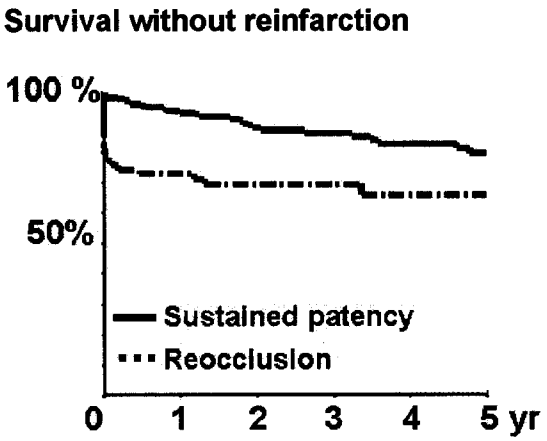
most probably due to a high prevalence (66%) of statin therapy.
Conclusions: In patients with acute coronary event HIV infection is associated with a higher incidence of recurrent coronary events and TVR independently of the metabolic effects of antiretroviral therapy.

1124-46 **Impact of Reocclusion on Six-Year Survival and Reinfarction Following Fibrinolytic Therapy: Long-Term Follow-Up of the Apricot-1 Trial**

Peter C. Kievit, Marc A. Brouwer, Albert Meijer, Gerrit Veen, Freek W. A. Verheugt, *University Medical Center Nijmegen, Nijmegen, The Netherlands, Free University Medical Center, Amsterdam, The Netherlands.*

Background: Whereas reocclusion within a week after demonstrated patency has been associated with a twofold increased risk of mortality, the prognostic impact of reocclusion after the acute phase remains to be determined.
Methods: In the APRICOT-1 trial 248 patients of 70 years or younger had TIMI 3 flow at coronary angiography, within 48 hours after fibrinolytic therapy. Follow-up angiography and ventriculography was scheduled at three months. Death and reinfarction were recorded using medical charts, telephone contact with the general physician and information from municipal registries.
Results: Reocclusion was observed in 71 patients (29%). Left ventricular ejection fraction increased from 51±10% to 55±11% with sustained patency ($p < 0.01$); in patients with reocclusion the change in ejection fraction(±sem) was -1.7±1.6% (p=ns). Mean clinical follow-up was 4.3±1.2 years. At five years, survival was 90% for patients with reocclusion compared to 92% for patients with a patent artery at follow-up angiography (p=ns). Death and reinfarction rates were 34% and 20%, respectively (fig.1, $p < 0.01$).
Conclusion: After demonstrated coronary patency following fibrinolysis for acute ST-elevation myocardial infarction, patients who survived the first 48 hours had an excellent 5-year prognosis. Although reocclusion was associated with a higher risk for reinfarction and impaired left ventricular contractile recovery, the potential adverse impact on long-term survival could not be demonstrated.



1124-47 **Resting Heart Rate as a Predictive Risk Factor for Sudden Death in the Population**

Xavier X. Jouven, Mahmoud Zureik, Laurent Sabbah, Dominique Courbon, Michel Desnos, Claude Guerot, Pierre Ducimetiere, *Hôpital Européen Georges Pompidou, Paris, France, INSERM U 258, Villejuif, France.*

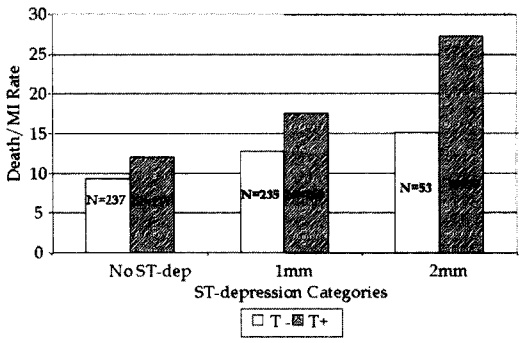
Objective: A relative hyperadrenergic tone related to abnormalities of the autonomic nervous system is suspected in the mechanisms of sudden death. Therefore, we assessed the role of an elevated resting heart rate in the occurrence of sudden death in a long-term cohort study (the Paris Prospective Study I).
Methods : 7746 subjects underwent ECG and physical examination conducted by a physician in standardized conditions, provided blood samples for laboratory tests, and answered questionnaires administered by trained interviewers. The vital status was obtained from specific inquiries until retirement and then by death certificates. Men with known ischemic heart disease were further excluded from analysis which was conducted on the 7079 remaining subjects.
Results : After an average follow-up period of 23 years of the population, there were 2083 deaths, among which 603 cardiovascular deaths including 118 sudden deaths and 192 fatal myocardial infarctions. The crude risk of sudden death increased proportionally with the level of resting heart rate and the relative risk associated with the higher quintile of heart rate was 3.8 fold that associated with the lowest quintile, whereas such a relative risk was approximatively 2 for fatal myocardial infarction, cardiovascular and total mortality (all $p<0.01$). When age, body mass index, systolic blood pressure, tobacco consumption, parental history of myocardial infarction and parental history of sudden death, cholesterol level, diabetic status, and sport activity were simultaneously entered into the survival model, resting heart rate remained an independent risk factor for sudden death (p=0.03) but not for fatal myocardial infarction.
Conclusion : An elevated heart rate at rest remained an independent risk factor for sudden death in middle-aged men.

