Myocardial Function/Heart Failure---Basic/ Molecular; Myocardial Function/Heart Failure--Clinical Pharmacological Treatment

Sunday, March 29, 2009, 9:30 a.m.-12:30 p.m.
Orange County Convention Center, West Hall D

9:30 a.m.

1015-165 Effect of Aging on MicroRNA Expression in the Fischer 344/NNia x Brown Norway/BiNia Female Rat Heart

Jacqueline C. Fannin, Megan Neal, Sunil Kakarla, Anjaiah Katta, Satyanarayana Paturi1, Anil Gutta, Kevin Rice, Miaozong Wu, Nalini Santanam, Eric Blough, Marshall University, Huntington, WV, Joan C. Edwards School of Medicine, Huntington, WV

Background: Cardiovascular disease (CVD) is responsible for more than 50% of deaths in American women. The risk increases in women after menopause. Although not well understood it is thought that the profound impact of age on the risk of the occurrence, severity and prognosis of cardiovascular disease is due, in part, to age-associated changes in cardiovascular structure and/or function. It has been recently postulated that these changes may be due to microRNAs (miRNAs) which are small, noncoding RNAs that regulate gene expression at the post-transcriptional level. MicroRNAs have been shown to regulate processes such as cardiomyocyte growth as the over expression of miRNA-21, miRNA-195, and miRNA-208 has been shown to induce cardiac hypertrophy. We hypothesize that age-related changes in cardiac structure and function may be related to alteration in miRNA expression.
Methods: Echocardiographic and ECG assessments were performed to assay cardiac function in 6-, 26-, and 30-month-old female Fischer 344/NNia x Brown Norway/BiNia (F344XBN) rats (n=4/group). The expression of microRNAs was measured using quantitative RT-PCR and normalized to 5s rRNA levels.
Results: Compared to 6-month animals, cardiac mass in 26- and 30-month females was 31% ± 3 and 51% ± 7 higher, respectively ($p < 0.05$). These age-associated changes in mass were accompanied by an increase in cardiac arrhythmias. The expression of miRNA-195 and miRNA-208 in 30-month hearts was found to be 51% ± 1 ($p < 0.001$) and 41% ± 2 ($p < 0.05$) higher than that observed in the hearts of 6-month animals. Compared to 6-month animals, the expression of miRNA-21 in 26- and 30-month hearts was 42% ± 4 and 13% ± 4 higher, respectively ($p < 0.05$).
Conclusions: These results indicate that expression of miR-21, miR-195, and miR-208 are altered in the aging hypertrophic female hearts of F344XBN rats. Further investigation of these microRNAs may help in understanding the etiology of CVD risk in the aging female.

9:30 a.m.

1015-166 The Urocortin 2-Induced Increase in Myocardial Distensibility Is Compromised in Heart Failure

Carmen Brás-Silva, Ana Patricia Fontes-Sousa, Susana Mendes, Monica Almeida, Adelino F. Leite-Moreira, Faculty of Medicine, Dept. of Physiology, Porto, Portugal

Background: The urocortin (Ucn) peptides are recently isolated members of the corticotropin-releasing factor family. It was previously demonstrated that Ucn2 acutely increases myocardial distensibility in healthy animals. In the present study it was our goal to characterize diastolic Ucn2 effects in the presence of heart failure.
Methods: New Zealand white rabbits were treated with Doxorubicin (1mg/kg, heart failure group) or with saline (control group), administered intravenously twice weekly for 8 weeks, into the marginal ear vein. The effects of increasing concentrations of Ucn2 (10^{-10} to 10^{-6} M) were evaluated in isolated right papillary muscles (Krebs-Ringer: 1.8mM $CaCl_2$, 35°C) from the heart failure group (n=7) and from the control group (n=11). Reported parameters include: active tension (mN/mm2), maximum velocities of tension rise and tension decline (dT/dtmax and dT/dtmin, respectively; mN/mm2/s), passive tension (mN/mm2) and muscle length (L; L/Lmax). Only significant results (mean±SEM, $p<0.05$) are given, expressed as % change from baseline.
Results: Ucn2 induced a concentration-dependent positive inotropic effect in muscles from the control group (at 10^{-6} M it increased 63.6±6.3% active tension and 185.1±14.6% dT/dtmax) that was exacerbated in the heart failure group (active tension increased 91.3±16.7% and dT/dtmax increased 275.5±37.3%). In the control group Ucn2 also promoted a concentration-dependent increase in resting muscle length up to 1.012±0.004 L/Lmax at the highest concentration. Correcting muscle length to its initial value resulted in a 27.7±8.3% decrease of passive tension, indicating a decrease in muscle stiffness and so an increase in myocardial distensibility. This effect was however attenuated in the presence of heart failure, once resting muscle length increase up to 1.0059±0.002 L/Lmax, corresponding to a decrease of passive tension of only 14.3%±5.0%.
Conclusions: The present study demonstrated that the physiologic adaptation mechanism induced by Ucn2, that may allow the heart to reach the same diastolic volume with up to 28% lower filling pressures, is attenuated in heart failure.

9:30 a.m.

1015-167 Human Cardiosphere-Derived Adult Stem Cells Originate Exclusively From In Situ Cardiac Cells

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Background: The aim of this study was to determine the origin of cardiosphere-derived cells (CDCs). CDCs are cardiac stem cells expanded in cell culture, from endomyocardial biopsies. An intermediate step involves formation of floating clusters of progenitor-rich cells (cardiospheres). Very large numbers of CDCs can reliably be produced in a matter of weeks. Intra-myocardial injection of CDCs results in improvement of LV function in rodent models of myocardial ischemia, and clinical trials are planned. A central unresolved issue is whether CDCs represent stem cells expanded from intrinsic cardiac progenitors, or stem cells seeded from an extra-cardiac site (contiguous tissue or blood borne).
Methods: Following informed consent, endomyocardial biopsies were obtained from cardiac transplant recipients (n=10, age 57±15 yr) during routine rejection screening biopsy procedures. CDCs were cultured from each biopsy. The origin of the CDCs was investigated by short-tandem nucleotide repeat (STR) testing, otherwise known as "genetic fingerprinting", performed on DNA from three sources - CDCs, donor heart, and recipient. In addition, in cases in which the donor was of the opposite sex to the recipient (n=2) the presence of X and Y chromosomes in the CDCs was examined using fluorescence *in situ* hybridization (FISH).
Results: Eight of the 10 subjects were male, with all transplanted hearts originating from male donors. The average time from transplantation to cardiac biopsy was 283±484 days. In all cases, no recipient DNA was detected in the CDCs by STR analysis. In the two cases in which a female patient had received a male donor heart, FISH staining indicated that all CDCs had an X and a Y chromosome (511 of 511 cells, and 74 of 74 cells respectively), similarly indicating exclusively donor origin.
Conclusions: CDCs originate from an *in situ* cardiac source, with no detectable extra-cardiac contribution. Our data indicate that cardiac tissue is required in order to grow CDCs for future clinical purposes.

9:30 a.m.

1015-168 Dimethyloxalylglycine-induced Hypoxia Inducible Factor-1α Stabilization and Akt Activation Contribute to the Protective Effect on Mesenchymal Stem Cells

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Background: Mesenchymal stem cell (MSC) transplantation is a promising approach in the therapy of ischemic heart diseases, however, the poor viability of MSCs after transplantation critically limits the efficacy of this new strategy. The goal of this study is to explore a method to enhance MSC survival. Here we hypothesized the prolyl hydroxylase inhibitor Dimethyloxalylglycine (DMOG) can promote MSC survival during serum deprivation.
Methods: The apoptotic model of serum deprivation was used in this study to mimic the microenvironment of ischemic heart diseases *in vivo*. MSCs were subjected to 24h serum deprivation in the presence or absence of DMOG. Apoptosis and cell death were assessed by caspase-3 staining and trypan blue staining respectively. The mitochondrial apoptotic pathway and PI3K/Akt cell survival pathway were evaluated by western blot to study the mechanisms.
Results: The apoptosis and cell death of MSCs were significantly inhibited by DMOG in a dose dependent manner. The peak of protection was achieved at 1000 μM which reduced apoptotic and total cell death rate from 25.3±2.1% to 10.2±0.6%, 29.8±1.5% to 12.9±0.6% after 24h serum deprivation respectively. Hypoxia inducible factor-1α expression and downstream protein glucose transporter-1 synthesis were remarkably induced after DMOG treatment. DMOG decreased cytochrome c release into cytosol and apoptosis inducing factor translocation into nucleus indicating both caspase dependent and independent apoptotic pathway were inhibited. Furthermore, DMOG promoted Akt phosphorylation which was blocked by a specific PI3K inhibitor wortmannin. Wortmannin abrogated the beneficial effect of DMOG on MSC survival.
Conclusions: DMOG can effectively protect MSCs against apoptosis and cell death induced by serum deprivation; DMOG-induced HIF-1α stabilization and PI3K/Akt pathway contribute to the protective effect on MSC survival.

9:30 a.m.

1015-169 Immunosuppression Reduces Immune Responses and Enhances AAV-mediated SERCA2a Expression in a Canine Model of Cardiac Gene Transfer

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Background: The SERCA2a Ca^{2+} pump plays a central role in cardiac contractile properties. SERCA2a expression is decreased in heart failure (HF). Restoring SERCA2a in animal HF models improves cardiac functions. A clinical trial delivering SERCA2a using adeno-associated virus (AAV) is underway (CUPID, Celladon Corp.). Recent studies suggest that AAV-mediated gene transfer may cause inflammation. In this study, we used a canine model to test a) the safety and efficacy of AAV6-mediated expression of human (h) SERCA2a and b) the role of immunosuppression in modulating expression.
Methods: Dogs were tachy-paced to induce HF, then received direct LV wall injection with $5x10^{12}$ viral genomes of AAV6-hSERCA2a (AAV) or saline (S). Pacing continued post-

injection, and dogs were euthanized after 2- (AAV, n=5; S, n=2) or 6-Wk (AAV, n=6; S, n=2). Tissue/serum samples were analyzed for hSERCA2a expression (Western blot), histology (H+E), and immune responses (AAV6-neutralizing antibodies (NAB), AAV-induced leukocyte production of interferon (IFN, Elispot)). Additional non-paced dogs were injected as above and analyzed at 12-Wk (AAV, n=6; S, n=2); a parallel cohort (AAV, n=5; S, n=2) received prednisone+cyclosporine (P+C) immunosuppression starting 4-Wk post-injection.
Results: Cardiac expression of hSERCA2a was detected at the injection sites, with expression peaking at 2-Wk. Echocardiographic LV end diastolic and end systolic diameters decreased in 6-Wk treated HF dogs (4.4+/-0.4 to 3.4+/-0.8 mm, 3.3+/-0.6 to 2.4+/-1.0 mm, p=0.05). Cardiac tissue from 12-Wk AAV injected P+C dogs had higher hSERCA levels (>2 times) relative to 12-Wk dogs without P+C. H+E analysis revealed cardiac infiltrates at AAV injected sites that were less marked in P+C dogs. Elispot showed development of AAV-reactive/IFNγ secreting T-cells. Dogs receiving AAV developed AAV6 NAB (>160) that were reduced to the baseline (<20) by 8-Wk P+C treatment.
Conclusions: Direct cardiac injection of AAV6-hSERCA2a in the dog promotes local robust hSERCA2a expression that is reduced by host immune responses. Immunosuppression alleviates the responses and sustains the hSERCA2a expression, which may be useful for human gene therapy.

9:30 a.m.

1015-170 Intermediate Dose of Pentaglobin Eradicates Inflammation in Parvo B19 and Adenovirus Positive Myocarditis

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Background: Effective treatment of viral myocarditis is a matter of controversy.
Methods: 152 consecutive pts with myocarditis according to the quantitative World Heart Federation Criteria (> 14 infiltrating cells/mm² by endomyocardial biopsy(EMB)) were analysed for infective cardiotropic agents. In 90 pts parvoviruses B19 (59,5%) and in 36 pts adenoviruses (23,8%) were assessed by PCR as causative viral pathogens. All virus positive patients were treated with 10 g/day Pentaglobin® i. v.(enriched IgG, IgA and IgM preparation, Biotest) at day 1 and 3. After six months all patients were reevalutated clinically, 73 patients (48%) in addition by EMB.
Results: After Pentaglobin therapy, all patients demonstrated a significant clinical improvement of the NYHA class, of exercise capacity and of LVEF (from 54,4 to 60,0%, p<0,005) independent from the respective virus. In 52 of 73 (71%) rebiopsied pts inflammation had resolved. In 17 of the 19 rebiopsied patients (90%) with a positive PCR for ADV before therapy no more virus DNA was recovered after treatment, inflammation had resolved completely. In Parvo B 19 myocarditis inflammation had resolved in 31 of the 44 pts (70%), whereas Parvo B19 DNA was eradicated in only in 18 out of 44 pts(40%). In patients in whom both virus and inflammation were eliminated enddiastolic LV dimension decreased and EF increased significantly (p<0,001).
Conclusions: Treatment with an intermediate dose of Pentaglobin is highly effective in resolving myocardial inflammation independent of the underlying viral etiology, but it eradicates adenoviral much better than Parvo B19 infection.

9:30 a.m.

1015-171 Molecular Imaging of Angiotensin Converting Enzyme-1 Expression in the Myocardium of Angiotensin Converting Enzyme-1 Overexpressing Transgenic Rats

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Background: Increased expression of angiotensin converting enzyme 1 (ACE-1) is observed in the failed myocardium and is a potential marker for disease severity. We used Technetium-99m labeled lisinopril (Tc-Lis) for ACE-1 over-expressing transgenic rats (Tg rats) to demonstrate the feasibility of noninvasive imaging of ACE-1 expression in the myocardium.
Methods: In this study, 21 Tg rats and 18 Sprague-Dawley (SD) rats were used. Non invasive images using micro SPECT/micro CT were obtained at 10min, 30min, 60 min, and 120min after Tc-Lis administration. Nine of 21 Tg and 8 of 18 SD received 0.6 mg/kg cold lisinopril (cold-Lis) 5 minutes prior to radiotracer administration. After in vivo imaging, the rat myocardium was explanted, ex vivo images acquired and the percent injected dose per gram (%ID/g) gamma-well counted, followed by assessment of ACE-activity and mRNA, and histological and immunohistochemical characterization.
RESULTS: Myocardial uptake of Tc-Lis was best observed at 120 min after tracer administration in the in vivo imaging. The quantitative uptake of Tc-Lis in the myocardium was higher in Tg than SD rats at each time-point after tracer injection; %ID/g uptake in Tg and SD rats at 30 min was 0.74 +/- 0.13 and 0.17 +/- 0.03%, respectively. The uptake reduced substantially in Tg and SD rats pre-treated with cold-Lis 0.05 +/- 0.008 and 0.05 +/- 0.008%, respectively.
Conclusions: The present study demonstrates the feasibility of molecular imaging of ACE-1 receptors in myocardium. If clinically applicable, it is expected that this strategy will help identify patients susceptible to development of heart failure and also allow optimization of pharmacologic intervention.

9:30 a.m.

1015-172 Intravenous Cell Therapy Given to Rats With Monocrotaline-Induced Pulmonary Artery Hypertension Reduces Right Ventricular Hypertrophy and Improves Right Ventricular Function by Restoring Precapillary Pulmonary Artery Patency

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Background: Pulmonary artery hypertension (PAH) is a life-threatening disease for which standard treatment is inadequate. Novel therapies like stem cell therapy have been demonstrated to be very effective in experimental animals and in patients with PAH.We investigated whether bone marrow-derived mesenchymal stem cells (MSCs) obtained from rats with advanced stage of monocrotaline (MCT)-induced PAH and given to rats at 14 days after MCT administration were able to (i) reverse PAH, (ii) reverse right ventricular (RV) hypertrophy, (iii) improve RV function, and (iv) improve precapillary pulmonary arterial diameters.
Methods: Thirty rats were divided in three groups, being healthy rats that received i.v. PBS (control, n=10), MCT (60 mg/kg, n=10), MCT (60 mg/kg) 14 days later followed by i.v. administration of one million MSCs per rat (n=10). MSCs were obtained from rats which have been treated with MCT (60 mg/kg) for 28 days. At 28 days after MCT or PBS administration, RV function was assessed by combined pressure-conductance catheter, RV hypertrophy was quantified by weighing the RV free wall, interventricular septum (IVS) and LV wall, and lung tissue was examined by histology.
Results: At 28 days after MCT-treatment, rats had PAH (36.2±7.0 vs. 26±2.2 mmHg in control; p<0.001) and RV hypertrophy (RV/(IVS+LV) weight ratio=0.59±0.15 vs. 0.25±0.04 in control; p<0.001). Lung tissue demonstrated severe narrowing of precapillary arterioles and concomitant thickening of arteriolar walls. If MSCs had been administered 14 days after MCT administration, PAH was strongly attenuated (30.2±2.4 mmHg; p<0.05 vs. MCT only), and RV/ (IVS+LV) weight ratio was near normal (0.32±0.07; p<0.005 vs. MCT only) and lung tissue demonstrated hardly any narrowing nor thickening of arterioles.
Conclusion: If rats with developing PAH were treated with MSCs obtained from rats with advanced stage of MCT-induced PAH, beneficial effects have been demonstrated, suggesting that patients with PAH can be treated successfully using autologous MSCs.

9:30 a.m.

1015-173 Cardiac Pro-Oxidant Gene Expression Patterns Are Altered by Chronic Exposure to Particulate Air Pollutants. A Gene Chip Study

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Background: Air pollution (AP) significantly increases cardiovascular morbidity and mortality in the general population. Whether chronic exposure to AP alters gene expression of the myocardium is unknown.
Methods: Therefore Fisher 344 rats for a period of 3 months were exposed to filtered air (FA), or ambient particles of different aerodynamic diameter (AD); i.e. coarse (CP, median AD 4 microns), fine (FP, median AD 0.7 micron) and ultrafine (UFP, median AD 0.06 micron, n=8 per group) in a particle concentrator equipped mobile unit located near a busy Southern California freeway. At the end of the exposure, hearts were subjected to gene expression profiling by using Illumina RatRef-12 bead chips covering over 22,000 rat transcripts.
Results: Fold ratio >1.5 (for both up- and down-regulated genes), and false discovery rate (FDR) adjusted p value of <0.05 were applied. In the UFP-treated group thioredoxin interacting protein (Txnip), a negative regulator of an antioxidant enzyme thioredoxin, and cytochrome P450 isoform (Cyp2e1) involved in primary metabolism of foreign substances including components of air pollutants, demonstrated significant up-regulation (fold ratios 1.79 and 1.57 respectively, FDR<0.05). No changes in the gene expression patterns were observed in the FP group. In the CP group there was also a trend towards increased Txnip expression (fold ratio 1.43, FDR>0.05) and significant increase in the Cyp2e1 expression (fold ratio 1.79, FDR<0.05). Changes in the expression patterns of both genes were confirmed by quantitative RT-PCR.
Conclusions: Up-regulation of Txnip, a negative modulator of antioxidant thioredoxin complex, may increase the heart's susceptibility to the damaging effects of air pollution-generated reactive oxygen species, while up-regulation in Cyp2e1 may indicate activation of a defense-related mechanism to eliminate toxic components of air pollutants. To the best of our knowledge this is the first study to show that chronic exposure to air pollutants alters the expression of genes within the myocardium - and one of these genes relates to the susceptibility to oxidative stress.

9:30 a.m.

1015-174 Congenital Absence of NOS3 Potentiates Left Ventricular Dysfunction in a Murine Model of Diet-Induced Obesity and Chronic Pressure Overload

Roien Ahmadie, Jon-Jon Santiago, Tielan Fang, Khuong Le, Nazila Azordegan, Sheri Bage, Amy Kroeker, Sydney Harris-Janz, Zhaohui Zhao, Kristie Walker, Matthew Lytwyn, Elissavet Kardami, Mohammed Moghadasian, Davinder S. Jassal, University of Manitoba, Winnipeg, MB, Canada

Background: A high lipid diet (HLD) is causal to the induction of cardiomyocyte hypertrophy, fibrosis, insulin resistance and hyperlipidemia leading to adverse left ventricular (LV) remodeling, which may be exacerbated in conditions of hemodynamic stress such as chronic pressure overload. Although nitric oxide (NO) and nitric oxide

synthase 3 (NOS3) plays a major protective role in LV remodeling after transverse aortic constriction (TAC), the nature of interaction between a HLD and NOS3 in a chronic heart failure model of metabolic syndrome remains undefined.
Objective: To determine whether the congenital absence of NOS3 potentiates LV dysfunction in a murine model of diet induced obesity and chronic pressure overload.
Methods: In total, 60 C57Bl/6 wild-type (WT) mice and 60 NOS3 knockout ($NOS3^{-/-}$) mice were randomized into four groups: a) WT+ low lipid diet (LLD); b) WT + HLD; c) $NOS3^{-/-}$ + LLD; d) $NOS3^{-/-}$ + HLD for a total of three months. After one week of randomization to either diet, TAC was performed, followed by monthly echocardiograms. Fasting lipid profiles were evaluated at baseline and at the end of the study. At month 3, the hearts were removed for histopathological and Western blot analyses.
Results: After TAC, echocardiography revealed a decrease in LVEF in WT and $NOS3^{-/-}$ mice fed a HLD compared to a LLD. $NOS3^{-/-}$ mice fed a HLD demonstrated a further reduced LVEF compared to WT mice fed a HLD after TAC (45±5% vs. 52±4%, p<0.05). Three months after TAC, LV weight was increased in WT and $NOS3^{-/-}$ mice fed a HLD as compared to a LLD respectively (0.25±0.01 g vs. 0.21±0.01 g (WT) and 0.28±0.1 g vs. 0.22±0.01 g ($NOS3^{-/-}$), p<0.05). There was increased myocyte hypertrophy and interstitial fibrosis in $NOS3^{-/-}$ mice fed a HLD three months post TAC as compared to the other groups. Total serum cholesterol was increased 2.0 fold in WT mice and increased 2.5 fold in $NOS3^{-/-}$ mice at three months post TAC. High FGF-2, a marker of cardiac hypertrophy, was upregulated in $NOS3^{-/-}$ mice fed a HLD compared to WT mice.
Conclusions: In a chronic pressure overload state and hyperlipidemia, $NOS3^{-/-}$ mice demonstrated greater LV dysfunction, cardiac hypertrophy and fibrosis as compared to WT mice.

9:30 a.m.

1015-175 Expression of MicroRNA-212 Is Increased in Left Ventricular Myocardium of Explanted Failed Human Hearts and in Dogs With Experimentally-Induced Heart Failure

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Background: MicroRNAs are regulatory molecules consisting of 22 noncoding nucleotides that regulate gene expression. MicroRNAs have been shown to play a fundamental role in diverse biological and pathological processes. Recent studies have suggested that microRNA-212 participate in the control of cardiac hypertrophy. Furthermore, expression of microRNA-212 in the adult heart is also believed to contribute to re-activation of the fetal gene program. Because compensatory cardiac hypertrophy and induction of the fetal gene program are characteristics of the failing heart, we tested the hypothesis that expression of microRNA-212 is increased in left ventricular (LV) myocardium of failed human and dog hearts.
Methods: LV tissue was obtained from 6 explanted failed human hearts due to ischemic cardiomyopathy (ICM), 6 failed human hearts due to idiopathic dilated cardiomyopathy (IDC), and 6 donor (DNR) hearts deemed not suitable for transplantation. LV tissue was also obtained from 6 dogs with coronary microembolization-induced heart failure and 6 normal dogs. Low-molecular-weight RNAs were isolated using the mirVana microRNA Isolation Kit. microRNA-212 (hsa-miR-212) and microRNA-92 (hsa-miR-92, used as an internal control) assay kits were used to determine expression of microRNAs using specific TaqMan Gene Expression Master Mix in Real-Time PCR. Results were expressed in fold increase or decrease relative to human DNR or normal canine myocardium.
Results: Expression of microRNA-92 was similar in LV myocardium of DNR, ICM and IDC human hearts as well as in normal and failed dog hearts. Expression of microRNA-212 was increased 5.43 fold in ICM and 4.66-fold in IDC hearts compared to DNR hearts. Similarly, expression of microRNA-212 was increased 5.13-folds in LV of heart failure dogs compared to normal dogs.
Conclusions: Expression of microRNA-212 is increased in failing human and dog LV myocardium regardless of etiology. Up-regulation of microRNA-212 in the failing LV can explain, in part, the processes that underlie the development of hypertrophy and induction of the fetal gene program in heart failure.

9:30 a.m.

