (7.6±5.9 ng/mg Cr) were increased over SA (4.0±1.0 ng/mg Cr $p=0.04$) but not control (4.5±1.9 ng/mg Cr $p=0.056$) pts. Mean peak MI values (44.5±60.0 ng/mg Cr) were higher than no CAD ($p<0.001$); SA ($p=0.002$) and UA pts ($p=0.03$). The UA pts with highest values (11.6,.29.2 ng/mg Cr) suffered MIs 2 and 4 days later. Using 6.1 ng/mg Cr as a cutoff value (no CAD mean +2 SD) 48% of UA admission and 53% of peak values were increased. For MI, 50% of admission and 91% of peak values were increased. We conclude: 1) Spot uFpA levels are elevated in unstable ischemic heart disease implying active thrombosis, 2) changes in uFpA levels in MI reflect the dynamic nature of coronary thrombosis, 3) high uFpA levels in UA may indicate impending MI.

S.T.A.I. (STUDY OF TICLOPIDINE IN UNSTABLE ANGINA)

F. Violi MD, D. Scrutinio MD, C. Cimminiello MD, G. Gamba MD, G. Rudelli MD, S.M. Chierichetti MD, P. Rizzon MD and F. Balsano MD on the behalf of Italian S.T.A.I. study group.

Treating pts with unstable angina (UA) with antiplatelet drugs is a therapeutic approach that has provided interesting results. Pts given aspirin, which inhibits the cyclooxygenase pathway, have shown a significant reduction of cardiovascular events. Surprisingly sulfinpirazone, which possesses a similar mechanism of action to aspirin, has not influenced cardiovascular complications of UA pts. To further investigate the role of platelets in UA pts, we studied if ticlopidine (T), which inhibits platelet function by blocking fibrinogen binding to platelets, influences the clinical course of UA. The trial was multicenter (53 centers), controlled, centrally randomized, with blind validation of both pts eligibility and primary events by an independent committee. Pts of both sexes with UA were randomly allocated to conventional therapy (CT) (beta-blockers, Ca-antagonists, nitrates etc.) or CT+T. T, 250 mg b.i.d., was started within 48 h of hospitalization. Pts were monitored monthly up to 6 mo. Nonfatal AMI and cardiovascular death constituted the primary end points. 2438 pts were screened, 652 (338 on CT, 314 on CT+T) were randomized; 599 pts (309 on CT, 290 on CT+T) were eligible. The results of the intention-to-treat analysis are shown in the table.

PRIMARY EVENTS

| | CT n=338 | T+CT n=314 | Risk reduct. | p value |
|---|---|---|---|---|
| AMI | 29 (8.6%) | 15 (4.8%) | 44.2% | 0.0531 |
| Fatal AMI + sudden death | 14 (4.1%) | 6 (1.9%) | 53.7% | 0.0988 |
| Overall mortality | 15 (4.4%) | 6 (1.9%) | 56.8% | 0.0678 |
| Total events | 44 (13.0%) | 21 (6.7%) | 48.5% | 0.0070 |

The drug-efficacy analysis will also be presented.

ANALYSIS OF THE ISCHEMIA RELATED CORONARY ARTERY AND ITS PREDICTIVE VALUE IN UNSTABLE ANGINA.

Andrea Pozzati M.D., Raffaele Bugiardini M.D. F.A.C.C., Filippo Ottani M.D., Gianluigi Morgagni M.D., Paolo Puddu M.D. Institute of Patologia Medica and C.C.U., University of Bologna, Italy.

To assess the factors predictive of an adverse clinical outcome in unstable angina, we related the 6 month follow-up of 50 patients (pts) with rest or crescendo angina, to their coronary angiograms obtained within 2 weeks from admittance in C.C.U. Quantitative (% stenosis) and qualitative (Ambrose criteria) analysis of the ischemia related coronary artery (IRA) was performed in all pts. Twentyfive of the 50 pts showed complicated (type II eccentric lesion) IRA stenosis; of these, 16 (64%) had an adverse clinical outcome (3 myocardial infarction, 4 sudden death and 9 need for urgent coronary revascularization). Severe stenosis (≥ 90% lumen narrowing) of IRA was present in 28/50 pts; of these, 17 (61%) had an unfavourable clinical course (4 myocardial infarction, 3 death, 10 revascularization). The occurrence of both complicated and severe IRA stenosis was observed in 20/50 pts, 16 of whom (80%) presented an adverse clinical outcome (4 myocardial infarction, 3 death, 8 revascularization). Only 6 of the remaining 30 pts (20% vs 80%; $\chi^2$: $p<.0001$) had major coronary events (1 myocardial infarction, 1 death, 4 revascularization). In conclusion, association between complicated morphology and severity of IRA stenosis is closely related to an adverse clinical outcome in pts with unstable angina; thus, an aggressive management of this subset of pts is recommended.

IMPACT OF ABNORMAL MYOCARDIAL PERFUSION ON VENTRICULAR FUNCTION IN PATIENTS WITH UNSTABLE ANGINA.
Anatoly Langer M.D., Michael R. Freeman M.D. FACC, Robert J. Howard M.D. FACC, Paul W. Armstrong M.D. FACC, Toronto, Canada.

To assess the impact of myocardial perfusion on left ventricular function in unstable angina we performed resting thallium$^{201}$ myocardial perfusion scans (Tl, anterior, lateral, and 45° LAO views) on admission and biplane left ventricular angiography (LVA, RAO 30° and LAO 60° views) 4±3 days following admission in 161 pts. The presence of a defect (D) in either anterior (apical, anterolateral, septal, and anteroseptal segments) or posterior (inferior and posterolateral segments) territories was assessed by quantitative analysis (> 2.5 S.D. below normal). Two independent observers, blinded to Tl results, assessed anterior and posterior wall motion abnormality (WMA) by LVA. Myocardial infarction (MI) on admission was ruled out by enzymes and in pts with previous MI, territories associated with infarction were not analyzed. The association of WMA with perfusion according to territory is shown in the table:

| | ANTERIOR | | POSTERIOR | |
|---|---|---|---|---|
| | no D(n=81) | D(n=48) | no D(n=82) | D(n=29) |
| WMA: | 27(33%) | 33(69%)* | 20(24%) | 16(55%)* |
| no WMA: | 54(67%) | 15(31%)* | 62(76%) | 13(45%)* |

*p<.005 vs no D

We then correlated D size with WMA score (for each segment: 1=normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic) combining anterior and posterior territories: r=.60, p<.005.

We conclude that resting thallium defects in unstable angina are evident early after presentation, potentially defining territory at risk, and have significant impact on ventricular function assessed later, suggesting myocardial stunning.

**NIFEDIPINE IN UNSTABLE ANGINA: BENEFICIAL EFFECTS IN THE ELDERLY AND IN PATIENTS WITH REDUCED LEFT VENTRICULAR FUNCTION.** Sidney O. Gottlieb, M.D., FACC, Pamela Ouyang, M.D., FACC, E. David Mellits, Sc.D., Gary Gerstenblith, M.D., FACC. The Johns Hopkins Medical Institutions, Baltimore, Maryland.

The beneficial effects of nifedipine therapy has previously been described for the broad spectrum of unstable angina pts. Recent reports, however, have raised concern about the safety of some calcium antagonists in subsets of pts with acute ischemic syndromes who have reduced LV function. There is also concern for the potential for adverse effects with combination therapy in elderly pts due to previously noted age-related changes in electrophysiological and beta-adrenergic responsiveness. In the Johns Hopkins Nifedipine Unstable Angina trial, 138 pts treated with beta blockers and nitrates were randomized to receive either nifedipine 80 mg/day (N) or placebo (Pl). Of these, 45 pts (21N, 24 Pl) had an initial LV ejection fraction < 55% (≤35% n=11, 36-40% n=7, 41-45% n=7, 46-50% n=10, 51-54% n=10). After 18 months 15 Pl pts and only 10 N pts experienced a clinical outcome (death, myocardial infarction, or requirement for bypass surgery for recurrent angina), and Kaplan-Meier analysis revealed a beneficial effect of N on the incidence and time dependence of these combined outcomes (p<.03). In the same trial, 42 pts (19 N, 23 Pl) were ≥ 65 years of age (range 65-87 years). Over 18 months, 15 Pl and only 7 N pts experienced one of the above clinical outcomes, and Kaplan-Meier analysis also revealed a beneficial effect of nifedipine (p<.04). No adverse electrophysiologic or hemodynamic effects occurred in either of these subgroups. Thus, nifedipine in combination with nitrates and beta blockers is well tolerated and beneficial in subsets of unstable angina pts who are elderly and who have reduced LV function.

# Thursday, March 23, 1989
# 8:30AM–10:00AM, California Room C
# Anaheim Convention Center
# Pediatric Cardiology Follow-Up Studies and Methods

VENTRICULAR VOLUME AND FUNCTION IN INFANT ORTHOTOPIC HEART TRANSPLANTATION

Mohammad S. Kanakriyeh, MD, Charles E. Mullins, MD, FACC, Marcos Cordoba MD, Leonard L. Bailey, MD, FACC
Loma Linda University, Loma Linda, CA

To study the growth and function of transplanted hearts donated from young infants and neonates, angiographic volume parameters were measured in the first five recipients who underwent cardiac catherization 17 ∓ 5.6 months post transplantation. Mean donor age was 0.8 (range 0.1 - 2.3) months. Mean recipient age was 1.4 (range 0.1 - 3.5) months. Angiographic ventricular end-diastolic volumes (AngEDV) were compared with donors' predicted EDV (DPrEDV) derived from previously published formulas according to body surface area. Volume increase from DPrEDV (ΔV) was used to evaluate ventricular growth. Ejection fraction (EF) and cardiac index (CI) were used to evaluate cardiac function.

| Results: | LV Mean ∓ SD | RV Mean ∓ SD |
|---|---|---|
| AngEDV (ml) | 23.3 ∓ 3.7 | 23.9 ∓ 6.6 |
| (% of predicted nl) | 90 ∓ 13 | 87 ∓ 17 |
| DPrEDV (ml) | 9.9 ∓ 2.5 | 10.3 ∓ 2.5 |
| ΔV (ml) | 12.9 ∓ 2.9 | 13.9 ∓ 6.1 |
| (% of DPrEDV) | 137 ∓ 43 | 140 ∓ 62 |
| EF (%) | 70 ∓ 10 | 68 ∓ 9 |
| ci (L/min/m) | 3.8 ∓ 1.1 | 3.5 ∓ 1.2 |

This is the first angiographic study to document growth and normal function after infant orthotopic heart transplantation.

RIGHT VENTRICULAR GROWTH AND FUNCTION FOLLOWING FONTAN PROCEDURE FOR TRICUSPID ATRESIA.
Edwin McGough, MD, FACC, Kent Thorne, MD, Mark Boucek, MD, Primary Children's Medical Center, Salt Lake City, Utah.

It has been shown that significant right ventricular (RV) growth can occur in patients with tricuspid atresia (TA) and ventriculo-arterial concordance. However, growth of the RV has been related to preoperative size, and problems with conduit obstruction have limited use of the RV. We have used preoperative selective RV angios to demonstrate the unique morphology of the RV in TA; usually not well visualized. Based on this information, we have evolved an operative approach to promote RV growth and minimize conduit obstruction. Operative technique includes enlarging the OS infundibulum to incorporate the trabecular portion of the RV. The trabeculations are excised and the VSD is closed. The right atrial to RV connection is accomplished with a homograft inserted in a manner to avoid obstruction of the conduit from compression of the sternum secondary to RV growth. Eight consecutive patients with an average age of 2.9 years (range 2.1 - 5.9 years) have been operated on using this approach. All patients have survived and six have been studied more than one year after operation. RV diastolic volume increased from 14.4±9.5 cc to 45.4±24 cc p 0.05 or 40±22% to 106±43% of predicted normal. The increase in the RV volume was not related to preoperative size. The postoperative RV ejection fraction was 52±3.9%.

We conclude that an operative approach directed toward inclusion of both portions of the RV and specific tailoring of the conduit will promote RV growth, systolic function and avoid conduit obstruction.

## REMODELING OF THE AORTA FOLLOWING SUCCESSFUL BALLOON COARCTATION ANGIOPLASTY

P. Syamasundar Rao, M.D., F.A.C.C., Patrick Carey, M.S., University of Wisconsin, School of Medicine, Madison, Wisconsin.

The purpose of this study was to examine if remodeling of aorta takes place following successful balloon angioplasty of aortic coarctation. During the 35-month period ending December 1987, 30 children, aged 14 days to 13 years underwent balloon angioplasty of unoperated aortic coarctation with resultant reduction in coarctation gradient from 44 ± 20 to 10 ± 8 mm Hg ($p<0.001$). On the basis of results of six to 30 months follow-up catheterization data in 20 children, they were divided into group A with good results (gradient ≤ 20 mm Hg and no recoarctation on angiography), 13 patients and group B with fair and poor results (gradient >20 mm Hg with or without recoarctation on angiography), 7 patients. Measurements of the aorta at five sites, namely ascending aorta, isthmus, coarctation segment and descending aorta distal to coarctation and at the level of diaphram were made in two angiographic views, corrected for magnification and averaged. A standardized variance of the diameter of the aorta at the five locations measured was calculated for each case prior to angioplasty and at follow-up. The variance between groups was compared with the use of Mann-Whitney U statistic and the effect of angioplasty was tested by Wilcoxon's signed rank test.. The variance of standardized aortic measures (0.233 vs 0.287) was similar ($p>0.05$) in both groups prior to angioplasty while at follow-up (0.057 vs 0.129) they were different ($p=0.01$). There was a significant improvement at follow-up (0.233 vs 0.057) in group A with good results ($p=0.002$) while there was a marginal improvement ($p=0.04$) in group B (0.287 vs 0.129). Anderberg's cluster analysis was also indicative of remodeling of the aorta in the group with good results. These data indicate a greater normalization of the aorta following successful balloon angioplasty of aortic coarctation suggesting that normalized flow across the dilated coarctation allows optimal growth of the aortic segments.

## FATE OF THE NEOAORTIC VALVE AFTER ARTERIAL REPAIR OF TRANSPOSITION OF THE GREAT VESSELS

Frank Smith M.D., Rae-Ellen Kavey M.D., Craig Byrum M.D., Bonnie Salisbury R.N., R.D.M.S., and John Dadario. SUNY Health Science Center, Syracuse, New York.

It remains unresolved whether neoaortic valve incompetence occurs late after arterial repair of transposition of the great vessels. To address this question we reviewed the most recent color doppler echocardiograms (CDE) and compared them to previous two dimensional studies in 17 Pts with this diagnosis. The patients were most recently studied at 7 mos-7½yrs of age (mean 2.4 yrs), 6 mos-6 yrs after repair (mean 2.3 yrs). All were asymptomatic and on no medications. Neoaortic incompetence (AI) was detected by CDE in 5/17 Pts, but was judged to be trace in 4 and only mild in 1. The latter Pt was the only 1/17 with AI by auscultation. Maximum neoaortic root diameter (AOD) could be measured on early postoperative studies (mean 5 months postop) as well as on later postoperative studies (mean 27 months postop) in 14/17 Pts. On the early studies the AOD averaged 1.16 x 95%ile for age and exceeded 95%ile in 11/14 Pts. On the recent studies the AOD averaged 1.18 x 95%ile for age and exceeded 95%ile in 9/14 Pts. Although AOD averaged large for age on early and late studies, the size relative to upper limits of normal for respective patient age did not change significantly over the interval. Although neoaortic incompetence remains uncommon, neoaortic root dilatation has persisted for up to 6 years after arterial repair of transposition of the great vessels. Progressive aortic root dilatation relative to patient age, however, did not occur. Further long term follow-up is needed to determine the significance of neoaortic root dilatation in this patient group.

