(PTCA). Reducing platelet accumulation at PTCA sites may attenuate NP and restenosis. Single antiplatelet agents are not effective, due to multiple platelet activation pathways. Previous work suggested that combined antagonism of 2 mediators of platelet aggregation — thromboxane A_2 (by *ridogrel*) and serotonin (by *ketanserin*), could reduce platelet-thrombus formation and lessen NP. We therefore tested the hypothesis that combined treatment with 3 agents (*ridogrel, ketanserin,* and an ADP antagonist — *clopidogrel*) would be more effective in reducing NP after PTCA. We studied 18 dogs with coronary flow probes and plastic constrictors chronically implanted on LAD arteries. All dogs underwent LAD PTCA and were sacrificed after 8 weeks of monitoring. Eight dogs were controls, while 10 dogs were treated with combined antiplatelet therapy for 3 weeks before and 3 weeks after PTCA. Compared to controls, ex vivo platelet aggregation was virtually abolished in treated dogs, and bleeding times during treatment were greater (>720 vs 119 ± 4 sec, $p < 0.001$). Cyclic flow variations (CFVs) after PTCA, from repetitive accumulation and dislodgement of platelet aggregates at PTCA sites, occurred in 7/8 controls but in only 1/10 treated dogs ($p < 0.01$). Platelet counts and hematocrit values were not different between treated and control groups. Quantitative coronary artery histology revealed that neointimal area was threefold less in the treated group (0.18 ± 0.07 cm^2 vs 0.52 ± 0.12, $p = 0.032$), as was the percent lumen stenosis (13 ± 4% vs 40 ± 13%, $p = 0.06$).

Conclusion: Combination antiplatelet therapy with these 3 antagonists inhibited several relevant measures of platelet function and reduced neointimal proliferation in a canine coronary artery angioplasty model.

2:30

751-3 Lovastatin and Probucol for the Prevention of Restenosis After Coronary Angioplasty

Patricia G. Cavero, James H. O'Keefe, Jr., Gregg W. Stone, Ben D. McCallister, Jr., Cheryl Dreiling, Robert Ligon, Ray L. Kacich. *Mid America Heart Institute, Kansas City, MO*

We hypothesized that combination lipid lowering therapy (Lovastatin) and anti-oxidant (Probucol) therapy might reduce restenosis following coronary angioplasty (PTCA). To address this question, 239 patients (pts) were enrolled in a multi-center, randomized trial whereby 2 out of 3 pts received Lovastatin 20 mg bid and Probucol 500 mg bid in combination; 1 out of 3 pts was randomized to double placebo. Pts were treated in a blinded fashion for 6 months. Total cholesterol (154 vs 211), LDL (98 vs 141) and HDL (31 vs 42) were lower in treated compared with placebo patients. Serious adverse effects from the medications were not observed.

EVENTS WITHIN 6 MONTHS

	Active (n = 163)	Placebo (n = 76)
Death	1 (1%)	1 (1%)
Myocardial Infarction	3 (2%)	1 (1%)
Repeat PTCA	51 (31%)	22 (29%)
Bypass Surgery	7 (4%)	3 (4%)

Quantitative coronary angiography was available in 147 lesions, the mean loss in luminal diameter was 27% ± 31% and 28% ± 34% in treated and placebo groups.

Conclusion: Combination Lovastatin and Probucol: 1) reduced total cholesterol (27%), LDL (29%) and HDL (27%) levels, but 2) did not prevent restenosis or clinical events during the first six months post-angioplasty.

2:45

751-4 Low Molecular Weight Heparin in the Prevention of Restenosis After Coronary Angioplasty. Results of the FACT Study

Jean-Marc Lablanche, The FACT investigators. *France, Belgium, Spain*

Restenosis after coronary angioplasty is a multifactorial process that may involve elastic recoil, thrombus incorporation, smooth muscle cell proliferation, and late vascular remodeling. Fraxiparine (nadroparin) is a low molecular weight heparin derivative that has potent antithrombotic and antiproliferative properties in animal models.

The FACT (Fraxiparine Angioplastie Coronaire Transluminale) study is a multicentre double-blind randomised trial designed to compare the effects of treatment with Fraxiparine or aspirin on the occurrence of restenosis after coronary balloon angioplasty. All patients received aspirin (250 mg, daily) before coronary angioplasty. Therapeutic doses of unfractionated heparin were used during coronary angioplasty in both groups. The active treatment group received subcutaneous injections of Fraxiparine (0.6 ml) daily for 3 days before coronary angioplasty that was continued for 3 months. The control group was treated with aspirin (250 mg) daily for 3 months.