1015-176 Improvement of Left Ventricular Remodeling and Function by Protease-Activated Receptor 1 Inhibition in Rats With Heart Failure After Myocardial Ischemia and Reperfusion

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Background: Protease-Activated Receptor 1 (PAR1) inhibition has been shown to acutely reduce infarct size during ischemia and reperfusion. The purpose of this study was to determine whether PAR1 inhibition continued to protect against long-term reperfusion injury after ischemia by decreasing cardiac remodeling and preventing left ventricular failure.
Methods and Results: Rats were randomly assigned to 7 different groups and received either 30 min of anterior myocardial ischemia followed by 28 d of reperfusion or a sham surgery. The Control and Sham group received no treatment. The treatment groups received one dose of the PAR1 antagonist, SCH either before or after ischemia alone or with a continuous 28 d infusion of SCH. Echocardiography was performed at baseline and post-operatively at 3 d and 28 days. Infarct size and inflammation was assessed at 28 d. Ischemia and chronic reperfusion in the Control group was associated with increased LV dimensions and volumes and decreased ejection fraction and fractional shortening when compared to the Sham group (EF: 41% Control vs. 79% Sham). SCH treatment inhibited these changes (EF:66-77%). The control rats also displayed decreased radial and circumferential strain when compared to the Sham rats. SCH treatment attenuated the decrease in myocardial strain. Furthermore, SCH treatment eliminated pulmonary remodeling and edema that resulted from 28 d of reperfusion. The attenuation of LV remodeling and failure with SCH was associated with a substantial decrease in infarct size and myocardial inflammation when compared to Control.
Conclusions: PAR1 inhibition preserves LV structure and function after ischemia and chronic reperfusion. The PAR1 antagonist also protected against clinical signs of heart failure including pulmonary edema. This protection is due to a decreased infarct size and associated myocardial inflammation. PAR1 may be an attractive and efficacious target for the clinical treatment of ischemic cardiomyopathy.

9:30 a.m.

1015-177 Angiotensin II Induces Cardiac Systolic and Diastolic Dysfunction via Toll-Like Receptor 4 Mediated Up-regulation of Oxidative Stress in Murine Heart

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Background: Toll-like receptor 4 (TLR4) is involved in cardiovascular events. Angiotensin II (Ang II) also play an important role in cardiac hypertrophy and the development of heart failure. However, the relationship between TLR4 and Ang II in regulating oxidative stress and cardiac function remains unknown. We compared the effects of TLR4 on the oxidative stress, cardiac hypertrophy and function in Ang II or norepinephrine (NE)-induced pressure overload in mice *in vivo*.
Methods: $TLR4^{-/-}$ and wild-type (WT) mice were randomized into two groups each, and given Ang II or NE for 2 weeks. Left ventricular end-diastolic dimension (LVEDd), LV end-systolic dimension (LVESd), fractional shortening (%FS), ejection fraction (EF), interventricular septum (IVS) as well as LV posterior wall thickness (LVPW) and transmitral flow (TMF) were assessed by transthoracic echocardiography under light anesthesia. In each heart, we evaluated the wall-to-lumen (W/L) ratio and the perivascular fibrosis. Superoxide content in the heart, we incubated frozen section of heart tissues with the dye hydroethidine staining.
Results: Both Ang II and NE induced a significant increase in systolic blood pressures (SBP) in WT and $TLR4^{-/-}$ mice (p<0.05), while SBP and heart rates were not significantly different among the four groups throughout the experiments. Ang II induced a significant increase in IVS, LVPW, and a significant decrease in EF, %FS and E/A ratio of TMF (p<0.05), and also demonstrated a greater LVESd (p<0.05) in WT mice, whereas $TLR4^{-/-}$ mice showed little effects of Ang II on these indices, and LVEDd were not different among the four groups. Ang II also increased perivascular fibrosis, W/L ratio, and heart weight/body weight in WT mice compared with $TLR4^{-/-}$ mice. Furthermore, Ang II induced 5-fold significant increase in superoxide content in the heart in WT mice, whereas only 2-fold increase in superoxide content in $TLR4^{-/-}$ mice. In contrast, NE treatment did not reach a statistical significance in these indices.
Conclusions: TLR4 is the critical determinant factor for the increase in oxidative stress, cardiac hypertrophy, fibrosis, and systolic and diastolic dysfunction in Ang II-induced hypertension *in vivo*.

9:30 a.m.

1015-178 Effects of Combination of Proliferative Agents and Erythropoeitin on Left Ventricular Remodeling Post-Myocardial Infarction

Rosemeire M. Kanashiro-Takeuchi, Lauro M. Takeuchi, Joshua M. Hare, University of Miami, Miami, FL

Background: Erythropoeitin (EPO) has been reported to improve cardiac function after MI through promoting mobilization of endothelial progenitor cells to the injured heart and enhancing neovascularization. Here we tested the hypothesis that adding either human chorionic gonadrotrophin (hCG) or prolactin (PRL) followed by EPO may provide additional therapeutic benefit through a regenerative mechanism.
Methods: MI induced by coronary artery ligation was performed in 6-month-old Wistar rats. Animals were randomly assigned to one of five treatment groups: control (n=6); human chorionic gonadotrophin (hCG, n=6); EPO (n=7); hCG + EPO (n=5) and prolactin + EPO (n=5). Cardiac structure and function was assessed by echocardiography at baseline, 24h, 1, 2, 4 and 8 weeks post-MI. Apoptosis and cell proliferation were determined by TUNEL assay and immunostaining for Ki67, respectively.
Results: At baseline and after MI, echocardiographic parameters of LV size and function were similar in treated and untreated animals. After MI, chamber systolic dimension increased from 4.2±0.3 to 8.1±0.3 mm, p<0.05 in controls. Over and 8-week period, hCG, EPO and hCG + EPO but not PRL+EPO groups attenuated this increase (from 8.1±0.3 to 7.2±0.2 mm, p<0.05 for each vs. control); however, in PRL+ EPO group (8.4 ±0.6 mm, p>0.05) it was not affected. Similarly a reduction in ejection fraction (EF) from 81±1 to 45±4% (p<0.05) due to MI was ameliorated in these groups (57±3 %, p<0.05 for each vs. control) but not in PRL group (39±7% p>0.05). Myocyte and non-myocyte apoptosis was markedly reduced in all treated groups (p<0.01); however, Ki67 positive cells were only reduced in groups treated with EPO (p<0.05). The reduction in LV size and functional decline as measured by repeated echocardiography was accompanied by reductions in MI size in the group treated with hCG (p<0.05).
Conclusion: Our findings revealed that hCG alone or in combination with EPO may be an effective therapeutic strategy to ameliorate post-MI remodeling. The absence of effect with PRL suggests a direct effect on the myocardium. Given the established safety profile of hCG in humans, clinical trials may be warranted.

9:30 a.m.

1015-179 **Decreased S-Nitrosylation of the Calcium Release Channel RyR2 and Increased SR Ca Leak in Heart Failure**

Adriana V. Treuer, Daniel R. Gonzalez, Joshua M. Hare, Interdisciplinary Stem Cell institute, Miller school of Medicine, University of Miami, Miami, FL

Background: In the cardiac muscle cell, the specific isoform of the ryanodine receptor (RyR2) mediates Ca2+ release from the sarcoplasmic reticulum. This channel is highly susceptible to redox modifications. Among these, S-nitrosylation has emerged as an important modification in health and disease. We have previously shown in a mouse model that deficiency in RyR2 S-nitrosylation is detrimental for excitation-contraction coupling. Consequently, we tested the hypothesis that the level of activity and S-nitrosylation of RyR2 are altered in heart failure.
Methods: We studied the redox state of the RyR2 from hearts of spontaneously hypertensive-heart failure (SHHF) rats (n=9, ~ 22 months old) and Wistar-Kyoto (WKY) rats, as control (n=4, ~19 months old). S-nitrosylation was studied using the biotin-switch method and the relative content of free cysteines by the bimane assay. Superoxide was detected using DHE staining and xanthine oxidase by Western blotting and immunohistochemistry. Isolated cardiomyocytes were obtained enzymatically. Ca2+ transients were measured using fura-2 as indicator. Sarcoplasmic reticulum (SR) Ca2+ was estimated superfusing caffeine and diastolic Ca2+ leak was evaluated using an established protocol using tetracaine as RyR blocker.
Results: RyR2 from the SHHF rat hearts showed decreased S-nitrosylation and contained fewer free cysteines ($p<0.05$ vs. WKY), findings consistent with oxidation of the channel in the failing hearts. Superoxide production along with the expression of the superoxide-producing enzyme xanthine oxidoreductase were increased in the failing hearts (fourfold, $p<0.05$ vs. WKY). By studying the diastolic Ca2+ leak in a range of Ca2+ contents, analysis showed that for a given Ca2+ load, Ca2+ leak was increased in SHHF myocytes, denoting increased RyR2 activity, associated with decreased contractility.
Conclusions: Our results show that increased oxidative stress in heart failure induced modifications in the RyR2, including decreased S-nitrosylation. These redox modifications of RyR2 are associated with increased SR Ca2+ leak and decreased myocyte contractility. This highlights the importance of restoring the redox milieu in heart failure.

9:30 a.m.

1015-180 **Expression of H11 Kinase Is Increased in Left Ventricular Myocardium of Explanted Failed Human Hearts and in Hearts of Dogs With Experimentally-Induced Heart Failure**

Ramesh C. Gupta, Hani N. Sabbah, Henry Ford Hospital, Detroit, MI

Background: Adenoviral-mediated overexpression of H11 kinase (H11K) in rat neonatal cardiomyocytes promotes cell hypertrophy and apoptosis. Over-expression of H11K was also shown to cause re-expression of the fetal gene program. We examined the expression of H11K in LV myocardium of failed human and dog hearts.
Methods: RNA was extracted and SDS-extract of homogenate, membrane and cytosol fractions was prepared from LV tissue of 6 explanted failed human hearts due to ischemic cardiomyopathy (ICM), 6 failed hearts due to idiopathic dilated cardiomyopathy (IDC), and 6 normal donor (DNR) hearts. RNA and SDS extracts were also prepared from LV of 6 dogs with microembolization-induced heart failure (HF) and 6 normal (NL) dogs. mRNA expression was measured with real-time PCR and protein expression with Western blotting and bands quantified in densitometric units (du).
Results: Data are shown in the table. mRNA expression of H11K increased significantly in ICM and IDC hearts compared to DNR hearts and in HF dogs compared to NL dogs. H11K protein expression increased significantly in homogenate and cytosol fractions but decreased in membrane fractions of ICM and IDC compared to DNR and in HF dogs compared to NL dogs.
Conclusions: mRNA and protein expression of H11K is increased in HF. The H11K translational modification in HF is localized to the cytosol and may act as an intracellular trigger for cell hypertrophy and apoptosis.

*=p<0.05 vs. NL; †= p<0.05 vs. DNR

	Dog		Human		
	NL	HF	DNR	ICM	DCM
H11K mRNA (108 molecules/mg of total RNA)	1.0 ± 0.2	2.7 ± 0.4*	9.0 ± 0.6	17.0 ± 1.0†	24.0 ± 2.0†
H11K Protein in LV Homogenate (du)(/b>	28 ± 4	86 ± 4*	54 ± 6	229 ± 47†	307 ± 44†
H11K Protein in Membrane Fraction (du)	0.36 ± 0.04	0.17 ± 0.01*	0.45 ± 0.03	0.21 ± 0.03†	0.20 ± 0.03†
H11K Protein in Cytosol Fraction (du)	2.42 ± 0.10	4.85 ± 0.18*	0.65 ± 0.06	3.94 ± 0.27†	3.90 ± 0.22†

9:30 a.m.

1015-181 **Cardiomyogenic Differentiation Potential of Mesenchymal Stem Cells Declines With Increase in Age: Rebuilding the Heart With Old or New Bricks?**

Arti A. Ramkisoensing, Daniel A. Pijnappels, John van Tuyn, Hector A. Farias, Carolina L. Gomez, Antoine A. de Vries, Dick L. Ypey, Arnoud van der Laarse, Martin J. Schalij, Douwe E. Atsma, Leiden University Medical Center, Leiden, The Netherlands

Background: In cardiac cell therapy often autologous stem cells from adult patients are used as therapeutic agent. Whether the cardiomyogenic differentiation potential of stem cells depends on the host's age is not studied in detail. Therefore we assessed, in an in vitro model, the capacity of neonatal and adult rat mesenchymal stem cells (MSCs) to differentiate into cardiomyocytes.
Methods: eGFP-labeled bone-marrow derived MSCs of 2-day old neonatal rats (nr) or 10-weeks old adult rats (ar) were co-cultured with nr ventricular cardiomyocytes (CMCs) up to 10 days. Immunocytochemical analysis for cardiac protein expression, and whole-cell patch clamp experiments to study action potential characteristics after gap junctional uncoupling were used to assess cardiomyogenic differentiation.
Results: After 3 days of co-culture, 34±5% and 30±6% of the nrMSCs showed positive diffuse staining for sarcomeric alpha-actinin and cardiac troponin-I, respectively, while less than 10% of the arMSCs stained positive. After 10 days, positive staining for these cardiac markers in nrMSCs increased to 63±6% and 60±4%, respectively, but now including 17±5% (n=65) in typical sarcomeric cross-striation without signs of cell fusion. In contrast, 20% (n=75) of the arMSCs showed positive diffuse staining for both cardiac markers. Interestingly, a fraction of arMSCs was fused with native nrCMCs (0.5% n=16), as indicated by the presence of heterokaryotic eGFP labeled, cross-striated cells. Importantly, at day 10 of co-culture, nrMSC-derived CMCs (16%, n=9) were found to beat independently from surrounding nrCMCs in the presence of the gap junction uncoupler 2-APB, while showing action potential characteristics comparable to those of native nrCMCs (n=10). However, arMSCs were non-beating and showed no cardiac-like action potentials.
Conclusion: Neonatal rat (nr) mesenchymal stem cells (MSCs) are able to undergo functional cardiomyogenic differentiation upon co-culture with nr cardiomyocytes, in contrast to adult rat (ar) MSCs. However, arMSCs are able to fuse with nr cardiomyocytes, which might contribute to the subtle therapeutic effects of autologous cell therapy observed in the clinical setting.

9:30 a.m.

1015-182 **Thrombomodulin Is Upregulated in Cardiomyocyte During Cardiac Hypertrophy and Promotes Cardiomyocyte Survival**

Yi-Heng Li, Hsing-Chun Chung, Kou-Gi Shyu, Guey-Yueh Shi, Hua-Lin Wu, National Cheng Kung University Hospital and College of Medicine, Tainan, Taiwan,ROC, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan,ROC

Background: Cardiac hypertrophy is a common response to pressure overload. It is associated with cardiomyocyte (CM) apoptosis and results in heart failure. Thrombomodulin (TM), traditionally known as an anticoagulant protein, was found to have unique effects on cellular proliferation, adhesion and inflammation. We examined TM expression in CM during cardiac hypertrophy and investigated the physiological significance. **Methods and Results:** Data are expressed as mean±SE. Statistical analysis was performed using ANOVA followed by Bonferroni test. In hypertrophic human and mouse hearts, immunohistochemical study showed a significant TM expression in CMs. In cardiac hypertrophy elicited by transverse aortic constriction (TAC) in mice, heart TM expression increased (baseline vs 1 vs 6 vs 12 wks after TAC, TM mRNA ratio: 1 vs 0.74±0.13 vs 1.09±0.07 vs 2.04±0.29, $p<0.05$) in association with the increased heart weight/body weight ratio (3.91±0.09 vs 4.61±0.22 vs 4.97±0.19 vs 6.01±0.38 mg/g, $p<0.01$). Cultured neonatal rat CMs were stretched by vacuum to 20% of maximum elongation at 60 cycles/min. TM mRNA increased to a maximum of 4-fold over the control at 14 hrs after stretch (baseline vs 6 vs 12 vs 14 vs 24 hrs after stretch, TM mRNA ratio: 1 vs 2.95±0.38 vs 3.43±0.26 vs 4.08±0.44 vs 3.55±0.25, $p<0.01$). Quantification of apoptotic DNA fragmentation was done using the Cell Death Detection ELISA kit in cultured neonatal rat CMs. TM reduced doxorubicin-induced CM apoptosis (saline vs 10 vs 30 vs 50 ng/ml TM pretreatment, apoptosis ratio: 1 vs 0.67±0.03 vs 0.64±0.01 vs 0.58±0.01, $p<0.01$). The CM caspase-3 activity was also reduced (saline vs 50 ng/ml TM pretreatment, caspase-3 activity ratio: 1 vs 0.74±0.06, $p<0.05$). The cell size of CM was increased after stimulation with TM for 5 days (saline vs 10 vs 30 vs 50 ng/ml TM treatment, cell area ratio: 1 vs 1.47±0.30 vs 1.89±0.39 vs 2.09±0.47, $p<0.01$). TM treatment significantly increased the extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation in CM. **Conclusions:** There is a significant TM expression in CMs during cardiac hypertrophy. TM promotes CM survival by reducing apoptosis and sustains CM hypertrophy in response to pressure overload.

9:30 a.m.

1015-183 **Impact of Enhanced Expression and Secretion of Cell Proliferation Related Genes and Proteins in Adipose-Derived Mesenchymal Stem Cells on Salvaging Vascular and Heart Failures: Insights From Microarray Analysis**

Chiaki Nakanishi, Toshinari Tsubokawa, Masaaki Kawashiri, Noritoshi Nagaya, Masakazu Yamagishi, Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Kanazawa, Japan, Department of Regenerative Medicine and Tissue Engineering, National Cardiovascular Center Research, Osaka, Japan

Background: Previous experimental studies indicated that adipose tissue-derived mesenchymal stem cells (A-MSC) has emerged as a possible alternative cell source to bone marrow-derived mesenchymal stem cell (B-MSC) for the treatment of vasular and heart failures. However, few data exist regarding the molecular foundation that explains the difference in biological behavior between A-MSC and B-MSC. Therefore, we examined expression of gene and secretory protein in A-MSC and B-MSC using microarray and ELISA.
Methods and Results: A-MSC and B-MSC were obtained from subcutaneous adipose tissue and bone marrow of adult Lewis rats weighing 200 ~ 250 g. During cultural process A-MSC proliferated 4-fold as rapidly as B-MSC, although A-MSC and B-MSC had comparable potential to differentiate into osteoblasts and adipocytes. In microarray analysis, 571 genes (1.8%) out of 31,099 genes were preferentially expressed (> 3-fold) in A-MSC, and a number of genes were associated with mitosis such as cyclin dependent kinase 2, cyclin B1, cyclin F and with immune response such as interleukin 1α, interleukin 6, chemokine (C-C motif) ligand 20. In contrast, other 571 genes (1.8%) highly expressed

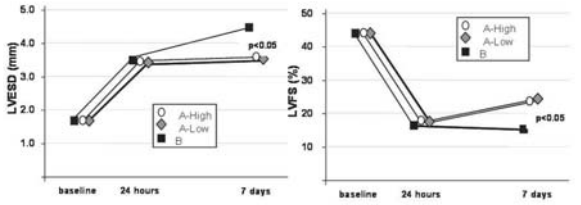
(> 3-fold) in B-MSC were associated with morphogenesis such as jagged 1, cadherin 13, elastin and with development such as transforming growth factor β2, WNT1 inducible signaling pathway protein 2, actin γ2. ELISA demonstrated that A-MSC secreted larger amounts of growth and antiapoptotic factors such as vascular endothelial growth factor and hepatocyte growth factor than B-MSC.
Conclusions: These results demonstrate that A-MSC expresses cell mitosis-related genes and secretes larger amounts of bioactive proteins than B-MSC, thus contributing to alternative cell source to B-MSC in the treatment of vascular and heart failures. The enhanced effects of combined treatment with A-MSC and B-MSC on these failures should further be sought.

9:30 a.m.

1015-184 Safety and Efficacy of High-Dose Anakinra in Experimental Acute Myocardial Infarction

Fadi N. Salloum, Nicholas N. Hoke, Amit Varma, Benjamin Van Tassell, Stefano Toldo, Antonio Abbate, Virginia Commonwealth University Pauley Heart Center, Richmond, VA

Background: Interleukin-1 (IL-1) receptor antagonist (Ra) is a naturally occurring IL-1 blocker with a cardioprotective effect during acute myocardial infarction (AMI). Anakinra, recombinant-human IL-1Ra, reduces heart failure in a mouse model of AMI. The aim of this study was to determine the optimal therapeutic dosing regimen for anakinra in experimental AMI.
Methods: Fifteen ICR mice underwent surgical coronary artery ligation. Five mice received anakinra 1 mg/kg daily, 5 received anakinra 100 mg/kg, and 5 received a matching volume of NaCl 0.9% for 7 days. All animals underwent transthoracic echocardiography before surgery, 24 hours and 7 days after surgery.
Results: Both doses of anakinra improved left ventricular end-diastolic diameter (LVEDD), end-systolic diameter (LVESD), and fractional shortening (LVFS) versus saline at 7 days (all p values <0.05 [see figure]). No significant differences in LVEDD, LVESD, and LVFS were found between high and low dose treatment groups.
Conclusions: Treatment with higher dose anakinra (100 mg/kg) is safe during AMI and prevents adverse cardiac remodeling when compared to inactive treatment. However, high-dose anakinra provides no additional benefits compared to standard dose anakinra (1 mg/kg).



9:30 a.m.

1015-185 Mitochondrial Dysfunction in Heart Failure Affects Interfibrillar but Not Subsarcolemmal Mitochondria

Michael Schwarzer, Andrea Schrepper, Paulo Amorim, Gracjan Pytel, Friedrich W. Mohr, Torsten Doenst, University Leipzig - Heart Centre, Leipzig, Germany

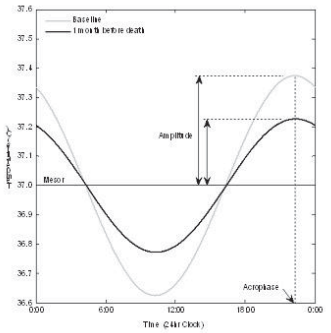
Objectives: Pressure overload induced heart failure is correlated with significant impairment in mitochondrial function. In normoxia >95% of the ATP is produced there. In heart muscle, two types of mitochondria exist. Subsarcolemmal mitochondria (SSM) presumably, providing ATP for basic cell function, and interfibrillar mitochondria (IFM), presumably providing energy for the contractile apparatus. We speculated that the respiratory capacities of these subpopulations are differentially affected by pressure overload.
Methods: Male Sprague-Dawley rats were subjected to transverse aortic constriction for 20 weeks. Contractile function was assessed by echocardiography. Mitochondria were isolated by differential centrifugation and respiratory capacity was analyzed using a Clark electrode.
Results: Left ventricular posterior wall diameter was increased (LVPWD: 2,6±0,2 vs. 1,4±0,2mm; p<0,05) after 10 weeks and resulted in reduced EF (53±8 vs. 75±6%; p<0,05) after 20 weeks, indicating heart failure. The mitochondrial marker enzyme, citrate synthase, was significantly reduced in heart failure (U/100mg tissue: 15,3±2,0 vs. 24,6±2,1). State 3 respiration of isolated SSM was unchanged with all substrates. In contrast respiratory capacity of IFM was impaired with complex-I substrates (natomsO/min/mg protein: glutamate 239±64 vs. 503±91, palmitoyl-carnitine 241±27 vs. 521±83 and pyruvate 198±14 vs. 615±107; p<0,05) but unchanged with succinate as complex-II substrate.
Conclusion: Contractile dysfunction in heart failure is associated with significant impairment of mitochondrial respiratory capacity. However this effect is limited to the interfibrillar mitochondria. The selective differences of the respiratory capacity of the IFM support the notion of IFMs main role in producing ATP for contractile function.

9:30 a.m.

1015-186 The Usefulness of Body Temperature Circadian Rhythm Variation as an Early Predictor of Decompensation in Cardiomyopathic Hamsters

Amany Ahmed, Sreedevi Gondi, Casey Cox, Shahzeb M. Munir, K. J. Shankar, Igor V. Stupin, Ed Sobash, Dejian Lai, Alan Brewer, James M. Wilson, S. Ward Casscells, Texas Heart Institute, Houston, TX, University of Texas HSC, Houston, TX

Introduction: We have previously shown that hypothermia is a significant predictor of death in heart failure patients. We hypothesize that variations in the body temperature circadian rhythm (BTCR) precede the temperature decline and will be an early predictor of decompensation and death.
Methods: We observed 48 male BIO-TO-2 Syrian dilated cardiomyopathic hamsters and continuously monitored their temperature with an intraperitoneal transmitter until death. We used group mean cosinor analysis to determine the mesor, amplitude, and acrophase of the BTCR sinusoid and to establish whether there was a difference between values at baseline and death.
Results: Of the 45 hamsters included in the final analysis, 44 had a decline in temperature 8±4 days before death. Group mean cosinor analysis of the temperature data revealed a significant (P<0.05) decrease in the amplitude of the BTCR 8 weeks before death (0.28; 95% CI, 0.26-0.31) compared to baseline (0.36; 95% CI, 0.34-0.39). A Student t test confirmed that the amplitude at 8 weeks before death was significantly lower than that at both baseline (P=0.005) and 4 weeks after baseline (P=0.03). The acrophase and mesor did not significantly change between baseline and death.
Conclusions: The decrease in the amplitude of the BTCR occurs before the temperature decline in cardiomyopathic hamsters. Continuous temperature monitoring may be useful in predicting decompensation in heart failure patients and in guiding treatment.



9:30 a.m.