## RIGHT VENTRICULAR SIZE AND PULMONARY FLOW IN PATIENTS AFTER FIRST STAGE SURGERY FOR PULMONARY ATRESIA: COMBINED ASSESSMENT BY CINE MAGNETIC RESONANCE IMAGING AND COLOR DOPPLER FLOW MAPPING.

Frederick Sherman, M.D., FACC, Iain Simpson, M.D., Jack Powell, M.D., Azucena Murillo, Richard Swensson, M.D., FACC, Lilliam Valdes-Cruz, M.D., FACC, David J. Sahn, M.D., FACC, Kyung Chung, M.D., FACC. Univ Calif, San Diego, CA

We used the combination of cine magnetic resonance imaging (MRI) and color Doppler flow mapping (CDFM) to assess RV and PA morphology and the derivation of PA flow in 9 Pts, ages 4 weeks to 2.5 yrs, with pulmonary atresia (PUL ATR) with intact ventricular septum (IVS) studied after pulmonary valvotomy and AO to PA shunts. Cine MRI was performed using a GE Signa system (1.5 Tesla). High resolution cine MRI images were obtained in all 9 Pts and accurately delineated RV and PA anatomy compared to observations by angiography in 8 Pts and at subsequent surgery in 1 Pt. The RV wall thickness (mm) and the area ejection fraction derived from diastolic and systolic RV areas ($cm^2$) on saggital and axial views by cine MRI also provided an assessment of RV size and function comparable to angio, including 1 Pt with RV cavity obliteration. CDFM delineated the shunt flow patterns in the PA in 7 Pts and the area of variance encoded shunt flow correlated well with the arterial oxygen tension. Forward RV-to-PA flow identified by acceleration proximal to the pulmonary valve was seen in 6 Pts with continuing valve patency, but the severity of residual stenosis was better assessed using CW Doppler of TV insufficiency (TI) velocities. The degree of TI and PI was similar on CDFM and MRI. Combined use of cine MRI and CDFM provides a comprehensive assessment of RV growth, PA size and hemodynamic results in Pts with PUL ATR and IVS after initial surgery and aids planning subsequent medical or surgical managment.

## PREVALENCE OF CONGENITAL HEART DISEASE IN OFFSPRING OF PARENTS WITH FALLOT'S TETRALOGY.

Thomas M. Zellers, M.D., David J. Driscoll, M.D., F.A.C.C., Virginia V. Michels, M.D., Section of Pediatric Cardiology, Mayo Clinic, Rochester, Minnesota.

Patients with Fallot's tetralogy (TOF) can be offered physiologic operative repair with low operative and late mortality. Because many of these patients marry and have children of their own, we conducted this study to determine the prevalence of significant congenital heart disease (CHD) in liveborn offspring of patients with TOF. We contacted 230 consecutive patients (mean age = 38 ± 10 years, range 24-78) with TOF who were evaluated at the Mayo Clinic between 1945-1968. Of these 230, 163 were married and 129 (63F; 66M) had 256 children (126F; 130M). Three (all F) of the 256 (1.2%) children had congenital heart disease (1 TOF, 1 VSD, 1 truncus). The occurrence rate between probands was similar in males (1.5%) and females (0.93%). The occurrence rate per family was 3 of 129 (2.3%). Neither the probands nor their spouses in the 3 involved families had additional first degree relatives with CHD.

The 63 women had 135 pregnancies; 20 of these women had 25 spontaneous abs and 3 therapeutic abs (maternal health). The 230 patients had 595 siblings, 15 (2.5%) of whom had congenital heart disease.

These data suggest that the occurrence rate of significant congenital heart disease in liveborn offspring of parents with TOF is low (1.2%) and consistent with the theory of multifactorial etiology.

# Thursday, March 23, 1989
# 10:30AM–12:00AM, California Room C
# Anaheim Convention Center
# Physiologic Effects of Exercise

## EXERCISE CARDIAC OUTPUT DECLINES WITH ADVANCING AGE IN NORMAL SUBJECTS

Dalane W. Kitzman M.D., Martin J. Sullivan M.D., Frederick R. Cobb M.D., Michael B. Higginbotham M.B., Duke University and V.A. Medical Centers, Durham, North Carolina.

In order to determine the effect of age on central cardiovascular function, we studied 82 healthy volunteers from a wide age range (54 men age 20-73 and 28 women age 21-67). All subjects had negative exercise electrocardiograms during a familiarization test. Subjects underwent maximal (MAX) bicycle exercise with simultaneous right heart and brachial artery catheterization, expired gas analysis, and radionuclide angiography for serial measurements of $O_2$ consumption ($VO_2$, ml/kg/min), cardiac index (CI, l/min/$m^2$) by direct Fick, stroke volume index (SVI, ml/$m^2$), LVEF, end diastolic volume index (EDVI, ml/$m^2$) calculated from SVI and LVEF, mean arterial pressure (MAP,mmHg) and pulmonary wedge pressure (PWP, mmHg). The correlation coefficients for the regression equations of these variables versus age at upright rest, 300 kpm/min, 600 kpm/min and MAX are displayed below ($^a$p<0.01, *p<0.001):

| | REST | 300 | 600 | MAX |
|---|---|---|---|---|
| $VO_2$ | -.27 | -.36* | -.37* | -.56* |
| HR | -.19 | -.15 | -.18 | -.72* |
| CI | -.24 | -.38* | -.40* | -.54* |
| SVI | -.17 | -.34$^a$ | -.29$^a$ | -.28$^a$ |
| LVEF | -.03 | .01 | -.04 | -.26$^a$ |
| EDVI | -.15 | -.30$^a$ | -.30$^a$ | -.15 |
| MAP | .46* | .45* | .46* | .35$^a$ |
| PCWP | .14 | .06 | .05 | .06 |

Thus, in normal subjects, aging is accompanied by significant alterations in central cardiovascular function during exercise, including reduced heart rate, cardiac output, and LVEF. EDVI and SVI do not compensate for the age related decline in maximal heart rate, and PWP is not age related.

## OSCILLATORY SHIFTS IN OXYGEN UPTAKE DIMINISH THE FUNCTIONAL RELEVANCE OF GAS EXCHANGE MEASUREMENTS DURING EXERCISE IN CHRONIC HEART FAILURE.

Rochelle L. Goldsmith MS, Gerald W. Neuberg MD, Marrick L. Kukin MD, Stephen S. Gottlieb MD, Milton Packer MD, FACC. Mount Sinai School of Medicine, New York, NY

Although oxygen uptake ($VO_2$) normally increases as workload ↑, we have observed pts with chronic heart failure (CHF) whose $VO_2$ (measured breath-by-breath) increases and decreases cyclically during exercise. Such shifts recurred every 1-2 min and resulted in an oscillatory (Osc) pattern of $VO_2$, which varied > 100% even when workload was constant. Oscillations of $VO_2$ in these pts appeared to be related to cyclical changes in minute ventilation (Cheyne-Stokes respiratory pattern, CSR).

To determine the significance of Osc, we evaluated 18 pts with CHF, of whom 9 had Osc and 9 did not (Non-Osc). In both groups, we measured: (1) cardiac index (CI, l/min/$m^2$), LV filling and mean right atrial pressures (LVFP and RA, mm Hg) at rest; (2) submaximal exercise capacity by the distance achieved during a 6 min walk (6minW, m); and (3) maximal exercise capacity by the duration (Tmax, s) and maximal oxygen uptake ($VO_2$max, ml/kg/min) achieved on an incremental bicycle test; * = p<.05.

| | CI | LVFP | RA | $VO_2$max | Tmax | 6minW |
|---|---|---|---|---|---|---|
| Osc | 1.5 | 29 | 13 | 10.5 | 326 | 347 |
| Non-Osc | 2.2* | 26 | 13 | 9.5 | 323 | 321 |

Osc pts had a lower CI than Non-Osc pts - suggesting that Osc (like CSR) could be related to delayed chemoreceptor signalling.

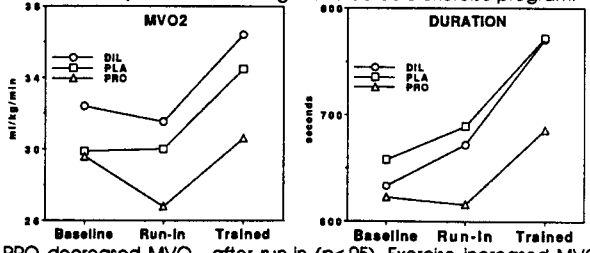
Values for 6minW, Tmax and $VO_2$max were similar in Osc and Non-Osc pts. In Non-Osc pts, there was a close relation between $VO_2$max and Tmax (r=0.85) and between $VO_2$max and 6minW (r=0.83). In contrast, in Osc pts, $VO_2$max did not correlate significantly with Tmax or 6minW (r=0.31 and r=0.21).

In conclusion, cyclical changes in ventilation occur during exercise in some CHF pts with a very low CI and may distort the expected relation between $VO_2$ and workload. Thus, $VO_2$max may not accurately reflect exercise tolerance in such pts.

## EXERCISE TRAINING VERSUS EXERCISE TRAINING WITH DILTIAZEM OR PROPRANOLOL: EFFECTS ON MAXIMAL OXYGEN UPTAKE AND EXERCISE DURATION IN MEN WITH MILD HYPERTENSION.

Michael H. Kelemen M.D. F.A.C.C., Mark B. Effron M.D., F.A.C.C., Stephen A. Valenti M.D., F.A.C.C., and Kerry J. Stewart Ed.D. Johns Hopkins School of Medicine, Baltimore, Maryland.

Beta blockers may impair exercise-induced increases in endurance capacity whereas calcium channel blockers have not been studied when combined with exercise training. 52 sedentary men, ages 25-59, with a DBP of 90 to 105 off drugs, and negative stress tests were randomized in a double blind fashion to diltiazem SR (DIL), propranolol (PRO), or placebo (PLA). Maximal oxygen uptake ($MVO_2$) and exercise duration were assessed on a Bruce treadmill test after a 4 week single blind placebo baseline, after 2 weeks of drug run-in, and after 10 weeks of exercise training. Daily run-in doses were increased to 240 mg of PRO and 360 mg of DIL. 51 men (DIL n=17, PLA n=19, PRO n=15) completed the 1 hour, 3 times/week, circuit weight and aerobic exercise program.



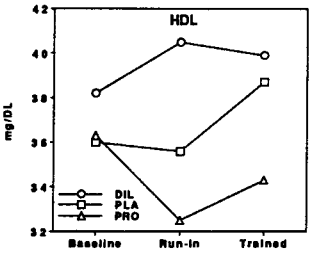

PRO decreased $MVO_2$ after run-in (p<.05). Exercise increased $MVO_2$ (p<.05) from run-in values in all groups. However, $MVO_2$ after training was not different from baseline in the PRO group. Exercise increased duration in all groups (p<.05). This increase from baseline was 22% for DIL, 19% for PLA, and 10% for PRO . While exercise with PRO produced a training effect, the reduction in $MVO_2$ consequent to PRO therapy limited the overall benefits of exercise. DIL did not interfere with exercise capacity and provides an advantage over PRO during exercise training when patients require drug therapy.

## EXERCISE TRAINING VERSUS EXERCISE TRAINING WITH DILTIAZEM OR PROPRANOLOL: EFFECTS ON LIPIDS IN MEN WITH MILD HYPERTENSION

Kerry J. Stewart Ed.D., Mark B. Effron M.D., F.A.C.C., Stephen A. Valenti M.D., F.A.C.C., and Michael H. Kelemen M.D., F.A.C.C. Johns Hopkins School of Medicine, Baltimore, Maryland.

Beta blockers may negate exercise-induced improvements in lipids. The effect of calcium channel blockers combined with training has not been studied. 52 sedentary men, with negative stress tests, ages 25-59, with a DBP of 90 to 105 off drugs, were randomized in a double blind manner to diltiazem SR (DIL), propranolol (PRO), or placebo (PLA). Lipids were measured after a 4 week single blind placebo baseline, after 2 weeks of drug run-in, and after 10 weeks of a 1 hour, 3 times/week circuit weight and aerobics program. Run-in total daily doses were increased to 240 mg PRO and 360 mg DIL. 51 men DIL(n=17), PLA (n=19), and PRO (n=15) completed the study. Mean weight loss was 1.7 kg. Baseline lipids (mg/dL) were not different among groups. Data analysis was performed on differences in changes from baseline among groups. Exercise decreased total cholesterol by 6% (p<.05) and LDL by 9% (p<.05) similarly in all groups. TG did not change significantly. HDL changes at run-in were greater for DIL and less for PRO compared with PLA (p<.05). Exercise with PLA increased HDL (p<.05). After training, HDL changes from baseline were similar for DIL and PLA groups and both were greater than PRO (p<.05). Thus, neither drug attenuated the exercise-induced improvements in total or LDL cholesterol. HDL changes before training were in a favorable direction with DIL. The overall effect of exercise with DIL on HDL was comparable to exercise with PLA whereas PRO had an opposite effect. The data show an advantage to using DIL rather than PRO during exercise training of patients who require concominant drug therapy.

| Baseline (mean±sd) | DIL | PLA | PRO |
|---|---|---|---|
| Total cholesterol | 198±33 | 183±43 | 190±29 |
| LDL cholesterol | 131±25 | 119±35 | 118±21 |
| HDL cholesterol | 38±07 | 36±11 | 36±09 |
| Trigylcerides | 172±138 | 180±136 | 167±72 |



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EXCESSIVE VENTILATORY RESPONSES TO CARBON DIOXIDE PRODUCTION DURING EXERCISE IN PATIENTS WITH CONGESTIVE HEART FAILURE

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To elucidate the mechanisms causing excessive ventilatory responses to carbon dioxide production ($VCO_2$) during exercise (Ex), ventilatory and hemodynamic responses were assessed in thirty-five Pts with chronic congestive heart failure (CHF). Minute ventilation (VE) increased proportionally with $VCO_2$ during Ex and individual linear regression analysis showed excellent correlations in all Pts ($r \geq 0.95$). VE at any given level of $VCO_2$ during Ex was significantly higher in Pts with more advanced CHF. Significant correlation was noted between excessive ventilation and dead space ratio (VD/VT)(r=0.77). Increased VD/VT was mainly due to abnormally widened arterial-end tidal $CO_2$ tension ($P(a-ET)CO_2$), indicating increased alveolar dead space with high ventilation/ perfusion ratio (V/Q). Calculated anatomical dead space was not different. There was virtually no difference in theoretical effective alveolar ventilation (=VE(1-VD/VT)) needed to eliminate $CO_2$, suggesting preserved neurochemical ventilatory drive to maintain normal arterial $CO_2$ tension despite increased dead space. Excessive ventilation also correlated with pulmonary capillary wedge pressure (r=0.42) and pulmonary vascular resistance (r=0.41). Conclusion: Abnormal lung units with high V/Q ratio which are associated with impaired pulmonary circulation account for increased VD/VT and wasted ventilation resulting in compensatory excessive ventilation in Pts with CHF. Excessive ventilatory response to $VCO_2$ is a frequent abnormal finding and may be an objective marker of altered ventilatory function in Pts with CHF.

COMPARISON OF EXERCISE PROTOCOLS: EVALUATION OF OXYGEN UPTAKE KINETICS IN HEART FAILURE

Ileana L. Pina M.D., F.A.C.C., Dean G. Karalis M.D., Rachel Zack R.N., William S. Frankl M.D., F.A.C.C., Likoff Cardiovascular Institute, Hahnemann University, Philadelphia, Pennsylvania.

