1144-132 **L-Type Calcium Channel Inhibitor Diltiazem Prevents Diastolic Dysfunction and Stress-Induced Cardiac Decompensation and Death in a Mouse Model of Familial Hypertrophic Cardiomyopathy**

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The cardiac troponin T (TnT) I79N mutation has been linked to familial hypertrophic cardiomyopathy (FHC) and a high incidence of sudden death. To investigate the effect of this mutation on left ventricular (LV) function, we determined LV pressure-volume (PV) relationships in transgenic mice expressing human wild type (Wt) and human mutant TnT (I79N). A micro-conductance catheter was introduced in the LV (n =8/group). Loadindependent enddiastolic PV relationships were obtained (EDPVR) under basal and stress conditions (0.25 mg/kg isoproterenol i.p.). After treatment with the calcium channel inhibitor diltiazem we investigated the LV function in another set of I79N mice.

Basal conditions: I79N mice showed increased systolic function compared to Wt : EF:63.3±.4.3* vs. 51.1±5.0%; SV:35±3.2* vs. 27.1±1.6µl; CO: 16950±1300* vs. 12119±1027µl/min; * p<0.05 without differences in HR and LVP. Load dependent diastolic pressure indices as LVEDP were unchanged, but the load independent EDPVR was increased (0.5±0.1* vs. 0.3±0.03; * p<0.05), showing increased LV stiffness leading to a diastolic dysfunction.

Stress conditions: HR (654±21 vs. 625±25 bpm) and LVP (159.9±8.6 vs. 169.5±11.3mmHg; p<0.05) response was similar in all groups, but systolic function of I79N mice decreased compared to Wt (EF: 25.1±5.5* vs. 51.7±8.4%; SV: 14.0±3.3* vs. 22.17±4.4µl; CO: 8916±1832* vs. 13915±1558µl/min; Ves: 42.2±3.6* vs. 25.8±5.6µl *p<0.05). Diastolic indices demonstrate diastolic dysfunction in I79N compared to Wt: (LVEDP: 17.1±2.2* vs. 8.4±2.2mmHg; *p<0.05). This cardiac decomensation due to stress conditions leads to death in all I79N, but in none of the Wt animals.

Diltiazem prevented the reduction in SV, EF, CO and the rise in LVEDP without affecting HR signifcantly compared to non treated I79N and decreased mortality due to stress to 25 %.

I79N mice show an increased cardiac stiffness under basal conditions, and a diastolic dysfunction leading to decompensation and death under stress. Diltiazem prevents cardiac decompensation and death. These data gain an inside into hemodynamic pathology of the I79N mutation leading to FHC and why sudden death is common in FHC.

1144-133 **β3-adrenergic Receptor Activation Decreases Peripheral Vascular Resistance in Heart Failure by Restoring Endothelial Dependent Vasorelaxation via Endothelial Nitric Oxide Synthase Upregulation**

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Background:Peripheral vascular resistance (PVR) is increased in heart failure (HF). Therapy designed to decrease PVR by restoring nitric oxide (NO) mediated endothelial dependent (ED) vasorelaxation may prove to be vital in improving survival. Recent data suggests that beta-3 adrenoreceptor (β3-AR) activation may increase NO bioavailability. This study was performed to evaluate whether β3-AR activation with BRL, a β3-AR agonist, decreases PVR via NO mediated ED vasorelaxation in HF.

Methods: Sprague-Dawley rats with HF after coronary artery ligation were randomized into untreated controls and BRL treatment. After four weeks of therapy, hemodynamics was obtained and aortic vasorelaxation in response to isoproterenol with and without L-NMMA were performed. Additionally, bovine pulmonary artery endothelial cells in culture were incubated for 24 hours with BRL at 10 µM and 20 µM concentrations. Western blots for endothelial NO synthase (eNOS) protein concentration was performed.

Results: In HF rats treated with BRL, heart rate, systolic blood pressure, and left ventricular (LV) dP/dt was decreased (P<0.05) compared to untreated HF rats. LV end diastolic pressure (LVEDP) was unchanged. BRL significantly improved endothelial dependent vasorelaxation (37.1 ± 15.3 versus 17.3 ± 6.8 %, P<0.05) compared to untreated HF rats at peak isoproterenol dose. Addition of L-NMMA completely blunted all vasorelaxation responses. Bovine cell cultures incubated with BRL resulted in greater (P<0.05) than two fold increases of eNOS compared to untreated cell cultures.

Conclusions: β3-AR activation decreases peripheral vascular resistance in heart failure by restoring endothelial dependent vasorelaxation via endothelial nitric oxide synthase upregulation.