1015-187 Intranasal Administration of Atrial Natriutetic Peptide May Be Useful for the Treatment of Chronic Heart Failure in Rats

Tatsuji Kono, Akiko Soyama, Kazuhiko Yamane, Takao Tanaka, Yasushi Kitaura, Osaka Medical College, Osaka, Takatsuki, Japan

Background: Atrial natriutetic peptide (ANP) and angiotensin II act as mutual antagonists in the brain. In rats with chronic heart failure (CHF), a substantial decrease of ANP was found in the paraventricular nucleus (PVN) and supraoptic nucleus (SON), which are involved in cardiovascular and fluid regulation. We have demonstrated that alpha-hANP administered intranasally may access the brain directly. We hypothesized that alpha-hANP administered intranasally may be useful for the treatment of CHF. **Methods:**At 1 month after coronary ligation, forty survived rats with left ventricular (LV) dysfunction were assigned to either alpha-hANP administered intranasally at a dosage 200μg in 10μL saline once a day for 1 month (ANP, n=20) or same amount of vehicle alone (CHF, n=20). Sham-operated rats (n=20) were used as controls.**Results:**In CHF compared with sham, although plasma ANP levels were elevated, immunohistochemical studies showed decreased expression of ANP and increased expression of angiotensin II type 1 receptor (AT-1) in PVN and SON. Compared with CHF, intranasal alpha-hANP significantly increased expression of ANP and decreased expression of AT-1 receptor in PVN and SON, attenuated activation of sympathetic nerve and improved LV function.(*=p<0.05 vs. Sham, †=p<0.05 vs. CHF) **Conclusions:** Alpha-hANP administered intranasally may counteract central angiotensin II, suppress activated sympathetic nerve and may improve LV function in CHF.

Table

	Sham (n=20)	CHF (n=20)	ANP (n=20)
LV end-diastolic dimension (mm)	7.0±0.9	12.0±1.0*	9.2±1.1* †
LV fractional shortening (%)	49±7	11±2*	20±7*†
Mean aortic pressure (mmHg)	69±11	71±9	78±9
LV end-diastolic pressure (mmHg)	7±2	25±3*	13±6*†
Peak dp/dt (mmHg/sec)	4440±540	3180±480*	4140±410†
Negative dp/dt (mmHg/sec)	3980±310	2220±530*	3180±680*†
LV/BW (mg/g)	2.03±0.11	3.66±0.58*	3.03±0.47*†
Plasma ANP (pg/mL)	0.9±0.4	9.5±3.9*	4.9±3.9†
Plasma norepinephrine(pg/mL)	96.2±33.1	241.0±108.2*	28.4±8.6†

9:30 a.m.

1015-188 Derivation and Validation of a Novel Load Independent Index of Isovolumic Relaxation

Leonid Shmuylovich, Sandor J. Kovacs, Washington University School of Medicine, St Louis, MO

Background: Isovolumic pressure decline is characterized by the monoexponential and logistic time-constants of isovolumic pressure decay (IVPD) τ, and τ_L. However, both τ, and τ_L are afterload dependent. In this work we derive a novel load-independent index of isovolumic pressure decay (LIIIVPD).

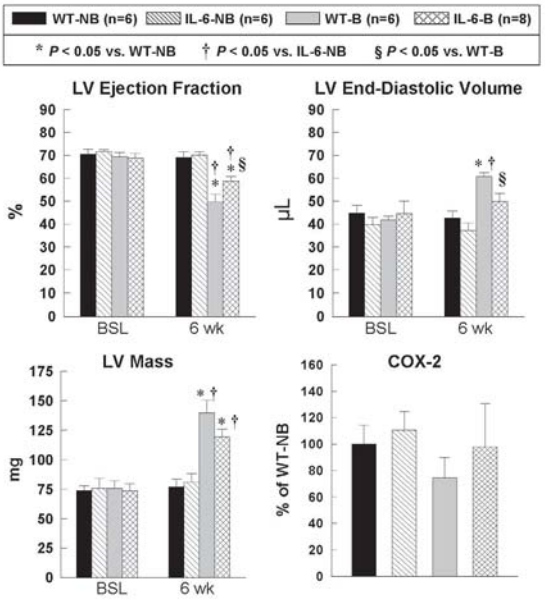
Methods: We applied kinematic modeling to predict and derive a pressure contour-based LIIIVPD. For each IVPD contour, we mathematically extract an effective peak-restoring force driving pressure decay ($F_{Restore}$) and peak-resistive force opposing pressure decay (F_{Resist}), thereby defining coordinates in the $F_{Restore}$ vs F_{Resist} plane. The LIIIVPD is defined as the dimensionless slope, called $M_{LIIIVPD}$, of the linear regression between a set of IVPD contours plotted as points in the $F_{Restore}$ vs F_{Resist} plane. To validate load-independence, an average of 107 IVPD contours were analyzed in 25 subjects undergoing diagnostic catheterization, and the linearity of each subject's $F_{Restore}$ vs F_{Resist} regression was assessed.
Results: The $F_{Restore}$ *vs* F_{Resist} relation was highly linear, with average r^2=0.993±0.006. For all subjects, $M_{LIIIVPD}$ was found to be linearly correlated to subject averaged τ (r^2= 0.65), τ_L(r^2=0.50), and dP/dt_{MIN} (r^2=0.63), as well as to ejection fraction (r^2=0.52).
Conclusions: We conclude that $M_{LIIIVPD}$ is a LIIIVPD because it is load-independent and correlates with conventional IVPD parameters. Further validation of $M_{LIIIVPD}$ in selected pathophysiologic settings is warranted.

9:30 a.m.

1015-189 Genetic Deletion of IL-6 Attenuates Pressure Overload-Induced Left Ventricular Hypertrophy and Dysfunction

Santosh K. Sanganalmath, Christine R. James, Hisham Taher, Greg Hunt, Robert J. Vincent, Rui Wu, Qianhong Li, Michael P. Flaherty, Roberto Bolli, Buddhadeb Dawn, Institute of Molecular Cardiology, University of Louisville, Louisville, KY

Background: Although interleukin (IL)-6 has been implicated in ischemic heart disease, its role in pressure overload-induced LV hypertrophy and dysfunction remains unclear.
Methods: We subjected IL-6-/- (IL-6-B, n=8) and age-matched wild-type (WT) (WT-B, n=6) mice to suprarenal aortic banding. Sham-operated (nonbanded) WT (WT-NB, n=6) and IL-6-/- (IL-6-NB, n=6) mice served as controls. Echocardiography was performed before (BSL) and at 6 wks after banding before euthanasia.
Results: Compared with sham controls, aortic banding increased LV end-diastolic volume (LVEDV) and LV mass, and decreased LVEF in WT mice (Fig). Compared with aortic-banded WT mice, the increase in LVEDV (61±1.7 μL vs. 50±3.4 μL in WT-B and IL-6-B, respectively, P<0.05) and LV mass (140±11 mg vs. 119±7 mg in WT-B and IL-6-B, respectively, P<0.05), and the decrease in LVEF (49.7±3.3% vs. 58.6±2.2% in WT-B and IL-6-B, respectively, P<0.05) were significantly attenuated in aortic-banded IL-6-/- mice (Fig). Compared with sham controls, the myocardial levels of COX-2 protein, which exerts potent antifibrotic effects, was reduced by 25% in WT-B mice. This reduction in myocardial COX-2 protein expression was attenuated in IL-6-B mice (Fig).
Conclusions: The absence of IL-6 signaling protects against LV hypertrophy and dysfunction during pressure overload possibly by preventing the downregulation of COX-2 expression. Thus, inhibition of IL-6 may potentially ameliorate LV hypertrophy and dysfunction in hypertensive patients.



9:30 a.m.

1015-190 A High Fat Diet Inhibits the Cardioprotective Effects of ω-3 Polyunsaturated Fatty Acids on Ventricular Hypertrophy

Keyur B. Shah, Monika K. Duda, David J. Chess, Karen M. O'Shea, Ramzi J. Khairallah, Isabelle Frayne-Robillard, Christine des Rosiers, Willem J. Kop, William C. Stanley, University of Maryland School of Medicine, Baltimore, MD

Background: The GISSI-HF study showed that dietary supplementation with ω-3 polyunsaturated fatty acids from fish (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), improves survival in patients with chronic congestive heart failure. EPA and DHA are incorporated into the cardiac membrane phospholipids where they exert metabolic and anti-inflammatory effects. It is unknown whether high dietary fat intake competitively displaces ω-3 PUFA in myocyte membranes, consequently inhibiting downstream beneficial effects.
Methods: We assessed the development of LV hypertrophy and pathology in rats subjected to aortic banding randomized to a diets consisting of (1) standard diet [14% of energy from fat] (2) standard diet + ω-3 PUFA [2.3% of energy intake as EPA+DHA], (3) high fat [60% fat]; or (4) high fat + EPA+DHA. Echocardiography was performed at 7 weeks, and tissue harvested at 8 weeks.
Results: Aortic banding increased LV mass in both diets without EPA+DHA (standard diet: 40%, P < 0.001; high fat diet: 43%, P <0.001). Treatment with EPA+DHA limited left ventricular hypertrophy in animals on the high in carbohydrate diet (4% increase), but not in those receiving diets high in fat (36% increase). Banding up-regulated expression of the fetal gene MHCβ (P < 0.001) and ANF (P < 0.001), which was significantly blunted by treatment with EPA+DHA (P = 0.003 and 0.033, respectively) in animals receiving diets high in carbohydrates, but increased expression MHCβ (P = 0.009) and ANF (P = 0.003) in animals consuming diets high in fat. Regardless of diet composition or surgical banding, supplementation increased EPA and DHA and decreased arachidonic acid in cardiac membrane phospholipids (all P's <0.001).
Conclusion: The cardioprotective effects of EPA+DHA on ventricular hypertrophy and expression of MHCβ and ANF are limited in rats fed diets high in fat, despite incorporation of EPA and DHA into the cardiac cell membranes.

9:30 a.m.

1015-191 Cardiorenal Actions of New Designer Natriuretic Peptide CD-NP in Experimental Heart Failure

Ondrej J. Lisy, Horng H. Chen, John C. Burnett, Jr., Mayo Clinic and Mayo Clinic College of Medicine, Rochester, MN

Background: Our aim was to define for the first time biological actions of a new designer natriuretic peptide CD-NP in a model of experimental heart failure (HF). We recently reported design, synthesis and potent biological actions of a designer peptide CD-NP which combines vascular and antiproliferative actions of C-type natriuretic peptide (CNP) with natriuretic, diuretic and cardiac unloading properties of newly discovered Dendroaspis natriuretic peptide (DNP).
Methods: Hemodynamic, renal, and hormonal parameters were obtained prior (Baseline), during and after (Recovery) intravenous infusion of 100 ng/kg/min of CD-NP in a canine model of chronic HF produced by rapid ventricular pacing (n=6). * p<0.05 vs. Baseline.
Results: CD-NP decreased right atrial pressure (from Baseline 2.9±0.7 to 2.1±0.9* and Recovery 3.5±0.9* mmHg), wedge pressure (from 11±1 to 9±1*and Recovery 12±1 mmHg) with a mild decrease in MAP (from Baseline 109±9 to 100±8* and Recovery 105±8 mmHg). CD-NP increased GFR (from 30±3 to 54±7* and Recovery 37±4 ml/min) and RBF (from 185±13 to 226±20* and Recovery 203±23 ml/min) and also produced significant natriuresis (UNaV from 5±2 to 96±35* and Recovery 60±17 μEq/min) and diuresis (UV from 0.1±0.0 to 1.3±0.6* and Recovery 0.6±0.2 ml/min). Distal fractional reabsorption of sodium decreased (DFRNa from 99±0 to 96±1* and Recovery 96±1* %) localizing the tubular actions of CD-NP to the distal nephron. These actions were associated with increase in plasma cGMP (from 15.8±2.6 to 36.1±4.3* and Recovery 26.1±5.3* pmol/ml) and urinary cGMP. CD-NP infusion was also associated with a marked decrease in plasma renin activity (from 16.6±3.4 to 4.8±2.1* and Recovery 8.4±3.1 ng/ml/hr).
Conclusions: Our study demonstrates that the new designer peptide CD-NP has cardiac unloading, natriuretic, diuretic and GFR enhancing properties together with a suppression of renin release with mild effects on blood pressure in an experimental model of HF. These beneficial properties warrant further evaluation of this designer peptide in a human HF.

9:30 a.m.

1015-192 Left Ventricular Torsion and Untwisting Are Correlated With Left Ventricular End-Diastolic Pressure: A Simultaneous Catheterization and Two-Dimensional STE

Sung-Ji Park, Rick A. Nishimura, Paul Sorajja, Barry A. Borlaug, GyeongSang National University Hospital, Jinju, South Korea, Mayo Clinic, Rochester, MN

Background: Left ventricular torsion (LVtor) and untwisting have been shown to be integral in systolic and diastolic mechanics of the heart.Our earlier study showed that LVtor surprisingly increases in patients with mild diastolic dysfunction and normal systolic function before decreases with worsening of diastolic function. We hypothesized that, LV torsion is dependent on filling pressure. However, there is limited information about relationship between LVtor and invasive hemodynamic parameters. The aim of this study was to evaluate the correlation between LVtor-derived parameters and invasive high-fidelity LV hemodynamic parameters.
Methods: Forty-three consecutive patients (age: 61.6±14.6 years, female 20) underwent simultaneous echocardiographic imaging (Toshiba Apolio XG) and LV pressure measurements (7F Millar catheters). All had normal ejection fraction (62.7±10.2%).
Results: Peak LV torsion was significantly correlated with LV end-diastolic pressure (LVEDP: r =-0.474, P=0.0013). Twisting rate and untwisting rate were significantly correlated with LVEDP (r =-0.426, P=0.0044, r =0.4562, P=0.0021, respectively). Close correlation were found between peak negative dp/dt and LVtor (r =-0.365, P=0.0161).
Conclusions: Higher LV torsion, TR and UTR are significantly correlated with lower LVEDP. LVtor-derived parameters are good correlated with LVEDP than conventional Doppler parameters. This finding gives additional hemodynamic insight in LV torsion and untwisting.

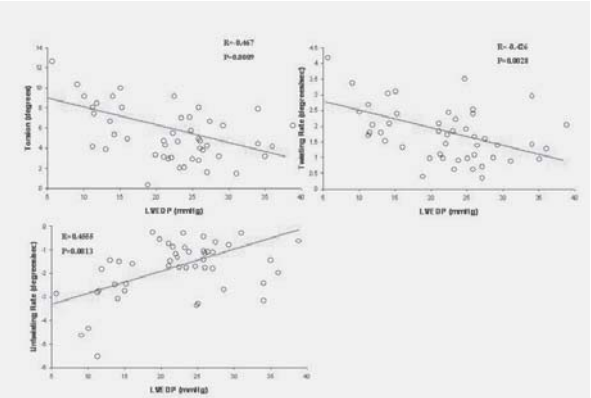


Figure 1. The correlation between LV torsion, TR and UTR and LVEDP.

9:30 a.m.

1015-193 Does Adverse Cardiac Remodelling Contribute to Clozapine-Induced Cardiac Injury?

Rachel Denver, Bing Wang, Jennifer Cooke, Gary Gordon, Paul Katz, Gishel New, Henry Krum, Box Hill Hospital, Box Hill, Australia, Monash University, Alfred Hospital, Prahran, Australia

Background: Clozapine is an atypical antipsychotic used for treatment-refractory schizophrenia. Despite its favourable side effect profile, clozapine may be associated with fatal cardiac sequelae. Myocarditis and dilated cardiomyopathy are estimated to occur in up to 8.5% and 0.1% of clozapine patients respectively. The mechanisms of cardiac injury are largely unknown. We examined the effect of clozapine on markers of cardiac remodelling in our *in vitro* model of human cardiac fibroblasts (VFs).
Methods: VFs were isolated from the left ventricle of explanted human hearts. Cells at passage 3-5 were seeded at medium density in 6- or 12-well plates for mRNA and proline analyses respectively, and rested for 24 hours. VFs were serum deprived for 48 hours then stimulated with clozapine (10nM to 10μM) or olanzapine (1nM to 1μM), a similar atypical antipsychotic not associated with cardiac injury. In separate experiments, the effect of clozapine on TGFβ_1 (60pM) stimulated collagen production by VFs was also assessed. Cells were harvested at 6-48 hours. Exogenous collagen production was estimated by incorporation of [^{3}H]-proline. Real-time PCR was used to quantitate α_1(I)-procollagen mRNA, CTGF mRNA and 18S rRNA. Unstimulated cells served as controls.
Results: Clozapine reduced basal collagen synthesis by VFs in a dose-dependant manner (p<0.001), maximal at 10μM with a 47% reduction in [^{3}H]-proline incorporation (p<0.001). TGFβ_1 stimulated collagen synthesis (195% of controls, p<0.001) was reduced to unstimulated levels with 10μM clozapine (p<0.001). Olanzapine had no effect on basal or stimulated collagen synthesis. α_1(I)-procollagen mRNA was reduced in a time dependent manner with clozapine treatment, maximal at 48 hours (48% of controls, p<0.001). CTGF mRNA was reduced by 38% at 6 hours (p<0.005) and 60% at 12 hours (p<0.001). VF viability was not affected by either antipsychotic.
Conclusion: Clozapine reduces basal and stimulated collagen synthesis and transcription in human VFs. Reduced production of fibrillar collagen with clozapine treatment may disrupt the myocardial collagen network, leading to slippage of cardiac myocytes and subsequent chamber dilation and systolic dysfunction.

9:30 a.m.

1015-194 Donepezil: An Acetylcholinesterase Inhibitor Against Alzheimer's Dementia, Prevents Remodeling and Improves Survival in Volume Overload Heart Failure Mice

Takemi Handa, Takayuki Sato, Yoshihiko Kakinuma, Mikihiko Arikawa, Shiro Sasaguri, Kochi Medical School, Nankoku, Kochi, Japan

Background: We previously reported that chronic Vagal nerve stimulation (VNS) markedly improved long-term survival after large myocardial infarction in rats through cardioprotective effects of Ach, a neurotransmitter at cardiac nerve endings. However, such an approach is invasive and its safety is unknown in clinical settings. To develop an alternative therapy with a clinical available drug, we examined the chronic effect of oral donepezil (DNP) on cardiac remodeling and survival with a mouse model of volume-overload heart failure (CHF).
Methods: The care and use of the animals were in strict accordance with the guiding principles of the Physiological Society of Japan. Four weeks after the surgery of aortocaval shunt, CHF mice were randomly assigned to untreated and DNP-treated groups. DNP was given at a dosage of 5 mg/kg/day. The dosage was selected without the bradycardiac effect. At the end of 4-week treatment, we evaluated left-ventricular (LV) pressure-volume relationships of Langendorff perfused hearts and LV function of in-situ hearts.
Results: When compared to the untreated group (n=20), the DNP-treated group (n=20) had significantly low LV end-diastolic pressures (EDP) and high end-systolic pressures in the operating range of in situ LV volumes (Ees: 0.98±0.03 vs 1.12±0.05 mmHg/μL, p<0.05). DNP significantly reduced the volume intercept of ESPVR (V0: 3.22±0.28 vs 1.44±0.33 μL, p<0.05), and heart weight (6.14±0.16 vs 5.68±0.17mg/g, p<0.05). And EDP was significantly lower (10.2±1.6 vs 14.9±0.8 mmHg, p<0.05), dp/dt max was significantly higher (5961±562 vs 4506±997 mmHg/s, p<0.05) in in-situ hearts. There were 13 survivors among 24 untreated mice, 22 survivors among 27 treated mice during 100-day treatment (54% vs 81%, p<0.05). In CHF mice, donepezil augmented ANP (1.85±0.11 vs 2.93±0.12, p<0.05), lowered BNP (5.55±0.83 vs 3.66±0.57, p<0.05). In vitro study, DNP upregulated ANP in HL-1 cells.
Conclusions: Our findings suggest that the upregulatory effect of DNP on ANP terminates the vicious circle of maladaptation in CHF through the natriuretic actions and that the hemodynamic improvement suppressed an increase in ventricular BNP mRNA. DNP improved cardiac remodeling and survival.

9:30 a.m.

1015-195 Alpha-Adrenergic Stimulation Increases Myocardial Distensibility Through PKC Activation in Health and Disease

Ana Patrícia Fontes-Sousa, Carmen Brás-Silva, Vera Monteiro-Cardoso, Nádia Pereira-Gonçalves, Luisa Lopes-Conceição, Adelino F. Leite-Moreira, Department of Physiology, Faculty of Medicine, Porto, Portugal

Bachground: Alpha$_1$-adrenoceptor (AR) stimulation has an important role in the regulation of cardiac function. Some neurohumoral agents acutely decrease myocardial stiffness, effect that could be altered in heart failure (HF). The present study was designed to determine the, yet unknown, acute effects of phenylephrine (FE), an alpha$_1$-AR agonist, on the diastolic properties of the myocardium in healthy rabbits and in the model of doxorubicin-induced HF.
Methods: Effects of increasing doses of FE ($3*10^{-7}$-10^{-4}M) were studied in papillary muscles of normal rabbits with (i) intact endocardial endothelium (control group), and in the presence of (ii) damaged endocardial endothelium (EE) (iii) NO synthase inhibitor, N^G-Nitro-L-Arginine (L-NNA; 10^{-5} M) and (iv) PKC inhibitor, chelerythrine (CHE; 10^{-5}M). Papillary muscles from rabbits injected with doxorubicin were also evaluated (HF group). Calculated parameters: passive tension (PT), active tension (AT), maximum velocity of tension rise and decline (dT/dt_{max} and dT/dt_{min}, respectively) and muscle length. Results presented as mean±SEM (p<0.05).
Results: FE induced concentration-dependent positive inotropic and lusitropic effects, with 10^{-4}M promoting an increase of 117.5±25.3% AT, 142.4±28.7% dT/dt_{max}, and 96.6±22.5% dT/dt_{min}. The same concentration of FE induced a significant increase on muscular length of 1.013±0.003 L/L_{max}, which corresponds to a 28±6% decrease of PT and represents a decrease of myocardial stiffness. This later effect was abolished by the inhibitor of PKC, while the other experimental protocols did not change any of the myocardial effects. Additionally, all the effects induced by FE were maintained in HF group.
Conclusion: The present study demonstrated that alpha$_1$-adrenergic stimulation promotes an increase of myocardial distensibility, modulated by the activation of PKC. On the other hand, this effect occurs even after EE removal, is independent of nitric oxide release and is preserved in HF, which might have important pathophysiologic implications in this syndrome where EE dysfunction occurs.

9:30 a.m.

1015-196 Eplerenone Attenuates Atrial Remodeling and Abolishes the Vulnerability to Induced Atrial Fibrillation in Experimental Heart Failure

Gordon W. Moe, Andrea Konig, George O. Naik, Andrew Ramadeen, Paul Dorian, St. Michael's Hospital, Toronto, ON, Canada

Background: Structural remodeling is a substrate for abnormal atrial mechanical function and the development of atrial fibrillation (AF) in the setting of heart failure (HF). Aldosterone is a key player in vascular pathology but its role in atrial remodeling and AF has not been elucidated. We therefore tested the hypothesis that aldosterone played a role in the development of atrial remodeling and AF by studying the effect of aldosterone inhibition in a novel dog model of atrial remodeling and AF in the setting of HF.
Methods: Mongrel dogs were randomized to 1) controls without pacing (CTRL, n=5), 2) simultaneous atrioventricular pacing (SAVP) for 2 weeks (SAVP, n=9) and 3) SAVP and treatment with eplerenone 10 mg/kg twice daily orally (SAVP-Epl, n=9).
Results: Data for LA pressure (LAP); LA area and shortening fraction from ultrasound (LA area and LAFS); measures of vulnerability to AF from rapid atrial stimulation; tissue collagen area fraction (CAF) (Picrosirius stain) and matrix metalloproteinase-9 (MMP-9) activity (gelatin zymography) are shown in the table.

	CTRL	SAVP	SAVP-Epl
LAP (mm Hg)	10±1	21±3*	16±2*†
LAA (cm2/kg body weight)	0.35±0.01	0.59±0.04*	0.55±0.03*†
LASF (%)	25±3	12±2*	18±2*†
Burst attempts leading to AF (%)	3.2 ± 1.8	20 ± 5*	3.2 ± 1.2†
Median AF duration (s)	191	1932*	504†
Collagen area fraction (%)	7±1	13±1*	10±1*†
MMP-9 (% of controls)	-	452±43	249±23†

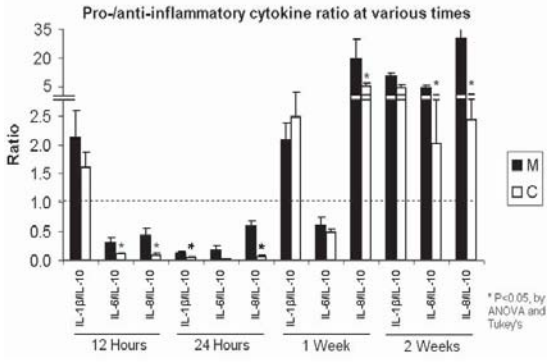
* p <0.05 vs. CTRL; † p <0.05 vs. SAVP
Eplerenone attenuated the LA chamber dilatation and partially restored the impaired function while abolishing the AF induced by SAVP. This was accompanied by a marked reduction in fibrosis and MMP activation in the LA.
Conclusion: Aldosterone plays a key role in mediating atrial remodeling and AF and may provide a novel therapeutic target against heart failure related arrhythmias.

9:30 a.m.