The purpose of this study was to determine which treadmill protocol would best assess aerobic capacity in Pts with Class III heart failure (HF). Six Pts were tested [mean age 65±9;mean ejection fraction(EF)22%] using 4 protocols[Bruce(B),Naughton in 2' and in 3' stages and a Ramp(15 watt/min)] with breath by breath $O_2$ uptake($VO_2$). Medications were at steady state. Testing was done at a mean of 3 hours post dose, to dyspnea/fatigue, and to a respiratory exchange ratio of >1.1. Mean hemodynamics were: [heart rate(HR); systolic pressure (SBP) mmHg; double product (DP) x $10^3$; $VO_2$cc/min/kg; time(mins).

| | peak hr | peak sbp | peak dp | peak $VO_2$ | time |
|---|---|---|---|---|---|
| Bruce | 126±15 | 154±36 | 19.4±5 | 11.2±3 | 4.0±1.2 |
| Ramp | 122±16 | 160±27 | 19.3±3 | 8.7±3.6 | 4.4±1.3 |
| 3min | 128±10 | 152±19 | 19.4±3 | 7.8±1.7 | 9.5±5.5 |
| 2min | 125±15 | 162±37 | 20.4±6 | 8.3±3.2 | 7.8±2.7 |

Anaerobic threshold (AT) was reproducible in each Pt regardless of protocol within a margin of 6.5-9%. All Pts achieved the highest $VO_2$ with the B. There was no significant correlation between EF and exercise time or between the protocol and the max DP in each Pt. The slope of $VO_2$ kinetics prior to AT ($\Delta VO_2/\Delta$ time) was highest in the B. Thus, in Pts with HF, the HR reserve is relatively fixed and a challenging test will give a better approximation of maximum $VO_2$ but a less demanding one will allow a greater duration. Peak $VO_2$ is effort and protocol dependent. AT, however,may be a better parameter to measure therapy response due to its reproducibility. Its prognostic capabilities are yet to be determined.

## Thursday, March 23, 1989
## 8:30AM–10:00AM, Santa Ana Room 1
## Anaheim Convention Center
## Cardiac Transplantation: New Insights

IS YEARLY CORONARY ARTERIOGRAPHY SUFFICIENT FOR DETECTION OF CORONARY ARTERY DISEASE IN HEART TRANSPLANT RECIPIENTS?

Milena J. Henzlova, MD, Hrudaya Nath, MD, James K. Kirklin, MD, FACC, Robert C. Bourge, MD, FACC, Connie L. White, RN, William J. Rogers, MD, FACC. University of Alabama at Birmingham, Birmingham, AL.

In order to determine whether routine yearly coronary angiography post-cardiac transplantation is adequate for detection of coronary artery disease (CAD), we reviewed the clinical course, serial coronary angiograms, and autopsy data from 73 transplanted patients who survived until the first yearly angiogram or later. Angiograms (n = 138) were read by 2 observers, projecting serial angiograms simultaneously for side-by-side comparison and assessment of interval change. CAD was detected in 7.1% (5/70) at 1 yr, in 14.3% (6/42) at 2 yr, in 36.8% (7/19) at 3 yr, in 66.7% (2/3) at 4 yr, and 75% (3/4) at 5 yr post-transplantation. Patients with CAD were longer post-transplant than patients without CAD (34 ± 17 mos vs 22 ± 11 mos, $p<0.003$). Of the 15 patients with CAD, 53% had lesions involving only 1 vessel, 40% 2 vessels and 7% 3 vessels. Only 2 patients had lesions comprising >50% luminal narrowing. Of the 13 patients having <50% luminal narrowing, CAD had been missed on previous "clinical" (non-simultaneous side-by-side) reading of the angiograms in 8 (62%). Among 7 patients who died 2-11 mos following coronary angiography, severe underestimation (or rapid progression) of CAD was noted in 2 patients (29%) and likely was the proximate cause of death. Not predictive of CAD development were other clinical variables including recipient's and donor's age, sex, race, primary disease, ischemic time, and number and severity of rejection episodes.

Thus, CAD becomes increasingly prevalent as survival post-transplantation lengthens; transplant CAD in its earliest stages is subtle and best detected by side-by-side angiogram analysis. However, even 1 yr serial coronary angiograms are inadequate to detect rapidly progressive transplant CAD in some patients. Alternate non-invasive detection methods are needed.

POSITRON EMISSION TOMOGRAPHY REVEALS DECREASED CORONARY FLOW RESPONSE TO EXERCISE AFTER CARDIAC TRANSPLANTATION

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The maximal exercise capacity for some pts after cardiac transplantation (CTx) is decreased compared to normals. To determine if a limitation in coronary flow reserve contributes to this problem, we measured coronary blood flow in 9 pts with CTx at rest and at peak supine exercise using dynamic positron emission tomography. Ejection fraction for CTx pts was 55±15% and recent coronary angiography showed no evidence of atherosclerosis except in 1 pt with distal 2-vessel disease. The flow tracer nitrogen-13 ammonia (NH3) was injected at rest and at 1 min prior to the end of supine exercise. A 2 compartment model was applied to the initial 90 sec of PET data to obtain average flow values. The average flow at rest was 1.16±.38 ml/min/g, 45% higher than normals (.80±.43 ml/min/g). The double product (DP) for CTx pts at rest was also 49% higher than the DP for normals. Despite an 80% increase in DP in CTx pts with exercise, the flow only increased 10% (1.28±.83ml/min/g, N.S.). In normals, with an identical peak DP, the flow increased 100% (1.53±.69 ml/min/g, $p<.001$). In conclusion, elevated resting flow rates were observed in CTx pts which may have resulted from their higher resting DPs. The cardiac flow response to exercise was decreased. These findings may result from cyclosporin-induced hypertension, the effects of denervation on heart rate and coronary vasomotion, and/or the effects of accelerated atherosclerosis on the microvasculature.

## CORONARY ARTERY TO RIGHT VENTRICLE FISTULAE IN HEART TRANSPLANT RECIPIENTS: A COMPLICATION OF ENDOMYOCARDIAL BIOPSY?

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Coronary artery fistula is a very rare congenital anomaly with an incidence of 0.1-0.2% (Hobbs, 1982; Gillebert, 1986). However, in a series of 74 cardiac transplant recipients undergoing annual follow-up coronary angiography, we observed a coronary artery to right ventricle fistula in 4 patients (incidence = 5.4%, C.L. 2.7% to 8.1%). In order to investigate an endomyocardial biopsy-related etiology of these fistulae, the clinical records and biopsy histopathological data of these patients were reviewed and compared with those of patients without fistulae. All fistulae were detected at the time of the first yearly coronary angiogram. Patients with fistula underwent more biopsies during the first year post-transplant than patients without fistula (20 $\pm$ 11 vs 14 $\pm$ 6, $p < .05$). However, during the entire observation period (25 $\pm$ 14 months) the total number of biopsies in patients with fistula (20 $\pm$ 11) was no different from that of patients without fistula ($19 \pm 7$)($p > .05$).

Histopathologically, at least one "large" arteriole (circumference > 0.5 mm) was found in the biopsy specimens of all patients with fistula (100%) but in only 2 of 12 randomly selected patients without fistula (16.7%, $p < .01$). All fistulae were located in the biopsy sampling area; in 2 patients fistulae involved the left anterior descending (LAD), in 1 patient the right coronary artery (RCA), and in 1 patient both LAD and RCA. Right heart pressures and cardiac index were normal in all 4 patients with fistula at the time of diagnosis.

Thus, more frequent endomyocardial biopsies during the first year post-cardiac transplant may predispose to fistula formation between right ventricle and a coronary artery, an apparently benign condition.

## PRESERVED ATRIAL NATRIURETIC PEPTIDE SECRETORY FUNCTION IN DENERVATED CARDIAC TRANSPLANT RECIPIENTS.

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The secretion of atrial natriuretic peptide (ANP) is regulated by atrial pressure and stretch and influenced by the autonomic nervous system via cardiac innervation. The purpose of this investigation was to determine if ANP secretory function is preserved in denervated, orthotopic cardiac transplant recipients (CTR). Ten cyclosporine treated patients performed supine bicycle exercise with simultaneous hemodynamic monitoring. The mean baseline ANP level (pg/ml) was 140±15 and the mean peak level was 430±37 ($p < .001$). Significant differences ($p<.001$) between hemodynamic measurements obtained at rest and peak exercise were observed: mean right atrial pressure (RAM) 5±1 and 12±1; pulmonary artery mean pressure (PAM) 19±2 and 35±3; pulmonary capillary wedge mean (PCW) 10±1 and 22±2. ANP levels correlate with the RAM $r=.66$, PAM $r=.63$, and PCW $r=.62$ (all $p<.005$). No correlation exists between mean arterial pressure and ANP levels ($r=.226$). All patients had therapeutic cyclosporine levels and the mean blood urea nitrogen was 28±7.7 mg/dl and serum creatinine 1.3±.23 mg/dl. In conclusion basal ANP levels are markedly elevated (normal< 20) in successful CTR. ANP levels increase with exercise, associated with increased PCW indicating that despite denervation, ANP secretory function is preserved in CTR.

## ONE HEART, TWO BODIES: INSIGHTS FROM THE TRANSPLANTED HEART'S NEW ELECTROCARDIOGRAM.

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Cardiac transplantation provides a unique opportunity for the study of the human heart in 2 hosts. To evaluate the significance of common accepted findings in the scalar electrocardiogram (ECG), 35 donor and recipient ECGs were coded and compared a mean of 57 (17) days after successful transplantation. There was no difference in height (173 (2.1) vs 171 (2.2) cm, pNS), but recipient weight 71 (2.5) vs 63 (2.2) kg, $p<0.025$) and body surface area (1.84 vs 1.72 $M^2$, $p<0.05$) were higher. The mean recipient age was also higher (44.2 vs 31.3 years, $p<0.05$). The ECG findings were as follows:

| ( ) = SEM | Donor | Recipient | p |
|---|---|---|---|
| Rate (bpm) | 107(3.7) | 104(4.4) | NS |
| PR interval (msec) | 146(2.9) | 138(3.0) | <0.025 |
| QRS(msec) | 107(3.0) | 868(3.0) | NS |
| QT(msec) | 350(8.0) | 320(11) | <0.05 |
| QRS Axis | +62(4.0) | +54(5.9) | NS |
| Transition (mean) | V3 | V4 | <0.0005 |
| SV1+RV5(mm) | 21.5(1.5) | 24.1(2.2) | NS |

Eight pts had new incomplete RBBB and 2 had new complete RBBB. Mean ischemic time for the new RBBB pts was 150.3 (14.6) min versus 150.0 (13.1) min for the pts with a normal QRS (pNS). Mean PA pressure and PVR were not significantly different. Conclusions: 1. Clockwise rotation detected on ECG has a true anatomic basis, 2. An acute increase in age or body mass does not result in a decrease in frontal plane voltage, 3. The PR, QRS, and QT intervals are shortened after denervation, and 4. New BBBs do not appear to be related to pulmonary hypertension prior to or preservation injury at the time of orthotopic cardiac transplantation.

## ECHOCARDIOGRAPHIC FEATURES OF THE TRANSPLANTED HEART IN WELL PATIENTS ONE YEAR POST TRANSPLANTATION.

John Gorcsan, M.D., Frank R. Snow, M.D., Walter J. Paulsen, M.D., FACC, James A. Thompson, M.D., FACC, Richard R. Lower, M.D., FACC, J. V. Nixon, M.D., FACC, Medical College of Virginia, Richmond, Virginia

The echocardiographic features of well orthotopic cardiac transplantation (Tx) recipients have not been previously characterized. Accordingly, echocardiography was performed on 28 Pts(aged 23-60 yrs) who were clinically well 12± 2 months post Tx. All had normal stress thallium scintigraphy, normal radionuclide left ventriculography, and no endomyocardial biopsy evidence of rejection within 48 hrs of the time of study. The following 2-dimensional and M-mode echocardiographic parameters were measured and compared to those of a group of 10 similarly aged (22-59 yrs) normal subjects (N): LV end-diastolic (D) volume (Simpson's Rule), LV ejection fraction, LV mass (Penn method), RV end-diastolic area and RV fractional area change during systole (FAC), RV wall thickness, and LA and RA areas. Values are mean ± standard deviation.

| | Tx | N | | Tx | N |
|---|---|---|---|---|---|
| LV mass g | 197±49* | 125±44 | RV Thickness cm | 0.6±.1* | 0.4±.1 |
| LV Volume (D) cc | 109±28 | 103±28 | RV Area (D) $cm^2$ | 23±4* | 16±3 |
| LV Ejection Fraction % | 63±3 | 63±4 | RV FAC % | 33±12 | 35±11 |
| LA Area $cm^2$ | 27±4* | 15±4 | RA Area | 21±4* | 12±3 |

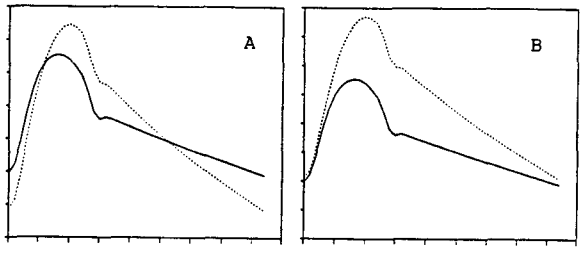
*$p<0.005$

At one year post Tx, clinically well recipients are characterized by increased LV mass but normal LV volumes and ejection fraction, increased RV wall thickness and cavity size but normal RV systolic function, and markedly dilated atria. These unique echocardiographic features of well orthotopic Tx recipients should provide a normal baseline from which recognition of pathologic states may be made in their long term follow-up.

# Thursday, March 23, 1989
# 10:30AM–12:00NOON, Santa Ana Room 1
# Anaheim Convention Center
# Arterial and Ventricular Compliance in HTN

CONCURRENT COMPLIANCE REDUCTION AND INCREASED RESISTANCE IN THE MANIFESTATION OF ISOLATED SYSTOLIC HYPERTENSION.
John K-J. Li, Ph.D., David S. Berger, B. S., Cardiovascular Research Lab, Biomedical Engineering, Rutgers University, Piscataway, New Jersey

Reduced compliance (C) of blood vessels has been suggested as a causative factor of the occurrence of isolated systolic hypertension (ISH). No consistent theoretical or experimental model has been proposed for the production of ISH. To investigate this, experiments were performed on open chested anesthetized dogs (n=6). Simultaneous measurements of ECG, aortic pressure (AOP), and flow (AOQ) were recorded. Increased systolic pressure (Ps) alone with insignificant change in diastolic blood pressure (Pd) was successfully produced in a modified windkessel model of the aterial system with AOQ as the input and AOP the output, as shown below. A reduction of C alone increases Ps, but also decreases Pd (A). A C decrease of 50% and a simultaneous smaller increase in peripheral resistance (< 25%) are necessary for the successful production of ISH from a normal dog (B). This finding suggests that a decrease in compliance alone is not responsible for ISH.




ANTIHYPERTENSIVE THERAPY IS IMPROVED BY CENTRAL EFFECTS OF ARTERIAL DILATION AND REDUCED WAVE REFLECTION.
Raymond Kelly M.B., Julie Daley R.N., Alberto Avolio PhD, Michael O'Rourke M.D., F.A.C.C. St. Vincent's Hospital, Sydney, Australia.