In total, 354 patients were randomized and constitute the intention-to-treat population. Angiographic follow-up was performed in 91% of patients with successful procedures at 3 months. There were no differences between groups in baseline clinical characteristics. The acute gain (0.96 ± 0.42 mm, 1.03 ± 0.40 mm) and late loss (0.36 ± 0.51 mm, 0.36 ± 0.57 mm) were similar in the Fraxiparine and aspirin groups. Restenosis, defined as a binary variable (stenosis >50% at angiographic follow-up) occurred in 41% of the Fraxiparine treated and 38% of the aspirin treated group ($p = 0.69$). At six months major clinical event rates, death (1% vs 2%), acute myocardial infarction (4% vs 2%) and repeat revascularization (26% vs 26%) were similar in both groups.

Despite, 3 days of pretreatment and 3 months of treatment with low molecular weight heparin (Fraxiparine), no statistical differences were observed in angiographic or clinical end points.

3:00

751-5 Rapid Angiographic Progression of "Target" and "Non-target" Stenoses in Patients Awaiting Coronary Angioplasty

Juan Carlos Kaski, Lijia Chen, Michael Chester. *St. George's Hospital Medical School, London, U.K.*

Coronary angioplasty (PTCA) is effective therapy for angina pectoris but coronary events occur after successful PTCA which may be caused by both restenosis and progression of mild pre-existing, *"non-target"*, stenoses. To compare the short-term evolution of *"target"* versus *"non-target"* stenoses in patients awaiting PTCA, we prospectively studied 161 consecutive stable angina patients (124 men and 37 women). After diagnostic angiography, *"target"* stenoses for PTCA and *"non-target"* lesions were identified. Patients were put on a routine waiting list and followed up regularly until repeat coronary arteriography (mean ± SD: 7 ± 3 months), which was performed immediately preceding angioplasty (138 patients) or soon after acute coronary events (23 patients) when these occurred. Stenosis diameters were measured using computerized arteriography. Progression was defined as ≥20% diameter reduction, new total occlusion, or development of "new" stenoses ≥30%. At study entry, diameters of *target* (n = 207) and *non-target* (n = 184) lesions were 68 ± 9% and 38 ± 9%, respectively ($p < 0.001$). Disease progression occurred in 33 patients (20%), in whom 18 *target* (9%) and 15 *non-target* stenoses (8%) progressed and 7 new lesions (1 total occlusion) developed. Total occlusion developed in 15 of the 18 (83%) *target* and in 6 of the 15 (40%) *non-target* stenoses; ($p = 0.03$). During follow up, 3 patients (2%) had a myocardial infarction and 20 (12%) developed unstable angina. These events were associated with progression of *target* stenoses in 10 patients, of *non-target* stenoses in 7 patients, and with new lesions in one patient. In 5 patients events were not associated with stenosis progression.

Thus a similar proportion of *target* and *non-target* lesions progressed rapidly. *Target* stenoses, however, were more likely to progress to total occlusion than *non-target* lesions. Progression of *non-target* stenoses may contribute to recurrence of angina and new coronary events after successful angioplasty and their role should be considered when developing strategies aimed at improving survival after angioplasty.

3:15

751-6 Multiple Repeat Coronary Angioplasty for Final Lesion Patency

Hidemasa Kitazume, Ichiro Kubo, Yoshio Ageishi, Toru Iwama, Akio Suzuki. *Bokuto Hospital, Tokyo, Japan*

To demonstrate that multiple repeat coronary angioplasty can be solely utilized to achieve final lesion patency after restenosis, such a protocol was prospectively applied for restenosis since 1983. Bypass surgery was only considered for 1) new left main trunk lesions, 2) symptomatic restenosis where angioplasty was either unsuccessful or unsuitable, and 3) patient preference. Between 1983 and 1992, 1455 lesions (acute myocardial infarction or total occlusion excluded) were successfully dilated for the first time. Although only 941 (68%) of the 1385 lesions studied showed satisfactory patency (≤70% stenosis) after the first procedure, 93% (1248/1345 studied) showed satisfactory patency after repeating angioplasty up to 3 times and 94% (1268/1354 studied) after repetition up to 6 times. Only 23 lesions (1.6%) required 4 or more procedures and 20 of them showed final patency. Disease aggravation (either impossible or failed repeat angioplasty, acute infarction, or sudden death) occurred in 43 lesions (3.2%). Bypass grafts were done for 11 lesions of 7 patients, mostly due to disease progression at the left main trunk.