1015-197 The Salutary Paracrine Effects of Antiinflammatory Cytokines May Play a Role in Cellular Cardiomyoplasty Using Mesenchymal Stem Cells

Guangyong Chen, Madhur Nayan, Minh Duong, Juan-Francisco Asenjo, Yin Ge, Ray C-J Chiu, Dominique Shum-Tim, McGill University Health Centre, Montreal, Canada

Background: Mesenchymal stem cells (MSCs) have been explored to treat myocardial infarction (MI) and heart failure, but the mechanism remains controversial. We hypothesized that changes in the pro-/anti-inflammatory cytokine ratio after MSCs therapy may improve cardiac function following MI.
Methods: 88 rats with coronary artery ligations were injected with culture media (Grp M) or MSCs (Grp C). All rats underwent echocardiography to assess left ventricular ejection fraction (LVEF). Gene expression of IL-1β, IL-6, IL-8 (pro-inflammatory) and IL-10 (anti-inflammatory) was quantified by Real-time PCR. Extra-cellular matrix (ECM) deposition, inflammatory cell infiltration and the ratio of matrix metallopeptidase 2 (MMP2) to metallopeptidase inhibitor 1 (TIMP1) were also analyzed.
Results: The ratio of pro-/anti-inflammatory cytokine gene expression (fig1) was significantly decreased in Grp C with times. In Grp C, LVEF improved significantly (M=57% vs C=75% at 1 wk*, M=52% vs C=70% at 2 wks*, *p<0.01); ECM deposition was significantly lower (M=19.3% vs C=9.3% at 1 wk*, M=24.4% vs C=7.5% at 2 wks*, *p<0.01); Inflammatory cell infiltration decreased after 24 hrs (C=1.7 vs M=2.1 at 1 wk, and C=0.9 vs M=1.7 at 2 wks, p<0.05); MMP2/TIMP1 ratio was lower at 12 and 24 hrs, and 2 wks (0.40-, 0.51- and 0.39-fold, p< 0.05).
Conclusions: Our data showed that MSCs therapy decreases the pro-/anti-inflammatory cytokine ratio in the infarct microenvironment. This may explain the early functional improvement after MI.



9:30 a.m.

1015-198 Different Mechanisms of Myocardial Insulin Resistance in the Diabetic and Failing Heart

Christina Kleinert, Stuart A. Cook, Anabel Varela-Carver, Takashi Matsui, Saumya Das, Ornella E. Rimoldi, Anthony Rosenzweig, Paolo G. Camici, Medical Research Council, Clinical Sciences Centre, London, United Kingdom, Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, MA

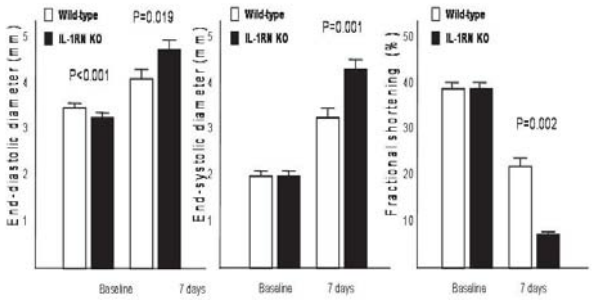
Background: Whole body and myocardial insulin resistance are features of type 2 diabetes mellitus (T2DM) and left ventricular dysfunction (LVD) in non-diabetic patients. The aim of the study was to determine whether abnormalities of insulin receptor substrate-1 (IRS1), different members of the PI3 kinase (PI3K) pathway and glucose transporter 4 (GLUT4) contribute to myocardial insulin resistance in these two disease states.
Methods: In patients awaiting cardiac surgery whole body and myocardial glucose uptake was measured using positron emission tomography and euglycemic-hyperinsulinemic clamp. Myocardial biopsies were used to examine IRS1-PI3K activity and protein expression levels of different members of the PI3K pathway. Additionally, GLUT4 expression was studied in cytosolic, intracellular vesicular pools and sarcolemmal fractions by sucrose gradient purification. In parallel, we examined the same parameters in leptin-deficient, insulin resistant *ob/ob* mouse hearts and a mouse model of LVD.
Results: Patients with T2DM or LVD had lower whole body and myocardial glucose utilization compared to controls. Myocardial IRS1-PI3K activity was significantly increased in both groups, while an increase in Akt activity was only seen in T2DM. Additionally, both PTEN and GLUT4 expression was decreased in T2DM (45.19%±26.29% for PTEN and 71.8±5.13%, *P*=0.012 for GLUT4, n=3) compared to controls. However, a significant increase in GLUT4 expression in patients with LVD (42.78±13.16%, *P*=0.01, n=4) compared to controls was observed. In the *ob/ob* mouse heart GLUT4 expression at the sarcolemma was also significantly reduced compared to controls but increased in the LVD model.
Conclusions: We observed a strong activation of IRS1-PI3K, elevated Akt and PTEN activity and diminished expression of GLUT4 at the sarcolemma in T2DM patients and diabetic mouse. However, in patients with LVD as well as in the mouse model of LV dysfunction, intermediate IRS1-PI3K activity, no increase in Akt activity but an increase in PTEN expression and GLUT4 at the sarcolemma under basal conditions was observed. Thus, we conclude that the mechanism underlying myocardial insulin resistance is different between T2DM and LVD.

9:30 a.m.

1015-199 Endogenous Interleukin-1 Receptor Antagonist Protects Against Severe Adverse Cardiac Remodeling After Acute Myocardial Infarction

Fadi N. Salloum, Nicholas N. Hoke, Amit Varma, Benjamin Van Tassell, Stefano Toldo, Vinh Q. Chau, Elena Vecile, Aldo Dobrina, Antonio Abbate, Virginia Commonwealth University Pauley Heart Center, Richmond, VA

Background: Interleukin-1 receptor antagonist (IL-1Ra) is a naturally occurring anti-inflammatory protein with anti-apoptotic activity. We hypothesized that knock-out (KO) mice lacking the IL-1Ra gene (IL-1RN -/-) may be at increased risk for adverse cardiac remodeling after acute myocardial infarction (AMI) due to lack of the protective effects of IL-1Ra.
Methods: Seven IL-1RN -/- mice and 8 age-matched wild-type (WT) mice with the same genetic background underwent surgical coronary artery ligation. All animals underwent transthoracic echocardiography before surgery and at day 7. Infarct size and cardiomyocyte apoptosis were measured using collagen staining and in situ detection of DNA fragmentation, respectively.
Results: Seven days after AMI, KO mice showed increased left ventricular (LV) end-diastolic diameter and LV end-systolic diameter with reduced fractional shortening vs WT mice [Figure]. An average of 5 aneurysmatic segments were seen in the KO mice vs 1 segment in the WT mouse (p=0.010). KO mice also had a significantly larger area of scar (35±2% vs 23±2%,p=0.009) and significantly greater cardiomyocyte apoptosis both in the peri-infarct myocardium (9.5±2.2% vs 1.9±0.1%, p=0.022) and remote myocardium (0.3±0.2% vs 0%, p=0.014) compared to WT mice.
Conclusions: IL-1Ra plays a protective role in the myocardium during AMI by preventing cell death, ensuing adverse cardiac remodeling and aneurysm formation.



9:30 a.m.

1015-200 Intracoronary Injection of Autologous Bone Marrow Mononuclear Cells Plus Granulocyte Colony Stimulating Factor Therapy or Granulocyte Colony Stimulating Factor Alone Improve Chagas' Chronic Heart Failure

Valeria B. Carvalho, Ricardo R. Santos, Carlos Eduardo S. Silva, Silvano Wendel Neto, Antonio Esteves Filho, Milton Godoy, Enis D. Silva, Vicente Amato Neto, Gilson S. Feitosa, Radi Macruz, Antonio Carlos C. Carvalho, Hospital Sirio Libanes, Sao Paulo, Brazil, FIOCRUZ, Bahia, Brazil

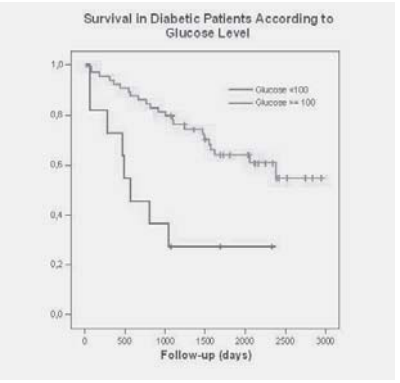
Background: Autologous bone marrow mononuclear cells (ABMMC) transplantation followed by Granulocyte Colony Stimulating Factor (G-CSF) therapy has been effective in Chagas` heart failure, but effects of G-CSF alone remain unknown. We sought to compare both therapies, after etiological and optimized medical treatment.
Methods: In a Double Blind study, 14 patients with New York Heart Association (NYHA) class III-IV and left ventricular ejection fraction (LVEF) < 35% were randomly assigned to intracoronary injection of ABMMC (10^8 cells) followed by G-CSF, 5mcg/kg/day, for 5 days (G1) Versus G-CSF alone, in the same dose (G2). Effects were assessed up to one year on LVEF (Simpson's formula), myocardial performance index (MPI) and velocity-time integral of LV outflow tract (VTI) in echocardiogram, also on NYHA class, quality of life, time walked and maximal physical work in treadmill test, arrhythmias in Holter (24 hours) and biochemical parameters. Friedman and Mann-Whitney non-parametric tests were used for statistics.
Results: LVEF changed from 24.9±3.8 to 29±9.3% (p>0.05) in G1 and from 26.4±7.6 to 37.4±5.0 (p=0.019) in G2; MPI and VTI changes were not significantly different in either group, but improvement was greater in G2 Versus G1 (p<0.05); 86% of the patients went to NYHA class I-II in G1, and 100% to class I in G2 (p>0.05). Minnesota Life Quality score, time walked and maximal physical work in treadmill test had prominent improvement in G1 and G2 (p<0.05). No significant differences were seen in arrhythmias, serum Na or BNP in either group, but BNP tended to increase in G1 and to decrease in G2. Overall data presented no differences in G1 Versus G2, except in MPI and VTI improvement in G2.
Conclusions: Clinical benefits of the therapies, within the regimens used, were similar, although significant cardiac function improvement was shown with G-CSF alone. Given its easy employment, G-CSF offers great potential use for cardiac repair in Chagas' disease.

9:30 a.m.

1015-201 **Prospective Study of the Influence of Fasting Glucose Level on Mortality of Patients With Heart Failure**

Victor S. Issa, Alexandre Amaral, Fatima D. Cruz, Guilherme V. Guimarães, Silvia MA Ferreira, Edimar A. Bocchi, Heart Institute (InCor) University of São Paulo Medical School, São Paulo, Brazil

Background: glucose level is associated with cardiovascular events in patients with diabetes. However, recent findings have identified a harmful effect of intensive glucose lowering. As conflicting data report on the role of glucose level in heart failure (HF) we tested the association between glucose level and mortality in HF patients.
Methods: 457 patients were prospectively followed from September 1999 through December 2007; ages ranged from 18 to 83 (50.3±11.5) years, 322 (70.5%) patients were male and 135 (29.5%) female; 142 (31%) were in NYHA III-IV, mean left-ventricle ejection fraction was 0.36±0.1, and 78 (17.1%) were diabetic.
Results: Death occurred in 202 (44.2%) patients and 27 (5.9%) were submitted to heart transplantation. Mean glucose was 110±7 mg/dL, and 254 (55.6%) had glucose ≥ 100. In diabetic patients, glucose level ≥ 100 was associated better survival free from death/transplant(LogRank 0.0006). In Cox Regression model including age, sodium, creatinine, ejection fraction and NYHA status, presence of glucose ≥ 100 was associated with better survival (p<0.001). No association between glucose and mortality was found in non-diabetic patients
Conclusions: hyperglycemia was frequent in HF patients, and lower glucose levels in diabetic patients were associated with increased mortality. Our findings identify a previously unknown association between glucose and mortality in diabetic patients with HF, and suggest that current treatment targets in this setting should be reviewed.



9:30 a.m.

1015-202 **Anthracycline Chemotherapy Impairs Left Ventricular Diastolic Function in Lung Cancer Survivors**

Dan Radulescu, Sorin Pripon, Elena Buzdugan, Sorin Dudea, Valer Donca, Laurentiu Stoicescu, Maria L. Radulescu, Andreea Parv, Gavril Saplacan, Gheorghe Sebestyen, Marian Mihaiu, Constantin Cosma, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania, Cardiology Department, 5th Medical Clinic, Municipal Hospital, Cluj-Napoca, Romania

Background: Anthracycline-induced alteration of the left ventricular (LV) performance is a serious consequence of chemotherapy in cancer patients. Epirubicin, a less cardiotoxic anthracycline isomer was less studied in this respect.
Methods: Forty-six patients with lung cancer, treated with a chemotherapy protocol containing epirubicin in low doses (mean cumulative dose 450 mg/m^2), associated with cyclophosphamide and vincristine (study group) and a gender and age-matched control group of 46 lung cancer patients who had not started oncologic treatment yet, were assessed by Doppler echocardiography. LV diastolic function was evaluated by measuring the transmitral inflow indices: maximal velocity of the E and A waves, E/A ratio, E wave pressure half time (PHT) and isovolumic relaxation time (IVRT). LV ejection fraction (LVEF) was also assessed. Analysis of data included between-group comparison of LV performance variations at baseline and at 6 months after treatment completion.
Results: No significant differences between the 2 groups were found at baseline. At 6 months after treatment, an alteration of LV diastolic performance was found in the study group: significant increase of A_{max} with a decrease of E_{max}, prolonged PHT and IVRT. The LVEF was within normal limits in both groups.
Conclusions: Epirubicin chemotherapy, even in low doses in lung cancer patients, alters diastolic filling parameters, impairment due to poor LV compliance, representing an early marker of infraclinical cardiotoxicity.

Echocardiographic parameters in the study and control group (mean ± standard deviation)

Parameter	Study group	Control group	p-value
Amax (cm/s)	56.02±4.66	36.76±8.44	<0.001
Emax (cm/s)	48.24±3.44	68.42±10.88	<0.001
PHT (ms)	67.01±12.44	53.68±12.64	<0.001
IVRT (ms)	97.21±12.20	85.68±12.16	<0.001
LVEF	59.44 ± 6.12	60.14 ± 6.18	NS

9:30 a.m.

1015-203 **Low-Dose β Blocker Therapy Improves Cardiac Function in Patients With Acute Heart Failure Partly Through Correction of Abnormal Intracellular Ca^{2+} Handling**

Shigeki Kobayshi, Takeo Tanaka, Takehisa Susa, Takeshi Suetomi, Makoto Ono, Hitoshi Uchinoumi, Shinichi Okuda, Masahiro Doi, Syuji Kawamura, Takeshi Yamamoto, Masafumi Yano, Masunori Matsuzaki, Yamaguchi University Graduate School of Medicine, Department of Medicine and Clinical Science, Ube, Japan

Background: Altough β blocker is considered to be inappropriate for the treatment of patients with acute heart failure (AHF), low-dose of β blocker, which has modest negative chronotropic (but less inotropic) effect, may improve myocardial performance in these patients. Here, we investigated whether low-dose of β blocker improves cardiac function in human AHF (Protocol 1), and if so, we clarified the cardiprotective mechanism using isolated canine failing cardiomyocytes (Protocol 2).
Methods and Results: In 15 AHF patients (Killip's classification;III(n=2) and IV(n=13), heart rate; 115±15 bpm, LVEF; 23 ±5%, Cardiac index(CI); 2.6±0.5 l/min/m^2, PCWP; 26±8mmHg), who first underwent conventional therapy by milrinon(<0.5 μg/kg/min) or dopamine(<3.0 μg/kg/min), vasodilators, and diuretics, we added landiolol (1.5-6.0 μg/kg/min;i.v., an ultra-short acting β1-selective blocker) to study the effect on hemodynamics. Low-dose of landiolol (1.5-3.0 μg/kg/min) significantly reduced heart rate by11-15% and rate pressure product without changing blood pressure (BP), CI and PCWP, whereas its higher dose (>3.0μg/kg/min) decreased BP and CI, suggesting that optimal (safety) dose of landiolol is 1.5-3.0 μg/kg/min. After the treatment with landiolol (3.0 μg/kg/min), hemodynamic parameters such as transmitral flow pattern, filling time/RR, E/Ea and Tei index were all improved (p<0.01), and interestingly, pulsus alternans, which had been observed in 4 patients, disappeared. For protocol 2, cardiomyocytes were isolated from the LV of canine HF model by 4-week's rapid RV pacing (250 bpm, LVEF 27±5%, n=6). Then, we investigated the effect of landiolol on the intracellular Ca2+ transient (CaT) and cell shortening. In the failing cardiomyocytes, both CaT and cell shortening were markedly impaired as compared with normal cardiomyocytes (p<0.01). After an incubation with low-dose landiolol (10 nM) for 4 hours, both CaT and cell shortening in the failing cardiomyocytes were substantially improved (p<0.01).
Conclusions: Low-dose of β blocker, by suppressing tachycardia and correcting abnormal Ca^{2+} handling, improves cardiac function in patients with AHF with severe LV systolic dysfunction.

9:30 a.m.

1015-204 **Relationship of Left Ventricular Systolic Function to Persistence or Development of Electrocardiographic Strain Pattern in Hypertensive Patients: Implications for the Development of New Heart Failure**

Peter M. Okin, Kristian Wachtell, Eva Gerdts, Kurt Boman, Markku S. Nieminen, Björn Dahlöf, Richard B. Devereux, Weill Cornell Medical College, New York, NY

Background: Persistence or development of ECG strain are associated with an increased risk of new heart failure (HF) compared with regression or continued absence of ECG strain. We postulated that this relationship might be in part mediated via worse left ventricular (LV) systolic function in patients with new and persistent ECG strain.
Methods: Baseline and year-1 ECG strain and LV midwall shortening (MWS) were examined in 725 patients in the LIFE echocardiographic substudy without HF. MWS <14.2% and stress-corrected MWS (scMWS) <89.2% were considered abnormal.
Results: Baseline mean MWS and scMWS were significantly lower in patients with persistent or new strain. Although both MWS and scMWS improved in all groups after 1 year of antihypertensive treatment, persistence or development of ECG strain were associated with significantly lower year-1 mean MWS and scMWS and with higher prevalence and odds of abnormal MWS and scMWS than absence of ECG strain, even after controlling for age, gender, race, treatment, diabetes, history of ischemic heart disease or MI, baseline and change from baseline to year-1 of systolic and diastolic pressure and ECG LVH by Cornell product and Sokolow-Lyon voltage.
Conclusions: Persistence or development of ECG strain during antihypertensive therapy are associated with increased risk of LV systolic dysfunction at baseline and after 1 year follow-up. These findings provide insight into a possible mechanism by which changes in ECG strain are associated with changing risk of HF.

Variable	No Strain Baseline/No Strain Year 1 Absence of Strain (n=603)	Strain Baseline/ No Strain Year 1 Regression of Strain (n=32)	No Strain Baseline/Strain Year 1 Development of New Strain (n=21)	Strain Baseline/ Strain Year 1 Persistence of Strain (n=73)	p value
Baseline MWS (%)	15.8±2.0	15.5±1.8	14.0±1.6	14.3±2.3	<0.001
Year-1 MWS (%)	16.8±1.8	16.4±2.3	15.7±1.7	15.6±2.2	<0.001
Year-1 MWS< 14.2% (%)	6.6	18.8	23.8	27.4	<0.001
Year-1 univariate odds ratio of MWS<14.2% (95% CI)	1	3.3 (1.3-8.4)	4.4 (1.5-12.6)	5.3 (2.9-9.7)	<0.001
Year-1 multivariate odds ratio of MWS<14.2% (95% CI)	1	2.8 (1.1-7.5)	4.0 (1.4-11.6)	3.7 (1.9-7.2)	<0.001
Baseline scMWS (%)	98.5±12.3	97.3±10.7	88.0±10.3	91.6±16.0	<0.001
Year-1 scMWS (%)	103.5±10.6	103.0±14.2	98.7±10.9	97.6±14.6	<0.001
Year-1 scMWS< 89.2% (%)	7.9	13.8	26.3	29.4	<0.001
Year-1 univariate odds ratio of scMWS<89.2% (95% CI)	1	1.9 (0.6-5.6)	4.2 (1.4-12.1)	4.9 (2.7-8.9)	<0.001
Year-1 multivariate odds ratio of scMWS<89.2% (95% CI)	1	1.4 (0.4-4.4)	3.1 (1.0-9.5)	3.7 (1.9-7.2)	0.001

9:30 a.m.

1015-205 **Occurrence of Hopitalization in Relation to Time of Follow-Up in Older Patients With Advanced Systolic Heart Failure Treated With Rosuvastatin: Experiences From the CORONA Trial**

Finn Waagstein, Peter Dunselman, Ake Hjalmarson, John Kjekshus, John JV McMurray, Hans Wedel, John Wikstrand, Wallenberg Laboratory, Gothenburg, Sweden

Background The CORONA trial in ischemic systolic heart failure with rosuvastatin (R) versus placebo (P) included only patients without statin indication. We analyzed if baseline NT-proBNP could predict effect.
Methods Table shows numbers of hospitalizations for cardivoascular and worsening heart failure reasons.Primary composite endpoint (PCE) of nonfatal myocardial infarction or stroke or CV death (time to first event) was analyzed after 12 and 24 months of FU.
Results After 12 months 297 patients in the P group had suffered a PCE compared to 265 Pts in the R group (HR 0.88 CI 0.75-1.04 p=0.13); after 24 months was 544 vs. 487 Pts (HR 0.88 CI 0.78-0.99 p=0.034); end of study data 732 vs. 692 Pts (HR 0.92 p= 0.12).

Follow-up time	Total n of CV hospitaizations		Total n of WHF hospitalizations	
	Placebo/Rosuvastastin	Difference	Placebo/Rosuvastastin	Difference
6 months	486/414	-72	219/233	+14
12 months	953/849	-104	455/452	-3
18 months	1399/1220	-179	697/635	-32
24 months	1856/1619	-237	931/834	-97
30 months	2243/1924	-319	1116/978	-138
36 months	2489/2117	-372	1254/1070	-184

The effect on both variables was strongest among patients in the lowest baseline tertile for NT-proBNP CV-H -33 %, p=0.009 and WHF-H -55%, p=0.0002. Less percentage effects but no harm were seen in upper two tertiles.
Conclusion Data suggest de NOVO use of R in pts with ischemic systolic heart failure. Selection of heart failure patients for therapy may be based on biochemical baseline variables such as NTproBNP.

ACC.POSTER CONTRIBUTIONS

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Myocardial Function/Heart Failure--Clinical Pharmacological Treatment

Sunday, March 29, 2009, 1:30 p.m.-4:30 p.m.
Orange County Convention Center, West Hall D

3:30 p.m.

1024-165 **Risk of Heart Failure and Peripheral Edema in Patients With Pre-Diabetes and Type 2 Diabetes With Use of Thiazolidinediones (TZD): A Systematic Review and Meta-Analysis of Placebo-Controlled Randomized Clinical Trials**

Anitha Rajamanickam, Ali Usmani, Amir Moheet, Abdul Rashid, Christina Heckathorn, Adrian V. Hernandez, Cleveland Clinic, Cleveland, OH

Background: A recent meta-analysis of randomized trials demonstrated a higher risk of heart failure (HF) with >12 month use of thiazolidinediones (TZDs) in comparison to an active control or placebo in patients with pre-diabetes and type 2 diabetes (DM-2). However, this effect may have been diluted by including active comparators, and the consistency of the risks was not explored with different methods. We quantified the risks of HF and peripheral edema with TZD usage in placebo-controlled trials of adult patients with pre-diabetes and DM-2.
Methods: We performed a systematic review and meta-analysis of published double-blind, placebo-controlled randomized trials that evaluated the effect of TZDs (roziglitazone [RSG] or pioglitazone [PIO]) on investigator-reported HF and edema. We included English language trials with ≥100 patients, and ≥2 months of follow-up. We quantified the effect of TZDs on HF and edema by using the Mantel-Haenzel (MH) fixed effects model. Heterogeneity of effects across trials was evaluated with Chi Square test, and the associations were shown as Odds Ratios (OR) and 95% confidence intervals (CIs). To evaluate the consistency of the risks we also used the Peto fixed effects and the MH random effects models.
Results: A total of 35 trials (n=22950) were evaluated. TZDs were significantly associated with both HF (TZD 328/6785 (4.8%) vs. placebo 207/6413 (3.2%), OR_{MH} 1.62; 95% CI, 1.35-1.94; p<0.00001), and edema (1457/12856 (11.3%) vs. 688/9597 (7.2%), OR_{MH} 2.04; 1.85-2.26; p<0.00001). There was no evidence of heterogeneity of HF risks across trials (p=0.6), but heterogeneity of edema risks was significant (p=0.0007). Both RSG and PIO were independently associated with HF and edema: the risk of HF was higher with RSG than with PIO (OR_{MH} 3.40; 1.94-5.94 vs. 1.49; 1.24-1.80, p=0.006), but the risk of edema was similar between PSG and PIO. HF and edema risks from the Peto and MH random effects models were consistent with the ones from the MH fixed effects model.
Conclusion: TZD therapy in adult patients with pre-diabetes and DM-2 is significantly associated with higher risk of HF and edema. The risk of HF is higher with RSG than with PIO, although the risk of edema was similar between these drugs.

3:30 p.m.