Systolic blood pressure is an important risk factor for cardiovascular morbidity and mortality. Its determinants include arterial distensibility and pulse wave reflection. The purpose of this study was to examine how these determinants of systolic pressure are affected by different types of antihypertensive therapy. We compared dilevalol (an isomer of labetolol), 200-400 mg daily, against atenolol, 50-100 mg, in a double-blind, cross-over, placebo-controlled trial with respect to effects on arterial distensibility (measured as pulse wave velocity, PWV) and wave reflection (assessed from carotid pressure wave contour). 12 pts (44-73 yrs) with essential hypertension (supine diastolic BP 95-114 mm Hg) took active therapy for 12 weeks, separated by a 2-4 week placebo period. Carotid pressure waveforms were recorded non-invasively by applanation tonometry using a Millar micromanometer-tipped probe. PWV was measured between carotid and femoral arteries (aortic PWV), carotid and radial (arm PWV), femoral and pedal pulses (leg PWV). Early wave reflection was calculated from the ratio of the height of the peak of the carotid wave above its shoulder to the pulse pressure and expressed as an index of augmentation (IA). Both drugs were equally effective in reducing brachial sphygmomanometric pressure and PWV in all 3 regions (active vs placebo $p < 0.001$) but there was no significant difference between the two active therapies. However, IA (averaged over the period of treatment) was significantly lower with dilevalol (19%) than atenolol (28%), $p < 0.01$, corresponding to a greater fall of 5-8 mm Hg in carotid systolic pressure compared to the brachial artery. While both drugs were equally effective in reducing arterial distensibility, the vasodilating action of dilevalol gave added benefit in reducing wave reflection. In conclusion: dilevalol is better than atenolol in reducing central systolic pressure and left ventricular load due to its effect on wave reflection.

NONINVASIVE ASSESSMENT OF ARTERIAL COMPLIANCE IN PATIENTS WITH SYSTEMIC HYPERTENSION.
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Arterial compliance (AC) is often abnormal in pts with systemic hypertension (HTN) resulting in a greater than normal ↑ in arterial pressure for any change in AO volume. Traditional approaches to measuring AC have required cardiac cath. Accordingly, we developed a noninvasive method (analogous to the invasive method of Yin et al) which is based on the Windkessel model of the arterial system. This assumes that AO diastolic pressure decays exponentially with time. In 12 normals and 18 untreated HTN pts, continuous wave Doppler was used to measure instantaneous AO flow while simultaneously recorded calibrated carotid pulse tracings were used to determine the rate of Ao pressure decay. Sustained HTN was confirmed by ambulatory 24 hr BP monitoring. The HTN pts were divided into those with normal (n = 9) vs low (n = 9) arterial compliance.

| | NORMALS | HTN (NL AC) | HTN (↓ AC) |
|---|---|---|---|
| Age (years) | 48 ± 16 | 47 ± 12 | 47 ± 20 |
| Mean 24 hr BP | 89 ± 10 | 112 ± 5* | 116 ± 9* |
| CI ($L/m/m^2$) | 2.9 ± 0.4 | 3.6 ± 0.7* | 2.8 ± 0.5‡ |
| SVR ($ds/cm^5$) | 1445 ± 281 | 1316 ± 313 | 1990 ± 487*‡ |
| AC (ml/mmHg) | 1.8 ± 0.5 | 1.8 ± 0.3 | 1.2 ± 0.3*‡ |

*$p < 0.01$ vs NL, ‡$p < 0.01$ vs HTN (NL AC)

The HTN patients with ↓AC had lower AO flow and higher SVR than HTN pts with normal AC. This was true despite similar mean 24 hr BP and age. Thus, this easily performed noninvasive method for determining arterial compliance can identify differences in LV-peripheral vascular coupling that are not evident from BP measurements alone. This may have important therapeutic implications for a physiologically based approach to treatment of systemic hypertension.

RELATIONSHIP BETWEEN LEFT VENTRICULAR MASS REGRESSION AND IMPROVED LEFT VENTRICULAR FILLING IN SEVERE HYPERTENSION.
Robert A Phillips MD PhD, Maria Ardeljan RN, Martin E Goldman MD FACC, Lawrence R Krakoff MD. Mount Sinai Medical Center, NY, NY

The relationship between LV mass regression and improved LV diastolic performance in severe hypertensives remains uncertain. We treated 11 severe hypertensives (age 58±4, mean±s.e.m.) with long-term monotherapy using Nifedipine-GITS (Nif-GITS), a sustained release preparation. Serial measurements by echo/Doppler to assess LV mass index (LVMI) and LV filling were made at entry (E) and after two months (2M) of blood pressure (BP) control (diastolic BP ≤95 mm Hg). The ratio of atrial to early LV filling velocity (A/E ratio) was used as an index of LV filling. At E, 55% had elevated LVMI and 60% had an elevated A/E ratio. Systolic (SBP) and Diastolic (DBP) BP were well controlled at 2M on Nif-GITS. LV mass regression (8%) was significant and there was a trend toward normalization of LV filling with a fall (18%) in the A/E ratio. There was no correlation between LV mass regression and improvement of LV filling.

| Phase | SBP | DBP | LVMI($gm/m^2$) | A/E ratio |
|---|---|---|---|---|
| E | 198±10 | 117±3 | 124±11 | 1.6±0.2 |
| 2M | 141±8 | 87±2 | 114±11 | 1.3±0.1 |
| | p<.0001 | p<.0001 | p<.05 | ns |

Conclusion: Sustained BP reduction by Nif-GITS for 2M leads to regression of LV hypertrophy. LV regression precedes and is not correlated with improved LV filling. This suggests that LV mass regression and improved LV filling may be dissociated in severe hypertensives who are treated long-term with nifedipine-GITS.

CONCENTRIC REMODELING OF THE LEFT VENTRICLE IN HYPERTENSIVE PATIENTS WITH NORMAL VENTRICULAR MASS.
Antonello Ganau M.D., Richard B. Devereux, M.D., FACC, Mary J. Roman, M.D., Peter Schnall, M.D., Thomas G. Pickering, M.D., Ph.D., John H. Laragh, M.D. Cornell Medical College, New York, N.Y.

To investigate whether modifications of LV geometry and inotropism play a role in LV adaptation to the pressure-overload in hypertensive pts (H) without LV hypertrophy, we studied by echocardiography 50 normal subjects (N) and 38 untreated mild H with LV mass index (LVMI) within sex-specific normal limits. Relative wall thickness (RWT) was increased more than 2 standard deviations above the normal mean (>.44) in 11/38 H, providing evidence of a subtle change in LV geometry. Cardiac index (CI: $l/min/m^2$), total peripheral resistance (TPR: $dynes \cdot sec \cdot cm^{-5}$), peak wall stress (PWS: $10^3 dynes/cm^2$), end-systolic stress/volume index ratio (ESS/ESVi: $10^3 dynes/cm^2$), and 2-dimensional LV short/long axis ratio (S/L) were compared in N and in H with increased (H1) or normal (H2) RWT. Systolic blood pressure was higher in H1 (142±11 mmHg; p<.01) and H2 (134±10; p<.05) than in N (128±9), whereas LVMI was similar in N (79±19 $g/m^2$), H1 (89±13) and H2 (85±15).

| | | RWT | CI | TPR | ESS/ESVi | S/L |
|---|---|---|---|---|---|---|
| N | (50) | .34±.0 | 2.7±.6 | 1480±357 | 3.2±.7 | .59±.06 |
| H1 | (11) | .45±.0* | 2.3±.5* | 1877±368* | 3.6±.6 | .52±.04* |
| H2 | (27) | .35±.0 | 2.7±.6 | 1610±457+ | 3.2±.5 | .57±.04 |

+ = p<.05 and * = p<.01 vs N.

Thus, increased RWT and more elliptic LV shape ( S/L) suggest that concentric remodeling of LV occurs in a number of H with normal LV mass. Low CI, high TPR and a trend toward increased inotropism are associated with this anatomic pattern. Since PWS is lower in this group (173±23; p<.05) than in N (207±36) or in H2 (221±29), LV concentric remodeling seems to eliminate the stimulus to increase of LV mass due to mild hypertensive overload.

SPONTANEOUS PROGRESSION AND REGRESSION OF CONCENTRIC HYPERTROPHY IN PATIENTS WITH BORDERLINE(BOH) OR MILD HYPERTENSION(MIH).
Nobutaka Doba M.D., Hiroshi Tomiyama, M.D., Toshio Kushiro M.D.,Nagao Kajiwara,M.D.,FACC,Shigeaki Hinohara,M.D.,FACC. Teikyo Univ.,Nihon Univ.,Life Planning Center,Tokyo,Japan.

BOH and MIH have been well known to reveal increased relative diastolic wall thickness (RDWT). In this study, we will demonstrate changes in RDWT for 44 ± 10 months and will discuss the possibility of prediction of its progression (PROG) or regression(REG). Of 155 male patients with BOH or MIH whose echocardiograms were eligible for routine measurements, 56 subjects (average age of 44 ± 5 years) who completed the second check-up after 3.7 years were selected for the study. Maximal treadmill stress testing was performed on all subjects. Subjects were divided into 3 groups based on changes in RDWT; progressive($\Delta$ RDWT $\geq$ 0.1), less progressive (0.1 > $\Delta$RDWT $\geq$ 0) and regressive ($\Delta$ RDWT < 0). Comparisons were made between 14 PROG and 13 REG subjects with regard to blood pressure (BP) levels at rest and maximal exertional stress, and echocardiographic parameters. While no significant differences were noted at the entry between the two groups with regard to rest BP, CI, EF, mVcf, TPRI, LVDd, LVDs or PWTd, significant differences were noted in maximal exertional systolic pressure, IVSTd and several echocardiographic diastolic functions. For 3.7 years, increased RDWT in PROG was associated with significantly increased IVSTd, PWTd, TPRI and decreased LDVd and LVDs without changes in BP levels. On the other hand, decreased RDWT in REG was characterized not by changes in BP levels, but by increased LVDd and decreased IVSTd and TPRI. Conclusions: (1) TPRI and diastolic functions at rest and BP response to maximal exertional stress were different between PROG and REG groups. Thus, (2) Progression or regression of concentric hypertrophy could be predicable at the entry to the program.

# Thursday, March 23, 1989
# 8:30AM–10:00AM, Santa Ana Room 2
# Anaheim Convention Center
# Neurohumoral Activation in Congestive Heart Failure

HEMODYNAMIC CORRELATES OF INCREASED CARDIAC ADRENERGIC DRIVE IN THE INTACT FAILING HUMAN HEART.
Anthony B. Sandoval, M.D., Edward M. Gilbert, M.D., Patti Larrabee, B.S. Randy Rasmussen, B.S., Kirk Volkman, R.N., Michael R. Bristow. University of Utah, Salt Lake City, Utah

Cardiac adrenergic drive (ADc) is increased in heart failure. Little is known about the hemodynamic or cardiac functional abnormalities that trigger the increase in ADc. To investigate possible afferent signals for an increase in ADc, we measured coronary sinus norepinephrine (CSNE) and hemodynamic variables in 60 subjects (group 1) with idiopathic dilated cardiomyopathy. In a separate group of 29 subjects (group II) we serially measured ADc with respect to hemodynamic changes: subgroup IIa, decrease in CSNE; IIb, no change in CSNE; IIc, increase in CSNE: (±SEM, *-p<.05).

| Group I: (n=60) | CSNE pg/ml | r values vs CSNE: RV Biopsy & Receptor Density | PWP | E.F. | C.I. |
|---|---|---|---|---|---|
| | 581±67 | -.60* | +.66* | -.26 | -.30 |

| Group II: | CSNE | | PWP | | C.I. | | E.F. | | MAP | |
|---|---|---|---|---|---|---|---|---|---|---|
| (n) | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| IIa (6): | 936 | *357 | 19 | *11 | 2.0 | 2.3 | .25 | .28 | 88 | 90 |
| | ±301 | ±106 | ±4 | ±1 | ±.2 | ±.2 | ±.03 | ±.04 | ±4 | ±4 |
| IIb(14): | 830 | 465 | 16 | 15 | 2.2 | 2.2 | .23 | .25 | 85 | 86 |
| | ±310 | ±154 | ±3 | ±4 | ±.1 | ±.2 | ±.02 | ±.02 | ±2 | ±3 |
| IIc (9): | 275 | *1136 | 10 | *18 | 2.4 | 2.3 | .23 | .25 | 83 | 87 |
| | ± 74 | ±483 | ±2 | ±11 | ±.2 | ±.2 | ±.03 | ±.03 | ±4 | ±3 |

Conclusion: Change in left ventricular filling pressure (PWP) is the best correlate of changes in ADc. One possible mechanism for the increased ADc is therefore increased ventricular volume and/or pressure, with the subsequent inhibition of inhibitory adrenergic reflexes mediated by either stretch or pressure receptors located in the ventricles, atria, or central veins.

RELATIONSHIP OF VENTRICULO-ARTERIAL COUPLING TO NEUROHUMORAL MECHANISMS IN HEART FAILURE.
Tomoki Kameyama M.D., Hidetsugu Asanoi M.D., Shinji Ishizaka M.D., Shigetake Sasayama M.D.F.A.C.C.. Toyama Medical & Pharmaceutical University, Toyama, Japan.

Circulatory adjustments to heart failure were evaluated by ventriculo-arterial coupling in relation to sympathetic nervous activity, as measured by plasma norepinephrine levels, and baroreflex sensitivity. Direct arterial pressure and LV echocardiogram were recorded simultaneously as the pressure was changed by phenylephrine and nitroprusside in 10 normals and 23 pts with chronic heart failure. Ventriculo-arterial coupling was defined by the relationship between the slope of the end-systolic pressure-volume relation (Ees) and the slope (Ea) of the end-systolic pressure-stroke volume relation ; Ea/Ees. Ea/Ees was 0.5±0.2 in normal subjects and markedly increase in pts with heart failure (1.7±1.1,p<0.05). Baroreflex sensitivity substantially fell with the increase in Ea/Ees. Pts with Ea/Ees greater than 1.0 had 2.4±1.7msec/mmHg of baroreflex sensitivity, while pts with Ea/Ees of 1.0 or less had 7.7±6.0msec/mmHg (p<0.05). Plasma norepinephrine was elevated more in pts with Ea/Ees of 2.0 or more (439±223pg/ml) than in pts with Ea/Ees less than 2.0 (221±73pg/ml,p<0.05) Thus, these results suggest that in the course of heart failure, circulatory adjustments result in three phases according to Ea/Ees; phase I with normal baroreflex and sympathetic activity (Ea/Ees≤1.0). phase II with depressed baroreflex and normal sympathetic activity (1<Ea/Ees<2) and phase III with depressed baroreflex and enhanced sympathetic activity (Ea/Ees≥2).

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CARDIOVASCULAR HORMONES IN RELATION TO MORTALITY IN SEVERE HEART FAILURE

Karl Swedberg M.D., FACC., Peter Eneroth M.D., John Kjekshus M.D., Steve Snapinn Ph.D., Lars Wilhelmsen M.D., Östra Hospital, Gothenburg, Sweden.

In the CONSENSUS TRIAL 253 patients with severe heart failure were randomised to placebo (P,n=127) or enalapril (E,n=126). Blood levels of noradrenaline, adrenaline, angiotensin II and atrial natriuretic peptide were determined at baseline. In the placebo group there was a significant relationship between each of these hormones and mortality. We used a stepwise linear discriminant analysis to evaluate how the combined interaction of these hormones could predict mortality. A prediction score was calculated. A higher score indicates high hormonal levels overall.

Results: There were 217 patients with all hormones determined.74 patients died within 6 months (primary objective).

6-month Mortality (%) by Prediction Score at Baseline

| | Score | | | | | | |
|---|---|---|---|---|---|---|---|
| | <23 | 23-25 | 25-27 | 27-30 | 30-40 | >40 | P |
| P | 11 | 32 | 30 | 36 | 58 | 93 | 0.002 |
| E | 42 | 24 | 18 | 19 | 18 | 41 | n.s. |

P vs E=0.003. Primarily death due to progressive heart failure was predicted.

Conclusion: The combined activation of the sympathetic nervous system and the reninangiotensin system is strongly correlated to mortality in patients with severe heart failure not treated with ACE-inhibitors. This relationship was not observed among patients treated with enalapril where mortality was much lower.

EVIDENCE FOR AN EARLY INCREASE IN CARDIAC SYMPATHETIC STIMULATION IN PATIENTS WITH DIASTOLIC DYSFUNCTION.