1124-48 **Does Troponin Positivity Add Prognostic Value to Quantitative ST Segment Depression in Predicting Death and Myocardial Infarction in Non-ST Elevation Acute Coronary Syndrome Patients?**

Padma Kaul, Yuling Fu, L. Kristin Newby, Kenneth W. Mahaffey, Robert A. Harrington, E. Magnus Ohman, Frans Van de Werf, Paul W. Armstrong, *Duke Clinical Research Institute, Durham, North Carolina, University of Alberta, Edmonton, Alberta, Canada.*

We have recently documented the ominous prognostic role of ST-depression (ST-dep) >=2mm among patients (pts) with non-ST elevation acute coronary syndromes (ACS). Since Troponin (TnT) is also associated with worse outcomes, we evaluated whether there was incremental value in combining ECG and TnT data for improved risk stratification. Core laboratory quantitative ST-segment analysis was performed in the 1160 pts prospectively assigned to the TnT sub-study of PARAGON-B which enrolled 5225 pts with non-ST elevation ACS.
Six-month death and/or re-MI rates by magnitude of ST-dep and positive or negative TnT [levels >=0.1 ng/mL = +TnT] are shown in the Figure. Individually, both increasing ST-dep and +TnT were associated with significantly higher six-month risk. Compared to all other pts, the odds of death/re-MI among pts with both ST-dep >=2mm and +TnT status were 3.4 [95% CI: 1.8, 6.6]. In a multivariable logistic regression model accounting for baseline characteristics known to predict death/re-MI in this pt population, both ST-dep and +TnT were significant predictors of six-month death/re-MI.
Quantitative ST-dep and +TnT status are complementary in assessing risk among ACS pts. Both should be employed to determine prognosis and assist in medical decision making.

Death/MI 6 Months by ST-segment category and Troponin Status



ORAL CONTRIBUTIONS

836 Basic Mechanisms of Myocardial Ischemia

Monday, March 18, 2002, 4:00 p.m.-5:30 p.m.
Georgia World Congress Center, Room 255W

4:00 p.m.

836-1 **Repetitive Brief Myocardial Ischemia and Reperfusion Induces a Cardiomyopathy With Features of Myocardial Hibernation in Mice: A Possible Role for Chemokines**

Oliver Dewald, Nikolaos G. Frangogiannis, Martin Zoerlein, Pascal Knuefermann, Thuy T. Pham, George Taffet, Lloyd H. Michael, Mark L. Entman, *Section for Cardiovascular Sciences, Department of Medicine, Baylor College of Medicine, Houston, Texas, Winters Center for Heart Failure Research, Baylor College of Medicine, Houston, Texas.*

