Background: Low risk patients (pts) presenting to our emergency department (ED) with chest pain undergo immediate exercise testing (IET). The mean number of negative IET during the study period was 2,656 which were obtained in 1,960 pts with single IET and in the multivisit (MV) subgroup of 289 pts who had 696 multiple visits and negative IETs. Results: Of 3,432 patients tested during a 7.5 year interval, IET was positive in 353 (10.3%), nondiagnostic in 830 (24.2%) and negative in 2,249 (65.5%). During the study period, 289 (13%) of the 2,249 pts with negative tests had multiple (≥2) IET for chest pain. The total number of negative IET during the study period was 2,656 which were obtained in 1,960 pts with single IET and in the multivisit (MV) subgroup of 289 pts who had 696 negative IET. Thus, the MV subgroup comprised 13% (289/2,249) of all pts with negative IET but accounted for 26% (696/2,656) of the total number of negative IET. In the MV subgroup (n=289), 261 (90.3%) pts had ≥3 IET and 28 (8.7%) had ≥4 IET. The mean number of IET in the MV subgroup was 2.7 (range 2-7). The MV negative subgroup was similar (p>0.05) in age (52 vs. 51 yr) and number of cardiac risk factors (1.5 vs. 1.5) to the single negative IET pts but the proportion of women was higher in MV (39% vs. 44%, p<0.05). In the MV negative IET pts, there was no cardiac mortality, 7 (2.4%) pts had myocardial infarction and after a mean of 3.7 tests, 25 underwent catheterization showing critical coronary artery disease and 4/3 (83%) of these pts had myocardial revascularization.

Conclusions: Although a minority of negative IET pts had multiple visits to the ED, they accounted for a disproportionate number of the IET by the entire negative group. An important minority of the MV negative subgroup was ultimately found to have coronary artery disease after multiple tests and were candidates for revascularization. Earlier definitive evaluation of MV pts could obviate repeat visits in many and afford appropriate therapy for coronary artery disease in an important minority.

ORAL CONTRIBUTIONS

Heart Failure, Basic Science, Animal Models, and Human Studies

Monday, Tuesday, March 09, 2004, 2:00 p.m.-3:30 p.m.
Morial Convention Center, Room 217

849-1 Uncoupling Proteins Shift During Cardiac Hypertrophy and Renin-Angiotensin System Suppression

Susan Marie Dallalonda, Maria Arni Ruepizich, Brigham and Women’s Hospital, Boston, MA. Children’s Hospital, Boston, MA.

Background: Improving energetics during heart failure may aid to preserve cardiac function. Uncoupling proteins (UCPs) are key regulators of energetics in skeletal muscle and adipose tissue. They reduce the proton electrochemical gradient across the innermitochondrial membrane. However, their role in cardiac tissue is poorly understood. In mice with heart failure, increased UCP2 coincides with reduced high-energy phosphates. In humans, reduced UCP3 in failing hearts is normalized with left ventricular assist devices. RAAS suppression with angiotensin converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor (AT1R) blockers improve cardiac function and reduce remodeling. We asked if these benefits were associated with improved cardiac energetics.

Methods: We examined UCP1, UCP2, UCP3 mRNA levels (real-time RTPCR in thyroid-hormone (T3)-induced cardiac hypertrophy (CS7BL/6 mice) and in mice given T3 plus an antiangiogenic drug, TNP-470 on 1-4, 14 d. We measured the effect of captopril or candesartan (14 d) on UCPs in CS7BL/6 mice. Body, heart/weight ratios, and atriaweights and tibia length were assessed.

Results: T3-induced hypertrophy increased left ventricle (LV) UCP2 and UCP3 mRNA levels, and reduced UCP1. Compared to controls, UCP1 increased 5 fold (1, 2 d), 10 fold (3 d), and 20 fold (4 d) with no further increases despite continued LV increases (14 d). The UCP2 increases coincided with the most angiogenic phase (1-4 d) of T3-induced hypertrophy. We examined the effects of an antiangiogenic agent, TNP-470, on UCP shifts and hypertrophy. We treated mice with T3 plus TNP-470 (1, 4 d). TNP-470 reduced UCP2 to normal and limited increases in LV mass (T3: 171±12 mg; T3+TNP-470: 94±6.0 mg). UCP2 decreased by LVAD support of the failing human heart, the ratio of beta-1/beta-2 adrenergic receptors remains at decreased after LVAD implant and explant. Total beta receptor density were quantified in the same tissue pairs by Scatchard analysis using radiolabeled cyanopindolol, while receptor subtype were determined by two-site competition binding curves using 15 doses of ICI 118,551.