Michel F. Rousseau M.D., F.A.C.C., Jean Etienne, Henri Van Mechelen, Hubert Pouleur M.D., F.A.C.C., University of Louvain, Brussels, Belgium.

The relation between left ventricular (LV) function and cardiac sympathetic drive at rest was studied in 19 patients with ischemic heart disease (Ejection Fraction ranging from 26 to 60 %, mean 45±13). No patient had clinical signs of congestive heart failure and all cardioactive drugs were stopped for 3 days before measuring arterial and Coronary Sinus (CS) norepinephrine (NE) and the indices of LV function (Millar + Angiography). CS NE concentrations ranged from 0.62 to 5.78 pmol/ml (mean 1.98±1.65 pmol/ml) and correlated slightly with the ejection fraction (r=-0.76*) but not with LV dP/dt Max (r=0.04). The best correlations, however, were found between CS NE and the indices of diastolic function such as LVEDP (r=0.91**) or the time-constant T of isovolumic relaxation (r=0.86**). Arterial NE levels (mean values 1.84±1.19 pmol/ml) were slightly lower than in the CS and the correlation of arterial NE with LV function indices were significantly weaker than with CS NE. Thus, CS NE is increased in the presence of diastolic dysfunction suggesting an activation of cardiac sympathetic drive before any signs of overt congestive heart failure. These data also indicate that systemic plasma levels of NE underestimate cardiac sympathetic stimulation in the presence of LV dysfunction and may explain the moderate $\beta$-adrenoceptor down-regulation reported in such patients. * P<0.01 ** P<0.001

DIFFERENCES IN NEUROHUMORAL ACTIVATION IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION WITH AND WITHOUT HEART FAILURE.

Gary Francis, MD, FACC, Claude Benedict, MD, PhD, FACC, David Johnstone, MD, Philip Kirlin, MD, FACC, Gerald Neuberg, MD, Spencer Kubo, MD, FACC, James Hosking, PhD, Chang-seng Liang, MD, PhD, FACC, Salim Yusuf, MD; Investigators for Studies of Left Ventricular Dysfunction. Minneapolis, MN.

Patients (pts) with congestive heart failure (CHF) are known to have neurohumoral activation. Comparative data in asymptomatic pts with left ventricular (LV) dysfunction are not available. We measured baseline plasma norepinephrine (PNE) and plasma renin activity (PRA) in pts with LV dysfunction (ejection fraction {EF} ≤0.35) with and without CHF. The mean EF was 0.29±5 (SD) in asymptomatic pts and 0.25±6 in symptomatic pts (p<0.0003). Although PNE was significantly (p<0.02) lower in the 87 asymptomatic pts (478±218 pg/ml) compared to the 56 pts with CHF (596±340 pg/ml), this difference was modest with considerable overlap. By contrast, the differences in PRA between the two groups were striking (1.16±1.13 ng/ml/hr in the asymptomatic group vs 2.58±2.95 in the CHF group, p<0.0005) with no asymptomatic pt (n=87) showing PRA elevation. Therefore, asymptomatic pts with LV dysfunction have lower PNE and PRA than pts with CHF, but have higher values of PNE than previously reported for non-age matched controls. Sympathetic activation may precede renin-angiotensin activation in pts with CHF.

NEUROHORMONAL ACTIVATION LIMITS THE LONG-TERM RESPONSE TO THE DOPAMINE-1 RECEPTOR AGONIST, FENOLDOPAM, IN CHRONIC HEART FAILURE.

Marrick L. Kukin MD, Stephen S. Gottlieb MD, Norma Medina RN, Madeline Yushak RN, Rochelle L. Goldsmith MS, Milton Packer MD, FACC. Mount Sinai School of Medicine, New York, NY

The selective dopamine-1 receptor agonist, fenoldopam (FEN), produces acute hemodynamic benefits in chronic heart failure (CHF), but its long-term effects are unknown. In 19 CHF pts, we measured stroke volume index (SVI, ml/m$^2$), heart rate (HR, bpm), mean arterial, pulmonary wedge and mean right atrial pressures (MAP, PWP & RA, mm Hg), systemic vascular resistance (SVR, d-s-c), plasma renin activity (PRA, ng/ml/hr) and norepinephrine (PNE, pg/ml) before (pre) and 1-3 months after therapy with FEN (100 mg orally every 8h), while digoxin and diuretics were kept constant; where * = p < 0.05.

| | SVI | MAP | PWP | RA | HR | SVR | PRA | PNE |
|---|---|---|---|---|---|---|---|---|
| Pre | 24 | 87 | 26 | 13 | 83 | 1760 | 5.0 | 703 |
| FEN | 29 | 73* | 22 | 11 | 91* | 1160* | 14.5* | 984* |

Although FEN ↓ MAP and SVR, the drug did not improve LV function (as assessed by SVI, PWP or RA). This may explain why FEN produced little clinical improvement in these pts. There was no ↑ in maximum $O_2$ consumption (bicycle) (9.7 to 10.1 ml/kg/min) or in distance walked in 6 min (308 to 284 m). Only 5 of 19 pts (26%) showed ↓ CHF symptoms; 14 did not.

Changes in neurohormonal activity paralleled the clinical response to FEN. The 5 responders had low values for PRA and PNE before FEN and showed no change in PRA (1.2 to 1.4 ng/ml/hr) or PNE (541 to 615 pg/ml) during FEN. In contrast, in the 14 nonresponders, pretreatment values for PRA and PNE were elevated, and both PRA (6.7 to 20.4 ng/ml/hr, p < .05) and PNE (821 to 1177 pg/ml, p < .05) ↑ further during FEN.

In conclusion, FEN does not produce hemodynamic or clinical benefits in most pts with severe CHF. This may be related to the ability of FEN to stimulate neurohormones, particularly in pts whose neurohormonal systems are activated before treatment.

# Thursday, March 23, 1989
# 10:30AM–12:00NOON, Santa Ana Room 2
# Anaheim Convention Center
# Inotropic Agents in Congestive Heart Failure

ACCELERATED ARTERIAL WAVE REFLECTION WITH DOPAMINE BUT NOT DOBUTAMINE IN CONGESTIVE HEART FAILURE

Philip F. Binkley M.D., F.A.C.C., Douglas B. VanFossen M.D., F.A.C.C., Enrico Nunziatta M.S.B.M.E., Carl V. Leier M.D., F.A.C.C. The Ohio State University, Columbus, Ohio

Reflected pressure and flow waves may significantly alter ventricular performance since reflected pressure adds to afterload and reflected flow subtracts from forward stroke volume. The effect of the positive inotropic agents dopamine (DOP) and dobutamine (DOB) on peripheral wave reflection was analyzed in 12 patients with congestive heart failure to determine whether these agents beneficially alter afterload by influencing reflected waves. Deconvolution of signal-averaged central aortic pressure and flow wave forms was performed using Fourier analysis to generate forward and reflected pressure and flow waves. The backward wave arrival time (BWAT) and BWAT normalized for left ventricular (lv) ejection time (BWATN) were determined at baseline and with infusion of DOP at 2, 4, and 8 ug/kg/min and DOB at 3, 6, and 12 ug/kg/min. DOP resulted in a progressive decrease in BWAT from 208±72 to 117±21 msec and in BWATN from 1,025±314 to 579±175 (both p<.05). However, DOB was associated with no change in BWAT (164±25 to 168±33 msec) and an increase in BWATN (.723±.124 to .821±.173; p=.09). Therefore, DOP administration is associated with earlier arrival of reflected arterial waves during lv ejection thus augmenting afterload and subtracting from forward flow. In contrast, DOB is associated with a later arrival of reflected waves relative to lv ejection thus beneficially influencing systolic loading conditions.

ABSENCE OF TACHYPHYLAXIS FOLLOWING CHRONIC THERAPY WITH XAMOTEROL IN HEART FAILURE.

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The chronic use of $B_1$-receptor agonists as inotropes in heart failure is limited by tachyphylaxis, possibly mediated by B-receptor down-regulation. Xamoterol (X) is a novel $B_1$-agonist with 43% of the intrinsic sympathomimetic activity of the full agonist isoprenaline. Its properties enable it to act as a $B_1$-agonist when sympathetic tone is low and as an antagonist when sympathetic tone is high. This modulation of sympathetic tone may be beneficial in preserving B-receptor function and maintaining therapeutic response to inotropes. Haemodynamic variables (Swan-Ganz catheter, intra-arterial blood pressure and radionuclide ejection fraction) were assessed at rest and on exercise before and after intravenous (IV) X (0.2mg/Kg), in 30 patients with heart failure NYHA II(13), III (17) due to ischaemic heart disease or congestive cardiomyopathy. The patients then entered a 3 month double blind crossover study comparing oral X with placebo and the haemodynamic response to IV X reassessed at the end of the study. At rest, initially X increased cardiac index (CI) (2.5±0.2 to 2.8±0.1 l/min/$m^2$, P<0.001) and stroke volume index (SVI) (33±2 to 40±3 mls/bt/$m^2$, P<0.001), with a small fall in heart rate (78±3 to 74±2, P<0.05). At peak exercise, X maintained CI at significantly lower heart rates (112±4 to 97±3, P<0.001) and double product (18640±920 to 15990±760 mmHg/min, P<0.01) due to an improvement in SVI(42±3 to 48±4 mls/bt/$m^2$, P<0.001). Following chronic oral therapy the haemodynamic responses to IV X both at rest and on exercise were preserved and showed no attenuation.
Conclusion. In this study there was no evidence of tachyphylaxis to either the agonist effect at rest or antagonist effect on exercise after chronic therapy with Xamoterol.

TACHYPHYLAXIS ASSOCIATED WITH DOPEXAMINE ADMINISTRATION IN SEVERE HEART FAILURE.

Edward M. Gilbert, M.D., Kirk Volkman, R.N., Patrice C. Mealey, R.N., Michael R. Bristow, M.D. University of Utah School of Medicine. Salt Lake City, Utah

Dopexamine (DPX) is reportedly a dopaminergic and $\beta_2$ agonist with combined inotropic and vasodilator effects. In isolated human heart DPX appears to also possess "indirect" action related to release of neuronal norepinephrine. In 7 patients (pts) with severe heart failure, hemodynamics were measured at baseline and with i.v. infusion of DPX at 1 to 8 μg/kg/min. DPX was then infused to maintain cardiac index 20-40% above baseline for 72 hours or until loss of efficacy or adverse events occurred. Infusion was prematurely discontinued in 3 pts with tachyarrhythmia and 3 pts with loss of efficacy. In 5 pts, DPX dose-response could be remeasured after 27.9±9.7 hrs of DPX infusion. For these 5 pts, cardiac index (L/min/$m^2$) response was:

| DPX Dose | Initial | Post-infusion |
|---|---|---|
| No DPX | 1.7 ± 0.3 | 1.6 ± 0.6 |
| 1 μg/kg/min | 2.3 ± 0.4 | 1.9 ± 0.5 |
| 2 μg/kg/min | 2.6 ± 0.4 | 2.2 ± 0.7 |
| 4 μg/kg/min | 3.1 ± 0.4 | 1.9 ± 0.6 |
| 6 μg/kg/min | 3.6 ± 0.6 | 2.5 ± 0.8 |
| 8 μg/kg/min | 3.6 ± 0.9 | 1.9 ± 0.4 |

The post-infusion dose response was significantly downward and right-shifted (p=0.013). Control pts receiving a 43±5 hr dobutamine (DBT) infusion exhibited no shift in DBT dose-response curve. CONCLUSION: Although DPX initially improves cardiac output, efficacy is rapidly lost during long-term DPX infusion. In contrast, early tachyphylaxis is not observed in DBT-treated pts. The mechanism of tachyphylaxis may be related to the indirect action of DPX.

ENOXIMONE IMPROVES MAXIMAL AND SUBMAXIMAL EXERTION IN PATIENTS WITH CHRONIC HEART FAILURE: A DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL.

Mariell Jessup, M.D., F.A.C.C., Susan C. Brozena, M.D., Arthur Jenkins III, Judianne Samaha, R.N. Temple University Hospital, Philadelphia, Pennsylvania.

An important goal in the treatment of patients with chronic heart failure (CHF) is to improve tolerance to the exertion of daily living. Accordingly, 14 patients with CHF, aged 58 ± 8 years, LV ejection fraction of 21 ± 9%, optimally treated with digitalis and diuretics, underwent 2 or more baseline maximal exercise tests with respiratory gas exchange to measure a reproducible baseline exercise duration (base) (seconds) and maximal oxygen uptake ($VO_2$ max) (ml/kg/min). At each stage of exercise, patients indicated a Borg Perceived Exertion score. Patients were then randomized, double blind to enoximone (enox), (n=7) at 1 mg/kg TID or placebo (plac), (n=7) for 12 weeks. All exercise testing and the Borg scale scores were repeated at the end of this time.
RESULTS:

| | Borg Scale | | | | | |
|---|---|---|---|---|---|---|
| exercise stage : | 0 | 1 | 2 | 3 | exercise duration | $VO_2$ max |
| base: | 9±2 | 11±4 | 13±4 | 14±3 | 505±183 | 14.5±5 |
| plac: | 8±2 | 11±3 | 13±4 | 14±3 | 534±177 | 15.4±5 |
| enox: | 8±1 | 9±2 | 11±3* | 12±3* | 608±248* | 16.2±5* |

(* p<.01, * p<.08 vs baseline)

CONCLUSION: Enoximone, added to digitalis and diuretics, significantly improves $VO_2$ max, exercise time and perceived exertion at submaximal loads in patients with chronic CHF.

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USE OF ENOXIMONE IN CARDIAC TRANSPLANT CANDIDATES; EFFECT ON β ADRENERGIC RECEPTORS

Howard R. Lee, M.D.,Ph.D., John B. O'Connell, M.D., F.A.C.C., Dale G. Renlund, M.D., F.A.C.C., Edward M. Gilbert, M.D., Patrice C. Mealey, R.N., Kirk Volkman, R.N., Patricia A. Larrabee, B.S., Michael R. Bristow, M.D.,Ph.D., and the UTAH Cardiac Transplant Program, Salt Lake City, Utah

We have used Enoximone (E), a phosphodiesterase inhibitor with positive inotropic and vasodilator effects, for stabilizing cardiac function in patients awaiting cardiac transplantation (Tx). 72 patients have been treated with E (58 transplanted with 84% 1 year survival; 6 died while awaiting Tx; 8 alive not Tx). In 10 patients awaiting Tx, the effect of E (mean treatment 25.5 days; range 4-64) on ventricular myocardial β adrenergic receptors (AR) was studied. The mean age was 46±4 (mean±SE) years and 7 were male. Five patients had dilated cardiomyopathy, 4 had coronary artery disease, and 1 had adriamycin cardiomyopathy. The explanted hearts (LV & RV) of patients treated with E alone, and hearts not requiring E or β agonists were analyzed for total βAR density ($\beta_{tot}$), $\beta_1/\beta_2$ AR density ($\beta_1/\beta_2$), dissociation constants ($K_d$), and norepinephrine (NE) content: (*p < 0.01)

| Group | $\beta_{tot}$ | $\beta_1$ (% $\beta_1$) | $\beta_2$ (% $\beta_2$) |
|---|---|---|---|
| | | fmol/mg protein | |
| (+)E (n=20) | 51.7±2.8 | 24.5±2.5* (46)* | 25.4±2.5* (51)* |
| (-)E (n=106) | 52.6±1.9 | 34.4±1.6 (63) | 18.8±0.9 (36) |

There was no significant difference in $K_d$ or NE levels (+E=377±69 ng/g tissue; -E=557±58). Conclusion: E is not associated with further down-regulation of the $\beta_{tot}$ in heart failure, but is associated with a decrease in $\beta_1$ and an increase in $\beta_2$ AR.

