3:15

718-6 Quantitative Dobutamine Stress Echocardiography Utilizing Doppler Tissue Imaging

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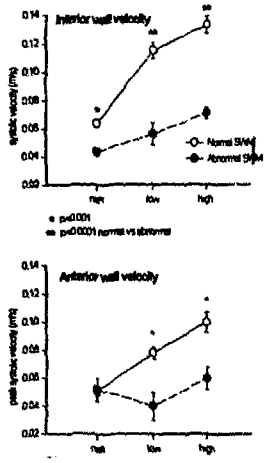
Detection of myocardial ischemia (MIS) by Dobutamine Stress Echo (DSE) is limited by qualitative, observer dependent analysis Doppler tissue imaging (DTI) (Acuson XPc 128) can measure myocardial velocities during DSE and may be useful to quantify wall motion abnormalities. Therefore, the purpose of this study is to determine whether pulsed wave DTI can detect and quantify stress induced MIS by changes in MV. *Methods:* 24 patients had DSE with DTI. Systolic velocities (SV) of the inferior(IW) and anterior walls(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 0.064 to 0.133 m/s ($p < 0.0001$); AW 0.05–0.10 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 ($p < 0.0001$); 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.

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

2:00

719-1 A Novel Inhibitor of Plasminogen Activator Inhibitor-1, T-686, Modulates Development of Atherosclerosis in Vivo in Rabbits

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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-(3,4,5-trimethoxy-benzylidene)-pyrrolidine-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) for 8 weeks attenuated the increase in plasma PAI-1 activity induced by vascular injury (2.7 ± 0.9 (SE) AU/ml, n = 7, vs 4.0 ± 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.

2:15

719-2 Prothrombotic Factors and Edothelial Dysfunction in Left Ventricular Hypertrophy: Implications for Thrombogenesis and Atherogenesis

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

Hypertensive patients with left ventricular hypertrophy (LVH) are at high risk of thromboembolism and atherogenesis. 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 turnover/thrombogenesis), plasminogen activator inhibitor (PAI, 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 to 47 normotensive healthy controls (mean age 55.0 years, s.d. 19.2).

Results:

	Hypertensive	Controls
Mean blood pressure (BP)	180/101	133/81 mmHg
P-selectin (ng/ml) *median* (IQR)	300@ (190–480)	212 (160–3500)
PAI (ng/ml) *median* (IQR)	31.0* (22.5–43.1)	19.6 (10.9–31.0)
D-dimer (ng/ml) *median* (IQR)	250* (190–340)	158 (100–231)
vWF (IU/dl) *mean* (s.d.)	115** *(30)*	97 *(27)*
fibrinogen (g/l) *mean* (s.d.)	3.39+ *(1.02)*	2.92 *(0.49)*

@p = 0.016, *p < 0.0001, **t-test; p = 0.0002, +p = 0.001

Patients with LVH (defined as LVMI > 134/m^2 in males or > 110 g/m^2 in females) had higher PF compared to those without LVH (3.51 vs 2.95 g/l; $p = 0.0006$). D-dimer levels were correlated with vWf (Spearman, $r = 0.45$; $p < 0.001$) and PF ($r = 0.20$; $p = 0.035$) levels. PF levels were correlated with systolic and diastolic BPs (both $r = 0.40$; $p < 0.001$), LVMI ($r = 0.23$; $p = 0.018$), left atrial size ($r = 0.32$, $p = 0.002$), P-selectin ($r = 0.17$; $p = 0.05$) and vWF ($r = 0.34$; $p < 0.001$). This study suggests that hypertensives have high PF 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 PF levels were related to BPs, LVMI (and 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.

2:30

719-3 Role of Factor Xa/Va in the Procoagulant Activity on Balloon-Injured Arteries

Giorgio Ghigliotti [1], Dana R. Abendschein, Christopher M. Speidel, Paul R. Eisenberg. [1] *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 contributions 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 of a 4F Fogarty catheter in 29 anesthetized rabbits. As a control group, eight other rabbits underwent the surgical procedures, but without balloon overinflation. Aortae were perfused *in situ* with phosphate-buffered saline to prevent intravascular clotting, excised and extensively washed in buffer. Injured aortic segments were incubated for 30 min with recalcified plasma depleted of vitamin K-dependent factors by adsorbtion 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 (26 ± 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