Conclusions: Serial PW-TDI and annual EBCT are reliable for timing of cardiac catheterizations. Thy can facilitate the early diagnosis of coronary stenoses or its aggravation, before the appearance of regional wall motion disturbances or alteration of the LV ejection fraction.

2:30 p.m.

855-3 **Dobutamine Stress Echocardiography Is Predictive of Events After Heart Transplantation**

Matthew Pincus, Tuan Nguyen, Anne Keogh, Christopher S. Hayward, Michael Feneley, Peter Macdonald, St. Vincent's Hospital, Sydney, Australia, Garvan Institute of Medical Research, Sydney, Australia

Background: Cardiac allograft vasculopathy (CAV) is the commonest cause of death in patients surviving more than one year after heart transplantation. Non-invasive diagnosis is made difficult by the absence of angina in most cases, the insensitivity of scintigraphy, and a diminished exercise response. Dobutamine stress echocardiography (DSE) has been shown to have good sensitivity relative to angiography and has become a commonly used non-invasive screening tool for CAV . There is less published information on the prognostic value of DSE in transplant recipients, although a study of 109 patients found it to be predictive of cardiac events. The aim of this study was to assess the predictive value of DSE in a larger patient population.
Methods: A retrospective study was made of 240 heart transplant recipients referred for screening DSE. Dobutamine infusion rate was started at 5mcg/kg/min and increased to a maximum of 50 mcg/kg/min or maximum predicted heart rate. The definitions of an abnormal resting and stress study were, respectively, a resting regional wall motion abnormality and a new or worsening regional wall motion abnormality with dobutamine. The primary endpoint was a combination of the following events: death, acute coronary syndrome, heart failure, percutaneous coronary intervention and coronary bypass surgery.
Results: 455 DSE examinations were performed with each patient having between one and five. The mean followup period was 3.5 years (range 1 month-7 years). 53 patients had a total of 68 events. The odds ratios of an event for any abnormality on DSE, a resting abnormality, and a stress abnormality were 3.1(95%CI 1.4-7.1), 3.2 (1.3-8.4) and 3.6 (1.4-9.5) respectively. The probability of being event free at 1 year was 95% in those with a normal DSE. The probability of having an event at 2 years was 10% in those with a normal and 32% in those with an abnormal DSE and this was significantly different ($p<0.05$).
Conclusions: DSE is predictive of events after heart transplantation. A normal DSE identifies patients at low risk of an event over the subsequent 12 months. In screening for CAV, invasive studies such as angiography could reasonably be restricted to those who have an abnormal DSE.

2:45 p.m.

855-4 **Transcriptional Profiling of the Vascular Smooth Muscle Cell Response to Allograft Injury**

Michael V. Autieri, Sheri E. Kelemen, Howard J. Eisen, Temple University School of Medicine, Philadelphia, PA

BACKGROUND: The activation of Vascular Smooth Muscle Cells (VSMC) is responsible for most of the obliterative arterial intimal thickening present in cardiac allograft vasculopathy (CAV). Characterization of proteins which regulate VSMC activation in response to vascular injury is an important approach to understanding the process leading to CAV formation.
METHODS: Primary human coronary artery VSMC were challenged with T lymphocyte conditioned media in the presence and absence of the immunosuppressive compounds cyclosporin A (CsA), mycophenolic acid (MA), and rapamycin (R), and the temporal program of gene expression was investigated by cDNA microarray analysis representing 60,000 sequences. The expression of several candidate proteins were investigated further by western blot and immunohistochemistry on normal, failing, and
transplanted human coronary arteries. RESULTS: Fold-change analysis revealed that inflammation-induced transcripts could be clustered into several categories based on their temporal pattern of expression. These included cytokine, cell cycle, cytoskeletal, and remodeling proteins. Additional clusters could be identified by their common or differing inhibition to CsA, MA, and/or R. The expression of one representative gene, the transcription factor Forkhead Activin Signal Transducer-1 (FAST-1), was upregulated in
activated VSMC but inhibited by CsA, MA, and R. FAST-1 is a
transcriptional regulator of TGF? signaling, and plays a role in tumorigenesis and maintenance of differentiated cell states. Western blots confirm increased FAST-1 expression in arteries with CAV versus normal and arteries from failing hearts. Immunohistochemical analysis determined that forkhead expression localized to medial and neointimal VSMC, and infiltrating leukocytes in these vessels. CONCLUSIONS: These results demonstrate differential gene expression in the VSMC response to inflammatory stimuli and immunosuppressive regimens, and suggest that the transcription factor FAST-1 may participate in the VSMC response to injury and may represent important molecular targets of antirestenotic therapy.

3:00 p.m.