1024-166 **Intravenous Iron Is Safe and Equally as Efficient as Darbepoetin Alpha for the Treatment of Anemia in Advanced Heart Failure**

Elisabeth Kaldara, John Terrovitis, John Kanakakis, Stavros Drakos, Argyris Ntalianis, Evangelos Repasos, Vasiliki Kontopidi, Despoina Barmparousi, John Nanas, 3rd Department of Cardiology, University of Athens School of Medicine, Athens, Greece

Background. Anemia is as a frequent and important co-morbidity in heart failure, associated with worse prognosis. Suppression of hematopoiesis, due to cytokine excess, has been considered as the main etiologic factor, however recently the prevalence of iron deficiency has been increasingly recognized. It is not known if the bone marrow of severely sick patients will demonstrate normal response to iron supplementation alone or concomitant use of erythropoietin stimulating agents (ESA) is needed.
Purpose. To investigate the optimal treatment strategy in patients with advanced heart failure, anemia and iron deficiency.
Methods. Twenty four patients, 56±1 yrs with advanced heart failure (NYHA class III or IV, EF<35%), anemia (hemoglobin-Hb-<12g/dl for men and <11.5g/dl for women) and iron deficiency (diagnosed by bone marrow aspiration and absence of iron in the erythroblasts) were randomized in two groups: Group A (n=12), was treated with IV intravenous iron sucrose alone (300mg) and Group B (n=12), treated with darbepoetin alpha (50μg weekly) and intravenous iron for 6 weeks. Patients were followed for 3 months.
Results. There were no differences in patients' baseline characteristics, between the two groups (NYHA: 3.5±0.5 vs 3.6±0.5, p=0.698, EF:25.8±9.4 vs 22.6±7.2, p=0.354, Hb:10.5±1.1vs10.5±0.7, p=0.88, creatinine:1.4±0.7 vs 1.7±0.9, p=0.459, for Group A and B, respectively). At 3 months, there was no difference in patients' functional class (2±0.6 vs 2.4±0.8, p=0.308) and EF (31.5±12.9 vs 28.9±7.5, p=0.64, for Group A and B respectively). Erythropoietic response started as early as two weeks from treatment initiation in both groups. At completion of treatment, Hb increased to 12.5±0.9.in Group A (p=0.001) and to 12.7±1.6 in Group B (p=0.001). The increase in Hb was similar in both groups (2.1±0.9 vs 2.3±1.4, p=0.822, for group A and B).
Conclusion. Iron supplementation alone is effective for patients with advanced heart failure, anemia and iron deficiency. In patients with severe heart failure and well documented iron deficiency, the bone marrow response to intravenously administered iron remains adequate and there is no need for additional ESA treatment

3:30 p.m.

1024-167 **Long-Term Adherence to Evidence-Based Care and Outcomes of Black and Whites With Heart Failure: A Review of the UT Southwestern Heart Failure Database, 1996-2005**

Faris Araj, David W. Markham, Lynn Fernandez, Brenda S. Thompson, Colby R. Ayers, Parag C. Patel, Pradeep PA Mammen, Mark H. Drazner, Clyde W. Yancy, UT Southwestern Medical Center, Dallas, TX, Baylor University Medical Center, Dallas, TX

Background: Racial disparities in heart failure (HF) include differences in prevalence, morbidity, and mortality. However, data are currently limited regarding the racial differences in quality of care and long-term outcomes in tertiary care HF management programs. We sought to evaluate adherence to evidence-based therapy (EBT) and outcomes in a single center tertiary care disease management program as a function of race.
Methods: We identified 405 patients referred to our HF disease management program between April 1996 and August 2005. Inclusion criteria required a minimum of two outpatient visits and one year follow up. Analyses were performed based on self-reported racial classification. Adherence to EBT was stratified by race, and the use of ISDN-hydralazine was examined before and after November 2004 (release of the A-Heft trial results). All-cause mortality was obtained by a search of the National Death Index.
Results: 109 African American (AA) and 227 white subjects were identified. Mean follow up was 4.8 years. In univariable analysis of the entire database, AA and whites had similar high rates of long term adherence of certain EBT: beta blockers (84% vs. 80%; p=0.4) and ACE-inhibitors (92% vs. 90%; p=0.6); prior to 2004, ISDN-hydralazine in AA vs. whites was 24% vs. 4% (p<0.01). Quality of care improved in both groups over time with excellent rates of long term adherence, especially for AA after 11/2004: beta blockers (82% to 100%), ACE-inhibitors (91% to 100%), and ISDN-hydralazine (24% to 64%, respectively). Multivariable analysis demonstrated that race was not a significant predictor of survival. Long term survival was not significantly different for AA or whites at five year follow up (76% and 75%, respectively; p=0.9).
Conclusions: In a tertiary care HF program, adherence to evidence-based care improved substantially for AA with HF. These data confirm that high rates of adherence with EBT and similar outcomes can be achieved in all patients with HF.

3:30 p.m.

1024-168 **Changes in Ventricular Systolic and Diastolic Function Over Time: Relationship to Incident Heart Failure in the Community**

Garvan C. Kane, Barry L. Karon, Doug W. Mahoney, Steven J. Jacobsen, Margaret M. Redfield, Richard J. Rodeheffer, Mayo Clinic, Rochester, MN

Background - Heart failure (HF) is a progressive disease that becomes increasingly prevalent as the population ages, with over half of patients having a normal left ventricular ejection fraction. Yet longitudinal changes in LV systolic and diastolic function and their relation to incident HF in population-based cohorts is unknown.
Methods - Subjects enrolled in the Olmsted County HF Study (1997-2001), an extensively characterized randomly selected population-based cohort of persons ≥45 years old, were

invited to participate in a follow-up evaluation. A total of 1,402 (69%) subjects returned for clinical and Doppler echo assessment of systolic and diastolic function 4 ± 0.3 years after their initial evaluation. An incident HF diagnosis was identified through medical record review and validated HF with Framingham criteria.

Results - At follow-up, there was a modest increase in mean LVEF, from 63.9 ± 6.6% to 65.9 ± 7.5% (p<0.001). The rates of systolic dysfunction (EF < 50%) remained low and unchanged. By contrast, the prevalence of *any* diastolic dysfunction increased over time, rising from 25.1% to 40.8% (p<0.001) and the prevalence of moderate-severe diastolic dysfunction increased from 9.1% to 18.3% (p<0.001). The prevalence of increased left ventricular filling pressures (E/e'≥10) increased from 25.7% to 56.2% (p<0.001). Factors associated with worsening diastolic function over time included age (p<0.01), female sex (p=0.08) and systemic hypertension (p=0.01). The annual incidence of new validated HF was 0.21% (95% CI, 0.1%-0.4%). 9/12 incident HF cases had an EF > 50% at the 2nd exam. All 12 HF cases had E/e' >10 at the 2nd evaluation with a mean E/e' of 15 ± 6. Factors associated with the development of incident HF included age (p<0.001 - with an incident annual HF rate of 0.73% in those > 75 years of age), incident myocardial infarction (2/12, p<0.05) and diabetes mellitus (4/12, p < 0.01).

Conclusions - Middle aged and elderly community subjects demonstrate significant progression of rates and severity of diastolic dysfunction while rates of systolic dysfunction remaining stable and relatively low. Incident HF occurs predominantly in the setting of normal LVEF and increases with age.

3:30 p.m.

1024-169 Erythropoiesis Stimulating Agents In Heart Failure: A Meta-Analysis Of Clinical Trials

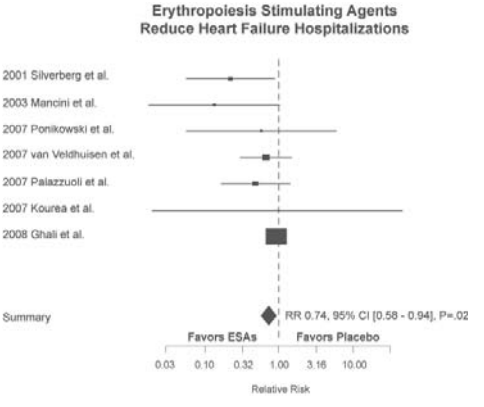
Eiran Z. Gorodeski, Dharam J. Kumbhani, Daniel J. Cantillon, Mazen A. Hanna, Cleveland Clinic, Cleveland, OH

Background: Anemia predicts poor outcomes in heart failure (HF). It is unknown if treatment with erythropoiesis stimulating agents (ESAs) reduces HF hospitalizations, increases thrombotic risks, or improves survival. Prior clinical trials did not primarily examine these end points.

Methods: We performed a pooled analysis of clinical trials that randomized HF patients to ESAs or placebo. We contacted authors where data was unavailable. Efficacy estimates were pooled using fixed effects models.

Results: We included 7 trials, of which 367 patients were randomized to ESAs and 303 to placebo. Ninety-two percent were NYHA class II or higher. Mean baseline hemoglobin was 11 g/dL. The weighted mean duration of follow-up was 9.5 months. There was a significant increase in hemoglobin after treatment with ESAs (Mean change 1.65 g/dL, 95% CI [1.47-1.83], p<.01). The incidence of HF hospitalizations was lower in the ESA group (20.3% vs. 29.7%, RR 0.74, 95% CI [0.58-0.94], p=.02). There was no significant difference in the incidence of death or transplantation (6.5% vs. 6.6%, RR 1.02, 95% [CI 0.6-1.73], p=.95), myocardial infarction (RR 0.86, 95% CI [0.29-2.54], p=.79), or venous thrombosis (RR 0.17, 95% CI [0.03-1.03], p=.054) between the two groups.

Conclusions: ESAs are efficacious (increase hemoglobin, reduce HF hospitalizations) and safe (no increase in mortality, MI, or thrombosis) in HF. Their use in treatment of anemia in HF should be studied in appropriately powered long-term randomized clinical trials.



3:30 p.m.

1024-170 All-Cause Mortality Endpoint Comparison in Large Beta-Blocker Heart Failure Trials: United States (US) Versus Rest of World (ROW)

Christopher M. O'Connor, Bruce Koch, Mona Fiuzat, Gordon Davis, Michael R. Bristow, Duke University Medical Center, Durham, NC, ARCA biopharma, Broomfield, CO

Background: Large randomized, controlled trials have shown that β-blockers reduce mortality by 34-35% in moderate to severe systolic dysfunction heart failure patients (COPERNICUS, MERIT-HF, and CIBIS-II). However, the majority of patients enrolled in these trials were from outside the US (i.e. Rest of World, ROW). BEST, the only intention-to-treat mortality trial which enrolled almost exclusively US patients, showed only a 13% reduction in mortality. We investigated whether or not improvement in survival was different due to enrollment of ROW populations.

Methods: We compared the primary endpoint of all cause mortality and annual placebo mortality rate for the 4 trials.

Results: Table 1.

Clinical Trial/ BB studied	# pts	Total ACM Results & HR	Actual # US Deaths/total (Rel. Risk)	Actual # ROW Deaths/total (Rel. Risk)	US HR's, (C.I.)	ROW HR's (C.I.)
COPERNICUS/ carvedilol	2289 (US=482)	191/1133 P 132/1156 C 0.65 (0.52-0.81) (p=0.0014)	50/233 P 44/249 C (0.82)	141/900 P 88/907 C (0.62)	0.80	0.60
MERIT-HF/ metoprolol	3991 (US =1071)	217/2001 P 145/1990 M 0.66 (0.53-0.81) (p=0.00009)	49/539 P 51/532 M (1.05)	168/1462 P 94/1458 M (0.56)	1.05 (0.71-1.56)	0.55 (0.43-0.70)
CIBIS-II/ bisoprolol	2647 (US=0)	228/1320 P 156/1327 B 0.66 (0.54-0.81) (p<0.0001)	No U.S. pts	228/1320 156/1327 (0.68)	No U.S. Pts	0.66 (0.54-0.81)
BEST/ bucindolol	2708 (US=2645)	439/1354 P 402/1354 B 0.87 (0.76-1.0) (p=0.053)	428/1322 P 391/1323 B (0.91)	11/32 P 11/31 B (1.03)	0.87 (0.76-1.00)	1.53 (0.55-4.30)
All Studies (Relative Risk)	11,635	1075/5808 (19%) P 835/5827 (14%) β-b Tx (0.774)	527/2094 (25.2%) P 486/2104 (23.1%) β-b Tx (0.918)	548/3714 (14.8%) P 349/3755 (9.3%) β-b Tx (0.635)		

Conclusions: The magnitude of beta-blocker (BB) survival effect was either reduced (HR 0.80) or non-existent (HR 1.05) in large US populations included in COPERNICUS and MERIT-HF, respectively. These effects are more comparative to BEST trial results with bucindolol in US patients. Such findings suggest that differences in BB survival benefit observed in clinical trials may be significantly influenced by inclusion of varying geopraphic populations (US vs. ROW).

3:30 p.m.

1024-171 Sleep Apnea Incidence and Outcomes in Heart Failure Patients: A Retrospective Study of Medicare Beneficiaries

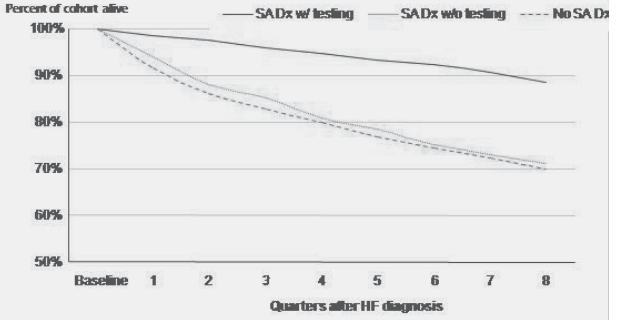
William T. Abraham, Shahrokh Javaheri, The Ohio State University, Columbus, OH

Background: Previous studies showed a high prevalence (40%-60%) of sleep apnea (SA) in patients with heart failure (HF) and that SA has adverse effects on the progression of HF, leading to higher mortality and higher healthcare utilization (HCU). We investigated the incidence, treatment, and outcomes of SA in new onset HF.

Methods: This retrospective cohort study used the 2003-2005 Medicare Standard Analytical Files (SAFs) that contain a 5 percent sample of randomly selected Medicare beneficiaries. The study population included newly diagnosed HF patients in the first quarter of 2004 without prior diagnosis of SA, stratified by SA diagnosis and SA testing status.

Results: Among a final study population of 30,719 newly diagnosed HF patients, only 1,263 (4%) were diagnosed with SA. Of these, 553 (only 2% of the total cohort) received SA testing. Among subjects diagnosed with SA, those tested and diagnosed had higher rates of treatment compared with those not tested and diagnosed (52.4% vs. 15.5%, P<0.001), lower overall mean payment ($42,859 vs. $63,747), and lower all cause mortality (7.8% vs. 26.3%, P<0.001).

Conclusions:SA was under-tested and therefore under-diagnosed in Medicare HF patients during 2004 and 2005. Newly diagnosed HF patients who were diagnosed with SA after testing had higher rates of treatment, lower mortality, and lower overall Medicare costs than HF patients diagnosed with SA without testing and those not diagnosed with SA. These results support SA testing for HF patients.



3:30 p.m.

1024-172 **How Does Exercise Affect Natriuretic Peptides in Heart Failure With Preserved Ejection Fraction?**

Barry A. Borlaug, Carolyn S.P. Lam, Thomas P. Olson, Kelly S. Flood, Bruce D. Johnson, Margaret M. Redfield, Mayo Clinic, Rochester, MN

Background Atrial (ANP) and B-type Natriuretic Peptides (BNP) are released in response to cardiac wall distention, stimulating synthesis of cyclic guanosine monophosphate (cGMP). Elevated BNP is common in Heart Failure with preserved Ejection Fraction (HFpEF), yet little is known regarding acute effects of exercise on natriuretic peptide (NP) signaling in HFpEF.
Objectives To compare basal and exercise (Ex) changes in NP and cGMP levels in patients with HFpEF and hypertensive (HTN) controls.
Methods Age/gender matched subjects with HFpEF (n=21) and HTN (n=19) underwent metabolic Ex testing. ANP, BNP and cGMP levels were measured prior to Ex and at peak. The ratio of A/BNP to cGMP was examined as a surrogate for NP resistance.
Results Exercise performance was impaired in HFpEF (p<0.0001, Table). ANP, BNP and cGMP rose with Ex, while NP/cGMP ratios fell. NP levels were higher in HFpEF at rest and Ex, but there were no differences in the change in ANP, BNP or cGMP between groups, and peak VO2 was not associated with ΔANP, ΔBNP or ΔcGMP (p=NS). BNP/cGMP was higher in HFpEF, while ANP/cGMP was not.
Conclusions ANP, BNP and cGMP levels increase with exercise, while NP/cGMP ratios decrease, suggesting enhanced NP sensitivity and/or alternative sources of cGMP are activated. While HFpEF display elevated resting NP levels compared with HTN, acute changes with exercise are similar and do not predict exercise performance. The ratio of BNP to cGMP is elevated in HFpEF, suggesting BNP resistance is present.

***p<0.05 vs base; †p<0.05 vs HTN; ‡p=0.09 vs HTN**

	Overall		HTN (n=19)		HFpEF (n=21)	
	Base	Ex	Base	Ex	Base	Ex
BNP(pg/ml)	98±84	126±111*	60±50	73±67*	143±94†	204±120†
ANP(pg/ml)	980±690	1110±720*	790±530	850±550	1210±810‡	1590±800*†
cGMP(nmol/L)	8.5±3.9	13.1±5.6*	7.8±2.4	12.0±4.9*	9.3±5.0	14.5±6.3*
BNP/cGMP	10.8±7.6	8.6±6.3*	7.5±5.6	6.0±5.1*	14.6±8.0†	12.6±5.9*†
ANP/cGMP	119±67	85±42*	110±66	78±45*	130±70	100±32*
Peak VO2(ml/min*kg)				18.6±3.7		12.7±3.0†

3:30 p.m.

1024-173 **Gender of Physicians and Patients: Risk Factor for Patients With Chronic Heart Failure?**

Magnus Baumhäkel, Ulrike Müller, Michael Böhm, University Hospital of the Saarland, Homburg, Germany

Background: To determine possible effects of patients' and physicians' gender on medical treatment of chronic heart failure (CHF).
Methods: Consecutive patients (n=1857) with CHF were evaluated regarding co-morbidities, NYHA-classification and current medical treatment as well as dosage of ACE-inhibitors and beta-receptor-blockers. Gender of treating physicians were documented. Multivariable regression analysis to determine association of patients and physicians gender (independent variables) and use of ACE-I and beta-blockers was adjusted to hypertension, coronary heart disease, NYHA-classification, ACE-I/ARB or beta-blocker use, specialization of physicians, age of patient, time since medical board examination and left ventricular ejection fraction as confounding variables.
Results: Baseline characteristics of patients were comparable in males and females. In female and male physicians, specialization (63.2% male vs. 68.0% female general practitioners, 29.0% male vs. 25.7% female internists, 7.8% male vs. 6.2% female cardiologists, p=0.105) and duration since medical examination (male: 23.9±9.1 years, female 23.5±8.8 years, n.s.) were not different. Female patients were less frequently treated with an ACE-inhibitor or an ARB (p=0.021) and tended to with beta-blockers (p=0.054). Achieved doses were smaller in female compared to male patients (ACE-I p=0.058, beta-blockers p=0.021). Drug use and achieved doses tended to be better in patients treated by female physicians. There was no different treatment of male or female patients by female physicians (n.s.), whereas male physicians significantly used less medication and lower doses in female patients (p<0.05). In multivariable linear regression, physicians' gender was an independent risk factor for using beta-blockers (p=0.029, 95%CI -1.000_0.055), but not ACE-I (n.s.).
Conclusions: Treatment of chronic heart failure is influenced by patients', but also physicians' gender with regard to evidenced based drugs and their dosage. Physicians should be aware of this problem, to avoid gender dependent medical treatment.

3:30 p.m.

1024-174 **Circulating Estradiol and Mortality in Men With Systolic Chronic Heart Failure**

Ewa A. Jankowska, Piotr Rozentryt, Waldemar Banasiak, Philip A. Poole-Wilson, Piotr Ponikowski, Cardiology Department, Military Hospital, Wroclaw, Poland, National Heart & Lung Institute, Imperial College London, London, United Kingdom

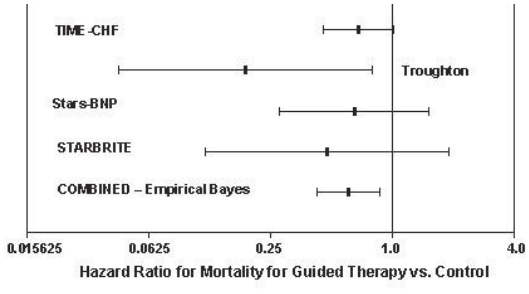
Background: Androgen deficiency is common in men with chronic heart failure (CHF), and is associated with increased morbidity and mortality. Estrogens are formed by the aromatization of androgens, so that abnormal estrogen metabolism would be anticipated in CHF. We sought to examine the relation between the serum concentration of estradiol (E2) and mortality in men with CHF.
Methods: Serum concentrations of E2 and androgens (total testosterone [TT], dehydroepiandrosterone sulfate [DHEAS]) were measured using immunoassays in 501 men with stable systolic CHF (age: 58±12 [mean±SD] years, LVEF [left ventricular ejection fraction]: 28±8%, NYHA [New York Heart Association] class [I/II/III/IV]: 52/231/181/37, ischemic CHF etiology: 71%).
Results: During follow-up (mean: 32±18 months), there were 194 (39%) deaths. In stepwise multivariable regression models, serum E2 predicted mortality in men with CHF (P<0.0001), independently of low serum TT and DHEAS, reduced LVEF, high plasma N-terminal pro-B type natriuretic peptide and high NYHA class. In multivariable models, men in the lowest and highest quintiles for serum E2 had an increased mortality as compared to the middle quintile (adjusted hazard risk: 3.33 (95% confidence interval [CI]: 2.05-5.40) and 2.62 (95% CI 1.57-4.38), both P<0.001, respectively). These two quintiles had different clinical characteristics. Men in the lowest quintile for serum E2 had increased serum TT, reduced serum DHEAS, advanced NYHA class, more prevalent ischemic etiology of CHF, lower hemoglobin concentration, reduced estimated glomerular filtration rate and lower total fat tissue mass as compared to a middle quintile (all P<0.05). Men in the highest quintile for serum E2 demonstrated a deterioration of liver function (increased serum bilirubin, increased serum activity of aminotransferases) as compared to a middle quintile (all P<0.05).
Conclusions: In men with systolic CHF, both high and low concentrations of serum E2 are related to an increased mortality. The mechanisms for the U-shaped outcome in relation to serum E2 concentrations require further studies. Modulation of steroid metabolism is a potential therapeutic target in selected male patients with CHF.

3:30 p.m.

1024-175 **Biomarker Guided Therapy in Chronic Heart Failure: A Meta-Analysis of Randomized Controlled Trials**

Gary Michael Felker, Victor Hasselblad, Christopher M. O'Connor, Duke Clinical Research Institute, Durham, NC

Background: Measurement of circulating natriuretic peptides (NP) has been shown to play an important role in diagnosis and prognosis in patients with chronic heart failure (HF). Whether using serial NP measurements to guide titration of therapy would improve HF outcomes remains uncertain.
Methods: We performed a meta-analysis of published or presented randomized controlled trials (RCTs) of NP guided therapy for chronic HF. A Medline search combining "natriuretic peptide", "BNP", "NTproBNP", and "heart failure" was used to identify potential studies. We searched proceedings of major cardiovascular meetings to identify studies not yet published. We included studies which randomized patients with chronic HF to a control group or a strategy of adjusting medical therapy that incorporated NP levels, and which reported mortality. For each study, we estimated the hazard ratio (HR) for all-cause mortality, and studies were combined using an empirical Bayes random-effects estimator.
Results: Four RCTs were identified which met criteria for inclusion, randomizing a total of 918 patients. HRs and 95% confidence intervals (CI) for each study are shown (Figure). The combined HR was 0.61, 95% CI = 0.43-0.86. There was no quantitative evidence of heterogeneity between studies (p=0.31).
Conclusions: Analysis of completed RCTs suggests that a strategy incorporating NP levels to guide therapy is associated with a significant reduction in all cause mortality compared to usual care in patients with chronic HF.



3:30 p.m.

1024-176 **Glucagon-Like Peptide-1 Increases Blood Pressure and Heart Rate in Heart Failure Patients**

Mads Halbirk, Helene Nørelund, Niels Møller, Jens Juul Holst, Ole Schmitz, Jens Erik Nielsen-Kudsk, Søren Steen Nielsen, Torsten Toftegaard Nielsen, Hans Eiskjær, Hans Erik Bøtker, Henrik Wiggers, Aarhus University Hospital, Skejby, Aarhus, Denmark, Aarhus University Hospital, Aarhus Hospital, Aarhus, Denmark

Objectives: The incretin hormone glucagon-like peptide 1 (GLP-1) and its analogues are currently emerging as anti-diabetic medications. GLP-1 improves left ventricular ejection fraction (LVEF) in dogs with heart failure and in patients with acute myocardial infarction. The influence of GLP-1 on blood pressure and heart rate (HR) is conflicting. We studied the effect of 48-hour GLP-1 infusion on hemodynamics in patients with congestive heart failure (CHF).

Methods: We included 20 non-diabetic ischemic CHF patients, LVEF 33% ±2%, NYHA II and III (n=14 and 6). Patients were hospitalized during infusions and blood samples were drawn regularly. On two separate occasions patients received native GLP-1 (0.7 pmol·kg^{-1}·min^{-1} intravenously) and placebo-infusion for 48 hours in a double-blind randomized cross-over design. Each infusion was separated by a time period of at least 14 days. At 0 and 48 hours LVEF was determined by echocardiography and cardiac index was measured using an inert gas rebreathing method. Blood pressure and HR was recorded every 4 hours.
Results: Fifteen (13 males) completed the protocol, 5 dropped out (side effects 1, cancer 1, withdrawal of consent 3). Two suffered side effects (hypoglycemia 1, nausea 1). HR (67 ± 2 beats/min vs. 65 ± 2 beats/min; p=0.016) and diastolic blood pressure (71 ± 2 mmHg vs. 68 ± 2 mmHg; p=0.008) increased during GLP-1 treatment. Systolic and mean arterial pressure remained unaffected. Cardiac index (1.5 ± 0.1 L·min^{-1}·m^{-2} and 1.7 ± 0.2 L·min^{-1}·m^{-2}; p=0.55) and LVEF (33 ± 2 % and 33 ± 3 %; p=0.95) were unchanged. Insulin levels were higher during GLP-1 infusion than during placebo (90 ± 17 pmol/L vs. 69 ± 12 pmol/L; p=0.025) and blood glucose concentration were lower (5.0 ± 0.1 mmol/L vs. 5.7 ± 0.2 mmol/L; p=0.005).
Conclusion: GLP-1 increases HR and diastolic blood pressure in CHF patients without altering LVEF or cardiac index. GLP-1 had blood glucose lowering effects in this non-diabetic population. The mechanisms and potential clinical consequences of the observed increases in HR and diastolic blood pressure require further studies.

