sclerotic lesions to determine the extent of apoptosis. Experimental atherosclerosis was induced by abdominal aorta deendothelialization followed by hyperlipidemic diet (HD) (.5% cholesterol+6% peanut oil) in 22 NZW rabbits. 5 unmanipulated rabbits, fed normal chow (NC), were used as controls. Animals were randomized as below: Gr.1 (n=5) NC 4 mo; Gr.2 (n=5) HD 4 mo; Gr.3 (n=6) HD 3 mo+NC 1 mo; Gr.4 (n=7) HD 4 mo+ Simvastatin (po 1mg/kg/day) last mo; Gr.5 (n=4) HD 4 mo+ ZVAD-fmk (polycaspase-inhibitor, iv 1 mg/kg) 6 and 1 H before imaging on last day. After Tc-99m Annexin-V administration iv, gamma images were obtained until 3 H.

Results: Atherosclerotic lesions were best visible in Gr.2; mean % injected dose/g Annexin uptake was significantly higher in Gr.2 compared to other groups (Gr.2: 0.050+/-0.009; Gr.3: 0.030+/-0.006: Gr.4: 0.029+/-0.007; Gr.5: 0.022+/-0.006; Gr.1: 0.006+/-0.001; P<0.05). Quantitative Annexin uptake in atherosclerotic lesions decreased most in rabbits treated with ZVAD-fmk. Histopathologic characterization revealed increasing % Annexin uptake, and proportionally increasing macrophage apoptosis and number of macrophages in AHA type II to IV lesions. Simultaneously injected biotinylated Annexin uptake was traced predominantly to apoptotic macrophages.

Conclusion: Broad -based caspase inhibitor reduces incidence of apoptosis in experimentally induced atherosclerotic lesions, even moreso than diet interruption and statin therapy. It is expected that abrogation of apoptosis may lead to plaque stabilization.

5:00 p.m.

835-5 **Prolonged but Reversible Sarcolemmal Phosphatidyl Serine Expression in Myocardial Ischemia Represents Ischemic Memory and Can Be Noninvasively Detected by Radiolabeled Annexin-V Imaging**

Leo Hofstra, Ewald Dumont, Artiom Petrov, Navneet Narula, Nezam Haider, Chris Reutelingsperger, Jagat Narula, Drexel University School of Medicine, Philadelphia, PA, Cardiovascular Research Institute, Maastricht, The Netherlands

Phosphatidyl serine (PS) is restrictively distributed to the inner leaflet of the sarcolemmal lipid bilayer in normal myocytes but gets externalized during apoptosis. Since apoptosis occurs commonly in ischemic stress and Annexin-V selectively targets exteriorized PS, we hypothesized that myocardial ischemia should be noninvasively detectable by radionuclide gamma imaging.

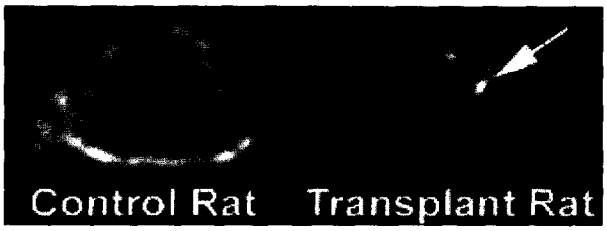
Severe myocardial ischemia was produced in 6 NZW rabbits by LCX coronary artery occlusion for 10 min followed by 30 min reperfusion. 99mTc-Annexin-V (~10 mCi) was injected intravenously and animals were sacrificed at 3H. Ex vivo imaging demonstrated significant Annexin uptake in ischemic zone. Maximum percent injected dose per gram was 0.27+/-0.16 in ischemic, compared to 0.03+/-0.01% in normal myocardium (ratio 9+/-3). However, histopathologic and histochemical analysis did not reveal apoptosis or necrosis, and ultracentrifugal isolation of subcellular components of ischemic myocardium from cell membrane revealed that 53+/-6% radioactivity had been internalized, possibly due to translocation of PS back to inner sarcolemmal leaflet upon reperfusion. To further characterize the reversibility of PS expression, we subjected mouse hearts to to 5-min ischemia, and allowed reperfusion for 0.5, 1, 1.5, 3, 6 and 24H and injected biotinylated Annexin-V 10 min before sacrifice. PS expression persisted for 6H. Internalization was traced to cytoplasm, mitochondria, and nucleus. These data indicate that persistent but reversible PS expression in ischemic myocardium offers an ischemic memory window for at least 6H. Noninvasive targeting of molecular alterations during severe ischemia, such as transient PS expression, should lead to development of newer hot spot imaging strategies, and after-the-fact recognition may provide novel means to differentiate cardiac from noncardiac origin of chest pain.

5:15 p.m.