# Thursday, March 23, 1989
# 8:30AM–10:00AM, California Room B
# Anaheim Convention Center
# Pharmacology of Antiarrhythmic Drugs—Basic I

EFFECTS OF COMBINED LOW DOSES OF QUINIDINE AND METOPROLOL ON INDUCIBLE VENTRICULAR ARRHYTHMIAS IN A CHRONIC CANINE INFARCT MODEL

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Quinidine (Q) and metoprolol (M) are given to treat ventricular arrhythmias (VA) and improve survival after myocardial infarction (MI), however, full dose therapy is frequently limited by intolerable side effects, toxicity or treatment failure. Thus, using the chronic canine occlusion-reperfusion model of inducible VA, we studied the ability of combined sub-therapeutic doses of Q+M to suppress inducible VA. Of 34 dogs, no VA were inducible in 9, sustained ventricular tachycardia (VT) was reproducibly initiated in 14 and ventricular fibrillation (VF) in 11. Alternating sub-therapeutic intravenous doses of Q (3.75-15 mg/kg) and M (0.1-1.0 mg/kg) were given until VA were suppressed. 2 VT dogs could not tolerate even low doses of Q hemodynamically and were eliminated from further study. Low dose Q alone suppressed VT in one dog. Low dose M alone suppressed VT in 2 dogs. Combined low dose Q+M suppressed VT in 8 of the remaining 9 dogs. Q slowed VT rates, M did not. Q alone suppressed VF in 3 cases. Prior studies demonstrated remarkably small doses of M to be completely effective at suppressing VF. It remained so here in the one case when it was given first. Low dose M remained effective against VF in the seven cases when low dose Q given first was ineffective. Conclusion: Combined low doses of Q+M are extremely successful at suppressing VT after experimental MI, with only rare treatment failure and no proarrhythmia. Neither drug alone suppressed VT. Low dose M remains effective against VF, even in the presence of Q.

LACK OF CORRELATION OF OUABAIN BINDING SITES AND INOTROPIC RESPONSE TO DIGITALIS IN EXPERIMENTAL HEART FAILURE.

Tai-Hwang M. Fan, Ph.D., Susumu Sakamoto, M.D., John Thompson Sullebarger, M.D., Chang-seng Liang, M.D., Ph.D., F.A.C.C., University of Rochester Medical Center, Rochester, New York.

Myocardial digitalis receptor numbers (DR) have been shown to be reduced in several pathologic conditions including congestive heart failure secondary to dilated cardiomyopathy. To study whether this reduction in DR causes a blunted inotropic response to digitalis, we measured DR and hemodynamic response to acetylstrophanthidin (AS, 50 μg/kg) in 8 dogs with right heart failure (RHF) induced by tricuspid avulsion and pulmonary artery constriction and 10 sham-operated dogs. Compare to sham dogs, RHF dogs exhibited a lower (p<0.05) baseline RV dP/dt (492±34 vs. 730±27 mmHg/sec), LV dP/dt (1950±115 vs. 3002±128 mmHg/sec) and CO (2.69±0.18 vs. 3.24±0.14 L/min). Ventricular DR was quantitated by radioligand binding assay with [3H]-ouabain which bound cardiac membranes with high affinity (Kd≈13 nM) and Scatchard analysis showed a homogeneous population of binding sites in both RHF and sham dogs. Results (mean±SE) of DR (pmol/mg)$_g$ and maximum AS-induced increases in dP/dt and CO are: *P<0.05 vs. sham.

| | RV DR | LV DR | RV dP/dt | LV dP/dt | CO |
|---|---|---|---|---|---|
| Sham | 4.7±0.2$_g$ | 5.8±0.3$_g$ | 247±25 | 1312±107 | 1.13±0.12 |
| RHF | 3.2±0.3 | 3.9±0.3 | 282±55 | 1491±232 | 0.93±0.10 |

HR responses to AS did not differ between the 2 groups. The results indicate that the reduction of DR is not specific to the failing myocardium, as it also occurs in the non-failing LV. Furthermore, since the ventricular dP/dt and CO responses to AS did not differ between the sham and RHF dogs, we conclude that DR can be reduced by as much as 30% without causing a demonstratable decrease in the inotropic response to digitalis.

COMBINATION OF CLASS IA AND IB ANTIARRHYTHMIC DRUGS MARKEDLY DEPRESSES Vmax WITH LITTLE CHANGE IN THE ACTION POTENTIAL DURATION IN CANINE PURKINJE FIBERS

Yoshio Watanabe M.D., F.A.C.C., Hideo Tanaka M.D., Nobuo Homma M.D., Hiroko Uchida M.D., Cardiovascular Institute, Fujita Gakuen Health University, Toyoake, Aichi, Japan

Cellular electrophysiologic mechanisms for the beneficial effects of combined class IA and IB antiarrhythmic drugs in the treatment of ventricular tachyarrhythmias were studied by recording transmembrane potentials of canine Purkinje fibers driven at 1 Hz. Drugs tested were (1) 5mg/L disopyramide (D) + 10mg/L lidocaine (L), and (2) D + 5mg/L mexiletine (M), with the perfusion sequence switched in both groups. In group 1, initial perfusion with D significantly (P < 0.05) decreased Vmax and prolonged the action potential duration at 90% repolarization ($APD_{90}$), and subsequent addition of L further reduced Vmax and restored $APD_{90}$ to normal (n=5). L alone significantly decreased Vmax and $APD_{90}$, and addition of D further reduced Vmax and prolonged $APD_{90}$ to the control level (n=5). In group 2, M showed exactly similar interactions with D, whether the perfusion sequence was D followed by D+M (n=8) or M followed by M+D (n=8). Shortening of $APD_{90}$ at shorter cycle lengths of stimulation (600 and 400 ms) as compared with 1,000 ms was less marked when D and M were combined, suggesting relative prolongation of APD during tachycardia. Use-dependent depression of Vmax on sudden shortening of the cycle length from 1,000 to 400-500 ms showed fast kinetics with L or M and slow kinetics with D, and their combination produced an intermediate response. These results suggest that combination of class IA and IB drugs are additive in depressing conduction and antagonistic in modifying refractoriness, and such interactions may cause an increased efficacy against ventricular tachyarrhythmias with less untoward effects on ventricular repolarization.

TERMINATION OF EPINEPHRINE-INDUCED VENTRICULAR TACHYCARDIA BY ADENOSINE IN HALOTHANE-ANESTHETIZED DOGS

W. Jerry Merrell M.D., William Rush B.S., Menno ter Riet, David G. Bjoraker M.D., Luiz Belardinelli M.D., University of Florida College of Medicine, Gainesville, Florida

Halothane sensitizes the heart to the effects of epinephrine and may lead to life-threatening ventricular arrhythmias, properties not shared by other commonly employed inhalational anesthetics. This catecholamine-induced arrhythmia is blocked by adrenergic blockers or adenosine triphosphate (ATP) but exacerbated by theophylline, an adenosine antagonist. Therefore, we sought to determine whether this arrhythmia is suppressed by adenosine, which has been shown to terminate isoproterenol-induced ventricular tachycardia (VT) in humans. In 8 dogs anesthetized with halothane, arterial pressure was measured and arrhythmias monitored by lead-2 ECG, RA, RV, and/or His-Bundle electrograms. Under stable anesthetic conditions, progressively larger doses of epinephrine were administered sequentially by constant intravenous (IV) infusion until VT occurred. Epinephrine, at a mean dose of 46.8 ± 13.1 μg/min (SEM), induced sustained VT in all dogs. In every case, IV administration of adenosine, 105 ± 65 μM/min (mean ± SEM), rapidly restored normal sinus rhythm. When adenosine was discontinued, VT promptly recurred. In 2 dogs, dipyridamole (250 μg/kg IV), an adenosine uptake blocker that increases myocardial adenosine levels, also restored normal sinus rhythm; this effect was reversed by the adenosine antagonist 8-sulpho-phenyltheophylline (5 mg/kg IV). Conclusions: Epinephrine-induced VT during halothane anesthesia: (a) can be terminated effectively and rapidly by exogenous adenosine and (b) is modulated by endogenous adenosine. Adenosine or agents with adenosine-like effects may be valuable in the treatment of catecholamine-induced VT.

AMIODARONE ON SUPPRESSION OF BARIUM-INDUCED TRIGGERED AUTOMATICITY AND EARLY AFTERREPOLARIZATIONS IN PURKINJE FIBERS RELATIVE TO EFFECTS OF VERAPAMIL AND CLASS I AGENTS.

Chiei Takanaka M.D., Bramah N. Singh M.D., Ph.D., F.A.C.C., Wadsworth VA Medical Center Los Angeles, CA.

Triggered automaticity (TA) and early afterdepolarizations (EADs) are implicated in the genesis of torsades. The effects on EADs of amiodarone (Am) which rarely causes torsades is unknown. TA and EADs were produced in isolated canine Purkinje fibers with 5 mM barium (Ba). Such action potentials (AP) were abolished in Tyrode devoid of $[Ca^{2+}]_o$ and by 10 μM verapamil. Effects of Am (50 μM) on maximal diastolic potential (MDP), AP amplitude (APA), Vmax, spontaneous frequency (SF) are shown as means ± SE (*p<0.01):

| | MDP (mV) | AMP (mV) | Vmax (V/sec) | SF (mV) |
|---|---|---|---|---|
| Control | 55.1 ±1.1 | 78.8 ±2.9 | 13.2 ±1.1 | 62.3 ±4.0 |
| Am | 55.4 ±1.2 | 60.0* ±2.7 | 7.3* ±0.8 | 35.5* ±2.8 |

Lidocaine (40μM) had no effect. Quinidine (10μM) decreased APA 6.9% (p<0.05) and Vmax 15.7% (p<0.01) but increased APD (p<0.05) and produced EADs. Am had no effect on APD but abolished EADs. Conclusions: (i) Slow Ca- but not fast-Na channel activity appears to mediate Ba- triggered APs and EADs; (ii) low incidence of torsades on Am may be due to associated inhibitory effects on Ca-channels.

## DISPARATE EFFECTS OF ACUTE AND CHRONIC AMIODARONE ON VENTRICULAR FIBRILLATION THRESHOLD IN DOGS.

Mario D. Gonzalez, M.D., Jaime J. Grin, M.D., Eduardo D. Venturini, M.S.E.E. College of Medicine, National University of Rosario, Argentina.

Chronic oral amiodarone (A) administration is effective in suppressing ventricular arrhythmias in patients at high risk for sudden death. However, intravenous administration of A is often less effective. The purpose of this study was to compare the effect of intravenous A with lidocaine on the ventricular fibrillation threshold (VFT) in anesthetized closed-chest dogs. In addition, serial studies during long-term oral A administration were performed to determine the time-course of VFT changes. VFT was determined by scanning the ventricular vunerable period with single RV endocardial stimuli of increasing current strength. Following intravenous administration of lidocaine (2 mg/kg followed by 20 μg/kg/min, n=10) VFT increased significantly from 46.5±6.3 to 80±15.3 mA (mean±SEM, $p < 0.025$). In contrast, intravenous A (3.6 mg/kg over 5 min, n=13) decreased the VFT from 35±5.5 to 27±3.6 mA ($p < 0.025$). The VFT was not modified after the administration of either saline solution (30±2 vs 31±2 mA, NS; n=10) or solvent of A ( 40±2 vs 45±8 mA, NS; n=5). Repeated measurements (at 2 to 8 week intervals) during chronic studies were analyzed by fitting a straight line to the data of each animal. The mean slope of these regressions ($\bar{b}$) was subjected to trend analysis ($t$-statistic, $t = \bar{b}\sqrt{n}/s_b$). In the control group, the VFT remained stable over a mean of 5.1±0.4 months ($\bar{b}$ = -0.9±0.6, not significantly different from zero). Prolonged oral A administration (17 mg/kg/day for 4.6±0.7 months, n=7) resulted in a progressive increase in the VFT ($\bar{b}$ = 12.7±2.18, $p<0.0005$). A 50% increase in the VFT was observed after 65±16days of A. In conclusion: The intravenous infusion of amiodarone, unlike lidocaine, increased the vulnerability of the ventricle to electrically induced ventricular fibrillation. Conversely, chronic amiodarone administration was required to produce an increase in the VFT. These data emphasize the disparate effects of acute and chronic amiodarone therapy.

'TORSADES DE POINTES' WITH QUINIDINE AND PROPRANOLOL IN CONSCIOUS DOGS WITH A-V BLOCK.

Jacques Weissenburger M.D., Frédérique Chézalviel, Jean-Marc Davy M.D., Antoine Ferry M.D., Gilbert Motté M.D. and Georges Cheymol M.D. Faculté St-Antoine, 75012-Paris (France).

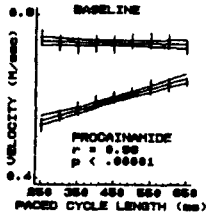
Quinidine (Q)-induced 'Torsades de pointes' (TdP) are known to be facilitated by hypokaliemia (HK) and bradycardia and prevented by isoproterenol infusion. In a recent model of conscious dog with permanent A-V block, non-toxic doses of i.v. Q have been shown to provoke frequent complex ventricular (V) arrhythmias mostly when chronic diuretic-induced HK was present. But TdP never occured.
In order to obtain TdP in this model, we administered propranolol (PPL, 0.5 mg/Kg i.v.) prior to Q (10 mg/Kg i.v.) in 7 dogs with normokaliemia (NK) and in 6 dogs with HK (3.1±0.1mMol/l). At baseline V cycle length were similar in both groups (RR: 1520±109ms). After Q and PPL, RR increased to 2325±76ms in NK and to 1965±190ms in HK, and QT intervals at V driven-rate (60/min) reached 382±16ms (NK) and 374±17ms (HK). TdP occured in 4 out of the 7 dogs in NK (with 2 V fibrillations) and in 2 out of 6 dogs in HK (all with V fibrillations). Other V arrhythmias (non-sustained tachycardia or couplets) occured in 4 dogs (1 in NK and 3 in HK dogs). Conclusions: In dogs with A-V block, PPL pre-treatment is required to observe TdP after non-toxic i.v dose of Q. Enhanced degree of bradycardia and/or direct adrenergic interactions could here be involved.

# Thursday, March 23, 1989
# 10:30AM–12:00NOON, California Room B
# Anaheim Convention Center
# Pharmacology of Antiarrhythmic Drugs—Basic II

RATE-DEPENDENT SLOWING OF INTRAVENTRICULAR CONDUCTION BY PROCAINAMIDE: DIRECT MEASUREMENT IN THE HUMAN HEART

E. Wayne Grogan, Jr., M.D., F.A.C.C. University of Wisconsin, Madison, Wisconsin

Sodium channel blocking agents decrease the slope of phase 0 of the action potential, thereby decreasing myocardial conduction velocity (CV). This blockade is rate dependent (RD), which may occur as a result of mechanisms postulated by the modulated receptor hypothesis. This study was performed to examine this phenomenon in man, by determining if procainamide causes RD slowing of intraventricular conduction, and if this phenomenon can be accurately measured by catheter recordings. At EP study, 11 patients were paced at 650-250 ms paced cycle length from electrode pair 1 of a catheter in the RV apex, and conduction time was measured from pairs 2 to 5 (33 mm apart) before and after 15 mg/kg IV procainamide (PA), level=9.7±2 µg/ml. The standard deviation of 5 measurements averaged ± 1.2 ms. Assuming linear conduction, mean baseline CV was 0.73 M/sec, and did not vary with rate. Mean CV on PA slowed with decreasing paced cycle length by 2.6x10-4 M/sec/ms, from 0.64 to 0.53 M/sec. The graph shows mean CV ± standard errors with linear regression lines and 95% confidence limits for baseline and PA. Thus: 1) Ventricular CV can be reproducibly measured by this method and is similar to reported ventricular CV measured in vitro; 2) CV in the absence of drugs is not RD; 3) PA slows CV in a linear, RD fashion; 4) this method may be useful to quantify RD effects of antiarrhythmic drugs in man.




