Role of Oxidative Stress in Diastolic Function in Patients With Hereditary Hemochromatosis

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Background: Abnormal diastolic function has been reported in patients with hereditary hemochromatosis (HH). Little is known about the mechanisms mediating this abnormality; however, it is possible that an increased oxidative stress related to iron overload is involved in this process. Thus, we evaluated relationships between biomarkers of oxidative stress and diastolic function in the patients with HH.

Methods: 27 consecutive HH patients (mean age 47±10, meanSD), were recruited from an NHLBI-sponsored Heart study of hemochromatosis protocol. All patients had confirmed C282Y homozygosity and a documented history of iron overload. The level of oxidative stress was evaluated by plasma MDA, erythrocysteine SOD and glutathione (GSH) levels. Diastolic function was assessed with early filling (E) and atrial contraction (A) diastolic tissue velocities measured with pulsed tissue Doppler (PWT) or strain rate imaging (SRI) in the apical four chamber views near the annuluses. Correlations between tissue Doppler velocities and oxidative stress markers were evaluated with the Spearman correlation method.

Results: A significant positive correlation was found between MDA and SRI values of the lateral mitral annulus (r=0.40, p=0.039) and between SOD and E velocities of the tricuspid annulus at the right ventricle free wall measured with PWT (r=0.453, p=0.021). In addition, a strong positive correlation was noted between GSH and E velocities of the septal mitral annulus measured with SRI (r=0.669, p=0.006). When the patients were divided into 2 groups by the average value of GSH, a significant difference of the septal annulus E measured with SRI (2.1±0.65 sec-1 in high group vs. 1.42±0.55 sec-1 in low group, p=0.005) was noted. However, the level of iron overload itself measured with ferritin failed to correlate with any of these measurements of diastolic function. These results indicate a trend that chronic exposure to oxidative stress manifesting elevated MDA and reduced SOD and GSH, attenuates E velocities and increases A velocities.

Conclusions: Our results suggest that oxidative stress per se, not the direct level of iron overload, may be affecting diastolic function in patients with hereditary hemochromatosis.
Cardiac Function and Heart Failure

1017-164 Contribution of Diastolic Dysfunction to Heart Failure Regardless of Ejection Fraction

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Background: Heart failure (HF) has been classified as systolic and diastolic based on the left ventricular (LV) ejection fraction (EF). We hypothesized that diastolic dysfunction is an important element of HF regardless of EF.

Methods: Two hundred six patients with clinical HF were compared to 72 age-matched controls. Results: Diastolic dysfunction assessed by tissue Doppler imaging as normal (grade 0), impaired relaxation (grade 1), pseudonormal (grade 2), or restricted (grade 3). Diastolic dysfunction (≥ grade 1) was present in 89% of patients with HF regardless of EF, and was more frequent and severe than in age-matched controls (P <0.001). In patients with HF, EF >0.40 correlated with the grade of diastolic dysfunction (≥ P=0.02, P<0.001), but not EF or end-diastolic volume index (EDVI).

The degree of diastolic dysfunction influenced survival (RR=1.64, P<0.05) where EF and EDVI did not. Systolic dysfunction measured by the systolic mitral annular velocity was reduced in HF patients with EF ≥0.40 (4.4±1.1 cm/sec) and to a lesser extent with EF ≥0.50 (6.1±1.8 cm/sec) compared to normals (8.0±2.1 cm/sec) (P<0.01). HF patients with EF ≥0.50 had increased mass/EDVI (2.6±1.0 vs 2.2±0.7 g/ml, P<0.05). HF patients with EF ≥0.40 had increased LV EDVI.

Conclusions: Patients with HF have diastolic dysfunction regardless of EF. Diastolic dysfunction is a better predictor of BNP and mortality than EF or LV EDVI. In addition to diastolic dysfunction, HF with EF ≥0.50 is associated with mid systolic dysfunction and increased LV mass/EDVI. In HF with EF ≥0.40 have both systolic and diastolic dysfunction and LV dilatation.

1017-165 Marked Increases in the Prevalence of Diastolic Heart Failure Amongst Community and Referral Patients Hospitalized With Heart Failure

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Background: Community-based studies report normal ejection fraction (EF) in 50% of heart failure (HF) patients (pts). This is termed diastolic HF (DFH). Differences in the prevalence of DFH over time or between Community and Referral HF cohorts have not been examined.

Objective: To hospitalized HF pts, determine if the prevalence of DFH has changed over time or is different in Community-based and Referral HF cohorts.

Methods: Electronic chart review of all consecutive unique HF pts (DRG 127) discharged from Mayo Clinic hospitals, Olmsted County, Rochester MN from 1/87 to 12/02. Pts were designated as Community (Olmsted County residents) or Referral (Non-Olmsted County residents). EF was available in 4610 of 6440 total HF pts. Pts with EF≥50% were considered DFH.

Results: Over 24% of pts were Community pts and 49% (n=2259) had DFH. The % HF pts with DFH increased over time (P<0.001, figure) and was higher in the Community cohort (20%) vs Referral cohort (14%). Community HF pts were older (78±13 yrs vs 72±14 yrs, P<0.001) and more likely female (65% vs 49%, P<0.01) than Referral HF pts. In univariate analysis, 3 month mortality was lower in DFH (odds ratio, OR, for DFH=0.84, P=0.03). However, controlling for age, sex, renal function and hemoglobin, mortality was higher in DFH (OR for DFH=1.98, P<0.001) but not different between Community and Referral cohorts (P=0.08).

Conclusion: We speculate that increased awareness of DFH as well as increases in the % of the population over age 65 contribute to the increased prevalence of DFH.

1017-166 Relationship of Electrocardiographic Strain Pattern to Left Ventricular Diastolic Function in Hypertensive Patients: The LIFE Study

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Background: Whether ECG strain pattern (ST+), associated with left ventricular hypertrophy (LVH) and risk of development of congestive heart failure, is independently associated with diastolic dysfunction is unclear.

Methods: The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study enrolled hypertensive patients with ECG-LVH, of whom 10% underwent Doppler echocardiography. ST+ was assessed in leads V5 and/or V6, LV diastolic function measures included diastolic filling pressure (A wave), and filling time (TAWP); A/F ratio; and left atrial volume index (LAVI).

Results: ST+ (in leads V5 and/or V6) was associated with male gender, African-American race, diabetes, history of coronary heart disease (CHD), and age. Age, diastolic BP, and LVH were more frequently seen in patients with ST+. LV systolic function measures included the ratio of peak E and A waves velocities (E/A), E deceleration time (EDT); atrial filling fraction (AFF); and isovolumic relaxation time (IVRT). A combined index of systolic-diastolic function was also computed (isovolumic relaxation time/ejection time, TEI-index).

Conclusion: Hypertensive patients with ECG-LVH, the ST+ pattern was not independently associated with LV diastolic abnormalities.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Renn Activity (ng/ml/hr)</td>
<td>7.1±1.8</td>
<td>8.2±1.4</td>
</tr>
<tr>
<td>Angiotensin (ng/dl)</td>
<td>8.4±1.1</td>
<td>8.4±1.4</td>
</tr>
<tr>
<td>Angiotensin II (pg/ml)</td>
<td>51±5</td>
<td>51±4</td>
</tr>
<tr>
<td>Vasoressin (pg/ml)</td>
<td>4.7±1.2</td>
<td>5.0±0.9</td>
</tr>
</tbody>
</table>

1021-167 ID was correlated with T1/2 (r = 0.678, p < 0.005) and it did not depend on the severity of the increase in wall thickness.

Conclusions: Reflecting myocardial perfusion, this greater is in LVH, especially in patients who symptoms disturb coronary microcirculation, contributing to impaired relaxation. MACE could reflect the difference of pathophysiology between HCM and hypertensive LVH.
Background:

While diastolic dysfunction (DD) is known to be prevalent in patients on dialysis, little is known about its prevalence in non-dialysis chronic kidney disease (CKD). Furthermore, the relationship between DD, coronary calcification, and arterial stiffness is not well characterized.

Methods:

Diastolic function was evaluated by echocardiography in a sub-cohort of patients enrolled in the RHR-CKD study; a prospective observational multicenter study of non-dialysis CKD patients at 4 centers. DD was graded as: none (E/A ≤ 1 and absence of LVH), mild (E/A > 1 and absence of LVH), or severe (E/A > 2). LVH was defined as LV mass index ≥ 104 g/m² for males and ≥ 110 g/m² for females. Coronary calcium (CC) scores were determined by computed tomography (n=90), and arterial stiffness was determined by measuring aortic pulse wave velocity (PWV) from carotid and femoral pressure wave contours (n=129). Statistical analysis was performed using t-test or Chi square as appropriate.

Results:

DD was present in 118 out of 171 patients (69%) in whom diastolic function was determined (mild = 52%, moderate = 11%, and severe = 6%). The table compares patients with normal vs. abnormal diastolic function. DD was associated with older age, higher CC score, greater carotid intima-media thickness (CIMT), and higher PWV.

Conclusions:

DD is highly prevalent in non-dialysis CKD patients, and is associated with markers of atherosclerosis and arterial stiffness.

Normal vs. Abnormal Diastolic Function

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>n (Normal)</th>
<th>Abnormal</th>
<th>n (Abnormal)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 17</td>
<td>53</td>
<td>61 ± 17</td>
<td>112</td>
<td>0.001</td>
</tr>
<tr>
<td>% Female</td>
<td>47 %</td>
<td>25/53</td>
<td>46 %</td>
<td>52/112</td>
<td>0.929</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 %</td>
<td>10/53</td>
<td>32 %</td>
<td>37/112</td>
<td>0.059</td>
</tr>
<tr>
<td>HTN</td>
<td>22 %</td>
<td>18/82</td>
<td>35 %</td>
<td>37/112</td>
<td>0.024</td>
</tr>
<tr>
<td>EFR</td>
<td>26 ± 12</td>
<td>32 ± 11</td>
<td>25 ± 11</td>
<td>40</td>
<td>0.738</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.1 ± 1.5</td>
<td>11.9 ± 1.5</td>
<td>66</td>
<td>0.440</td>
<td></td>
</tr>
<tr>
<td>CC Score</td>
<td>166 ± 342</td>
<td>29</td>
<td>501 ± 846</td>
<td>46</td>
<td>0.020</td>
</tr>
<tr>
<td>Max CIMT (mm)</td>
<td>1.7 ± 0.69</td>
<td>34</td>
<td>1.95 ± 1.08</td>
<td>63</td>
<td>0.042</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>7.76 ± 2.71</td>
<td>44</td>
<td>8.38 ± 3.64</td>
<td>85</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Stress-induced impairment in diastolic relaxation leads to increased LVEDP reducing exercise tolerance in patients with HF and PWLV.

1017-179 Unique Features of Patients Hospitalized with Heart Failure and Truly Normal Ejection Fraction (EF)

Nancy K. Sweitzer, Clyde W. Yancy, Margarita Lopatin, Lyme W. Stevenson, University of Wisconsin, Madison, WI, Brigham and Women’s Hospital, Boston, MA

Background:

Studies of diastolic heart failure (DHF) utilize widely varying EF cutoffs (40-55%), which may result in mixing two distinct groups into one analysis and dilute treatment effects specific to particular etiologies. We hypothesized that patients (pts) with high (≥55%, highEF) vs. mildly impaired EF (40-55%, midEF) would be more often female and less often have coronary artery disease (CAD).

Methods:

Data from 105,388 hospitalized patients in the ADHERE registry as of January 2004. Of these, 74,863 had in- or prehospital assessment of EF; 17,022 were highEF and 17,045 midEF. Characteristics and outcomes of the groups were compared using Chi-square and ANOVA tests.
Results: High EF pts were more often female, slightly older and more often on Medicare than mid EF pts (Table). High EF pts had less history of HF, CAD, diabetes, and renal insufficiency. Echocardiographic failure was more often hypertensive and less often ischemic for high vs mid EF. Both groups had similar systolic BP and BUN. High EF pts had higher pulse pressure. No differences in length of stay or mortality were found.

Conclusions: High EF patients are predominantly female and hypertensive with lower CAD and more frequent mid EF pts. When designing clinical trials of DHF one must determine EF cutoff to carefully improve understanding of the pathophysiology and treatment of this important condition.

1017-174 Diastolic Dysfunction Is Accompanied With Increased Arterial Wave Reflections and Prolonged Mechanical Systole

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Background: In patients with diastolic heart failure, exercise capacity has been linked to arterial stiffness. Moreover, slowed relaxation in diastole is associated with increased arterial wave reflections and increased pulse pressure. No differences in length of stay or mortality were found.

Methods: Brain natriuretic peptide (BNP) levels were measured in patients at the time of entry into an 18-month, community-based, randomized clinical trial of heart failure (HF) disease management. The 318 patients with DD (HF signs and symptoms with ejection fraction ≤ 40%) were compared with 751 patients with SD (HF signs and symptoms and EF > 50%).

Results: DD patients were older, had less coronary disease, and were more likely to have hypertension compared with SD patients (p < 0.0001). Significant predictors of mortality in SD (after Bonferroni correction) included age (HR 1.93 per year increase), and estimated pulmonary artery (PA) pressure (1.58 per 10 mm Hg increase). The only significant predictor of mortality for DD was PA pressure (1.94 per 10 mm Hg increase). Hospitalization or death in SD increased with mild MR (HR 1.49), mild tricuspid regurgitation (HR 1.33), diastolic dimension (HR 1.28 per cm increase), left atrial dimension (HR 1.36 per cm increase), fractional shortening (HR 0.96 per % increase), LV mass index (HR 1.30 per 10 gm/m2 increase), and PA pressure (HR 1.33 per 10 mm Hg increase); while for DD, LV systolic dimension (1.58 per cm increase) and PA pressure (1.55 per 10 mm Hg increase) were significant.

Conclusions: In a community-based cohort of patients with HF, different echo features predicted survival and event-free survival in patients with SD vs DD. Estimated PA pressure appears similarly predictive of hospitalization and mortality in both SD and DD. Attempts to estimate PA pressure should be a routine step in the echo assessment of patients with heart failure, and may identify patients at particularly high risk for clinical events.
Background: Endothelial progenitor cells (EPCs) have been shown to selectively home to ischemic or inflamed tissues and may have therapeutic potential.

Methods: EPCs, obtained from peripheral blood mononuclear cells of normal, ischemic and inflamed mice up to 8 hr (average 1.32%ID/g in the normal muscle), were characterized by UEA-1 binding and Dil-AcLDL uptake and angiogenesis capability on Matrigel. Radioactivity, labeled with $^{111}$In-oxine and $^{125}$I, was routinely determined at 8 and 24 hr. Immunohistochemical (IHC) analysis for EPC markers was performed. Results are expressed as % injection dose (n=8). EPC biodistribution was evaluated in normal mice 2, 8 and 24 hr after injection; in ischemic or inflamed animals at 8 and 96 hr. Results are expressed as % injection dose (n=8). EPC biodistribution was evaluated in normal mice 2, 8 and 24 hr after injection; in ischemic or inflamed animals at 8 and 96 hr. Results are expressed as % injection dose (n=8).

Conclusions: Radioactive labelling of EPCs provides a satisfactory noninvasive imaging approach able to assess in vivo biodistribution of transplanted EPCs and a possible basis for external imaging. Non selective recruitment of EPC needs of thinking it over.

Tissue Imaging Of $^{111}$In-Oxine Labeled Human Endothelial Progenitor Cells in Muscle Ischemia and Inflammation

Rossella Di Stefano, Paola Erba, Tatiana Santoni, Chiera Armani, Maria Chiara Barsotti, Daniele Barone, Paola Collecchi, Giuliano Maroni, Alberto Balbarini, University of Pisa, Pisa, Italy

Background: Endothelial progenitor cells (EPCs) have been shown to selectively home to ischemic foci and contribute to neovascularization. Aim of this study was to evaluate $^{111}$In-oxine labeled EPCs in a murine model of ischemia or inflammation.

Methods: EPCs, obtained from in vitro culture of peripheral blood mononuclear cells, were labeled with $^{111}$In-oxine and $^{125}$I. EPCs and radiolabeled EPCs were tested for cell viability, endothelial marker expression and angiogenesis capability and injected (3.7 to 4.8 MBq) via tail vein into male Balb-c mice 72 hr after the induction of hindlimb ischemia through artery ligation (n=8), after aseptic right hindlimb ischemia or inflammation (n=8), and in normal, ischemic or inflamed muscles up to 8 hr (average 1.32 %ID/g in the normal muscle). Radiolabeled EPCs biodistribution was evaluated in normal, ischemic and inflamed mice up to 8 hr (average 1.32 %ID/g in the normal muscle).

Results: Early biodistribution (2 hr) of labeled EPCs showed high radioactivity content in the lungs, spleen, liver and bladder, followed by later increase in the kidneys, thyroid and stomach (possibly due to release of free radioactive label). Blood radioactivity peaked at 8 hr, while no radioactive accumulation was found in the bone marrow. A consistent pattern of overall tissue biodistribution was obtained in normal, ischemic and inflamed mice up to 8 hr (average 1.32 % ID/g in the normal muscle).

Conclusions: Early biodistribution of labeled EPCs in a murine model of ischemia or inflammation was comparable to that of younger patients. In conclusion, LVAD BTT in older patients is equivalent to that of younger patients. In conclusion, LVAD BTT in older patients is associated with excellent conditional post-transplant as well as graft survival.

Post-Transplant Survival Is Equivalent in Older Versus Younger Patients Bridged to Heart Transplant with Left Ventricular Assist Device Support

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BACKGROUND: Left ventricular assist device (LVAD) support has become an accepted therapy for end-stage heart failure patients. However, the prognosis for older patients who undergo LVAD BTT is unknown.

METHODS: In order to determine patient survival characteristics for older vs. younger patients who undergo LVAD BTT, a retrospective analysis was performed on our population of LVAD recipients. Older patients were defined as age greater than or equal to 60 years. Statistical analysis was performed using the Kaplan-Meier method with log rank test comparison of time-to-events between the two groups of patients. A Cox's regression model was employed in order to adjust for covariates.

RESULTS: Between May 1997 and May 2004, a total of 139 intra- and para-corporeal LVADs have been implanted at UMHS. Of these patients, 33 (24%) were 60 years or older. Between May 1997 and May 2004, a total of 139 intra- and para-corporeal LVADs have been implanted at UMHS. Of these patients, 33 (24%) were 60 years or older. Statistical analysis was performed using the Kaplan-Meier method with log rank test comparison of time-to-events between the two groups of patients. A Cox's regression model was employed in order to adjust for covariates.

CONCLUSION: LVAD survival include male sex (p=0.002), pre-LVAD need for IABP, hemodialysis, ECMO, or mechanical ventilation (p=0.02), and higher pre-LVAD heart rate (p=0.002).

A Novel Use of Optical Coherence Tomography to Distinguish Pericarditis and Its Extent from Healthy Atrium

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Sterile pericarditis (SP) after open heart surgery (OHS) provides an important substrate for initiation and maintenance of atrial fibrillation and flutter (AFL). Using Optical Coherence Tomography (OCT), which provides high resolution and cross sectional imaging of internal structures, we tested the hypothesis that conduction delay or pulse blood pressure between LVAD and non-LVAD pts, but there was a trend toward greater aortic systolic blood pressure in the LVAD group (107 ± 12 vs. 97 ± 9 mmHg, p=0.09). There was no significant difference between LVAD and non-LVAD pts in the roundtrip travel time of the aortic reflected pressure wave to periphery and back (146.2 ± 13 vs. 148.1 ± 11 ms, p=NS), but aortic systolic tension time index, an index of LV function, was higher in the LVAD group (2655 ± 298 vs. 1748 ± 303 mmHg/sec/min, p<0.01).

Conclusion: Despite normalization of cardiac output and stroke volume, pts with end-stage HF on LVAD support have increased arterial stiffness compared to patients on intravenous inotropic drugs. We believe that the LVAD-related improvement in aortic flow leads to increased reflected wave amplitude and increased LV function in the setting of HF-related peripheral arterial stiffness. This may have clinical relevance for antihypertensive management of HF pts post-LVAD placement.

Arterial Stiffness Is Increased in End-Stage Heart Failure Patients on a Left Ventricular Assist Device


Background: Chronic heart failure (HF) is associated with increased arterial stiffness leading to increased pulse wave velocity and an early return of reflected aortic pressure waves from the peripheral reflecting sites to the ascending aorta. This may contribute, in part, to increased left ventricular (LV) afterload and myocardial oxygen demand (MVO$_2$) in HF. However, the effects of left ventricular assist device (LVAD) placement on the amplitude and timing of reflected aortic pressure waves in end-stage HF patients (pts) are unknown.

Methods: High-fidelity radial artery pressure waveforms were recorded non-invasively by applanation tonometry and ascending aortic pressure waveforms were generated using a validated general transfer function (Spynormor$^{\text{TM}}$ device) in five end-stage HF pts on LVAD support (age 47 ± 9 yrs; 3 male), and in 10 HF pts on intravenous inotropic agents (age 58 ± 4 yrs; 7 male) awaiting cardiac transplant.

Results: Aortic augmented pressure and aortic augmentation index corrected for heart rate of 75 bpm, were significantly greater in LVAD compared to non-LVAD pts (9.4 ± 9 vs. 4.1 ± 3 mmHg, p=0.05; and 28.2 ± 10 vs. 7.9 ± 9%, p<0.01, respectively). There was no significant difference between LVAD and non-LVAD pts in the roundtrip travel time of the aortic reflected pressure wave to periphery and back (146.2 ± 13 vs. 148.1 ± 11 ms, p=NS), but aortic systolic tension time index, an index of LV function, was higher in the LVAD group (2655 ± 298 vs. 1748 ± 303 mmHg/sec/min, p<0.01).

Conclusion: Despite normalization of cardiac output and stroke volume, pts with end-stage HF on LVAD support have increased arterial stiffness compared to patients on intravenous inotropic drugs. We believe that the LVAD-related improvement in aortic flow leads to increased reflected wave amplitude and increased LV function in the setting of HF-related peripheral arterial stiffness. This may have clinical relevance for antihypertensive management of HF pts post-LVAD placement.
First Human use of a 16 F Axial Flow Pump (AMED) in Cardiogenic Shock and High-Risk PCI

Markus Ferranti, Gerald S. Werner, Markus Schlösser, Walid Aboudhousn, Klaus Pethig, Hans R. Fugita, Friedrich-Schiller-University, Jena, Germany, Amed Inc., Sacramento, CA

Background: Axial flow pumps with flow rates > 2 l/min. require a surgical approach to the femoral artery. But percutaneous implantation with sufficient flow rates is desirable.

Methods: The novel axial flow pump (AMED) can be implanted percutaneously creating a flow of 3.3 l/min. After advancing a 16 F sheath by Seldinger’s technique with its tip in the left ventricle the inner guiding pigtail catheter is replaced by the impeller pump. We percutaneously implanted the device in 3 patients. The left ventricular ejection fraction (LVEF) was measured before insertion of the pump. Free hemoglobin (FHB) and haptoglobin (HGB) were analyzed every 2 hours after the insertion to monitor the amount of hemolysis. A follow-up examination was performed 30 days after the procedure.

Results: The AMED pump was implanted within 14.6 min. in all 3 patients without any complication. Two patients were on inotropic support and had an IABP implanted before due to cardiogenic shock. The third patient had a left main stenosis and an occluded right coronary artery but refused cardiac surgery. All patients had severe 3 vessel disease. A PCI was performed on an average of 2.3 vessels without hemodynamic compromise during any procedure. After 1 month all patients were able to perform daily activities without angina pectoris.

Conclusions: The novel 16 F turbine pump provides sufficient circulatory support in cardiogenic shock and for high-risk PCI. The amount of hemolysis is relatively low. The device can be implanted easily within 15 minutes.

Salvage Ventricular Assistance for Patients Undergoing Cardiopulmonary Resuscitation: Long Term Results

Gi Bulos, Jaishchand Raman, Neil Thomas, Vallavan Jeevanadam, University of Chicago, Chicago, IL

Background: It is possible to transfer patients undergoing cardiopulmonary resuscitation (CPR) with closed chest compressions or open massage to the operating room (OR), place them emergently on cardiopulmonary bypass and continue with ventricular assist device as a bridge to transplant or recovery. We retrospectively reviewed short and long term results of these salvage procedures.

Methods: Between March 2000 and July 2004 eighty eight patients underwent left, right or biventricular assist device implantation in our institute. Thirteen of those patients (14.8%) had CPR at the time of the implantation. In five patients the CPR was started during the transfer to or while entering the OR, while in the other eight patients the CPR was initiated on the floor or in the ICU.

Results: Mean time of CPR was 61±31 (range: 15-120) minutes. Twelve of the 13 patients (92%) survived the operation and nine (69%) were neurologically intact. Five patients were transplanted (38%), seven patients (54%) were discharged from the ICU and four (31%) were discharged home. However, only three (23%) survived past 6 months. The common causes of death included: GI complications (31%), smoldering sepsis (31%), cardiac failure (17%), and coagulopathy with bleeding (15%).

Conclusions: A significant number of patients undergoing salvage ventricular assist device implantation survive the operation without neurological compromise. However, long term survival was low due systemic complications, related to the GI tract and persistent sepsis. Better strategies are required to protect other organs during the CPR and the assist device implantation.
Heart Rate Recovery Predicts Better Mortality Than Chronotropic Response In Patients With Chronic Heart Failure

Stavros Dimopoulos, Maria Anastasou-Nana, George Alexopoulos, Konstantinos Stamatakopoulos, Dimitrios Sakellarakis, Smaragdo Kapsimalakou, Konstantinos Kritikos, Sotiris Gytopoulos, Serafim Nanas, Charalampos Roussos, Cardiopulmonary Exercise Laboratory and Rehabilitation Center, Athens, Greece

Background: Imbalance of the autonomic nervous system is a common finding in patients with chronic heart failure (CHF) and is strongly related to their high cardiac mortality risk. However, exercise- and recovery-related chronotropic response and heart rate recovery reflect autonomic abnormalities during and after exercise, but their prognostic role in these patients hasn’t been well established yet.

Methods: Ninety-two (83M/9F) consecutive CHF patients underwent symptom-limited cardiopulmonary exercise test. We measured maximal oxygen uptake (Vo2peak, ml/kg/min), anaerobic threshold (AT,ml/kg/min) and ventilatory response to exercise (VE/VCO2 slope). Heart rate recovery (HRR) was defined as the HR difference from peak to 1 min after exercise and chronotropic response was evaluated by percentage proportion of chronotropic reserve (CR%). Peak HR-retesting HR / (220-age-retesting HR x 100). The mean follow-up period was 21±6 months and the primary end-point was cardiac mortality.

Results: Twenty-four (23M/1F) patients (26.1%) died from cardiac events during follow-up period. HR% and CR% were lower in non-survivors than in survivors (11.4±6.4 vs 20.6±8.1; p<0.001 and 32.9±21.5 vs 70.2±18.2; p<0.001, respectively). Both HRR and % CR as continuous variables were univariate predictors of mortality (OR:0.871; 95%CI:0.82-0.93; p<0.001 and OR:0.97; 95%CI:0.95-0.98; p<0.001, respectively). In a Cox regression multivariate survival analysis, including HRR and % CR as continuous variables were univariate predictors of mortality (OR:0.87; 95%CI:0.82-0.93; p<0.001). Conclusions: In patients with chronic heart failure, both chronotropic response and heart rate recovery are related to a higher cardiac mortality risk, but only heart rate recovery is an independent prognostic risk factor in CHF patients and may play an important role in their risk stratification.

Prognostic Value of Exercise Versus Recovery Electrocardiographic Analysis

Riccardo Bigi, Laura Cornigliano, Davide Gregori, Benedetta Chiara, Cesare Fiorentini, University Medical School and A.DeGasperi Foundation, Milan, Italy

Background. Heart rate-adjusted ST-segment depression (ST/HR) analysis improves diagnostic accuracy of exercise testing, but its prognostic value has not been evaluated in unselected populations. We prospectively used comparative exercise-recovery ST/HR analysis to predict outcome in a consecutive cohort of outpatients referred for exercise testing.

Methods. Stress-Recovery Index (SRI), defined as the difference between ST/HR areas during exercise and recovery was derived in 1,163 subjects, median age 60 (interquartile range 54 to 65) years. All-cause mortality and the combination of death or non-fatal myocardial infarction were target end-points. The individual effect of clinical and exercise testing data on outcome was evaluated by Cox’s regression analysis using separate models for each group of variables. Model validation was performed by bootstrap adjusted by the degree of optimism in estimates. Survival analysis was performed using product-limit Kaplow-Meier method.

Results. During 33-month follow-up 48 deaths and 72 non-fatal myocardial infarctions occurred. After adjusting for confounding variables, hypertension (hazard ratio 1.8, 95% confidence interval [CI] 1.26-2.59), ST/HR index (hazard ratio 1.32, 95%CI 1.04-1.66 for interquartile difference in kilopounds per minute), and SRI (hazard ratio 0.79, 95% CI 0.65-0.86 for interquartile difference) were predictive of death or non-fatal myocardial infarction, whilst hypertension (hazard ratio 3.67, 95% CI 2.00-6.73) and SRI (hazard ratio 0.55, 95% CI 0.48-0.63 for interquartile difference) were predictive of all-cause mortality. SRI increased the prognostic power of the model on top of clinical and exercise testing variables and provided significant discrimination of survival.

Conclusions. Exercise-recovery ST/HR analysis improves the prognostic capacity of standard exercise electrocardiography.

Early Heart Rate Recovery Kinetics is Related To Exercise Capacity, Ventilatory Response And Resting Hemodynamic Measurements In CHF Patients

Stavros Dimopoulos, Maria Anastasou-Nana, Dimitrios Sakellarakis, Smaragdo Kapsimalakou, Petros Roditis, Konstantinos Kritikos, Christina Mpatziou, George Maroulidis, Konstantinos Stamatakopoulos, Serafim Nanas, Charalampos Roussos, Kapodestrian University of Athens, Athens, Greece

Background: Patients with chronic heart failure (CHF) seem to present a delayed heart rate decline during recovery period immediately after peak exercise reflecting a withdrawal of parasympathetic activity. However, early recovery heart rate kinetincs in CHF patients hasn’t been thoroughly studied in relation to exercise capacity, ventilatory response to exercise and hemodynamic measurements at rest.

Methods and Materials: Ninety-two (83M/9F) consecutive CHF patients underwent symptom-limited cardiopulmonary exercise test, right catherization and radionucleide ventriculography. We measured maximal oxygen uptake (Vo2peak,ml/kg/min), anaerobic threshold (AT,ml/kg/min), ventilatory response to exercise (VE/VCO2 slope), left ventricular ejection fraction [LVEF (%)] and pulmonary capillary wedge pressure (PCWP,mmHg). Early heart-rate recovery (HRR) kinetics was evaluated by HR difference from peak to 1 min after exercise, considered “abnormal” if 12 or less, and by the first degree slope of HR for the 1st min of recovery period (HR1slope,b/min), calculated by a linear regression model using an appropriate computerized statistical program.

Results: Patients with “abnormal” HR1slope (<12b/min) presented a lower Vo2peak (14.9±3.9 vs 20.3±8.6; p<0.001), AT (11.2±2.9 vs 14.6±3.7; p<0.001), a higher VE/VCO2 slope (34.6±7.8 vs 29.1±5.3; p<0.001), a lower UEF (24.9±11.3 vs 32.9±11.4; p<0.002), a higher PCWP (19.3±9.9 vs 11.5±5.9; p<0.001) and a lower HR1slope (12.3±5.7 vs 26.2±6.9; p<0.001) than patients with “normal” HR1slope (>12b/min). HR was correlated with Vo2peak (r=-0.47; p<0.01), AT (r=-0.45; p<0.01), VE/VCO2 slope (r=-0.4; p<0.01), UEF (r=-0.37; p<0.01) and PCWP (r=-0.45; p<0.01). There was also a strong positive correlation between HR and HR1slope (r=0.79; p<0.01).

Conclusions: Early heart-rate recovery kinetics was delayed in CHF patients with an impaired exercise capacity and ventilatory response, as well as with severe hemodynamic measurements. These findings suggest that HR and HR1slope expressing early heart rate recovery kinetics are related to functional status of CHF patients and may be used in their global clinical assessment.
Myocardial Function and Heart Failure: Basic and Molecular I

Sunday, March 06, 2005, 1:30 p.m.-5:00 p.m.
Orange County Convention Center, Hall E1
Presentation Hour: 1:30 p.m.-2:30 p.m.

Tissue Inhibitor of Matrix Metalloproteinase-3 (TIMP-3) Cell-Based Gene Delivery After Myocardial Infarction Preserves Heart Function

Denis Angoulvant, Shafie Fazel, Richard D. Weisel, Paul W. Fedak, Amy P. Wong, Shahin Rafati, Charit K. Seneviratne, Liwen Chen, Rama Khokha, Ren-Ke Li, Toronto General Hospital, Toronto, ON, Canada, Ontario Cancer Institute, Toronto, ON, Canada

Background: We have recently reported that knock out mice lacking Tissue Inhibitor of Matrix Metalloproteinase (TIMP-3) serve as a model of dilated cardiomyopathy. We hypothesized that cell based gene therapy designed to restore regional TIMP-3 expression in TIMP-3-/- mice would prevent progression to overt heart failure following myocardial infarction (MI).

Methods: Bone marrow cells (BMC) from C57BL/6 mice were harvested and expanded before being transfected with murine TIMP-3 cDNA. Quantity and activity of TIMP-3 transfected (BMC T3+) and untransfected (WT BMC) BMC were evaluated by Western blot and reverse zymography. BMC T3+ were injected in the anterior wall of TIMP-3-/- BL/6 mice hearts immediately after coronary ligation. WT BMC or media injections served as controls. Heart function was assessed by echocardiography calculating fractional shortening (FS) at baseline, day 3, 7 and 28 after MI. Biochemical, morphometry, and activity of TIMP-3 transfected (BMC T3+) and untransfected (WT BMC) BMC were evaluated by Western blot and reverse zymography. BMC T3+ were injected in the anterior wall of TIMP-3-/- BL/6 mice hearts immediately after coronary ligation. WT BMC or media injections served as controls. Heart function was assessed by echocardiography calculating fractional shortening (FS) at baseline, day 3, 7 and 28 after MI.

Results: Western blot showed a significant 53% increase in TIMP-3 expression after BMC transfection. Gelatine zymography showed a lower activity of matrix metalloproteinases (MMP)-9 and MMP-2 in the BMC T3+ mice hearts at day 3 after a bounce effect at day 7. Tunnel staining at day 7 showed less apoptosis in the border zone of BMC T3+ and WT BMC mice compared to medium. At day 3, BMC T3+ mice, compared to WT BMC and Medium, showed significant preservation in systolic function (FS 29.4±6.1 vs 22.8±6.3, 19.1±2.5%, all P<0.05). FS at day 28 was close to baseline for BMC T3+ mice (38.1±6 vs 38.9±2%), non significantly lower for WT BMC mice (32.5±4%) and significantly altered for medium mice (17.1±1%, P<0.05). Morphometry analysis at day 28 showed significantly smaller left ventricle volume (2.4 and 2.1 vs 6.3 m/kg) and % of scar area (10.4 and 10.7 vs 37.1%) in BMC T3+ and WT BMC mice compared to medium (all P<0.05). Conclusion: These data suggest an intricate dose- and time-dependant effect of TIMP-3 over expression in modulating post MI cardiac remodeling and systolic function. The results highlight the efficacy and the synergistic benefit of cell-based gene therapy for prevention of heart failure after MI.

Delayed Regional Activation After MI Increases Borderzone Work

Lanli M. Parish, Hiroaki Sakamoto, Benjamin M. Jackson, Bradley Leshnower, Ahmad Zeehan, Joseph H. Gorman, III, Robert C. Gorman, University of Pennsylvania School of Medicine, Philadelphia, PA

Background: After infarction, increased strain in the normally-perfused borderzone (BZ) contributes to adverse remodeling. We hypothesized that increased BZ strain after infarction is caused by delayed initiation of BZ and WT BMC mice compared to medium (all P<0.05). Morphometry analysis at day 28 showed significantly smaller left ventricle volume (2.4 and 2.1 vs 6.3 m/kg) and % of scar area (10.4 and 10.7 vs 37.1%) in BMC T3+ and WT BMC mice compared to medium (all P<0.05). Conclusion: These data suggest an intricate dose- and time-dependant effect of TIMP-3 over expression in modulating post MI cardiac remodeling and systolic function. The results highlight the efficacy and the synergistic benefit of cell-based gene therapy for prevention of heart failure after MI.

Safety and Feasibility of Endocardial Autologous Skeletal Myoblast Transplantation in a Porcine Model of Myocardial Infarction

Nabil Daj, Ann Campbell, Thomas Mattioni, Vijendra Swarup, Amir Gahremanpour, Brigitte Meizybrockki, Alice Dayouz, Shaun Opie, Noreen Goodwin, Edward Diethrich, Arizona Heart Institute, Phoenix, AZ

Background: Cell therapy is a promising new treatment for myocardial infarction (MI). Although direct epicardial cell injection has been successful, a less invasive approach is preferred. Methods: Six swines underwent a randomized, controlled study. A skeletal muscle biopsy was excised from the hind limb of each animal and myoblasts were expanded. MI was induced by coil deployment in the left anterior descending artery. An implantable loop recorder was placed to continuously monitor the heart rhythm and intragated 29 times. One month after MI, cells or medium were delivered to the infarcted myocardium by endocardial injection using the Biosense system. Swines were separated into control, low and high dose treatment groups (Table). Echocardiography, left ventriculography and NOGA mapping were done at baseline, transplant and harvest. Results: All animals survived after transplantation and there were no complications related to the procedures. No arrhythmias were detected post-transplant. Two months after cell delivery, the unipolar voltage of the transplanted zone improved by 27.5% (p<0.04) in the treated group and deteriorated by 6.5% (p>NS) in the control group. There was a trend toward improvement in EF by echocardiography from 45.5% to 52.5% in the treated group and a deterioration from 48.5% to 43.5% in the control group. Conclusion: Endocardial cell delivery is feasible and safe. There was a trend toward improvement in heart function and voltage.
Biodistribution and Bioretention of Autologous Skeletal Myoblast After Percutaneous Transplantation in a Coll-injected Swine Myocardium Using The Biosens® System

Nabel Oha, Amr Campbell, Amir Gahremanpour, Shaun Opie, Brigitte Medzynbskki, Alice Daphnis, Edward Jehle, Jonathan J. Dimsom, Phoenix, AZ
Background: Epicardial cell transplantation is feasible and safe. Bioretention and biodistribution of stem cells by endocardial delivery is not known. We evaluated the bioretention and biodistribution of iridium-labeled autologous skeletal myoblast (ASMB) following percutaneous delivery to a swine model of myocardial infarction.

Methods: An apical myocardial infarction was created by percutaneous coil deployment into the anterior descending artery. Skeletal muscle biopsy was taken from the hind limb of the animal to isolate and expand myoblast. Forty million myoblasts were mixed with 13.4 x 10^11 iridium particles and incubated for 2.5 hrs at 37 °C. Unabsorbed particles were removed by centrifugation. The remaining cells (6 x 10^8 viable cells) were mixed with unlabelled cells to form the final product (79 x 10^6 viable cells/ml, 23 x 10^9 total cells, 59.6% viability). One month after infarction, the iridium-labeled ASM were transplanted into the infarcted zone via endocardial delivery using NOGA mapping and the Biosense injection catheter. After 2 hours the animal was sacrificed, samples from the heart, brain, kidneys, liver, lungs and spleen were analyzed for the presence of iridium particles. The samples were exposed to high-energy neutrons allowing the iridium atoms in the cells to capture incident neutrons. Then the samples were placed in a high-resolution gamma-detection system to detect [101x262]mRNA (du) 20 ± 2 73 ± 1* 45 ± 1**

Results: All pigs developed chronic severe MR. At sacrifice, LVEF increased with SERCA2a versus controls (60 ± 8 vs 41 ± 10 %, p=0.02); there was no change in LVED (48 ± 8 vs 46 ± 10 mm, p=n.s) or LVES (26 ± 6 vs 36 ± 11 mm, p=n.s). With SERCA2a, peak systolic tissue velocity (TV), peak strain (S), and peak strain rate (SR) improved in the anterior wall; in the inferior wall, only TV and SR increased with SERCA2a.

Conclusions: Percutaneous adenoviral gene transfer of SERCA2a resulted in improved global and regional LV systolic function parameter in a porcine model of chronic heart failure with a greater regional effect in the anterior wall.

Anterior Wall

<table>
<thead>
<tr>
<th>Time to peak velocity (cm/s)</th>
<th>SERCA2a</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.18 ± 0.30</td>
<td>2.75 ± 1.48</td>
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<table>
<thead>
<tr>
<th>Time to peak strain (%)</th>
<th>SERCA2a</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>7.12 ± 4.66</td>
<td>28.15 ± 14.17</td>
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<tr>
<th>Time to peak strain (s)</th>
<th>SERCA2a</th>
<th>p value</th>
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<tr>
<td>0.29 ± 0.05</td>
<td>0.25 ± 0.06</td>
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<th>Peak strain rate (1/0)</th>
<th>SERCA2a</th>
<th>p value</th>
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<tr>
<td>0.57 ± 0.49</td>
<td>1.61 ± 0.59</td>
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<th>Peak strain rate (s)</th>
<th>SERCA2a</th>
<th>p value</th>
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<tr>
<td>0.15 ± 0.01</td>
<td>0.09 ± 0.04</td>
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Inferior Wall

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<th>Peak tissue velocity (cm/s)</th>
<th>SERCA2a</th>
<th>p value</th>
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<td>2.49 ± 0.29</td>
<td>4.34 ± 4.46</td>
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<th>Time to peak velocity</th>
<th>SERCA2a</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12 ± 0.05</td>
<td>0.05 ± 0.05</td>
<td>0.02</td>
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<table>
<thead>
<tr>
<th>Peak strain</th>
<th>SERCA2a</th>
<th>p value</th>
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<tbody>
<tr>
<td>1.65 ± 0.50</td>
<td>40.28 ± 11.72</td>
<td>0.01</td>
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<tr>
<th>Time to peak strain (s)</th>
<th>SERCA2a</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.06 ± 0.28</td>
<td>28 ± 0.06</td>
<td>0.56</td>
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<tr>
<th>Peak strain rate</th>
<th>SERCA2a</th>
<th>p value</th>
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<tbody>
<tr>
<td>1.44 ± 0.76</td>
<td>2.27 ± 0.72</td>
<td>0.09</td>
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<table>
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<tr>
<th>Time to peak strain (s)</th>
<th>SERCA2a</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>0.11 ± 0.05</td>
<td>0.07 ± 0.08</td>
<td>0.42</td>
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1047-1150 Role Of MCP-3 As A Mesenchymal Stem Cell Homing Factor For Myocardial Regeneration

Soren Schenk, Ming Zhang, Nidali Mal, Zoran Popovic, Reiner Koerfer, Matthew Kiedrowski, Patrick McCarthy, Marc S. Peng, Cleveland Clinic Foundation, Cleveland, OH

Increased engraftment of mesenchymal stem cells (MSC) has been shown to improve cardiac function in acute MI. We hypothesized that sustained expression of a MSC homing factor could allow for serial infusions of MSC in order to increase cardiac function in ischemic cardiomyopathy (ICM). However, to date, no MSC homing factor has been identified. MSC do home transiently to the freshly infarcted myocardium. In order to identify a MSC homing factor, we determined the expression profile of an array of chemokines as a function of time after MI. We merged this database with an array of chemokine receptors that are expressed at least 10 fold greater on MSC compared to cardiac fibroblasts (CF). Chemokine receptor expression significantly greater in MSC than CF were considered to be potentially involved in MSC homing since MSC do home infarcted myocardium, and CF do not. This analysis revealed CCR1, CCR2 and CCR5 as potential receptors involved in MSC homing, and MCP-1, MCP-3, MIP-1α and MIP-1β as potential MSC homing factors. We made CF that were stably transfected with an MCP-3 expression vector. To determine if MCP-3 can served as an MSC homing factor, 1 million control or MCP-3 expressing CF were transplanted into the infarct border zone 2 months after MI. Three days later 4 million BrdU labeled MSC were infused via the tail vein. Three days later, we observed a greater number of MSC in the infarct zone of those animals that received MCP-3 expressing CF compared to control (18.6 ± 4.7 vs. 7.4 ± 3.0 MSC/mm², n=4 per group, p<0.05). We then studies animals 2 months post-MI and 1 week post injection of control or MCP-3 expressing CF. The animals received 6 intravenous infusions over 14 days of 1 million MSC per infusion. In those animals that received MCP-3 expression CF, we observed a significant increase in shortening fraction 4 weeks later in those animals that received MCP-3 expressing CF (10.0 ± 1.5% vs. 16.6 ± 3.2%, p=0.005). However, we did not see this same trend in those animals that received control CF. These data indicate that MCP-3 may be an MSC homing factor, and that transplantation of MCP-3 expressing cells may serve as a strategy to optimize MSC engraftment in CHF.