1144-134 **Direct Comparison of Bone Marrow Stromal Versus Mononuclear Cells in Murine Cardiac Function After Cellular Cardiomyoplasty**

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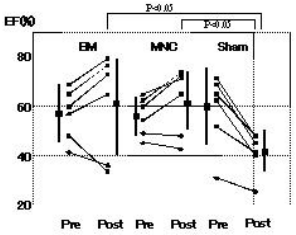
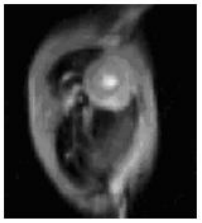
Background: Cellular cardiomyoplasty, transplantation of bone marrow cells into injured myocardium, has been reported to improve cardiac function but the mechanism is unknown. Thus, in a mouse cryoinjury model, we compared the functional effects of potentially myogenic bone marrow stromal cells (BM), potentially angiogenic bone marrow mononuclear cells (MNC), or media alone (sham) with historical myoblast (Mb) controls where myogenesis is clear. Methods: C57BL/6 mice (n=6, each group) were subjected to LV cryoinfarction. Animals received myocardial injections of 10^7 BM, MNC or media 7 days after injury. Contiguous short-axis (2mm) ECG-gated segmental FLASH images were acquired on a 1.5T clinical scanner (eyecoil) immediately before, and again 4 wks after injection. Result: After infarction, all animals showed poor ejection fraction (EF, %) (57±11 in BM, 56±8 in MNC and 60±16 in sham) and all infarction areas were detectable. At 4 wks EF was improved in BM (61±20) and MNC (62±14) similar to Mb, yet deteriorated in the sham group (56±8). Conclusions: Although both MNC and BM cells stabilize cardiac function to a similar degree as myoblasts, histological evidence suggests differing mechanisms of angiogenesis versus myogenesis, respectively.





POSTER SESSION

1145 Heart Failure: Miscellaneous Topics

Tuesday, March 09, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1145-115 **Congestive Heart Failure in Rheumatoid Arthritis Patients: Rates, Predictors, and the Effect of Antitumor Necrosis Factor Therapy**

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Background: Cardiovascular morbidity (e.g. pericarditis, diastolic dysfunction) is increased in rheumatoid arthritis (RA) patients though data on rates of congestive heart failure (CHF) in RA patients is unknown. Elevated tumor necrosis factor (TNF-alpha) levels have been identified as potential factors in CHF development. However, clinical studies have demonstrated limited value of anti-TNF blockade in patients with CHF. This study examined background CHF risk factors in RA and osteoarthritis (OA) patients, CHF prevalence and incidence rates in RA patients, and evaluated the relationship of anti-TNF agents and rates of CHF. **Methods:** Cohorts of RA patients (n = 13,171) and OA patients (n=2,568) in a longitudinal outcome study of the National Data Bank for Rheumatic Diseases were assessed via questionnaire and medical record review for CHF during a two-year period ending in 6/2002. Propensity scores were used to adjust for the risk of anti-TNF prescription. **Results:** Adjusted prevalence of CHF in RA patients was increased over that in OA patients (3.9% vs. 2.2%). CHF risk factors (e.g., hypertension, prior MI, diabetes, advanced age) were similar between RA and OA patients though measures of RA severity (HAQ, education, weight) were contributory to CHF rates. Adjusted rates of CHF were lower in anti-TNF treated RA patients (n = 5,832) than in non anti-TNF RA treated patients (2.8% vs. 3.9%, average treatment effect –1.2%[-1.9 to -0.5]). The rate of new-onset incident cases was low (0.2%) and unrelated to anti-TNF therapy. **Conclusion:** In 13,171 RA patients, rates of CHF were increased compared to concomitant OA patients. Non-RA factors predicting CHF are the same in RA patients as in patients from general population studies, but RA activity/severity measures also predicted heart failure. Patients receiving anti-TNF therapy had lower rates of prevalent CHF compared to non anti-TNF treated patients. Incidence rates of CHF were low and unrelated to treatment.

1145-116 **Prevalence and Mechanism of Functional Mitral Regurgitation in Dilated Cardiomyopathy: Baseline Data From the Acorn Trials**

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Background: Functional mitral regurgitation (MR) in dilated cardiomyopathy has significant prognostic implication, but its mechanism needs to be elucidated. The aim of the study was to determine the prevalence and the main echocardiographic factors determining the severity of MR in theses patients. Method: From the baseline echocardiographic results of Acorn cardiac support device trials, 154 patients with dilated cardiomyopathy without organic mitral valve disease were identified. Echocardiographic parameters were correlated with the severity of MR assessed by color flow imaging. Results: There were 96 males and the mean age was 55 ± 12 years. Mitral regurgitation was detected in 111 patients (72%); 29 in grade I (26%), 22 in grade II (20%), 29 in grade III (26%), and 31 in grade IV (28%). In univariate analysis, systolic and diastolic left ventricular dimensions (p<0.01), systolic and diastolic spherical indices of left ventricle (p<0.0005), systolic and diastolic mitral annulus size and area (p<0.0001), left atrial area and volume (p<0.0001), tethering distance from papillary muscle to annulus fibrosa (p<0.0001), tenting height (p<0.0001) and tenting area (p<0.0001) of mitral valve, and stroke volume (p<0.005) showed significant correlation with the severity of MR. Left ventricular volume or ejection fraction did not show significant correlation. In multivariate analysis, only tenting area showed significant correlation with severity of MR (p<0.0001). Conclusion: Functional MR was found in more than two thirds of patients with dilated cardiomyopathy, and severity of MR was mainly related with the tenting area of the mitral valve. Therefore, treatment interventions for functional MR may have to be directed to reduce the tenting area of regurgitant valve in addition to reducing the size of the mitral annulus.