DEVELOPMENTAL CHANGES IN LIDOCAINE ACTION OCCUR AT NEUTRAL BUT NOT ACIDIC pH.

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Previous studies have shown that lidocaine induces use-dependent depression of $\dot{V}_{max}$ in adult canine Purkinje fibers (PF) to a greater extent than in neonates, and that acidosis augments lidocaine's use dependent actions. We studied the interactions of lidocaine (5 mg/L) and pH (7.3 and 6.8) on $\dot{V}_{max}$ of adult and neonatal PF, to determine if acidosis altered the developmental differences previously seen. PF were driven at stimulus cycle lengths = 1300 and 300 ms. Control maximal diastolic potential (MDP) and $\dot{V}_{max}$ = -83±1mV and 623±16V/sec, respectively (adults); and -83±1mV and 550±36 V/sec (neonates) (p>.05). We studied the effects of lidocaine on tonic block (% reduction of $\dot{V}_{max}$ from control); use-dependent block (% reduction of $\dot{V}_{max}$ from tonic); the "on" rate (number of stimuli to establish steady state use dependent block); and the off rate representing recovery from use-dependent block ($\tau_{off}$). Results were as follows:

| | pH 7.3 | | pH 6.8 | |
|---|---|---|---|---|
| | adults | neonates | adults | neonates |
| tonic block(%↓) | 12±2 | 11±2 | 14±4 | 17±3 |
| use-dependent block(%↓) | 10±1 | 7±2 | 23±3 | 28±2 |
| "on" rate (beats) | 2±.3 | 6±.8 | 5±.8 | 7±1 |
| $\tau_{off}$ (ms) | 133±10 | 81±8 | 210±15 | 193±10 |

At pH 7.3 tonic and use dependent block were equivalent in adults and neonates, but "on" rate was shorter and $\tau_{off}$ longer in adults (both P<.05). Acidosis increased use-dependent block and $\tau_{off}$ in both groups (P<.05) and eliminated the differences between adult and neonate in "on" rate and $\tau_{off}$. To attain this required a greater prolongation of "on" rate and $\tau_{off}$ in the neonate. These results suggest that the interactions between lidocaine and the developing cell membrane are influenced by pH such that at neutral pH ionized lidocaine is more effective in inducing local anesthetic action in the adult.

ELECTROPHYSIOLOGIC EFFECTS OF A CHEMICAL DEFIBRILLATORY AGENT: DIBENZEPIN

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We studied the effects of dibenzepin (D), a tricyclic antidepressant, which spontaneously terminates electrically induced ventricular fibrillation. Its defibrillatory action is enhanced by elevated catecholamines. Using standard microelectrode techniques the following measurements were made in vitro in canine papillary muscle: action potential amplitude and duration, effective refractory period, maximum diastolic potential, overshoot, Vmax (V/sec) and conduction time (CT) between 2 electrode sites spaced 1-2mm apart (msec/mm). Measurements were made at 3 cycle lengths both before (C) and after dibenzepin. A cycle length of of 200 msec was studied in order to approach cycles that may occur during fibrillation.

| Cycle length | Vmax( C) | Vmax(D) | CT(C) | CT(D) |
|---|---|---|---|---|
| 1000(msec) | 195±29 | 187±25 | 1.85±.45 | 1.54±.45 * |
| 400(msec) | 182±26 | 166±27 * | 1.92±.48 | 1.61±.48 * |
| 200(msec) | 163±25 | 136±27 * | 2.08±.44 | 1.70±.51 * |

Significant reductions occurred in Vmax and CT (n=8;*p<.05) even at the very short cycle length. The paradoxical shortening of CT with a decreased Vmax may be due to indirect effects of dibenzepin. It inhibits reuptake of catecholamines. Therefore, propranolol (P) (200 nanoM) was used. (n=6).

| Cycle length | Vmax(C) | Vmax(D+P) | CT(C) | CT(D+P) |
|---|---|---|---|---|
| 1000(msec) | 192±30 | 167±27 * | 1.59±.22 | 1.79±.28 * |
| 400(msec) | 177±27 | 158±26 * | 1.64±.26 | 1.85±.35 * |
| 200(msec) | 165±24 | 145±26 * | 1.69±.28 | 2.03±.35 * |

Propanolol alone caused no significant changes in any measurment. When combined with dibenzepin Vmax was still significantly reduced but CT was increased. Therefore, the paradoxical effect of dibenzipin alone to decrease Vmax but inprove conduction may be mediated by the ability of catecholamines to increase intercellular coupling. Thus, the defibrillatory effects of dibenzepin seem to be due to its ability to improve conduction during fibrillation and thereby decrease the critical number of asynchronous fibrillatory wavelets.

CHRONIC AMIODARONE ADMINISTRATION PROTECTS AGAINST GLOBAL MYOCARDIAL ISCHEMIA IN THE RAT

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Patients who have had therapy for arrhythmia with Amiodarone (A) frequently require cardiac surgery.

To evaluate the effect of chronic administration of A on cardiac function after surgery with global ischemia, normotensive (n=6) and spontaneously hypertensive (n=6) rats were administered A intraperitoneally for 4 weeks. An equal number of normotensive and hypertensive controls were injected with sterile saline solution on the same schedule.

Normotensive rats received a total dose of 240 mg/kg of A over 4 weeks, at which time the myocardial concentration of A was 3.73 ± 1.98 µg/gm wet weight. Hypertensive rats received 500 mg/kg of A over 4 weeks, at which time myocardial A was 1.74 µg/gm wet weight. The hearts from these rats were excised and perfused in a Langendorff apparatus for 30 min, then subjected to 15 min global ischemia followed by 45 min reperfusion, all at normothermia. Heart rate and LV developed pressure were measured using an LV balloon and LV work was calculated before and after ischemia. During the reperfusion period, A treated hearts had significantly better LV function than controls, and treated hearts had recovered 97 ± 13% of preischemic work after 45 min, compared to 76 ± 17% for control hearts (p<0.005).

There was no difference in the post-ischemic functional recovery of normotensive and hypertensive hearts. Chronic A administration protects against functional deterioration after global ischemia under these conditions.

EPICARDIAL MAPPING OF RATE-DEPENDENT VENTRICULAR CONDUCTION SLOWING BY PROCAINAMIDE.
Stanley Nattel, M.D., F.A.C.C., Wuhua Jing, M.D., Montreal Heart Institute, Montreal, Quebec.
While antiarrhythmic drugs are known to produce rate-dependent sodium channel blockade, little quantitative work has been done to evaluate the consequences for drug effects on conduction. The purpose of these experiments was to study interval-dependent effects of procainamide on epicardial activation in anesthetized dogs. Formalin-induced AV block was used to study the effects of 3 stable procainamide concentrations over a wide range of coupling intervals. Computer-based mapping was performed using data from 56 simultaneously acquired epicardial electrograms. Results: Overall conduction pattern and time were constant over a wide range of test intervals ($S_1S_2$) under control conditions. Procainamide produced a concentration and interval-related slowing in conduction velocity ($\theta$). Quantitative analysis of conduction pattern showed it to be unchanged by procainamide, even in the presence of substantial drug-induced conduction slowing. Mathematical modelling of conduction slowing caused by procainamide showed it to be more consistent with an underlying proportional relationship between $\dot{V}max$ and $\theta 2$ (least sum of squares of curve fits 4.8±0.9*10-3) than with a linear relationship between $\dot{V}max$ and $\theta$ (least sum of squares 7.2±1.7*10-3, $p<.05$). Drug-induced epicardial conduction time changes correlated closely with changes in QRS duration ($r=0.95$, $p<.001$), indicating that QRS is a valid index of drug effects on ventricular conduction. Conclusions: 1) Procainamide causes rate-related conduction slowing suggesting that $\dot{V}max \propto \theta 2$, without altering overall epicardial activation pattern; 2) QRS is a valid noninvasive index of drug effects on ventricular conduction.

RETROGRADE CONDUCTION PROPERTIES DETERMINE RATE-DEPENDENT EFFICACY OF DILTIAZEM FOR AV REENTRANT TACHYCARDIA.
Demetrios Papadatos, Mario Talajic, MD, Christine Villemaire, BSc, Mohsen Nayebpour, PharmD, Stanley Nattel, MD, FACC, Montreal Heart Institute, Montreal, Canada.
Molecular models predict rate-dependent effects of diltiazem (D) on AV nodal conduction. This study was designed to evaluate the potential clinical significance of this property in treating orthodromic AV reentrant tachycardia (AVRT). Sensing and pacing circuits were used to mimic a retrograde accessory pathway in 10 autonomically-blocked dogs. In each dog, AVRT was induced over a range of retrograde intervals (VA) between 300 and 10 msec. Under control conditions, the rate of AVRT increased as VA decreased, and sustained AVRT (sAVRT) was observed until atrial refractoriness limited induction at VA≤31±8 msec. In the presence of D, decreases in VA resulted in rate-dependent AV conduction slowing, manifesting as a secondary phase of AH prolongation after tachycardia onset which prevented or slowed sAVRT. This phase had a time constant averaging 24 beats, similar to that of D effects on Isi in vitro, and a magnitude determined by VA and AVRT rate ($p<.001$). Consequently, the ability of D to prevent sAVRT depended on VA, with an efficacy of 0,37, and 81% (low dose) and 29,86, and 100% (high dose) at VA's of 200, 100, and 50 msec respectively. The rate-related secondary phase of AH prolongation depended on D dose, and was absent under control conditions. We conclude that retrograde conduction properties determine D's efficacy in AVRT by controlling rate-dependent slow channel blockade. This confirms predictions based on pharmacologic models suggesting selective depression of tachycardias by drugs with use-dependent blocking actions.

# Thursday, March 23, 1989
# 8:30AM–10:00AM, California Room A
# Anaheim Convention Center
# Cellular Metabolism and Cardiac Injury

IN VIVO NEAR INFRARED MONITORING OF MYOCARDIAL OXYGENATION DURING ISCHEMIA AND REPERFUSION.
William J. Parsons, MD, Judith C. Rembert, PhD, Robert P. Bauman, MD, Jack A. Griebel, MD, Claude A. Piantadosi, MD, Duke and VA Medical Centers, Durham, NC.
The use of near infrared (NIR) spectroscopy to assess cardiac oxidative metabolism in vivo is reported for the first time. NIR spectroscopy detects changes in redox state of the copper complex of mitochondrial cytochrome $\underline{a},\underline{a}_3$ and oxygenation of tissue hemoglobin (Hb) and myoglobin (Mb). We employed the NIR method in open chest dogs (n=6) to assess oxidative metabolism in normally contracting, ischemic, and reperfused myocardium. Complete occlusion of the LAD artery for 1 min was associated with an abrupt drop in myocardial $O_2$ stores (tissue $HbO_2$ + $MbO_2$) and tissue Hb volume, reaching a nadir in ~30 sec. The cyt $\underline{a},\underline{a}_3$ oxidation level decreased in parallel, due to an imbalance between electron flux and $O_2$ supply in ischemia. Upon reperfusion, reactive hyperemia was reflected in increases in tissue Hb volume and myocardial $O_2$ stores. Reoxidation of cyt $\underline{a},\underline{a}_3$ was observed within 30 sec to above preocclusion levels, followed by return to baseline within 1 min. Reperfusion after 15 min of LAD occlusion led to more prominent optically detected hyperemic changes. Of note, cyt $\underline{a},\underline{a}_3$ remained at an elevated state of oxidation for up to one hour post occlusion. Thus, in contrast to isolated mitochondria in vitro, cyt $\underline{a},\underline{a}_3$ is not fully oxidized in contracting myocardium. Also, reperfusion after prolonged coronary occlusion is associated with a persistent hyperoxidized state in terms of enhanced $O_2$ availability relative to electron flux at the oxidase. The NIR method provides important and unique information regarding changes in myocardial oxidative metabolism associated with ischemia and reperfusion.

ESTIMATION OF THE CONCENTRATION AND FUNCTION OF THE ADP/ATP CARRIER IN THE MYOCARDIUM OF PATIENTS WITH DILATED CARDIOMYOPATHY (DCM)
G. Ulrich, H.-P. Schultheiss, and B. Kemkes
Med. Klinik I, University of Munich, FRG
Recent studies from our group described the ADP/ATP carrier (ADP/ATP c.) of the inner mitochondrial membrane as an autoantigen in DCM. After isolation of mitochondria from explanted hearts the adenine nucleotide exchange was monitored using an inhibitor stop method combined with back exchange. In 14 out of 27 DCM the ATP-transport rate was significantly lower than in coronary heart disease (CHD) (after 40 sec.: 44.2±3.5 vs. 61.7±3.6 %). Although the transport capacity of the ADP/ATP carrier was decreased, its concentration in DCM was markedly increased as measured with a dot immunobinding assay (DCM 72.5±10.6; CHD 51.0±3.7 µg/mg protein). In these 14 patients autoantibody (AB) deposition in cardiac myocytes was clearly visible in direct immunofluorescence (CHD negative). To substantiate these findings, myocardial biopsies from patients with DCM (n=40) and CHD (n=10) were examined for ADP/ATP c. concentration and for deposition of AB in the tissue. In DCM the ADP/ATP c. concentration was significantly higher than in CHD (70.5±16.6 vs. 50.2±3.5 µg/mg protein). In 67% the elevated ADP/ATP c. titer was paralleled by a deposition of AB in cardiac myocytes. These data suggest that as a consequence of the autoimmune reaction against the ADP/ATP c. and its functional impairment the concentration of the carrier protein is up-regulated.

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SARCOLEMMAL PHOSPHOLIPID TURNOVER: A CRITICAL MEDIATOR OF MYOCARDIAL INJURY

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The biochemical events responsible for the transition from reversible to irreversible myocardial ischemic injury are not yet well understood. Increased turnover of membrane phospholipids with release of arachidonic acid (AA) and toxic, amphiphilic metabolites has been implicated. To delineate specific subcellular loci of augmented AA turnover in order to determine whether this process occurs in particularly vulnerable sites such as the sarcolemma, we characterized the subcellular distribution of $^{3}$H-AA in neonatal rat myocytes (n = 24 preparations) incubated with 5 nM $^{3}$H-AA for 24 hr before (prelabeled) or during (concomitantly labeled) exposure to iodoacetate to simulate either reversible (3 hr) or irreversible (5 hr) ischemic injury. Reversibly injured prelabeled cells released only minimal amounts of $^{3}$H-AA and resumed contracting in control media. Irreversibly injured prelabeled cells released massive amounts of $^{3}$H-AA and lactate dehydrogenase and did not recover. TLC did not identify marked changes in the percentage of $^{3}$H-AA in specific lipid pools despite injury. Quantitative ultrastructural autoradiography showed that the specific radioactivity of sarcolemma in prelabeled cells increased by 8% with reversible and by 56% with irreversible injury. The percentage of total $^{3}$H-AA in sarcolemma of concomitantly labeled cells increased from 0.2% in controls to 4.0% in reversibly injured and 19.2% in irreversibly injured cells. Thus, markedly augmented turnover of sarcolemmal phospholipids presages and appears likely to contribute to irreversible hypoxic injury of cardic myocytes.