1048 Natriuretic Peptides

Sunday, March 06, 2005, 1:30 p.m.-5:00 p.m.
Orange County Convention Center, Hall E1
Presentation Hour: 1:30 p.m.-2:30 p.m.

1048-105 Effects of Human Atrial Natriuretic Peptide on Myocardial Performance and Energetics in Patients With Heart Failure Due to Previous Myocardial Infarction

Tori Otsuka, Jyunie Shilla, Toshiba Shinke, Satoshi Watanabe, Hirotsune Otake, Daiiuke Matsumoto, Mitsuo Yokoyama, Cardiovascular and Respiratory Medicine, Kobe University Graduate School of Medical Science, Kobe, Japan

Background: Human atrial natriuretic peptide (hANP) and nitric oxide (NO) share cyclic guanosine monophosphate (cGMP) as a second messenger and modulate myocardial performance. We examined the effects of hANP on left ventricular (LV) myocardial energetics and myocardial contractility compared to NO donor, sodium nitroprusside (SNP) in patients with heart failure (HF).

Methods: Eight patients with HF due to previous myocardial infarction (MI) (LV ejection fraction; 40±2%) were instrumented with conduitance and coronary sinus thermodilution catheters for CO (E), coronary arterial and collateral parameters in conditions of end-systolic pressure-volume relation, time constant of LV pressure decay (Tau) and mechanical efficiency (the ratio of LV stroke work (SW) to myocardial oxygen consumption (SW/MVO2)) were measured in response to the intravenous infusion of hANP (0.05 µg/kg/min) and SNP (0.3µg/kg/min). In patients with heart failure (HF).

Results: Compared to SNP, hANP did not alter coronary CO or coronary flow reserve. Coronary arterial and collateral responses to hANP were similar to SNP.

Conclusion: hANP had no effect on myocardial effector function (CO and dP/dt) or myocardial energetics (SW and MVO2) compared to SNP in patients with HF.
Cardiac Function and Heart Failure

**Results:** The infusion of SNP did not change E\textsubscript{a}, Tau, SW nor MVO\textsubscript{2} resulting in unchanged SW/MVO\textsubscript{2}. Whereas, the infusion of HANP increased E\textsubscript{a} shortened Tau and decreased MVO\textsubscript{2} with preserved SW, resulting in increased SW/MVO\textsubscript{2}. Plasma levels of cGMP elevated after infusion of HANP, whereas they did not change after infusion of SNP.

**Conclusion:** HANP enhances LV contractility and relaxation as well as improves myocardial efficiency in patients with HF due to previous MI. HANP-dependent elevation of cGMP may ameliorate myocardial isocytosis, lusitropy and energetics in HF.

*P<0.05 versus control, #P<0.05 versus SNP

**Operating Characteristics for NT-proBNP**

<table>
<thead>
<tr>
<th>Threshold (pg/mL)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>81 pg/mL (75)</td>
<td>91</td>
<td>18</td>
</tr>
<tr>
<td>126 pg/mL (90)</td>
<td>93</td>
<td>84</td>
</tr>
<tr>
<td>198 pg/mL (95)</td>
<td>97</td>
<td>68</td>
</tr>
<tr>
<td>368 pg/mL (97.5)</td>
<td>99</td>
<td>67</td>
</tr>
<tr>
<td>881 pg/mL (99)</td>
<td>98</td>
<td>68</td>
</tr>
</tbody>
</table>

**Using Changes in B-Type Natriuretic Peptide Levels Between Hospital Admission and Discharge to Predict Mortality of Patients with Heart Failure**

Thom G. Dahle, Leslie W. Miller, University of Minnesota, Minneapolis, MN

**Background:** When determining the appropriate time for discharge of patients with heart failure, physicians rely on improvement of clinical exam and symptoms. This study was designed to determine whether change in B-type natriuretic peptide (BNP) levels from admission to discharge of heart failure patients may be used as a predictor for death or re-admission and thus a guide for discharge.

**Methods:** BNP levels were measured at the time of admission and discharge of patients admitted with decompensated heart failure. Patients were followed for up to one year for death or re-admission.

**Results:** Of the 46 patients who completed the study, 14 patients died during the follow up period and 22 patients were readmitted. Proportional hazard regression analysis revealed statistically significant increased risk of death associated with increased percentage change in BNP (hazard ratio [HR] = 1.13 [95% confidence interval (CI) 1.03 to 1.22], p = 0.006), increased absolute change in BNP (HR = 1.08 [95% CI 1.02 to 1.15], p = 0.009) and increased discharge BNP level (HR = 1.05 [95% CI 1.01 to 1.09], p = 0.007). There was no significant association with readmission. The percent change of BNP (figure 1) and the discharge BNP were the strongest predictors for mortality of the variables.

**Conclusion:** The percentage and absolute change in BNP levels from admission to discharge as well as the discharge BNP level may be used as reliable markers to identify patients with heart failure who are at higher risk for mortality following discharge.

**Echocardiographic Determinants of NT-proBNP Levels in Dyspneic Patients: the Importance of Right Heart Structure and Function. Results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Echocardiographic Substudy**

Anabel A. Chen, Malissa Wood, Roderick Tung, Daniel G. Krauser, Aaron L. Baggish, Saif Awanuddin, James L. Januzzi, Massachusetts General Hospital, Boston, MA

**Background:** N-terminal pro-B-natriuretic peptide (NT-proBNP) levels may be elevated in patients with right ventricular (RV) dysfunction; the relative importance of RV structure and function on NT-proBNP levels is not known.

**Methods:** NT-proBNP (Elecys<sup>®</sup> proBNP Roche Diagnostics, Indianapolis, IN) was measured in 599 dyspneic patients. Transthoracic echocardiography (echo) was performed as standard of care in 134 patients an average of 51 ± 42 hours after enrollment. Congestive heart failure (CHF) was the final diagnosis in 66%. Echo measurements, including cardiac chamber size/function and cardiac valve function, were obtained by observers blinded to NT-proBNP level and clinical diagnosis. Associations between NT-proBNP and echo parameters were assessed with Spearman correlation.

**Results:** Comparisons between groups were performed using nonparametric testing. Multivariable linear regression analysis identified independent predictors of NT-proBNP levels.

**Results:** The average RV fractional area change was 40±10%. Twenty-seven patients had RV hypokinesis. Tricuspid regurgitation (TR) was absent or trace (n = 66), mild (n = 26), moderate (n = 26) or severe (n = 10). Average TR velocity for all patients was 2.9±0.5 m/s. Several right heart factors correlated with NT-proBNP levels, including RV hypokinesis (p<0.004), TR severity (p<0.001) and TR velocity (RV 0.460, p<0.001).

While RV size did not significantly correlate with NT-proBNP levels, RV fractional area change was inversely related (RV = 0.169, p=0.06). In multivariate analysis including echo parameters, RV hypokinesis (p<0.006), TR severity (p<0.001) and TR velocity (p=0.007) all remained independent predictors of NT-proBNP levels.

**Conclusion:** RV abnormalities are highly prevalent in dyspneic patients with elevated NT-proBNP levels. Right heart structure and function are important independent determinants of NT-proBNP levels.
NT-proBNP is Superior to BNP for the Evaluation of Patients with Dyspnea and non-Systolic Congestive Heart Failure: A ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Substudy

Michelle D’Onofrio, Annabel Chen, Aaron Bagghis, Saffi Anwaruddin, Daniel G. Krauser, Rodger Woods, James L. Januzzi, Massachusetts General Hospital, Boston, MA

Background: Congestive heart failure (CHF) with preserved left ventricular ejection fraction is common. The performance of N-terminal pro-brain natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) in the presence or absence of impaired left ventricular ejection fraction has not been compared. We used the data from the ProBNP Investigation of Dyspnea in the Emergency Department study to determine the relationship between NT-proBNP, BNP and left ventricular ejection fraction in subjects with acute CHF.

Methods: Of 209 study subjects diagnosed with acute CHF, 153 (73%) had left ventricular ejection fraction data. These subjects were subdivided into those with non-systolic CHF (NS-CHF, EF=50%), and those with systolic CHF (S-CHF, EF<50%). Median NT-proBNP (Eleycsy® ProBNP, Roche Diagnostics, Indianapolis, IN) and BNP (Advia BNP, Bayer Inc., Tarrytown, NY) levels for both categories were compared utilizing non-parametric testing. The relationship between left ventricular ejection fraction and natriuretic peptide levels was analyzed using multivariable linear regression analysis.

Results: 49.7% of the 209 total study subjects had NS-CHF. Median NT-proBNP and BNP levels were significantly lower in subjects with NS-CHF compared to those with S-CHF (p <0.005). There was a significant inverse relationship between NT-proBNP, BNP, and left ventricular ejection fraction in subjects with acute CHF.

Conclusion: NT-proBNP remains a useful marker for patients with heart failure (CHF) with preserved left ventricular ejection fraction.
persistent left ventricular filling pattern at Doppler-echocardiography (rest) and with the lack of improvement in clinical signs (clin) from BSL to DS.

Results: BSL, median NT-proBNP levels, median (25th - 75th percentiles), were 5843 (1724-12440) pg/mL in the 45 pts with acute worsening of chronic HF; 2514 (1276-3989) pg/mL in 7 pts with pulmonary edema and 274 (254-380) pg/mL, (p<0.001 versus the others) in 3 pts with non cardiac (pulmonary) causes of dyspnea. Nine pts (16%) died during the initial hospitalization (hosp), 2 after discharge, 13 other pts (24%) had another HF hosp.

Time course of NT-proBNP (median, 25th-75th percentiles)

<table>
<thead>
<tr>
<th>BMI (kg/m2)</th>
<th>No events</th>
<th>12 hs</th>
<th>24 hs</th>
<th>48 hs</th>
<th>Discharge</th>
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<tr>
<td>&lt;30</td>
<td>5843 (1724-12440)</td>
<td>5843 (1724-12440)</td>
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</tr>
<tr>
<td>30-35</td>
<td>2514 (1276-3989)</td>
<td>2514 (1276-3989)</td>
<td>2514 (1276-3989)</td>
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<tr>
<td>&gt;35</td>
<td>274 (254-380)</td>
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Amongst the 24 pts with death or hosp, 17 (71%) had a BSL NT-proBNP > 5000 pg/mL and 13 (54%) had a DS NT-proBNP > 3000 pg/mL (median values of all pts). Similarly, 19 pts had restra only 9 (38%) had lack of clin. The negative predictive values of BSL NT-proBNP <5000, DS NT-proBNP <3000, no restra and clin were 75%, 79%, 79% and 63%, respectively.

Conclusions: NT-proBNP plasma levels decline < 48 hs. after treatment of acute HF and they are powerful predictors of major events.

**1048-176**

**Amino-Terminal pro-B-type Natriuretic Peptide and B-Type Natriuretic Peptide: Determinants and Detection of Systolic Dysfunction in the Community**

Lisa C. Costello-Boerrigter, Margaret M. Redfield, Richard J. Rodenhiser, Lynn H. Urban, Douglas W. Mahoney, Steven J. Jacobsen, Guido Boerrigter, Denise M. Heublein, John C. Burnett, Jr., Mayo Clinic and Mayo College of Medicine, Rochester, MN

**Background:** Amino-terminal pro-BNP (NT-proBNP), a BNP prohormone fragment, is a new heart failure biomarker that complements the use of BNP as a diagnostic tool. We hypothesized that NT-proBNP would have equal or superior diagnostic characteristics compared to BNP in the detection of left ventricular systolic dysfunction in a large community sample. We also evaluated the impact of factors such as gender, age, and renal function on NT-proBNP levels in normal subjects.

**Methods:** A random Olmsted County, MN sample (n=2042; age 44) was clinically characterized and underwent detailed echocardiography as previously reported. Plasma NT-proBNP was measured with the Elecsys® proBNP sandwich immunoassay (Roche Diagnostics). BNP was measured by immunoassay (Bisocite) as reported. The ability of BNP and NT-proBNP to detect subjects with an EF<40% and an EF<50% was determined by receiver operator characteristic (ROC) curves. Areas under the curves (AUC) were compared for the two assays. The influence of age, gender, creatinine (Cr), and calculated glomerular filtration rate (GFR) was assessed by linear least-squares regression analysis with log-transformed NT-proBNP values.

**Results:** 1989 subjects had both assays performed, of whom 37 had an EF<40% and 115 had an EF<50%. For detecting an EF<40%, NT-proBNP had a significantly higher AUC than BNP overall (0.94 vs. 0.89; p=0.01), in males (p=0.02), and in subjects<65 years (p=0.04). For detecting an EF<50%, the AUC for NT-proBNP was significantly higher than that for BNP in all subjects (0.78 vs. 0.72; p<0.001), subjects<65 years (p=0.001), males (p=0.001), males<65 years (p=0.002), and females<65 years (p=0.03). On multivariate analysis in a clinically normal subgroup (n=746), gender and age were strongly and positively associated with NT-proBNP. After accounting for age and gender, no independent correlation with Cr or calculated GFR existed in this population.

**Conclusions:** We report here that in a large community sample NT-proBNP is affected by gender and age, as is seen with BNP. Most importantly, NT-proBNP outperforms BNP in the detection of reduced left ventricular systolic function.

**1048-177**

**Body Mass Index Is Inversely Related to Both Amino-Terminal Pro-Brain Natriuretic Peptide and B-Type Natriuretic Peptide in Acute Congestive Heart Failure: A ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Substudy**

Daniel G. Krauser, Donald M. Lloyds-Jones, Claudia U. Chae, Renee Cameron, Saff Anwaruddin, Aaron L. Bagghis, Annabel Chen, Roderick Tung, James L. Januzzi, Jr., Massachusetts General Hospital, Boston, MA

**Background:** Obesity is associated with lower B-type natriuretic peptide (BNP) levels in healthy individuals. Whether obesity affects natriuretic peptide levels among patients with acute congestive heart failure (CHF) is not known.

**Methods:** The associations of amino-terminal pro-BNP (NT-proBNP) and BNP with body mass index (BMI) were examined in 204 subjects with acute CHF. Multivariable regression analyses were performed to identify factors independently related to NT-proBNP and BNP levels.

**Results:** Across clinical strata of normal (<25 kg/m²), overweight (25-29.9 kg/m²), and obese (>30 kg/m²) patients, median NT-proBNP and BNP levels decreased with increasing BMI (p<0.001). In multivariable analyses adjusting for covariates known to affect B-type natriuretic peptide levels, the inverse relationship between BMI and both NT-proBNP and BNP remained (p<0.05). Using a cut-point of 900 pg/mL, NT-proBNP was falsely negative in up to 10% of CHF cases in overweight patients and 15% in obese patients. Using the standard cut-point of 10 pg/mL, BNP testing was falsely negative in 20% of CHF cases in both overweight and obese patients. NT-proBNP and BNP exhibited similar overall sensitivity for the diagnosis of CHF.

**Conclusions:** When adjusted for covariates, compared to lean counterparts, overweight and obese patients with acute CHF have lower NT-proBNP and BNP levels, suggesting a BMI-related defect in natriuretic peptide secretion. When used as a diagnostic tool both marks may have reduced sensitivity.
Using B-Type Natriuretic Peptide to Diagnose Heart Failure in Obese Patients

Lori B Daniels, Paul Clifton, Albert Chu, James McCord, Judd E. Hollander, Philippe Duc, Torgeorn Omland, Alan B. Sorrow, Alan H.B. Wu, Gabriel Steg, Arne Westheim, Catherine Wold Knudsen, Howard C. Herrmann, Peter A. McCullough, Alan S. Maisel, University of California at San Diego Medical Center, San Diego, CA, Veteran’s Affairs San Diego Healthcare System, La Jolla, CA

Background: B-type natriuretic peptide (BNP) is valuable in the diagnosis of heart failure (HF), but its utility in obese patients is unknown. Studies have suggested a cut-off point of BNP > 100 pg/mL for the diagnosis of HF; however there is an inverse relation between BNP levels and body mass index (BMI). This study sought to determine whether the optimal cut-point for BNP in diagnosing acute HF changes with BMI, and if so to develop an algorithm to improve diagnosis.

Methods: The Breathing Not Properly Multinational Study was a 7-center, prospective study of 1,586 patients who presented to the Emergency Department with acute dyspnea and had BNP measured on arrival. Data on height and weight were available for 1,368 participants. The final diagnosis, which was adjudicated by 2 cardiologists who reviewed all clinical data and were blinded to BNP results, was HF in 631 patients (46.1%).

Results: Mean BNP levels (pg/mL) in lean, overweight/obese, and severely/obesity obese patients were 643, 462, and 247 for those with acute HF, and 52, 35, and 25 in those without HF, respectively (p<0.05 for all comparisons except 35 and 25). The optimal cut-point to maintain 90% sensitivity for the diagnosis of CHF in each BMI group is shown in the Figure.

Conclusion: BMI influences the optimal cut-point for BNP in diagnosing acute heart failure such that a lower cut-point (BNP > 54 pg/mL) should be used in severely obese patients. A higher cut-point in lean patients (BNP > 170 pg/mL) could be used if increased specificity was needed.

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1048-180

organ-specific (O-s) autoantibodies in 37 IRAP patients, 22 male, aged 38±16 years. All patients had typical chest pain with or without a pericardial friction rub, abnormal electrocardiogram, pericardial effusion, normal biventricular function and no regional wall motion echocardiographic abnormalities, normal myocytolytic enzymes. AHA were detected by indirect immunofluorescence on human myocardium and skeletal muscle. AHA control groups included patients with non-inflammatory cardiac disease (NICD) (n=160), with ischemic heart failure (n=141) and normals (n=278). Other O-s autoantibodies, including anti-thyroid, gastric parietal cell, islet cell, adrenal cell, were tested by indirect immunofluorescence. Non-O autoantibodies, e.g. anti-nuclear (ANA) and anti-mitochondrial autoantibodies were detected by indirect immunofluorescence on rat liver and kidney, anti-Ro/SSA, anti-La/SSB by ELISA (Inova Dgn, USA). AHA were detected by indirect immunofluorescence included 200 normals. Frequencies of autoantibodies in IRAP vs controls were compared by ANOVA.

Results. AHA were found in 22 (59%) IRAP patients (cross-reactive-1 in 46%, cross-reactive-2 in 18% and O-s in 5%). The frequency of cross-reactive-1 AHA was higher (p=0.001) in IRAP than in NICD (4%), ischemic (1%) and normal subjects (3%)(p=0.001). Conversely, the frequency of cross-reactive-2 and O-s AHA were similar in IRAP (8%; 5%), in NICD (3%; 1%), IHD (6%; 1%) and normals (3%; 2.5%) respectively (p<0.05). Other O-s antibodies were all negative, but 2 (5%) parietal cell antibody positive patients. IRAP patients and controls were negative for anti-mitochondrial autoantibodies; ANA frequency tended to be higher in IRAP (16%) vs normals (7.5%, p=0.08). Anti-Ro/SSA autoantibodies were positive in 2 IRAP patients (5%), anti-La/SSB were positive in 1 (2.5%). Overall 27% (87) IRAP patients were positive for O-s autoantibodies (cross-reactive-1 or O-s).

Conclusion. The finding of AHA and other autoantibodies supports the involvement of autoimmunity in 2/3 of patients with IRAP.

1048-185

The New Diagnostic Role of Brain Natriuretic Peptide in the Differentiation of Constrictive Pericarditis From Restrictive Cardiomyopathy.

Dinesh Arab, Ferdinand Leya, Leslie Cho, Bruce E. Lewis, Lowell H. Steen, Jr., Loyola University, Chicago, IL

Background: The differential diagnosis of constrictive pericarditis and restrictive cardiomyopathy is a source of debate, with considerable overlap of hemodynamic criteria.

Objective: To determine the role of plasma brain natriuretic peptide (BNP) in the diagnosis and differentiation of constrictive pericarditis (CP), from restrictive cardiomyopathy (RC).

Methods: We prospectively studied the plasma levels of BNP in patients undergoing cardiac catheterization, to help differentiate CP and RC. A total of 10 patients were identified. All patients underwent trans-septal catheterization to measure the left atrial (LA) pressure. BNP levels were drawn during the procedure.

Results: Seven patients were diagnosed as having CP and 3 patients had RC by history, non invasive evaluation and traditional invasive hemodynamic criteria. All patients had elevated and equalization in all four cardiac chamber pressures, which is a hallmark of CP. All patients were positive for anti-thyroid autoantibodies; 5 patients had a history of autoimmune thyroiditis. RC patients and controls had normal LA pressures. The mean LA pressure and left ventricular end diastolic pressure was not significantly different in the two groups (4.8±3 vs 3.3±0.8; p=0.07) The mean pulmonary arterial pressure was higher in the RC group (4.8±3 vs 3.3±0.8; p=0.07). The BNP was significantly higher in the RC group when compared to the CP group (8±15 vs 16±4; p=0.02 by the student t test).

Conclusions: 1) The BNP levels are low in CP, when compared to RC for a similar LA pressure and left ventricular end diastolic pressure. We postulate that this is due to inability of the chambers to stretch, as they are encompassed by rigid pericardium. BNP levels have been shown to be grossly elevated in RC in previous studies. 2) BNP levels can be used to differentiate CP from RC. This is the first study to describe the new role of BNP to help evaluate this complex disorder.

1049-149

Initial Report of the initiative to investigate the optimal Management of Tuberculous Pericarditis in Africa (IMPI) Registry

Charles Shy Wavonge, Mpiko Ntobeke, Bongani M. Mayosi, The IMPI Registry Study Group, University of Cape Town, Cape Town, South Africa

Background: Tuberculous (TB) pericarditis is a major public health problem in Africa as a result of the HIV/AIDS epidemic. There are no evidence-based guidelines for the diagnosis and management of the disorder. Furthermore, the clinical characteristics, morbidity and mortality associated with TB pericarditis in the HIV era are not known. We have established a multi-centre registry to document the clinical presentation, management, and outcome of TB pericarditis in Africa.

Methods: Fifteen hospitals in Cameroon, Nigeria, and South Africa are participating in the registry. Incident cases who presented between March 1, 2004 and August 31, 2004 were identified consecutively on commencement of treatment for suspected TB pericarditis.

Each patient is followed up at three-, six- and 12-months intervals to establish the vital status and response to treatment.

Results: 162 patients were recruited in the 6 month enrolment period. Mean age was 28 years (78% 48%) were male. Sixty-four patients (40%) were clinically immunocompromised, 44 (27%) tested HIV-positive; 82 (51%) were of unknown HIV status. The diagnosis was based on clinical evaluation and echocardiography (without microbiological confirmation of TB) in the majority of cases (74%). Pericardiocentesis was performed in 60 patients. Six percent had bacteriological confirmation of TB infection of the pericardial fluid, while eighteen percent had adenosine deaminase level above 40 U/l, which is suggestive of TB pericarditis. The pericardial syndrome was effusive in 83%, effusive-constrictive in 16% and constrictive in 2% of patients. Ninety-six percent were put on the 4-drug anti-TB regimen. Ninety-seven patients (60%) received an adjuvant oral steroid treatment. Three-month follow-up information, which was available for 50 participants, indicated 20% mortality rate.
Acute Pericardial Disease as First Evidence of Malignancy

Massimo Imazio, Brunella Demichelis, Enrico Cicchetti, Federico Beqaraj, Elisa Favro, Federica Romani, Daniela Demarte, Aldo Ghisio, Riccardo Belli, Rita Trinchero, Cardiology Department, Maria Vittoria Hospital, Turin, Italy

Background: Most patients with a malignant pericardial disease are known to have a malignant tumour but sometimes an acute pericardial disease has been described as the first manifestation of cancer. Aim of this work is to evaluate the frequency and clinical features of acute pericardial disease as first manifestation of malignancy, and to identify clinical criteria for diagnosis.

Methods: We prospectively studied all consecutive patients with a diagnosis of an acute pericardial disease (acute pericarditis and cardiac tamponade) from January 1996 to December 2003. Results: In the study period we recorded 450 patients (mean age 52.6 ± 18.1, range 16-90 years, 237 males) with a diagnosis of acute pericarditis (440 new cases of acute pericarditis, and 10 patients with isolated cardiac tamponade). A neoplastic etiology was found in 440 (52.5%) cases in patients with acute pericarditis without pericarditis. Altogether neoplastic etiology was found in 33 of 450 cases of acute pericardial disease (7.3%). An acute pericardial disease was the first manifestation of a previously unknown malignancy in 18 of 450 patients (4.0%). Detected malignancies were primary neoplastic diseases in 17 of 18 cases (94.4%), carcinomas of the colon and rectum (6 cases), breast cancer in 2 cases, and lymphomas in 2 cases) and primary neoplastic disease of the pericardium in a case of pericardial mesothelioma (5.6%). Lung cancer was the most common etiology in these patients (72.2%, p=0.02). After multivariate analysis the following clinical characteristics were associated with a higher probability of a neoplastic etiology: history of malignancy (OR 19.8, 95% CI 7.0-60.0, p<0.001), cardiac tamponade at presentation (OR 7.0, 95% CI 1.3-38.2; p=0.023), lack of response to non-steroidal anti-inflammatory drugs and recurrent or incessant course (OR 10.0, 95% CI 3.6-27.1; p=0.001). Conclusion: Acute pericardial disease may be the initial clue to malignancy and this is not uncommon in lung cancer. Malignancy must be excluded in every case of an acute pericardial disease with cardiac tamponade at presentation, lack of response to non-steroidal anti-inflammatory drugs and incessant or recurrent course.

Expression of E-selectin in Coxsackievirus B3 Myocarditis

James SM Yeh, Steven Tracy, Kristen M. Drescher, Jason Sunde, Ken Kono, Nora Chapman, Joseph Boyle, Tracy Russell, Charles Semmoga, Robert Eckerleisy, Martin Blomley, Donie Haskard, Petros Ntanosmopoulos, National Heart Lung Institute, Imperial College University of London, London, United Kingdom, University of Nebraska Medical Center, Omaha, NE

Background: Myocarditis is a classic inflammatory condition of the heart, commonly due to coxsackievirus B3 (CVB3) infection. The progression from acute myocarditis to chronic myocarditis and dilated cardiomyopathy, or resolution is not well understood. The study helps to an important role of Th2-dominated responses in the pathogenesis of myocarditis, whilst Th2-dominated responses are associated with enhanced recovery.

Recent evidence indicates that E-selectin (an endothelial adhesion molecule expressed only on activated endothelium) is involved in the selective recruitment of TH1 cells in vivo. However, to date, the expression of E-selectin during the course of CVB3 myocarditis has not been studied.

Methods: We inoculated 5-6 week old male C3H/HeJ mice intraperitoneally with 1x10^5 50% tissue culture infective dose (TCID50) of CVB3/28 in a volume of 100 µl or an equal amount of viral diluent. Animals were sacrificed at day 7 post inoculation. Hematoxylin and eosin staining and immunohistochemistry were performed on the frozen hearts.

Results: Extensive acute myocarditis was present in all infected C3H/HeJ mice (3 out of 3), accompanied by E-selectin expression that was spatially more widespread than the distribution of the myocardial lesions. The expression of E-selectin was predominantly on endothelial cells of the intra-myocardial capillaries, suggesting that these vessels are the route of transmigration of leukocytes to the myocardium. Myocarditis and E-selectin were absent in all non-infected controls (0 out of 2 animals).

Conclusion: These data demonstrate that E-selectin is expressed in acute CVB3 myocarditis in C3H/HeJ mice, that it may play a role in the selective recruitment of helper T cell subsets in CVB3 myocarditis. Furthermore, E-selectin is a good target for imaging of activated endothelium in the assessment of inflammatory activities in myocarditis using novel techniques such as E-selectin targeted microbubble contrast enhanced echocardiography.

Assessment of Vaccinia-Associated Myopericarditis with Cardiac Magnetic Resonance Imaging

Sean P. Javaheri, Eric Shry, Robert Eckart, Sr., Dimitri Cassimatis, Jr., Edwin Atwood, Sr., John Grabenstein, Sr., Brooke Army Medical Center, San Antonio, TX

OBJECTIVES: The purpose of this study was to assess the value of radionuclide labeled (111)In white blood cell (WBC) scan on the evaluation of patients with smallpox vaccine-associated myopericarditis.

BACKGROUND: On December 13, 2002, the Department of Defense described widespread smallpox vaccination. At that time, DoD identified an elevated risk of myocarditis and pericarditis among vaccinees, especially young men given smallpox vaccine for the first time. We describe a cohort of these myopericarditis patients who underwent testing with an (111)In-WBC scan to assess for recurrent or persistent myocardial inflammation.

METHODS: Patients with a history of recurrent myopericarditis or following resolution of symptoms had radionuclide studies performed using autologous leukocyte administration with (111)In-WBC and (111)In-Tc-Sestamibi (In WBC).

RESULTS: From December 2002 to July 2004, 78 military personnel were diagnosed with myocarditis or pericarditis following smallpox vaccination. Of these, 9 patients had persistent chest discomfort on follow-up. Seven patients underwent 111In-WBC imaging. The average length of time from vaccination to imaging was 298 ± 239 days (median 345 days). Of the 8 studies performed on patients with continuing clinical symptoms, 6 demonstrated focal areas of inflammation. Three of these areas were in the proximal septum and apex, one in the apex, one in the lateral wall and one in the distal anteroseptal wall and apex. Of the three patients who were imaged following symptom resolution, none had inflammation on (111)In-WBC.

CONCLUSIONS: (111)In-WBC imaging has been previously evaluated in patients with vaccinia-associated myocarditis, but may be a useful adjunct in the evaluation of recurrent or ongoing vaccinia-associated myopericarditis. In this preliminary evaluation, most patients who have persistent chest discomfort appear to have objective evidence of myocardial inflammation by (111)In WBC while inflammation was not seen in (111)In WBC scans following symptom resolution.
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of GJs are considered to be an important factor in the origin of reentrant arrhythmias. We investigated the alterations in connexin (Cx)43 during transition to heart failure in UM-X7 cardiac myopathic hamster (CM) hearts: Methods: We analyzed Cx43 expressions (protein and mRNA) of the left ventricular (LV) myocardium by western blotting and RTPCR at the age of 6, 10, and 20w. Echocardiographic and electrophysiological data were obtained. Results: In CM, LV hypertrophy had developed at 10w, LV global hypokinesis started at 20w, and dilated cardiomyopathy at 40w. The relative expression level of Cx43 protein and mRNA were significantly lower in CM at 20w than in G (0.52±0.29 vs. 1.20±0.12, 0.58±0.14 vs. 0.87±0.12, p<0.05, respectively). In CM, Cx43 expressions at the transverse portion of cardiomyocytes were significantly decreased. Interestingly, the relative expression level of serine255-phosphorylated Cx43, which initiates the down-regulation of gap junctional intercellular communication, was markedly increased in CM (1.1±0.4) compared with G (0.4±0.4, p<0.01) at 20w. Serine255-phosphorylated Cx43 was over-expressed at cytoplasmic area in CM. Conclusions: In cardiomyopathic hearts, in addition to interstitial fibrosis, down-regulation and absent serine-phosphorylation of Cx43 may result in abnormal cell-to-cell communication and alter the electrophysiological properties of the ventricle, leading to the initiation and perpetuation of ventricular arrhythmias.

**Down Regulation of Connexin43 is Associated with Sudden Death and Conduction Abnormalities in Transgenic Mice with Cardiac Restricted Over Expression of Tumor Necrosis Factor**

Sam E. Sawaya, Yadavendra S. Rajawat, Tapan G. Rami, Gabor Szalai, Robert L. Price, Vissegmentamarian Natarajan, Dirir S. Khoury, Douglas L. Mann, Baylor College of Medicine, Houston, TX, University of South Carolina, Columbia, SC

Background: The incidence of sudden death increases in cardiac conditions associated with hypertrophy. In cardiac hypertrophy, the mechanism is unknown. Based on previous reports that tumor necrosis factor (TNF) down regulates the gap junction protein connexin43 (Cx43), we examined Cx43 expression in transgenic mice with targeted over expression of TNF (MHC-TNF). Western blot analysis and immunohistochemistry showed decreased phosphorylation and dispersion of Cx43 away from the intercalated disks of cardiomyocytes. We hypothesized that Cx43 disruption causes ventricular conduction abnormalities and sudden death in MHC-TNF mice.

Methods: We recorded ECGs, measured ventricular conduction velocity during LV epicardial mapping, and performed intracardiac electrophysiology (EP) studies in 6 MHC-TNF mice and in 6 wild type (WT) mice.

Results: The ECG showed diminished heart rate and wide QRS complex in MHC-TNF mice compared to WT (RR = 171 vs. 120 ms, p = 0.01; QRS = 23 vs. 9 ms, p < 0.001). Although Cx43 was disrupted in MHC-TNF mice, LV conduction velocity in MHC-TNF mice was similar to WT (0.6 vs. 0.6 m/s), suggesting that the disruption in Cx43 was not functionally significant in MHC-TNF mice. Additional EP studies showed that MHC-TNF mice developed AV junctional rhythm and bundle branch block along with sinus and AV nodal dysfunction. While no ventricular tachyarrhythmias were induced in MHC-TNF mice, atrial tachycardia was induced in 3/6 mice and ventricular bigeminy in 2/6 mice. However, no arrhythmias were induced in WT mice. Since Cx43 is known to be present in regions where the electrical abnormalities were observed, we performed further immunohistochemistry and found that Cx43 was down regulated in MHC-TNF mice compared to WT.

Conclusion: Contrary to our initial hypothesis, disruption of Cx43 expression does not appear to alter ventricular conduction velocity or engender ventricular arrhythmias in MHC-TNF mice. Electrical abnormalities observed in the atrium and the ventricle underlying ventricular conduction system are consistent with down regulation of Cx43. Therefore, inflammation-induced abnormalities in atrial and AV conduction may predispose MHC-TNF mice to sudden death.

**POSTER SESSION**

1075 Heart Failure: Prognosis

Monday, March 07, 2005, 9:00 a.m.-12:30 p.m.
Orange County Convention Center, Hall E1
Presentation Hour: 11:00 a.m.-Noon

1075-143 Inability to Tolerate Optimal Neurohumoral Blockade Predicts Poor Survival in Heart Failure

Catherine Fallick, Jon Fryzek, Suzanne Wingate, Colleen Healey, Pam Barnett, Deborah Grider, Cecelia Gramsky, John Golden, Kaiser Permanente Mid-Atlantic States, Rockville, MD, International Epidemiology Institute, Rockville, MD

Background: Though the concept of neurohumoral blockade is well-established in heart failure (HF) treatment, associated therapies remain underutilized. This has impeded the development of a fuller understanding of the current natural history of HF progression. We evaluated patients (pts) in a large HMO HF disease management program who emphasized optimization of therapy in an effort to determine the extent to which optimal neurohumoral blockade has modified disease course.

Methods: We retrospectively analyzed data on 1121 pts referred to our Heart Failure Treatment Program (HTFP) with a history of heart failure systolic dysfunction (mean LVEF 23.5 ±7.9%). Mean age was 62.4±13.3 years, 66% were male, 55% African American, and 42% diabetic. 93% were treated with an ACE-inhibitor (ACE-I) or angiotensin receptor

**POSTER SESSION**

1047 Rodent Models of Heart Failure and Hypertrophy

Monday, March 07, 2005, 9:00 a.m.-12:30 p.m.
Orange County Convention Center, Hall E1
Presentation Hour: 11:00 a.m.-Noon
Increased Levels Of C-Reactive Protein Are Related To Reduced Regional Left Ventricular Function Detected By Tagged MRI In Asymptomatic Individuals: The Multi-ethnic Study Of Atherosclerosis (MESA)

Boaz D. Rosen, Mary Cushman, Khurram Nasir, David A. Bluemke, Thor Edwardsen, Veronica Fernandes, Shergan Lai, Russell Tracy, Joao AC Lima, Johns Hopkins Hospital, Baltimore, MD, University of Vermont, Burlington, VT

Background: C-reactive protein (CRP) is a marker of increased risk for heart failure, but the impact of CRP on subclinical LV dysfunction has not been evaluated. We investigated the association between CRP and regional LV function in participants of the Multi-Ethnic Study of Atherosclerosis.

Methods: Regional function was determined by peak systolic circumferential strain (Ecc) using Harmonic Phase method in 1,164 study participants who underwent tagged MRI. Relationship between CRP levels and Ecc was studied by stepwise regression. Multi-Ethnic Study Of Atherosclerosis (MESA)

Table: Relationship between regional peak systolic strain and log-CRP

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<th>Women</th>
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<td>0.37</td>
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<td>0.01</td>
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<tr>
<td>RCA</td>
<td>0.37</td>
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<tr>
<td>Mean Ecc</td>
<td>0.34</td>
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*Regression coefficient is defined as difference in Ecc(%) per 1 unit increase in log-CRP. CRP is in mg/L.

Conclusions: Higher CRP levels were associated with regional LV dysfunction in men, but not women, after controlling for traditional risk factors and protective therapy for coronary artery disease.

Pacing-Induced Mechanical Alternans Is a Good Predictor of Poor Prognosis in Idiopathic Dilated Cardiomyopathy With Sinus Rhythm

Akhiro Hirashiki, Hideo Izawa, Fuji Sosuma, Kohzo Nagata, Tomoko Kato, Hikuyuki Asano, Satoru Oshihama, Akira Yamada, Yousuke Murase, Akiko Noda, Koji Obata, Masahiko Maeda, Toyoko Murohara, Mitsuhiro Yokota, Chita City Hospital, Chita, Japan, Nagoya University, Nagoya, Japan

Background: Little studies have attempted to find prognostic indicators in ambulatory patients with idiopathic dilated cardiomyopathy (IDCM) in sinus rhythm. The relation between pacing-induced mechanical alternans and prognosis was investigated in patients with IDCM in sinus rhythm. We also investigated the myocardial expression of Ca2+-handling protein genes associated with the mechanical alternans.

Methods: Left ventricular (LV) pressure was measured during atrial pacing in the 36 IDCM patients and 8 controls. LV endomyocardial biopsies were performed and the abundance of Ca2+-handling protein mRNAs in the biopsy specimens were determined by quantitative RT-PCR. We also followed these IDCM patients for a mean period of 3.7 years.

Results: Under baseline conditions, no patient exhibited mechanical alternans. We could identify two groups of IDCM patients. Group A consisted of 22 IDCM patients who did not develop mechanical alternans at heart rates up to 140 bpm. Group B consisted of 14 IDCM patients who developed pacing-induced mechanical alternans. There were no significant differences in LV ejection fraction or plasma brain natriuretic peptide between Groups A and B. In endomyocardial biopsy specimens, the ryanodine receptor-2 mRNA level was significantly lower in patients with Groups A and B than in controls, but there were no significant differences between Groups A and B. The sarcoplasmic reticulum Ca2+-ATPase mRNA level was significantly lower in Group B than in Group A. The 3- and 5-year cumulative event-free survival rates in Group A were 62.5% and 31.3%, respectively. The event-free survival rates in Group A was significantly higher than that in Group B by the log-rank test (p=0.022).

Conclusions: Pacing-induced mechanical alternans is a good indicator of poor prognosis in IDCM patients with sinus rhythm. Abnormal expression of Ca2+-handling proteins resulting in altered intracellular Ca2+-levels may play a central role in pacing-induced mechanical alternans in IDCM patients.
Improvement in Hyponatremia During Hospitalization for Worsening Heart Failure Is Associated With Improved Outcomes: Insights From the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF)

Mihai Gheorghiade, Kirkwood Adams, Christopher O'Connor, Christopher Zimmer, Frank Czerwiec, Gungay John, Orianda Cesare, Feinberg School of Medicine–Northwestern University, Chicago, IL

Background: Hyponatremia (HYPO) is a known predictor of mortality in pts hospitalized for worsening heart failure. However, it is not known whether improving sodium levels in hyponatremic patients would lead to improved outcomes. We studied the relationship between changes in serum sodium during hospitalization and mortality in hyponatremic patients admitted for decompensated heart failure (HF) in a post-hoc analysis of the ACTIV in CHF trial.

Methods: The ACTIV in CHF trial randomized 433 pts with systolic dysfunction hospitalized for worsening HF to receive placebo or 30, 60, or 90 mg tolvaptan, a novel vasopressin type 2 receptor antagonist. Cox proportional hazards regression analysis was used to explore the relationship between HYPO (Na<136 mEq/L) at baseline and improvements ≥2 mEq/L in serum sodium by hospital discharge, and mortality within sixty days.

Results: Mild to moderate HYPO was observed in 69 patients (21.6%), with median (IR) levels of 133 (131, 134) mEq/L at baseline. After adjustment for other covariates, HYPO was a highly statistically significant predictor of mortality at 60 days post hospital discharge (p=0.005). At hospital discharge, 45 out of 69 pts (66.2%) had improvements in serum sodium ≥2 mEq/L. These pts had a median Persistent HYPO was defined as Na≤133 (131, 134) mEq/L, as compared with 133 (132, 135) mEq/L in those who did not improve by hospital discharge. Pts with a serum sodium improvement at discharge had a mortality rate of 15.6% at 60 days post discharge, as compared with a 30.4% mortality rate in those showing no improvement (p=0.062). After adjustment for other covariates, change in serum sodium at hospital discharge was a statistically significant predictor of mortality at 60 days post hospital discharge (p=0.0269).