Dilatation (stenosis)	Patent (0–50%)	Mild (55–70%)	Re-do (75%-)	Grafts (75%-)	Medical (75%-)	Aggravated#	Withdrawal	Cumulative 0–70%	Cumulative No.*
1st	874	67	384	9	16	32	73	941	1382
2nd	221	22	97	0	6	7	31	1184	1351
3rd	53	11	23	0	1	3	6	1248	1345
4th	11	1	8	1	0	1	0	1261	1345
5th	3	3	2	0	0	0	0	1267	1345
6th	1	0	0	1	0	0	0	1268	1345

*:1763- Σ Withdrawal, #:sudden death, acute infarction or irreversible occlusion

Conclusion: These findings indicate that 1) repeat angioplasty can be the main treatment strategy for restenosis, 2) multiple repeat angioplasties (up to 6 times) can be effective and rarely aggravate coronary anatomy and 3) disease aggravation must be prevented to improve the final patency rate of repeat angioplasty.

752 Clinical Applications of Myocardial Contrast Echocardiography

Tuesday, March 21, 1995, 2:00 p.m.–3:30 p.m.
Ernest N. Morial Convention Center, Room 90

2:00

752-1 Microcirculatory Flow Dynamics During Peripheral Intravenous Injection of Echogen™: Microscopic Visualization of Mesenteric Microcirculatory Flow with Simultaneous Transthoracic Echo Imaging in Cats

Shuping Ge, George G. Giraud, Takahiro Shiota, George A. Pantely, Jinping Xu, Zheng Gong, Masahiro Ishii, Xiaodong Zhou, Arthur Hall, David J. Sahn. *Oregon Hlth Sci Univ, Portland, OR*

Echogen™, a phase shift, fluorocarbon gas echo contrast agent, has been shown capable of producing left ventricular and robust myocardial opacification, persisting up to 35 to 40 mm after peripheral venous injection. We investigated the microcirculatory flow dynamics of this agent in the cat mesenteric vascular bed using microscopic visualization of capillary flows. Four cats (weight 2 to 5.2 kg, mean = 3.2 kg) were anesthetized and ventilated. Systemic arterial blood pressure was monitored by cannulation of the carotid artery. Microscopic examination (x 400) with an instrument calibrated for scale was performed by placing a loop of small intestine on a warm water bath stage and transilluminating the mesentery with a xenon light source while videotape recording the images for off-line analysis. Transthoracic echocardiography was performed simultaneously using a TOSHIBA 140A system with a 7 MHz transducer. Doses of 0.4, 0.6, 0.8 ml/kg (a total of 15 injections) of Echogen were administered intravenously. For all the injections, visually apparent left ventricular and intense myocardial opacification was achieved lasting up to 20 minutes. A transient drop in arterial blood pressure (25 ± 13.2 mmHg) was observed with the high dose (0.8 ml/kg), which returned to baseline within 5 mins. Capillary flow velocities of the red blood cells before and after Echogen injection were 4.3 ± 1.7 mm/sec dropping to 2.3 ± 0.9 mm/sec, the drop occurred 5 to 20 seconds following injections and recovery was within 40–70 seconds. Transient slowing and periodicity of flow was noted in the venule side of the capillaries, but arteriolar capillary flow changed little during brisk transit of the observed bubbles. There was no significant difference in flow velocity changes associated with different doses ($p > 0.05$). Also, margination and endothelial adhesion of bubbles observed in larger arteriolar feeding vessels without slowing of central RBC flow suggests a mechanism for the long persistence of echo contrast bubbles in the tissue without vascular blockage or evidence of myocardial tissue damage.

2:15

752-2 Intra-coronary Contrast Echocardiography Predicts Myocardial Viability Prior to PTCA

Martyn Thomas, Ray Wainwright, Stephen Holmberg, Richard Wray, David Jewitt, Mark Monaghan. *King's College Hospital, London, UK*

A rapid method for predicting myocardial viability prior to revascularisation remains elusive. Intra-coronary contrast echocardiography (ICE) evaluates myocardial perfusion and may have a role in predicting myocardial viability by demonstrating flow at a microvascular level. ICE was performed before PTCA in 14 patients who had a wall motion abnormality associated with the index artery (LAD = 11 RCA = 3). There were 10 men and 4 women with a mean age of 63 years (range 54–74 years). Echo derived wall motion score and global ejection fraction were calculated before PTCA and again at 1 month. Linear ultrasound contrast echo data was digitally stored on optical disc and quantified using a specially developed software package. Measured parameters were peak contrast effect (P), area under the contrast echo curve (A), time to peak contrast effect, contrast half-time and mean transit time. Contrast effect in the myocardial bed of the index artery (i) was also compared with that in a reference bed supplied by a normal artery (r). Nine patients ("viable group") had an improvement in echo score at 1 month while 5 patients ("non-viable" group) had no improvement. The "viable" patients had an improvement in ejection fraction (52.1% to 55.5%, $p < 0.02$) as well as wall motion index score (1.4 to 1.1, $p < 0.04$) while the "non-viable" patients had no significant improvement in either parameter (49.0% to 42.8% and 1.5 to 1.6). Significant contrast data was:

