**718-5**

### Quantitative Dobutamine Stress Echocardiography Utilizing Doppler Tissue Imaging

Hector L Fontanet, John A. PuteO, Mifct~ll G. Davis, Ma~ Lockeby, South Florida, Tampa, Florida

Detection of myocardial ischemia (MIS) by Dobutamine Stress Echo (DSE) is limited by qualitative, observer dependent analysis Doppler tissue imaging (DTI) (Acuson XPc 128) can measure myocardial velocities during DSE and may be useful to quantify wall motion abnormalities. Therefore, the purpose of this study is to determine whether pulsed wave DTI can detect and quantify stress induced MIS by changes in MV. Methods: 26 patients had DSE with DTI. Systolic velocities (SV) of the inferior (IW) and anterior wall(AW) were examined. 16 patients had a normal response and 8 had inducible ischemia. The abnormal group had angiographic evidence of coronary disease (CAD) (RCA or LAD > 70%). Results: There was a significant dose dependent increase in SV in the normal group: IW 0.054 to 0.133 m/s (p < 0.0001); AW 0.04-0.06 m/s (p < 0.001). Compared to normals, patients with CAD had lower resting SV and a blunted increase during DSE: IW 0.043 to 0.069 m/s (p < 0.001); AW 0.04-0.06 m/s (p < 0.01) (figure).

Conclusions: Patients with CAD have impaired augmentation of systolic myocardial velocities during DSE. Thus, DTI may be useful in the quantitative analysis of stress induced myocardial ischemia.

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**718-6**

### Prothrombotic Factors and Endothelial Dysfunction in Left Ventricular Hypertrophy: Implications for Thrombogenesis and Atherogenesis

Gregory YH Lip, Andrew Blann, Peck Lin Lip, Gareth Basterva. University Department of Medicine, City Hospital, Birmingham, England

Hypertensive patients with left ventricular hypertrophy (LVH) are at high risk of thromboembolism and atherosclerosis. To investigate this further, we measured plasma levels of the soluble adhesion molecule P-selectin (ELISA, R&D Systems; associated with platelet adhesion and atherosclerosis), von Willebrand factor (vWF; ELISA, DAKO; a marker of endothelial dysfunction), fibrin D-dimer (AGEN-ELISA; an index of fibrin formation), tissue-type plasminogen activator inhibitor (PAI-1, an index of impaired fibrinolysis & increased thrombogenesis) and fibrinogen (PF; CLAUSs) in 159 patients (74 male; mean age 54.1 years, s.d. 14.8) with essential hypertension, in whom the left ventricular mass index (LVMI) was determined using echocardiography. Levels were compared at 47 nonvoltage healthy controls (mean age 55.0 years, s.d. 19.2).

Results:

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure (BP)</td>
<td>133/81 mmHg</td>
<td>133/71 mmHg</td>
</tr>
<tr>
<td>P-selectin (ng/ml) (median (IQR))</td>
<td>3100 (190-480)</td>
<td>212 (160-350)</td>
</tr>
<tr>
<td>PAI (ng/ml) (median (IQR))</td>
<td>31.0 (25.5-43.1)</td>
<td>19.8 (10.3-31.0)</td>
</tr>
<tr>
<td>vWF (IU/ml) (mean &amp; s.d.)</td>
<td>115.0 (30)</td>
<td>77 (27)</td>
</tr>
<tr>
<td>fibrinogen (g/l) (mean &amp; s.d.)</td>
<td>3.39 (1.02)</td>
<td>2.92 (0.49)</td>
</tr>
</tbody>
</table>

Student's t-test: p = 0.016. This study suggests that hypertensives have high PAI levels, thrombogenesis and impaired fibrinolysis (as indicated by high D-dimer and PAI levels), platelet dysfunction (raised P-selectin) and endothelial dysfunction (high vWF). The high PAI levels were related to LVH and left atrial size. These factors may act synergistically to increase the risk of thrombogenesis and atherosclerosis and may explain the high risk of vascular disease in hypertensives with LVH.