Conclusions: Hyponatremia appears to be a modifiable therapeutic target and not purely a marker of disease severity. Improvements in serum sodium levels during hospitalization were associated with improved mortality at 60 days. Prospective studies are necessary in this population to assess if therapies aimed at increasing serum sodium will result in improved outcome.

Hemodynamic Characterization and Prognostic Value of Persistent Hyponatremia in Patients With Severe Heart Failure in the ESCAPE Trial

Mihai Gheorghiade, Anne S. Hellkamp, Ileana L. Pina, Gregg C. Fonarow, Teresa De Marco, Daniel F. Pashy, Joseph Rogers, Thomas DiSalvo, Javed Butler, Joshua M. Hare, Corrin S. Francis, Christopher M. O’Connor, Northwestern Feinberg School of Medicine, Chicago, IL

Background: the significance of hyponatremia (HN) and its correlation with hemodynamics have not been studied in heart failure (HF) patients (pts).

Methods: the ESCAPE trial randomly assigned 433 pts with severe HF to receive therapy guided by pulmonary artery catheter or by clinical assessment alone. Of these, 400 pts had serum Na levels ≤130 mEq/L. These pts had a median Persistent HN was defined as Na≤134 mEq/L throughout hospitalization. Cox proportional hazards models, with discharge Na as a continuous variable and adjusted for other predictors, were used to examine the association of Persistent HN with discharge end-points (p=0.017) had HN; 71 of them had HN at discharge. Also at baseline 318 pts (79%) had normal Na; of these, 266 had normal Na throughout hospitalization, while 52 had a decline by discharge. Persistent HN was a significant predictor of subsequent mortality (p=0.003; HR=1.25; 95% CI=1.08-1.46 for each 3-mEq/L decrease) (Table) and of rehospitalization for HF (p=0.004; HR=1.11; 95% CI=1.01-1.23 for each 3-mEq/L decrease). Conclusions: In pts with severe HF, HN is relatively common and usually not corrected during hospitalization. Compared with pts with normal Na, pts with HN have a higher pulmonary capillary wedge pressure and right atrial pressure after treatment, despite receiving higher diuretic doses and undergoing similar reductions in body weight. HN at discharge is associated with a very high risk of early mortality and rehospitalization for HF.

Total Hospitalizations in Advanced Heart Failure: Results from COMPANION

Peter Carson, Christopher O’Connor, JoAnn Lindenfield, Jalal Ghali, Brian Jaski, Jonathan Steinberg, Jodi Barnett, Inder Anand, Department of Veterans Affairs Medical Center, Washington, DC

Background: Despite frequent hospitalizations in heart failure (HF) pts, little data is available on the all cause hospitalization (AHC) burden. No clinical trial has ever reported a total database of adjudicated hospitalizations. Most data concern HF hospitalizations, as part of a primary endpoint.

Methods: The COMPANION study, in an advanced HF population, offers a unique opportunity to examine AHC database as adjudicated by an endpoint committee. The current analysis involves the optimal pharmacologic therapy (OPT) cohort of COMPANION (308 pts) followed for a median of 11.7 months. Hospitalizations were required to be of 24 hours duration or involve a calendar date change.

Results: A total of 210 pts (68% of total pts experienced 523 ACH. 176 pts had a cardiac admission (75% of all hospitalizations) and 106 had a HF admission (42% of all hospitalizations). Cardiac procedures accounted for 19% of total events. Non cardiac hospitalizations comprised 24% with pulmonary and GI the leading causes.

Conclusion: In an advanced HF population with GRS widening, ACH occurred frequently. While HF was the highest single category, non HF hospitalization predominated. The nature of the population and study contributed to more hospitalizations for cardiac procedures than anticipated but this may be an accurate reflection of the effect of recent device trials on current clinical practice. This data emphasizes the importance of non HF and non-cardiac morbidity in this population.

Serum Level of Uric Acid, Partly Secreted From The Failing Heart, is a Prognostic Marker in Japanese Patients with Congestive Heart Failure

Hiroshi Sakai, Takayoshi Tsutsutomo, Takashi Tsutsumi, Chisato Ishikawa, Keiho Onjin, Minoru Horie, Shiga University of Medical Science, Otsu, Japan

Background: Serum uric acid (UA) is reported to be elevated and may be a prognostic indicator in congestive heart failure (CHF). Activation of xanthine oxidase (XO) is a mechanism for elevation of serum UA in CHF. Activated XO, in the failing heart, produces free radicals and may contribute to oxidative damage in the failing myocardium and the progression of heart failure. However, whether UA is secreted from the failing heart remains unknown.

Objective: To evaluate serum UA is secreted from the failing heart and to estimate the prognostic role of UA in Japanese patients with CHF.

Methods: 1. We measured the serum UA in the Aortic root (AO) and in the coronary sinus (CS) in 58 patients with CHF and 13 control subjects. In 150 CHF patients, we measured plasma levels of xanthine nucleotide, brain natriuretic peptide (BNP), UA, and left ventricular ejection fraction (LVEF) and monitored for more than one year prospectively (mean follow-up periods>3 years).

Results: In 58 CHF patients, serum UA level in the AO increased with the severity of CHF and serum UA level was significantly higher in the CS than the AO (6.7±0.23 vs. 6.9±0.21, p<0.0001). The transcardiac gradient of UA (CS-AO) increased with severity of CHF and inversely correlated with LVEF and positively correlated with LV end-diastolic volume index. During the long-term follow-up, 16 patients died of cardiac event. In 150 CHF patients, high plasma levels of UA (p<0.001) and BNP (p<0.001) were shown to be independent predictors of mortality by multivariate stepwise analysis. Twenty patients died (mortality rate=40%) in 49 patients (BNP+30 pg/ml and UA≥6 mg/dL). Only one patient died in 53 patients (BNP+UA≥16 mg/dL).

Conclusions: These findings suggest that activated XO system in the failing heart contributes to the left ventricular dysfunction and the high plasma UA level is an independent prognostic predictor of BNP in Japanese patients with CHF.

Elevated Troponin T is Associated With Increased Left Ventricular End-diastolic Pressure and Electrocardiographic Left Ventricular Hypertrophy in Congestive Heart Failure Patients With No Coronary Artery Disease

George O. Anghelou, Mohammad H. Yamani, Randall C. Starling, James B. Young, The Cleveland Clinic Foundation, Cleveland, OH, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Congestive heart failure (CHF) can be a cause of elevated troponin T (tNT). Little is known about the etiology of tNT elevation in CHF patients free of coronary disease.

Methods: We studied the records of 525 CHF patients that visited the Cleveland Clinic emergency department between 1998-2002, had at least one tNT value measured and subsequently underwent cardiac cath. Patients with no disease on coronary angiogram were entered into the study. We recorded 17 clinical and laboratory variables, and investigated the association between them and tNT greater than 0.1 and 0.01 ng/ml respectively.

Results: Seventy-eight patients were included. Peak tNT values were greater than 0.1 and 0.01 ng/ml in 13 and 50 patients respectively. Five variables were associated with tNT greater than 0.1 ng/ml and three with tNT levels of 0.01 ng/ml or more (Table). After comparing the effects of these variables by means of multivariate analysis, increased left ventricular end diastolic pressure (LV EDP) was associated with tNT greater than 0.1 ng/ml (P=0.01), electrocardiographic left ventricular hypertrophy (ECG-LVH) with tNT of 0.01 ng/ml or greater (P=0.03), and the combination of these two variables with tNT greater than 0.1 ng/ml and LVH (P=0.01).
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than both 0.1 and 0.01 ng/ml (P=0.04 and 0.05 respectively).

**Conclusion**: Increased LV EDP and ECG-LVH are associated with elevated tnT levels in CHF patients. The presence of ECG-LVH, no matter what the cause, that left ventricular load and hypertrophy are a cause for myocardial ischemia and tnT release.

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>mTnT &lt; 0.1 ng/ml</th>
<th>mTnT &gt; 0.1 ng/ml</th>
<th>mTnT &lt; 0.01*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>54%</td>
<td>59%</td>
<td>0.33</td>
<td>0.82</td>
</tr>
<tr>
<td>Age</td>
<td>59%</td>
<td>59%</td>
<td>0.29</td>
<td>0.77</td>
</tr>
<tr>
<td>SBP &gt; 160 mm Hg</td>
<td>30%</td>
<td>35%</td>
<td>0.47</td>
<td>0.41</td>
</tr>
<tr>
<td>DBP &gt; 100 mm Hg</td>
<td>23%</td>
<td>27%</td>
<td>0.41</td>
<td>0.30</td>
</tr>
<tr>
<td>ECG-LVH</td>
<td>36%</td>
<td>39%</td>
<td>0.08</td>
<td>0.30</td>
</tr>
<tr>
<td>C-reactive protein &gt; 1.2 mg/L</td>
<td>13%</td>
<td>19%</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>LV mass &gt; 300 g/m²</td>
<td>79%</td>
<td>84%</td>
<td>0.01</td>
<td>100%</td>
</tr>
<tr>
<td>LV EF &lt; 35%</td>
<td>55%</td>
<td>59%</td>
<td>0.74</td>
<td>0.44</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>57%</td>
<td>44%</td>
<td>0.22</td>
<td>0.44</td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>36%</td>
<td>26%</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>RVSP &gt; 40 mm Hg</td>
<td>67%</td>
<td>67%</td>
<td>0.17</td>
<td>0.30</td>
</tr>
<tr>
<td>LV EF &gt; 12 mm Hg</td>
<td>83%</td>
<td>86%</td>
<td>0.06</td>
<td>100%</td>
</tr>
<tr>
<td>LV SP &gt; 160 mmHg</td>
<td>33%</td>
<td>30%</td>
<td>0.54</td>
<td>0.63</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34%</td>
<td>39%</td>
<td>0.59</td>
<td>0.19</td>
</tr>
<tr>
<td>HTN</td>
<td>71%</td>
<td>79%</td>
<td>0.18</td>
<td>0.85</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>59%</td>
<td>59%</td>
<td>0.22</td>
<td>0.15</td>
</tr>
<tr>
<td>Smoking</td>
<td>18%</td>
<td>24%</td>
<td>0.62</td>
<td>0.15</td>
</tr>
</tbody>
</table>

### Chromogranin A is an Independent Prognostic Marker in Postinfarction Heart Failure

Mette Else Estensen, Aina Hognestad, Unni Syversen, Iain Squire, Leong Ng, Kenneth Dickstein, Torbjörn Omland, Akerhus University Hospital, Nordbyhagen, Norway, Central Hospital in Rogaland, Stavanger, Norway

**Background**: Chromogranin A (CgA) is widely distributed throughout the neuroendocrine system and may, due to its long in vivo and in vitro half-life, be an attractive candidate for assessment of overall neuroendocrine activity. Recently, increased plasma levels of CgA have been found in patients with chronic heart failure and related to the severity of symptoms and prognosis. The prognostic value of CgA in postinfarction heart failure is unknown.

**Methods**: We assessed the association between serum CgA levels obtained during the subacute phase and time to hospitalization or death in 217 patients with postinfarction heart failure included in the OPTIMAAL trial. This trial evaluated the effect of losartan vs ACE-I treatment.

**Results**: The median follow-up time was 37.7 months. Investigators completed a structured report on electrocardiographic findings on all patients at baseline. The relationship between ECG-LVH and outcome was examined in a Cox model, adjusting for up to 30 co-variables of prognostic importance.

**Conclusion**: The prevalence of ECG-LVH was similar in all 3 CHARM trials (overall 15.7%), despite a more frequent history of hypertension in CHARM-Preserved. However, in each trial, patients with ECG-LVH had a higher baseline blood pressure than those without (difference 4.9-2.2 mmHg overall, P<0.0001). In the overall CHARM programme, ECG-LVH was an independent predictor of worse prognosis: relative risk of primary outcome 1.13 (95% confidence interval 1.02-1.26), P=0.023. ECG-LVH was also associated with an increased risk of non-fatal myocardial infarction: 1.52 (1.12-2.06), P=0.02 and hospitalization for CHF: 1.13 (0.99-1.30), P=0.10.

**Conclusion**: ECG-LVH was equally common in patients with CHF regardless of LVEF. The simple clinical finding of ECG-LVH was an independent predictor of a worse clinical outcome in a broad spectrum of patients with CHF receiving extensive contemporary treatment.

### Prognosis Determination in Heart Failure: Effects of Aggressive Therapy

Carrie Geisberg, Joann Goring, Ghazanfar Khadim, Kimberly Champney, Javed Butler, Vanderbilt University, Nashville, TN

**Background**: Most recent studies assessing heart failure (HF) prognosis have been cross sectional in design where medical therapy was not maximized in all eligible patients. In this study, we sought to assess the relative prognostic value of peak VO2 in relation to medical therapy in a contemporary group of HF patients treated from 1999-2003.

**Methods**: We assessed the event-free (death-ventricular assist device placement) survival, based on peak VO2, at one year among 362 HF patients. Outcomes were also assessed in two subgroups: group I (n=156) patients on maximal care defined as: on therapeutic dose specific agent or intensively documented with ACE inhibitor (ACE-I), at least 50% of recommended dose of beta-blockers (BB) unless hypotensive or bradycardic, spironolactone (RALES criteria plus BB criteria), and defibrillator (MADIT II criteria with QRS duration >120 msec), and group II (n=206) comprising group I patients with IVB pacer implantation (COMPANION criteria).

**Results**: Mean duration of follow-up was 48±295 days. Mean age of the study population was 55±11 years, ejection fraction was 23±8%, and peak VO2 was 12.4±3.6 ml/kg/min. One-year event-free survival for patients based on peak VO2 was as follows: peak VO2 <10 ml/kg/min (n=87, 24%) 65%, peak VO2 10-14 ml/kg/min (n=156, 43%) 81%, and peak VO2 >14 ml/kg/min (n=119, 33%) 90%. Sub-group analysis of Group I patients with peak VO2 <10 ml/kg/min (n=40) showed 72%, those with peak VO2 10-14 ml/kg/min (n=74) 91%, and those peak VO2 >14 ml/kg/min (n=42) 94% one-year event free survival.

**Conclusion**: Assessment of adequacy of medical therapy is essential prior determining HF prognosis for e.g. transplant eligibility. Cross sectional determination without therapy consideration may be misleading. Aggressive medical therapy in many patients currently considered eligible for transplant is associated with outcomes similar to or better than with medical therapy as compared to transplantation.

### Long-Term Prognosis of Patients With CHF Associated With Depression

Wei Jiang, Maragatha Kuchibhatla, Michael S. Cuffe, Greg L. Clary, Eric Christopher, Jude Alex, Ranga R. Krishnan, Christopher M. O’Connor, Duke University Medical Center, Durham, NC

**Background**: Results of previous studies demonstrated that depression is associated with increased short-term mortality in patients with chronic heart failure (CHF). This study designed to examine the effects of depression on the long-term prognosis of CHF patients
and to explore which cut-off value of Beck Depression Inventory (BDI) scale to better predict the outcome of CHF.

Method: We measured symptoms of depression using the BDI scale in a sample of 1005 patients with CHF when they were hospitalized because of various cardiac events.

We then followed these patients for all cause mortality during a 7-year period. Cox-proportional hazard model was utilized to assess the predictability of depression for long-term mortality. We compared the mortality of CHF patients with the existing cut-off BDI score (≥10) as well as with other possible cut-off points to explore the best predictability of depression. The interaction of other risk factors with depression and mortality were also investigated.

Result: The mean BDI score is 8.0±6.95 for the entire sample. The average days of follow-up was 971±730. BDI score was linearly associated with increased long-term mortality (Hazard ratio (HR) = 1.02, p=0.002); HR was 1.44 for patients whose BDI scores ≥10 (p=0.0004). The highest HR (HR=1.51) was yielded when the cut-off BDI score was set at ≥17 (p=0.0003). The adverse association of depression and increased long-term mortality was independent of age, marriage, cardiac function, and etiology of CHF.

Conclusion: The results of this study demonstrate a long term adverse impact on the prognosis of patients with HF. Furthermore, the negative impact of depression on mortality begins at a low depression level as measured by BDI, suggesting that even mild forms of depressive illness identify a subset of HF patients at high risk who may benefit from aggressive HF/antidepressant therapy.

Comparison of the Effects of Xanthine Oxidase Inhibitor, Allopurinol, and Uricosuric Agent, Benzobromarone, on Clinical Outcome in patients with Chronic Heart Failure and Hyperuricemia

Takahisa Yamada, Naoyuki Misaki, Mitsutoshi Asai, Nobuhiro Makino, Hitadaka Kikou, Yasumasa Tsukamoto, Shunsuke Tamaki, Masaharu Masuda, Takashi Matsumoto, Keiji Okuda, Masatake Fukunami, Osaka General Medical Center, Osaka, Japan

Background: Echocardiographic (echo) diagnosis of Arrhythmogenic Right Ventricular Dysplasia (ARVD) is increasing in frequency, but this disorder often remains underdiagnosed. The purpose of the current study was to assess the utility of the RV MPI in ARVD. Methods: Detailed echocardiograms were performed in 19 probands and analyzed at a core laboratory and compared to 19 normal controls matched for age, sex, body size and year of echo. RV systolic function was calculated as RV fractional area change (FAC). RV MPI was calculated as the ratio of Doppler-derived tricuspid regurgitation duration minus pulmonary outflow duration (PVD) divided by PVD. Results: The mean age was 35.6 ± 14.5 years and 68% were male. There were significant differences in RV dimensions and FAC between the 2 groups. The MPI was significantly increased in ARVD probands compared with controls (Table). In the subgroup of probands with normal FAC (n=6), the MPI was significantly increased compared with the matched controls (p=0.03). ROC curves show that an RV MPI >0.14 (AUC=0.94) is significantly greater than the Doppler-derived RV FAC >0.45 (AUC=0.78) for comparison between ARVD and controls. Conclusions: RV MPI is significantly increased in ARVD probands versus controls and could differentiate probands from controls even when FAC is normal. The RV MPI may be useful as an adjunct to 2-D imaging for the assessment of RV function in ARVD.

Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy by 3 Different Sets of Criteria.

Philippe Kiss, Marianne Bootema, Jeroen J. Bax, Katja Zeijnen, Annamarie E. de Koninck, Fleur Vriend, Ernst E. van der Walt, Martijn J. Schalij, Leiden University Medical Center, Leiden, The Netherlands

Introduction: Diagnosis of arrhythmogenic right ventricular dysplasia / cardiomyopathy (ARVD/C) has major implications for the management of patients and their first-degree relatives. Diagnosis may be difficult and is based on a set of criteria proposed by the International Task Force (TF) for Cardiomyopathies in 1994. More recently, diagnostic criteria based on MRI or ECG only have been suggested in the literature. We evaluated the consistency in outcome between 3 different sets of diagnostic criteria.

Methods and Results: A total of 52 patients (33 male, mean age 46±11 yrs) were evaluated for the possible occurrence of ARVD. Patients were evaluated because of ventricular arrhythmias (16), palpitations (13) syncope (3), ECG changes during routine analysis (4) or a family history of ARVD (1). All patients were analysed based on the TF-, MRI- and ECG criteria and their concordance was calculated. According to the TF-criteria 27 (52%) patients were diagnosed with ARVD. MRI. MRI was performed in 45 (86%) patients (7 patients were excluded because of prior ICD implant) of whom 20 (45%) were diagnosed with ARVD. According to the MRI criteria, 20 (45%) patients fulfilled the ECG criteria for ARVD. A moderate concordance was found between diagnoses based on the TF- and the MRI criteria (kappa = 0.49) and a fair concordance was found between the TF- and the ECG-criteria (kappa = 0.25). We found only a slight concordance between the MRI- and ECG-diagnoses (kappa=0.08).

Conclusion: These results indicate that there is not a strong concordance between the 3 diagnostic sets. Therefore we conclude that the clinical diagnosis of ARVD has to be based on TF-criteria, and cannot be replaced by a single diagnostic technique.

Regional Contractility is Reduced and Phase Heterogeneity of Tissue Doppler Is Increased in Isolated Noncompaction of the Ventricular Myocardium

Brian D. Hoit, Oleg Chebotarev, Keith Fox, Rebecca Ameduri, Frank V. Brozovich, Mark T. Johnson, Case Western Reserve University, Cleveland, OH, University Hospitals of Cleveland, Cleveland, OH

Background: Isolated noncompaction of the ventricular myocardium (INVM) is an increasingly recognized form of heritable cardiomyopathy characterized by highly trabeculated myocardium and LV chamber dysfunction. However, myocardial contractile abnormalities in this disorder are poorly defined.

Methods: Affected members from a kindred with INVM (n=6) were compared to age-matched controls (n=8) with tissue Doppler strain analysis using a GE Vivid 7 and dedicated software. Tissue Doppler velocity, longitudinal strain (S), strain rates (SR, 1/s) from the 4-and 2-chamber apical views were averaged over 3 cycles at base, mid, and apical LV sites. In addition, basal and mid lateral LV tissue Doppler velocities curves were correlated over 3 cycles every 10 ms to obtain a novel index of cardiac phase heterogeneity.

Results: S and SR were regionally and only modestly reduced in INVM compared to controls, affecting the basal and apical (but not mid-LV) segments:

<table>
<thead>
<tr>
<th>B Base</th>
<th>B Mid</th>
<th>B Apex</th>
<th>SR Base</th>
<th>SR Mid</th>
<th>SR Apex</th>
</tr>
</thead>
<tbody>
<tr>
<td>INVM</td>
<td>15.7±6.5</td>
<td>16.9±6.8</td>
<td>8.9±5.8</td>
<td>3.5±3.5</td>
<td>1.4±1.1</td>
</tr>
<tr>
<td>Controls</td>
<td>20.9±4.8</td>
<td>17.9±6.3</td>
<td>14.1±6.9</td>
<td>7.0±6.0</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>Controls</td>
<td>20.9±4.8</td>
<td>17.9±6.3</td>
<td>14.1±6.9</td>
<td>7.0±6.0</td>
<td>1.4±0.3</td>
</tr>
</tbody>
</table>

Conclusion: Phase heterogeneity correlation coefficients were significantly and strikingly lower in INVM than control (.76/ .09 (SD) vs .93/ .02, p<0.001), suggesting dysynchronous contraction and relaxation. The correlation between LV ejection function (range: 23-61%) and heterogeneity coefficient was poor (r=0.41, p=0.1)

Regional myocardial contractility is impaired in INVM, and with spatiotemporal heterogeneity of contraction and relaxation, may underlie the abnormal chamber function in this disorder.
Corticosteroid Therapy Prevents Cardiac Remodeling and Improves the Prognosis in Patients with Cardiac Sarcoidosis

Hideo Okumura, Shiro Nakatani, Kazukiho Satomi, Kazuhiro Sugaya, Wataru Shimizu, Takashi Kurita, Naohiko Ahara, National Cardiovascular Center, Suita, Japan

Background: Corticosteroid therapy for patients with cardiac sarcoidosis is widely accepted, but how much it affects on the cardiac function and the prognosis is not fully investigated. In this study, we compared patients treated with corticosteroid to those treated without aiming to confirm its beneficial effect and to provide the information on the patient selection.

Methods: We studied 23 patients who were treated with oral corticosteroid (steroid group) and 15 patients treated without it (control group) retrospectively on their echocardiographic data and the incidences of death on any cause or repeated hospitalization due to heart failure. Patients were divided into two subgroups according to the diastolic diameter of the left ventricle (LVDD) ≤54mm or >54mm at the point of diagnosis. The changes of LVDD and percent fraction of shortening (%FS) in each group and in each subgroup were examined.

Results: LVDD increased from 49 to 57 mm in the control subgroup (p=0.043) in contrast to the steroid subgroup decrease by 54mm (p=0.29). On the other hand, LVDD increased in the steroid subgroup >54mm from 61 to 68 mm (p<0.01), not in the control subgroup >54mm (p=0.36). The change of %FS did not reach the statistical difference. The event-free survival was 22% in the control group and 59% in the steroid group (p=0.014). More patients in the control group suffered the events in the early period than in the steroid group.

Conclusion: Corticosteroid therapy not only prevents the cardiac remodeling but also improves the prognosis in patients with cardiac sarcoidosis.

Genotype-Phenotype Correlations in Familial Amyloidotic Cardiomyopathy

Letizia Riva, Enrica Perugini, Fabrizio Salvi, Letizia Bacchi Reggiani, Paolo Ciliberti, Alessandra Ferlini, Marinella Ferlito, Angelo Branzi, Claudio Rapezzi, University of Bologna, Bellaria Hospital, Bologna, Italy, S.Anna Hospital, Ferrara, Italy

Background: Transthyretin related amyloidosis (ATTR) is highly heterogeneous both genetically and phenotypically. We investigated associations between genotype and frequency/symmetry of cardiac involvement.

Methods: We analyzed clinical and echocardiographic findings of three groups of consecutive ATTR patients (follow-up, 24±26 mo) with different mutations.

Results: Definite cardiomyopathy was present in 4/8 (50%) patients with Val30Met/77 (100%) with Glu89Gln, and in 15/21 (71%) with other mutations. Data on these patients are shown in the Table and Figure.

Conclusion. The Glu89Gln mutation is associated with a particularly high frequency of severe myocardial involvement with major cardiovascular events. Combined heart/liver transplantation should be strongly considered for this subgroup.

Selective Myocardial Uptake of 99mTc-DPD in Transthyretin-Related Amyloidosis: Implications for Recognition of Cardiac Involvement and Differential Diagnosis with AL Amyloidosis

Enrica Perugini, Claudio Rapezzi, Fabrizio Salvi, Letizia Riva, Paolo Ciliberti, Francesco Fallar, Pierluigi Guidiatti, Cinzia Pettinato, Letizia Bacchi Reggiani, Angelo Branzi, Policlinico S.Orsola, Bologna, Italy, Ospedale Bellaria, Bologna, Italy

Background: We investigated the diagnostic value of 99mTc-DPD scintigraphy in the recognition of cardiac involvement in transthyretin-related, TTR, vs AL amyloidosis.

Patients and Methods: Group A (TTR CA): 12 pts (56±16 yr) with DNA-proven TTR amyloidosis and echocardiographically demonstrated cardiac amyloidosis (CA). Group B (AL CA): 6 pts with AL amyloidosis (56±7 yr) and CA. Group C (normal controls): 10 subjects (64±2±12.2 yr) without any evidence of cardiac disease. Group D (amyloidosis without CA): 6 pts (46±15 yr) with either TTR mutations (n=4) or systemic AL amyloidosis (n=2) but no cardiac involvement. The study population received 740 MBq of 99mTc-DPD and to assess therapeutical effects on microcirculation.

Corticosteroid therapy for patients with cardiac sarcoidosis is widely accepted, but how much it affects on the cardiac function and the prognosis is not fully investigated. In this study, we compared patients treated with corticosteroid to those treated without aiming to confirm its beneficial effect and to provide the information on the patient selection.

Methods: We studied 23 patients who were treated with oral corticosteroid (steroid group) and 15 patients treated without it (control group) retrospectively on their echocardiographic data and the incidences of death on any cause or repeated hospitalization due to heart failure. Patients were divided into two subgroups according to the diastolic diameter of the left ventricle (LVDD) ≤54mm or >54mm at the point of diagnosis. The changes of LVDD and percent fraction of shortening (%FS) in each group and in each subgroup were examined.

Results: LVDD increased from 49 to 57 mm in the control subgroup (p=0.043) in contrast to the steroid subgroup decrease by 54mm (p=0.29). On the other hand, LVDD increased in the steroid subgroup >54mm from 61 to 68 mm (p<0.01), not in the control subgroup >54mm (p=0.36). The change of %FS did not reach the statistical difference. The event-free survival was 22% in the control group and 59% in the steroid group (p=0.014). More patients in the control group suffered the events in the early period than in the steroid group.

Conclusion: Corticosteroid therapy not only prevents the cardiac remodeling but also improves the prognosis in patients with cardiac sarcoidosis.

Genotype-Phenotype Correlations in Familial Amyloidotic Cardiomyopathy

Letizia Riva, Enrica Perugini, Fabrizio Salvi, Letizia Bacchi Reggiani, Paolo Ciliberti, Alessandra Ferlini, Marinella Ferlito, Angelo Branzi, Claudio Rapezzi, University of Bologna, Bellaria Hospital, Bologna, Italy, S.Anna Hospital, Ferrara, Italy

Background: Transthyretin related amyloidosis (ATTR) is highly heterogeneous both genetically and phenotypically. We investigated associations between genotype and frequency/symmetry of cardiac involvement.

Methods: We analyzed clinical and echocardiographic findings of three groups of consecutive ATTR patients (follow-up, 24±26 mo) with different mutations.

Results: Definite cardiomyopathy was present in 4/8 (50%) patients with Val30Met/77 (100%) with Glu89Gln, and in 15/21 (71%) with other mutations. Data on these patients are shown in the Table and Figure.

Conclusion. The Glu89Gln mutation is associated with a particularly high frequency of severe myocardial involvement with major cardiovascular events. Combined heart/liver transplantation should be strongly considered for this subgroup.

Selective Myocardial Uptake of 99mTc-DPD in Transthyretin-Related Amyloidosis: Implications for Recognition of Cardiac Involvement and Differential Diagnosis with AL Amyloidosis

Enrica Perugini, Claudio Rapezzi, Fabrizio Salvi, Letizia Riva, Paolo Ciliberti, Francesco Fallar, Pierluigi Guidiatti, Cinzia Pettinato, Letizia Bacchi Reggiani, Angelo Branzi, Policlinico S.Orsola, Bologna, Italy, Ospedale Bellaria, Bologna, Italy

Background: We investigated the diagnostic value of 99mTc-DPD scintigraphy in the recognition of cardiac involvement in transthyretin-related, TTR, vs AL amyloidosis.

Patients and Methods: Group A (TTR CA): 12 pts (56±16 yr) with DNA-proven TTR amyloidosis and echocardiographically demonstrated cardiac amyloidosis (CA). Group B (AL CA): 6 pts with AL amyloidosis (56±7 yr) and CA. Group C (normal controls): 10 subjects (64±2±12.2 yr) without any evidence of cardiac disease. Group D (amyloidosis without CA): 6 pts (46±15 yr) with either TTR mutations (n=4) or systemic AL amyloidosis (n=2) but no cardiac involvement. The study population received 740 MBq of 99mTc-DPD and to assess therapeutical effects on microcirculation.
Background: Although many studies have demonstrated a decrease in aerobic function with aging, few have examined the influence of gender, and none have characterized the combined effects of aging, gender and training on exercise efficiency (energy output/energy input).

Methods: 61 healthy subjects, divided into 4 groups of young women (20-33 years, n=15), younger men (20-30 years, n=12), older women (65-79 years, n=16), and older men (65-77 years, n=18), underwent cardiopulmonary exercise testing (CPET) to analyze aerobic parameters before and after 3-6 months of supervised aerobic exercise training.

Results: Younger subjects had a 42% higher peak VO2 (ml/kg) than older subjects (p<0.001) before exercise training. At baseline, the elderly had an 8% lower efficiency (20.4 ± 3.7% vs. 22.2 ± 2.4%, p<0.05) and a 17% higher O2 debt (20.8 ± 4.3% vs. 17.7 ± 5.0%, p=0.012) than the young. Peak VO2 was 32% higher (p<0.001) in men than in women at baseline. In all subjects, training resulted in an increase in peak VO2 (+14%, p<0.001), an increase in peak Watts/kg (+21%, p<0.001), a decrease in the O2 debt (-24%, p<0.0001), and an improvement in exercise efficiency (+17%, p<0.001). An age effect was seen in combination with these training effects, with older subjects displaying a larger increase in peak Watts/kg (+27% vs. -12%, p<0.001) and a larger decrease in O2 debt (-28% vs. -17%, p<0.01) than the young. The older subjects also showed a significantly larger increase in exercise efficiency (absolute increase of 6% vs. 1%, p<0.0001), but a smaller increase in peak VO2 (+11% vs. +15%, p<0.001) with training as compared to the young.

Conclusion: Older age is associated with a marked decline in aerobic capacity. The age-related decline is also associated with decreased exercise efficiency and an increased O2 debt. This translates into a higher VO2 and a greater O2 debt during matched absolute workloads in the elderly. These age-related changes may be reversed with aerobic exercise training, which improves exercise efficiency and lowers the O2 debt to a greater degree in the elderly than in the young.

Biochemical Evidence of Myocardial Injury Among Participants in Endurance Sports
Malissa Wood, Tom G. Nelan, Danita Yoerg, Kent Lewandrowski, Arthur Siegel, Elizabeth Lewandrowski, Michael Picard, James Januzzi, Massachusetts General Hospital, Boston, MA

Background: Rare deaths have been reported with marathon running. While some deaths have been attributed to hypertonia, the contribution of myocardial injury remains unclear. We sought to determine whether biochemical evidence of myocardial injury could be demonstrated following completion of a marathon and its possible association with hypertonia.

Methods: We recruited 35 Boston Marathon runners. Testing, including serum N-terminal proBNP (NTproBNP), troponin T (cTnT), C-reactive protein (CRP), ischemia modified albumin (IMA) and serum Na, was performed prior to and immediately after marathon.

Results: The group included 22 males and 13 females with a mean age of 34.3±9.3 years and mean finish time of 4 hours 24±48 min. Significant changes in mean heart rate (356±12 bpm in SO) and improvement in TR (4.4±0.6 vs 2.8±0.4 bpm/mmHg in SO) and BR (2 ± 0.1 vs. -1.2 ± 0.2 bpm/mmHg in SO) were observed. The myocardium and gastrocnemius CRP were not related to change in Na. The mechanism of cardiac injury may not be due to myocardial ischemia, as IMA, a sensitive marker of ischemia, fell following exercise. Biochemical evidence of myocardial injury was demonstrated in marathon runners and was not related to change in Na. The mechanism of cardiac injury may not be due to myocardial ischemia, as IMA, a sensitive marker of ischemia, fell following exercise.
Doppler Evaluation of Cardiac Allograft Dysfunction in Long-Term Heart Transplantation Recipients With Normal Coronary Angiograms

Francesco Tong, Alida LP Calafio, Antonio Gambino, Giuseppe Feltrin, Giuseppe Tomasino, Diego Calziato, Cristiano Saras, Omar Pacagellina, Anna Lisa Vinci, Maria Grazia Leon, Annalisa Angelini, Angelo Ramondo, Gaetano Thiene, Gino Gerosa, Sabino Iliceto, Cardiology, University of Padova, Padova, Italy, Cardiovascular surgery, University of Padova, Padova, Italy

Background. Chronic cardiac allograft dysfunction with normal coronary angiograms is poorly understood. We studied Doppler-derived systolic and diastolic function indexes in long-term heart transplantation, to identify early non-invasive markers of allograft dysfunction.

Methods. We studied 154 stable heart transplantation recipients (125 male, aged 51 ± 13 years) with normal left ventricular echocardiographic ejection fraction (63 ± 6%), free from acute rejection and without allograft vasculopathy. Doppler parameters were: mitral E and A wave velocities, E/A ratio, mitral deceleration time (DT), isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), ejection time (ET) and Tei index (IVCT + ET/ET). Mean follow-up from heart transplantation to Doppler examination was 6.6 ± 4.3 years. Rejection scores (RS) on endomyocardial biopsy were calculated (ISHLT grades: 0=0; 1A=1; 1B=2; 2=3; 3A=4; 3B=5; 4=6) in the first year, in the second year and during the whole follow-up. RS including only severe grades (≥3A) were also calculated. Pearson’s test was used to correlate quantitative data.

Results. E/A ratio and Tei index were inversely related with donor age (r=-0.198, p=0.02 and r=-0.232, p=0.004 respectively) and directly related with mean time from heart transplantation (r=0.090, p=0.03 and r=0.305, p=0.001 respectively). IVRT was inversely related with ischemic time (r=-0.172, p=0.01) and with RS in the second year (r=-0.213, p=0.01 and r=-0.202, p=0.02). DT was inversely related with RS in the first year, in the whole follow up, and with RS including only severe grades in the first year and in the whole follow-up (r=-0.052, p=0.261, p=0.01; r=-0.224, p=0.006 and r=-0.220, p=0.04 respectively). Tei index was directly related with all RS and SR for severe grades in the first year (r=0.298, p=0.001 and r=0.242, p=0.005 respectively).

Conclusion. These correlations suggest a progressive impairment of myocardial performance, directly associated with acute rejection burden, in long-term heart transplantation recipients free from cardiac allograft vasculopathy and with normal left ventricular ejection fraction. This may indicate early graft dysfunction, reflecting subtle diastolic function changes.

Coronary Endothelial Dysfunction in Cardiac Transplant Recipients is Related to Elevated Levels of ADMA

William F. Fearon, Bing-yin Wang, Atsushi Hirohata, Mamoo Nakamura, Luciano Potena, Hamath A. Valantine, Alan C. Yeung, John P. Cooke, Stanford University, Stanford, CA

Background: The pathophysiology and course of coronary endothelial dysfunction after cardiac transplantation (Tx) remains incompletely defined. Elevated levels of asymmetric dimethylarginine (ADMA), the endogenous inhibitor of the nitric oxide synthase (NOS) pathway, may play a role.

Methods: Coronary angiography was performed in 56 recent cardiac transplant recipients. Quantitative coronary angiography of the proximal left anterior descending artery (LAD) was performed at baseline and after an intracoronary bolus of acetylcholine (Ach; 50μg). Aortic and coronary sinus blood was drawn for calculation of basal and stimulated plasma nitric oxide (NOx) levels using the Griess reaction, and ADMA levels using ELISA.

Results: Of the 55 cases, 28 were within 6 months of Tx, 19 were 1 year post-Tx and 7 were 2 years post-Tx. In the entire cohort there was significant endothelial dysfunction based on paradoxical LAD vasodilatation after Ach (mean LAD diameter decreased from 3.12 ±0.49 to 3.31 ±0.38 mm, p<0.001). The 19 cases which were 1 year post-Tx had a similar degree of significant endothelial dysfunction. By contrast, the 7 cases which were 2 years post-Tx had less prominent vasodilatation after Ach (2.75 ±0.58 to 2.58 ±0.53 mm, p<0.05), on a change in transmyocardial NOx generation (3.63 ±1.25 vs. 52.3±25.4 μM, p<0.26). The mean ADMA level was significantly lower at 2 years post-Tx compared to the level within 8 weeks of Tx (0.58 ±0.18 vs. 0.85 ±0.25 μmol/L, p<0.03).

Conclusion: Endothelial dysfunction is present early and persists after cardiac transplantation with gradual improvement over time. The observed impairment of the NOS pathway is likely due to elevated levels of ADMA, the endogenous inhibitor of NOS.
and 55% (1.5-7 years) vs. 89%, 75% and 69% for CCB pts post-TX (p<0.001 by log-rank method). Freedom from cardiac death for all no CCB pts was 98%, 89% and 87% vs. 99%, 95% and 93% in CCB pts (p=0.018). Comparison of all CCB pts, no CCB with statins pts and no CCB and no statins pts showed pts in the CCB group had lowest risk for all cause mortality (p<0.0001) and cardiac death (p=0.013), independent of statin use. Risk factors including recipient and donor age, rejection episodes, CMV infection and lipids were comparable between groups.

Conclusion: Diltiazem in heart Tx recipients lowers all cause and cardiac mortality rates.

**ORAL CONTRIBUTIONS**

**811 Experimental Models of Heart Failure and Hypertrophy**

Monday, March 07, 2005, 11:00 a.m.–12:15 p.m.
Orange County Convention Center, Room 230B

**811-5 mRNA Gene Expression and Protein Levels for Granulocyte Colony Stimulating Factor Are Increased in Left Ventricular Myocardium of Dogs With Heart Failure**

Meiyi Huang, Sharad Rastogi, Victor G. Sharov, Ramesh C. Gupta, Makato Imai, Han N. Sabbah, Henry Ford Health System, Detroit, MI

**Introduction:** Granulocyte colony stimulating factor (G-CSF) is a cytokine that stimulates the survival, proliferation, and differentiation of primitive bone marrow stem cells. In mice with acute myocardial infarction secondary to coronary artery ligation, G-CSF-mediated translocation of bone marrow stem cells was shown to result in significant myocardial tissue regeneration. In this study, we tested the hypothesis that mRNA and protein expression of G-CSF is increased in the failing left ventricle (LV) of dogs as a possible response to ongoing injury, degeneration and loss of cardiomyocytes.

**Methods:** mRNA and protein expression of G-CSF were measured in LV myocardium of 6 dogs with heart failure (HF) induced by multiple sequential intracoronary microembolizations (LV ejection fraction <30%) and in LV myocardium of 6 normal (NL) dogs. Tissue samples from both groups were used to isolate total RNA, mRNA expression for G-CSF was measured using reverse transcriptase polymerase chain reaction (RT-PCR). Protein expression was determined in SDS-extract of LV tissue homogenate using Western blots. P-NCX was normalized to total NCX protein.

**Results:** mRNA expression of G-CSF was significantly increased in the failing left ventricle (LV) of dogs as a possible response to ongoing injury, degeneration and loss of cardiomyocytes. SDS-extract of LV tissue homogenate using Western blots. P-NCX was normalized to total NCX protein.

**811-6 Undifferentiated Human Embryonic Stem Cells Are Not Guided to Form New Myocardium by Transplantation into Normal and Infarcted Heart**

Jonathan Leq, Sharon Gerecht-Nir, Smadar Cohen, Liron Miller, Parvin Zarir, Radka Holbova, Anna Ziskind, Michal Shachar, Esther Guetta, Joseph Itskovitz-Eldor, Neufeld Cardiac Research Institute, Tel-Hashomer, Israel

**Background:** We aimed to test the hypothesis that both the normal and infarcted heart tissue can provide specific guidance to guide differentiation of undifferentiated human embryonic stem cells (hESCs) into mature myocardium.

**Methods:** Human ES cell lines H9 and I6 were grown on inactivated mouse embryonic fibroblasts or cultivated in suspension to form differentiating human embryoid bodies (hEBs). hESCs (0.5-1x10^6); hEBs (4-8 days; 0.5-1x10^6); 0.1 mm pieces of ES-derived myocardial beating tissues or PBS (control) were injected into normal (n=18) or infarcted (n=9) myocardium of athymic nude rats either by direct injection into normal heart muscle, or into pre-implanted 3-D alginate scaffold sutured onto the heart. By two to four weeks after transplantation, heart sections were processed and examined to detect the presence of human donor cells and differentiation of myocardium with hESC-derived cardiomyocytes, typical teratoma had been developed at the site of implantation.

**Conclusion:** Unidifferentiated human embryonic stem cells or ES-derived cardiomyocytes can survive transplantation into normal or infarcted myocardium of athymic nude rats. The implanted cells, however, are not directed to form new myocardium and may rarely form teratomas. Our work suggests that elimination of undifferentiated cells is critical prior to ES-derived cardiomyocyte transplantation into the heart.

**811-7 Non-Excitatory Cardiac Contractility Modulation Electric Signals Normalize Phosphorylation and Expression of the Sodium Calcium Exchanger in Left Ventricular Myocardium of Dogs with Heart Failure**

Ramesh C. Gupta, Sudish Mishra, Sharad Rastogi, Makato Imai, Walid Haddad, Yuval Mika, Han N. Sabbah, Henry Ford Health System, Detroit, MI

**Background:** The sodium-calcium exchanger (NCX) is hyperphosphorylated in heart failure (HF) and its mRNA and tissue protein expression are up-regulated; maladaptations that may contribute to progression of HF. In HF dogs, delivery of non-excitory cardiomyocytes can survive transplantation into normal or infarcted myocardium of athymic nude rats. The implanted cells, however, are not directed to form new myocardium and may rarely form teratomas. Our work suggests that elimination of undifferentiated cells is critical prior to ES-derived cardiomyocyte transplantation into the heart.