	P (i)	P(i)/P(r)	A (i)	A(i)/A(r)
"Viable"	1.84	0.54	66.1	0.51
"Non-viable"	0.64	0.22	20.0	0.22
p value	$p < 0.04$	$p < 0.01$	$p < 0.02$	$p < 0.05$

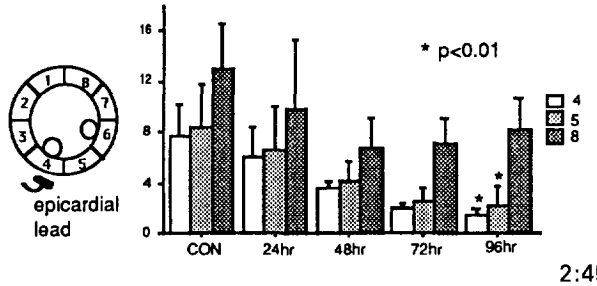
P and A were significantly greater in the index myocardial bed in the "viable" group compared to the "non-viable" group. Despite a patent epicardial index coronary artery, 4/5 patients in the "non-viable" group demonstrated minimal contrast effect in the index myocardial segment. These initial results suggest that ICE prior to PTCA may be rapidly used to predict improvement in both regional and global left ventricular function. The contrast data is additive to that obtained by angiography and identification of a contrast "watershed" value should enable a valuable echo predictor of myocardial viability.

2:30

752-3 Evaluation of Regional Myocardial Perfusion in Early Pacing-induced Left Ventricular Dysfunction Using Myocardial Contrast Echocardiography

Shiro Nozaki, Anthony N. DeMaria, Valmik Bhargava, Bruno Cotter, H. Kirk Hammond. *UCSD and VAMC-San Diego, CA*

Sustained rapid left ventricular (LV) pacing has been used to induce congestive heart failure, but whether regional myocardial perfusion contributes to the development of myocardial dysfunction is unknown. Therefore, we examined 4 pigs before and sequentially during sustained rapid LV pacing (225 bpm) from the at posterolateral epicardium. We performed myocardial contrast echocardiography (MCE) with left atrial injection of an investigational galactose contrast agent prior to pacing and daily for 4 days after onset of pacing. Pacemakers were inactivated for 60 min prior to data acquisition. The ratio of peak intensity after injection and baseline intensity of region of interest (peak intensity ratio) was measured at 8 segments (Fig) in the short axis view at the tip of papillary muscle using video intensitometry. Percent wall thickening (%WTh) in the interventricular septum (IVS) and posterolateral wall (PLW) were assessed by M-mode echo. Over the 4 days of pacing, the peak intensity ratio progressively decreased in the PLW [region 4 ($p < 0.01$), 5 ($p < 0.001$), 6 ($p < 0.05$)] but did not decrease in other regions. Significant regional-specific changes were observed between region 4 vs 8 ($p < 0.0002$), and region 5 vs 8 ($p < 0.0001$). Similarly, %WTh in the PLW progressively decreased ($p < 0.0001$) but was unchanged in the IVS. *Conclusion:* These data suggest that sustained rapid LV pacing produces regional myocardial dysfunction in the initial development of LV failure. Myocardial contrast echocardiography suggests that relative hypoperfusion may contribute to regional myocardial dysfunction in this model.



2:45

752-4 Transient Intracoronary Infusion of ATP After Reperfusion Reduces the Extent of No-reflow and Infarct Size in Dogs

Kazuo Komamura, Hiroshi Ito [1], Shin Takiuchi [1], Katsuomi Iwakura [1], Atsushi Maruyama [1], Tohru Masuyama, Tetsuo Minamino, Koichi Node, Masafumi Kitakaze, Masatsugu Hori. *The 1st Dept. of Med., Osaka Univ. School of Med., Osaka, Japan;* [1] *Sakurabashi Watanabe Hospital, Osaka, Japan*

It is now widely acknowledged that preconditioning (PC) before severe ischemic insults reduces infarct size (IS) and may attenuate the extent of no-

TUESDAY PM