Results: At time of LVAD explant, the inotropic response to isoproterenol was greater (149±29% as compared to the time of implant (68±14%, p<0.05), and the response tended to improve with increased duration of support (p<0.05). Total receptor density was increased after LVAD (72.3±7.8 vs 42.4±3.6 fmol/mg protein; p<0.001), whereas the percent of beta-1 receptors was not different between the two groups (46.4±6.1% at implant; 68.4±2.0% at explant). While the percent of beta-1 receptors was not different, the absolute number of both beta-1 (50.3±6.4 vs 19.4±3.5 fmol/mg protein, p<0.001) and beta-2 receptors (21.9±2.2 vs 10.8±2.6 fmol/mg protein, p<0.05) was increased after LVAD.

Conclusion: Although the total density of beta-adrenergic receptors recovers following LVAD support of the failing human heart, the ratio of beta-1/beta-2 receptors remains at decreased after LVAD (60/40) rather than non-failing (80/20) levels. The larger percentage of beta-2 receptors after LVAD may contribute to delayed recovery of the inotropic response.

849-4 Extracellular Matrix Remodeling During Left Ventricular Assist Device Support: Relation Between Collagen and Passive Pressure-Volume Relations

Stefan Klotz, Marc L. Dickstein, Jeffrey A. Morgan, Robert F. Fonroy, Angou Gu, Jeanine D Armentrio, Daniel Burhoff, Columbia University, New York, NY.

Introduction: Left ventricular assist device (LVAD) support of failing hearts induces reverse remodeling, manifest as shifts towards lower volumes of the passive pressure-volume relationship (PVR). This may be a consequence of regression of hypertrophy and/or changes in myocardial properties due to extracellular matrix remodeling. However, the relative contributions of these factors to reverse remodeling are unknown.

Methods: LV tissue samples were collected from idiopathic dilated cardiomyopathic (DCM) hearts at the time of cardiac transplantation in patients requiring (n=16) or not requiring (n=16) prior LVAD support and from 5 normal hearts not suitable for transplantation. Total collagen (hydroxyproline), soluble collagen and insoluble collagen were quantified. Chamber capacitance and myocardial stiffness were calculated from ev-ro PVRs and measured LV wall volume.

Results: Compared to normals, total collagen and soluble collagen were increased in DCM (3.1±1.5 vs 6.1±3.4 μg/g, p=0.014; 1.4±0.3 vs 4.1±0.9 μg/g, respectively). LVAD support further increased total collagen (9.3±3 vs 18.2±5 μg/g, p<0.001), which was due to an increase of insoluble collagen (2.0±3.5 vs 5.1±3.1 μg/g, p=0.008) with no change in soluble collagen (4.1±0.9 vs 3.9±1.0, p=NS). LV mass was decreased by LVAD support (296±73 vs 234±60 g, p=0.014), the PVR shifted towards lower volumes with a chamber capacitance (volume at a pressure of 30 mmHg) decreasing from 266±132 mL to 192±87 mL (p=0.024). However, myocardial stiffness constant was not affected (9.9±0.7 vs 10.6±0.9, p=NS).

Discussion: LVAD-support of the failing human heart leads to increased total collagen and cross-linking of collagen, suggestive of increased tensile strength of the extracellular matrix. Despite these changes, however, global myocardial stiffness constant was unaffected. These lead to the provocative hypothesis that the profound changes induced by LVADs indicate of reverse structural remodeling are mainly due to regression of myocyte hypertrophy, with relatively little impact of the changes in collagen matrix on passive myocardial properties.

2:45 p.m.

855-5 Soluble Tumor Necrosis Factor Receptor (Etanercept) Treatment Enhances Left Ventricular Dysfunction in an Experimental Model of Chronic Chagas Disease Cardiomyopathy

Angelina M. Bilat, Vera C. Salesim, Felix J. Ramires, Daniel Gregio, Jorge Kalil, Edécio Cunha-Neto, Heart Institute- University of São Paulo Medical School, São Paulo, Brazil.

Background: chronic Chagas’ disease cardiomyopathy (CCD), caused by the protozoan Trypanosoma cruzi, affects ca. 3 million patients in Latin America. The lack of proven effi- cacious therapy is associated with increased restrictions of the extracellular matrix, which is as- sociated to increased production of proinflammatory cytokines such as TNF-alpha. The aim of this study was to evaluate Etanercept, a TNF-blocking agent, as a potential therapeutic approach in the control of CCD development. For that matter, we used as a model the