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**719**

### Vascular/Coronary Artery Disease/Thrombosis—Basic: Platelets and Soluble Clotting Factors

Monday, March 25, 1996, 2:00 p.m.–3:30 p.m.
Orange County Convention Center, Room 222

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**719-1**

### A Novel Inhibitor of Plasminogen Activator Inhibitor-1, T-686, Modulates Development of Atherosclerosis in Vivo in Rabbits

Boris Vinogradsky, Stephen P. Beil, Hitoshi Okada, Amy S. Guia, Dagmija Thornton, Satoshi Fujii. Washington University School of Medicine, St. Louis, MO; University of Vermont, Burlington, VT

We have previously shown that plasminogen activator inhibitor-1 (PAI-1), the major inhibitor of tissue-type plasminogen activator and urokinase, is abundantly expressed in atherosclerotic vascular wall. To determine the role of PAI-1 in vascular wall, we have used a novel inhibitor of PAI-1, (3E, 4E)-3-benzylidene-4-(4,5,5-trimethyl-2-benzylidene-4-pyridol-2,5-dione (T-686). In rabbits with aortic atherosclerosis induced by hypercholesterolemia and implantation of indwelling plastic tubing, oral administration of T-686 (30 mg/kg body weight per day) for 8 weeks attenuated the increase in plasma PAI-1 and fibrinogen induced by vascular injury (2.7 ± 0.3 (SE) AU/ml, n = 7, vs 4.9 ± 0.8 AU/ml in control, n = 8) without altering blood triglyceride and cholesterol. This was accompanied by the reduction in aortic PAI-1 mRNA expression (relative absorbance PAI-1/GAP, 0.21 ± 0.04, n = 7 vs 0.86 ± 0.20 in control, n = 8, p < 0.05, Northern) and the inhibition of development of atherosclerosis lesions (lesion area over total aortic area, 25 ± 2%, n = 8, vs 44 ± 7% in control, n = 9, p = 0.05). T-686 prevented the accumulation of PAI-1 within the aortic lesions (immunohistochemistry) and expansion of extracellular matrix (maximal intimal thickness, 124 ± 10 μm, n = 8, vs 155 ± 22 μm in control, n = 9). In contrast, PAI-1 mRNA expression in liver was not altered (Northern). Thus, T-686 not only decreased PAI-1 synthesis selectively in vascular cells but also protected against the development of vascular lesions in vivo. This compound may be useful in defining the role of PAI-1 in atherothrombotic states.

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**719-2**

### Role of Factor Xa/Va in the Procogulant Activity on Balloon-Injured Arteries

Giorgio Ghiglotti, Dania R. Abendschein, Christopher M. Speldel, Paul R. Eisenberg. University of Genoa, Italy; Washington University School of Medicine, St. Louis, MO

We and others have shown that balloon-induced deep arterial injury exposes tissue factor (TF), which initiates thrombosis. However, the contribution of thrombin and Xa/Va activity elaborated and bound at the site of injury to the progression of thrombosis is not known. To determine their relative role, deep injury to the abdominal aorta was induced by overinflation (Norm) of a 4F Fogarty catheter in 29 anesthetized rabbits. As a control group, eight other rabbits underwent the surgical procedures, but without balloon overinflation. Aortas were perfused in situ with phosphate-buffered saline to prevent intravascular clotting, excised and extensively washed in buffer. Injured arterial segments were incubated for 30 min with recalcified plasma depleted of vitamin K-dependent factors by adsorption with barium chloride (Ba plasma) to characterize thrombin activity, followed by incubation with Ba plasma containing 0.9 μM prothrombin to characterize Xa/Va activity. Concentrations of fibrinopeptide A (FPA) were measured in the incubated plasma as a marker of thrombin-mediated fibrin formation. Uninjured segments did not induce significant increases in FPA in Ba plasma with (28 ± 20 ng/ml, mean ± SD) or without (9 ± 5 ng/ml) added prothrombin. Injured segments also did not induce fibrin formation in Ba plasma (19 ± 13 ng/ml, consistent with little
or no bound thrombin activity at the injury site. However, injured segments induced significant elaboration of FPA in Ba plasma containing prothrombin (203 ± 186 nM, p < 0.01 vs Ba plasma alone), consistent with Xa/Va complex bound to the site of injury. Thus, the factor Xa/Va complex rapidly associates at the site of deep arterial injury, presumably on platelets, and is the principle determinant of persistent procoagulant activity on the luminal surface.