835-6 **Positron Emission Tomography Imaging of Cellular Cardiomyoplasty**

Joseph C. Wu, Ian Y. Chen, Abhijit De, Jung-Joon Min, Gobalakrishnan Sundaresan, Jian-Hua Qiao, Michael C. Fishbein, Sanjiv S. Gambhir, UCLA School of Medicine, Los Angeles, CA

Background: Cell transplantation is actively investigated as potential treatment for end-stage heart failure. However, traditional methods of determining engraftment rely on postmortem analysis. Development of an imaging technique to quantify, localize, and optimize transplant protocols would be beneficial. **Methods:** 1) Cell Culture: Rat cardiomyoblast cell line (H9C2) was transfected with Ad-CMV-HSV1-sr39tk to assess expression level of a PET reporter gene (mutant viral thymidine kinase (sr39tk)). 2) *In Vivo*: Transfected myoblasts (3x10^6) were injected into anterolateral wall of nude rats (n=5) via thoracotomy. Control rats (n=3) received myoblasts expressing firefly luciferase. MicroPET imaging on living rats was performed on days 2 and 5 using tracer for viral thymidine kinase enzyme ([^{18}F]-FHBG). **Results:** 1) Transfected myoblasts yield robust sr39tk activity: 3x10^6 myoblasts (4.42±1.79), 2x10^6 (3.92±1.26), and 1x10^6 (1.86±0.28 % conversion/ug protein/min) versus control (0.02±0.01). 2) MicroPET images show [^{18}F]-FHBG uptake by transplanted myoblasts at anterolateral wall on day 2 (0.046±0.008) and day 5 (0.038±0.013 %ID/g) versus control (0.019±0.002) (p<0.05). Immunohistochemistry and autoradiography confirm presence of transplanted myoblasts. **Conclusion:** This is the first proof-of-concept study on noninvasive PET imaging of cardiac cell transplantion. Further validation and refinement of the approach described may lead to wider research and clinical application.



POSTER SESSION

1165 Doppler Hemodynamics: New Insights

Tuesday, April 01, 2003, 9:00 a.m.-11:00 a.m.
McCormick Place, Hall A
Presentation Hour: 10:00 a.m.-11:00 a.m.

1165-31 **Doppler Gradient Estimations Across Tunnel Obstructions: An In Vitro Study Including Flow Visualization**

Raphael Rosenhek, Julia Mascherbauer, Leopold Huber, Heinrich Schima, Gerald Maurer, Helmut Baumgartner, University of Vienna, Vienna, Austria

Background: Underestimation of pressure gradients across tunnel obstructions by Doppler (Do) as well as marked overestimation have been observed. The latter was found in tunnels as short as 5 mm and in settings where relevant pressure recovery distal to the obstruction could be excluded.

Methods: To define mechanisms that determine the Do - catheter gradient relation in this setting, tunnels (L = 20 mm, Ø = 5.5 mm) with gradually tapering inlet and/or outlet (20°) or with abrupt narrowing and/or expansion were studied in a pulsatile flow model. Do and catheter measurements were simultaneously performed. Catheter gradients were estimated with the distal pressure port either at the tunnel entrance (dp C1), at the tunnel exit (dp C2) or 10 cm downstream (dp C3). Flow was visualized with a Laser system and recorded with a high-speed video camera.

Results: Doppler gradients (dp Do) showed excellent agreement with dp C1 in all settings (mean diff. 0.8+/-2.4 mmHg). In tunnels with abrupt narrowing, dp Do overestimated dp C2 by 54+/-19%. Flow visualization demonstrated that this dramatic change in lateral pressure within the tunnel was caused by marked flow contraction at the tunnel entrance resulting in a high velocity and low pressure field followed by readaption of the flow to the full cross-section with only little turbulence resulting in significant pressure recovery within the tunnel itself.

In contrast, in tunnels with gradually tapering inlet, dp Do underestimated dp C2 by 8+/-2%. In this setting, flow contraction was totally avoided and the neglection of viscous resistance in the simplified Bernoulli equation caused this Doppler – catheter gradient discrepancy. Due to various extent of distal pressure recovery, dp C3 was 30+/-7% lower than dp C2 in tunnels with gradually tapering outlet but only 9+/-1% lower in abruptly expanding tunnels.

Conclusion: The Doppler-catheter gradient relation in tunnel obstructions is determined by the individual extent of flow contraction with pressure recovery within the tunnel, viscous resistance, and pressure recovery distal to the tunnel. Depending on inlet and outlet geometry, tunnel length, and diameter, overestimation as well as underestimation by Do may occur.

1165-32 **Degree of Pulmonary Hypertension Predicts the Severity of Functional Tricuspid Regurgitation: New Findings Based on Invasive Measurements of Pulmonary Artery Pressure**

Sachin M. Navare, Carol Y. Gemayel, Cynthia Taub, Ahmad Habboub, Linda D. Gillam, Hartford Hospital, Hartford, CT

Background: Functional tricuspid regurgitation (FTR) is a common clinically important complication of left-sided heart disease. While prior studies have linked FTR to tricuspid annular dilation, there is little information concerning the importance of pulmonary artery pressure (PAP) in this setting. The only previous study of this issue showed no significant association between PAP and FTR. However PAP was measured using a Doppler method since shown to be inaccurate in the setting of severe TR. (PAP = 4[TR jet velocity]^2 + 10 mm Hg). **Methods:** To revisit this issue using more robust methods, we simultaneously measured PAP (Swan-Ganz catheter) and quantitated the severity of FTR echocardiographically. The study group consisted of 14 pts with FTR complicating mitral valve disease. As previously reported, FTR was defined by presence of apical tethering or incomplete closure of a structurally normal valve. FTR was quantified using proximal isovelocity surface area based methods yielding values for effective regurgitant orifice and regurgitant volume (reader blinded to the PAP). **Results:** There was a strong linear correlation between the measured mean pulmonary artery pressure and the severity of