**Methods:** Total NCX mRNA expression was significantly increased in LV myocardium of HF dogs compared to NL dogs (37 ± 1 vs. 24 ± 2 du, p<0.05). Similarly, protein expression of NCX was determined using RT-PCR and normalized to GAPDH. Tissue homogenate was used to isolate phosphorylated proteins using a Phosphoprotein enrichment kit. Total and P-NCX protein were quantified using Western blots. P-NCX was normalized to total NCX protein.

**Results:** Total NCX mRNA expression for NCX increased in untreated HF dogs. CCM normalized mRNA expression of NCX. Total and P-NCX protein increased in untreated HF dogs compared to NL. CCM normalized total and P-NCX (Table).

**Conclusions:** In HF dogs, short-term CCM therapy normalized P-NCX and NCX mRNA and protein expression. This finding may explain, in part, improvement of LV function seen in HF dogs during CCM therapy.

**811-8 C-flip, A Protein Required For Embryonic Heart Development, Is Markedly Increased In Pressure Overload Myocardial Hypertrophy.**

Antonio Rapaccio, Emma Sanzari, Giovanni Esposito, Elisa di Pietro, Francesco Borgia, Luigi Di Sarra, Emilina Mayo, Dario Leoco, Gerolama Condorelli, Massimo Chiancone, Division of Cardiology, Federico II university, Naples, Italy

**Background:** Cardiac hypertrophy (CH) is an independent risk factor in the development of heart failure (HF). A number of molecular mechanisms could be involved in the transition from CH to HF. C-flip is a protein expressed mostly in kidney and heart. Both forms of C-flip (long and short) have an antiapoptotic role interfering with caspase 8 downregulation. C-flip knock-out mice embryos do not survive past day 10.5 of embryogenesis exhibiting impaired heart development. No data are available regarding the actual role of C-flip in the normal adult heart and in pathophysiological settings such as pressure overload CH.

**Methods and results:** 7 days after transverse aortic constriction (TAC) in C57B16 mice, a significant increase in left ventricle to body weight ratio (3.20 in control animals (N=9) vs 4.82 in TAC animals (N=7), p=0.05) was associated to an increase of p-NCX and NCX mRNA and protein expression. This finding may explain, in part, improvement of LV function seen in HF dogs during CCM therapy.

**811-9 Non-excitatory Cardiac Contractility Modulation Electric Signals Normalize Phosphorylation and Expression of the Sodium Calcium Exchanger in Left Ventricular Myocardium of Dogs with Heart Failure**

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**Conclusion:** Total and P-NCX protein increased in untreated HF dogs compared to NL. CCM normalized total and P-NCX (Table).
for efficacy of G-CSF induced PBSC mobilization in healthy bone marrow donor. We examined the safety and feasibility of G-CSF stimulated peripheral blood apheresis for stem cell source in MI patients.

**METHODS AND RESULTS:** From Feb 2003 to Aug 2004, 51 MI patients were included in this study. PBSC apheresis product collections after G-CSF stimulation were performed with a COBE cell separator. FACS analysis was done with apheresis products. Study group was comprised of 20 AMI and 31 CMI patients, with a mean age of 58.7±10.3 years. During G-CSF injection and peri-apheresis period, we did not observe aggravation of angina, any ECG changes suggesting ischemia or substantial arrhythmia, or thrombotic complication. We collected 7.6±2.7x10^7 leukocytes (mononuclear cells:86.5±12.0%, CD34+ cells: 9.7±7.4%) during apheresis, and infused 1.4±0.4x10^7 collected leukocytes (9.3±9.1 mL;3.7±1.32±3.4x10^7 CD34+ cells) by over-the-wire balloon angioplasty catheter after PCI. In FACS analysis, apheresis cells were comprised of subpopulation of cells:KDR+(10.3±10.9%), CD31+(50.5±13.2%), VWF+(24±4.9%), VE-cadherin+(1.8±3.6%)[endothelial marker]. AC133+(1.1±1.2%), CD34+(9.7±9.8%)[stem cell]; CD14+(38.8±19.3%)[monocyte]; CD45+(84.1±3.3%)[common leukocytes]; SH2+3H3+(3.4±0.5%)[mesenchymal stem cells]; and KDR+/CD34+(3.4±5.3%)[endothelial progenitor cells]. Age, diabetes, hypertension, presence of acute ischemia, and LV dysfunction did not show any difference with collected stem cell population regardless of age, diabetes, presence of acute ischemia and LV dysfunction. This study suggests that G-CSF based PBSC therapy in MI is safe and feasible.

**POSTER SESSION**

**1103**

**Heart Failure: Therapy**

**Monday, March 07, 2005, 1:30 p.m.-5:00 p.m.**

Orange County Convention Center, Hall E1

Presentation Hour: 3:30 p.m.-4:30 p.m.

**Clinical Safety and Feasibility of G-CSF mobilized Peripheral Blood Stem Cell Therapy in Myocardial Infarction patients: MAGIC Cell investigator [Myocardial Regeneration and Angiogenesis in MI with G-CSF Mobilization and Intra-Coronal Cell Infusion]**

Sang-Hoon No, Hyun-Jai Cho, Shu-Ying Zhang, Hwa-Pyung Kim, Jin-Wook Chung, Joo-Yong Hahn, Hae-Young Lee, Hye-Jin Kang, Bon-Kwon Koo, Dae-Won Sohn, Byung-Hee Oh, Myoung-Mook Lee, Young-Bae Park, Yun-Sik Choi, Hyo-Soo Kim, Seoul National University Hospital, Seoul, South Korea

**BACKGROUND:** Intra-coronary infusion of peripheral blood stem cells (PBSC) mobilized with G-CSF stimulation has been shown to improve cardiac function in myocardial infarction (MI) patients. Aging and other risk factors have been reported modifying factors for stem cell engraftment and differentiation. The purpose of this study was to examine if autologous peripheral stem cell transplant in myeloma patients would improve left ventricular ejection fraction.

**Methods and Results:** Retrospective review of 193 patients receiving autologous peripheral blood stem cell transplantation (CD34+) at the University of Arkansas for Medical Sciences was performed. All patients had pre and post transplant quantitative left ventricular ejection fraction (LVEF) assessments by multiple gated acquisition scan (MUGA). At 3-5 months, there was no significant change in overall LVEF (63±2 vs 63±2% mean ± SE). 8 (mean age 62 ± 10 years) out of 193 patients had baseline LVEF (< 50%). In 7 of these 8 patients, there was an improvement in global LVEF (from 47±1% to 54±2%). No changes were made in medical therapy for their baseline cardiac conditions. When correlated with the number of coronary risk factors (prior myocardial infarction, diabetes, hypertension, dyslipidemia, smoking and family history as potential homing factors) the percentage improvement in LVEF revealed a correlation with the risk factor score (R=0.05).

**Conclusions:** Stem cell transplantation has the potential to improve cardiac function in patients with low LVEF. These data also suggest that traditional coronary risk factors may serve as homing factors for stem cells into the dysfunctional myocardium.
**Table 1:**

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**Conclusions:**

- Testosterone improves insulin sensitivity and body composition in men with congestive heart failure.
- There was a significant reduction in serum fasting glucose (-0.61 ± 0.2mmol/L, p=0.03) and a significant increase in insulin sensitivity (0.8 ± 0.3kg, p=0.02).
- Testosterone therapy reached a high physiological range (mean ± sem) 14.3 ± 2.9nmol/L who completed the study and were evaluated by intention to treat using univariate analysis of the variance, the data are presented as the mean delta (difference between study groups) at 1 year.
- The effect of testosterone therapy on haemodynamic and echocardiographic parameters in men with congestive heart failure (mean ± s.e.m; age 64 ± 1.2 years; ejection fraction 32.5% ± 1.3%, treatment with an aldosterone antagonist with maximum follow up to 12 months. Analysis was by intention to treat using univariate analysis of the variance, the data are presented as the mean delta (difference between study groups) at 1 year.
Cardiac Function and Heart Failure

TFS in HF pts and hence may contribute to better management of these HF pts.

Conclusion:

These events could be predicted by changes in intra-thoracic Z.

Male sex, ischemic etiology and HF with ISF were features associated with increased use.

Conclusion.

with ISF (p<0.001; fig. 1), —2. The HF was of ischemic etiology (p=0.001) or —3. the pt was

was not related to admission BNP, creatinine, hemoglobin level, diabetic status or age. Pts

black pts with HF.

Mean age 70 ±13 (male: 65 ±12 and female: 72 ±14, p<0.001), 64% female, 46%

A total of 44 patients have been enrolled, with a mean follow-up time of 32.5
days. Thirty-two of the patients were followed > 1 month; of those 32, 7 patients had a HF
event. The 7 patients with HF events (0±0.001 ± 2.73±). had significantly higher daily Z then
the 25 HF event free patients (P<0.001, 6.12± ±2.2±). In addition, the average change in
daily Z 3 days pre and post CR hosp was 2.17± (N= 4, 5.5% change), suggesting that these
events could be predicted by changes in intra-thoracic Z.

Results:

as a useful tool to monitor the TFS in HF pts and hence may contribute to better management of these HF pts.

Results.

In Sauna group, repeated thermal therapy for 2 weeks improved cardiac function (ejection fraction: 31±8 to 36±9%, P<0.01, LV Tei index: 0.82±0.29 to 0.69±0.22, P<0.01). Repeated thermal therapy decreased serum levels of ANP (138±27 to 103±19 pg/ml, P<0.01), BNP (43±102 to 32±85 pg/ml, P<0.01), and noradrenaline (44±212 to 313±160 pg/ml, P<0.05), and increased serum levels of ghrelin (110±26 to 156±35 fmoi/ml, P<0.05) and GH (2.4±0.9 to 3.6±1.1 ng/ml, P<0.05). In addition, appetite-loss improved with 11 (85%) of the 13 patients in Sauna group. On the other hand, in Control group, there were no significant changes in indices of cardiac function, serum levels of indices of cardiac function in patients with CHF.

Methods:

Twenty four patients (68±8 years old) with NYHA functional class II or III HF were studied. They were divided into Control (n=11) and Sauna group (n=13). Sauna group underwent the thermal therapy in a far infrared-ray dry sauna system at 60 degrees centigrade for 15 minutes and then kept on bed rest with a blanket for 30 minutes, daily for 2 weeks. Before and after 2-week treatment, serum levels of ghrelin, growth hormone (GH), atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP), and noradrenaline were measured, and a self-assessment questionnaire for appetite-loss was performed.

Repeat Thermal Therapy Increases Serum Level of Ghrelin, and Improves Appetite-Loss in Patients With Chronic Heart Failure

Tsuoyoshi Fukudome, Masaki Miya, Takashi Kihara, Takuro Shinsho, Akinori Masuda, Yoshikiyo Ikeda, Sadatoshi Biro, Shinichi Minogoe, Chuaa Tei, Kagoshima University, Kagoshima, Japan

Background: We have previously reported that repeated thermal therapy improves cardiac function and vascular endothelial function in patients with chronic heart failure (CHF). Ghrelin, a novel growth hormone-releasing peptide isolated from stomach, stimulates food intake and growth hormone secretion. It was reported that ghrelin levels were elevated in patients with CHF and infusions of ghrelin decreased systemic vascular resistance and increased cardiac output in patients with heart failure. Therefore, we investigated the effect of repeated thermal therapy on serum ghrelin levels and indices of cardiac function in patients with CHF.

Beta-Blocker Use and Associated Outcomes Among Hospitalized Heart Failure Patients

Judith E. Mitchell, John Feng, Mian F. Caboral, Locquessa Okpala, Luther T. Clark, David J. Cohen, Harvard Clinical Research Institute, Boston, MA

Background: We have previously reported that repeated thermal therapy improves cardiac function and vascular endothelial function in patients with chronic heart failure (CHF). Ghrelin, a novel growth hormone-releasing peptide isolated from stomach, stimulates food intake and growth hormone secretion. It was reported that ghrelin levels were elevated in patients with CHF and infusions of ghrelin decreased systemic vascular resistance and increased cardiac output in patients with heart failure. Therefore, we investigated the effect of repeated thermal therapy on serum ghrelin levels and indices of cardiac function in patients with CHF.

Methods: Twenty four patients (68±8 years old) with NYHA functional class II or III HF were studied. They were divided into Control (n=11) and Sauna group (n=13). Sauna group underwent the thermal therapy in a far infrared-ray dry sauna system at 60 degrees centigrade for 15 minutes and then kept on bed rest with a blanket for 30 minutes, daily for 2 weeks. Before and after 2-week treatment, serum levels of ghrelin, growth hormone (GH), atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP), and noradrenaline were measured, and a self-assessment questionnaire for appetite-loss was performed.

Results: In Sauna group, repeated thermal therapy for 2 weeks improved cardiac function (ejection fraction: 31±8 to 36±9%, P<0.01, LV Tei index: 0.82±0.29 to 0.69±0.22, P<0.01). Repeated thermal therapy decreased serum levels of ANP (138±27 to 103±19 pg/ml, P<0.01), BNP (43±102 to 32±85 pg/ml, P<0.01), and noradrenaline (44±212 to 313±160 pg/ml, P<0.05), and increased serum levels of ghrelin (110±26 to 156±35 fmoi/ml, P<0.05) and GH (2.4±0.9 to 3.6±1.1 ng/ml, P<0.05). In addition, appetite-loss improved with 11 (85%) of the 13 patients in Sauna group. On the other hand, in Control group, there were no significant changes in indices of cardiac function, serum levels of indices of cardiac function in patients with CHF.

Conclusion: Repeated thermal therapy increased serum concentration of ghrelin, and improved cardiac function and appetite-loss in patients with CHF. It seems to be a promising comprehensive therapy of CHF.

Black Women Hospitalized With Heart Failure Treated Less Often With Beta-Blockers

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Background: Black Beta blockage (BB) therapy reduces morbidity and mortality in patients with heart failure (HF) and impaired systolic function (ISF), EF< 40%. Despite the documented benefits of the therapy, national HF registries report only 50-60% use in pts with HF.

Methods: We sought to examine the pattern of BB utilization in S29 consecutively admitted black pts with HF.

Results: Mean age 70 ±13 (male: 65 ±12 and female: 72 ±14, p<0.001), 64% female, 46% diabetic and 64% with ISF (of which 57% were female). Somewhat higher than the national statistics, 71% of black pts admitted with HF were treated and discharged on a BB. Its use was not related to admission BNP, creatinine, hemoglobin level, diabetic status or age. Pts were more likely to be treated and discharged on a BB if: —1. they were admitted with HF with ISF (p<0.001; fig. 1), —2. the HF was of ischemic etiology (p<0.001) or —3. the pt was male (79% vs. 67%; p=0.004; fig. 2). Allergy, bradycardia, hypotension, significant airway disease and heart block were the most commonly recorded reasons for not using BB, but combined, cited only 5% of the time. “Contradication” was noted without clarification 9% of the time. But in 80% of cases no reason for withholding the drug could be found.

Conclusion: Seventy-one percent of black pts admitted with HF were treated with a BB. Male sex, ischemic etiology and HF with ISF were features associated with increased use. The disparity in the use of BB in black women requires further studies to identify barriers to this treatment.
Consistent Survival Benefit of Carvedilol Over Metoprolol Irrespective of Baseline Characteristics of Heart Failure Patients - Mode of Death Evaluation in COMET

Willem J. Remme, John G. Cleland, Christian Torp-Pedersen, Marco Metra, Andrew Charlesworth, Beatrix Lutger, Philip A. Poole-Wilson, STICARED - Cardiovascular Institute, Rhoon, The Netherlands, University of Hull, Kingston upon Hull, United Kingdom

Background: In the COMET study carvedilol resulted in better overall survival than metoprolol tartrate in 3209 patients with NYHA II-IV heart failure and EF < 35%, followed for an average of 58 months. Whether this effect is consistent irrespective of mode of death and patients baseline characteristics is unknown.

Methods: Of the 1112 total deaths, 972 were adjudicated as cardiovascular (CV), 480 sudden (SD), 365 circulatory failure (CF) and 51 stroke deaths. For each mode of death, the effect of the following baseline variables were assessed: sex, age, NYHA class, ischemic etiology, left ventricular ejection fraction (LVEF), systolic blood pressure, EF, diastolic cardiomyopathy, diabetes, atrial fibrillation, previous myocardial infarction or hypertension, hemoglobin, creatinine, sodium, and ACE inhibitor, spironolactone, digitalis, aspirin/anticoagulant and statin use, and study treatment allocation.

Results: In univariate analyses, carvedilol reduced total and CV mortality, SD and stroke death more than metoprolol in all subgroups (hazard ratios (RR) varying between 0.81-0.85, 0.78-0.81, 0.78-0.82 and 0.31-0.35, resp), but for CHF only in patients with low serum sodium or on digitalis treatments. In multivariate Cox regression analyses carvedilol remained significantly better than metoprolol for total death (RR 0.80, 95% CI 0.77-0.91, p<0.0007), CV mortality (RR 0.80, CI 0.77-0.91, p<0.0009), SD death (RR 0.77, CI 0.64-0.93, P=0.0073) and stroke death (RR 0.37, CI 0.19-0.71, p=0.0227), and showed a non-significant trend for CHF death (RR 0.83, CI 0.66-1.04, p=0.1). There were no interactions between treatment allocation and any of the prespecified baseline characteristics.

Conclusion: Carvedilol results in significantly better survival in most modes of death and a positive trend for CHF death, irrespective of baseline characteristics. This consistent better effect of carvedilol in all prespecified subgroups suggests it to be the preferred beta-blocker in the treatment of heart failure.

Beneficial Effect of Beta Blockers on Survival in Congestive Heart Failure with Normal Ejection Fraction

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Background: Beta blockers have been shown to prolong survival in congestive heart failure (CHF) patients with reduced ejection fraction (EF). However, its effect on survival in CHF patients with normal EF is not well known.

Methods: Detailed chart reviews of 2246 patients with a discharge diagnosis of CHF from a university medical center were performed by medical residents. The diagnosis of CHF was confirmed (definite 87%, probable 13%) by Framingham criteria. Details of clinical, echocardiographic and discharge pharmacy data were collected. Effect of beta blockers on survival was analyzed.

Results: Of the 2246 patients with CHF, 1079 (48%) had normal EF (≥50%). Baseline patient characteristics in beta blocker patients with CHF and normal EF, LVEF 64±8%, age 75±14 years, males 47%, Caucasians 78%, hypertension 56%, diabetes mellitus 28%. Of these patients 62% were on aspirin, 13% on beta blockers, 59% on diuretics, 33% on digoxin and 36% on ACE inhibitors at the time of discharge. The 5 year survival for patients treated with beta blocker therapy was 65% compared to 55% for those receiving no beta blockers (p=0.0017). Adjusting for all comorbidities including age, gender, hypertension, diabetes mellitus and presence of coronary artery disease using the proportional hazards model, use of beta blockers was associated with a better survival (adjusted p=0.01).

Conclusion: Our observational data supports an independent survival benefit with beta blocker therapy in CHF patients with normal EF.

Carvedilol corrects Interventricular And Interventricular Dysynchrony In Chronic Heart Failure.

Pablo F Castro, Sr., Paul Mc Nab, Sr., Alex Blittner, Sr., Douglas Greig, Sr., Juan Carlos Quintana, Sr., Mario Chiong, Sr., Guillermo Diaz-Araya, Sr., Rodrigo Valenzuela, Sr., Ismael Vergara, Sr., Ramon Corbalan, Sr., Sergio Lavandero, Sr., P. Catholic University of Chile, Santiago, Chile, University of Chile, Santiago, Chile

Carvedilol as an adrenergic antagonist, improves left ventricular (LV) remodeling and reduces morbidity and mortality in chronic heart failure (HF) patients. These salutary effects could be related to restoration of cardiac synchrony.

B-type Natriuretic Peptide and Doppler Echocardiography for Identifying CHF patients at Risk of Acute Heart Failure Decompensation during Beta-blockade Titration

Ahmed Ben Driss, Jean-Yves Tabet, Philippe Meurin, Helene Weber, Nathalie Renaud, Anne Grosdemouge, Claude Bourmany, CRCB, Villeuneuve-Saint-Denis, France

Background: As plasma BNP concentrations and Trans Thoracic Echocardiography (TTE) parameters are strongly related to outcome of patients with chronic heart failure (CHF), we hypothesized that BNP and TTE may predict tolerance during beta-blockade titration in stable CHF.

Methods and results: Fifty consecutive stable CHF patients (age: 61±2 years, male: 88%) with Left Ventricular Ejection Fraction (LVEF) <40% and creatinemia <250 µmol/l were included in the study. Beta-blockers were started and/or increased as recommended by ESC Guidelines. Plasma BNP (Biostel) and TTE (GE Vivid 5) were performed the same day in a blind manner, at admission and once a week during 3 weeks.

At admission, NYHA class was 2.3±0.1, mean creatinemia: 99±3 µmol/l, plasma BNP: 49±13 pg/ml, UVEF: 28±1%, E/A ratio: 1.9±2.2, EF/A ratio : 9±0.9, Echocardiographic severity of pulmonary artery pressure by the CW Doppler (PAP): 42±7 mmHg and inferior vena cava diameter (IVC): 16±5 mm. Acute heart failure (HF) occurred in 32% of the study population (16/50). On univariate analysis, age and admission values of NYHA class, plasma BNP concentration, log BNP, E/A ratio, EDV, systolic PAP and PAP diameter predicted increased risk of acute HF during beta-blockade titration. On multivariate analysis, only BNP concentration predicted acute HF decompensation. The combination of infrahuman BNP (44±9 pg/ml) and supramedian EDT value (147 ms) was associated with 100% negative predictive value of acute HF decompensation during beta-blockade titration.

Conclusion: Carvedilol in patients with heart failure and LV dysfunction improves intraventricular synchrony.

POSTER SESSION

1104 Cardiac Transplantation: Basic and Clinical

Monday, March 07, 2005, 1:30 p.m.-5:00 p.m.
Orange County Convention Center, Hall E1
Presentation Hour: 3:30 p.m.-4:30 p.m.

1104-105 Influence of Donor Transmitted Atherosclerosis on the Development of Cardiac Allograft Vasculopathy

Haikun Li, Koji Tanaka, Hitoshi Arzai, Brandy Oesser, Jon Kobashigawa, Jonathan M. Tobis, University of California at Los Angeles, Los Angeles, CA

Background: Following orthotopic heart transplantation (OHT), coronary artery disease is a common cause of impaired allograft function. Transmitted atherosclerosis may contribute to disease development.

Methods: Intravascular ultrasound imaging was performed in 301 recipients at 1.3±0.6 months and again at 12.2±0.8 months after OHT. 1103 segments were matched from 333 coronary arteries between studies 1 year apart. In each segment, maximum intimal thickness (MIT), lumen area (LA), external elastic membrane area (EEM area) and internal area (IA) were measured. Segments with MIT of ≥0.5mm in MIT (progression of DL); 78% had a change >0.5mm

Results: The mean donor age was 29.6±12.7 years old and 197 segments from 95 arteries in 89(30%) hearts demonstrated DL. At 1 year after OHT, 16% of recipients with HF, NYHA class III-IV, LVEF <40%, under usual treatment, except by β-blockers or pacemaker were included. Multigate equilibrium blood pool scintigraphy was used to measure intraventricular and intraventricular synchrony and LVEF at baseline and after 6 months of carvedilol. Phase image analysis was applied to the scintigraphic data and mean for the phases calculated for the ventricle. LV intraventricular synchrony was calculated as the difference between the mean phase angle of each ventricle and the intraventricular synchrony using the standard deviation of the phase angles.

Results: Mean age was 55±13 years, 22 (71%) male, 11 (35%) patients had ischametic etiology of death (9.2% LBBB). After 6 months of therapy with carvedilol (maintenance dose = 25 mg, range 6.25 to 50 mg per day), there was an improvement in functional class and the 6-min-walk-distance (499±18 to 534±17 meters, p=0.032). The LVEF increased from 24%±8 to 31±13% (p<0.001). Patients with the worst synchrony under 50 percentile at baseline improved after treatment: intraventricular (113±7 vs. 94±10 msec, p= 0.02) and interventricular (62.8±7 vs. 39 ± 9 msec, p=0.02).

The patients with non-ischametic etiology had a significant improvement in both intraventricular (105.3±8 vs. 78.3±12 msec, p=0.04) and interventricular synchrony (68.1±3 vs 35.3±12 msec, p=0.02). Patients without LBBB improved the intraventricular synchrony (112.1±8 vs. 88.5±11.2 msec, p=0.01 ). No significant changes were observed in patients with ischametic etiology or LBBB.

Conclusion: Carvedilol in patients with heart failure and LV dysfunction improves intraventricular synchrony. These findings could be related to favourable effects in cardiac remodeling.

Fondetcy 1091092 and FONDAP 1501006
in MIT, 6% had a decrease ≥ 0.5 mm in MIT (regression of DL); and 10.1% of patients with DL developed NL. Of the 333 arteries, 16 segments had progression of DL and 51 segments had NL; 18 of 69 segments came from 14 of 95 (15%) arteries with DL, and 49 of 67 segments came from 36 of 108 (33%) arteries without DL (p=0.9). Lumen loss and intimal growth in NL were greater than in DL (ΔLA: -3.5±2.7mm² vs. -0.89±3.0mm², p<0.0001; ΔA: 4.5±2.1mm² vs. 0.54±2.1mm², p<0.0001). For the same degree of increase in LA (ΔA: 4.5±2.1mm² vs. 1.2±2.9mm², p=0.6), the NL tended to have vessel enlargement (ΔEEM area=0.93±2.6mm², p=0.01), and the segments with progression of DL had no significant change in EEM area (ΔEEM area=0.10±2.0mm², p=0.8). The presence of NL was similar in arteries with and without progression of DL (14.3% vs 8.6%, p=0.6).

Conclusions: In the first year after OHT, DL do not act as a nidus for further intimal growth and may not be as susceptible to CAV as segments without DL. The presence of a DL also does not accelerate intimal thickening elsewhere in the artery. The presence of DL may impede compensatory positive remodeling as intimal thickening progresses.

1104-160
High Rejection Score Is Associated With Lower Coronary Flow Reserve in Heart Transplantation Recipients With Normal Coronary Angiography

Francesco Tona, Aida Linda Caforio, Antonio Gambino, Cristiano Sarais, Giuseppe Feltin, Giuseppe Toscario, Diego Calzolari, Annalisa Vinci, Maria Grazia Leone, Annalisa Angelini, Angelo Ramondo, Gaetano Thiene, Gino Gerosa, Sabino Illiceto, University of Padova, Padova, Italy, University of Cagliari, Cagliari, Italy

Background. Coronary flow reserve (CFR) is increasingly used to assess the functional significance of cardiac allograft vasculopathy (CAV). The factors determining CFR in heart transplant recipients with normal coronary angiography are ill defined.

Methods. 36 consecutive recipients (24 male, aged 50±13 years at heart transplantation) were studied at 6±4.5 years after heart transplantation. Rejection scores (RS) on endomyocardial biopsy were calculated (ISHLT grades: 0=0; 1A=1; 1B=2; 2=3; 3A=4; 3B=5; 4=6) in the first year and during the whole follow-up. RS including only severe grades (≥3A) were also calculated. Coronary blood flow velocity in the left anterior coronary descending artery was noninvasively detected by contrast-enhanced transthoracic echocardiography (CE-TTE) at rest and during intravenous infusion of adenosine (0.14mg/kg/min). CFR was obtained as the ratio of hyperemic diastolic peak velocity (DPV) to resting DPV. All patients had normal findings on left ventricular angiography and normal coronary angiography at a normal left ventricular mass. Comparison of means was made by Student’s t test. A p value <0.05 was considered to be significant.

Results. 7 patients (19%) had a CFR < 2.9 (group A) and 29 (81%) had a CFR ≥ 2.9 (group B). Systolic and diastolic blood pressure, heart rate and blood haemoglobin were similar in the two groups. Group A had a higher number of treated rejections in the first year (4.5±2.6 vs 2.3±2.2, p=0.01) and in the whole follow-up (5.1±3 vs 2.6±2, p=0.01). RS in the first year and in the whole follow-up were higher in group A (1.71±0.49 vs 1.2±0.64, p=0.04; 1.69±0.59 vs 1.16±0.49, p=0.02, respectively) as well as RS including only severe grades (≥3A) in the first year (0.26±0.14 vs 0.14±0.13, p=0.04) and in the whole follow-up (0.23±0.17 vs 0.13±0.09, p=0.04).

Conclusions. In heart transplant patients with angiographically normal coronary arteries, CFR by CE-TTE was inversely related to the number of previous rejection episodes. Since a high rejection burden is associated with increased risk of CAV, a CFR reduction may be an early marker of CAV. Prospective studies are warranted.

1104-167
Anemia is Associated with a Significant Increase in Mortality in the Orthotopic Heart Transplant Population

Ashley A. Bucelli, Tamara B. Horwich, Gregg C. Fonarow, Jignesh Patel, Jon A. Kobashigawa, University of California, Los Angeles, Los Angeles, CA

Background. Reduced hemoglobin (Hb) in orthotopic heart transplant (OHT) patients is frequently observed. There is limited data, however, analyzing the relationship between anemia and survival in this population. The aim of our study was to evaluate this relationship.

Methods. We analyzed a cohort of 813 heart transplant recipients from 1984-2004. The cohort was divided into 2 groups of anemic and non-anemic. Anemia was defined as Hb<11.0g/dL in women and <12g/dL in men. Hb values were taken from 12-20 weeks post OHT.

Results. Mean age was 53 years. The cohort was 74.7% male and 25.3% female. Mean Hb was 12.2±2; values ranged from 5.9 to 16.8. 33.7% of the cohort was anemic. Hb groups were similar in gender, BMI, CAD pre-OHT, and use of myophenolate mofetil and tacrolimus. Lower Hb was associated with increased age, higher creatinine (Cr), and use of prednisone and cyclosporine. Kaplan-Meier survival curves at 1 year showed improved survival in non-anemic versus anemic patients (94.5% and 89.4%, respectively; p value 0.0051). In multivariate analysis adjusted for recipient age, gender, pre-OHT heart failure etiology, BMI, Cr, and immunosuppressive regimen, anemia was an independent predictor of mortality (relative risk 2.5, 95% CI 1.1 to 5.6).

Conclusions. In the post OHT population anemia is associated with worsened 1-year survival independent of renal function. Further investigation into the significance of this association should be considered.

1104-168
Effects of Gender on Peak Oxygen Consumption and Survival in Ambulatory Heart Failure Patients

Sammy Elmariah, Lee R. Goldberg, Michael T. Allen, Andrew Kao, Hospital of the University of Pennsylvania, Philadelphia, PA, Mid-America Heart Institute, Kansas City, MO

Background. The predictive ability of peak exercise oxygen consumption values (PVO2) in heart failure patients (HF pts) is not well established. This study examines gender effects on PVO2 and survival in HF pts.

Methods. 694 consecutive ambulatory HF pts (mean age 59±12 yrs; 28% female; mean LVEF 26±12%; 73% on β blocker) underwent symptom-limited exercise tests with breath-by-breath expired gas analyses using ramped treadmill protocols. Comparisons between groups were made using χ² tests or chi-square analyses. Kaplan-Meier survival curves were generated for each gender and compared using log rank tests. Results. Women had significantly lower PVO2 than men (14.0±4.8 vs 16.6±7.1 ml/kg/min; p<0.0001); despite being younger (48±11.5 vs 53±22.14 yrs; p=0.0001), they had a higher LVEF (29±13 vs 25±11%; p=0.0003). The 1 year survival was significantly lower for men than for women (81 vs 94%, p=0.0001). This lower survival in men was seen across each Weber functional class.

One Year Transplant-Free Survival (%)  

Weber Class | Men | Women  
---|---|---  
A | 85 | 85  
B | 90 | 95  
C | 77 | 85  
D | 29 | 84  

Cox regression analyses confirmed the predictive effects of gender on survival when controlling for PVO2, age, β blocker use and type of cardiomyopathy. The PVO2 associated with 85% 1 year survival was significantly higher in men than in women (11.5 vs 10.0 ml/kg/min). Conclusion. Women had significantly lower PVO2 than men, but had a better survival at all levels of exercise capacity. The current practice of uniform application of PVO2 to determine optimal timing of cardiac transplantation should be re-examined.

1104-169
Human Menstrual Blood Is a Potential Cell Source for Cardiac Stem Cell Therapy

Shunichiro Miyashita, Naoko Hida, Nobuhiro Nishiyama, Tomoko Tanaka, Tohru Kyono, Saturo Kyo, Satoshi Ogawa, Akira Umekaze, Keio University School of Medicine, Tokyo, Japan, National Research Institute for Child Health and Development, Tokyo, Japan

Mesenchymal stem cell (MSC) transplantation slightly improved impaired cardiac function but the improvement was insufficient, because the main effect of MSC was attributable to neovascularization, not to cardiomyogenesis (CM). To achieve CM, in vitro selection of a monoclonal cell-line with a high rate of CM would be required, because not all MSC have the potential for CM. In the present study we focused on the endometrium as a source of MSC, because endometrial MSCs (E-MSCs) can be repeatedly, painlessly, and easily obtained from a younger and large population than marrow derived MSCs, and thus a cell bank system covering all HLA types can be established.

Method and Results. Endometrium-derived cells were obtained from a 52-year-old woman by the limiting dilution method. We attempted to prolong the life span of the endometrium-derived cells by infecting them with retrovirus encoding HPV16 E6/E7 and HNTER. The E-MSCs that were established were co-cultured with fetal murine cardiomyocytes without treating 5-azaCydine (5-azaCdC). On day 3 of co-cultivation, the GFP-labeled E-MSCs began spontaneously beating, and on day 5 almost all of the E-MSCs contracted rhythmically and synchronously, suggesting the presence of electrical communication between the E-MSCs. The cardiomyocyte-specific pacemaker-like and plateau action potentials were recorded with a microelectrode containing fluorescent dye (Alexa568), which was simultaneously injected into the cell to confirm the electric potential recorded from the E-MSC. The E-MSC-derived cardiomyocytes stained positive for cardiac troponin-I (clear striation was observed) and connexin 43 (diffuse dot-like staining at the margin of cell) by the immunohistochemical method. Cardiac troponin-I-positive cardiomyocytes accounted for 35 % of the nucleated E-MSCs. E-MSCs were co-cultivated in the same dish with mouse cardiomyocytes separated by a collagen membrane, and thus cell-fusion was not a major cause of CM in the E-MSC.

Conclusion. For the first time we established a human E-MSC cell-line from the endometrium whose CM rate was very high without 5-azaCdC. Human menstrual blood may be a major cell source for stem cell therapy to achieve cardiomyogenesis.
Using Flow Cytometry to Eliminate High Risk Donors Without the Need for a Direct Prospective Crossmatch for Sensitized Pediatric Heart Transplant Recipients

Steven Zarepski, Thomas M. Ellis, Jane Zlotucha, Robert D. Jaques, James S. Tedwell, Kathy A. Marshall, Shulberger, Medical College of Wisconsin, Milwaukee, WI, Blood Center of Southeast Wisconsin, Milwaukee, WI.

Background: HLA sensitization is a problem for heart transplant (HTx) recipients. To limit risks, one may require a prospective crossmatch (CMX) severely limiting the donor pool. We used flow cytometry donor phenotyping to predict CMX results.

Methods: A bead-based flow cytometry was used to identify anti-HLA Ab in a child listed for HTx. "Donors" were chosen from a pool of CMX negative blood donor samples. Using recipient phenotyping, direct T and B cell CMX studies were run for potential donors against whose HLA type the recipient had specific Ab (Group 1, n=7) and those without donor specific anti-HLA Ab (Group 2, n=7). Results were expressed as MCD (mean channel difference between control and recipient serum). A positive T cell CMX was defined as MCD>50 whereas MCD>100 constituted a positive B cell result. These are our clinically validated standards.

Results: Table 1: T cell reactivity was lower in Group 2 than Group 1 (29% vs. 100%, p=.02). B cell reactivity was also lower for Group 2 (14% vs. 100%, p=.005). The predicted CMX was 100% specific in detecting a positive CMX for T and B cells.

Conclusions: Sensitized patients are at risk either due to the wait for a CMX negative donor or undergoing HTx with a positive CMX. Currently, potentially suitable donor organs are declined for lack of a CMX; these organs may then be allocated to more distant recipients or not used at all. While further studies are needed, flow cytometry guided screening has the potential to improve organ availability for sensitized patients as well as the overall allocation process.

Table 1: Group 1 = Positive Predicted CMX, Group 2 = Negative Predicted CMX.

<table>
<thead>
<tr>
<th>Donor HLA Type</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T Cell</td>
<td>B Cell</td>
</tr>
<tr>
<td>A2,1A9,25,B9,D8,D12</td>
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<td>A22,23,30,B18,D9,D3</td>
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<tr>
<td>A29,2B13,45,DR,D17</td>
<td>107</td>
<td>147</td>
</tr>
</tbody>
</table>

Rate of positivity 77/100 vs. 77/100%

T104-177 Calcineurin Inhibitor-Free Renal Sparing Protocol For Patients with Renal Insufficiency After Heart Transplantation: Trouble On the Horizon?

Jan A. Kobashigawa, Jignesh K. Patel, Angela Marquez, Brandy T. Oser, Angela Velazco, Rowella Camara, Hillary Liles, University of California at Los Angeles, Los Angeles, CA.

Background: One of the major complications after heart transplantation is renal dysfunction due to the chronic use of calcineurin inhibitors (CI). Recent reports in small number of patients have suggested that cyclosporine can be withdrawn safely with subsequent decrease in serum creatinine (Scr). We report our experience in heart transplant patients on cyclosporine (15) or tacrolimus (3), mycophenolate mofetil (MMF), prednisone with regard to withdrawal of CI in patients experiencing renal dysfunction.

Methods: Between 11/02 and 2/04, 18 patients (11-12 years after transplant) with Scr >2.4 mg/dl began our renal sparing protocol (RSP). To start the RSP, CI dose was halved with the initiation of sirolimus 1-2 mg/day added to pre-existing MMF prednisone. After target levels of sirolimus (4-6 ng/mL) and MMF (2-5 mcg/mL) were documented, CI was discontinued (d/c). After d/c of CI, an echo was performed 4 weeks later and a biopsy was performed 6 weeks later.

Results: 1/11 (9%) patients experienced a decrease in Scr within ten months after d/c of CI. Seven patients had complications that led to the d/c of RSP. Three patients had acute decrease of left-ventricular ejection fraction (40% at 4 mos, 40% at 7 mos, and 20% at 10 mos), which required anti-rejection therapy; 1 patient had worsening renal failure that led to hemodialysis at 1 mos; 1 patient with profound diarrhea at 7 mos; 1 patient with severe sepsis that led to death at 3 mos; 1 patient with severe anemia at 4 mos after d/c of CI. For the remaining 11 patients in the group, the average peak Scr (between 3 mos prior to the start of the RSP and 1 mos after the start of the RSP), significantly decreased by 10 mos after d/c of CI (8.4 vs. 0.8 decreased to 2.5 vs. 0.8, p=0.000). Echocardiograms for these 11 patients at 4 weeks after d/c of CI were normal. Biopsies for these 11 patients at 6 weeks after d/c of CI were negative for rejection.

Conclusion: Renal sparing protocols involving withdrawal of cyclosporine/tacrolimus with maintenance mycophenolate mofetil and sirolimus immunosuppression should be performed with careful follow-up to detect any adverse effects. For many patients, this protocol appears to be effective in preserving renal function.
Achieving Optimal Stress Level During Exercise Testing: Should We Revisit Our Cutoff Points?

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Background: The age-predicted maximal heart rate (PMHR) equation (220 - Age) is commonly used as a criterion for predicting maximal heart rate possible during exercise testing. Adequate stress level is when the patient achieves ≥85% of this equation. Recently, the equation (208 - 0.7 x Age) has been suggested to better estimate PMHR especially in elderly patient by 10-20 beats. We tested the hypothesis that 208−0.7×Age

Methods: The study population comprised of 310 patients referred for a routine bicycle exercise ECG test at Tampere University Hospital. Of these, 112 had angiographically proven CAD, whereas 50 had no CAD according to angiography and 148 were clinically normal with respect to cardiac diseases. For each patient, the maximum values of ST/HR hysteresis, ST/HR index, end-exercise ST depression and ST depression at 3 minutes of recovery were determined from the 12-lead system (avL, avR, and V1 excluded). In addition, the heart rate recovery from peak exercise to 1 minute of recovery (HR Recovery) was calculated. The data were analyzed off-line by a modified CASE® (GE Medical Systems).

Results: The diagnostic properties were compared by receiver-operating characteristic (ROC) analysis. The area under the ROC curve (AUC) of ST/HR hysteresis was 88.1 %, which was significantly (p<0.001) larger than that of the other variables, indicating the superior overall diagnostic performance of the ST/HR hysteresis (Fig. 1).

Conclusion: The ST/HR hysteresis can significantly improve the diagnostic performance and clinical utility of the exercise ECG test for the detection of CAD.
pain and ECG changes were classified high risk by the DTS but intermediate risk by the modified DTS. For the low and intermediate risk group, 100% of the time the modified equation agreed with the DTS.

Conclusion: Our modification of the DTS agrees with the DTS 100% of the time in low and intermediate risk patients and eliminates the need for the use of the nomogram. The modified equation is easier to use than the nomogram and conforms to the practice of using MET as universal measure of work capacity.

Noninvasive Assessment Of Hemodynamic Response To Moderate Physical Activity In Patients Undergoing Resynchronization Therapy

Thomas Berger, Ralf Harun Zwic, Franz Xaver Rothinger, Gerhard Poetl, R. Pister, H. Hoernmag, Olmar Pachinger, Florian Hintinger, Internal Medicine, Innsbruck, Austria

Background: Cardiac resynchronization therapy (CRT) offers beneficial effects on exercise tolerance and quality of life in patients with congestive heart failure. However, little is known about the hemodynamic response to CRT in patients undergoing moderate physical activity. The aim of our study was to evaluate noninvasively the immediate effects of CRT during submaximal exercise on hemodynamic parameters.

Methods: Eleven patients (4F, age 68±6y; NYHA II-III; UFE130±30sec; biventricular DDSR pacemaker implantation >3 months) underwent treadmill exercise testing using the modified Bruce protocol (2.7km/h; 9% elevation; 4.6 METS).

Heart rate (HR), mean blood pressure (MBP), mean cardiac output (CO) and total peripheral resistance (TPR) were obtained noninvasively by means of biopendence cardiography (TaskForceMonitor™, CNSystems). Measurements were performed during a 3-minute exercise period followed by a 10-minute resting period for right-(RV), left-(LV) and biventricular (BV) ativoventricular-synchronized pacing (VDD100) as well as during sinus rhythm (VVI100) in each patient. Complete hemodynamic recovery in-between the different pacing modes was proven by measurements of blood lactate levels.