Background: Repetitive brief myocardial ischemia, in the absence of myocardial infarction and permanent necrosis has been implicated in the pathogenesis of the ventricular dysfunction associated with myocardial hibernation. We have previously demonstrated in a murine model that a single brief episode of myocardial ischemia followed by reperfusion (I/R) is associated with free radical generation and induction of chemokines. In this study we examine the effects of repetitive I/R in the murine heart.
Methods: C57BL6 mice underwent daily 15 minute left anterior descending coronary occlusions followed by reperfusion. After 7, 14, 21 and 28 days, echocardiography studies were performed, and hearts of I/R and sham operated animals were processed for RNA and histological studies.
Results: Echocardiographic studies showed a decreased fractional shortening in the I/R animals (sham 46.3±1.5 %, 7 days I/R 35.2±2.5 %, 28 days I/R 40.83±0.8 %, both $P<0.05$; n=7). Histological studies showed no necrosis area in the ischemic region. Quantitative assessment of the collagen stained area revealed a marked interstitial deposition of collagen after 7 days of repetitive I/R in anterior left ventricular wall (sham vs. I/R: 4.6±2.0 % vs. 21.5±6.5 %, $P<0.05$; n=8). Collagen expression remained high after 28 days of repetitive I/R (sham vs. I/R: 6.2±2.8 % vs. 22.9±6.0 %, $P<0.05$; n=8). One month after discontinuation of the I/R protocol (7 days of repetitive I/R) mice showed a reversal of fibrotic process and ($P<0.05$; n=8). α-smooth muscle actin increased in myofibroblasts at 7 days I/R, but was normal by 28 days I/R. Similarly, RNA expression of chemokines MIP-1α, MIP-1β, MIP-2 and MCP-1 peaked at 7 days I/R, and was reduced at 28 days.
Conclusions: Repetitive brief I/R in the murine heart induces fibrotic remodeling and systolic dysfunction of the left ventricle, in the absence of myocardial infarction and

necrosis leading to a cardiomyopathy with feature of hibernation. Early chemokine induction and interstitial fibrosis due to frequent sublethal ischemic episodes may have a role in mediating left ventricular dysfunction in ischemic cardiomyopathy.

4:15 p.m.

836-2 Serum Levels of Unbound Free Fatty Acids Reveal High Sensitivity for Early Detection of Acute Myocardial Infarction in Patient Samples From the TIMI II Trial

Alan M. Kleinfeld, Kevin J. Kleinfeld, Jesse E. Adams, III, *Torrey Pines Institute for Molecular Studies, San Diego, California, Jewish Hospital, Louisville, Kentucky.*

Background: Levels of unbound free fatty acids (FFAu) have been found to increase with myocardial cellular ischemia in patients undergoing balloon angioplasty (Kleinfeld et al, Am J Cardiol 1996;78:1350). To assess whether FFAu are an effective marker of ischemia in acute myocardial infarction (AMI), levels of FFAu were determined in serum samples from patients enrolled in the TIMI II trial (TIMI Study Group, N Engl J Med 1989;320:618). Methods: Patients in this trial were treated with tissue plasminogen activator (t-PA) for AMI. Blood samples were drawn upon presentation, and then 50 minutes, 5 h and 8 h after t-PA. These samples have been maintained at -70°C by the National Heart Lung Blood Institute. FFAu measurements and partial data analysis has been completed on 458 patients (75 F, 383 M). Measurements were done at 22°C using the ADIFAB2 (Richieri et al, J Biol Chem 1996;271:11291) fluorescent probe of FFAu (healthy controls = 2.6 ± 0.6 nM). Results: FFAu values for the TIMI patients ranged from 2 to 5000 nM. Average values and standard deviations for each of the 4 blood draws, from time of admission to 8 h were: 13 ± 17, 22 ± 25, 11 ± 13, and 10 ± 11 (nM). These results indicate, relative to the control population, an approximately 4 fold increase upon admission, a further 2 fold increase following t-PA with a gradual decrease within 5 h of t-PA. Using a 5 nM cutoff, the predicted sensitivity for detection of AMI was 91% using samples at time of admission only, and 98% using time of admission and the 50 minute sample. Only 19 % of patients had elevated levels of creatine kinase on admission. Specificity was estimated as 93% by comparison with a distribution that includes healthy individuals plus patients with non cardiovascular diseases. FFAu values for samples drawn at presentation were found to be highly ($p<0.025$) correlated with mortality; an increase of 4 fold in mortality rate is predicted from lowest to highest FFAu levels. Conclusions: These data indicate that levels of FFAu are: 1) a sensitive indicator of ischemia in AMI, 2) elevated well before markers of cardiac necrosis, 3) an indictor of reperfusion therapy, and 4) a predictor of mortality in these patients.

4:30 p.m.