719-4 Decreased Platelet and Neutrophil Deposition Despite Persistent Vasoconstrictive Response During L-Arginine Infusion Following Balloon Angioplasty

Daniel Hébert, Jules Y.T. Lam, Yannick Beaulieu. Montreal Heart Institute, Montreal, Quebec, Canada

Reduction of endothelial cell and vascular nitric oxide (NO) synthesis and release can be induced by mechanical injury to the vessel wall. Diminished NO may contribute to the increased platelet (PLT) and neutrophil (PMN) deposition and the distal vasoconstrictive response following balloon angioplasty. Whether administration of L-arginine (1.5 g bolus + 10 mg/kg/min infusion), the NO precursor, may be able to reverse these events was studied. Normal Yorkshire pigs underwent carotid artery injury by balloon angioplasty (5 inflations of 30 sec at 6 atm, with 1 min interval) prior to administration of L-arginine (n > 9) for a period of 15 min and compared to pigs who were administered saline (control; n = 8). Impaired platelet aggregation induced by ADP was significantly reduced during L-arginine infusion. Autologous GpIIb/IIIa labelled platelet and L-arginine labelled neutrophil deposition at the site of deep arterial injury, and the degree of angiographic vasoconstriction at the site of endothelial denudation induced by the tapering distal end of the balloon, are shown below (mean ± SEM):

<table>
<thead>
<tr>
<th>Group</th>
<th>PLT deposition (x 10^8/cm^3)</th>
<th>PMN deposition (x 10^3/µl)</th>
<th>Vasoconstriction (%) baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>44.3 ± 8.7</td>
<td>398.3 ± 64.1</td>
<td>30.0 ± 3.6</td>
</tr>
<tr>
<td>L-arginine</td>
<td>18.9 ± 5.1*</td>
<td>186.0 ± 52.4*</td>
<td>40.8 ± 5.6</td>
</tr>
</tbody>
</table>

*p < 0.05 vs control

Thus, infusion of L-arginine influences platelet and neutrophil deposition at the site of deep arterial injury without affecting the distal vasoconstrictive response induced by endothelial denudation as assessed in our pig model. L-arginine may have a differential effect on circulating blood cells and the vasculature.

719-5 The Elevated NF-kB Activity and MCP-1 Expression In Endothelial-Injured Arteries From Hypercholesterolemic Rabbits Are Prevented by Quinapril

Miguel H. Presa, Carmen Bustos, Mónica Ortega, José Turón, Marta Ruiz-Ortega, Julio G. Puente, Jesús Egido. Fundación Jiménez-Díaz. U.A.M. Madrid. Spain

Although Angiotensin II (AngII) seems to participate in the pathogenesis of atherosclerosis, its role in this setting remains unclear. In a model of endothelial damage and atherogenic diet in rabbits, we studied the effect of quinapril (Q) on the arterial nuclear factor NFkB activity and monocyte chemotactic protein-1 (MCP-1) mRNA expression. Two days before the endothelial damage (day 0), animals were randomized to no treatment (NT) (n = 9) or Q (1 mg/kg/day) (n = 9) and were killed on day 7. On this day, serum vascular ACE activity was inhibited by 70% and 50% respectively in Q vs NT group. NFkB activity (gel shift assay) was increased in the arteries of NT animals vs controls, and Q markedly reduced this activity. MCP-1 expression (RT-PCR) was also elevated in the arteries of NT vs Q (6.3 ± 1.2 vs 3.4 ± 1.4 a.u.; p < 0.04). The reduction in MCP-1 mRNA induced by Q paralleled that of intimal infiltration of macrophages (immunohistochemistry). Since macrophages are the main cells implicated in the increase of MCP-1 observed in atherosclerotic lesions, we studied the effect of Ang II on NFkB activity and MCP-1 expression on the monocytic cell line U937. Ang II (10^{-8} M) increased NFkB activity and MCP-1 expression (3-fold; Northern blot), being maximal at 2 and 6 h of incubation, respectively. Precipitation of cells with the NFkB inhibitor pyrrolidine dithiocarbamate abolished the AngII-induced MCP-1 expression. Our results show that AngII increases the MCP-1 expression through the induction of NFkB and therefore may participate in the cell recruitment to the injured vessel wall. ACE inhibitors might have a beneficial effect in the earliest phases of atherosclerosis by modulating those AngII effects.