LOW DOSE OF ANTITUMOR AGENTS PREVENTS SMOOTH MUSCLE CELL PROLIFERATION AFTER ENDOTHELIAL INJURY

Peter Barath, M.D., Ko Arakawa, M.D., Jin Cao, M.D., Michael Fishbein, M.D., FACC, James Fagin, M.D., Aldon Lusis, M.D., James Forrester, M.D. FACC, Cedars-Sinai Medical Center, Los Angeles, CA

The cellular basis of restenosis after balloon angioplasty (BA) is dedifferentiation of smooth muscle cells (SMC) (shift from the contractile to synthetic phenotype) followed by proliferation accompanied by and production of connective tissue. We hypothesize that early administration of low dose cytostatic agents could prevent restenosis by selectively damaging the active and proliferating SMCs. We gave mitosis phase specific Vincristine (0.075 mg/kg) and transcription inhibitor Actinomycin D (0.015 mg/kg) i.v. during balloon denudation of rabbit aorta. Control (C), denuded (D), treated (Rx) and denuded + treated (D-Rx) animals were sacrificed at 3d. The number of subintimal SMCs after intervention was compared with the that of control and the proportion of mitotic figures in 2,000 SMCs was expressed in percentage in semi-thin sections. Electron microscopic signs of cell activity (euchromatinization of nuclei, pronounced endoplasmic reticulum), cellular damage and the presence or absence of myofibrils were scored on a 4 point ordinal scale.

| | C(n=9) | D(n=9) | Rx(n=9) | D-Rx(n=9) |
|---|---|---|---|---|
| #SMC (% of control) | - | 223% | 100% | 155% |
| Mitotic figures | 0.15% | 17% | 24% | 34% |
| Activity | - | +++ | - | - |
| Cell Damage | - | - | - | +++ |
| Myofibrils | +++ | - | +++ | ++ |

**CONCLUSION:** Cytostatic agents in single low doses administered at the time of the injury prevent SMC proliferation without damaging normal SMCs. Therefore, these drugs may prevent post-angioplasty restenosis.

HYPOXIA AND GLUCOSE DEPRIVATION INDEPENDENTLY INDUCE UNCOUPLING OF $\alpha_1$-ADRENERGIC SIGNAL TRANSDUCTION IN CULTURED MYOCARDIAL CELLS

Toshifumi Kagiya M.D., Krishna Rocha-Singh M.D., Norman Honbo M.S. and Joel S. Karliner M.D., F.A.C.C. VA Medical Center and Cardiovascular Research Institute, University of California, San Francisco, CA

Supplement of glucose could be of critical importance in supporting ischemic myocardium. And it is still unclear how altered adrenergic receptor regulation during myocardial ischemia influences the second messenger system. We investigated the effects of hypoxia and/or deprivation of glucose on myocardial $\alpha_1$-receptors and phosphatidylinositol(PI) hydrolysis in single-cell cultures from neonatal rat myocardium. Cells were incubated under normoxic (95% $O_2$+5% $CO_2$) or hypoxic (95% $N_2$+5% $CO_2$) conditions in combination with glucose deprivation in media at 37°C for 2 hr. Inositol phosphates(IPs) were measured using anion exchange chromatography. Hypoxia increased the number of $\alpha_1$-receptors (18.1±2.5 (SE) to 26.9±3.4 fmol/mg protein; n=12, p<.001) and the basal level of inositol trisphosphate (48.1±6.9 to 68.5±14.8 fmol/mg protein; n=5, p<.05), but norepinephrine (NE)-stimulated PI hydrolysis was not enhanced (72.7±14.7 to 77.5±16.6 fmol/mg protein; n=5). Glucose deprivation without hypoxia increased $\alpha_1$-receptor density (12.5±3.0 to 23.0±4.1 fmol/mg protein; n=4, p<.05) and hypoxia produced further increase (27.2±2.7 fmol/mg protein; n=5). During glucose deprivation, NE-stimulated PI hydrolysis was also not enhanced either with or without hypoxia. Hypoxia resulted in a shift of NE competition curve for $^{125}$I-HEAT binding to the right, the Ki increasing significantly 2.97 fold (n=3, p<0.01). These results suggest that hypoxia increased the number of $\alpha_1$-receptors but decreased agonist affinity, and that both hypoxia and glucose deprivation independently result in uncoupling of $\alpha_1$-receptor mediated signal transduction.

## Thursday, March 23, 1989
## 10:30AM–12:00NOON, California Room A
## Anaheim Convention Center
## Recent Advances in Myocarditis

ENHANCED PHOSPHOINOSITIDE METABOLISM DURING REPERFUSION OF ISCHEMIC RAT HEART: A NOVEL MECHANISM OF REPERFUSION INJURY.

Hajime Otani, M.D., Ph.D., M. Renuka Prasad, Ph.D., Richard M. Engelman, M.D., Hitomi Otani, Ph.D., Dipak K. Das, Ph.D., Kansai Medical University, Moriguchi City, Osaka, Japan.

We examined phosphoinositide (PI) metabolism in ischemic and reperfused rat heart. The incorporation of [$^{3}$H]-inositol into PI increased significantly during reperfusion after 30 min of ischemia compared to that observed during nonischemic perfusion. In the heart prelabeled with [$^{3}$H]inositol, 30 min of ischemia did not increase accumulations of [$^{3}$H]inositol phosphates (IP), but reperfusion caused a several-fold increase in [$^{3}$H]IP accumulations. Reperfusion of the ischemic heart prelabeled with [$^{14}$C]arachidonate increased [$^{14}$C]diacylglycerol (DAG) and [$^{14}$C]phosphatidic acid. The enhanced accumulations of [$^{3}$H]IP during reperfusion were not affected by either prazosin plus atropine or indomethacin, but were inhibited by hypoxic reperfusion, reperfusion with $Ca^{2+}$-free buffer, or by mepacrine.

Conclusions: 1, myocardial reperfusion enhances PI metabolism via stimulation of $Ca^{2+}$-dependent, PI-specific phospholipase C activity; 2, the second messenger roles of $IP_3$ and DAG in elevating intracellular $Ca^{2+}$ suggest that enhanced PI metabolism may represent a novel mechanism of reperfusion injury.

INSENSITIVITY OF RIGHT VENTRICULAR ENDOMYOCARDIAL BIOPSY IN THE DIAGNOSIS OF MYOCARDITIS: WHITHER THE GOLD STANDARD? Lawrence H. Chow, MD, Thomas D. Sears, MD, FACC, & Bruce M. McManus, MD, PhD, FACC. University of Nebraska Medical Center, Omaha, NE.

Clinical suspicion of myocarditis relies heavily on the endomyocardial biopsy for confirmation, yet the sensitivity of the procedure in this setting has not been clearly defined. This uncertainty has assumed greater importance in the face of decisions about therapy for recent-onset, rapidly progressive heart failure of unknown cause. Biopsy sensitivity was determined in the present study in 14 hearts with histologically proven myocarditis investigated ex vivo, including 12 autopsies and 2 native hearts of allograft recipients. An average of 4-5 RV endomyocardial biopsies was obtained from the apical ventricular septum of each heart, using both the Cordis™ and Stanford bioptomes, and sampling was repeated at 3-5 specific RV sites in the rest of the septum. Corresponding diagnostic sensitivities, considered casewise for each bioptome, either inside or outside the apical area, ranged from 43-57%. By combining the results of both bioptomes in each septal region (a mean of 8-9 biopsies/region), sensitivity improved to 64%. Only by combining all available samples in each heart did sensitivity reach 79%, but this required an average of 17.2 pieces/heart, a number clinically unattainable. Furthermore, disease severity was underestimated in almost one-third of cases, and the nature of the inflammatory infiltrate was inaccurately represented in an equivalent proportion. Clearly, continuing revision of ideas about the diagnosis of myocarditis must include careful attention to the sufficient number of biopsies to be obtained, as well as further approaches to examine the tissue to make this number clinically applicable.

PORCINE MODEL OF MYOCARDITIS LEADING TO DILATED CARDIOMYOPATHY. Mara T. Slawsky, M.D., Ph.D., Judith K. Gwathmey, V.M.D., Ph.D., Patricia C. Come, M.D., F.A.C.C., Walter H. Abelmann, M.D., F.A.C.C., Beth Israel Hospital, Harvard Medical School, Boston, Mass.

We have developed a large animal model of myocarditis/cardiomyopathy using outbred pigs infected with encephalomyocarditis virus. Twenty-five pigs were studied over a thirty day period following infection. Cumulative mortality post infection was 39%; the majority of deaths occurred within one week post infection. Histopathological findings in seven animals which died during this period and in six of seven animals sacrificed between two and three weeks after infection, revealed active myocarditis as defined by the Dallas criteria. In the four animals sacrificed at the end of thirty days, histopathological examination revealed no active myocarditis and little to no fibrosis. M-mode echocardiography was used to measure end-diastolic and end-systolic left ventricular diameters (EDD and ESD). Fractional shortening (FS) was then calculated as a measure of systolic function. Each animal served as its own control. Left ventricular dilatation occurred in infected pigs: EDDi/EDDc=1.2±0.04 (mean ± SE; n=24; $p<0.001$); i=infected and c=control. There was no significant difference between EDD in animals which died following infection and those which survived (1.1 ± 0.09 vs 1.3 ± 0.06; $p=0.12$). However, animals which succumbed showed a significant decrease in FS (FSi/FSc=0.4 ± 0.06) compared with animals which survived (FSi/FSc=0.9 ± 0.08); $p<0.01$. In conclusion, these data suggest that animals surviving acute myocarditis showed recovery of resting ventricular function but persistent left ventricular dilatation. These changes occurred despite the absence of significant fibrosis on histopathological examination.

EFFECT OF CARDIAC TRANSPLANTATION ON ANTI-BETA-RECEPTOR AUTOANTIBODIES
Constantinos Limas, M.D., Catherine Limas, M.D., Irvin Goldenberg, M.D., University of Minnesota and Minneapolis Heart Institute, Minneapolis, Minnesota

Patients with idiopathic dilated cardiomyopathy (IDC) have serum autoantibodies directed against cardiac $\beta_1$-receptors, as determined by ligand binding inhibition, immunoprecipitation, and immunoblotting assays. Fourteen of forty-two IDC patients (30%) evaluated for heart transplantation were positive for anti-β-receptor autoantibodies (more than 20% inhibition of [$^3$H]dihydroalprenolol binding to cardiac membranes at 100-fold serum dilution). Following cardiac transplantation, eleven of the fourteen patients showed a decline in the degree of ligand binding inhibition (from 40±5% before, to 12±3% after, transplantation). Immunoblotting of β-receptors on cardiac membranes showed a quantitative decline in the titer of autoantibodies following transplantation. In addition, two of the three patients in whom autoantibodies against β-receptor persisted following transplantation had rejection episodes compared to two of the eleven patients with declining titer. These results suggest that removal of the immunogen (diseased heart) and/or immunosuppressive therapy effectively lowers the incidence and titers of antiβ-receptor antibodies with possibly positive functional consequences on the recipient heart.

SHARING OF ANTIGENIC DETERMINANTS BETWEEN COXSACKIE B3 VIRUS AND AUTOANTIGENS IN VIRAL MYOCARDITIS AND DILATIVE CARDIOMYOPATHY.
Peter L. Schwimmbeck M.D., Heinz-Peter Schultheiss M.D., Bodo E. Strauer M.D., Michael B.A. Oldstone M.D., Dept. of Internal Medicine/Cardiology, University of Duesseldorf, Duesseldorf, F.R.G.

Both myocarditis (MC) and dilative cardiomyopathy (DCM) are characterized by an autoimmune response against specific autoantigens. We studied if these autoantibodies may be due to molecular mimicry, i.e. the sharing of antigenic determinants between a host and an invading microbe, such as a virus. As coxsackie B3 virus (CB3) has been shown to induce myocarditis in mice and man, we searched for homologous determinants shared between the recently determined sequence of CB3 and proteins identified as the main autoantigens in viral heart disease. Utilizing the Dayhoff Data Bank, computer search and computer predictions of the secondary structure of proteins, the best homologies are as follows:

- -CB3, res. 1895-1905, and myosin, res. 400-410
- -CB3, res. 1220-1227, and adenine nucleotide carrier, res. 28-35
- -CB3, res. 1311-1320, and connexon, res. 168-177

Subsequently, we synthesized peptides of up to 25 amino acids covering the homologous regions by the "tea-bag" method and raised antibodies against them. By immunochemical analysis we could demonstrate that homology also translated into immunological cross-reactivity. Conclusion: These results show that the sharing of cross-reacting antigenic determinants between CB3 and known autoantigens in MC and DCM occurs and may play a role in the pathogenesis of MC and DCM.

## CYCLOSPORINE IN AVIREMIC COXSACKIEVIRUS B3 MYOCARDITIS IN MICE.

Chiharu Kishimoto, M.D., Walter H. Abelmann, M.D., F.A.C.C. Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts.

To investigate the effects of cyclosporine (CS) upon postviremic myocarditis, we analysed myocardial lymphocyte subsets (LS) in BALB/c mice inoculated with coxsackievirus B3 (CB3). CS, 25 mg/kg, was administered sc daily, starting on day 10 (Exp I) or 30 (Exp II) for 3 weeks. LSs (Thy 1.2=pan T, Lyt 1=effector T, Lyt 2=suppressor T, L3T4=activated T, M7/20=interleukin-2 receptor (IL-2R)) were examined by an immunoperoxidase method. Mortality appeared high in Exp I (15/25 vs 24/25, $p<0.05$) and Exp II (32/34 vs 34/34, NS). There was no decrease in cardiac pathology (infiltration, necrosis and calcification) compared to infected controls (C) in either Exp.

| | Days 15-18 | | Day 31 | |
|---|---|---|---|---|
| LS(%,±SD) | C (n=5) | CS (n=5) | C (n=4) | CS (n=4) |
| Thy1.2$^+$ | 21.5±7.3 | 18.8±12.0 | 8.9±4.3 | 9.0±0.4 |
| Lyt 1$^+$ | 17.1±8.9 | 13.0±5.5 | 8.1±2.3 | 7.4±2.7 |
| Lyt 2$^+$ | 5.5±1.1 | 5.3±1.7 | 2.7±0.1 | 2.0±0.6 |
| L3T4$^+$ | 3.3±1.0 | 3.8±1.0 | 1.7±1.6 | 1.3±1.0 |
| IL-2R$^+$ | 1.4±2.1 | 0.8±0.9 | 0.2±0.2 | 0.2±0.4 |

Histologically, cellular depletion was evident in the thymus, not in the spleen, of CS groups. The failure of CS to ameliorate aviremic myocarditis may be due to the paucity of CS-sensitive cells (Lyt 2$^+$, L3T4$^+$, IL-2R$^+$) in the diseased myocardium. Significant depression of thymus may account for the high mortality in CS groups. In conclusion, the use of CS in clinical CB3 myocarditis may be ineffective if not deleterious.

## MYOCARDIAL IGA DEPOSITION: A POSSIBLE MARKER FOR ALCOHOL RELATED MYOCARDIAL DISEASE.

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The contribution of chronic alcohol consumption to left ventricular dysfunction in patients with idiopathic dilated cardiomyopathy (IDCM) and coronary artery disease (CAD) has been difficult to assess. One difficulty is the lack of a pathological marker for alcohol related myocardial disease. Recent immunological studies suggest that in alcohol related liver disease IgA may be such a marker.

We examined right ventricular endomyocardial biopsies from 50 patients; age 27-65 years. The indication for biopsy was IDCM (20), ventricular dysfunction disproportionate to the extent of CAD (24) and ventricular arrhythmias in (6). In addition to the routine histology, sections were stained using an indirect immunoperoxidase technique for the presence of immunoglobulins (IgG, IgM and IgA). These were then examined by an observer with no prior knowledge of the patients clinical details. 14 patients were heavy drinkers (>30u/week), 8 were moderate (15-30u/week), 9 were light (1-15u/week) and 19 drank occasionally (<1u/week). 12 patients had evidence of IgA deposition on myocardial cell membranes. The diagnoses in these patients were IDCM in 5 and coronary heart disease in 7. Of these, 9 admitted to heavy and 3 to moderate alcohol consumption. IgA deposition on myocardial cell membranes is a highly specific and moderately sensitive marker of alcohol related myocardial dysfunction and may also have a role in the pathogenesis of this condition.