836-3 A Cardioprotective Agent, JTV519, Inhibits Apoptotic Cell Death of Postischemic Reperfused Myocardium Through _PKC-Mediated ERK Activation

Hiroyuki Takenaka, Yasuki Kihara, Koichi Inagaki, Takeshi Yoneda, *Department of Cardiovascular Medicine, Kyoto University, Kyoto, Japan.*

Objective: JTV519 (JTV), a 1,4-benzothiazepine derivative, confers cardioprotective effects on the post-ischemic, reperfused myocardium through a specific activation of δ-isoform of protein kinase C (PKC) (Inagaki et al., *Circulation*, 2000). In this study, we further tested the hypothesis whether the downstream of δ-PKC activation may link to its inhibitory effects on the apoptotic cell death. **Methods:** Hearts were isolated from male SD rats (n=7, for each group), and were coronary-perfused in a Langendorff setup at a constant coronary flow under electrical pacing at 3.33Hz. The preparation was treated with 1μM JTV or vehicle for 5 min, and then subjected to a 30-min global ischemia and the subsequent 60-min full reperfusion protocol. On the other hand, isolated ventricular myocytes from neonatal rats (n=6, for each group) were treated with JTV or vehicle before an exposure to 50μM H_2O_2 for 80 min. Both the heart and cell preparations were subjected to TUNEL staining, DNA fragmentation assay, and immunoblotting for phosphorylated forms of JNK, ERK1/2, and p38-MAPK. **Results:** In the reperfused heart preparations, JTV ameliorated the recovery of left ventricular developed pressure by 80% ($p<0.01$), which was associated with a reduction of TUNEL-positive ventricular myocytes by 10% ($p<0.05$). In isolated cells, JTV reduced the H_2O_2-induced TUNEL staining from 43% to 30% ($p<0.05$). JTV also showed substantial decreases of DNA fragmentation in both preparations. These anti-apoptotic effects of JTV were inhibited either by GF109203X (GF, a PKC inhibitor) or by PD98059 (PD, a MEK inhibitor). In the cell preparations, JTV further increased H2O2-induced phosphorylation of ERKs by 55% ($p<0.01$). This ERK activation was decreased by pretreating the system with 50μM PD, 5μM GF, and 1μM rottlerin(a δ-PKC specific inhibitor) to the levels of 18.0%, 55.2%, and 31.5%, respectively ($p<0.05$). JTV did not show significant effects on JNK and p38-MAPK phosphorylation. **Conclusion:** JTV519 protects the post-ischemic reperfused myocytes from the apoptotic cell death through a specific activation of the δ-PKC/ERK cascade.

4:45 p.m.

836-4 Hearts of Stat 6 Knockout Mice Are Resistant to Ischemia Reperfusion Injury

Genbu Yamaura, Shoji Fukuda, Kazuhisa Kishima, Jianhua Cui, Richard M. Engelman, Dipak K. Das, *University of Connecticut Medical Center, Farmington, Connecticut.*

Background: STATs (Signal transducers and Activators of Transcription) comprise a family of transcription factors that reside in the cytoplasm of resting cells. Recently, ischemia/reperfusion was found to rapidly activate JAK (a group of tyrosine kinases)/STAT signaling pathway which play a crucial role in myocardial ischemic injury. Specifically, JAK2 and STAT 6 were activated even after 15 min ischemia and remained activated during subsequent reperfusion.

Methods: To confirm the role of STAT 6 in ischemic injury, we examined if STAT 6 knockout mice devoid of any copies of STAT 6 gene was resistant to ischemic injury. STAT 6 knockout mice (n=10) and control wild-type mice (n=10) were anesthetized with pentobarbital, hearts excized, and perfused via working mode with KHB buffer. The working mouse hearts were made globally ischemic for 25 min followed by 2 h of reperfusion. Left ventricular function was monitored at the baseline and during post-ventricular reperfusion and infarct size was determined at the end of the reperfusion.

Results: Heart rates of the STAT 6 knockout (KO) mice were lower compared to wild-type (WT) mice at baseline and at 15 min of reperfusion (15R). Knockout mouse hearts displayed significantly better ($p<0.05$) post-ischemic ventricular recovery as evidence by higher left ventricular pressure (LVP) (mm Hg) [BL: 86.5±0.7 (WT) vs. 97.3±1.7 (KO); 15R: 75.2±1.4 (WT) vs. 82.2±2 (KO); 30R: 71.8±1.4 (WT) vs. 77.8±2.1 (KO)]; higher dp/dtmax (mm Hg/sec) [BL: 4518±76 (WT) vs. 5085±120; 15R:3807±130 (WT) vs. 4288±134 (KO); 30R: 3529±131 (WT) vs. 4026±133 (KO). Infarct size determined by TTC staining was lower in STAT 6 KO mouse hearts (41.1±1.6%) compared to those for the WT mice (48.6±2.3%).