Results: BV and LV pacing increased CO (107±14% and 107±12%; P<0.05) as compared to RV pacing (given as 100%) and sinus rhythm (99±14%). BFmean was increased during RV and LV pacing (110±22% and 104±15%; P<0.01 in comparison to CO) in non-responders (103±3%) compared to responders (103±3%; P<0.05). Interestingly, the increase in CO between BV and RV was slightly augmented during exercise as compared to resting conditions (11% vs. 14%, n.s.); HR, TPR and blood lactate levels did not show any changes within the different pacing modes as compared to sinus rhythm.

Conclusion: Biventricular pacing significantly increased CO but did not seem to improve hemodynamics in patients with congestive heart failure during rest as well as during physical exercise. The beneficial effect of CRT may be augmented during moderate physical activity.

Evidence That Cerebral Oxygenation Is Impaired During Exercise In Patients With Left Ventricular Dysfunction

Akira Koiita, Osamu Nagayama, Masayo Hoshimoto, Akihiko Tajima, Keiko Okawa, Tadamon Azaawa, Long Tai Fu, Hanuki Itoh, The Cardiovascular Institute, Tokyo, Japan

Background: Quite recently, we reported that the cerebral oxyhemoglobin (O2Hb), a parameter reflecting cerebral blood flow and cerebral oxygenation, decreased during exercise in nearly half of patients with dilated cardiomyopathy. The rate of the decrease was even higher among those with lower left ventricular ejection fraction (LVEF). These findings strongly suggest that the decrease in cerebral O2Hb during exercise in these patients reflects a cerebral hypoxia resulting from impaired O2 transport to the brain. In the present study we evaluated whether the inhibition of supplementary O2 diminishes the decrease in cerebral O2Hb during exercise in patients with left ventricular dysfunction.

Methods: Ten patients with LVEF of less than 50% (Age, 62 ± 13 years; mean LVEF, 33 ± 11%)-were included. A clear observable decrease in cerebral O2Hb during premaximal exercise testing underwent additional two symptom-limited incremental exercise tests in the present study. Cerebral O2Hb was continuously monitored during exercise using near-infrared spectroscopy.

Results: In the control exercise test, cerebral O2Hb initially remained constant at lower work rate, and then began to decrease at higher work rates. When the subjects breathed 50% O2, this decrease in cerebral O2Hb was diminished. The change of cerebral O2Hb from rest to peak exercise during the test under 50% O2 was significantly higher than that during the control test (-0.23 ± 1.89 vs. -2.47 ± 1.57 µmol/ml, p=0.002). Similarly, the change of the cerebral tissue oxygenation index was significantly higher in the test under 50% O2 (0.45 ± 4.46 vs. -3.33 ± 3.06 µmol/ml, p=0.023).

Conclusion: Our present findings strongly suggest, firstly, that exercise of moderate to high intensity can impair cerebral oxygenation in patients with left ventricular dysfunction, and secondly, that breathing of supplemental O2 sets off this impairment.

Prognostic Value of Cardiopulmonary Exercise Testing in a Group of Female Patients With Heart Failure

Ross Arena, Marco Guazzi, Jonathan Myers, Virginia Commonwealth University, Richmond, VA, University of Milano, Milano, Italy

Background: Cardiopulmonary exercise testing clearly holds prognostic value in the heart failure (HF) population. Peak oxygen consumption (VO2) and the relationship between minute ventilation (VE) and carbon dioxide production (VCO2) have emerged as the most frequently assessed variables. Studies supporting the clinical value of these variables in HF have been primarily using male subjects. Specifically, peak VO2 and VE/VCO2 slope are prognostically similar in an all-female HF group compared to previous investigations using male subjects. The purpose of the present study is to examine the prognostic value of peak VO2 and VE/VCO2 slope in an all-female HF group.

Methods: Sixty-one female subjects diagnosed with HF participated in this study. Mean age and ejection fraction were 58.8 years (±11.3) and 31.3% (±12.2). Cox regression analysis examined the ability of peak VO2 and VE/VCO2 slope to predict all-cause mortality. Receiver Operating Characteristic (ROC) analysis determined optimal prognostic threshold values for peak VO2 and VE/VCO2 slope.

Results: Mean peak RER, peak VO2, and VE/VCO2 slope values were 1.0 (±0.1), 13.0 ml/kg/min (±4.0), and 35.9 (±8.1) respectively. There were 16 deaths during the tracking period (mean = 27.2 months (±8.1)). Peak VO2 (Chi-square: 5.5; p=0.02) and VE/VCO2 slope (Chi-square: 14.1; p=0.001) were both univariate predictors of mortality. Peak VO2 did not add additional predictive value to VE/VCO2 slope in a multivariate model (Residual Chi-square: 0.63; p=0.40). The optimal prognostic threshold values for peak VO2 and VE/VCO2 slope were 12.1 ml/kg/min (60% sensitivity, 62% specificity) and 35.5 (71% sensitivity, 69% specificity) respectively.

Conclusion: The results of the present study indicate peak VO2 and VE/VCO2 slope hold similar prognostic characteristics in an all-female HF group compared to previous investigations primarily using male subjects. Specifically, peak VO2 and VE/VCO2 slope are prognostically similar although the latter variable outperforms the former. Optimal threshold values for these variables were also found to be similar to findings reported in other investigations. Separate, gender-based, prognostic classification schemes may therefore not be necessary for individuals with HF undergoing cardiopulmonary exercise testing.
METHODS: 17 consecutive pts (all with LBBB,QRS≥160msec (193±14msec), 13 with idiopathic dilated cardiomyopathy, 4 with ischemic cardiomyopathy, 16 males, aged 46-70 years, left ventricular ejection fraction (LVEF):24% left ventricular end-diastolic diameter (LVDD):74±13 mm) were studied without (Nopace) and with Biv. CFR in the distal LAD territory (modified 2 chamber apical view, 7MHz transducer) was estimated post adenose infusion 140mg/kg/min for 4 min (CFR=ratio of velocity-time integral of VTIs of diastolic phase post adenose infusion/baseline). CFR was evaluated at No pace and Biv. Study conditions were changed on a random sequence.

RESULTS: Diastolic velocity profiles were similar between Nopace/Biv at rest (cm: 7.4±2.8/7.5±2.8). However, they were greater post adenose in Biv (11±7 vs 13.4±9, p=0.06) resulting in greater CFR (1.4±0.5 vs 1.7 ±9.6, p=0.001). The % increase of CFR (%ID) was lower when Biv (25±35 vs 0.05). CFR Biv was related to CFR Nopace (CFR Biv/No = 0.8±0.8%CFRNopace, n=7, p=0.01). Moreover, the %CFR was inversely related to the degree of LV dilatation: (%CFR vs LVDD=0.70, p=0.024) as well as to the EF (±0.56, p<0.001). CFR was not related to any of the CFR parameters.

CONCLUSION: In patients with severe left ventricular systolic dysfunction and left bundle branch block, biventricular pacing was related to an improvement of CFR at the LAD. Baseline CFR as well as the degree of LV dilatation and dysfunction affected the CFR changes. Thus, changes of microvascular hemodynamics in the LAD territory, related to the respective CFR, might be a parameter contributing to the beneficial effects exerted by biventricular pacing since decreased CFR is the hallmark of myocardial hibernation.

2:30 p.m.

31T-75 Heart Rate Variability Predicts Adverse Outcome Among Cardiac Resynchronization Therapy Patients
F.R. Gilliam, Maureen McGuire, Gerrard M. Carlson, Tim Pratt, Duke University Medical Center, Durham, NC, Guidant Corporation, St. Paul, MN

Background: Cardiac resynchronization therapy with defibrillation (CRT-D) provides therapy in treatment of congestive heart failure (HF). Decreased heart rate variability (HRV) is an indicator of autonomic dysfunction and is regarded as a predictor of HF mortality. The present study evaluated the utility of HRV measured via the implanted CRT-D device in predicting future mortality.

Design: The Heart Failure-Heart Rate Variability (HF-HRV) Registry is an ongoing study that has enrolled 1409 HF patients who received a Guidant CONTAK RENEWAL CRTD. Patients are followed for one-year post-implant. Patients’ Activity Log (a device measure of activity level) and quality of life (QOL; Minnesota Living with Heart Failure Questionnaire) data were obtained at implant, HRV measures included: mean, minimum, and maximum heart rate, SDANN (standard deviation of average five-minute intrinsic RR intervals), and HRV Footprint; these measures were collected at the 2-week follow-up. These baseline measures were used to predict mortality.

Results: Independent baseline predictors of mortality are shown in the Table. Stepwise logistic regression analysis indicated that, together, baseline HRV Footprint and Activity Log were the most significant predictors of future mortality.

Conclusion: These data suggest that HRV and activity levels soon after implant predict future mortality. Future analyses will evaluate how changes over time in these variables are related to mortality and morbidity.

3:00 p.m.

31T-76 Left Ventricular Dysynchrony Predicts Prognosis After Cardiac Resynchronization Therapy
Gabe B. Bleeker, Jeroen J. Bax, Sander G. Molhoek, Eduard R. Holman, Paul Steendijk, Ernst E. van der Wall, Martin J. Schalij, Leiden University Medical Center, Leiden, The Netherlands

Background: Cardiac resynchronization therapy (CRT) is considered a major breakthrough in the treatment of patients with dilated cardiomyopathy and advanced heart failure, however, not all patients respond and therefore pre-implantation identification of responders is needed. In the present study, the prognostic value of LV dysynchrony in patients undergoing CRT was assessed.

Methods: Eighty-five patients with end-stage heart failure, QRS duration >120 ms and LBBB were evaluated by tissue Doppler imaging before CRT. At baseline and 6 months follow-up, NYHA class, quality of life and 6-minute walking distance, LV volumes and LV ejection fraction (EF) were determined. Events (death, hospitalization for decompensated heart failure) were obtained during 1-year follow-up.

Results: Responders (74%) and non-responders (26%) had comparable baseline characteristics, except for a larger dysynchrony in responders (87±49 ms versus 35±20 ms, P=0.01). Patients with no or minimal dysynchrony (<40 ms) had a low likelihood of improvement in clinical parameters and reverse remodeling, whereas patients with extensive dysynchrony (>80 ms) had a high likelihood of response. Using a cutoff value of 65 ms for LV dysynchrony, a sensitivity of 81% and specificity of 81% to predict response to CRT were obtained. Patients with dysynchrony >65 ms had an excellent prognosis (6% event-rate) after CRT, as compared to a 50% event-rate in patients with dysynchrony <65 ms (P=0.001).

Conclusion: Patients with extensive LV dysynchrony (>65 ms) responded well to CRT and had an excellent prognosis at 1 year follow-up.

3:15 p.m.

31T-77 Cost-Effectiveness of Cardiac-Resynchronization Therapy With and Without a Defibrillator in COMPANION Heart Failure Patients
Arthur M. Feltman, Gregory de Lissogny, Michael R. Bristow, Leslie A. Saxon, Teresa De Marco, David A. Kass, John Boehner, Steven Singh, David J. Whellan, Peter Carson, Audra Boscoe, Timothy Baker, Matthew R. Gunderman, Jefferson Medical College, Philadelphia, PA, University of Colorado Health Sciences Center, Denver, CO

Background: The COMPANION trial concluded that cardiac-resynchronization therapy with either a pacemaker (CRT-P) or defibrillator (CRT-D) in combination with optimal pharmacological therapy (OPT) decreased combined risk of death from any cause or first hospitalization compared with OPT alone. We analyzed hospitalization costs and incremental cost-effectiveness ratios (ICER) of CRT-P and CRT-D relative to OPT for COMPANION patients.

Methods: Intent-to-treat trial data were modeled to project the ICER of CRT-D and CRT-P relative to OPT over a base case 5-year treatment episode from a third-party payer (Medicare) perspective. Mortality for CRT-P, CRT-D, and OPT was modeled using an exponential function that achieved good fit with observed survival data. Monthly probability of hospital admission for each arm was derived by averaging 24 sequential months of adjudicated case report form data. Cost of hospital admission was calculated by mapping adjudicated data to an appropriate DRG and corresponding physician fees. All-cause hospitalization and all-cause mortality were used in base case analysis and both were discounted at 3% per annum. The beneficial impact of CRT-P or CRT-D on quality of life was not incorporated into this analysis.

Results: In the 5-year base case analysis, CRT-D was associated with a 20% (or $7,698) reduction in cost of follow-up hospitalization. CRT-D analysis also demonstrated increased survival of 0.50 years with additional costs of $18,612 and a resultant ICER of $36,870/life-year saved relative to OPT. CRT-P resulted in a similar reduction in cost of follow-up hospitalization. CRT-D analysis also demonstrated reduced hospitalization rates, and episode duration yielded a range of results, e.g., increasing significant mortality benefit. Sensitivity analysis examining effects of varying survival rates, $36,870/life-year saved relative to OPT, well within the accepted range for innovative therapy.
Evidence that Hypertrophic Cardiomyopathy is a Disease Characterized By Predominantly Left Ventricular Outflow Tract Obstruction

Martin S. Maron, Iacopo Olivotto, Andrea G. Zenovich, James E. Udelson, Mark S. Link, Natalie G. Pandian, Jeffrey T. Kuhn, Susan A. Casey, Stefano Nistico, Franco Cecchi, Barry Maron, Tufts-New England Medical Center, Boston, MA, Minneapolis Heart Institute Foundation, Minneapolis, MN

Background: Most patients with hypertrophic cardiomyopathy (HCM) are thought to have the nonobstructive form of the disease without a subaortic gradient. However, this characterization is based predominantly on measurement of left ventricular (LV) outflow tract obstruction under resting conditions. However, the proportion of patients without obstruction at rest who exhibit mechanical impedance to LV outflow with physiologic provocation remains unresolved.

Hypothesis: Define prevalence and clinical profile of LV outflow obstruction (i.e., ≥ 30 mmHg) in a large HCM cohort. Methods: We analyzed 221 consecutive HCM patients from 3 centers in U.S. and Italy (mean age 43±16 years) and measured LV outflow gradient at rest by continuous wave Doppler. Patients with LV outflow gradient ≥ 50 mmHg at rest were also evaluated with Valsalva, and Bruce protocol stress echocardiography.

Results: Of 221 patients, 91 (41%) had an outflow gradient ≥ 50 mmHg at rest. Of the other 130 patients with rest gradient < 50 mmHg, ≥ 65 (ie., 50%, and 29% of the 221) developed physiologically significant ROC mechanical impedance to LV outflow following cessation of exercise with gradient ≥ 30 mmHg (including 45 patients with gradients 50 to 120 mmHg) measured with CW Doppler; the remaining 65 patients had no gradient at rest or exercise. Therefore, for the overall study group (n=221), 156 or 70% of 221 HCM patients exhibited mechanical obstruction to LV outflow at rest and/or with exercise. Most patients with latent gradients evident only with exercise (38/65; 58%) had no or mild symptoms; only 27 (41%) had severe for this evolution which carries on an ominous prognosis.

Conclusions: HCM is most appropriately characterized as a predominately obstructive disease (ie.,70% of patients) in which physiologically relevant LV outflow gradients are commonly identified by exercise testing. These prospective data justify routine stress echocardiography to define obstruction in HCM patients with obvious application to management strategies.

Gender-Related Differences in the Clinical Presentation and Outcome of of Hypertrophic Cardiomyopathy

Iacopo Olivotto, Martin S. Maron, A. Selcuk Adabag, Susan A. Casey, Daniela Vargiu, Mark S. Link, James E. Udelson, Franco Cecchi, Barry Maron, Referral Center for Cardiomyopathies, Azienda Ospedaliera Universitaria Careggi, Florence, Italy, The Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minneapolis, MN

Background: Little is known regarding the impact of gender on the clinical expression of hypertrophic cardiomyopathy (HCM). We have assessed gender-related differences in a multicenter HCM patient population from Italy and the US.

Methods: A total of 969 consecutive HCM patients were studied over 6.2±6.1 years. Results: Males had a 3.2% predominance (59%) similar in Italy and the US (p=0.24) and were more often diagnosed fortuitously by routine medical examination (41%, versus 23% in females, p<0.001). At initial evaluation, females were older and more symptomatic than males (47±23 vs. 38±18 years; p<0.001; mean NYHA functional class 1.8±0.5 vs. 1.4±0.6; p<0.001), suggesting delayed diagnosis, and also more frequently showed outflow obstruction at rest (37% vs. 23%; p<0.001). Female gender was independently associated
with the risk of symptom progression to NYHA classes III-IV or heart failure death (relative hazard 1.5, p<0.001), particularly in patients ≥50 years old (p<0.005). Overall HCM-related mortality and risk of sudden death aged 40 was similar in the two genders. Conclusions. Female patients with HCM were diagnosed less frequently, later in life and with more advanced disease states; had greater propensity toward symptom progression to NYHA functional classes III-IV or heart failure death. These findings suggest potential biases against timely clinical diagnosis for female patients with HCM, as well as the possibility of gender-specific differences in patient susceptibility to disease complications. The data underscore the need for a heightened index of suspicion for HCM in women.

**Methods:**

**Background:** Mid-ventricular obstruction due to systolic asystole of left ventricular (LV) wall is a less common variant of hypertrophic obstructive cardiomyopathy (HOCM). We studied the effects of mechanical asynchrony induced by pacing for relieving mid-LV obstruction.

**Methods:** 8 patients (pts) (mean age 57 ± 16 yrs) were diagnosed with significant mid-cavity HOCM had pacemaker implanted. Standard and tissue Doppler echocardiogram were performed at follow-up (mean 42 ±26 mths). Myocardial velocities and timings were measured from 12 LV segments: time intervals from onset of QRS to peak systolic (Ts) were compared during pacing and intrinsic rhythm. Coefficient of variation (SD/mean) of time intervals were used as index of systolic asynchrony.

**Results:** There was significant reduction in mid-cavity gradient during pacing (119 ± 33 vs 62 ±20 mmHg: p<0.001) at mean optimal AV delay of 108 ± 18 msecs. Chronic pacing resulted in significant prolonged Ts at anteroseptal wall.(graph) There were fixed delay in LV apical segment after pacing was turned off. The LV end diastolic (53 ±5 vs 38±4 ml; p=0.03) and end systolic volumes increased during pacing. The systolic asynchrony index (mean -0.96 vs 0.01; p<0.001) and ESV changes (mean -0.86 vs 0.03) were independent factors correlated with intracavity gradients.

**Conclusions:** Chronic pacing limited cavity obliteration and improved systolic reserves in pts with midLV HOCM by inducing asynchronous delayed contraction along anteroseptal wall.

**ORAL CONTRIBUTIONS**

**826**

**Coronary Revascularization and Heart Failure**

**Monday, March 07, 2005, 4:00 p.m.-5:30 p.m.**

**Orange County Convention Center, Room 414C**

**4:00 p.m.**

**826-3**

**Percutaneous Versus Surgical Revascularisation in Patients With Low Left Ventricular Ejection Fraction: The Results of Revascularisation in Ischaemic Heart Failure Trial (REHEAT).**

Pawel E. Bujsman, Iwona Szkrobka, Zofia Tendera, Agata Gruszka, Radoslaw Parma, Bozena Balicka, Miroslaw Wilczynski, Wojciech Wojakowski, Stefan Radoslaw Klesz, Jack Martin, Andrzej Bochenek, Michal Tendera, Silesian Medical School, Katowice, Poland, American Heart of Poland, Ustron, Poland

**Revascularisation in Ischaemic Heart Failure Trial (REHEAT) is a case controlled, prospective study to compare recent and late result after percutaneous and surgical revascularisation in patients with severe ischaemic left ventricular impairment.**

**Methods:** Patients with multivessel coronary artery disease, left ventricle ejection fraction (LVEF) <40% and suitable for percutaneous (PCI) and surgical (CABG) revascularization were eligible for the study. The primary end-point of the study was LVEF improvement and long term survival. Secondary end-points included angina status and the risk of major adverse cardiac events (MACE) at 12 month follow-up. LV function was evaluated based on 2-D echo and myocardial viability was assessed according to Selvester QRS injury score.

**Patient population:** Two-hundred seventeen patients (166 males, 76.5%) were screened with 5+3 segments/patient recovering function. At the same time, after revascularization was present. Viability was present in 6+3 segments/patient. Revascularization was accompanied by extensive recovery of ejection fraction (EF, from 33±6% to 44±11%, p<0.0001), and wall motion score index (WMSI, from 2.39±0.32 to 1.75±0.45, p<0.0001). There was significant improvement of end-systolic volume index (ESVI, from 79±23 to 56±24 ml/m2, p<0.0001), end-diastolic volume index (EDVI, from 120±26 to 102±27 ml/m2, p<0.0001), and LV SI (from 0.69±0.13 to 0.53±0.11, p<0.0001) was observed. Improvement in ESVI, EDVI, and SI were all significantly correlated to the number of segments showing recovery of function after revascularization.

**Conclusion:** In the present study, myocardial hibernation was associated with major alterations in LV volumes and geometry, which significantly reverted upon revascularization. Thus, our data show that severe impairment of regional function per se is sufficient to induce ischemic LV remodeling in patients, in the absence of scar formation.

**826-4**

**Impact of Myocardial Viability Testing With PET and Revascularization on Long-Term Prognosis in Patients With Ischemic Left Ventricular Dysfunction**

Carole Pollack, Jens P. Hellenkamp, Mehdi Namdar, Pascal Koedel, Patrick T. Siegrist, Nina Bartenstein, Ulrich Schurr, Rolf Jeni, Philipp A. Kaufmann, University Hospital, Zurich, Switzerland

**Background:** Most outcome studies in patients with ischemic left ventricular dysfunction (LVD) and hibernating myocardium as assessed with PET are limited by short-term follow-up or small patient populations.

**Aim:** To assess the impact of myocardial viability testing with PET and revascularization (revasc) on long-term prognosis in a large study population with LVD.

**Methods:** The baseline characteristics and the follow up (FU) of 346 consecutive patients (age 60±10 years) with ischemic LVD who underwent FDG and NH3 PET scan for evaluation of hibernating myocardium (+H3/FDG mismatch) were assessed. Conclusion: Our results demonstrate a strong association between myocardial viability based on PET testing and improved survival after revascularization in patients with chronic ischemic LVD. Viable tissue seems to represent a risk factor, as lack of revascularization is associated with increased mortality. Absence of viability is associated with no significant difference in outcomes, irrespective of treatment strategy.
Background: In patients with ischemic cardiomyopathy and substantial amount of viable myocardium, left ventricular ejection fraction (LVEF) does not always improve after coronary revascularization. Whether patients with viable myocardium and improvement in baseline differences revascularization have a different prognosis than those patients who do not improve in LVEF was evaluated in this study.

Methods: Before revascularization, myocardial viability was assessed by dobutamine stress echocardiography. Patients with 4 or more viable segments were considered to have substantial myocardial viability (viable patients). Patients with <4 viable segments were defined nonviable patients. Before and at 12 months after revascularization, radionuclide ventriculography was performed to assess changes in LVEF. An improvement in LVEF ≥5% was considered clinically significant. Heart failure symptoms were also assessed before and at 12 months after revascularization. Cardiac events were obtained during a 4 years follow-up.

Results: Patients were divided into 3 groups: Group 1, viable patients with LVEF improvement (n=27); Group 2, viable patients without LVEF improvement (n=15); Group 3, nonviable patients (n=48). Preoperative clinical characteristics and baseline LVEF were comparable in the 3 groups. After revascularization, the LVEF increased from 32 ± 9 to 42±10% in Group 1 (P < 0.001), but did not change significantly in Group 2 and in Group 3. Heart failure symptoms improved both in Groups 1 (NYHA class from 3.1±0.9 to 1.7±0.7) and (2) from 3.2±0.7 to 1.7±0.9), but not in Group 3 (from 2.8±1.0 to 2.7±0.5), P<0.001 by ANOVA. During the follow-up, the cardiac event rate was low (4%) in Group 1, intermediate (21%) in Group 2 and high (33%) in Group 3 (P<0.01).

Conclusion: The findings in the present study demonstrate that in patients with ischemic cardiomyopathy the best prognosis after revascularization may be expected in those viable patients who improve in LVEF. Conversely, viable patients without functional improvement have an intermediate prognosis. Nonviable patients have the worst prognosis despite coronary revascularization.
and (2) a 12-hour ambulatory cardio-respiratory recording in free-living patients by means of a multi-sensor portable system (LifeShirt®, VivosMetrics, USA).

Results: Results of the neuro-hormonal profile were indicative of neurohormonal activation (norepinephrine = 460±46 pg/ml; ANP = 121±16 pg/ml; BNP = 268±42 pg/ml; PRA = 2.96±.47 ng/ml/h, aldosterone = 1886±52 pg/ml, cortisol = 17.58±1 ng/ml). Nighttime cardiorespiratory recordings revealed CSR in all patients, while 25 subjects exhibited daytime breathing abnormalities. Abnormal breathing time, as defined by presence of CSR or periodic breathing, was observed during 40±4% of the time for the total recordings. The apnea-hypopnea index was 20±2 events/hr (hypopneas 67±6; apneas = 223±26; mean maximum apnea duration = 40±3 sec; mean minimum oxygen saturation = 85.9±0.9). The presence of CSR was significantly related to BNP (r=0.57, p=0.001), ANP (r=0.52, p=0.0007) and norepinephrine (r=0.35, p=0.03).

Conclusions: These data indicate that breathing pattern abnormalities are frequent in patients with CHF and support an association between neuro-hormonal and ventilatory dysregulation. The identification of neuro-hormonal and ventilatory impairment provides additional insight into the multi-systemic complexities of patients with CHF and, ultimately, may serve as therapeutic targets to help retard the progression of heart disease.

8:45 a.m.

335-5 Elevated Brain Natriuretic Peptide In Symptomatic Acute Cerebral And Peripheral Vascular Syndromes

Robert V. Kelly, Walter A. Tan, Hyunsoo Cho, Allan D. Struthers, University of North Carolina, Chapel Hill, NC, University of Ninevalwells Hospital, Dundee, Scotland, United Kingdom

Background: Brain natriuretic peptide (BNP) has been shown to be elevated in heart failure, acute coronary syndrome and LVH patients. It is a valuable marker for diagnosing, treating and risk stratifying non-vascular CHF and left ventricular systolic dysfunction (LVSD) patients. We have previously showed that CHF occurs in five times more stroke, TIA and daytime breathing abnormal (PAD) patients than in age and sex matched controls. We sought to examine the role of measuring BNP in patients presenting to hospital with their first non-cardiac vascular event.

Methods: Baseline BNP levels were measured in 216 prospective consecutive patients presenting with their first stroke, TIA or new onset of claudication and in 161 age and sex matched control patients. LV systolic dysfunction (LVSD) was defined as an ejection fraction (EF) < 45%.

Results: BNP levels >100 pg/ml were significantly higher in patients presenting with stroke (28%), TIA (23%) and PAD (70%) patients when compared to age and sex matched controls (6%). Patients presenting with their first stroke, TIA or PAD had significantly higher BNP levels than age and sex matched controls, when they were classified as NYHA class II-IV. Cardiologists were blinded to BNP plasma levels.

Conclusions: BNP is significantly elevated in all patients with non-cardiac vascular disease compared with controls. However BNP is more elevated in cerebrovascular disease than in PAD patients despite a similar prevalence of LVSD and of diastolic heart failure.

9:00 a.m.

335-6 Change in BNP Level Unrelated to Wall Stress, Echocardiographic Indices of Filling Pressure, and Volume of Intravenous Fluid Infusion

John B. Fournier, Craig Verch, Jeffrey C. Hill, Girishar Logsetty, Dennis A. Tighe, Theo E. Meyer, Gerard P. Aurigemma, University of Massachusetts, Worcester, MA

Background: Increased LV filling pressure and wall stress are proposed stimuli for elevated BNP. Administering medications is known to alter filling pressures and loading conditions. Accordingly, we examined BNP levels and echo hemodynamic indices before and after IV conscious sedation (IVCS) and TEE.

Methods: 23 out-pits (16 male, 61±16 yrs) underwent examination, transthoracic echo, and after IV conscious sedation (IVCS) and TEE. Pre- and post-BNP levels were obtained 49±13 min apart. PCWP was estimated by previously validated regression technique.

Results: (see table) IVCS was associated with decreased systolic and diastolic BP, Ml/min E wave, PASP and wall stress. Deceleration time increased. There were trends towards lower E/E' ratio and estimated PCWP. There was no correlation between IV fluid received and change in BNP. Mean BNP level increased, and no ph had a fall in BNP Diastolic wall stress did not change.

9:30 a.m.

335-7 B-Type Natriuretic Peptide and Diastolic Function Influence Exercise Tolerance in Patients With Stable Congestive Heart Failure

Quirino Ciampi, Gabriele Borzillo, Emanuele Barbato, Bruno Petruzelli, Michele Della Porta, Bruno Villari, Fatebenefratelli Hospital, Benevento, Italy, Villa Margherita Hospital, Benevento, Italy

Background: B-type natriuretic peptide (BNP) is a diagnostic and prognostic maker in patients with congestive heart failure (CHF). We evaluated the relation between BNP levels (at baseline and at peak exercise), echocardiographic systolic and diastolic function and aerobic exercise capacity in CHF patients.

Methods: 25 CHF patients (age 68±6 yrs, 55% with an ischemic etiology), underwent exercise cardiopulmonary test and standard echocardiography: LV diastolic function was evaluated with transitimal filling patterns and Tissue Doppler. A sample of venous blood was taken at rest and at peak exercise to determine the BNP level.

Results: Ejection fraction was 35±8% and NYHA class 2.04±0.6. 10 CHF patients with lower peak oxygen consumption (peak VO2 <14 ml/kg/min) showed: a) higher baseline (figure) and peak exercise BNP levels (2.6±0.4 pg/ml vs 2.1±0.4 pg/ml p<0.02); b) lower
increase in BNP levels during exercise (ΔBNP, figure); c) impaired diastolic function: major incidence of transmural pattern with elevated LV filling pressure (pseudonormal and restrictive vs normal and abnormal relaxation) (6/10 vs 2/15; p=0.15) and higher value of ratio E wave mitral flow and early diastolic velocity mitral annulus (17.1±8.6 vs 10.8±3.8; p=0.03); d) no difference in ejection fraction.

Conclusions: In patients with stable CHF, BNP levels (at baseline and at peak exercise) and worse diastolic function predict lower exercise tolerance. BNP increase during exercise was directly related to O2 consumption.

Rapid Assay B-type Natriuretic Peptide (BNP) Predicts Outcomes and Hemodynamics in Patients Hospitalized with Decompensated Heart Failure

Monica R. Shah, Vic Hasselblad, Gudaye Tasissa, Cynthia Binanay, Christopher M. O'Connor, E. Magnus Ohman, Lynne W. Stevenson, Robert M. Califf. Califium University Medical Center, New York, NY, Duke Clinical Research Institute, Durham, NC

Background: Rapid assay biomarkers are bedside tools that may predict outcomes in patients (pts) with decompensated (decomp) heart failure (HF). We assessed if rapid assay BNP (Triage®BNP) and troponin I (TnI) would 1) predict length of stay (LOS) and mortality and 2) correlate with pulmonary artery catheter (PAC)-derived hemodynamics (HD).

Methods: There were 105 pts in this cohort study of ESCAPE, which tested PAC in pts with severe, decomp HF. Biomarkers were drawn at baseline and discharge (dis), and during 1st, 2nd, and final HD in 38 pts with PAC. We used logistic regression to model mortality, Cox analysis to model LOS, and correlations to describe relations between BNP, TnI, and PAC-derived HD.

Results: Median (25th, 75th) BNP was 783 (329, 1565) pcg/mL at baseline and 468 (240, 946) pcg/mL at dis. After HF tx, BNP decreased 144 pcg/mL (-653, 55; p=.004). Median (25th, 75th) BNP was 10.8±3.8, p=.035); d) no difference in ejection fraction.

BNP correlated with final RAP, r= .63, (p=.001). BNP correlated with 1st pulmonary capillary wedge pressure, r=.54 (p=.001). Final BNP correlated with final RAP, r=.63, (p=.001). Conclusions: HF pts with BNP >1500 pcg/mL had higher mortality at 6 mos (Fig) and almost 2) correlate with pulmonary artery catheter (PAC)-derived hemodynamics (HD).

1132-144 Selective Upregulation of TGFβ1 in the Rat Heart to Induce Cardiac Protection From Ischemia-Reperfusion Injury

Kui Cheng, Yong Liu, Jiawei Chen, Dayuan Li, Paul L. Hermomat, Jawahar L. Mehta, University of Arkansas for Medical Sciences, Little Rock, AR, Central Arkansas Veterans Healthcare System, Little Rock, AR

Background: Although there is upregulation of TGFβ1 during ischemic injury to the heart, its conversion to active form (TGFβ1ac) which is cardio-protective is lacking. To examine the modulation of cardiac function by TGFβ1, we developed a model of selective upregulation of TGFβ1 in the rat myocardium. Methods and Results: First, we cloned rat TGFβ1 cDNA (position 413-1593, 1172 bp), with mutation of cysteine at position 223 and 225 into serine resulting in TGFβ1ACT. We developed a model of selective upregulation of TGFβ1ACT in the rat myocardium.

We infused TGFβ1ACT into the left side of the heart of rats. We observed that TGFβ1ACT is expressed in the heart and can prevent ischemia-reperfusion injury. Conclusions: TGFβ1ACT is a potential target for the development of cardiac protection from ischemia-reperfusion injury.

1132-145 Effects of AT1 Receptor Blockade on Oxidative Stress and Uncoupling Protein-2 Expression in Rat Hypertensive Heart Failure

Pepa Guo, Akira Nishiyama, Matubhar Rahman, Makoto Ichihara, Kazushige Murakami, Akira Miyatake, Koji Ohmori, Katsufumi Mizushige, Youichi Abe, Takanosha Noma, Masakazu Kohno, Kagawa Medical University, Kagawa, Japan.

Background: Uncoupling proteins, inner mitochondrial membrane protein transporters, are important for regulating myocardial energy efficiency. We recently demonstrated that left ventricular dysfunction and reduction in high-energy phosphate production are accompanied by the elevated expression of uncoupling protein-2 (UCP-2) in failing rat hearts, indicating the potential roles of UCP-2 in the progression of heart failure. In this study, we examined the effects of angiotensin II receptor blocker (ARB) on the expression of UCP-2 and left ventricular (LV) heart failure in Dahl salt-sensitive (DS) hypertensive rats. We also investigated the contribution of reactive oxygen species (ROS) to the effects of ARB.

Methods: DS rats were maintained on a high (7.8%NaCl, n=7), low (1.0% NaCl, n=6) salt diet, H + candesartan cilexetil (10 mg/kg/day, n=7) or H + a superoxide dismutase...
mimetic, tempol (3 mMol, in drinking water, n=7) from 7-week-old, and all data were collected at age 17-weeks.

Results: DSH rats represented increases in LV end-diastolic pressure and lung weight, indicating the presence of pulmonary congestion caused by congestive heart failure. The hemodynamic deterioration was associated with increases in LV mass index, the areas of fibrosis and myocardial stiffness and relaxation abnormality. As compared with DSS, LAD rats showed p22phox and gp91phox mRNA expression (by 2.3 and 2.9-fold, respectively), NADPH oxidase activity (by 1.9-fold) and thiobarbituric acid-reactive substance (TBARS) contents (19±2 vs 52±9 microg/ml in LV tissue. UCP-2 mRNA expression in LV tissue was also 2.6-fold higher in DSH rats. In DSH rats, treatment with carvedilol resulted in improved LV end-diastolic pressure contributed to the progression of LV heart failure in DSH rats, and that the cardioprotective effects of ARB may be partly due to the suppression of ROS-dependent UCP-2 expression.

Background: In heart failure or ischemia-reperfusion injury, intracellular calcium overload occurs in the myocardium and triggers the subsequent signaling to deteriorate the cardiomyocyte function. Additionally, failing myocardium have source of oxygen free radicals from mitochondrial electron transport complex I. This study is designed to demonstrate the key role of mitochondrial complex I as a target of calcium overload induced superoxide production and the inhibitory effect of carvedilol and metoprolol on the mitochondrial superoxide production.

Methods: Isolated mitochondria from SD rat hearts were loaded in the cuvette mounted with Clark oxygen sensor to measure the mitochondrial oxygen consumption. The amount of malondialdehyde (MDA) was measured as an index of superoxide production. NADPH was used to energize the mitochondria at 37°C. Calcium concentration was varied at 10, 100 µM and carvedilol and metoprolol concentration was varied at 1, 10, 100 µM. Rotenone was used for inhibiting complex I.

Results: The oxygen consumption was significantly augmented by increasing the calcium concentration from 10 to 100 µM (527±139 vs. 6.7±138 nmol/mg protein, P<0.05). This increase of oxygen consumption was significantly suppressed by even 1 µM carvedilol (522±88 nmol/mg protein, P<0.01), but no suppression was observed by metoprolol. The amount of MDA was not augmented by increasing the calcium concentration from 10 to 100 µM (6.1±1.5 vs. 6.3±1.0 nmol/mg, ns.), but significantly augmented with rotenone (522±88 nmol/mg protein, P<0.01), but no suppression was observed by metoprolol. The increase of oxygen consumption was significantly suppressed by even 1 µM carvedilol concentration from 10 to 100 µM (527±139 vs. 671±138 nmol/mg protein, P<0.05). This indicates that MDA was significantly suppressed by carvedilol dose-dependently (P<0.05), but not attenuated by metoprolol.

Conclusion: These data strongly suggest that the modification of mitochondrial oxygen consumption or superoxide production during complex I injury caused by calcium overload is suppressed by carvedilol but not by metoprolol, which may explain the distinct efficacy of carvedilol with antioxidant effect for treating heart failure.

Background: Urotensin II, a somatostatin-like cyclic peptide was recently identified as a potential hormone that is released in the peri-arterial space (RPA), n=7). Saline was injected in RPA in the control group (n=3).

Methods and Results: U-II (400 pmol/kg, iv) caused rightward shifts and decreased peak systolic [Ca2+]i (49.5±5.7 vs. 91.0±2.3%, P<0.05) and calcium ionophore (79.7±62.4 vs. 99.7±0.1%, P<0.05) but sodium nitroprusside was attenuated in N+PSI compared to N. As assessed by in-vivo electron-beam-CT, baseline left ventricular ejection fraction (LVEF, 40.3±2.4% vs. 55.7±4.9%, P<0.05) and cardiac output (CO, 4.1±0.5 vs. 6.3±1.1, P<0.05) were reduced in N+PSI compared to N, as well as percent increase in myocardial perfusion to adenosine (9.3±1.67 vs. 52.6±7.3, P<0.05) and dobutamine (38.1±3.4 vs. 54.9±2.3, P<0.05) was higher in N+PSI compared to N. As assessed by 3D-micro-CT, myocardial spatial microvessel density was not different between N and N+PSI. Quantified trichrome staining showed higher collagen content in field in the myocardium of N+PSI compared to N (13.8±0.5 vs. 0.9±0.1, NS). Myocardial apoptotic index, assessed by TUNEL-positive cells, was higher in N+PSI compared to N (1.97±0.29 vs. 0.12±0.05, P<0.001).

Conclusion: These data suggest that NAD(P)H oxidase-mediated ROS production and associated UCP-2 gene expression contributes to the progression of LV heart failure in DSH rats, and that the cardioprotective effects of ARB may be partly due to the suppression of ROS-dependent UCP-2 expression.

Results: Although systemic hemodynamics were not altered, both UOPI and UOPT were poor predictors of the response to carvedilol with antioxidant effect for treating heart failure. A statistically significant difference was found for concentrations between 10^-7 M and 10^-4 M by 14.3±5.6%, for 10^-5 M vs. N+PSI compared to N (529±11 vs. 91.0±2.3, P<0.05) for 10^-10 M, p<0.05 compared to control experiments with the utilized solvent (DMSO) in corresponding concentrations. In addition we could show a decrease of the diastolic cell length with increasing sirolimus-concentrations probably indicating an increased diastolic intracellular calcium concentration.

The negative inotropic effect can presumably be explained by a altered function of the sarcoplasmic reticulum as it has been shown that sirolimus can modulate cardiac ryanodine receptor function by inhibition of FKBP12.6. This leads to a decreased systolic calcium concentration and an increased diastolic calcium-leak which explains the reduced diastolic cell length.

Conclusion: Our experiments show for the first time an acute dose-dependent negative inotropic effect of sirolimus on isolated human cardiomyocytes which is probably due to altered function of cardiac ryanodine receptors.
Conclusions: Unilateral RSNA blockade significantly increased UOP via both an increase in aquaresis and natriuresis in acute HF without alterations of regional RBF or significant effects on GFR or systemic hemodynamics. These findings may provide a new approach to optimize patient’s volume status in HF. Further investigation into the underlying mechanisms responsible for this unique diuresis is warranted.

POSTER SESSION

1133 Heart Failure: Miscellaneous Topics

Tuesday, March 08, 2005, 9:00 a.m.-12:30 p.m.
Orange County Convention Center, Hall E1
Presentation Hour: 10:00 a.m.-11:00 a.m.

1133-165 Changes in Vasoactive Therapy and In-Hospital Outcomes in Patients Hospitalized with Acute Decompensated Heart Failure: An ADHERE® Analysis

J. Thomas Heywood, Gregg C. Fonarow, Clyde W. Yancy, Margarita Lopatin, ADHERE Scientific Advisory Committee and Investigators, Loma Linda University Medical Center, Loma Linda, CA

Background: The relationship between changes in intravenous (IV) vasoactive therapy and outcomes over time in patients (pts) with acute decompensated heart failure is unknown.

Methods: Data from 273 US hospitals and 109,546 hospitalizations from the Acute Decompensated Heart Failure National Registry (ADHERE®) were analyzed. The use of inotropes (INO), nitroglycerin (NTG), nesiritide (NES), as well as mechanical ventilation (MV), % pts hospitalized in ICU, and mortality were measured over 8 quarters (1/2002-12/2003). Q1 vs Q8 were compared using chi-square test; trends were assessed using Cochran-Armitage. Multiple linear regression was used to assess relationships between changes in therapy and outcomes across hospitals.

Results: INO use decreased 25%, NTG use decreased 5%, and NES use increased 238% (p<0.0001), MV decreased 21%, and % ICU patients decreased 5% (both p<0.0001) (Figure). In-hospital mortality decreased from 4.5% to 3.9% (RR 0.86, p=0.03). Trend analysis confirmed significant changes in INO, NTG, NES, MV and % ICU pts with borderline trend in mortality (p=0.06). Changes in IV therapy alone explained 6%, 16% and 22% of variability in per hospital changes in mortality, MV and % ICU pts, respectively.

Conclusions: Reductions in INO and NTG with an increase in NES use occurred over time. Concurrently, reductions in MV and % pts hospitalized in the ICU were observed. These data suggest that changes in IV vasoactive therapies may partially explain improvements in outcomes.