855-5 **Elevated Interleukin-1 Levels, Nuclear Factor κB Activation, and Arterial Intercellular Adhesion Molecule-1 Expression Are Associated With Development of Transplant Coronary Artery Disease**

Carlos A. Labarrere, Rodney W. Benner, Steven J. Miller, Edward J. Brizendine, Joshua B. Lee, Douglas E. Pitts, David A. Hormuth, Methodist Research Institute at Clarian Health, Indianapolis, IN, Indiana University School of Medicine, Indianapolis, IN

Background: Intercellular adhesion molecule-1 (ICAM-1) on arterial endothelium and in circulation are implicated in the development of transplant coronary artery disease (CAD). We studied the relationships among interleukin-1ß (IL-1ß), which stimulates ICAM-1; nuclear factor κB (NFκB); ICAM-1; and subsequent CAD. **Methods**: Using a sandwich ELISA we measured IL-1ß and ICAM-1 in a median of 6 serial serum samples obtained during the first 3 months post-transplantation from 139 heart transplant patients. The median IL-1ß value over the serial samples was estimated and subsequently classified as low, moderate or high levels, based on the distribution quartiles. Matching endomyocardial biopsies were studied immunohistochemically for IL-1ß, NFκB and ICAM-1. Yearly serial coronary angiograms (median: 2/patient) were assessed for CAD. **Results**: A significant association was found between IL-1ß levels and subsequent development of transplant CAD ($p=0.01$). Patients with increased IL-1ß levels developed more severe disease ($p=0.02$). A significant association was found between increased IL-1ß and ICAM-1 levels in the biopsies ($p=0.02$) and in circulation ($p<0.01$). IL-1ß was found in macrophages and endothelium of biopsies from patients with high soluble levels but not in biopsies from patients with low levels. NFκB was localized in endothelial nuclei of patients with high IL-1ß levels but not in those with low levels. **Conclusion**: Elevated soluble IL-1ß levels during the first 3 months after transplantation are associated with (a) endothelial IL-1ß expression and NFκB nuclear localization within the allografts, (b) elevated levels of tissue-associated and soluble ICAM-1, and (c) subsequent development of transplant CAD. Endothelial activation within the allografts could be mediated by IL-1ß expression and NFκB translocation, and this can result in development of transplant CAD.

POSTER SESSION

1206 Novel Methods: Therapies

Tuesday, April 01, 2003, 3:00 p.m.-5:00 p.m.
McCormick Place, Hall A
Presentation Hour: 4:00 p.m.-5:00 p.m.

1206-70 **Intrathoracic Impedance: A Surrogate Measure of Fluid Retention and Predictor of Hospitalization in Patients With Heart Failure**

Cheuk-Man Yu, Elaine Chau, Chu-Pak Lau, Wai-Fat Lam, Man-Oi Tang, Shun-Ling Kong, Qing Zhang, Hong Lin, Jill Christensen, Macrina Wong, Jenny Fong, Li Wang, The Chinese University of Hong Kong, Hong Kong, Hong Kong, Medtronic Inc., Minneapolis, MN

Background: A significant portion of patients implanted with pacemaker or ICD has congestive heart failure (CHF). The ability of an implantable device to better monitor fluid status and provide early warnings of fluid overload may help prevent CHF hospitalization. As fluid accumulates in the lung, intra-thoracic impedance (Z) is decreased. This study investigated the feasibility of using the Z sensor to measure pulmonary congestion and predict CHF admission. Methods: A special pacemaker and an ICD lead were implanted in 32 CHF patients with NYHA class III-IV. A download-software was used for Z measurement (between the RV electrodes and pacemaker can) and storage. Z was stored in the pacemaker 4 times/day during chronic monitoring and every 30 minutes during CHF hospitalization where pulmonary capillary wedge pressure (PCWP) measurement was performed, and the fluid status of the patients was carefully monitored. The maximum changes of Z and PCWP, and the net fluid input/output (FIO), within 6 hours after intravenous diuretics, were calculated and averaged. Results: With a mean follow-up of 8.4±4.6 months, 9 patients developed 20 episodes of CHF hospitalizations. Over 2.0±1.2 weeks (5 days to 4 wks) prior to CHF admission, Z reduced 14±7% ($p<0.0001$) from the relative "baseline". The 2-3 days of intravenous diuretic therapy resulted in a mean PCWP reduction of 21±9 mmHg ($p=0.02$) with a corresponding Z increase of 20±10% ($P<0.001$). Z increase correlated well with PCWP reduction ($r=-0.7$, $p<0.001$) and with FIO ($r=-0.95$, $p=0.0003$). The average reduction of PCWP within 6 hours of intravenous diuretic therapy was 3.5±4.7mmHg ($p=0.03$), while Z increased by 6±4.5% ($p<0.01$) and FIO was -656±580 ml ($p=0.02$). Conclusion: Device-based Z started to decrease with a mean reduction of 14% 2 weeks prior to CHF admission. The good correlation between Z and PCWP as well as volume status suggests that Z may be a surrogate measure of pulmonary congestion/edema in CHF patients. In patients with pacemakers or ICD, the intrathoracic Z sensor may provide a chronic diagnostic indicator of patient fluid status, and an early prediction of CHF admission.