Conclusion: The results of this study demonstrate that hearts of STAT 6 knockout mice are resistant to ischemia/reperfusion injury suggesting a role of STAT 6 gene in the mediation of cardiac injury.

5:00 p.m.

836-5 Glucagon-Like Peptide-1 (GLP-1) Limits Myocardial Stunning Following Acute Coronary Occlusion and Reperfusion in Conscious Canines

Lazaros A. Nikolaidis, Teresa Hentosz, Aaron Doverspike, Rhonda Huerbin, Lee Zourelias, Carol Stolarski, Dariush Elahi, Richard P. Shannon, *Allegheny General Hospital, Pittsburgh, Pennsylvania, Massachusetts General Hospital, Boston, Massachusetts.*

Background: Myocardial ischemia is associated with increased glucose utilization. Glucose Insulin K+ infusion has been shown to improve outcomes. We hypothesized that the insulinotropic peptide GLP-1 facilitates recovery of post-ischemic contractile dysfunction (stunning).

Methods: We studied 13 conscious dogs, instrumented with LV pressure gauges, aortic and coronary flow (CBF) probes, piezoelectric crystals to measure regional systolic wall thickening (WTh) and a hydraulic coronary artery occluder. All dogs underwent a 10 min coronary occlusion (CAO) followed by reperfusion (CAR). Five dogs received a 24-hr infusion of GLP-1 (1.5 $pmol \cdot kg^{-1} \cdot min^{-1}$) initiated 1 min prior to CAR; 8 dogs received placebo. We obtained serial recordings for the first 3 hrs and at 24-hr post-CAR.

Results: Hemodynamic responses and global LV function during CAO and CAR were similar in the two groups. Baseline regional WTh (2.6±0.3mm) and initial hyperemic responses were similar. Despite comparable changes in CBF, GLP-1 treated dogs demonstrated significantly (*$p<0.01$) less post-ischemic contractile dysfunction. The salutary effects of GLP-1 were sustained for 24-hrs.

	Regional CBF (ml)		Regional WTh (% baseline)	
	Control	GLP-1	Control	GLP-1
Baseline	21±1	20±2	100%	100%
CAO	3±2	5±2	12±8%	16±11%
CAR-1min	113±9	93±11	76±6%	84±8%
5 min	49±8	41±9	60±4%	81±4%*
10 min	22±2	18±2	57±5%	84±2%*
15 min	18±1	17±2	57±5%	87±2%*
30 min	19±2	19±2	60±6%	86±3%*
1 hr	17±1	18±3	69±5%	97±3%*
2 hr	17±2	18±2	70±5%	97±3%*
3 hr	17±2	17±3	76±6%	98±2%*
24 hr	22±2	22±1	78±4%	98±4%*

Conclusions: When administered at the time of reperfusion, GLP-1 limits myocardial stunning following brief coronary occlusion. The salutary outcome is sustained for at least 24 hrs. GLP-1 may be a promising adjuvant therapy in post-ischemic myocardial dysfunction.

5:15 p.m.

836-6 Cardiac Serum Marker Release After Percutaneous Transluminal Septal Myocardial Ablation: A Human Model

Patricia A. Gum, Steven R. Steinhubl, Harry M. Lever, F. Van Lente, E. Murat Tuzcu, A. Michael Lincoff, *The Cleveland Clinic Foundation, Cleveland, Ohio.*

Background. Multiple cardiac serum markers are available for determining myocardial cell death, but the comparative kinetics of these markers in humans have not yet been fully described due to the inability to precisely correlate symptom onset with vessel closure. Percutaneous transluminal septal myocardial ablation (PTMSA) for hypertrophic obstructive cardiomyopathy permits a unique opportunity to identify the time of vessel closure in a series of patients experiencing a MI and compare the course of cardiac serum marker elevation.

Methods. We obtained blood samples every 2 hrs for 48 hrs from 11 pts after PTMSA and measured the serum markers: creatine kinase MB (CK MB)(normal 0.0-8.8 ng/ml), myoglobin (30-90 mg/L), troponin-I (0.0-2.0 ng/ml), and troponin-T (0.0-0.1 ng/ml).

Results. Mean marker values are displayed in the figure below. In all patients studied, all markers were elevated above normal by 2 hrs after vessel closure. Mean peak measure-