3:30 p.m.

1024-177 Liver Failure Is Mainly Related to Increased Central Venous Pressure in Patients With Heart Failure

Kevin Damman, Vincent M. Van Deursen, Hans L. Hillege, Dirk J. van Veldhuisen, Adiraan A. Voors, University Medical Center Groningen, Groningen, The Netherlands

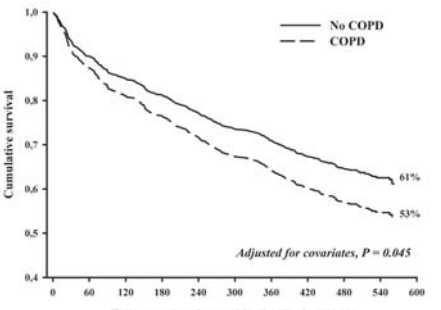
Introduction. Heart failure is often accompanied by liver failure. However, the relation between liver failure, cardiac output (cardiac forward failure) and central venous pressure (cardiac backward failure) has not been well established. We assessed the hypothesis that liver failure in patients with heart failure is dependent of both reduced perfusion and increased congestion, and is associated with poor prognosis.
Methods. We evaluated central venous pressure (CVP), cardiac output (CO) and clinical outcome in 340 patients with heart failure that underwent right heart catheterization between 1989 and 2006. Chart review was done to investigate follow up and demographics and laboratory liver function tests. These included aspartate and alanine aminotransferase (AST and ALT), alkaline phosphatise (ALP), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), direct and total bilirubin (Bili dir, and Bili tot). Liver failure was defined as values above the upper limit of normal.
Results. Mean age was 53±14 years, amd 61% were male. Abnormal liver function tests were prevalent: 19% ALP, 24% AST, 28% Bili tot, 37% GGT, 51% ALT, 68% LDH and 69% Bili dir. In univariate regression analysis, almost all liver function tests were associated with higher CVP and lower CO. However, in multivariate analysis, only AST remained associated with both CVP and CO, while all other were only related to CVP. Especially GGT (r=0.341), Bili tot (r=0.334) and Bili dir(r=0.369) (all P <0.001) were strongly associated with CVP. In univariate analysis, GGT, ALP, AST and LDH were significant predictors of all cause mortality. However, after adjustment for CO and CVP, none remained independently associated with prognosis.
Conclusion. Liver failure in patients with heart failure is mainly dependent of increased CVP. Liver failure is associated with reduced survival, but this is attributable to impaired hemodynamics, suggesting that liver failure in heart failure is a reflection of poor hemodynamic status.

3:30 p.m.

1024-178 Chronic Obstructive Pulmonary Disease Is Independently Associated With Adverse Clinical Outcome in Patients With Heart Failure: A Substudy of the COACH Study

Kevin Damman, Hans L. Hillege, Adriaan A. Voors, Dirk J. van Veldhuisen, Tiny Jaarsma, University Medical Center Groningen, Groningen, The Netherlands

Background. Comorbidities in heart failure are prevalent and increase the risk for adverse clinical outcome in heart disease such as mortality and high medical costs. There is however surprisingly little information on the association between the presence of Chronic Obstructive Pulmonary Disease (COPD) and adverse clinical outcome in patients with heart failure.
Methods. The Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH) included 1023 HF patients. Presence of COPD and other comorbidities, were assessed at baseline. Primary outcome was a composite of all-cause mortality and heart failure admissions after discharge.
Results. Mean age was 71±11 years and 62% were male. Mean LVEF was 33±14%, and 50% were in NYHA III/IV. In total 268 (27%) had coexisting COPD at admission. Patients with COPD were older, more often men, had lower renal function and more likely coexisting atrial fibrillation. In univariate analysis, the presence of COPD was associated with worse outcome: Hazard ratio (HR): 1.39 (95% confidence interval (CI) 1.13 - 1.71), P = 0.002. COPD especially predisposed to increased heart failure admissions: HR 1.42 (95% CI 1.09 - 1.84), P = 0.008). In multivariate analysis, the presence of COPD remained independently associated with on the composite end point of death and hospitalization: HR 1.29 (95% CI 1.01 - 1.65), P = 0.043 (Figure).
Conclusion. COPD is highly prevalent in patients with HF and independently associated with adverse clinical outcome.



Adjusted for age, gender, Hx of myocardial infarction, stroke, atrial fibrillation, diabetes, hypertension, peripheral artery disease, medication, NYHA class, BMI, LVEF, hospital stay, blood pressure, heart rate, presence of renal impairment, anemia and smoking

3:30 p.m.

1024-179 NT-proBNP Keeps Its Predictive Ability During Several Years of Follow-Up Experiences from CORONA

Hans Wedel, John McMurray, John Wikstrand, John Cleland, Peter Dunselman, Ake Hjalmarson, John Kjekshus, Nodic School fo Public Health, Gothenburg, Sweden

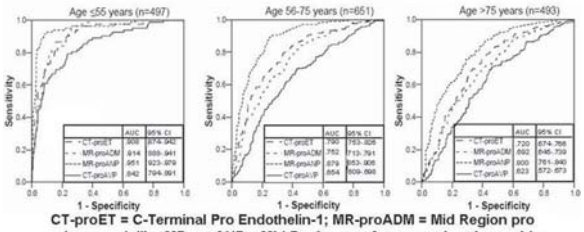
Background To analyze the importance of the biomarker NT-proBNP (BNP) by time of follow up after adjustment for other well-known risk factors in patients with stable advanced systolic heart failure.
Methods Patients in CORONA with BNP available from baseline (n= 3366) were analyzed. The hazard function of death from heart failure (and of other events) was estimated by Poisson models as a continuous function of time in study and BNP together with other risk variables. The event hazard was of the form $\exp(\beta_0+\beta_1 \cdot x_1+\beta_k \cdot x_k)$, where β_0, β_1, etc, were constants and x_1, x_2, etc, were the values of the variables. More precisely the time in study was modeled by connected linear pieces in specified intervals and interaction between logBNP and time in order to investigate whether the predictive power changed (decreased) with time. Endpoints were all-cause mortality (n= 940 deaths) and for death due to worsening of heart failure (n= 230 deaths).
The HR for a difference in logBNP of one standard deviation was calculated by time of follow up. The HR for EF is given for a difference of 5%. The following variables at baseline have been used in the model: logBNP, ejection fraction (EF), diabetes mellitus (DM), age, sex, New York Heart Association (NYHA) class, hypertension and MI. Median follow up time was 32.8 months
Results lnBNP was the strongest predictor of outcome both early and later during follow up. In the first six months of follow the HR for all cause mortality was 2.3 decreasing to 1.6 after 3 years with both p<0.001, for EF the figures were 1.2 p=0.003 and n.s at 3 years. Corresponding figures for death due to worsening of heart failure was 3.6 and 2.0 with both p<0.001, and 1.3 p=0.007 and 1.1 at 3 years p=0.04, respectively.
Conclusions Adding the biomarkers NT-pro-BNP to routine clinical variables can improve estimating the cardiovascular risk in older patients with advanced systolic heart failure. NT-proBNP added substantial information as regards risk estimation both in the short and longer term prediction. Interestingly, even a three year old BNP carries a stronger risk for death than a recent measurement of EF.

3:30 p.m.

1024-180 Impact of Age on the Levels and Utility of Novel Cardiac Biomarkers in Diagnosing Acute Heart Failure: Results From the BACH Multinational Study

Lori B. Daniels, Kimberly Tran, Paul Clopton, Stefan D. Anker, Inder Anand, Robert Christenson, Salvatore DiSomma, Gerasimos Filippatos, Christopher Hogan, Michael Hudson, James McCord, Martin Möckel, Christian Müller, Sean-Xavier Neath, Leong Ng, Richard Nowak, W. Franklin Peacock, Piotr Ponikowski, Mihael Potocki, A. Mark Richards, Alan Wu, Alan S. Maisel, University of California, San Diego, San Diego, CA, Veterans Affairs San Diego Healthcare System, La Jolla, CA

Background: B-type natriuretic peptide (BNP) levels are useful in the diagnosis of heart failure (HF) in patients with acute dyspnea, but their diagnostic value is confounded by age. We examined the impact of age on the levels and utility of novel cardiac biomarkers in a secondary analysis of the **B**iomarkers in **AC**ute **H**eart Failure (BACH) study**.**
Methods: The BACH study was a multinational 15-center prospective study of the use of novel cardiovascular prohormone fragments in diagnosing HF among dyspneic patients presenting to the ED. HF diagnosis was determined by 2 independent cardiologists who were blinded to the ED physicians' diagnoses and to the biomarker levels being examined in this study.
Results: The mean age of the 1641 subjects was 64±17 years; the 568 (35%) patients with a final diagnosis of HF were older than those with alternate diagnoses (71 vs. 60 years, p <0.001). In patients without acute HF, median levels of all BACH markers (CT-proET, MR-proADM, MR-proANP, CT-proAVP) increased significantly with increasing age group (p <0.001), as did levels of MR-proADM (p=0.001) and MR-proANP (p=0.025) in subjects with HF. The area under the ROC curve was largest in the youngest age group and decreased with age, suggesting that the BACH markers were stronger predictors in younger patients (Figure).



CT-proET = C-Terminal Pro Endothelin-1; MR-proADM = Mid Region pro adrenomedullin; MR-proANP = Mid Region pro A-type natriuretic peptide; CT-proAVP = C-Terminal Pro Arginine Vasopressin

Conclusions: The utility of the studied prohormone biomarkers for diagnosing acute HF varies by age. The BACH biomarkers proved to be a powerful adjunct to the diagnosis of HF, especially in younger patients.

3:30 p.m.

1024-181 The Effect of Pioglitazone on Sympathetic and Baroreflex Function in Type Two Diabetes Mellitus After Myocardial Infarction

Hiroshi Yokoe, Fumio Yuasa, Masue Yo, Reisuke Yuyama, Tetsuro Sugiura, Toshiji Iwasaka, Kansai Medical Univercity Hospital, Osaka, Japan, Kochi Univercity Hospital, Kochi, Japan

Background: Pioglitazone has been shown to reduce the occurrence of fatal and nonfatal cardiovascular events in type2 diabetes mellitus (DM) after myocardial infarction (MI). However the mechanisms of such favorable effects remain speculative. The aim of this study was to investigate the effect of pioglitazone on the sympathetic and baroreflex function in the type2 DM patient after MI.
Methods: Thirty patients with type2 DM after MI were assigned to a pioglitazone group (n=15) or control group (n=15). Baroreflex sensitivity(BRS) and muscle sympathetic nerve activity (MSNA) (microneurography at peroneal nerve) were measured at rest and during baroreceptor stimulation (phenylephirine infusion) and baroreceptor deactivation(nitroglycerin infusion). Insulin resistance and plasma adiponectin were measured. Insulin resistance was evaluated using the homeostasis model assessment insulin resistance (HOMA-IR). These measurement were performed at baseline and after 3 months.
Results: Resting MSNA reduced significantly (from 37±7 to 25±8 burst/min ; p=0.007) and BRS improved significantly (from 6.7±3.0 to 9.9±3.2 msec/mmHg ;p=0.01) after pioglitazone. MSNA response to baroreceptor activation (change of integrated MSNA from -26±13 to-45±11%;p=0.001) and baroreceptor deactivation (change of integrated MSNA from 115±14 to 153±23%;p=0.01) improved significantly after pioglitazone. Adiponectin (6.9±3.3 to 12.2±7.1μg/ml ; p=0.01)and HOMA-IR (4.0±2.7 to 2.1±0.9; p=0.006) improved significantly after pioglitazone. The change in resting MSNA was related significantly to the changes in HOMA-IR (r=0.6 ;p<0.05)and plasma adiponectin (r=0.7 ;p<0.05) after pioglitazone. However, there were no significant changes in measured variables in the control group.
Conclusions: Pioglitazone treatment increased arterial BRS and decreased sympathetic nerve traffic through the improvement of insulin resistance and adiponectin in the patients with type2DM after MI, which indicate that the sympathoinhibitory effects of this agent may contribute to the benefical effects of pioglitazone in type 2 DM after MI.

3:30 p.m.

1024-182 Safety and Usefulness of G-CSF in Patients With Ischemic Heart Failure: The Cell Option for Recovery in the Non-eligible Patients for Revascularization(CORNER) Study

Antonio Maria Leone, Maria Benedetta Giannico, Isabella Bruno, Matteo Perfetti, Alessandro Giordano, Giampaolo Niccoli, Italo Porto, Luigi Marzio Biasucci, Filippo Crea, Department of Cardiovascular Medicine, Rome, Italy, Nuclear Medicine, Rome, Italy

Background: Despite recent advances in pharmacological and mechanical treatment of post-infarction heart failure, mortality and morbidity remain high. After the demonstration that the heart is not a post-mitotic organ but can be regenerated from cardiac and non-cardiac cells, several clinical trials have been accomplished aimed to obtain myocardial repair even in patients with ischemic congestive heart failure. Aim of the study: To evaluate the cytokine-induced cell mobilization, in particular using granulocyte colony-stimulating factor (G-CSF) , as a less invasive method for promoting cardiac repair. **Methods:** We enrolled 13 patients with ischemic heart disease (IHD) and stable refractory angina and/or stable severe heart failure (NYHA III or IV) for at least 1 month, in spite of optimal medical therapy and we added G-CSF at a dose of 10μg/Kg/die, evaluating changes in cardiac perfusion and function at Gated SPECT. Quality of life was assessed by Seattle Angina Questionnaire (SAQ), Minnesota Living with Heart Failure Questionnaire (MLHF) and visual scale of Quality of Life (QoL). **Results:** G-CSF was well tolerated. At SAQ we found improvement of physical limitation (from 39.25+ 30.69% to 64.34+29.45%, p=0.03), angina stability (from 41.67+ 28.87% to 64.09+28.44%, p=0.05), angina frequency (from 53.33+ 33.12% to 72.73+25.73%, p=0.04), treatment satisfaction (from 67.28+ 29.23% to 82.87+20.66%, p=0.07), disease perception (from 36.80+ 29.17% to 66.39+26.50%, p=0.01). MLHF improved from 52.58+ 27.02 to 39.36+26.24, p=0.15, QoL improved from 32.82+ 23.99 mm to 64.55+20.55 mm, p=0.003. Segmental stress and differential perfusion significantly improved at follow up (respectively from 1.78+ 1.38 to 1.66+1.38, p=0.05 and from 0.35+ 0.68 to 0.23+0.53, p=0.02).
Conclusions: In patients with refractory angina or post-ischemic heart failure, treatment with G-CSF appears to improve symptoms, possibly through improvements of stress-induced ischemia.

3:30 p.m.

1024-183 Depression in Men With Chronic Heart Failure: Prevalence, Hormone Determinants, Detrimental Impact on Exercise Capacity and Survival

Ewa A. Jankowska, Beata Ponikowska, Anna Drohomirecka, Jolanta Maj, Bartosz Biel, Waldemar Banasiak, Philip A. Poole-Wilson, Piotr Ponikowski, Cardiology Department, Military Hospital, Wroclaw, Poland, Physiology Department, Wroclaw Medical University, Wroclaw, Poland

Background: Men with androgen deficiencies (testosterone, dehydroepiandrosterone sulfate [DHEAS]) are prone to development of late-onset depression. We investigated links between circulating androgens and depressive symptoms, and their combined impact on prognosis in men with chronic heart failure (CHF).
Methods: We examined 203 men with stable systolic CHF (age: 60±10 years [y], NYHA class [I/II/III/IV]: 36/101/60/6; LVEF: 31±9%) and 328 healthy men aged 35-80 living in the same area.
Results: The prevalence of Beck Depression Inventory (BDI) score above 15 points (at least moderate depression) was higher in CHF men as compared to healthy peers in all age groups (35-45 y: 22% vs 3%, p<0.01, 46-55 y: 36% vs 3%, p<0.0001, 56-65 y: 26% vs 9%, p=0.01, 66-80 y: 48% vs 26%, p<0.05). In a multivariable regression, in men with CHF severe affective-cognitive depressive symptoms were related to advanced NYHA class, high serum high sensitivity C-reactive protein, low hemoglobin, reduced serum total testosterone [TT] and DHEAS, marked somato-wegetative depressive symptoms correlated with reduced glomerular filtration rate and high plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) (all p<0.05). During follow-up (mean: 24±12 months), there were 74 (47%) cardiovascular deaths and unplanned hospitalizations. There were the following independent predictors of unfavorable outcome in men with CHF: TT deficiency and DHEAS deficiencies (below the 10th percentile of healthy peers), high plasma NT-proBNP (above 3242 pg/mL, median), BDI above 15 points (all p<0.05). The higher the number of risk factors, the worse prognosis (HR [95% CI] for 1, 2, 3, 4 vs. 0 risk factors, respectively: 1.01 [0.50-2.04], p=0.99, 3.41 [1.69-6.88], p<0.001, 8.05 [3.90-16.63], p<0.0001, 15.27 [6.03-38.67], p<0.0001).
Conclusions: Depression in common in men with CHF, and reduced serum TT and DHEAS are accompanied by more severe depressive symptoms. Depression together with neuro-hormonal activation and androgen deficiencies are related to poor outcome in these patients. Whether androgen therapy would ameliorate depressive symptoms and improve prognosis in CHF men, requires further studies.

3:30 p.m.

1024-184 Beta-Blocker Evaluation of Survival Trial (BEST) Findings Show Benefit of Bucindolol in Moderate to Severe HF Patients, According to Prespecified Statistical Analysis Plan

Michael Bristow, Eric Eichhorn, Hector Ventura, Bruce Koch, Mona Fiuzat, Gordon Davis, A. Douglas Robertson, University of Colorado Health Sciences Center, Denver, CO, Dallas Heart Group, Dallas, TX

Background: Preliminary results from the Beta-Blocker Evaluation of Survival Trial (BEST) were reported in 2001, following early termination of the study for loss of investigator equipoise. However, results analyzed according to the FDA-negotiated pre-specified statistical analysis plan (SAP) have never been reported. This paper presents results from that analysis.
Methods: A total of 2708 patients with heart failure (HF) designated as New York Heart Association (NYHA) functional class III (92%) or IV (8%) and a left ventricular ejection fraction ≤35% were randomly assigned to double-blind treatment with either bucindolol (1354 patients) or placebo (1354 patients) and followed for the primary endpoint of death from any cause, and the highest ranking secondary endpoint of HF progression.
Results: Analysis of study results according to the pre-specified SAP indicated a near significant reduction in all cause mortality with bucindolol compared to placebo (HR 0.87, p=0.053), despite the availability of only 92% of the projected number of primary endpoints based on the pre-trial sample size calculations. Analysis of the composite endpoint of HF progression indicated that bucindolol was significantly superior to placebo for slowing progression of HF (HR 0.80, p=0.00003), and its components of HF-related mortality (HR 0.85, p=0.042), HF-related hospital admission (HR 0.77, p=0.00002), and HF-related ER visit (HF 0.74, p=0.024). Bucindolol also demonstrated significant superiority over placebo for eight secondary endpoints.
Conclusions: In a demographically diverse group of primarily U.S. patients with NYHA class III and IV heart failure, bucindolol resulted in near significant overall survival benefit as well as significant benefit in slowing progression of HF, despite premature termination of the study. These findings are contrary to the common belief that BEST was terminated early due to futility.

3:30 p.m.

1024-185 Human Umbilical Cord Blood Stem Cells Decrease Fibrosis and Increase Cardiac Function in Cardiomyopathy

Robert J. Henning, Darrell Sawmiller, Masood Shariff, Jeffrey Aufman, Vincent DeLostia, Holly Hayden, Michael Morgan, James A. Haley Hospital/University of South Florida, Tampa, FL

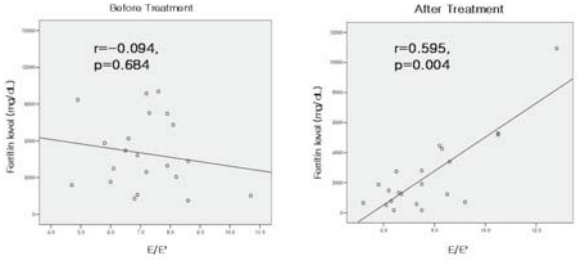
BACKGROUND: We have reported that human umbilical cord blood stem cells (HUCBC) decrease LV infarct size and increase wall thickening and ejection fraction (EF) after LV infarction in rats. We hypothesize that HUCBC would be beneficial in treating the dilated cardiomyopathy due to progressive ventricular fibrosis in TO2 hamsters. **METHODS:** In Group I we compared the effects of $4X10^6$ HUCBC injected into the LV myocardium at 1 month of age in 22 TO2s with 17 TO2s injected with only Isolyte and 16 F1B normal hamsters. In Group II in 4 month old hamsters, we compared the effects of $4X10^6$ HUCBC injected into the myocardium of 8 TO2s with 8 TO2s treated with Isolyte and 16 normal F1B hamsters. Immunosuppression therapy was not given to any hamster. Echocardiograms for EF and fractional shortening (FS) were done prior to and after treatment at 1 to 3 months in Group I and at 4 to 6 months in II then LV dP/dtmax was determined by catheterization. LVs were then examined for fibrosis and myocyte loss with H&E, trichrome and dystrophin stains. **RESULTS:** In Group I between 1 and 3 months the control F1B EF and FS were 90.5 $\pm$ 0.6% and 55.7 $\pm$ 1.0%. The Isolyte TO2s decreased their EF from 89.5 $\pm$ 1.4 to 66.7 $\pm$ 2.2% and FS from 55.2 $\pm$ 1.4% to 32.3$\pm$ 1.5% (p<0.0001). In contrast, the HUCBC TO2s decreased their EF from 90.8 $\pm$ 0.6 to only 76.0 $\pm$ 2.5 and FS from 56.2 $\pm$ 0.8 to 39.4 $\pm$ 2.6 which were larger than Isolyte treated TO2s (p<0.05). In Group II between 4 and 6 months the F1B EF and FS were 86.0 $\pm$ 1.5% and 49.7 $\pm$ 1.8%. Isolyte TO2s decreased their EF from 66.8 $\pm$ 2.7 to 37.8 $\pm$ 5.1% and their FS from 33.4 $\pm$ 2.2% to 15.7 $\pm$ 2.4% (p<0.0002). In contrast, the EF in HUCBC TO2s decreased only slightly from 64.3 $\pm$ 2.7 to 57.6.0 $\pm$ 2.4 and the FS from 30. 7 $\pm$ 1.9 to 26.2 $\pm$ 1.5 which were larger than Isolyte TO2s (p<0.05). HUCBC TO2s had greater LV dP/dtmax (3990 $\pm$ 258 vs. 3389 $\pm$ 423 mmHg/sec) and 51% less fibrosis and LV myocyte loss between 3 and 6 months compared with Isolyte TO2s which showed progressive LV fibrosis (p<0.02). The changes in LV fibrosis correlated inversely with the EF, FS, and dP/dtmax. **CONCLUSION:** HUCBC can limit LV fibrosis and myocyte loss and LV dysfunction, without requirements for immunosuppressive therapy, when administered early in course of dilated cardiomyopathy.

3:30 p.m.

1024-186 Oral Iron Chelation Therapy Prevents Diastolic Dysfunction in Chronic Iron Overload: Two-Year Follow-Up in Patients With Aplastic Anemia

Woo-Baek Chung, Ho-Joong Youn, Eun-Ju Hong, Youn-Seok Choi, Yong-Seog Oh, Wook-Sung Chung, Jae-Hyung Kim, Jong-Wook Lee, St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea

Purpose: In patients (pts) with aplastic anemia (AA), chronic iron overload due to multiple transfusions can lead to cardiac hemochromatosis. The aim of this study was to elucidate whether deferasirox (Exjade®), an oral iron-chelating agent, can prevent cardiac dysfunction in chronic iron overloading conditions.
Methods: Twenty-one AA pts (age 31±8 years, M:F=12:9) were recruited and divided into two groups [Deferasirox responder (DR) group, serum ferritin level <1500 mg after treatment; Deferasirox non-responder (DnR) group, serum ferritin level ≥1500 mg after treatment]. The serum ferritin level was measured regularly, and the deferasirox dosage was adjusted. Transthoracic echocardiography was performed during the 1st, 25th, 50th, and 100th weeks, and parameters including left ventricular ejection fraction (LVEF), LV mass, left atrial (LA) volume, and LV filling indices were measured. **Results**: 1. The serum ferritin level did not correlate with E/E' before treatment, but it was positively correlated with E/E' after treatment (Figure) 2. E/E' changed from 7.3±1.6 to 6.9±1.1 in the DR group and from 6.9±1.1 to 8.6±2.1 in the DnR group (p=0.041) 3. LA volume changed from 46.2±16.6 mL to 47.8 ±11.6 mL in the DR group and from 61.3±17.9 mL to 68.3±15.4 mL in the DnR group (p=0.004). **Conclusion**: The iron-chelating agent deferasirox prevents deterioration of diastolic function in patients with chronic iron overload.