1133-166 A High Prevalence of Left Ventricular Systolic Dysfunction in Rheumatoid Disease Patients

Gurber S. Bhatti, Michael D. Sosin, Jeestesh V. Patel, Karl A. Grindulis, Fazal H. Khattak, Gregory Y. Lip, Russell C. Davis, University Department of Medicine, City Hospital, Birmingham, United Kingdom

Background: Cardiovascular mortality is increased in Rheumatoid Disease (RD) patients, who are at an increased risk of developing chronic heart failure and ischaemic heart disease (IHD). However, there have been few large echocardiographic studies to identify objective evidence of cardiac dysfunction in RD. We hypothesised that left ventricular systolic dysfunction (LVSD) would be more prevalent in RD patients than in the general population.

Methods: 226 hospital out-patients with RD (65% women) underwent clinical evaluation, electrocardiography (ECG) and echocardiography. Prevalence ratios standardised for age, sex and gender were calculated for the RD population using estimates derived from a large (n=3960) study of the general population in this region.

Results: The table shows that any LVSD (left ventricular ejection fraction, LVEF <50%) occurred in 10.2% of RD patients: standardised prevalence ratio (SPR) 1.92, 95% CI 1.22-2.88. ‘Definite’ LVSD (LVEF<40%) occurred in 5.3% of the RD group, and was three times more prevalent than in the general population: SPR 3.20, 95%CI 1.85 - 5.59.

Conclusion: Any LVSD occurred almost twice as often in RD compared to the general population. Of note, definite LVSD was three times more common, and was particularly prevalent among RD women. Given the prognostic benefits of treatment of LVSD, echocardiographic screening of RD populations may be worthwhile. Absolute and standardised prevalence of LVSD in RD patients.
Comparison Between Cases of New Onset Heart Failure and Acutely Decompensated Heart Failure: An ADHERE® Analysis

Greg C. Fonarow, Lynne Warner Stevenson, J. Thomas Heywood, Margarita Lopatin, ADHERE Scientific Advisory Committee and Investigators, University of California Los Angeles, Los Angeles, CA

Background: Little is known as to whether patients (pts) hospitalized with a new-onset of heart failure (HF) differ in characteristics, treatments, and outcomes from pts with acute decompensation of pre-existing HF.

Methods: We used Acute Decompensated Heart Failure National Registry (ADHERE®) data to compare pts with no history of HF (new-onset) to those with decompensation of pre-existing HF by ANOVA, Wilcoxon, or chi-square tests. Logistic regression was used to adjust mortality analysis for gender, age, and previously identified mortality risk factors (BUN, systolic BP and serum creatinine).

Results: Of 105,386 pts, 25,832 (25%) were new-onset. Compared with pre-existing HF pts, new-onset pts had less history of CAD and atrial fibrillation. New-onset pts had higher systolic BP, lower BUN, similar hemoglobin, and higher LVEF at presentation. New-onset pts more often received ACE inhibitors (80% vs 56%, P<0.0001) as in pts; beta-blocker use was similar (60%). Mean ICU length of stay (LOS) and total LOS were similar between groups. Fewer new-onset pts died in-hospital (3.0% vs 4.3%, OR=0.67, P<0.001). Risk-adjusted mortality was, however, similar between groups (OR=1.0, P=0.95).

Conclusions: One in four HF hospitalizations is for new-onset HF. Medical therapies and cardiac procedures were employed at the same or higher frequency in new onset HF. Despite differences in characteristics and management, new onset HF pts had comparable LOS and risk-adjusted hospital mortality to pre-existing HF pts.

Pulmonary Artery Catherization and Mortality in Acutely Decompensated Heart Failure Patients: An Observational Analysis From ADHERE®

Clyde W. Yancy, James A. Hill, Lynne Warner Stevenson, Gregg C. Fonarow, Margarita Lopatin, ADHERE Scientific Advisory Committee and Investigators, University of Texas Southwestern Medical Center, Dallas, TX

Background: The safety and utility of pulmonary artery catheterization (PAC) use in HF management is inconclusive. This analysis compared in-hospital outcomes in patients with and without PAC using data from the ADHERE® Registry.

Methods: Previous classification and regression tree risk score defined patients at high-risk (HR) for in-hospital mortality. Patient characteristics and in-hospital outcomes (mortality, total LOS, and ICU LOS) were compared in HR patients with and without PAC. Chi-square tests, ANOVA, multiple logistic and linear regressions were utilized.

Results: 1,965 out of 102,524 ADHERE patients were identified as HR. 7.6% of HR pts were discharged without PAC. PAC was associated with increased mortality (OR=3.54, p<0.0001) but still had longer mean ICU length of stay (LOS) and total LOS; ICU LOS was shorter (OR=1.40, p=0.10) but still had longer mean ICU LOS (7.5 vs 4.3 days, p<0.001) and mortality adjusted was, however, similar between groups (OR=1.0, p=0.95).

Conclusions: The disconnect between the perceived severity of CHF by physicians and the severity as determined by BNP levels. Whether ethnicity plays a role in this discrepancy is unknown.

Effect of Ethnicity on Likelihood of Admission for Heart Failure

Lost B. Daniels, Paul Clotton, Judd E. Hollander, David Guza, Peter McCulloch, Richard Nowak, Gary Green, Mitchell Saltsberg, Stefanie R. Ellison, Meenakshi Awasthi Bhalla, Vikas Bhalla, Robert Jesse, Alan Maisel, University of California at San Diego Medical Center, San Diego, CA, Veteran's Affairs San Diego Healthcare System, La Jolla, CA

Background: Previous studies have shown that in patients presenting to the Emergency Department (ED) with heart failure, there is a disconnect between the perceived severity of CHF by physicians and the severity as determined by BNP levels. Whether ethnicity plays a role in this discrepancy is unknown.

Methods: The Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT) was a 10-center trial of 464 patients seen in the ED with acute dyspnea and BNP level >100 pg/mL upon arrival. Physicians were blinded to BNP levels. Patients were followed for 90 days after discharge.

Results: 151 patients identified themselves as Caucasian (32.5%), and 292 as African American (62.9%). Of these, 90% were hospitalized. African Americans were more likely to be age 65 or older (p<0.001). African Americans had higher hospitalization rates (207 vs 144, p<0.001). After adjusting for age, weight, and gender, the difference persisted (p=0.003). The median BNP of African Americans who were admitted was actually lower than the median BNP of those who were discharged (769 vs 1293, p=0.044); the same did not hold true for Caucasians.

Conclusions: In patients presenting to the ED with heart failure, the disconnect between perceived severity of CHF and severity as determined by BNP levels is most pronounced in African Americans.

Early Enalapril Therapy Confers Long-Term Protection Against Cardiac Ischemic Events: Evidence for a 15-Year Benefit on Platelet Stability

Michel F. Rousseau, Sylvie A. Alm, Philip Jong, Hubert G. Poulter, University of Louvain, Brussels, Belgium

Background: The Studies of Left Ventricular Dysfunction (SOLVD) demonstrated that, over 3-4 years, enalapril therapy decreased mortality and morbidity in patients with low ejection fractions and reduced the incidence of cardiac ischemic events. The aim of this study was to determine if early benefit of enalapril on atherosclerotic complications confers long-term protection.

Methods: From the initial cohort of 558 Belgian patients included in SOLVD, data on post-trial deaths or morbid events were collected on all 433 survivors at close-out (enalapril n=218, placebo n=215). At the end of follow-up (December 2003-February 2004), 145 patients were still alive (80 enalapril vs 65 placebo). Use of ACE-inhibitor (85% vs 79%, p=0.40) and other cardiovascular drugs post-trial were similar between enalapril and placebo groups. No patients were lost to follow-up.

Results: The median duration of follow-up was 15.5 years from randomization or 12.2 years from close-out. The risk of death or non fatal cardiac ischemic events (myocardial infarction, coronary angioplasty, coronary bypass surgery) was significantly lower in the early enalapril group than in the delayed enalapril group [148/218 (68%) vs 167/215...
was suspended. benefit diminished after trial completion, the effect was maintained after the intervention through the impact of the educational intervention on patients’ behaviors. Although the completion, and is maintained at one year. The sustained benefit could be explained with intervention as time dependent covariate: time-intevention interaction p<0.05). Of the intervention on primary end point from trial completion to 6 months the RR was 0.81 (0.69-0.96) p=0.013). This benefit was attributable to a reduction in HF admissions.

were performed: 1) Beginning to 6 months after trial completion, 2) Beginning to one year intervention program vs. control), the incidence of admission for worsening HF or all cause (QOL). We utilized the CHARM experience to test the hypothesis that there is no difference in QOL between pts with HF-PSF and those with HF and low ejection fraction (HF-LEF). In QOL between pts with HF-PSF and those with HF and low ejection fraction (HF-LEF).

Mark E. Dunlap, Eileen O’ Meara, Karl Swedberg, Jean L. Rouleau, Marc A. Pfeffer, From DIAL trial (n=1518, randomized controlled clinical trial of a nurse telephone registry data of HF pts. HD/HF pts are younger, have higher presenting systolic BP, lower Hgb, lower weight and less use of ACEI/ARB/AA. Findings have important implication for pt outcome and treatment management and warrant further studies. The initial in-trial use of enalapril was associated with a statistically significant risk reduction in cardiac ischemic events (HR: 0.43, 95%CI: 0.20 to 0.90, p=0.04).

Conclusions: Our data indicate that, beyond the original trial period, a significantly lower risk of cardiac ischemic events is present for at least 15 years in early enalapril group as compared to delayed enalapril group. This suggests that earlier treatment initiation produces sustained beneficial effect on plaque stability.

was performed: 1) Beginning to 6 months after trial completion, 2) Beginning to one year intervention group showed lower rate of events. However, this effect tapered in function of time. Considering the effect of the intervention on primary end point from trial completion to 6 months the RR was 0.700(0.46-1.06) p=0.082, and to one year RR 0.870(0.63-1.19), p=0.380. (Cox regression with intervention as time dependent covariate: time-intevention interaction p<0.05).

Conclusions: the benefit continues to increase during the first 6 months after trial completion, and is maintained at one year. The sustained benefit could be explained through the impact of the educational intervention on patients’ behaviors. Although the benefit diminished after trial completion, the effect was maintained after the intervention was suspended.

Quality of Life Among Patients with Heart Failure and Preserved Ejection Fraction versus Low Ejection Fraction: Does Ejection Fraction Matter?

Eldrin F. Lewis, Gervasio A. Lamas, John McMurray, JonasCarlsson, Chris Granger, Mark E. Dunlap, Eileen O’Meara, Karl Swedberg, Jean L. Rouleau, Marc A. Pfeffer, Brigham and Women’s Hospital, Boston, MA, Mount Sinai Medical Center, Miami, FL

Background: Despite the large number of patients (pts) with heart failure with preserved systolic function (HF-PSF), little is known about the impact of disease on their quality of life (QOL). We utilized the CHARM experience to test the hypothesis that there is no difference in QOL between pts with HF-PSF and those with HF and low ejection fraction (HF-LEF).

Methods: CHARM enrolled 7599 pts with chronic HF (NYHA Class II-IV) randomized to candesartan or placebos. A subset of 2709 (36.6%) completed the Minnesota Living with Heart Failure questionnaire (LHF). Differences in LHF scores were assessed between HF-PSF (EF>40%) and HF-LEF (EF≤40%) using t-test.

Results: There were 1097 pts with HF-PSF and 1612 pts with HF-LEF. HF-PSF pts were more likely women, more often NYHA Class II, had a higher systolic BP, and less likely to have a prior MI (Table). There was no difference in overall LHF scores (40.8±23.9 vs. 40.3±23.8, p=0.61) or emotional dimension scores (8.3±7.2 vs. 8.4±7.2, p=0.61) in HF-PSF pts compared with HF-LEF. HF-PSF pts had more impaired physical limitations than HF-LEF pts (19.3±11.1 vs. 18.2±10.9, p=0.02). The correlation coefficient between LHF scores and EF was 0.02.

Conclusion: Pts with HF-PSF have similarly impaired overall QOL as pts with HF-LEF despite more pts with NYHA Class II. There is no correlation between EF and QOL. These findings warrant further studies to better characterize the determinants of QOL and impact of therapies on QOL in this growing patient population with HF-PSF.
Background: Renal insufficiency is prevalent in patients admitted with acute decompensated heart failure (ADHF). However, the incidence of worsening renal function (WRF) in relation to the degree of baseline renal insufficiency at admission is not clear.

Methods: We identified 342 consecutive patients (mean age 66±14 years, 51% male, mean serum creatinine 1.4±0.5 mg/dl) admitted for ADHF between 10/02 - 5/03, and followed their sequential serum creatinine and glomerular filtration rates (GFR in ml/min/1.73m², by MDRD equation). WRF was defined by change in serum creatinine ≥0.3 mg/dl (Gottlieb criteria).

Results: In our cohort, 17% had underlying severe (GFR <30), 50% had moderate (GFR-30-59), and 33% had normal or mild renal insufficiency (GFR ≥60) at admission. The 3 groups had similar utilization rates for hemodynamically-guided therapy (33% vs 28% vs 35%), Overall, 31% and 26% of patients experienced WRF during hospitalization and at discharge, respectively. Lower admission GFR was associated with higher incidence of WRF, both at peak creatinine rise and at discharge (Figure). In patients with moderate or severe renal insufficiency, 39% experienced WRF, while 35% showed improvement in serum creatinine at discharge.

Conclusion: Over one-fourth of patients admitted for ADHF experienced WRF at discharge. Over two-thirds of patients admitted for ADHF had moderate or severe renal insufficiency, among them 39% experienced WRF while 35% showed improvement in serum creatinine at discharge.
The G212A Polymorphism of the APJ Receptor Gene for the Potent Inotropic Apelin Has a Prognostic Influence in Idiopathic Dilated Cardiomyopathy.

Riccardo Sarzani, Cinzia Forte, Francesca Pietrucci, Alessandro Capesto, Elii Soura, Francesca Masserano, Pietro Guida, Sandro Sorrentino, Massimo Iacoaciolo, Paolo Dessi-Fulgheri, Alessandro Rappelli, Mariavittoria Pitzalis, Mariavittoria Pitzalis, Bari, Italy, Riccardo Sarzani, Ancona, Italy

Apelin and its receptor APJ increase inotropic at cardiac level and seem to have a role in idiopathic dilated cardiomyopathy (IDC) pathophysiology. No data are available on APJ gene mutations responsible for IDC and on the role of G212A and T445A APJ receptor polymorphisms in predicting heart failure (HF) progression. We prospectively evaluated 176 consecutive pts (49±14 yrs, 134 men) with IDC, NYHA class II-IV. Pts were randomized to 2 groups: Ia (n=90, simvastatin 40 mg/day or to a tolerated dose) and Ib (n=86, placebo). APJ gene for mutations in 90 pts by direct sequencing. The correlation between APJ polymorphisms in predicting heart failure (HF) progression.

In conclusion, APJ is unlikely to be a disease-causing gene responsible for IDC. Moreover, we could not observe any correlation between the APJ receptor polymorphisms and the concentrations of CRP, sIL-2R, IL-6, or ANP, which are known to be increased in IDC pts. Therefore, the role of the APJ in IDC seems to be limited and complex; further investigations are needed to confirm our results.

**RESULTS:**

CRP levels were significantly higher in Group I patients vs. Group II patients (19.5±34 μg/ml vs. 3.0±3.5 μg/ml, P<0.01), and Group II CRP levels were significantly higher in Group I patients vs. Group II patients (1136.5±441.1 pg/ml vs. 599.2±234.7 pg/ml, P<0.001). No significant differences in the follow-up CRP values between Groups I and II. Group (a simvastatin therapy) showed a significant reduction of CRP and sIL-2R levels (p<0.045 and <0.001 respectively) after statin therapy. No such difference is observed in Group Ib (diet therapy).

**CONCLUSIONS:** DCM patients with dyslipidemia have increased inflammatory response compared with normolipidemic DCM patients which is reduced after 6 months of simvastatin therapy.
172A ABSTRACTS - Cardiac Function and Heart Failure
We studied 48 subjects: 12 unaffected offspring (24±6 years, 6 males) of FDCM pts; 12 unaffected offspring (24±6 years, 6 males) of NFDCM pts, and 24 age and sex-matched healthy unrelated subjects. All of them underwent echo-Doppler recordings. Indexed left ventricular end diastolic diameter (LVEDD), left ventricular relative wall thickness (RWT) and left ventricular fractional shortening (FS) were obtained; predicted left ventricular end-diastolic diameter (pLVEDD) was calculated using Henry’s formula; the ratio between predicted and observed LVEDD (pLVEDD/LVEDD) was finally calculated; the ratio between the early and late peak flow velocity (E/A) of transmitral flow was also assessed. FS values were significantly lower in FDCM offspring. The RWT and pLVEDD values were significantly different in FDCM offspring in comparison with those of control subjects (*p<0.05 vs second night). These differences were found in the LVEDD and E/A ratio.

Although still within normal ranges, unaffected offspring of FDCM pts show cardiac structural and functional modifications. These findings suggest the need for wide screening of kindred members with FDCM.

Table

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<td>FS (%)</td>
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<td>LVEDD (mm)</td>
<td>45.7±1.6</td>
<td>45.5±1.1</td>
<td>45.7±1.8</td>
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<tr>
<td>LVEDD (U)</td>
<td>0.09±0.04</td>
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</table>

1132-164
Obese Subjects With Heart Failure Have Lower N-Terminal pro-Brain Natriuretic Peptide Plasma Levels Irrespective of the Ischemic and Dilated Etiology
Raquel Cortes, Miguel Rivero, Antonio Salvador, Vicente Bermejo, Fernando Garcia de Burgos, Rafael Paya, Francisco Salvador, Ricardo Valero, Maria Jose Sancho Tello, Begoña Sevilla, Vicente Clement, Alejandro Jordan, Luis Martinez Dotz, Francisco Marin, Rafael Basel, Vicente Mira, Vicente Mora, Raquel Tolens, Andres Gonzalez Molina, Jose L Perez Bosca, Luis Mainero, Jose L Diago, Manuel Portoles, La Fe Hospital, Valencia, Spain

Background: N-terminal pro-brain natriuretic peptide (NT-proBNP) may be useful in the diagnosis of heart failure (HF) and ventricular dysfunction and is an independent cardiovascular risk factor. The purpose of this study was to compare NT-proBNP plasma levels in obese and non-obese subjects with HF of ischemic and dilated etiology.

Methods: We have studied 111 patients (34 obese), age 64±13, diagnosed of HF. A specific questionnaire and echo-Doppler study were performed. Blood samples were also taken and NT-proBNP levels were analysed. Patients were classified according to the New York Heart Association (NYHA).

Results: For the whole population (NYHA 2.1±0.5), plasma levels of NT-proBNP were 1206±1689 pg/ml. In multivariate analysis body mass index (BMI) was inversely associated with NT-proBNP plasma levels (p<0.05) and obesity was associated with a 17% decrement in natriuretic peptide levels (p<0.01). In both the ischemic and dilated groups of patients we found a 35% decrease in NT-proBNP plasma levels when comparing obese and non-obese patients.

Conclusion: This multicenter study shows that obese subjects with HF have lower NT-proBNP plasma levels than non-obese subjects. Obesity is an independent prognostic factor of NT-proBNP levels, so BMI has to be taken into account when using NT-proBNP in obese and non-obese subjects.

ORAL CONTRIBUTIONS
843 HEART FAILURE AND THE KIDNEY
Tuesday, March 08, 2005, 10:30 a.m.–Noon
Orange County Convention Center, Room 414C
843-3 Continuous Recording of the Hemodynamic Response to Dialysis in Patients with Impaired Left Ventricular Function
Cecilia Linde, Frieder Braunschweig, Mats Soderhall, Barbro Kjellstrom, PierreAndre Grandjean, Karolinska University Hospital, Stockholm, Sweden

Background: Intermittent and chronic volume overload might contribute to the onset and progression of cardiovascular disease in patients on maintenance hemodialysis. Continuous monitoring of central hemodynamic parameters may provide valuable information, particularly in patients with left ventricular dysfunction.

Methods: 9 patients with end-stage renal disease, age 53-76, with left ventricular dysfunction (EF < 50%) received an implantable echo-Doppler and E/A ratio monitor (IMHCHRONIC model 9520, Medtronic). The IMH consists of a memory device implanted subcutaneously and a transvenous right ventricular (RV) lead with a pressure sensor. It continuously records heart rate (HR), RV systolic (RVSP) and diastolic pressure (RVDP) and estimated pulmonary artery diastolic pressure (ePAD). All patients underwent hemodialysis 3 times/week. Average of hemodynamic data from the first, second and third night after dialysis were calculated.

Results: Progressive pressure increments were seen between the first, second and third and in 7 of 9 patients. The RVDP increased 9%, RVDP 19%, ePAD 11% from first night to second night after dialysis. The third night the increments were more pronounced - RVDP 12%, RVDP 28%, ePAD 16%.

843-4 The Prevalence of Cardiorenal Syndrome is Similar in Systolic and Diastolic Heart Failure
Theophilus E. Owan, Regina M. Herges, David O. Hodge, Veronica L. Roger, Margaret M. Redfield, Mayo Clinic, Rochester, MN

Background: Worsening renal function with heart failure (HF) therapy (cardiorenal syndrome, CRS) is common and predicts length of stay (LOS) and mortality in HF patients (pts). Pts with HF and normal (≥60%) ejection fraction (EF) (diastolic HF, DHF) may differ from those with reduced EF (systolic HF, SHF).

Objective: We sought to determine if the severity of renal dysfunction or the prevalence of CRS is different in DHF versus SHF.

Methods: Electronic chart review was performed on all consecutive unique HF pts discharged from Mayo Clinic hospitals Rochester MN from 1/18/01 to 12/31/02 (DRG 127) (n=6440). EF (measured within 30 days of admission) was available in 4610 pts. Creatinine (CrT) was examined on and for 14 days after admission. Three month mortality and LOS were examined.

Results: See Table. Pts with DHF were older, more likely female and had lower baseline CrT. Mean CrT clearance (Gault equation) was lower in DHF. The mean change in CrT was similar in DHF and SHF. The prevalence of CRS (increase in CrT of > 0.3 mg/dl or ≥ 25%) was similar to higher in DHF pts. Controlling for the type of HF and other pertinent covariates, baseline CrT was predictive of mortality (odds ratio, OR=1.01 per mg/dl increment in baseline CrT, p<0.001) but not LOS. Change in CrT was predictive of mortality (OR=1.38 per 1.0 mg/dl increase in CrT, p<0.004) and LOS (value = 1.04, p<0.001).

Conclusion: CRS is not less common in DHF and the presence of CRS is predictive of mortality and LOS regardless of type of HF.

843-5 Formulas estimating Renal Function give imprecise estimates in Heart Failure
Tom D. Smilde, Hans L. Hillege, Gerwin Nasj, Adriaan A. Voors, Dirk J. Van Veldhuisen, University Hospital Groningen, Groningen, The Netherlands

Background, Glomerular filtration rate (GFR) as an index of renal function has consistently been found to be an independent risk factor for CVD outcomes in patients with chronic heart failure (CHF). In clinical practice a variety of formulas have been used to estimate GFR. To date, no study has compared multiple methods of measuring renal function in CHF patients.

Objective, We validated in CHF patients three commonly used formulas estimating glomerular filtration rate (GFR) with the gold standard 125I-iodate clearance (GFR). A comparison between the GFR and GFRc was performed for body surface area. The Bland-Altman method was used to compare these formulas with the true GFR.

Methods, In 50 CHF patients; age 58 ± 10 years, LVEF 0.28 ± 0.10 and NYHA I/IV, GFR, glomerular filtration rate (GFR) with the gold standard 125I-iothalamate clearance (GFRc) were measured. In all patients gender and serum creatinine were the most prominent variables for inaccuracy estimating GFR.

Results, Although, the formulas appeared to correlate well with the GFR, the Bland-Altman method showed there were important differences and a wide variability in the estimated GFR (table). Furthermore, in all formulas gender and serum creatinine were the most prominent variables for inaccurately estimating GFR.

Conclusions, In CHF, formulas estimating GFR appeared to be biased and imprecise in estimating true GFR, especially in the upper and lower ranges.

True and estimated renal function in CHF (n=50)

<table>
<thead>
<tr>
<th>Mean</th>
<th>Min/Max</th>
<th>Correlation</th>
<th>Bland-Altman</th>
<th>Bland-Altman</th>
<th>Bland-Altman</th>
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<tr>
<td>GFR</td>
<td>77.8±26.8</td>
<td>14.6-132.5</td>
<td>0.768</td>
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<td>Cockcroft-Gault</td>
<td>87.5±53</td>
<td>24.1-123.5</td>
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<td>MDRD</td>
<td>64.5±20.0</td>
<td>32.1-123.5</td>
<td>0.001</td>
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<td>26.046</td>
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<td>Simplified MDRD</td>
<td>33.7±75</td>
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<td>0.001</td>
<td>0.792</td>
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</table>
Adrenomedullin (AM) Reflects Cardiac Dysfunction Better Than Brain Natriuretic Peptide (BNP) in Hemodialysis (HD) Patients With Cardiovascular Disease

Fumiki Yoshishara, Takeshi Horio, Masahyoshi Yoshii, Satoko Nakamura, Hajime Nakahama, Takashi Inenaga, Kenji Kangawa, Yuhei Kawano, National Cardiovascular Center, Suita, Osaka, Japan

Background: Plasma AM has been reported to reflect cardiac dysfunction and predict survival after myocardial infarction in non-HD patients. The present study was designed to investigate whether AM reflects cardiac dysfunction in HD patients, comparing to BNP, and whether mortality and additional cardiovascular events can be predicted by AM.

Methods: Plasma mature AM and BNP levels before HD were measured in 67 HD patients with cardiovascular disease along with two-dimensional and Doppler echocardiographic variables.

Results: By univariate regression analysis, log [AM] was positively related to LV end-diastolic and end-systolic volume indices (LVEDVI: r=0.32, LVEFSVI: r=0.36) and negatively to LV ejection fraction (LVEF). LV inflow velocity rate (A/E), deceleration time of the early diastolic filling wave (DcT) and pulmonary venous flow velocity rate (PVs/PVd) (r=0.34, r=0.37, r=0.40, r=0.34). Log [BNP] also was positively related to LVEFSVI (r=0.31) and negatively to LVEF and PVs/PVd (r=0.34, r=0.30). Multivariate stepwise regression analysis revealed that log [AM] reflected all variables better than log [BNP].

Conclusions: Using renal function compromising medication were excluded. All patients used renin-angiotensin system inhibiting medication. AM was related to mortality and morbidity (HR 4.96 [95% CI 1.4 to 17.7] p<0.013).

Increased Urinary Albumin Excretion in Non-Diabetic CHF is associated with Impaired Renal Function.


Background. The prognostic value of renal function for mortality is well established in diabetics and non-diabetics. Urinary albumin excretion (UAE) is a known marker for overt renal disease in diabetics. It is unknown whether increased UAE is also present in patients with chronic heart failure (CHF). We determined the UAE in CHF patients, without primary renal disease and evaluated the association between UAE and renal function.

Methods. In 47 CHF patients, age 58±10 years, mean UEF 0.29±0.10 and mean NYHA 2.3±0.8, we collected 2x24xours urine and measured the mean UAE. We measured glomerular filtration rate (GFR), as the golden standard of renal function, with 125I-iodotulamidine clearance. Patients with a history of hypertension, diabetes, nephropathy or using renal function compromising medication were excluded. All patients used renin-angiotensin system inhibiting medication.

Results. Median albumin excretion was 10.2 mg/L (6.8-21.8). MA (30-300 mg/L) was significant RD (p=0.0056). By Cox proportional hazards analysis, AM was related to mortality and additional cardiovascular events. Kaplan-Meier survival curves based on the median AM (4.6 pmol/L) showed that patients with high AM had higher mortality and morbidity than those with low AM (p=0.0056).

Conclusions: Significant RD is very common in patients admitted with decompensated CHF, with most having at least moderate (Stage III) decrease in eGFR. Simple measurement of serum creatinine significantly underestimates the degree of RD. RD is a very common comorbidity with CHF and it may play an important role leading to decompensation and hospitalization.

Myocardial Function and Heart Failure: Basic and Molecular III

Tuesday, March 08, 2005, 1:30 p.m.-5:00 p.m.
Orange County Convention Center, Hall E1
Presentation Hour: 2:30 p.m.-3:30 p.m.

1160 Myocardial Function and Heart Failure: Basic and Molecular III

Ghrelin Improves Biventricular Function And Attenuates Autocarpe/paracrine Activation In Monocrotaline-induced Pulmonary Hypertension

Tiago Henriques-Coelho, Jorge Correia-Pinto, Roberto Roncon-Albuquerque Jr, Ana Beteza-Moreiras, Andre Pedro Lourenco, Antonia Teles, Adelino F. Leite-Moreira, Serviço de Fisiologia, Faculdade de Medicina, Porto, Portugal

Background: We recently showed that ghrelin (ghr) attenuates pulmonary hypertension (PH), right ventricular and pulmonary vascular remodelling in monocrotaline (MCT) rats. In this model of right ventricular (RV) overload, there is failure of the non-overloaded left ventricle (LV). In the present study we evaluated the effects of ghr on biventricular function and autocrine/paracrine activation in MCT-induced PH.

Methods: Adult Wistar rats were injected with MCT (60 mg/Kg, sc) or just the vehicle (day 0). One week later, animals treated with MCT were randomly divided and treated with ghr (100 µg) or saline intraperitoneal plus a similar volume of vehicle. The study resulted in 3 groups: (i) Control (Cfr, n=7), (ii) MCT (n=9), (iii) MCT+ghr (n=9). At days 21-25 the animals were instrumented to record RV and LV peak systolic (Pays) pressures, dp/dmax and time constant Tau. RV and LV systolic free-wall samples were collected to quantify, by real time RT-PCR, IGF-1, pEF-T and ACE mRNA levels, which were normalized for GAPDH and expressed in arbitrary units (AU).

POSTER SESSION
Cardiac Function and Heart Failure

Results: Presented as means±SEM, are summarized in the table (P<0.05: a vs. Ctrl; b vs. MCT).

Conclusion: Ghr attenuation LV systolic dysfunction, biventricular diastolic dysfunction and increased expression of p53 and ACE induced by MCT. Therefore, Ghr has beneficial effects on cardiac remodelling independently of local IGF-1 expression and cardiac overload, but potentially related with blunting of local activation of ET-1 and renin-angiotension systems.

T1160-145

Caldomin Kinase II Inhibition Protects Against Isoproterenol-Induced Cardiomyocyte Death In Vivo

Yingbo Yang, Rong Zhang, Michelle S. Khoo, Yue Hou, Jinying Yang, Roger J. Colman, Mark E. Anderson, Vanderbilt University Medical Center, Nashville, TN

Background: Beta-adrenergic receptor activation contributes to the progression of human heart failure partly by inducing myocyte death. Here we test the hypothesis that cardiac CaMKII inhibition reduces isoproterenol (Iso)-induced cardiomyocyte death in vivo.

Methods: We developed transgenic mice with heart-restricted CaMKII inhibition (AC3-I) and control mice (AC3-C) by over-expressing a CaMKII inhibitory peptide or a control peptide. Mice were treated with intraperitoneal injection of iso or saline and sacrificed 2 hours after a single high dose Iso (150mg/kg) or 10 days after low dose Iso (15mg/kg/day) or saline. Myocyte and non-myocyte necrosis and apoptosis were measured as a percentage of endocardial fibrosis and by TUNEL assay on transverse mid left ventricle sections.

Results: After 10 days, AC3-I significantly reduced Iso-induced myocyte necrosis (AC3-C vs AC3-I, 8.8±1.8% vs 1.9±0.3%, P<0.001, n=4). AC3-I inhibited Iso-induced myocyte apoptosis after two hours (P=0.007, n=3-6). After 10 days of Iso, the difference in myocyte apoptosis between AC3-I and AC3-C was no longer evident; however non-myocyte apoptosis was significantly reduced in AC3-I compared to AC3-C (figure, p=0.02, n=4-8). Conclusions: Cardiac CaMKII inhibition protects against both Iso-induced cardiomyocyte necrosis and apoptosis in vivo. There are important time and cell type variations to the antinecrosis and antiapoptosis actions of CaMKII inhibition.

T1160-146

The Impact of Angiotensin-Converting Enzyme Inhibition on Stiffness and Collagen Cross-Linking During LV Assist Device Support

Stefan Kierzk, A.H. Jan Danzer, Robert F. Foronyi, Mehmet C. Oz, Jeanine D'Armiento, Daniel Burkoff, Columbia University, New York, NY, Erasmus Medical Center, Rotterdam, The Netherlands

Background: Mechanical unloading increases LV collagen content and myocardial stiffness and might contribute to the low rate of LV functional recovery following left ventricular assist device (LVAD) support. Angiotensin-converting enzyme inhibitors (ACE-I) reduce extracellular collagen matrix (ECM) synthesis and we therefore hypothesized that ACE-I therapy in LVAD patients might prevent this potentially detrimental ECM remodelling.

Methods and Results. LV myocardial samples were obtained in 22 patients with end-stage congestive heart failure before and after LVAD support, and divided into groups who did or did not receive ACE-I (ACE-I and Control_group) during similar periods of LVAD duration. Measurements were made of tissue angiotensin (Ang) II, and collagen characterization. Chamber and myocardial stiffness constants were determined from ex vivo pressure-volume relationships.

Conclusions: ACE-I therapy reduces tissue Ang II levels, myocardial collagen content and myocardial stiffness during LVAD support. The extent to which the markedly increased stiffness that occurs during LVAD support may inhibit myocardial recovery, ACE-I treatment may be beneficial.

T1160-147

The Role Of The Chromatin Remodelling Enzyme p300 In Cardiac Function and Heart Failure

Jian Qin Wei, James Mitrani, Alex Llanos, Keith Atkinson Webster, Nanette H. Bishopric, University of Miami School of Medicine, Miami, FL, Miami Heart Research Institute, Miami, FL

Background: The histone acetyl transferase (HAT) transcription factor p300 is critical in regulating cardiac growth and gene transcription during development. However, the role of p300 in the heart is unknown.

Objective: To determine the functional significance of p300 in the heart.

Methods: We have demonstrated that glucagon-like peptide-1 (GLP-1 [7-36] amide) improves myocardial glucose uptake (MGU) and LV hemodynamics in conscious dogs with established congestive heart failure (CHF). GLP-1R is a 7 transmembrane G-protein coupled receptor whose functional significance in the heart is unknown.

Conclusions: GLP-1R in the conscious heart may mediate the cardiac effects of GLP-1.

T1160-148

Dilated Cardiomyopathy (DCM) Is Associated With Increased Myocardial GLP-1 Receptors and Enhanced Myocardial Glucose Uptake in Response to GLP-1 Infusion in Conscious Dogs

Indu G. Poomma, Lazarus A. Nikolaidis, Aaron Doverspike, Lee Zourelia, Laurie Machen, Carol Stolarzki, Teresa Hentzos, Richard P. Shannon, Allegheny General Hospital, Pittsburgh, PA

Background: We have demonstrated that glucagon-like peptide-1 (GLP-1 [7-36] amide) improves myocardial glucose uptake (MGU) and LV hemodynamics in conscious dogs with established congestive heart failure (CHF). GLP-1R is a 7 transmembrane G-protein coupled receptor whose functional significance in the dog heart is unknown.

Objective: We sought to determine if the benefits of GLP-1 on MGU are mediated through the insulin signaling cascade in dogs with CHF.

Methods: We performed hyperinsulinemic-euglycemic clamps in 8 conscious dogs with DCM, chronically instrumented to measure LV function, coronary flow and transmyocardial substrate extraction, and compared to 6 normal dogs. Clamps were performed before and after a 48-hour infusion of GLP-1 [7-36] amide (5 pmol/kg/min) during which myocardial glucose uptake (MGU) was measured during hyperinsulinemia. Myocardial tissues were obtained to measure GLP-1 receptors and the effects of GLP-1 infusion on cellular insulin signaling using Western blots.

Results: There was a significant increase (+160±23%, p<0.005) in the 65-kDa GLP-1 receptor isoform in DCM. GLP-1 infusion was associated with significant increases in basal MGU (2.6±0.4 to 8.5±1.0 pmol/min, p<0.05) in DCM, where as GLP-1 had no effect in normal dogs (4.7±0.7 to 5.1±0.5 pmol/min). The increase in MGU seen with GLP-1 in DCM was not associated with an increase in myocardial GLP-1 receptor expression. During clamps, MGU was markedly (p<0.02) impaired in DCM (8.3±0.7 pmol/min) compared to normal dogs (17.2±2.3 pmol/min). GLP-1 treatment in DCM improved MGU (12.4±1.8 pmol/min, p<0.05) during clamp. DCM was associated with impaired ser 473-Akt phosphorylation (-73±10%, p<0.01) and GLUT -4 translocation (-51±5%, p<0.05). Notably, GLP-1 treatment in DCM did not increase Akt-1 phosphorylation or GLUT-4 translocation, despite increases in MGU.

Conclusions: GLP-1R are present in the canine myocardium in their active form (65-kDa) in DCM. GLP-1R increases MGU in DCM, despite marked insulin resistance. Furthermore, the insulinomimetic effects of GLP-1 in DCM are not mediated by activation of Akt-1, suggesting a unique GLP-1 mediated mechanism.
Effect of b-blocker Administration on Coronary Sinus Blood Temperature Measurements

Konstantinos Toutouzas, John Mitropoulos, Maria Drakopoulou, Sophia Vaina, Eleftherios Tsiamis, Manolis Vavouranakis, Dimitris Toussoulis, Christodoulos Stefanadis, Hippokration Hospital, Athens, Greece

Background: Coronary sinus (CS) temperature is increased in patients (pts) with coronary artery disease (CAD) or heart failure. Aim of our study was to investigate the Effect of b-blocker on CS blood temperature in pts without angiographically documented CAD and normal ejection fraction.

Methods: In the study we enrolled 7 pts undergoing electrophysiological study for evaluation of the atrioventricular conduction (EPS). Five minutes after EP lab a CS thermography catheter was advanced 2-4 cm distally to the CS orifice and blood temperature was measured without the tip of the catheter being in contact with the vessel wall (background temperature). Thereafter, esmolol was administered IV with a rate of 100mg/kg/min for 5 min. Temperature difference (TD) was designated as the blood temperature in the CS during and after esmolol infusion minus the background temperature.

Results: All procedures were successful and uncomplicated. TD at the end of esmolol administration was -0.12 ± 0.03°C and 5 minutes after the end of administration was -0.21 ± 0.04°C, p<0.001 (mean CS temperature was 37.1 ± 0.03°C at baseline and dropped to 36.98 ± 0.04°C at the end of esmolol infusion, reaching finally a minimum of 36.89 ± 0.03°C). Heart rate was reduced maximally by 26% at the end of esmolol infusion.

Conclusion: CS blood temperature is decreased during b-blocker administration, possibly as a result of decreased heat production from the myocardium.

Neonatal Cardiomyocytes Do Not Require a Cardiac Milieu to Establish Contractile Units

Wendye Dai, Sharon L. Hale, Robert A. Kloner, The Heart Institute, Good Samaritan University, Hospital of Southern California, Los Angeles, CA

Purpose: To investigate whether immature neonatal cardiomyocytes (Cs) grafted outside of a fetal cardiac environment, that is in the outer wall of an aorta, can mature and contract in a hostile and xenogenic environment.

Methods: Recipient adult female Fischer rats received medium only (n=9), or Cs isolated from neonatal Fischer rat pups (n=12, 5×10⁶ cells each). The injection site was the outer wall of the abdominal aorta. Six weeks later, the intra-aortic pressure at the grafted site, the pulse pressure generated by spontaneous beating and the response of the grafted tissue to pacing was assessed after excision of the abdominal aorta. Six weeks later, the intra-aortic pressure at the grafted site, the pulse pressure generated by spontaneous beating and the response of the grafted tissue to pacing was assessed after excision of the abdominal aorta. Six weeks later, the intra-aortic pressure at the grafted site, the pulse pressure generated by spontaneous beating and the response of the grafted tissue to pacing was assessed after excision of the abdominal aorta. Six weeks later, the intra-aortic pressure at the grafted site, the pulse pressure generated by spontaneous beating and the response of the grafted tissue to pacing was assessed after excision of the abdominal aorta. Six weeks later, the intra-aortic pressure at the grafted site, the pulse pressure generated by spontaneous beating and the response of the grafted tissue to pacing was assessed after excision of the abdominal aorta.

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Conclusion: CS blood temperature is decreased during b-blocker administration, possibly as a result of decreased heat production from the myocardium.

Abstracts - Cardiac Function and Heart Failure

Neonatal Cardiomyocytes Do Not Require a Cardiac Milieu to Establish Contractile Units

Functional Capacity as Assessed by Six-Minute Walk Test Is Strongly Associated With Cardiac Fibrosis in Patients With Chronic Heart Failure

Anca Radescu, Jean-Marc Virion, Camille Ducki, Josette Capiaumont, Li Mingjiang, Oh, Donna Mancini, Columbia Presbyterian Medical Center, New York, NY, Mayo Clinic, Rochester, MN

Background: Functional mitral regurgitation (MR) is common in patients with chronic heart failure (CHF) and contributes to rest and exertional symptoms. In the multicenter trial with the ACORN-CARD, 264 patients (age 62 ± 12 yrs; 79% male; 46% female) with Class II to IV CHF from 19 centers underwent screening echocardiogram and cardiopulmonary exercise testing (CPET). We investigated if resting echocardiographic measurement of MR severity could predict peak exercise performance and ventilatory response.

Methods: Exercise testing included bicycle and treadmill protocols. Anaerobic threshold (AT) was identified using the nadir of the ventilatory equivalent for VO₂ and end-tidal O₂. Ventilatory response to exercise was measured using the ventilatory equivalent for CO₂ (VE/VO₂) at AT (normal VE/VO₂ = 25). This technique has previously been shown to be independent of exercise protocol used. Severity of MR was visually estimated from 0 to 4+. Core lab personnel analyzed all data.

Results: Using ANOVA, increasing severity of MR predicted a lower Peak VO₂ (p<0.0001), a higher VE/VO₂ at AT (p<0.0002) and a decreased O₂ pulse (p=0.0001).

Conclusion: Severity of mitral regurgitation at rest is associated with diminished exercise capacity and a more abnormal ventilatory response to exercise. The results of the ACORN-CARD trial will elucidate whether correction of mitral insufficiency improves both exercise capacity and ventilatory efficiency in patients with CHF.

Long-Term β-Blockade Therapy Down-Regulates mRNA Gene Expression of Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1α in Left Ventricular Myocardium of Dogs With Chronic Heart Failure

Sharad Rastogi, Gudishw Mishra, Ramesh C. Gupta, Sidney Goldstein, Hani N. Sabbah, Henry Ford Health System, Detroit, MI

Background: Myocytes of humans and dogs with heart failure (HF) manifest ultrastructural and functional abnormalities of mitochondria including hyperplasia, reduced organole volume and abnormal oxidative capacity. Peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) is a regulator of mitochondrial biogenesis and function. Overexpression of PGC-1α in mice results in uncontrolled mitochondrial biogenesis, loss of sarcomeric structure and dilated cardiomyopathy. This study examined mRNA expression of PGC-1α in LV of normal (NL) dogs, dogs with HF and dogs with HF treated with β-blockers.