720 Computer Algorithms for ECG Analysis

Monday, March 25, 1996, 2:00 p.m.—3:30 p.m.
Orange County Convention Center, Room 230C

2:15 TACHY, a Computer Expert System for the Management of Supraventricular Tachycardia in the Elderly

ShaoSun Wang, Juming Xie, William J. French, Jr. Beijing Hospital, China;
1 Saint John’s Cardiovascular Research Center, Harbor-UCLA Medical Center, Torrance, CA

Doctors in training and non-cardiologist often find the management of supraventricular tachycardia (SVT) in the elderly difficult. An interactive computer expert system to recommend therapies and remind the physician of potential

2:20 A New Method for P Wave Signal Averaging

Cheng Xiao Ming, Neshe E. North, Ronald Oller, John H. McNulty, Blair D. Halperin, Merritt H. Ratt. Oregon Health Sciences University, Portland OR

A new method for accurate temporal alignment and template matching designed for P wave averaging is described.

Methods: Signal averaging was performed using waveforms digitized at 2000 Hz. The template included the entire waveform of interest and was defined relative to the peak of the QRS. The fast Fourier transform was used to derive an autocorrelation wave (ACW) for the entire template and a crosscorrelation wave (CCW) from the template and each incoming beat. The timing of the peaks of the ACW and CCW was used to adjust temporal alignment correcting for any variation in the PR interval. A new CCW was derived post realignment. The difference between the ACW and new CCW was used to determine beat acceptance. This method was compared to the standard correlation coefficient method by analyzing synthesized sine, square and triangle waves which varied in frequency and/or amplitude, and surface P waves from pigs pre and post isoproterenol (ISO) infusion.

Results: Our method resulted in rejection of synthesized waveforms that were not identical to the template while the standard method accepted waves that varied in frequency and amplitude from the template. ISO infusion resulted in clear morphologic changes in the surface P wave and shortening of the PR interval. Using the baseline P wave template the new method rejected all P waves during ISO infusion while the standard method continued to accept many P waves for averaging resulting in a signal averaged P wave which varied significantly from the template.

Conclusion: This new algorithm is more sensitive to changes in waveform morphology compared to standard correlation coefficient methods and is especially advantageous for P wave averaging in that it allows for adjustment on a beat by beat basis for changes in the PR interval.

3:15 Differential Expression of Collagen Subtypes III and IV In Human Vein Graft Atherosclerosis

Stephen M. Denning, Keith M. Chantron, Kevin G. Peters, Brian H. Annex. Division of Cardiology, Duke University Medical Center, Durham, NC

Collagen comprises the major mass of atherosclerotic lesions and accumulates in models of vein graft (VG) atherosclerosis. However, collagens are a family of genetically distinct proteins with different physiologic roles and potentially different mechanisms of regulation. We used immunohistochemistry to study the expression of type III (fibrillar) collagen and type IV (basement membrane) collagen in 18 control saphenous vein (CSV) segments and in 53 freshly excised VG segments from 31 patients. In CSV, collagen III and IV were present in the intima in only 2 (11%) of 18 segments compared to 35 (70%) of 51 segments for collagen III and 46 (82%) of 51 segments for collagen IV. Intimal collagen III and IV expression tended to increase when vessel segments were classified as mild (n = 21, 43% vs 67%), moderate (n = 11, 73% vs 100%), and severely (n = 21, 90% vs 100%) diseased. Also, different spatial patterns of collagen III and IV expression were frequently observed on serial sections. Collagen III predominated in regions of fibrous caps while type IV was diffusely present in the intima and often was associated with areas of neovascularization. In conclusion, these studies provide the first description of collagen subtype expression in human VG atherosclerosis and suggest that collagen subtypes may be differentially regulated in this disease process. Changes in collagen expression may provide insights into potential mechanisms involved in VG atherosclerosis.