3:30 p.m.

1024-187 Physiogenomic Comparison of Edema and BMI in Patients Receiving Rosiglitazone or Pioglitazone

Gualberto Ruano, James Bernene, Andreas Windemuth, Bruce Bower, Detlef Wencker, Richard L. Seip, Mohan Kocherla, Theodore R. Holford, Steven Hanks, Genomas, Inc., Hartford, CT, The Hospital of Central Connecticut, New Britain, CT

Background: The thiazolidinediones (TZDs) improve tissue sensitivity to insulin in patients with type II diabetes, resulting in reduced levels of fasting blood glucose and glycated hemoglobin. However, TZDs unpredictably demonstrate adverse effects of increased body weight, fluid retention, and edema. The balance of efficacy and safety of TZD varies widely from patient to patient. Genetic variability may reveal pathophysiological pathways underlying weight gain associated with TZD therapy and due to adiposity and/or edema.
Methods: We analyzed 384 single nucleotide polymorphisms (SNPs) from 222 cardiovascular and metabolic genes in 87 outpatients with type 2 diabetes receiving thiazolidinedione therapy. Physiogenomic analysis was used to discover associations with body mass index (BMI) and edema.
Results: The five most significant gene associations found between BMI and SNPs were *ADORA1*, adenosine A1 receptor (rs903361, p<0.0003), *PKM2*, pyruvate kinase-muscle (rs2856929, p<0.002); *ADIPOR2*, adiponectin receptor 2 (rs7975375, p<0.007); *UCP2*, uncoupling protein 2 (rs660339, p<0.008); and *APOH*, apolipoprotein H (rs8178847, p<0.010). For edema, the five most significant gene associations were *NPY*, neuropeptide Y (rs1468271, p<0.006); *GYS1*, glycogen synthase 1-muscle (rs2287754, p<0.013); *CCL2*, chemokine C-C motif ligand 2 (rs3760396, p<0.015); *OLR1*, oxidized LDL receptor 1 (rs2742115, p<0.015); and *GHRH*, growth hormone releasing hormone (rs6032470, p<0.023). After accounting for multiple comparisons, *ADORA1* was significantly associated with BMI at a false discovery rate (FDR) of < 10%.
Conclusions: Physiogenomic associations were discovered suggesting mechanistic links between adenosine signaling and BMI, and between vascular permeability and drug-induced edema.

3:30 p.m.

1024-188 Influence of Body Mass Index on Patients Presenting Characteristics, Treatment Practices, and Mortality in Patients Hospitalized With Decompensated Heart Failure: A Communitywide Perspective

Armen A. Chalian, Timothy P. Fitzgibbons, Olga T. Hardy, Darleen Lessard, Joel M. Gore, Jorge Yarzebski, Robert J. Goldberg, UMASS Medical School, Worcester, MA

Background: Obesity is associated with an increased risk of mortality and cardiovascular disease, including heart failure (HF). The effect of body weight on clinical characteristics, treatment regimens, and prognosis in acute HF patients is largely unknown, however, particularly from a community - wide perspective. **Methods:** 3,722 patients admitted with acute HF to all 11 greater Worcester, MA, hospitals were categorized as being of either normal weight, overweight, or obese based on their body mass index (BMI). **Results:** The average patient age was 76 years. 55% of patients were overweight or obese. Obese patients were younger, and more likely to have diabetes and a history of PCI (Table 1). Obese patients were more likely to have received lifestyle recommendations during hospitalization and be treated with an ACE inhibitor. They were less likely to receive Digoxin (Table 1). Although normal weight patients had a higher hospital death rate than obese patients, this effect was not significant in multivariate analyses (OR 0.88, 95% CI 0.60-1.31). **Conclusion:** In this community based study of patients with acute HF, there were important differences in treatment practices among HF patients of different body weight. Although normal BMI patients have a greater mortality rate than obese patients, this effect is not significant after controlling for confounding factors. Our results suggest that an "obesity paradox" in acute HF does exist, and that it may be related to older age and cachexia in the normal weight HF group.

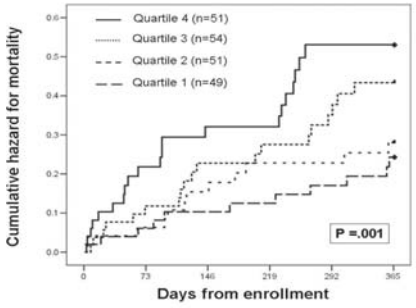
		BMI <25 (n=1,681)	BMI25-29.9 (n=1,007)	BMI >30 (n=1,034)	P Value
AGE (%)	< 65 years old	8.2	13.6	28	<0.001
	65-74 years old	17.7	27.1	28	
	> 74 years old	74.1	59.3	44.1	
GENDER (%)	Male sex	40.6	50.7	38.5	0.74
MEDICAL	Coronary HD	58.2	58.1	54.6	0.08
HISTORY (%)	PCI	5.6	9.0	10.3	<0.001
	CABG	19.0	22.7	17.3	0.48
	Hypertension	62.9	67.9	68.9	<0.01
	Diabetes	30.2	43.6	54.8	<0.001
	Atrial fibrillation	39.9	33.9	29.0	<0.001
MEDICATIONS	ACE inhibitors	51.3	52.4	55.3	<0.05
(%)	Beta blockers	39.7	45.1	40.6	0.41
	Diuretics	97.9	97.9	98.7	0.15
	Nitrates	65.9	68.2	65.2	0.84
	Digoxin	57.5	51.5	41.6	<0.001
LIFESTYLE	Low fat diet	55.7	61.7	65.5	<0.001
ADVICE (%)	Fluid restriction	21.7	20.8	26.3	<0.05
	Reduce salt intake	80.4	82.1	86.0	<0.01
MORTALITY (%)	Hospital case-fatality rate	7.2	6.0	4.2	<0.01

3:30 p.m.

1024-189 **Red Cell Distribution Width and One-Year Mortality in Acute Heart Failure**

Asim A. Mohammed, Roland RJ van Kimmenade, Shanmugam Uthamalingam, Peter van der Meer, Michael Felker, James L. Januzzi, Jr., Massachusetts General Hospital, Boston, MA, University Hospital Maastricht, Maastricht, The Netherlands

Background: Red blood cell distribution width (RDW) predicts mortality in chronic heart failure (HF). The prognostic value of RDW in acute HF, and its relative prognostic value compared to established measures such as amino-terminal pro-B type natriuretic peptide (NT-proBNP) is unknown.
Methods: In 206 patients with acute HF, independent predictors of RDW were identified using linear regression analysis. The association between RDW and 1 year survival in the context of other known predictors was assessed using Cox proportional hazards analysis.
Results: RDW was elevated in 116 (56%) patients (figure - cumulative hazard curves showing rates of mortality by 1 year as associated with quartiles of RDW); RDW was independently associated with hemoglobin (T-score= 9.97; P<.001), loop diuretic (T-score=2.77; P=.006) and β-blocker (T-score=2.46; P=.015) on presentation, but not to nutritional deficiencies, recent transfusion or inflammatory parameters. log-transformed RDW values independently predicted mortality in multivariable Cox proportional hazards analysis (HR 1.03, 1.00-1.06 95% CI; P=.04); when stratified on the basis of RDW and NT-proBNP status, the combination of markers provided additional prognostic information.
Conclusions: RDW is frequently high in patients with acute HF and was not associated with folate or iron deficiencies or inflammation. RDW independently predicts 1 year mortality in acute HFand appears to be additive to established prognostic variables like NT-proBNP.



3:30 p.m.

1024-190 **The Effects of Sildenafil on Hemodynamic Parameters and Exercise Capacity in Patients With Chronic Lung Disease and Secondary Pulmonary Hypertension**

Hye-Sun Seo, Tae Soo Kang, Jon Suh, Yoon Haeng Cho, Nae-hee Lee, Soonchunhyang university hospital, Bucheon, South Korea

Background: Sildenafil is a selective phosphodiesterase type 5 inhibitor which leads to nitric oxide-mediated vasodilatation decreases pulmonary vascular resistance. Sildenafil also significantly improves exercise tolerance and hemodynamic parameters in patients with idiopathic pulmonary hypertension (PAH), chronic congestive heart failure and consequent pulmonary hypertension. We hypothesized that sildenafil would improve pulmonary vascular resistance in patients with secondary pulmonary hypertension by chronic lung disease and could augment exercise capacity by improving right ventricular (RV) function. **Methods:** Fifteen patients who had chronic lung disease and pulmonary hypertension (peak pulmonary artery pressure (PAP) > 40 mmHg & mean PAP > 25mmHg by echocardiography) without other left heart problem were included. Thirteen patients (mean age: 68.6 years, 9 men) tolerable to drug were given sildenafil 25mg tid everyday during 4weeks. BNP, hs-CRP, ABG, pulmonary function test and 6M walk test were also performed before and after treatment.
Results: Pulmonary vascular resistance index was reduced by sildenafil (-21.3%, 5.02 to 3.32 Wood units, p=0.075). Peak PAP (-20.4%, 57.9 to 46.1 mmHg, p=0.043) and mean PAP (-8.7%, 39.3 to 35.9 mmHg, p=0.042) were all reduced after treatment. Exercise capacity measured by 6M walk test was also improved by sildenafil. (+10.5%, 190m to 210m, p=0.066). However RV fractional area change and RV diastolic, systolic function measured by tissue Doppler image (TDI) were not different. The hs-CRP level had tendency to be lower after treatment and concentration of O_2, CO_2 levels were not significantly changed during sildenafil administration. There were no adverse events.
Conclusion: Sildenafil improves pulmonary vascular resistance, decreases pulmonary artery pressure and improves exercise tolerance in patients with chronic lung disease and secondary pulmonary hypertension.

3:30 p.m.

1024-191 **Do Patients With Advanced Heart Failure Benefit From Defibrillation Threshold Testing at the Time of CRT Implantation?**

Grace Lin, Nandan Anavekar, Daniel Couri, Robert F. Rea, David L. Hayes, Peter A. Brady, Mayo Clinic, Rochester, MN

Background: Defibrillation threshold (DFT) testing is routinely performed at the time of implantable cardioverter defibrillator implantation to determine adequate safety margin. Cardiac resynchronization therapy defibrillator (CRT-D) has established benefit in patients (Pts) with advanced heart failure (AHF), however in some cases DFT testing cannot be performed due to hemodynamic instability.
Methods: To determine the likelihood of achieving adequate DFT in Pts with AHF, we reviewed clinical and follow up data of all Pts who underwent implantation of a CRT-D device at Mayo Clinic between 1999 and 2005. High DFT was defined as DFT >15 J.
Results: A total of 413 Pts (mean age 68 ± 11 years; 337 males, 82%) underwent implantation of a CRT-D device during the study period. Baseline ejection fraction was 21% ± 7%, and etiology of AHF was ischemic in 270 (65%) Pts. Indication for defibrillator placement was for primary prevention of sudden cardiac arrest in 315 (76%) patients. The CRT-D device was implanted on the left side in 377 (91%) Pts and on the right side in 36 (9%) Pts. In 3 Pts, the defibrillator lead was placed in the right ventricular (RV) outflow tract; in the remaining 410 (99%) Pts the lead was placed in the RV apex. DFT testing was performed at implant in 315 (76%) Pts and was successful at the initial RV lead location in 98% of Pts. Mean DFT was 15 ± 4J, with high DFT in 60 (19%) Pts. Although right sided CRT-D implant was not associated with high DFT, DFT of the 3 Pts with RV outflow tract leads was 24 J (p<0.01). Subsequent RV lead revision was not required in any Pts to improve DFT. Clinical characteristics (age, etiology and severity of AHF, ejection fraction, hemoglobin, serum sodium, estimated GFR) of Pts with high DFT were similar to Pts with DFT ≤ 15 J (p>0.05 for all). One year survival of Pts with high DFT was 76% compared with 85% in Pts with DFT ≤ 15 (p> 0.05).
Conclusions: Adequate DFT was achieved in 98% of patients undergoing CRT-D without need for RV lead revision either at the time of implantation or subsequently. This suggests a high likelihood for adequate safety margin in Pts with AHF in whom DFT testing is deferred due to hemodynamic instability or other concerns.

3:30 p.m.

1024-192 **Restrictive Cardiomyopathy With Preserved Ejection Fraction: Outcomes of Inotropic Support**

Aisling J. Carroll, Barry A. Boilson, John A. Schirger, Sudhir S. Kushwaha, Alfredo L. Clavell, Krishnaswamy Chandrasekaran, Robert P. Frantz, Richard J. Rodeheffer, Brooks S. Edwards, Naveen L. Pereira, Mayo Clinic, Rochester, MN

Background: Cardiac inotropes have traditionally been used in patients with severe systolic dysfunction as a bridge to cardiac transplantation. Occasionally patients with preserved ejection fraction (EF) demonstrate low cardiac output states and are determined to be inotrope dependent. We sought to investigate the clinical response of patients with heart failure preserved EF to inotropes while awaiting cardiac transplantation.
Methods: We identified 145 consecutive patients with a diagnosis of restrictive cardiomyopathy referred for transplant evaluation between January 1,1988 and August 29, 2008. 21 patients met inclusion criteria: EF >50%, intravenous inotrope use as a bridge to transplantation. Hemodynamics pre and 24 hours post treatment were documented. Metabolic parameters, adverse cardiac and non-cardiac outcomes were reviewed.
Results: All patients were admitted for monitoring and initiation of milrinone, dopamine or dobutamine with mean duration of inotrope use 74 days. Average age at start of treatment was 50 years with 7 patients discharged for ambulatory therapy.
PCWP improved from 24.9 ± 1.3 to 17.7 ± 2.1 mmHg 24 hours after inotrope initiation (p=0.01). There was no significant difference between cardiac output, pulmonary artery pressure, BUN, serum creatinine or bilirubin.
There was a subjective improvement in symptoms in all patients. There were no deaths in the sub-group of patients maintained on outpatient treatment; 4/7 had implantable cardioverter defibrillators and no shocks or anti-tachycardia pacing therapies were administered.
In the severely ill group of patients who remained in hospital awaiting transplantation, there were 4 deaths and one episode of clinically significant VT requiring electrical therapy. Only one patient required mechanical assist device support. There was no new requirement for renal replacement therapy following inotrope initiation.
Conclusion: Cardiac inotropes can improve symptoms and hemodynamics in patients with preserved EF awaiting cardiac transplantation. The majority of patients can be bridged successfully to transplantation. Further study is needed to elucidate the role of inotropes in heart failure with preserved EF.

3:30 p.m.

1024-193 **Predictors of the Improvement in Left Ventricular Ejection Fraction in Nonischemic Dilated Cardiomyopathy During Beta-Blocker Therapy**

Yoko Masukata, Kazuhiko Hashimura, Masataka Watanabe, Makoto Amaki, Takahiro Ohara, Takuya Hasegawa, Hideaki Kanzaki, Masafumi Kitakaze, National Cardiovascular Center, Suita, Japan

Background: Although beta-blocker therapy results in a significant improvement in left ventricular ejection fraction (EF) and prognosis in patients with chronic heart failure, little information is available to predict which patients will be responder or non-responder. Therefore, we sought to clarify specific predictor(s) for improvement in EF in patients with non-ischemic dilated cardiomyopathy, who are treated with standard pharmacotherapy and subsequent beta-blocker (carvedilol) therapy.

Methods: 154 patients with non-ischemic dilated cardiomyopathy (EF≤30%), who were under carvedilol therapy for one year, were retrospectively analyzed. Echocardiographic parameters, including end-diastolic dimension (Dd), end-systolic dimension (Ds), EF, wall thickness (Th), and wall stress (Dd/Th) and brain natriuretic peptide (BNP), and maintenance carvedilol dose were followed up. Responder was defined as an absolute improvement of 10% or more in EF (Group A: responder 76 patients, group B: non-responder 78 patients).
Results: Although there were no differences in age, gender, New York Heart Association functional class, and EF at baseline, group A was associated with lower BNP (142.6±286.9 vs. 358.5±362.7 pg/ml, p<0.001), higher carvedilol maintenance dose (15.3±8.0 vs. 10.4±6.8 mg/day, p<0.001), thicker wall thickness (8.5±1.7 vs. 8.0±1.6 mm, p=0.05), and lower wall stress (8.4±2.1 vs. 9.6±2.6, p=0.002). In multivariate analysis, wall stress (HR 1.17; 95%CI 1.02-1.34, p=0.03) and carvedilol dose (HR 0.92; 95%CI 0.87-0.97, p<0.01) independently predicted cardiac events after adjusting age, gender, EF and BNP. In addition, Kaplan-Meier analysis showed that the group A had better prognosis than group B (cardiac death, re-hospitalization due to heart failure, left ventricular assist device implantation, and cardiac transplantation).
Conclusion: Wall stress and carvedilol dose used are strong predictors of the improvement in left ventricular EF and prognosis during beta-blocker therapy in patients with non-ischemic dilated cardiomyopathy.

3:30 p.m.

1024-194 Reduced Renal Function Is Associated With Increases in Arterial Stiffness and Left Ventricular Contractility in Patients With Coronary Artery Disease: A Ventricular Arterial Coupling Pattern Similar to Heart Failure With Normal Ejection Fraction

Hidekatsu Fukuta, Nobuyuki Ohte, Seiji Mukai, Kaoru Asada, Kazuaki Wakami, Toshihiko Goto, Genjiro Kimura, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

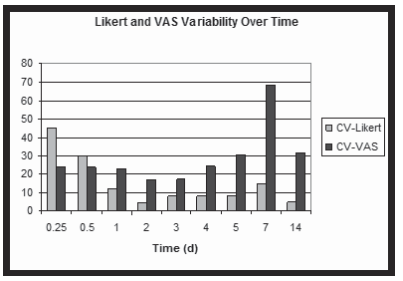
Background: Although reduced renal function is associated with increased risk for heart failure (HF) in various populations, including patients with coronary artery disease (CAD), mechanisms underlying the association remain to be fully elucidated. We tested the hypothesis that altered arterial and left ventricular (LV) function and their interaction may contribute to HF risk associated with reduced renal function.
Methods: We examined the relation of estimated glomerular filtration rate (eGFR) with augmentation index (AI) of ascending aortic pressure, effective arterial elastance (a ratio of LV systolic pressure to stroke volume index, Ea), an estimate of LV contractility (a ratio of LV systolic pressure to end-systolic volume index, Ees), and indices of LV diastolic function (time constant of decrease in LV pressure [Tau] and end-diastolic pressure [EDP]) in 147 consecutive patients without prior myocardial infarction undergoing cardiac catheterization for coronary artery disease (CAD; age, 66±9 years; males, 67%; eGFR, 65.5±17.4 ml/min/1.73m^2; ejection fraction [EF], 0.72±0.08).
Results: AI, Ea, and Ees increased with reducing eGFR (All P<0.001). Ea/Ees, EF, Tau, or EDP did not correlate with eGFR (All P>0.1). Findings were similar after considering potential confounders, including age, gender, other cardiovascular risk factors, and the severity of CAD.
Conclusions: Reduced renal function is associated with increases in arterial stiffness and LV contractility in CAD patients. This ventricular-arterial coupling pattern is similar to that seen in HF with normal EF and may provide a mechanistic link between reduced renal function and increased risk for HF in this population.

3:30 p.m.

1024-195 How Should Dyspnea Be Measured in Acute Heart Failure?: A Comparison of Visual Analog and Likert Scales in an International Clinical Trial

Marco Metra, John R. Teerlink, Adriaan A. Voors, G. Michael Felker, Elaine Unemori, Beth Weatherley, Sam L. Teichman, Gad Cotter, Section of Cardiovascular Diseases, Department of Experimental And Applied Medicine, Univ of Brescia, Brescia, Italy, Section of Cardiology, Veterans Affairs Medical Center, University of California, San Francisco, CA

Relief of dyspnea is an important therapeutic goal in acute heart failure (AHF), and patient reported dyspnea is a key endpoint in AHF clinical trials. However, there has been little comparison of methods that quantify dyspnea.
Methods: In PreRELAX-AHF, the vasodilator relaxin was given for 48 h to 234 patients hospitalized for dyspnea due to AHF. The 7-pt Likert and 100-mm VAS were used to assess dyspnea at baseline (VAS only), 6, 12, 24, 48 h, and days 3, 4, 5, 6, 7 and 14. We compared mean change from baseline in VAS to the proportion of patients reporting moderate or marked improvement by Likert.
Results: There was moderately good overall correlation between the two scales (r=0.69). The coefficients of variation (CV, 100 x SD/mean), an indication of the discriminatory power of each scale, were larger for the VAS at later time points, suggesting more discriminatory ability later, while the Likert tended to be more discriminatory at earlier time points (See figure).
Conclusion: Although they correlate moderately well overall, these results suggest that the Likert may be preferable for earlier assessments of dyspnea, while the VAS may be better for later assessments. This may be due to the frequent early report of the maximum categorical Likert scores of +2 and +3 (moderate or marked improvement), leaving no possibility for measuring subsequent improvement, while the VAS continuous scale offers a wider range over a longer period. These data are important for the choice of end-points related to symptoms in future AHF trials.



3:30 p.m.

1024-196 The Selective Cardiac Myosin Activator, CK-1827452, Increases Systolic Function in a Concentration-Dependent Manner in Patients with Stable Heart Failure

Roxy Senior, Fady Malik, Khalil G. Saikali, Jacqueline Lee, Gerrit Brand, Andrew A. Wolff, CK-1827452 in Heart Failure Investigators, Northwick Park Hospital, Harrow, United Kingdom, Cytokinetics Inc., South San Francisco, CA

Background: CK-1827452 (CK-452) increases systolic function by activating cardiac myosin. In healthy subjects CK-452 increases systolic ejection time (SET), stroke volume (SV), fractional shortening (FS), and ejection fraction (EF).
Methods: This first Phase II trial of CK-452 is a multi-center, double-blind, randomized, placebo-controlled study in patients with EF < 40% and treated with stable HF medication. In Cohorts 1 - 4, patients received 3 escalating i.v. doses of CK-452 and 1 placebo treatment. Infusions were 2 h in Cohorts 1 & 2 and 24 h in Cohorts 3 & 4, and 72 h in Cohort 5.
Results: For 28 completed patients in Cohorts 1 to 4, echocardiographic data were paired with coincident plasma concentrations of CK-452.

Placebo Corrected Changes from Baseline								
[CK-452] (ng/mL)		1-100	>100-200	>200-300	>300-400	>400-500	>500-883	
(n per bin)		(69)	(50)	(32)	(19)	(30)	(20)	
	Baseline							Correlation vs[CK-452]
SET (ms)	318	3 ± 4	24 ± 5‡	54 ± 5‡	65 ± 7‡	72 ± 8‡	98 ± 7‡	‡
LVOT SV (mL)	68	1 ± 2	1 ± 2	6 ± 2*	12 ± 3‡	14 ± 3‡	14 ± 3‡	‡
FS (%)	17	1 ± 1	2 ± 1*	3 ± 1†	4 ± 1†	3 ± 1#	4 ± 1‡	‡
EF (%)A	32	0 ± 1	0 ± 1	1 ± 1	1 ± 1	1 ± 1	2 ± 1	#
EF (%)B	30	1 ± 1	1 ± 1	1 ± 2	7 ± 2†	8 ± 2†	5 ± 2#	‡

± SEM; # p < 0.05 * p ≤ 0.01 † p<0.001 ‡p<0.0001
[A]EF = ([LVEDV-LVESV]/LVEDV)*100 (Bipl MOD)
[B]EF = (LVOT SV/LVEDV)*100 (Doppler, Bipl MOD)
Increases in SET, SV, and FS were statistically significant. The significance of increases in EF differed between methods of calculation. Statistically significant concentration dependence was observed for increases in EF and for decreases in heart rate and left ventricular end systolic volume. Treatments were well tolerated at pre-specified dosages. Results from the completed trial will be available at the time of presentation.
Conclusions: CK-452 increases systolic function in stable HF patients during intravenous administration. Data from this first Phase II trial supports translation of this mechanism into populations with more advanced heart failure.

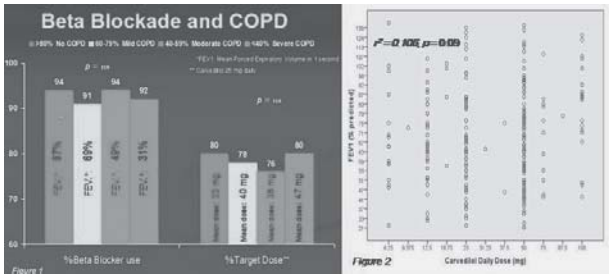
3:30 p.m.