Methods: Total RNA was isolated from LV tissue of 12 dogs with HF randomized to 3 months therapy with extended release metoprolol (ER-MET 100 mg, once daily, n=6) or to placebo (PL, n=6), 12 dogs with HF randomized to 3 months therapy with carvedilol (CARV 1.0 mg/kg, twice daily, n=6) or to PL (n=6) and from 6 NL dogs. mRNA expression for PGC-1α was measured using RT-PCR and bands quantified in densitometric units (du).

Results: mRNA expression of PGC-1α increased in PL-treated dogs compared to NL (table). Treatment with ER-MET or CARV reduced mRNA expression of PGC-1α compared to PL (table).

Conclusions: The increase in mRNA expression of PGC-1α in LV of dogs with HF may explain the observed abnormalities in mitochondria. Long-term therapy with β-blockers reduces mRNA expression of PGC-1α. This suggests another molecular mechanism by which β-blockade therapy elicits functional improvement in HF.

Poster Session

Heart Failure: Prognostic Markers

Mary Jane Far, Seung W. Park, Jennifer Haythe, John LaManca, Spencer Kuo, Jye K. Oh, Donna Mancini, Columbia Presbyterian Medical Center, New York, NY, Mayo Clinic, Rochester, MN

Background: Functional mitral regurgitation (MR) is common in patients with chronic heart failure (CHF) and contributes to rest and exertional symptoms. In the multicenter trial with the ACORN-CARD, 264 patients (age 62 ± 12 yrs; 79% male; 46% female) with Class II to IV CHF from 19 centers underwent screening echocardiogram and cardiopulmonary exercise testing (CPET). We investigated if resting echocardiographic measurement of MR severity could predict peak exercise performance and ventilatory response.

Methods: Exercise testing included bicycle and treadmill protocols. Anaerobic threshold (AT) was identified using the nadir of the ventilatory equivalent for VO₂ and end-tidal O₂. Ventilatory response to exercise was measured using the ventilatory equivalent for CO₂ (VE/VO₂) at AT (normal VE/VO₂ = 25). This technique has previously been shown to be independent of exercise protocol used. Severity of MR was visually estimated from 0 to 4+. Core lab personnel analyzed all data.

Results: Using ANOVA, increasing severity of MR predicted a lower Peak VO₂ (p<0.0001), a higher VE/VO₂ at AT (p<0.0002) and a decreased O₂ pulse (p=0.0001).

Conclusion: Severity of mitral regurgitation at rest is associated with diminished exercise capacity and a more abnormal ventilatory response to exercise. The results of the ACORN-CARD trial will elucidate whether correction of mitral insufficiency improves both exercise capacity and ventilatory efficiency in patients with CHF.

Functional Capacity as Assessed by Six-Minute Walk Test Is Strongly Associated With Cardiac Fibrosis in Patients With Chronic Heart Failure

Anca Radescu, Jean-Marc Virion, Camille Ducki, Josette Capiaumont, Li Mingjiang, Oh, Donna Mancini, Columbia Presbyterian Medical Center, New York, NY, Mayo Clinic, Rochester, MN

Background: The 6-minute walk test (6MW) has been recommended as a simple and safe indicator of prognosis in patients with chronic heart failure (CHF). So far, the mechanisms underlying the relationship between 6MW and prognosis in CHF are unknown. We hypothesize that one possible mechanism could be the excessive extra-cellular matrix collagen matrix (ECCM) turnover leading to fibrotic cardiac remodeling.

Methods: Evaluate the association between 6MW and serum collagen biomarkers assessing ECM turnover, in patients with mild-to-severe CHF.

Results: In 1009 patients included in the RECOVER trial (IIb-IV NYHA, LVEF <= 30%, 6MW <= 375m, diuretics 99%, ACEI 85%, β-blockers 64%, spironolactone 36%) we measured the IL1α (IL-1α, ELISA) in the triceps-Superior of collagen synthesis (zymo-terminal propeptide of type III collagen (PILNP)) and degradation [total matrix metalloproteinase 1 (MMP1)] total tissue inhibitor of metalloproteinase 1 (TIMP1)].
Conclusions: We showed that patients with excessive ECM turnover exhibited a lower 6MWT performance level. These results suggest that fibrotic cardiac remodeling could represent the “missing link” explaining the increased risk of death in patients with a short 6MWT.

Association of ECCM biomarkers to functional capacity

### Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>DWT</th>
<th>UVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHILNP (p/ml)</td>
<td>r = -0.12 (p&lt;0.01)</td>
<td>r = -0.01 (p=0.58)</td>
</tr>
<tr>
<td>MMP1 (ng/ml)</td>
<td>r = -0.14 (p&lt;0.01)</td>
<td>r = -0.07 (p=0.04)</td>
</tr>
<tr>
<td>TIMP1 (ng/ml)</td>
<td>r = -0.12 (p&lt;0.01)</td>
<td>r = -0.02 (p=0.61)</td>
</tr>
</tbody>
</table>

### T161-167 Six-Minute Walk Distance at Hospital Discharge Predicts Mortality in Patients With Advanced Heart Failure: An Analysis From the ESCAPE Study

**Stuart D. Russell**, Lynne W. Stevenson, Mark H. Drazner, Joshua M. Hare, Illeana L. Pita, Christopher M. O’Connor, Johns Hopkins Hospital, Baltimore, MD

**Background:** The 6-minute walk test can predict both mortality and hospitalization in stable heart failure (HF) patients (pts) in clinical trials and outpatient settings. Yet the test has not been examined as a predictive tool at time of admission or discharge for inpts hospitalized for acute decompensation.

**Methods:** ESCAPE was a prospective, randomized, NHLBI-funded trial comparing hemodynamically guided therapy using pulmonary artery catheterization versus standard care in pts with acute decompensated HF. Six-minute walk tests were performed at enrollment and discharge.

**Results:** The mean distance for 380 pts who underwent a baseline 6-minute walk test was 416 feet. For 315 patients who completed a predischarge 6-minute walk test, the mean was 690 feet. Both baseline and discharge 6-minute walks predicted readmission and mortality (Fig), but changes in 6-minute walk scores from baseline to discharge did not (r=0.07; p=0.8476). The 6-minute walk test remained predictive after adjusting for other covariates including pulse pressure, BUN, and hemoglobin. Based on a Cox model analysis, the hazard ratio per 100 feet for time to death or re-hospitalization was 0.995 (p=0.0053).

**Conclusion:** The 6-minute walk distance can be easily conducted in the majority of pts with congestive HF and can be easily conducted in the majority of pts with congestive HF.

### T161-168 Exercise Ventilation Inefficiency and Cardiovascular Mortality in Heart Failure: The Critical Independent Prognostic Value of the Arterial CO2 Partial Pressure

**Marco Guazzi**, Giuseppe Reina, Gabriele Tumminello, Maurizio D. Guazzi, Cardiopulmonary Laboratory, University of Milano, San Paolo Hospital Milano, Italy, Institute of Biometry and Statistics, Italy

**Background:** In chronic heart failure (CHF) patients, the ventilation (VE) needed to eliminate metabolically produced CO2 during exercise (i.e. VE/VCO2 slope) is a strong prognosticator: VE/VCO2 slope determinants are the dead space-tidal volume (VD/VT) ratio and the arterial CO2 partial pressure (PaCO2). We probed the prognostic role of these two variables.

**Methods:** In 1168 stable CHF patients (average left ventricular ejection fraction=34±10%) underwent cardiopulmonary exercise testing and blood gas analysis. The prognostic relevance of VE/VCO2 slope, VE/T and PaCO2 at peak exercise was evaluated by Kaplan-Meier approach with log-rank testing and by multivariate Cox regression analysis.

**Results:** During a mean follow-up of 31.3±20 months, 249 patients died for cardiac reasons. Non-survivors vs survivors, showed a smaller peak VO2 (14.3±4.0 vs 17.0±4.0 mL/min*kg⁻¹; p<0.01), a steeper VE/VCO2 slope (42±10 vs 32±6; p<0.01), a lower PaCO2 (33±5 vs 37±4; p<0.01), and a higher VE/T (0.24±0.04 vs 0.22±0.04; p<0.01), at peak exercise. Multivariate analysis identified a low PaCO2 as the strongest independent prognostic indicator (HR=4.65, 95% CI 1.695 to 12.751, p=0.003) that primarily accounts for the VE/VCO2 slope prognostic power.

**Conclusions:** Findings imply that regulatory mechanisms involved in the tight control between blood gas tension and ventilatory command, rather than lung abnormalities, play a critical pathophysiologial role in the exercise ventilation inefficiency of CHF patients.

### T161-169 Direct Bilirubin and Red Cell Distribution Width (RDW) Are Powerful Independent Predictors of Outcome in Chronic Heart Failure: Results from the CHARM Program

**Christopher Granger**, John McMurray, Marc Pfeffer, Karl Swedberg, Duolao Wang, Salim Yusuf, Eric Michelson, Stuart Pocock, Duke University Medical Center, Durham, NC

**Background:** While clinical factors predicting outcome in chronic heart failure (CHF) have been defined, less is known about how standard laboratory tests relate to outcome in CHF.

**Methods:** We evaluated data from 2679 patients in the CHARM program (from the US and Canada with baseline blood laboratory values) with symptomatic chronic heart failure randomized to candesartan or placebo for 38 months. A multivariable Cox regression model was developed using baseline variables to predict the composite of cardiovascular (CV) death and heart failure hospitalization (862 events).

**Results:** In order of amount of prognostic information (based on chi-square), the most important clinical predictors were age, NYHA class, diabetes, cardiomegaly on chest x-ray, ejection fraction, previous hospitalization for heart failure, and treatment with candesartan (all p<0.001). The most predictive laboratory values were higher direct bilirubin (HR 1.24 per 10 umol/L, p=0.001), red cell distribution width (RDW) (HR 1.5 per 5%, p=0.001), uric acid and lymphocyte count (p=0.001). Hazard ratios for quintiles of bilirubin (square for unadjusted, circle and 95% CI for adjusted) are shown in figure. Hemoglobin, creatinine, and glycosylated hemoglobin were also independent predictors. RDW was only modestly correlated with hemoglobin (correlation coefficient -0.27).

**Conclusions:** In a large contemporary CHF population, bilirubin and RDW were found to be surprisingly strong independent predictors of morbidity and mortality.

### T161-170 Dobutamine Related Eosinophilia Leads To Cardiac Decompensation By TNF-Alpha Deployment

**Gustavo A. Cardenas**, Patricia A. Uber, Mandeep R. Mehra, Ochsner Clinic Foundation, New Orleans, LA

**Background:** Dobutamine may lead to the development of idiosyncratic eosinophilia associated with clinical decompensation. We sought to evaluate whether eosinophilia was accompanied by the upregulation of the pro-inflammatory cytokine, Tumor necrosis alpha (TNF-alfa).

**Methods:** We examined 77 inotropic therapy-bound patients awaiting transplantation. Peripheral eosinophil counts were measured at baseline and weekly until transplantation. TNF-alfa was measured serially at baseline and at the time of heart explant. Explanted hearts were examined histologically to determine eosinophil infiltration (n=54 evaluable patients).

**Results:** The patients were 53 ± 1 years, 78% men, 53% ischemic, LVEF 16.3 ± 5%. Absolute Eosinophilia (>440 mm³) was diagnosed in 33 patients (43%) but eosinophilic myocardial infiltration was documented in only 3 of 54 patients (6%). A significant increase in TNF alpha levels (50%) was noted among those with eosinophilia who developed cardiac decompensation (table). Stepwise logistic regression found eosinophilia to be the most significant predictor of cardiac decompensation while type, dose and duration of inotropic therapy were not.
Conclusions: Peripheral eosinophilia, without eosinophilic cardiac infiltration is frequently found in inotropic therapy-bound patients and predicts impending cardiac decompensation. We suggest that the eosinophilia is associated with deployment of TNF-alpha, which may mediate the syndrome of cardiac decompensation.

<table>
<thead>
<tr>
<th>Eosinophilia (n=33)</th>
<th>No eosinophilia (n=44)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abs Eosinophilia</td>
<td>243 ± 131</td>
<td>1220 ± 918</td>
</tr>
<tr>
<td>% Eosinophilia</td>
<td>168 ± 111</td>
<td>999 ± 790</td>
</tr>
<tr>
<td>hTNF-a (%)</td>
<td>49 ± 9</td>
<td>49 ± 10</td>
</tr>
</tbody>
</table>

Incidence, Prevalence and Recovery of Anaemia in Heart Failure

Background: A high prevalence of anaemia has been reported amongst patients with chronic heart failure (CHF) but few data exist on its incidence and persistence. Methods: We assessed 254 consecutive patients attending a community heart failure clinic who were diagnosed with left ventricular systolic dysfunction and survived one year. Each patient underwent a full assessment including symptom scores, ECG, blood tests for electrolytes and creatinine and echocardiographic assessment of cardiac function. Haemoglobin (Hb) and haematinic indices were also measured at baseline and after 1 year of optimal medical therapy for heart failure with ACE inhibitors and beta-blockers. Anaemia was defined as a Hb <130 g/l in men and <120 g/l in women and <10 mmol/l in women.

Results: The mean age of the patients was 70 years, 30% were women and the mean left ventricular ejection fraction was 31±9%. 69 (27%) patients were anaemic at baseline; 14 (20%) cases resolved by one year. Of the 185 patients who were not anaemic, 45 (24%) became anaemic by one year; with the prevalence of anaemia increasing from 27% at baseline to 39% at 1 year. The prevalence of renal dysfunction at baseline was 34% ranging to 39% at one year. At baseline, 31% patients had a low serum iron of which 5% also had low serum ferritin concentrations. 32 (13%) patients had low B12 and 12 patients (5%) had low cell folate levels. Hb level correlated with serum iron (r=0.6, p < 0.001) and ferritin (r=0.2, p < 0.001), but did not correlate with B12 or red cell folate levels. Few patients were prescribed specific haematinic therapy. On multivariate analysis by logistic regression, only serum iron (p < 0.0001) and creatinine (p < 0.0001) were independent predictors of anaemia at baseline and only baseline serum iron of anaemia at 1 year (p=0.05) with an odds ratio of 6 comparing the upper and lower teriles.

Conclusions: Anaemia is common in patients with heart failure and its prevalence rises with longer duration of disease. It does not commonly resolve without specific therapy. Renal impairment and low serum iron are independent predictors of anaemia in heart failure.

Diminished T Helper and B Cell Numbers and Attenuated Antigen Presentation Capacity in Chronic Heart Failure

Stephan von Hehling, Ewa A. Jankowska, Darlington O. Okonko, Kristin Strohschein, Wolfam Doehnng, Stefan D. Anker, National Heart and Lung Institute, London, United Kingdom

Background: Chronic heart failure (CHF) is a state of chronic immune activation. Although the role of pro-inflammatory cytokines has been studied in detail, the role of leukocyte subsets and their antigen presenting capacity remains unclear.

Methods: We prospectively enrolled 32 CHF patients (age 69.3±1.8 y [meansEM], NYHA class II, left ventricular ejection fraction 33±4%, white blood cell count [WBC] 7±0.4 x 10^9/L, CRP 13.2±2.2 mg/L, creatinine 128±85 µmol/L) and 8 healthy control subjects (age 65.8±3.4, WBC 7.3±0.5, CRP 8.2±1.2, creatinine 77±6). Flow cytometry was performed using EDTA anticoagulated whole blood after staining with CD4/CD8/CD3, CD4/CD20/CD19, and CD3/CD5/white blood cell leukocyte (HLA)-DR. Data were analysed using scatter plot gating.

Results: Lymphocytes from CHF patients were enlarged in size (mean fluorescence intensity [MFI], CHF vs. control: 274±4 vs. 254±5, p<0.04). Lymphocyte distribution differed between CHF patients and controls: CD3 positive T cells 14±1 vs. 21±3%, p<0.004, CD4 positive T helper cells 9±0.7 vs. 14±2%, p<0.004, CD8 positive cytotoxic T cells 5.9±1.5 vs. 4.2±0.5%, p<0.01. The relative number of CD45 positive lymphocytes in CHF patients was reduced compared to controls (21±1 vs. 31±5%, p<0.007). The relative number of HLA-DR positive lymphocytes was reduced in CHF patients as compared to controls (21±1 vs. 31±5%, p<0.01). In monocytes, there was no difference in absolute number, cell size, CD54 or HLA-DR expression.

Conclusions: CHF is associated with attenuated specific immunity as characterized by reduced T helper and B cell numbers and diminished T cell antigen presenting capacity. The latter is reflected by reduced HLA-DR expression. Innate responses, which are important for this phenomenon.

Plasma Concentrations of the Novel Peptide Apelin are Decreased in Patients With Chronic Heart Failure

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Background: Apelin, the novel endogenous ligand for the G-protein coupled receptor APJ, has positive inotropic, vasodilatory and diuretic properties. Differential expression and the presence of apelin and APJ receptor were also observed in normal and failing hearts, suggesting an important role in cardiovascular homeostasis. Changes in plasma apelin concentrations in relation to chronic heart failure (CHF) have been described in small studies with conflicting results. We studied plasma apelin concentrations in a large cohort of patients with CHF across a broad spectrum of disease severity.

Methods: We studied 200 patients with CHF secondary to left ventricular systolic dysfunction and 22 normal controls. We report on the characteristics of this novel peptide in patients with CHF compared to normal controls.

Results: Plasma apelin concentrations were significantly lower in patients with left ventricular systolic dysfunction, irrespective of NYHA class (0.85 [0.53-2.04] versus 3.33 [0.85-6.60] ng/ml, p<0.01), ejection fraction or aetiology when compared to age-matched controls. Apelin concentrations were seen to correlate with peak VO2 and right ventricular ejection fraction, but not with age, sex, body mass index, renal function or NT-proBNP concentrations.

Conclusions: Plasma concentrations of apelin are decreased in patients with chronic heart failure. Apelin might play an important role in the pathophysiological processes of heart failure and has potential therapeutic implications.
Serum and clinical data was obtained for clinically controlled CHF outpatients (n=175). Serum levels of adiponectin, C-reactive protein, N-terminal pro-brain natriuretic peptide, IL-beta, IL-6, IL-10, TNF-alpha and CD45 ligand were determined. The association of adiponectin with the clinical severity of CHF was sought as well as the predictive value of this adipokine on mortality. CHF hospitalizations or the occurrence of each of these end points. Levels of adiponectin were significantly increased in patients with CHF. Patients with higher New York Heart Association class had significantly higher serum levels of adiponectin. Adiponectin serum levels were lower in diabetic CHF patients as well as in patients with ischemic cardiomyopathy and positively associated with age. A positive association was found between serum adiponectin and NT-ProBNP whereas a negative correlation was found with regard to cardiac troponin. Adiponectin above the 75th percentile was found to be an independent predictor of total mortality, CHF hospitalizations or either of these composite endpoints over a 2-year prospective follow-up. Adiponectin is increased in CHF patients and predicts mortality and morbidity.

**1116-176**

**Serum Acid, Left Ventricular Mass Index, and Creatinine Clearance as Predictors for Congestive Heart Failure in Essential Hypertension**

Yoshihisa Takashia, Takeshi Horaki, Hiroshi Sugahara, Yuhei Kawano, Osaka University Graduate School of Medicine, Suita City, Osaka, Japan, National Cardiovascular Center, Suita City, Osaka, Japan

**Background:** Hypertension and left ventricular hypertrophy (LVH) are principal precursor of congestive heart failure (CHF), and elevated serum acid (UA) and decreased creatinine clearance (CrCl) are associated with worse functional status and adverse prognosis in CHF. In this study, we examined the association between serum UA and CrCl, and investigated prospectively whether UA and left ventricular mass index (LVM) assessed by echocardiogram can predict the incidence of CHF in asymptomatic essential hypertensive subjects.

**Methods and Results:** A total of 713 subjects (mean age 62 years, 50 % female) free of prior myocardial infarction and CHF were included in this study. After adjustment for comorbidities, decreased CrCl and significantly elevated serum UA (UA > 270 µmol/l; vs. CrCl < 90 ml/min/m²; p=0.04) were independently associated with CHF. During follow-up (mean 32 months), 32 subjects (13 female) developed CHF. Kaplan-Meier curves showed a significantly lower event-free survival rate in subjects with UA (OR 2.11, p<0.01) and CrCl (OR 1.17, female: <102.2 g/m2) (p=0.001, respectively). Cox regression analysis showed that the incidence of CHF increased when UA (≥421, female: ≥350 µmol/l) and LVM (male: ≥143.4, female: ≥113.4 g/m²) were increased (UA: OR 2.58, CrCl: OR 2.11, p<0.01). Baseline serum UA was significantly increased in patients with LVH, and independently associated with CrCl. Increased UA and LVMI, and decreased CrCl are independent predictors for CHF.

**Conclusion:** In patients with essential hypertension, both UA and LVMI are independent predictors for CHF.
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Conclusion: These data suggest that myocardial ischemia is more strongly associated with impaired coronary endothelial function in patients with hypertensive heart disease and reduced basal and maximum coronary blood flow per unit LV mass in patients with hypertrophic cardiomyopathy.

1162-159 Percutaneous Septal Ablation for Hypertrophic Obstructive Cardiomyopathy: How Much CK is Necessary for Significant Reduction of the Outflow Gradient?

Dirk Weiste, Dieter Fassbender, Henning K. Schmidt, Dieter Hordkotte, Lothar Faber, Heart Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany

Background: A less agressive approach to outflow obstruction (LVOTO) using smaller doses of ethanol is increasingly used in percutaneous septal ablation (PTSSMA).

Methods: In a cohort of 244 patients (pts.), who had a complete follow-up over 12 months after PTSSMA we studied whether the hemodynamic effect differed between pts. groups with different CK peaks (group A: <300 UI; group B: 300-800 UI years, group C: >800 UI, normal: <80 UI).

Results: Mean NYHA functional class improved from 2.9±0.4 to 1.5±0.7, accompanied by a LVOTO reduction from 58±34 to 9±16 mm Hg at rest, and 122±45 to 27±32 mm Hg with provocation. The effect of PTSSMA in the three different groups according to CK release is shown in the table.

Conclusions: A higher CK peak resulting from a higher ethanol dose leads to a more pronounced septal thinning 12 months after percutaneous septal ablation. The clinical effect and the complication rates were comparable in our cohort of exclusively echo-guided procedures using ethanol doses in the range of 2.5-ML. Our results do not support a "bigger is better" approach with respect to the post-interventional CK rise but suggest adjustment of the ethanol dose to baseline septal thickness.

<table>
<thead>
<tr>
<th>A (n=31)</th>
<th>B (n=187)</th>
<th>C (n=26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NYHA class</td>
<td>2.9±0.3</td>
<td>2.9±0.4</td>
<td>2.9±0.5</td>
</tr>
<tr>
<td>Baseline septum (mm)</td>
<td>19±3</td>
<td>21±4</td>
<td>22±4</td>
</tr>
<tr>
<td>Baseline watts</td>
<td>97±49</td>
<td>90±50</td>
<td>94±55</td>
</tr>
<tr>
<td>Ethanol dose (ml)</td>
<td>2.5±0.8</td>
<td>2.7±0.9</td>
<td>4.3±2.3</td>
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<tr>
<td>Pacemaker rate (%)</td>
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<td>9</td>
<td>9</td>
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<tr>
<td>NYHA class improvement</td>
<td>1.3±0.7</td>
<td>1.4±0.7</td>
<td>1.3±0.5</td>
</tr>
<tr>
<td>Septum thinning (mm)</td>
<td>5±3</td>
<td>5±4</td>
<td>5±6</td>
</tr>
<tr>
<td>LVOTO reduction (%)</td>
<td>70±46</td>
<td>84±29</td>
<td>88±18</td>
</tr>
<tr>
<td>Wallst improvement</td>
<td>20±31</td>
<td>19±42</td>
<td>30±52</td>
</tr>
</tbody>
</table>

1162-158 Evidence Against Myocardial Bridging As A Determinant Of Sudden Death In Hypertrophic Cardiomyopathy

Cristina Basso, Barry Maron, Domenico Corrado, Jack Titus, Gaetano Thiene, Pathology, University of Padua Medical School, Padova, Italy, Minneapolis Heart Institute Foundation, Minneapolis, MN

Background. Although myocardial bridging (MB) of the left anterior descending (LAD) coronary artery has been associated with myocardial ischemia and sudden death (SD) in young patients with hypertrophic cardiomyopathy (HCM), its prevalence in different age groups is unresolved and its overall significance remains controversial.

Methods. The files of two pathology cardiac registries were searched for diagnosed cases of HCM. A total of 105 hearts were enrolled (32 female and 73 male, ages ranging 1-day-90 yrs, mean 30±11). Heart weight and septal thickness were 465±208 g and 19±6 mm, respectively. Mode of death/failure was SD in 67 (64%), heart failure (HF) in 27 (27%) (14 with heart transplantation), early postsurgical death in 2 (myectomy), infective endocarditis in 1 and extracardiac causes in 6.

Results. A MB of LAD was present in 40 (38%) HCM pts., compared to 21 (21%) of 100 consecutive controls who died of causes unrelated to HCM (p=0.01). MB was present in 39% of SD, 41% of HF, and 33% of pts who died of extracardiac causes (p=NS). The prevalence of MB in different age groups ranged from 20% in pts aged <10 yrs to 57% in pts aged 20-30 yrs. A higher prevalence was found in pts aged >20 yrs (46%) than in pts <20 yrs (28%, p=0.05), whereas no difference was found specifically among SD pts aged >20 (41%) as compared to those <20 yrs (38% p=NS). No correlation was found between the presence of MB and either septal thickness or heart weight. MB had a mean length of 14.8±6.6 mm and a mean thickness of 2.0±1.5 mm. No correlation was found between MB thickness and heart weight and septal thickness, whereas the longer the MB the greater the MB thickness. At histology, MB more frequently consisted of a sheath of myocardial fibers totally encompassing the LAD (71%) than of a few superficial fibers transversally oriented (29%).

Conclusions. In HCM, MB was present at postmortem in a sizeable minority of pts (i.e., more than one-third). However, MB prevalence in HCM was only modestly greater than in controls with other heart diseases and did not differ between HCM pts with sudden or other modes of death, nor with respect to age and gender. Our findings do not support the hypothesis that MB represent a prognostic marker for sudden death in young HCM pts.
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Malignant Clinical Profiles and Heterogeneous Morphological Pattern Associated With Two Mutations of Myosin Binding Protein C Gene in Hypertrophic Cardiomyopathy

Chiara Pedroni, Lotte E. de Laat, Dennis Doosje, Marcel J. Kofflard, Folkert J. ten Cate, Ballena Hospital, Bologna, Italy, Thoraxcenter Erasmus MC, Rotterdam, The Netherlands

Background: Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by cardiac hypertrophy caused by mutations of genes encoding for sarcromeric proteins. More than 50 myosin binding protein C (MYBPC) mutations have been identified, most of them related to late onset and benign or intermediate prognosis. We analysed clinical features of two MYBPC mutations to enrich the spectrum of known genotype-phenotype correlations.

Methods: R943X and 2864delCT mutations, involving C-terminus of the protein, have been identified respectively in 4 and 6 not related HCM patients out of 50 not screened for MYBPC mutations. Detailed phenotype analysis was obtained from clinical data, rest and 24 hours electrocardiography, stress test and two-dimensional echocardiography.

Results: Among the 4 patients (men) carrying 2864delCT mutation 2 different clinical profiles could be identified. Three patients had an obstructive form, with moderate hypertrophy (maximal wall thickness [MWT] 19±7mm), severe symptoms (NYHA class = III and angina) refractory to maximal medical therapy and requiring myectomy or non surgical septal reduction therapy. None had major risk factors for sudden death (SD). Differently one patient had severe non obstructive form (MWT=32 mm), no symptoms and a family history for SD.

The 6 patients carrying R943X had also an heterogeneous clinical phenotype. Three males had no obstructive form, massive hypertrophy (MWT 32±4 mm) and moderate symptoms (NYHA class I). Three patients (1 male and 2 females) had mid-range hypertrophy and different degree of dyspnoea (NYHA class from I to III). Five out six patients had an high risk profile for SD. In all the 10 cases the diagnosis was made in adulthood (mean age 45±12 and 43±9 in patients carrying 2864delCT and R943X respectively, p=0.469).

Conclusion: These preliminary data show that MYBPC C mutations may carry severe clinical features associated with a broad range of hypertrophy degree. In patients sharing the same mutation adverse clinical course can proceed along different pathways: high risk for SD and severe heart failure due to obstruction or diastolic dysfunction.

Left Ventricular Outflow Tract Planimetry By Cardiovascular Magnetic Resonance Correlates With Doppler Pressure Gradient and predicts the obstruction In Patients With Hypertrophic Cardiomyopathy

Hassan Abdel-Aty, Matthias G Friedrich, Rainer Dietz, Jeannette Schulz-Menger, Franz-Volhard-Klinik, Helios-Klinikum Berlin, Kardiologie, Charité Campus Berlin-Buch, Humboldt-Universität, Berlin, Germany

Background: Measurement of the left ventricular outflow tract (LVOT) using cardiovascular magnetic resonance (CMR) in hypertrophic cardiomyopathy (HCM) is feasible and correlates with disease severity. Data relating this measurement to Doppler derived pressure gradient (PG) applying echocardiography (ECHO) are lacking. Whether rest/PG measurement can differentiate between the obstructive and non-obstructive HCM remains elusive.

Methods: We studied 37 HCM patients (22 males, 56±15 y) and 14 healthy subjects (7 males, 28±10 y) using CMR and Echo (median inter-study duration= 2 days). Minimal symptoms of LVOT obstruction (1 male and 2 females) were confirmed by steady state free precession sequence. PG was quantified at rest and after Valsalva maneuver. Patients were divided into 3 groups based on their PG: a) non-obstructive HCM (PG<30 at rest and after provocation, n= 11) b) Latent obstructive HCM (PG>30 at rest and >30 after provocation, n= 10) and c) Obstructive HCM (PG>30 at rest, n= 16).

Results: LVOT measurements in patients showed a significant inverse correlation with the Doppler-derived PG both at rest (Spearman correlation coefficient=- 0.6, p<0.001) and after provocation (>0.71, p<0.0001). Compared to volunteers with a mean LVOT area of 4.8±0.8 cm², the area was smaller in patients with non-obstructive HCM (3.5±1.1 cm², p<0.002), latent obstructive (2.2±1.5 cm², p=0.002) and obstructive HCM (1.6±0.6 cm², p<0.001). Patients with non-obstructive HCM had larger LVO than latent (3.5±1.1 cm² vs. 2.2±1.5 cm², p<0.013) or obstructive HCM (3.5±1.1 cm² vs. 1.6±0.6 cm², p<0.0001). When the latent obstructive and obstructive forms were considered together as obstructive HCM, significant differences in LVOT still existed between obstructive and non-obstructive HCM (1.8±0.3 vs. 3.5±1.1 cm², p<0.0001).

Conclusion: LVOT-derived LVOT area measurements correlate with pressure gradient as assessed by Echo. Measuring the LVOT area by CMR has the potential to differentiate between obstructive and non-obstructive HCM and to identify latent LVOT obstruction without the need for provocation.

Electrophysiological Evaluation Does not Predict Adequate ICD Interventions in Patients With Hypertrophic Cardiomyopathy Implanted for Primary Prevention

Helga Busch, Lothar Faber, Juergen Vogt, Johannes Heintze, Cornelia Hoppe, Christoph Wachter, Martin Cheung, Barbara Lamp, Dieter Horstkotte, Heart Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany

Background: Sudden cardiac death (SCD) is a feared complication of hypertrophic cardiomyopathy (HCM). Due to the fact that nearly all patients (pts) fail to survive their first episode of ventricular fibrillation (VF), risk stratification is important. A family history of SCD, recurrent syncope, nonsustained ventricular tachycardia (VT) on Holter monitoring, severe left ventricular hypertrophy, and abnormal blood pressure response to exercise have been identified as main risk factors (RFs). The purpose of this study was to investigate the impact of VT/VF inducibility during EPS on the frequency of adequate ICD interventions in HCM pts. implanted for primary prevention.

Methods: Since 2001, 27 pts with at least two main RFs received an implantable cardioverter-defibrillator for primary prevention. Before implantation EPS was performed with a cycle length of 500 ms with up to 3 extrastimuli at the right ventricular apex and outflow tract. The decision to implant the ICD was independent from the EPS result. After implantation the ICDs were interrogated at 3 to 6 months intervals.

Results: Sustained polymorphic VT or VF was induced in 14 pts. (group A). Group B consists of 13 pts. with negative EPS. Clinical characteristics are shown in the table. The distribution of RFs was comparable in both groups.

Conclusions: In our cohort of pts. with HCM and ICD implantation for primary prevention the inducibility of VT or VF during EPS did not correlate with the frequency of adequate ICD intervention during follow-up.

Cardiovascular Screening Practices of Major North American Professional Sports Teams

Kevin M. Harris, Austin Spoon, Adolph M. Hutter, Jr., Barry J. Maron, Minneapolis Heart Institute Foundation, Minneapolis, MN, Massachusetts General Hospital, Boston, MA

Background: Professional athletes represent the pinnacle of sports achievement and excellence in society; sudden unexpected death of such individuals due to cardiovascular disease, albeit rare, is particularly tragic and counterintuitive. Therefore, detecting the responsible diseases in such athletes becomes crucial. While preparticipation screening strategies are detailed for high school and college competitive sports, customary practice in professional sports has not been examined systematically.

Methods: Each of 122 teams comprising the Major League Baseball (MLB), National Basketball Association (NBA), National Football League (NFL) and National Hockey League (NHL) were contacted to complete a standard questionnaire summarizing their screening practices. History and physical examination items were compared to recommendations of the AHA consensus panel (12 items).

Results: Of the 122 teams (101 (83%) returned the questionnaire, allowing a detailed profile to be developed of personal and family history (100%); complete physical examination (91%); specific focus on tobacco (96%) and drug/nutritional supplement use (88%). Diagnostic testing with ECG was common (90%). An emphasis on screening for atherosclerotic coronary disease was evident by lipid panels (88%). Routine use of echocardiography (20%) and stress ECG was uncommon (16%). Uniform medical screening history and physical forms were available for MLB (10/12 AHA items); NFL (8/12 AHA items); and NHL (3/12 AHA items). Of the 101 teams, 33% reported previous disqualification of ≤ 1 athlete for cardiovascular disease; 5% reported a sudden death.

Conclusions: Preparticipation screening for cardiovascular disease is widespread customary practice among U.S. professional sports teams. Strategies vary considerably, but are generally superior in MLB and NFL. While screening practices for athletes take into account atherosclerotic coronary disease, equal emphasis is placed on the identification of syncope. Of value to athletes is the potential to under diagnose heart disease capable of causing sudden death in young athletes. Closer adherence to AHA screening recommendations for history and physical would be advantageous.

ORAL CONTRIBUTIONS

849 Novel Mechanisms of Cardiomyopathy

Tuesday, March 08, 2005, 2:00 p.m.-3:30 p.m.
Orange County Convention Center, Room 304E

Identification of a Metavinculin Missense Mutation, R975W, Associated With Both Hypertrophic and Dilated Cardiomyopathy

Vlad C. Vasile, Melissa L. Will, Steve R. Oommen, Timothy M. Olson, Michael J. Ackerman, Mayo Clinic College of Medicine, Rochester, MN

Background: Hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) are partially allelic disorders (identical or closely linked to pathogenic mutations in the same gene). Mutations in metavinculin, a muscle-specific isoform of vinculin and a key component of adherens junctions, were identified previously in DCM and were shown to alter optotactic behavior of actin filaments. Here, we tested the hypothesis that perturbations in metavinculin may also provide a pathogenic substrate for HCM.

Methods: Using DHPLC and direct DNA sequencing, mutational analysis of the metavinculin-specific exon of vinculin (exon 19) was performed in a cohort of 389 unrelated patients with clinical HCM, previously genotyped for the 8 most common HCM-associated sarcomere genes.

Results: Overall, 5 patients were found to host a non-synonymous single nucleotide polymorphism (amino acid variant). Among the subset of 147 sarcomere gene-positive
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Result: LV ejection fraction improved dramatically during follow-up period (47±9 versus 65±11%, p<0.001) mainly due to reduction of LV end-systolic volume (36±9 versus 23±11 ml, p<0.05). Deceleration time of diastolic CFV (DdT) and CFVR increased in all cases during follow-up period (457±178 versus 882±211 msec, p<0.001 and 1.7±0.5 versus 2.6±0.6, p<0.001, respectively). DdT in the acute phase was correlated with the LV ejection fraction and LV end-systolic volume index at 3 weeks later (r=0.82, p<0.01 and r=0.85, p<0.01, respectively).

Conclusion: Transient coronary microvascular dysfunction demonstrated by rapid DdT and restricted CFVR might be considered to be a main mechanism of tako-tsubo-like LV dysfunction. DdT in the acute phase can predict the recovery of LV function.

849-6

Statin Therapy Improves Indices of Left Ventricular Function and Serum Markers of Inflammation in Nonrandomized Patients with Chronic Heart Failure

Muhammad Mir, Srikanth Sola, Stamatios Lenakis, Amar Patel, Tarek Helmy, Bobby V. Khan, Emory University School of Medicine, Atlanta, GA

Background: In addition to cholesterol lowering, statins have significant effects on cellular and molecular mechanisms in vascular and myocardial tissue. We hypothesized that the use of statins in patients with heart failure (HF) and normal serum lipids would improve left ventricular function and serum markers of inflammation.

Methods: We followed 446 patients with NYHA class II-III HF. Left ventricular ejection fraction (EF) >35%, and an LDL cholesterol = 100mg/dL in a prospective, non-randomized fashion for 24 ± 3 months. Patients were classified according to treatment with a statin, which was prescribed at the discretion of their treating physician. Left ventricular EF, left ventricle end diastolic diameter (LVEDD) and end systolic diameter (LVESD) were determined by echocardiography. Serum markers of inflammation were also determined.

Results: Statin therapy was associated with an increase in EF from 0.33 ± 0.05 to 0.37 ± 0.05 (p<0.01), whereas those patients not treated with a statin experienced a decrease in EF from 0.34 (p=0.01). LVEDD was reduced from 57.1 ± 5.9 to 53.4 ± 5.1 mm (p=0.007) and LVESD was reduced from 42.4 ± 3.8 to 39.1 ± 3.8 mm (p=0.02) in the cohort of patients treated with statins. There was no change in these dimensions in the non-statin cohort. Statin therapy was also associated with a decrease in serum levels of interleukin-6 (13.3±0.8 vs. 17.3±1.4 ng/ml, p<0.001) and tumor necrosis factor-alpha receptor II (24.3±1.0 vs. 34.5±3.0 ng/dL, p=0.001) compared with the non-statin cohort.

Conclusions: The use of statin therapy in normolipidemic patients with HF due to left ventricular systolic dysfunction in this non-randomized trial was associated with a significant reduction in left ventricular EF and an improvement in left ventricular dimensions. The improvement in levels of several serum inflammatory markers with statin therapy suggests in part mechanisms by which these agents may exert their beneficial effects.

3:00 p.m.

Acute Hypertension Results in an Exaggerated Elevation of Left Ventricular Diastolic Pressures in a Canine Model of Diastolic Heart Failure

Steven J. Lavine, University of Florida, Jacksonville, FL

Background: Decompensation of diastolic heart failure (DHF) is often accompanied by hypertensive episodes. We hypothesized that markedly elevated LV systolic pressures result in both early and late diastolic LV pressures due to further impairment of LV relaxation from pressure loading.

Methods: To test this hypothesis, we created a model of chronic DHF with preserved ejection fraction (EF) (>50%) in 8 dogs with increased LV mass and interstitial fibrosis using coronary microsphere embolization. Prior to embolization and with chronic DHF, each dog was paced 10 beats above baseline and high fidelity LV pressures, echo LV volumes, and transmural Doppler were obtained. The dogs were then pressure loaded >40 mm Hg with methoxamine, and the above parameters were obtained.

Results: At baseline, LV pressures (mm Hg) at peak - dP/dT (+17), LV pressure minimum (-3.6), and at the end of the rapid filling period (+5) increased (all p<0.05). The timing of these events from the R wave were unchanged. LV end diastolic pressure (LVEDP) increased (52±3 vs 70±4 mmHg, p<0.01). Tau increased from 26±3 msec to 35±2 msec (P<0.01). EF was unchanged though EDV increased 21% (p=0.003). Pressure loading with DHF resulted in greater increases in LV pressures (mm Hg) at peak - dP/dT (+44). LV pressure at miral opening (+17), LV minimal pressure (+8), and at the end of rapid filling (+10) were decreased from baseline pressure loading (all p<0.05). The timing of each of these pressure events were delayed by 25% (p=0.001). LV dP/dT was reduced from 24±10 to 13±9 mmHg (p<0.001) and the diastolic filling period shortened (268±51 to 240±64 msec, p<0.001). EF increased from 26±3% to 34±3% (p<0.05) and LV size increased 22% (p<0.05).

Conclusions: We conclude that pressure loading with normal LV function and with DHF result in increases in LV diastolic pressures that are further exaggerated with DHF. This exaggeration is associated with prolonged relaxation, delay in the onset and shortening of the diastolic filling period resulting in the LV filling volume entering a poorly relaxed left ventricle. Acute hypertension is an important pathophysiologic factor in decompensation in DHF.

2:30 p.m.

Assessment of Coronary Microvascular Function in Patients With Takox-Tsubo-Like Left Ventricular Dysfunction (Transient Left Ventricular Apical Ballooning Syndrome)

Teruyoshi Kume, Takashi Akasaka, Takahiro Kawamoto, Nozomi Watanabe, Eiji Toyoda, Yoji Neshi, Nozomi Wada, Kyoshi Yoshida, Kawasaki Medical School, Kurashiki, Japan

Background: Takox-tsubo-like left ventricular (LV) dysfunction is characterized by acute onset and reversible LV wall motion abnormality in the rare, conservative polymorph, coronary angiography. The precise mechanism of this syndrome is still unclear, but coronary microvascular dysfunction has been reported to be one of the possible mechanisms of this syndrome. The purpose of this study was to evaluate coronary microvascular function by measuring coronary microvasculariy (CFV) pattern and CFV reserve (CFVR), using Doppler guidewire, in patients with tako-tsubo-like LV dysfunction.

Methods: We examined 11 consecutive patients (10 women and 1 man; mean age, 71 ± 11 years old) who were diagnosed to be tako-tsubo-like LV dysfunction according to the following criteria: 1) LV wall motion abnormality at the apices on left ventriculography; 2) ST segment elevation or T-wave abnormality at least 2 leads on the ECG; 3) no prior history of myocardial infarction; 4) normal coronary angiogram. Immediately after admission and 3 weeks later, left ventriculography and coronary angiography were performed. After LV apical wall motion abnormality and normal coronary angiogram were confirmed, CFV was recorded at the middle portion of the coronary artery with a 0.014-inch Doppler guidewire at rest and during hyperemia induced by an intravenous injection of 0.15mg/kg/min adenosine 5'-triphosphate.
Results: Animals fed iron-rich chow showed significantly higher DOX cardiotoxicity at a lower cumulative dose as evident from greater weight loss (66 ± 29 gm loss versus 29 ± 36 gm gain, P<0.05), higher mortality (5 out of 11 versus 1 out of 8) and higher myocardial Annexin uptake (0.13 ± 0.02 vs 0.09 ± 0.00 injected dose per gram, P<0.05). Electron microscopy showed most severe myocyte injury in the iron-rich chow fed animals with more frequent areas of myocyte loss and sarcoplasmic swelling compared to regular chow fed animals. Caspase-3 (cleaved) staining was markedly increased in iron-rich chow animals on DOX treatment. Feeding iron-rich chow alone did not result in any cardiotoxicity.

Conclusion: Dietary iron loading resulted in a substantial increase in DOX cardiotoxicity in rats. Body iron stores as well as bioavailability in tissue may be important predictors of susceptibility to DOX cardiotoxicity. Clinical studies are warranted to study the relationship between body iron stores and susceptibility to DOX cardiotoxicity in man.

ORAL CONTRIBUTIONS

851 Heart Failure and Statins

Tuesday, March 08, 2005, 2:00 p.m.-3:30 p.m.
Orange County Convention Center, Room 414C

2:00 p.m.

851-1 Statins Shorten Qtc Interval Without Affecting Plasma Bnp Levels in Patients With Advanced Heart Failure
Bojan Vrtovec, Renata Okraskel, Alenka Golincik, Mateja Ferjan, Paula V. Juanes, Barbara Radij, Ljubljana University Medical Center, Ljubljana, Slovenia, Texas Heart Institute, Houston, TX

Background. Qtc interval duration and plasma BNP levels predict outcomes of patients with advanced heart failure (HF). Since statin therapy appears to be related to improved survival of such patients, we analyzed the effect of statins on Qtc interval duration and plasma BNP levels in these patients.

Methods. A prospective randomized trial included 80 patients with advanced HF (NYHA III-IV) (statin group); the remaining 40 patients served as controls. We measured Qtc interval duration and plasma BNP levels at baseline and at 3 months. Qtc interval duration was determined by averaging 3 consecutive beats through leads II and V4 on a standard ECG, then correcting the resulting value using the Bazett formula.

Results. Overall 3-month mortality was 5% (3% in the statin group vs. 8% in the control group, P=0.30). The two groups did not differ significantly in age (66±16 years in the statin group vs. 68±13 years in the control group, P=0.52), male gender (56% vs. 51%, P=0.66), ischemic etiology (56% vs. 68%, P=0.32), or LVEF (24.0±4.9% vs 24.2±3.6%, P=0.88). At baseline, Qtc interval duration was similar in both groups (450±30 msec in the statin group vs. 446±27 msec in controls, P=0.59). After 3 months, Qtc interval had decreased in the statin group (436±29 msec, P=0.0001), but not in controls (450±25 msec). Qtc interval shortening with statin therapy was more pronounced in patients with a baseline Qtc interval >440 msec (from 470±21 msec at baseline to 450±26 msec at 3 months, P<0.001), and in patients with non-ischemic HF (from 452±32 msec at baseline to 435±28 at 3 months, P=0.004). Plasma BNP levels at baseline were comparable in both groups (713±303 pg/ml in statin group vs. 791±271 pg/ml in controls, P=0.25) and remained relatively unchanged after 3 months (695±340 pg/ml vs. 809±331 pg/ml, P=0.13).

Conclusions. Statins shorten Qtc interval, but do not change plasma BNP levels in advanced HF. Statin therapy may be of particular benefit to patients with non-ischemic HF and a prolonged Qtc interval, thereby the HF morbidity can be improved.
Methods: Thirty-seven patients with heart failure (aged 69±2.3 yrs, NYHA II-IV with ejection fraction<35%) were enrolled. Nineteen pts received atorvastatin 10mg/day while 18 (controls) received no statin for 4 weeks. Forearm blood flow was measured by strain-gauge plethysmography. Endothelium dependent dilation (EDD) and endothelium independent dilation (EID) were expressed as the % change of flow from baseline to the maximum flow during reactive hyperemia or after sublingual nitroglycerin administration respectively. Serum sVCAM-1, IL-6, MCP-1 and TNF-a were determined by ELISA.

Results: Basal forearm blood flow remained unchanged in both groups after treatment. EDD was significantly increased in atorvastatin group (from 44.2±4.5 to 89.5±12.0%, *p<0.01) but not in controls (from 47.2±4.3 to 47.1±5.4%, *p=NS). Levels of sVCAM-1, IL-6 and TNF-a were significantly decreased in atorvastatin group (from 650.7±61.7, 7.76±0.69 and 3.8±0.35 to 471.6±44.5 ng/ml, 6.02±0.81 pg/ml and 2.8±0.22 pg/ml respectively, *p<0.05 for all) but not in controls (from 65.2±7.0, 7.32±0.72 and 4.5±0.62 to 64.9±7.21 ng/ml, 6.53±0.81 pg/ml and 4.53±0.61 pg/ml respectively, *p=NS for all). EID and levels of MCP-1 remained unchanged in both atorvastatin-treated (from 66.8±20.8 and 305.9±29.7 to 65±6% and 291.4±26.1 ng/ml respectively, *p=NS for both) and control group (from 66.8±20.8 and 311.0±26.0 to 60±7% and 321.5±19.6 ng/ml respectively, *p=NS for both).

Conclusions: Atorvastatin improves endothelial function and decreases the expression of IL-6, TNF-a and sVCAM-1 in patients with heart failure. These findings indicate that statins may have further antiinflammatory effects in patients with heart failure, beyond their lipid-lowering effects.

3:00 p.m.

Statin Use Is Associated with a Marked Improvement in Survival in Patients with Congestive Heart Failure: A study on 32,000 U.S. Veterans
Sathya Jaganmohan, Vikas Khurana, LSJ Health Sciences Center, Shreveport, LA, Overton Brooks VA Medical center, Shreveport, LA.

BACKGROUND: Though HMG CoA reductase inhibitors (Statins) have been proven to be beneficial in reducing coronary events, their effect on patients with congestive heart failure is inconclusive.

METHODS: Using patient data from the VA’s VISN 16 database from 4 states (LA, MS, TX, AK), we performed a retrospective case-control study on 32,463 people with a diagnosis of congestive heart failure. The use of statins was correlated with the primary outcome of all cause mortality.

RESULTS: The mean age of the cohort was 62.72±10.04. 19,838 (61.1%) patients were on statin therapy and 10,137 (31.2%) patients had a diagnosis of ischemic heart disease (IHD). A total of 9,028 deaths were recorded in the cohort, of which 4,186 (46%) patients were on statins. Cox proportional hazards model was used to adjust for covariates including age, sex, smoking, IHD, diabetes, beta blocker use, ACE Inhibitor use and aspirin use. The unadjusted hazards ratio (HR) for statin use was 0.85 (95% CI:0.83-0.86) and the adjusted HR for statin use was 0.90 (95% CI:0.88-0.92). The mean length of follow up was 2.7±1.5 years. The mean percentage of patients were on statin therapy and 10,137(31.2%) patients had a diagnosis of ischemic heart disease (IHD). In a multivariable analysis controlling for baseline characteristics and use of CRT/CRT-D devices, statin use was associated with a 28% relative risk reduction in mortality (HR 0.72, CI 0.56-0.92, *p=0.008). There was no interaction for mortality demonstrable between statin use and either etiology of heart failure or CRT/CRT-D therapy.

Conclusions: Statin use is associated with a marked improvement in survival in patients with advanced heart failure. The mortality benefit persists after adjusting for use of CRT/ CRT-D and etiology of heart failure.

Tuesday, March 08, 2005, 4:00 p.m.-5:00 p.m.
Orange County Convention Center, Room 230B

Erythropoietin Increases Capillary Density and Improves Cardiac Function in Rats with Heart Failure After Myocardial Infarction

Introduction: Erythropoietin (EPO), traditionally known as a hematopoietic growth factor, has been linked to angiogenesis in vitro and in vivo. After myocardial infarction (MI), acute administration of EPO, has been shown to reduce infarct size and to improve cardiac function. However, its role in the failing heart is unknown. Therefore, we assessed the effects of EPO treatment in a rat model of post-MI heart failure.

Methods and Results: Male Sprague Dawley rats underwent coronary ligation (n=50) or sham surgery (n=8). Rats with MI were randomly assigned to one of four treatments: untreated (MI), a single bolus of EPO immediately after MI induction (MI-EPO-early), EPO treatment immediately after MI and once every three weeks (MI-EPO-early+late) and EPO treatment starting three weeks after induction of MI, once every three weeks (MI-EPO-late). After nine weeks, hemodynamic parameters, infarct size and capillary density were measured. Treatment with EPO immediately after myocardial infarction (MI-EPO-early) resulted in a 23-30% reduction in infarct size and improved hemodynamic parameters, compared to MI (p<0.01). EPO treatment, started three weeks after MI (MI-EPO-late), did not affect infarct size, but resulted in an improved cardiac contractility (systolic dp/dt) and relaxation (diastolic dp/dt) (p<0.05). Furthermore, we observed a 34% reduction in left ventricular end-diastolic pressure (p<0.05) and a 46% decrease in ANP levels (p<0.05) in MI-EPO-late compared to MI. The improved cardiac function, was accompanied by an increased capillary density (p<0.01 vs. MI) and an increased capillary to myocyte ratio (p<0.05 vs. MI) in all treated groups, indicating newly formed capillaries.

Conclusion: EPO treatment improves cardiac function in a rat model of post-MI heart failure. This observation could be explained by the increased capillary density and capillary to myocyte ratio, indicating actual capillary growth.

4:15 p.m.

Cardiac Myocyte Apoptosis is Associated with Left Ventricular Hypertrophy in Murine Models of Obesity
Lili A. Barouch, Daquing Gao, Lei Chen, Shakil A. Khan, Shubha V. Y. Raju, Koenraad Vandegraaf, Christopher P. O’Donnell, Dan E. Berkowitz, Chiming Wei, Joshua M. Hare, The Johns Hopkins University School of Medicine, Baltimore, MD, University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: Cardiac myocyte apoptosis increases in heart failure and normal aging. Disruption of leptin signaling is associated with obesity, heart failure and cardiac hypertrophy, but the role of leptin in cardiac myocyte apoptosis is unknown. We tested the hypothesis that apoptosis increases in leptin-deficient ob/ob and leptin-resistant ob/db mice, and is associated with aging and LV hypertrophy.

Methods and Results: We performed echocardiography on young (2-3 month) and old (13-15 month) ob/ob, db/db and WT mice (n=2). Septal wall thickness was similar among young mice of all strains, but increased in old ob/ob (1.12±0.01mm) and db/db (1.09±0.04mm) vs. WT (0.76±0.03mm, P<0.0001 for both). Fractional shortening and chamber dimensions were similar among all groups. An additional group of 6-month-old ob/ob mice received leptin (0.3mg/kg/day SC) for 4 weeks. Heart weights were higher in old ob/ob (17±1g) and db/db (15±1g) hearts vs. old WT (9±2g, P<0.005 for both). We assessed apoptosis by TUNEL staining (% positive nuclei per 10 high-powered fields) and apoptosis inducing factor (AIF; 0-4 scale: 0=no staining, 4=50-80% positive).

3:15 p.m.

Statin Use Is Associated with a Marked Improvement in Survival in an Advanced Heart Failure Population from the COMPANION Trial
Andrew D. Sumner, John Boehmer, Leslie A. Saxon, Arthur M. Feldman, Michael R. Bristow, Penn State College of Medicine, Hershey, PA.

Background: Statin use reduces mortality in patients with ischemic heart disease. The beneficial effect of statins in advanced heart failure (HF) patients of various etiologies receiving cardiac resynchronization therapy (CRT) is unknown. The objective of this study was to assess the effect of statin use on survival in patients with advanced HF of various etiologies receiving CRT.

Survival Curve Comparing All Cause Mortality with Statin Use

3:30 p.m.
Cardiac Function and Heart Failure

Calpain Inhibition Prevents Acute Myocardial Dysfunction and Apoptosis Associated With Reperfusion Injury

Jeffrey M. Pearl, Jefferson M. Lyons, Connie J. Wagner, Jodie Y. Duffy, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH. University of Cincinnati College of Medicine, Cincinnati, OH

Background: Myocardial ischemia-reperfusion stimulates cytochrome proteins called calpains. Calpain activation is associated with interruption of calcium-regulated contraction by degrading contractile proteins and initiating cell death. Immature myocardium has elevated levels of calpain suggesting an enhanced role in neonatal tissues. We hypothesized that calpain inhibition could reduce myocardial injury from reperfusion of ischemic neonatal piglets.

Methods: Neonatal piglets (n=8, controls) were cooled to 18°C on cardiopulmonary bypass, underwent 2 hr of deep hypothermic circulatory arrest, then were re-warmed and recovered for 2 hr. Another 6 animals received 1 mg/kg of the peptide calpain inhibitor (2-Leu-Leu-Tyr-FMK) 1 hr before circulatory arrest. Hemodynamics were continuously monitored and myocardial tissue collected at 2 hr of recovery for analyses of NF-B activation and pro-apoptotic pathways.

Results: Oxygen delivery was significantly depressed in controls at the end of recovery (260 ± 5 ml/min), but was maintained in calpain inhibitor-treated animals (955 ± 17 ml/min, p<0.05). Myocardial calpain activity was decreased in treated animals compared with controls (102 ± 22 vs 185 ± 27 fluorescent units, p<0.05). Calpain inhibitor-treated animals had higher cytosolic Ca2+ protein levels compared with controls (0.61 ± 0.2 vs 0.18 ± 0.16 Ca2+/GAPDH protein ratio, p<0.01), and decreased NF-B DNA binding activity (80 ± 22 vs 137 ± 27 densitometry units, p<0.05) at end-recovery. Treated animals also demonstrated reduced cleavage of Bid, an early indicator of the apoptosis cascade, 37 ± 10 vs 59 ± 3.5% (expressed as percent 15 kDa of total Bid protein, p<0.05). Caspase-3 activity was reduced after calpain inhibitor (0.47 ± 0.03 vs 0.8 ± 0.48 pmol/min/µg protein DEVDase activity, p<0.05).

Conclusions: Calpain inhibition decreased cardiac dysfunction associated with reperfusion and prevented activation of NF-B pathways. Decreased Bid cleavage and caspase-3 activity were evident with calpain inhibition, which along with decreased NF-B activity, indicated less cell death and possible prevention of permanent cardiac myocyte loss.

860-5

Correlation Between Cell-to-cell Uncoupling And Remodeling In An Ovine Model Of Ischemic Heart Failure

Carlos L. del Rio, Patrick I. McConnell, Roger Dzwonczyk, Pawel Kwatowski, Bradley D. Clymer, Michael B. Howie, Robert E. Michler, The Ohio State University, Columbus, OH

Introduction: Heart Failure (HF) is associated with sudden death due to VF. Electric uncoupling is suggested as a mechanism for these arrhythmias. However, the altered expression of Connexin43 in HF, studies linking remodeling and uncoupling are lacking. Myocardial electrical impedance (MEI) detects uncoupling, as induced by ischemia. Hence, we studied the relationship between uncoupling and remodeling during HF.

Methods: Adult sheep were instrumented with sonomicrometry crystals and bipolar pacing electrodes for left ventricular (LV) geometry and MEI measurements. The pacing wires were stitched in the LAD and LCX distributions. Ischemic HF (EF<35% and EF > 40%). Spironolactone and other diuretics are associated with similar survival and 95% CI, 0.435-0.624). Cox Model: Chi sq=254.5, p <0.0001. (Figure)

Spironolactone, Diuretics or None in Ischemic Heart Failure: Use and Outcomes from the Duke Databank

Adrian P. Hernandez, Olcay Aksoy, Robert H. Tuttle, Linda Shaw, Christopher M. O'Connor, Duke Clinical Research Institute, Durham, NC

Background: Spironolactone use is controversial outside patients studied in clinical trials and some have argued other diuretics may be harmful. Therefore, we evaluated the use of spironolactone and diuretics in patients with ischemic heart failure (HF).

Methods: HF patients with CAD on catheterization between 1998 and 2002 were identified from the Duke Databank. We divided the cohort into 3 groups based on diuretic use: a) spironolactone b) other diuretics c) no diuretics. Using a Cox proportional hazards model (covariates: age, HF class, ejection fraction, Charlson index, mitral insufficiency), we examined long-term survival in each group.

Results: Of 2136 HF patients who consistently reported medication use, 20.3% were on spironolactone, 57.8% were on other diuretics and 19.9% were on none. The median EF was 32% in spironolactone users, 48% in other diuretic users and 51% in those on none (p<0.001). An EF > 40% was present in 36.2% of spironolactone users, 47.5% in other diuretic users and 51.1% in no diuretic users (p<0.001). With a median follow-up of 2.9 yrs, spironolactone was associated with lower mortality (HR, 0.512; 95% CI, 0.408-0.642) compared to no diuretic use. Similarly, other diuretics had a lower mortality (HR, 0.521; 95% CI, 0.436-0.642).

Conclusions: Spironolactone is used commonly in ischemic HF including patients with EF > 40%. Spironolactone and other diuretics are associated with similar survival and better than none.
Acute Tumor Necrosis Factor Antagonism Improves Left Ventricular Function and Exercise Performance in Heart Failure: Assessment by Left Ventricular Pressure-Volume Analysis

Hiroshi Hasegawa, Hideo Tachibana, Atsushi Morimoto, Hiroshi Hasegawa, Akihiko Iwaga, William C. Little, Che-Ping Cheng, Wake Forest University School of Medicine, Winston-Salem, NC

Background: Abnormal cardiac response to β-agonist stimulation contributes to exercise (Ex) intolerance in heart failure (HF). Previous studies indicate that elevated levels of tumor necrosis factor-α (TNF-α) in HF patients diminish cardiac positive inotropic response to β-agonist stimulation. Thus, antagonizing TNF-α with Etanercept (ETA) may improve Ex performance in HF.

Methods: We compared left ventricular (LV) systolic and diastolic responses and plasma TNF-α levels at rest and during Ex before and after receiving ETA (0.3 mg/kg) at 1, 7, and 24 hours (H) in 9 dogs with pacing-induced HF.

Results: After ETA, ETA caused a 40% reduction of plasma TNF-α (control: 24 pg/ml ETA: 1.5 pg/ml) in patients with an increased LV pressure volume relationship, significantly increased (E\(_\text{d}\); 7.1 versus 4.3 mmHg/ml M\(_\text{s}^{-1}\), 70.5 versus 62.4 mmHg/ml M\(_\text{s}^{-1}\)).

Conclusions: In a dog model of HF, ETA improves LV systolic and diastolic function and Ex performance. ETA reduces TNF-α, which may improve myocardial contractility and Ex function.

9:00 a.m.

D-Ribose Supplementation Improves Peak Exercise Capacity and Ventilatory Efficiency in Heart Failure Patients

Olly Carter, Dean MacCartner, Steve Mannebach, Joseph Biskupski, Greg Stoddard, Edward M. Gilbert, Mark A. Munger, University of Utah, Salt Lake City, UT

Background: Many clinicians and scientists concur that the failing heart is energy starved. D-Ribose (dR), a naturally occurring monosaccharide, has been shown to increase myocardial high-energy phosphate stores and improve post-ischemic myocardial function in the heart. This study was designed to determine whether dR could improve maximal exercise capacity and ventilatory efficiency, a powerful independent predictor of heart failure (HF) survival, in subjects with NYHA III HF.

Methods: Fourteen subjects with HF of ischemic etiology (LVEF: 32±8%) completed a single-center study using a randomized, double-blind, placebo-controlled (PL) cross-over design. Each subject underwent maximal cycle ergometry with gas exchange monitoring, quality of life (QOL, DASI questionnaire), and BNP levels at baseline and the end of each 8-week cross-over phase with a 2-week washout phase. Ventilatory efficiency was assessed using the linear VE/VCO2 slope (0-2 or PL) was administered on a 5 gram TiD schedule in addition to standard systolic HF drug regimens.

Results: dR significantly maintained VO\(_{2}\) max vs. PL, while improving the VE/VCO2 relationship, upper to the respiratory compensation point (RCP), and the RCP (Table 1) was not significant difference in QOL scores.

Conclusions: dR maintains maximal exercise capacity while improving ventilation efficiency, a strong predictor of HF survival, in NYHA III-II HF. dR may offer adjunctive, metabolic therapy for HF.

9:45 a.m.

Continuous Aerobic Flow Augmentation Using Orgis® Cancion® Cardiac Recovery System in Patients with Severe Heart Failure: Determinants of the Hemodynamic Response

Michael R. Zile, Ron M. Oren, Michael Bohm, Jerzy Sadowski, Adrian B. Van Bakel, Barbara Czernia, William T. Abraham, Andrzea Waseier, Sanaraj Kanhai, Barry Cabuayu, Krzysztof Baryta, Marvin A. Kostam, Emory University, Atlanta, GA

Background: Continuous aerobic flow augmentation using the Cancion® Cardiac Recovery System (CRS) has been shown to improve both cardiac index (CI) and pulmonary capillary wedge pressure (PCWP) in patients with decompensated chronic heart failure (CHF). We hypothesized that the magnitude of this hemodynamic response is determined by pretreatment cardiac index and creatinine.

Methods: Entry criteria included: 1) recently exacerbating CHF; 2) sustained (>24hr) elevated PCWP despite IV inotropes; 3) reduced creatinine clearance and/or diuretic resistance. CRS was placed in 23 patients for an average of 72 (24-112) hrs. Pumps averaged 1.33 (1.21-1.5) l/min.

Results: PCWP decreased from 28 ± 5 to 20 ± 7 mmHg and CI increased from 1.97 ± 0.46 to 2.24 ± 0.45 (mmHg/m2) 72 hrs post implant (p<0.05). Hemodynamic benefits were sustained after removal of CRS. Cumulative volume loss averaged -3.5L and weight loss averaged -2.2 kg.

Conclusions: Higher baseline CI and the higher the baseline creatinine, the greater the fall in PCWP.

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with a prescription for spironolactone were compared to those who were not. Comparisons were made using ANOVA for continuous and/or categorical variables. Adjustment for 33 baseline characteristics was made using a multivariate regression model.

Results: A total of 7816 patients were identified. Average age was 76 years, 52% were female and the median ejection fraction was 40%. Of these, 644 (8%) were discharged on spironolactone. Patients discharged on spironolactone were more likely to be younger, male, and diabetic. Furthermore, 6% had a creatinine ≥2.5 mg/dL, 9% had K+ ≥5.0, and 5% were given concomitant therapy with non-steroidal anti-inflammatory drugs (NSAIDs). After adjusting for clinical covariates, spironolactone use did not emerge as an independent predictor of long-term survival (Odds Ratio (OR) 0.87, p=0.80). When only patients enrolled in a HF clinic were included (n=981), spironolactone was associated with improved survival (OR 0.52, p=0.003).

Conclusion: In the HF population, spironolactone was not associated with improved survival, in contrast to those followed in HF clinics. These data suggest spironolactone should be prescribed to HF patients in a disease management setting.
At baseline, mean weight (± SE) for PIO vs ROSI was 93.7 ± 1.1 kg and 92.5 ± 1.0 kg (p = 0.25) or oral monotherapy. After 4 weeks of placebo treatment, subjects were treated with background anti-diabetic medications were uptitrated as required to achieve the glycemic target of fasting plasma glucose <126 mg/dL and CHF medications were changed as appropriate. Endpoints were adjudicated by an independent committee.

Results: 224 patients were randomized in the study (110 RSG, 114 PLB). Ejection fraction was similar in both groups at baseline (RSG 35.3 ± 6.2%, PLB 35.7 ± 7.8%) and was not significantly different following 52 weeks of treatment (RSG 37.8 ± 6.5%, PLB 36.8 ± 8.4%, 95% confidence interval -0.32% to 3.30%, p = 0.1). In addition, there were no differences between the groups in cardiac structure at 52 weeks. There were few adjudicated events of worsening or possible worsening of CHF (RSG n = 7 [8%]; PLB n = 4 [4%]), but more adjudicated events in the RSG group of worsening edema (RSG n = 28 [26%]; PLB n = 10 [9%]) and dyspnea (RSG n = 29 [26%]; PLB n = 19 [17%]). More adjudicated events of worsening or possible worsening of CHF (RSG n = 7 [8%]; PLB n = 4 [4%]) following chronic angiotensin-II receptor blockade. Consequently, the diabetic (DM) group consisted of 58 males and 20 females (mean age 61.7 and 60.2 years) while there were 87 males and 39 females (mean age 58.3 and 59.5 years) in the non-diabetic (NDM) group. The level of activity was similar as ascertained by the proportion of patients who were sedentary retirees (55.1% vs. 53.5%), involved in physical labor (23.7% vs. 24.6%) and desk job (22.4% vs. 22.2%) in the DM and NDM groups respectively. The DM and NDM patient groups were matched with respect to age, sex, LV Ejection Fraction (28.7 ± 4.2% vs. 29.2 ± 3.9%), proportion of smokers, presence of chronic kidney disease (68.6% vs. 64.9 %), use of beta-blockers (92.3% vs. 86.5 %) and ACE inhibitors (92.3% vs.88.1%). The mean BNP level in the DM group was 319 ± 343 pg/ml and NDM group was 275 ± 343 pg/ml (p = 0.368). DM patients had lower peak VO2 than NDM patients: 13.0 ± 3.5 ml/kg/min vs. 15 ± 3.84 ml/kg/min attained at similar respiratory exchange ratios (> 1.10). There was a higher prevalence of coronary artery disease (CAD) and hypertension (HTN) in the diabetic group. Multivariate analysis determined diabetes to be an independent predictor for peak VO2 after adjusting for the effect of age, sex, CAD and HTN (p = 0.027).

Conclusion: DM patients with CHF due to LV systolic dysfunction attained a lower peak VO2 than age, gender and activity matched NDM patients. Whether abnormal skeletal muscle metabolism, limited oxygen delivery to exercising muscles or both limit peak VO2 in DM patients remains to be investigated.

10:45 a.m.

874-3 A Comparison of Edema and Weight Gain Effects of Pioglitazone and Rosiglitazone in Patients With Type 2 Diabetes and Diastolic Dysfunction

David M. Kendall, John B. Buse, Ronald B. Goldberg, Mark A. Deeg, Anthony J. Zagar, Steve McMorn, Jeremy N. Roberts, Andrew Zambanini, Murray W. Stewart, Western Infirmary, Glasgow, United Kingdom

Background: Although thiazolidinediones have been shown to have potentially beneficial effects on some markers of cardiovascular risk in patients with type 2 diabetes (T2D), an important consideration in patients with established congestive heart failure (CHF) is a possible manifestation of fluid retention which may precipitate or exacerbate symptomatic CHF.

Methods: Patients with T2D and New York Heart Association (NYHA) III CHF were randomized to receive rosiglitazone (RSG 4-8 mg daily) or placebo (PLB) in addition to background anti-diabetic agents for 52 weeks. Background anti-diabetic medications were uptitrated as required to achieve the glycemic target of fasting plasma glucose <126 mg/dL and CHF medications were changed as appropriate. Endpoints were adjudicated by an independent committee.

Results: 224 patients were randomized in the study (110 RSG, 114 PLB). Ejection fraction was similar in both groups at baseline (RSG 35.3 ± 6.2%, PLB 35.7 ± 7.8%) and was not significantly different following 52 weeks of treatment (RSG 37.8 ± 6.5%, PLB 36.8 ± 8.4%, 95% confidence interval -0.32% to 3.30%, p = 0.1). In addition, there were no differences between the groups in cardiac structure at 52 weeks. There were few adjudicated events of worsening or possible worsening of CHF (RSG n = 7 [8%]; PLB n = 4 [4%]), but more adjudicated events in the RSG group of worsening edema (RSG n = 28 [26%]; PLB n = 10 [9%]) and dyspnea (RSG n = 29 [26%]; PLB n = 19 [17%]). More adjudicated events of worsening or possible worsening of CHF (RSG n = 7 [8%]; PLB n = 4 [4%]) following chronic angiotensin-II receptor blockade. Consequently, the diabetic (DM) group consisted of 58 males and 20 females (mean age 61.7 and 60.2 years) while there were 87 males and 39 females (mean age 58.3 and 59.5 years) in the non-diabetic (NDM) group. The level of activity was similar as ascertained by the proportion of patients who were sedentary retirees (55.1% vs. 53.5%), involved in physical labor (23.7% vs. 24.6%) and desk job (22.4% vs. 22.2%) in the DM and NDM groups respectively. The DM and NDM patient groups were matched with respect to age, sex, LV Ejection Fraction (28.7 ± 4.2% vs. 29.2 ± 3.9%), proportion of smokers, presence of chronic kidney disease (68.6% vs. 64.9 %), use of beta-blockers (92.3% vs. 86.5 %) and ACE inhibitors (92.3% vs.88.1%). The mean BNP level in the DM group was 319 ± 343 pg/ml and NDM group was 275 ± 343 pg/ml (p = 0.368). DM patients had lower peak VO2 than NDM patients: 13.0 ± 3.5 ml/kg/min vs. 15 ± 3.84 ml/kg/min attained at similar respiratory exchange ratios (> 1.10). There was a higher prevalence of coronary artery disease (CAD) and hypertension (HTN) in the diabetic group. Multivariate analysis determined diabetes to be an independent predictor for peak VO2 after adjusting for the effect of age, sex, CAD and HTN (p = 0.027).

Conclusion: DM patients with CHF due to LV systolic dysfunction attained a lower peak VO2 than age, gender and activity matched NDM patients. Whether abnormal skeletal muscle metabolism, limited oxygen delivery to exercising muscles or both limit peak VO2 in DM patients remains to be investigated.

10:45 a.m.

874-4 Role Of Activated Renin-angiotensin System In Myocardial Fibrosis And Left Ventricular Diastolic Dysfunction In Diabetic Patients: Reversal By Long-term Angiotensin II Blockade

Daiso Kawasaki, Keisuke Kosugi, Hidetoh Waki, Kazuhiro Yamamoto, Takeshi Tsujino, Tomo Masaayama, Hyogo College of Medicine, Nishinomiya, Japan, Osaka Police Hospital, Osaka, Japan

Background: LV diastolic dysfunction is a commonly observed cardiovascular manifestation even in the absence of coronary artery disease in diabetic patients. Myocardial fibrosis is one of the most important mechanisms for the diastolic dysfunction, and activation of local renin-angiotensin system has been shown to contribute to myocardial fibrosis in animal models of LV diastolic dysfunction. We attempted to test the hypothesis that long-term angiotensin-II receptor blockade alters collagen turnover in the myocardium leading to an improvement of diastolic dysfunction in diabetic patients. Methods: We assessed pulsed Doppler LV diastolic filling, plasma B-type natriuretic peptide (BNP) level and biomarkers of collagen type I synthesis and degradation in 38 diabetic patients (mean age, 68 years) before and after administration of candesartan for 6 months.

Results: 1) Mitral E/A ratio increased from 0.64±0.10 to 0.76±0.18 (p<0.01) without a change in LV diastolic diameter, indicating an improvement of LV diastolic dysfunction. 2) Plasma BNP level tended to decrease from 27.7±27.5 to 23.6±20.2 pg/ml. 3) Carboxy-terminal propeptide of procollagen type I (PICP), an index of collagen type I synthesis, tended to decrease from 99±29 to 94±39 ng/ml and carboxy-terminal telopeptide of collagen type I (ICTP), an index of collagen type I degradation, increased from 5.9±3.5 to 3.8±1.2 ng/ml (p<0.01) following chronic angiotensin-II receptor blockade. Consequently, the PICP/ICTP ratio, an index of coupling between the synthesis and degradation of collagen type I, decreased from 1.8±1.1 to 1.6±1.4 (p<0.01) after treatment. Conclusion: Chronic blockade of angiotensin-II-mediated signaling pathway improves LV diastolic dysfunction in diabetic patients, at least partially through the attenuation of myocardial fibrosis by regulating both collagen synthesis and degradation.

11:15 a.m.
Impact of Heart Failure on Survival Among Diabetics with Coronary Artery Disease

Jeffrey S. Berger, David L. Brown, Beth Israel Medical Center, New York City, NY

Background: The impact of heart failure (HF) on survival of patients with coronary artery disease (CAD) is not well understood. We sought to evaluate the effect of HF on survival of patients undergoing coronary interventions (PCI).

Methods: Three hospitals in New York City contributed prospectively defined data on 1142 consecutive diabetic patients undergoing PCI in 1998-9. HF was defined by treatment for HF prior to the admission for PCI. All cause mortality at a mean follow-up of 3 years was the primary end point.

Results: Among diabetics, HF was present in 187 patients (16%). Diabetics with HF were older and more likely to be female. Diabetic patients with HF had a greater prevalence of vascular disease (18% vs. 9.4%, P=0.001), renal insufficiency (11.2% vs. 2.4%, P=0.001) and end-stage renal disease (10.7% vs. 2.6%, P=0.001). Diabetics with HF were more likely to have a previous MI (47% vs. 34%, P<0.001) and prior cardiac surgery (32% vs. 21%, P=0.001). At clinical presentation, diabetics with heart failure were more likely to be hemodynamically unstable than those without heart failure. Diabetics with HF presented more often with 3-vessel disease (36% vs. 21%, P=0.001). Mean ejection fraction was lower in diabetics with HF (44% vs. 51%, P=0.001). Stent placement and glycoprotein IIb/IIIa inhibitor use were similar between groups. An angiographic success rate of 72% was observed for both elderly and younger patients who had abnormal baseline risk factor profiles.

Conclusions: Impact of heart failure on survival among diabetics with coronary artery disease is significant. The aging of the American population and improving survival of patients with cardiovascular disease (CVD) has created a large population of elderly patients (>65 years of age) eligible for cardiac rehabilitation. However, no comprehensive data are currently available on the effect of a contemporary phase II cardiac rehabilitation program on multiple CVD risk factors in elderly versus younger patients.

Patients with a normal HRR at baseline and an abnormal HRR at exit had the highest mortality when compared to patients whose HRR stayed abnormal, patients who improved and those who remained normal (29% vs. 22% vs. 17% vs 6%, P<0.0001). Cox analyses that accounted for clinical and socioeconomic confounders showed that preserved FC and normal HRR on the exit stress test were predictive of lower mortality (HR 0.77, 95% CI: 0.69 - 0.85; HR 0.95, 95% CI: 0.99 - 0.99, respectively).

Conclusions: Improvement of functional capacity and heart rate recovery during a cardiac rehabilitation program predicts improved long-term survival.

Multicenter Study of the Clinical Effectiveness of a Contemporary Cardiac Rehabilitation Program in Elderly Versus Younger Patients


Background: The aging of the American population and improving survival of patients with cardiovascular disease (CVD) has created a large population of elderly patients (>65 years of age) eligible for cardiac rehabilitation. However, no comprehensive data are currently available on the effect of a contemporary phase II cardiac rehabilitation program on multiple CVD risk factors in elderly versus younger patients.

Methods: In this multicenter study, we investigated the effect of a contemporary phase 2 cardiac rehabilitation program on multiple CVD risk factors in 5,418 consecutive patients >65 years of age (Group A; n=2,526; age>74±6 years) and >65 years of age (Group B; n=2,892; age<65±10 years). Outcome measures were evaluated at baseline and after approximately 12 weeks of participation in a phase 2 cardiac rehabilitation program at 30 centers in the U.S.

Results: On program exit, improvements (p<0.05) in multiple CVD risk factors were observed for both elderly and younger patients who had abnormal baseline risk factor values (based on national clinical guidelines), as follows: systolic blood pressure (Group A, -19 mmHg; Group B, -22 mmHg; p<0.05 for Group A versus Group B); diastolic blood...
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pressure (Group A, -17 mmHg; Group B, -14 mmHg; p < 0.05 for Group A versus Group B); LDL cholesterol (Group A, 28 mg/dl; Group B, 18 mg/dl; p < 0.05 for Group A versus Group B); HDL cholesterol (Group A, 4 mg/dl; Group B, 4 mg/dl; p=NS for Group A versus Group B); triglycerides (Group A, -41 mg/dl; Group B, -43 mg/dl; p=NS for Group A versus Group B); fasting glucose (Group A, -14 mg/dl; Group B, -17 mg/dl; p=NS for Group A versus Group B); and weight (Group A, -4 lbs; Group B, -4 lbs; p=NS for Group A versus Group B).

Conclusion: To our knowledge, these are the first multicenter clinical trial data to demonstrate that elderly patients derive similar improvements in multiple CVD risk factors as compared to younger patients during participation in a contemporary phase 2 cardiac rehabilitation program. Increased efforts should be devoted to providing these important services to elderly patients.

11:15 a.m.

879-3

Plasma Lipoprotein Lipids Do Not Regulate Exercise Training-Induced Changes in Coagulation Factor VIII Antigen and Prothrombin Fragment 1+2 Levels in Sedentary, Dyslipidemic Individuals

Rakesh Gopinathannair, Michael M. Lockard, Chad Paton, Joon Y. Park, Dana A. Phares, James M. Hagberg, Drexel University College of Medicine, Philadelphia, PA, University of Maryland, College Park, MD

Background: Elevated plasma factor VIII antigen (FVIII:Ag) and prothrombin fragment 1+2 (F1+2) levels have been shown to result in a hypercoagulable state, thus increasing the risk for thrombotic events. Aerobic training may decrease thrombotic risk by reducing activity of the coagulation cascade at rest. We analyzed the effect of 6 months of standardised exercise training on resting levels of FVIII:Ag and F1+2 in dyslipidemic men and women. A second objective was to assess whether training-induced changes in plasma lipoprotein-lipid levels were associated with training-induced changes in FVIII:Ag and F1+2.

Methods: Forty-four sedentary men (n=16, 58±2 y) and post-menopausal women (n=28, 59±1 y), with at least one lipid abnormality (total cholesterol > 200 mg/dl, LDL > 130 mg/dl, HDL < 40 mg/dl, or triglycerides > 200 mg/dl), underwent supervised aerobic training 3 times per week for 6 months, while maintaining a low-fat diet. All subjects had FVIII:Ag, F1+2, lipoprotein-lipid levels, and maximal oxygen consumption measured at baseline and after the training period.

Results: At baseline, there were no significant differences in FVIII:Ag and F1+2 levels between genders. Mean F1+2 (1.49±0.1 nmol/l) to 1.42±0.1 nmol/l, n=41, p=0.83) and FVIII:Ag (152.5±6.7% to 156.0±6.1%, n=44, p=NS) levels did not change significantly with 6 mo of training. There was a significant decrease in F1+2 levels with training when adjusted for baseline levels (p=0.035). There were significant improvements in plasma triglyceride and HDL levels (161±11.6 to 142.7±9.6 mg/dl, p<0.0001 and 45.1±2.3 to 49.5±2.4 mg/dl, p=0.01 respectively) with training. F1+2 and FVIII:Ag changes with training showed no significant association with training-induced changes in plasma lipoprotein-lipid levels.

Conclusions: Long-term aerobic training has a significant impact on the common pathway of coagulation, reducing thrombin formation and hypercoagulability at rest. This suggests a reduced risk for atherosclerotic disease progression. Aerobic training induces favorable changes in the coagulation cascade, independent of changes in plasma lipoprotein-lipids, in elderly dyslipidemic individuals.

11:30 a.m.

879-7

Even Short-Duration Exercise Training Improves Brain Natriuretic Peptide and C-Reactive Protein Levels in Severely Deconditioned Patients With Coronary Disease

Richard A. Krasnow, Sandra A. Black, Ara M. Maranian, Wilford Hall Medical Center, San Antonio, TX

Background: Serum levels of brain natriuretic peptide (BNP) and C-reactive protein (CRP) predict future cardiovascular events and mortality in patients with coronary artery disease (CAD). Similarly, lack of exercise has been associated with a shorter lifespan. We sought to examine if short-duration exercise training could reduce BNP and CRP levels in deconditioned CAD patients.

Methods: Forty-two consecutive patients with chronic CAD and significant deconditioning were recruited into a six-week graded-exercise program. Fasting bloodwork were collected at study entry and within 1 week of completion.

Results: Baseline characteristics included age 69 ± 10 years, echo ejection fraction 52 ± 16%, 32% women, 76% hypertensives, 88% dyslipidemics, 31% diabetics, and 14% active smokers. Medication use included aspirin 83%, beta-blockers 90%, angiotensin converting enzyme inhibitors 81%, and statins 76%. Tolerated exercise levels increased by 2.2 ± 1.9 metabolic equivalents over the 6-week period (p<0.001). There was no appreciable difference in body mass or any lipid panel component after 6 weeks. Percent body fat dropped from 32.8 ± 10.2 to 31.4 ± 10.2 (p<0.04). Levels of BNP and CRP significantly decreased from baseline values (see below).

Conclusions: Short-term exercise leads to significant reductions in serum BNP and CRP in deconditioned patients with coronary disease. These changes appear to be independent of changes in body mass or any individual lipid panel component.

11:45 a.m.

879-8

Association of Metabolic Syndrome With Poor Exercise Capacity and Heart Rate Recovery in Patients With Coronary Disease: the Heart and Soul Study

Christian Spies, Christian Otte, Alka Kanaya, Sharon S. Pipkin, Nelson B. Schiller, Mary A. Wholley, University of California San Francisco, San Francisco, CA, Rush University Medical Center, Chicago, IL

Background: Metabolic syndrome (MS) is associated with incident cardiovascular disease. However, it is unknown whether MS is associated with poor cardiac function among patients with established coronary heart disease (CHD). We evaluated the association of MS with treadmill exercise capacity and heart rate recovery among patients with CHD using data from the Heart and Soul Study.

Methods: We measured treadmill exercise capacity (metabolic equivalent tasks) and heart rate recovery at one minute (beats per minute) in 943 subjects with known CHD. Of these, 377 (40%) had MS, as defined by the National Cholesterol Education Program criteria.

Results: Participants with MS were more likely to have poor exercise capacity (METES <5) (33% vs. 18%; p<0.0001), and poor heart rate recovery (+16 beats/minute) (34% vs. 21%; p<0.0001), than those without metabolic syndrome. In ordinal logistic regression analyses, MS was associated with worse exercise capacity (odds ratio (OR) 2.2; 95% CI, 1.7-2.8; p<0.0001) and worse heart rate recovery (OR 1.6: 95% CI, 1.4-2.3: p<0.0001). These associations remained strong after adjusting for potential confounding variables (OR 1.6: 95% CI, 1.2-2.1: p<0.003 for worse exercise capacity; OR 1.4: 95% CI, 1.1-1.9; p<0.02 for worse heart rate recovery).

Conclusions: MS is independently associated with poor exercise capacity and poor heart rate recovery in patients with established CHD. Poor cardiac function may contribute to the adverse outcomes associated with the MS.

11:30 a.m.

Association of Metabolic Syndrome With Poor Exercise Capacity and Heart Rate Recovery in Patients With Coronary Disease: the Heart and Soul Study

Christian Spies, Christian Otte, Alka Kanaya, Sharon S. Pipkin, Nelson B. Schiller, Mary A. Wholley, University of California San Francisco, San Francisco, CA, Rush University Medical Center, Chicago, IL

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Conclusions: MS is independently associated with poor exercise capacity and poor heart rate recovery in patients with established CHD. Poor cardiac function may contribute to the adverse outcomes associated with the MS.

11:45 a.m.