1024-197 Use of High Dose Carvedilol in Chronic Heart Failure With Chronic Obstructive Pulmonary Disease: CIM-HF Registry Analysis

Michelle M. Harris, Linda Houston-Feenstra, Jun R. Chiong, Loma Linda University, Loma Linda, CA

Background: Use of Beta-blocker (BB) in Chronic Obstructive Pulmonary Disease (COPD) is controversial, associated with the belief that BB will exacerbate dyspnea. BB has been shown to reduce mortality in CHF. Our experience, using newer generations of BB, has shown that with carefully managed titration, in a dedicated CHF program, patients with both COPD and CHF benefit from this therapy. However, limited data exist on the long-term use of high dose BB therapy in patients with CHF and COPD.
Methods: This study evaluated the use of non-selective BB therapy in patients with both CHF and COPD as part of the Clinical Information Manager for Heart Failure (CIM-HF) registry. Designed as a prospective observational study, the proportion of BB use in patients with different degrees of COPD was evaluated.
Results: Data from 880 patients were reviewed, 312 patients had pulmonary function tests (PFT) as part of their dyspnea workup and 249 (80%) were on carvedilol. Mean duration of follow up was 4.4 years. Figure 1 demonstrates the well tolerated use of BB following long term, upward titration. Figure 2 shows poor correlation between carvedilol dosage and FEV$_1$ (% predicted). Mean and median daily carvedilol dosages were 40.25 mg and 50 mg, respectively.

Conclusion: CHF Patients with COPD tolerated long-term use of high dose BB with out exacerbation of symptoms. This study suggests that the severity of COPD should not dictate the initiation and dose titration of BB therapy.

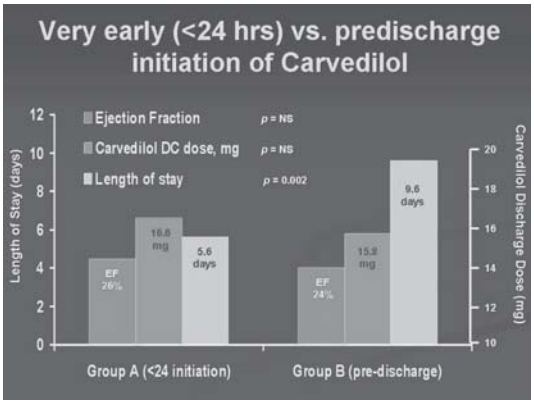


3:30 p.m.

1024-198 **Very Early Initiation (<24 Hours) of Carvedilol Shortens Length of Stay Compared to Pre-discharge Initiation in Acute Decompensated Heart Failure**

Jun R. Chiong, Jasmine Putnam, Christopher Hauschild, Loma Linda University, Loma Linda, CA

Background: The latest heart failure (HF) guidelines recommend delaying beta-blockade (BB) in acute setting. A gap exists regarding the timing of carvedilol. This may be due in part to persisting perceptions, despite recent evidence to the contrary, that BB worsens acute HF symptoms by bronchoconstriction.
Carvedilol use at the time of hospital discharge has been repeatedly shown to be well tolerated, and is associated with an early survival benefit. The aim of this study is to evaluate the strategy of early (<24 hours) vs. pre discharge (DC) initiation of carvedilol and the length of stay in acute decompensated HF.
Methods: There were 756 patient with systolic dysfunction (EF < 40%) who had carvedilol during hospitalization in 2007. We divided patients into 2 groups: Group A: Carvedilol initiated within 24 hours of admission. Group B: carvedilol given anytime prior to discharge. Patients who were already on carvedilol prior to admission and during hospitalization were excluded.
Results: Both groups have similar ejection fraction, age and discharge dose of carvedilol. Despite the similarities, early carvedilol initiation resulted in a shorter length of stay.
Conclusion: This study demonstrated that very early (<24 hours) initiation of carvedilol is associated with shorter length of stay. This finding is of significant clinical importance as it provides patients the protective benefits of therapy sooner and reduces the cost of care by shortening the length of the hospitalization.



3:30 p.m.

1024-199 **Inferiority of Insulin Sensitivity Indices From Single Time Point Assessment in Metabolic Studies in Patients With Chronic Heart Failure**

Wolfram Doehner, Stephan von Haehling, Mathias Rauchhaus, Mitja Lainscak, Dirk Habedank, Anja Sandek, Tibor Szabo, Stefan D. Anker, Charite University Medical School, Berlin, Germany

Background: Impaired insulin sensitivity (Si) indicates abnormal energy metabolism in chronic heart failure (CHF) and contributes to symptomatic status and mortality. Several indices of Si are based on mere single time assessment of fasting glucose and insulin. We aimed to assess the discriminatory power of such indices in comparison to more physiologic assessments of Si using dynamic glucose and insulin profiles.
Methods: In 105 CHF patients (NYHA I/II/III/IV 10/40/43/12, age 62±1y, peak VO2 18.2±0.7ml/kg/min, LVEF 28±2%, all mean±SEM). Si was assessed by minimal modelling using glucose and insulin profiles of a 3h intravenous glucose tolerance test. The Si indices HOmeostasis Model Assessment (HOMA: Insulin x Glucose /22,5), Fasting Insulin Resistance Index (FIRI: Insulin x Glucose / 25), and QUick Insulin CheckK Index (QUICKI: 1/ (log insulin log Glucose) were calculated from single time fasting glucose and insulin assessment.
Results Si was lower in CHF vs controls (2.53±0.26 vs 3.58±0.34, p<0.01) and decreased stepwise with NYHA class (I/II/III/IV 5.02±1.8 / 2.49±0.26 / 2.24±0.35 / 1.61±0.38, ANOVA p=0.0007). Si correlated with body mass index (BMI) (r=0.34, p<0.001) and total (r=0.28) and central (r=0.31, both p<0.01) Fat mass (DEXA scan) and with peakVO2 (r=0.23, p=0.02). Si was a prognostic marker in multivariate analysis independent of age, NYHA class, peak VO2, BMI, and LVEF (RR 0.38 [95%CI 0.21-0.67]; p=0.001). Si by minimal modelling correlated moderately with indices of HOMA, FIRI (both r=0.31, p=0.0003) and QUICKI (r=0.29, p=0.0008). HOMA identified impaired insulin sensitivity in CHF vs controls (3.45±0.29 vs 1.39±0.19) as did FIRI (3.10 vs 0.26) and QUICKI (0.34±0.01 vs 0.39±0.004, all p<0.0001). All three indices related to BMI and total and regional fat tissue in CHF (all p<0.01) but did not discriminate between NYHA classes, did not relate to peak VO2 and did not predict prognosis.
Conclusion: HOMA, FIRI and QUICKI are surrogate estimates of Si with poor discriminatory power in pathophysiologic studies in patients with CHF. Indices based on single time point estimates of Si are inferior to the physiological profile-derived assessment of insulin sensitivity by minimal modelling.

3:30 p.m.

1024-200 **Asymptomatic Left Ventricular Dysfunction in Idiopathic Dilated Cardiomyopathy: Long-Term Prognosis and Comparison Between Subgroups of Patients**

Marco Merlo, Andrea Di Lenarda, Giulia Barbati, Alberto Pivetta, Elisabetta Dalefffe, Gastone Sabbadini, Biancamaria D'Agata, Gianfranco Sinagra, Cardiovascular Department, "Ospedali Riuniti" and University of Trieste, Trieste, Italy

Background: Few data are available regarding characteristics and prognosis in patients (pts) with asymptomatic idiopathic dilated cardiomyopathy (AIDC).
Methods and Results: 744 pts with idiopathic dilated cardiomyopathy (IDC) have been enrolled in the Trieste Heart Muscle Disease Registry from 1978 to 2007: males were 75%, mean age 45±14 years; 68% were symptomatic for heart failure (HF): 307(41%) in II NYHA class, 198(27%) in III-IV NYHA class. 239 pts(32%) were asymptomatic despite impaired LV ejection fraction (LVEF<50%): 134 (56% Group A) had no previous symptoms of HF, 105 (44%, Group B) had previous symptoms of HF. In all pts without controindications treatment with ACE-inhibitors and beta-blockers were chronically used. Compared to Group B, at first evaluation Group A presented younger age (37±14 vs 42±14 years, p= 0.045), more frequent familial disease (39% vs 18%, p<0.001), less advanced heart disease (LVEF 39±7% vs 33±9%, p<0.001; LV end-diastolic diameter 62±7 vs 66±9mm, p=0.011; moderate-to-severe mitral regurgitation 7 vs 28%, p<0.001); LVEF≤30% 10 vs 43%, p<0.001). ACE inhibitors were used in 75 vs 87%, p=0.002, Beta-blockers 65 vs 79%, p=0.02. Data on medical treatment are significantly worse if compared with our symptomatic patients. During a mean follow-up of 112±63 months, 46 pts (21%) out of 239 pts with AIDC, experienced death/heart transplantation (D/HTx): 16 pts (7%) were transplanted, 7 pts (3%) died for refractory HF, 13 (6%) for unexpected sudden death/major ventricular arrhythmias (SD/MVA). At Cox analysis LVEF≤30% predicted both D/HTx (HR 3.15, 95% CI 1.5-6.7, p=0.003) and SD/MVA (HR 3.9, 95% CI 1.7-9.3, p=0.002). Kaplan-Meier analysis showed a non signifcant trend between Group A and B concerning D/HTx (at 120 months 7 vs 16%, p=0.06) and SD/MVA (17 vs 23%, p=NS).
Conclusions: in our experience the proportion of pts with AIDC at first evaluation is noteworthy. Severe LV dysfunction, present in 29% of AIDC pts, independently predicted a worse prognosis. AIDC pts demonstrated less advanced disease with respect to those who previously experienced symptoms of HF but similar prognosis on optimal medical treatment.

3:30 p.m.

1024-201 **Optimal Beta-Blocker Therapy and Lower Achieved Heart Rate Are Independently Associated With Better Survival in Heart Failure Patients That Are in Sinus Rhythm**

Damien Cullington, Kevin M. Goode, Thanjavur K. Bragadeesh, Ahmed A. Tageldien, Andrew L. Clark, John G F Cleland, University of Hull, Kingston-Upon-Hull, United Kingdom

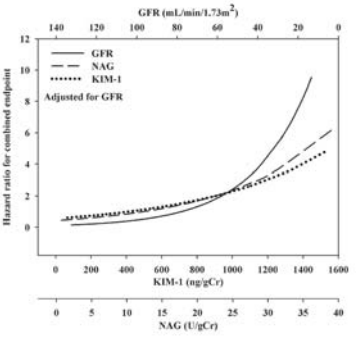
Background: Randomised controlled trials show that treatment with beta blockers (BB) reduces morbidity and mortality in patients with heart failure (HF). Whether these benefits are mediated primarily by adrenergic blockade or heart rate reduction remains uncertain. To investigate this further, we assessed the hypothesis that lower heart rate is associated with improved survival and whether this was independent of BB use in non-trial heart failure patients with left ventricular systolic dysfunction and in sinus rhythm.
Methods: Patients attending a HF clinic (Hull, UK) were recruited to a prospective cohort study. Heart rate was evaluated at 4 months following attempted optimisation of HF treatments to target doses. BB therapy was expressed as % of maximal target dose and split into those receiving no BB (0%), low target dose (0-33%) and moderate to target dose (>33%). Cox-regression models were used to determine the independent association of BB and heart rate with all cause mortality after adjusting for age, sex, and other co-morbidities commonly associated with HF.
Results: Of 937 patients, 689 (74%) patients were treated with BBs (60% carvedilol, 31% bisoprolol). Of those on BB, 272 (39%) were on low dose and 417 (61%) on moderate-to-target dose. Median age 72 (IQR 65-78), 72% male, 47% LVEF <35% and median follow-up 50 (IQR 38-60) months with 233 (25%) deaths. On adjusted Cox-regression, higher achieved heart rate (HR 1.16 per 10 bpm increase, p=0.005) and no-to-low target dose of BB therapy (HR 1.80, p=0.001) were independently associated with worse survival. Achieved heart rate was higher in the no-to-low BB group compared to the moderate-to-target BB group (median (IQR) 68 (59-80) vs 62 (56-70) bpm, p=0.0001).
Conclusions: Lower achieved heart rate and optimal BB therapy are both independently associated with better survival in HF patients in sinus rhythm. Reaching target BB therapy improves outcome independently of achieved heart rate, confirming that benefit is mediated through mechanisms other than just heart rate control.

3:30 p.m.

1024-202 Tubular Damage Is Common and Associated With Reduced Survival in Patients With Chronic Heart Failure

Kevin Damman, Dirk J. van Veldhuisen, Gerjan Navis, Vishal S. Vaidya, Tom D. Smilde, Daan B. Westenbrink, Joseph V. Bonventre, Adriaan A. Voors, Hans L. Hillege, University Medical Center Groningen, Groningen, The Netherlands

Background. Reduced glomerular filtration rate (GFR) is common in chronic heart failure (CHF). However, there is little information on the prevalence of tubular damage, and the association with renal function and prognosis in patients with CHF.
Methods. Ninety patients with CHF underwent GFR measurement by Iothalamate clearance. In addition, we studied 20 age and gender balanced controls. Kidney Injury Molecule 1 (KIM-1), Neutrophil gelatinase associated lipocalin (NGAL) and N-acetyl-β-D-glucosaminidase (NAG) were determined as selective markers of tubular damage in 24 hours urine collection. The primary endpoint consisted of the first occurrence of either all cause mortality, HTx or admission for CHF.
Results. Mean age was 58 ± 11 yr, 78% was male. Mean GFR was 78 ± 26 ml/min/1.73m^2. Urinary KIM-1 (277 (188-537) vs 136 (63-195) ng/gCr), NGAL (175 (70-346) vs 37 (6-58) µg/gCr) and NAG (12 (6-17) vs 1.6 (0.7-2.2) U/gCr) levels were highly elevated compared to controls (all $P < 0.001$). NAG but not NGAL and KIM-1 was related to GFR (r =-0.34). Both urinary NAG and KIM-1 were strong predictors of outcome, even independent of GFR: NAG HR 1.42 (1.02-1.94) per 5 U/gCr, P=0.039 and KIM-1 HR 1.15 (1.02-1.30) per 100ng/gCr, $P = 0.025$ (FIGURE).
Conclusion. Tubular damage is prevalent in patients with CHF. Both increased urinary NAG and KIM-1 levels are associated with reduced survival, independent of GFR.



3:30 p.m.

1024-203 Quality of Care for Atrial Fibrillation Among Patients Hospitalized for Heart Failure

Jonathan P. Piccini, Adrian F. Hernandez, Xin Zhao, Manesh R. Patel, William R. Lewis, Eric D. Peterson, Gregg C. Fonarow, Duke Clinical Research Institute, Durham, NC

Background: Atrial fibrillation (AF) is common in heart failure (HF) and guidelines recommend discharge on warfarin for stroke prophylaxis. However, the frequency and factors associated with the guideline adherence are poorly described.
Methods: We analyzed 72,534 HF admissions at 255 hospitals participating in the AHA Get With the Guidelines^{SM} HF program. Multivariable logistic regression was used to identify independent factors associated with warfarin use at discharge.
Results: In this HF population, 20.5% (n=14,901) had AF on admission; while another 13.7% (9918) had a prior history of AF but were in a regular rhythm at admission. Contraindications to warfarin therapy were documented in 9.2%. Among eligible HF patients without contraindications, the median prevalence of warfarin therapy at discharge was 64.9% (IQR 55.5 - 73.4) and did not improve during the 3.5 years of study. After adjustment, major factors associated with lower odds of warfarin use at discharge included increasing age, non-white race, anemia, and treatment in the south (Table). Warfarin use also varied inversely with $CHADS_2$ risk (70.9% to 59.5% for $CHADS_2$ 1-6, p<.0001).
Conclusions: Guideline recommended warfarin use in patients with AF and HF is suboptimal, has not improved over time, and varies significantly according to age, race, risk profile, region, and hospital site.

Table. Independent predictors of warfarin use at discharge.

	Odds ratio (95% CI)	P Value
Age (per 10 years increase)	0.83 (0.80-0.88)	<.001
Female (vs male)	0.93 (0.87-1.00)	0.067
Race (Non-white vs white)	0.68 (0.60-0.78)	<.001
Renal insufficiency	0.8 (0.73-0.88)	<.001
Anemia	0.70 (0.63-0.78)	<.001
Prior stroke or transient ischemic attack	1.17 (1.04-1.31)	0.008
Hospital size (per 100 beds increase)	1.06 (1.03-1.10)	<.001
Geographic Region		0.047
Midwest vs Northeast	0.92 (0.75-1.13	
South vs Northeast	0.77 (0.64-0.93)	
West vs Northeast	0.82 (0.63-1.07)	

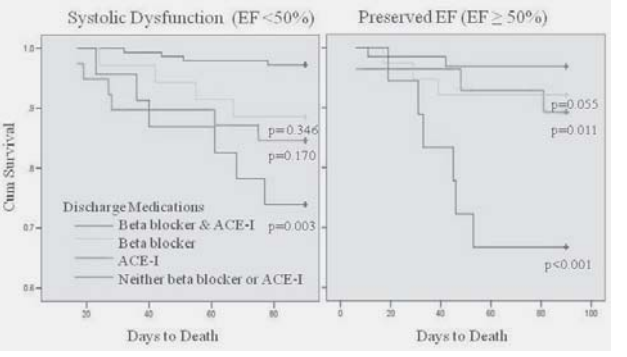
*Eligible patients without documented contraindications or other reason for not prescribing

3:30 p.m.

1024-204 Improved Mortality Associated With ACE-I and Beta Blocker Treatment in Heart Failure With Preserved Ejection Fraction: An Exploratory Analysis of the Biomarkers in ACute Heart Failure (BACH) Trial

Niraj Parekh, Kabir Singh, Daniel Jones, Paul Clopton, Inder Anand, Robert Christenson, Lori B. Daniels, Salvatore DiSomma, Gerasimos Filippatos, Christopher Hogan, Martin Möckel, Michael Hudson, Christian Müller, Sean-Xavier Neath, Leong Ng, Richard Nowak, W. Franklin Peacock, Piotr Ponikowski, A. Mark Richards, Mihael Potocki, Alan Wu, Stefan D. Anker, Alan Maisel, Veterans Affairs San Diego Health Care System, San Diego, CA, University of California San Diego, San Diego, CA

Background: There is limited evidence on the optimal management of preserved ejection fraction (EF) heart failure (HF). We compared outcomes of patients hospitalized with acute HF based on their systolic function and discharge medications.
Methods: This study was an exploratory analysis of the Biomarkers in ACute Heart Failure (BACH) trial, a multi-center study assessing novel biomarkers in dyspneic patients presenting to emergency department. Enrolled patients who were admitted to the hospital were followed for 90-days for all-cause mortality.
Results: Of 1641 enrolled patients, 429 had a primary diagnosis of HF and EF data, and 50 of these patients died during follow-up. 162 of these patients had preserved EF with an EF ≥ 50%. In both reduced and preserved EF groups, patients discharged on either ACE-I or beta blocker had better survival (see figure containing Kaplan-Meier survival curves). Survival benefit was greatest in patients discharged on dual therapy, and this persisted after adjusting for age, gender, history of HF, diabetes and chronic renal insufficiency.
Conclusions: After hospitalization for acute HF, discharge on ACE-I and beta blockers is associated with substantial survival benefit in patients with preserved ejection fraction. This strongly suggests a new therapeutic approach for acute HF patients with preserved EF.



3:30 p.m.

1024-205 Inferior Vena Cava Inspiratory Collapsibility as a Predictor of Change in Renal Function During Hospitalization for Acute Decompensated Heart Failure

Jeffrey Testani, Lee Goldberg, Julio A. Chirinos, Amit Khera, James N. Kirkpatrick, University of Pennsylvania, Philadelphia, PA

Background: The presumed pathophysiology of cardiac renal interactions traditionally assumed that reduced cardiac output lead to a reduction in renal perfusion with a cause and effect relationship. These assumptions have recently been challenged and the possibility of multiple distinct mechanisms of the cardiorenal syndrome have been raised. Animal models support renal venous hypertension as one of the candidate mechanisms for the syndrome.
Methods: We reviewed consecutive admissions to the general cardiology or medicine services with a primary discharge diagnosis of congestive heart failure. Inclusion required an echocardiogram day 1 or 2 of the hospitalization, a B-type natriuretic peptide (BNP) level >400 pg/ml, intravenous diuretic use > 50% of the hospitalization, length of stay 3 to 10 days, and the non-use of inotropes. The degree of inspiratory collapse of the inferior vena cava (IVC) was used as a noninvasive surrogate of renal venous pressure and was evaluated for its association with changes in renal function. IVC collapse was classified into groups as no collapse (G1), <50% collapse (G2), >50% collapse (G3), and full collapse (G4).
Results: 130 patients met the entry criteria with 18 patients in G1, 47 in G2, 40 in G3, and 25 in G4. Between groups there were no statistically significant differences in BNP, serum sodium, volume overload on chest X-ray, length of stay, systolic blood pressure (SBP), ejection fraction, hemoglobin, or maximum diuretic dose. By the time of discharge mean glomerular filtration rate (GFR) increased by 26.7% in G1 but had decreased by 2.7% in G2, 0.1% in G3, and 7.3% in G4 (p=0.0004). Worsening renal function, defined as a decrease in GFR by 25%, did not occur in any patients in G1 but occurred in 17.9% of non-G1 patients (p=0.04). Adjusting for SBP, blood urea nitrogen, BNP, baseline GFR, hemoglobin, and maximum diuretic dose IVC collapse remained a significant predictor of change in GFR.
Conclusion: IVC non-collapsibility predicts improvement in renal function during treatment of acute decompensated heart failure despite otherwise similar patient characteristics. These data suggest a role of renal venous hypertension in the pathogenesis of the cardiorenal syndrome.

3:30 p.m.

1024-206 **Effects of the Selective PPAR Gamma Modulating Angiotensin Receptor Blocker Irbesartan on Impaired Insulin Sensitivity in Patients With Chronic Heart Failure IRIS-HF: A Placebo-Controlled, Double Blinded, Randomized Study**

Wolfram Doehner, Cornelia Kenneke, Johanna Todorovic, Mathias Rauchhaus, Stephan von Haehling, Stefan D. Anker, Charite University Medical School, Berlin, Germany

Background: Impaired insulin sensitivity (Si) is common in chronic heart failure (CHF), contributes to symptomatic status and independently predicts prognosis. It has been suggested that the angiotensin II-receptor antagonist irbesartan can improve insulin sensitivity via selective activation of the peroxisome proliferator-activated receptor gamma (PPAR gamma). We aimed to assess the effect of irbesartan on impaired insulin sensitivity in patients with CHF.
Methods: In a prospective, placebo-controlled, double-blinded, randomized single center study we included 36 non-diabetic patients with stable ischemic CHF (age 63±9y, BMI 28.2±3.9kg/m^2, peakVO_2 16.6±4.8mL/kg/min all mean ±SD). Irbesartan (target dose 300mg/d) or placebo was given on top of standard optimum CHF therapy including ACE inhibitor and beta-blockers for 16 weeks. Change of insulin sensitivity from baseline to week 16 (primary endpoint) was assessed using the minimal modelling technique from glucose and insulin profiles of a frequently sampled intravenous glucose tolerance test.
Results: At baseline both groups were similar for age, NYHA class, peak VO_2, BMI, body composition (DEXA scan), Si (p=0.2), and main clinical characteristics. Si was 2.51±1.58 $min^{-1}.\mu U.mL^{-1}.10^4$ in the study population, which is 30% lower than in healthy controls of similar age (P<0.05). In the irbesartan treated group S_I increased by 26% (p<0.001 within group), but it decreased by 15% in the placebo group (p=0.17 within group). Change in S_I from baseline was significantly different between groups (mean difference 1.044 $min^{-1}.\mu U.mL^{-1}.10^4$; 95%CI 0.45 to 1.64, p=0.001). Treatment with irbesartan was well tolerated. NYHA class, peak VO_2 and body composition did not change but blood pressure significantly decreased on irbesartan (-5±2 mmHg, p<0.002).
Conclusion: Our study shows that 16 weeks of added therapy with irbesartan compared to placebo significantly improves impaired insulin sensitivity in non-diabetic patients with chronic heart failure. Whether this metabolic effect of irbesartan translates into additional clinical benefits for heart failure patients should be tested in larger studies.

3:30 p.m.

1024-207 **Relaxin, A Novel, Multiple Mechanism Vasodilator, for the Treatment of Acute Heart Failure - The PreRELAX-AHF Study**

John R. Teerlink, Marco Metra, G. Michael Felker, Adriaan A. Voors, Beth Weatherley, Elaine Unemori, Sam L. Teichman, Gad Cotter, Section of Cardiology, Veterans Affairs Medical Center, University of California, San Francisco, CA, Section of Cardiovascular Diseases, Department of Experimental And Applied Medicine, Univ of Brescia, Brescia, Italy

Relaxin is a naturally-occurring peptide that is known to affect multiple vascular control pathways. In preliminary studies, it reduced wedge pressure and increased cardiac output.
Objective: PreRELAX-AHF is the pilot for a phase 3 trial evaluating safety and dose-response to 48h of IV relaxin in patients with acute heart failure (AHF) and normal to high systolic blood pressure (SBP).
Methods: Eligible patients were hospitalized for AHF with dyspnea, congestion on chest X-ray, NTproBNP >1,400 pg/ml, SBP >125 mmHg and eGFR 30-75 mL/min. Randomization (double-blind) was <16 h from presentation to placebo (PBO) or relaxin 10, 30, 100 or 250 mcg/kg/d. Endpoints of interest were dyspnea (by 7-pt Likert and Visual Analog Scales [VAS]), clinical outcomes and renal function.
Results: In this interim analysis, 209 patients in 8 countries were followed for >14 days. Baseline characteristics were balanced across groups. Improvement in dyspnea was greater in the relaxin arms vs PBO, with greater efficacy seen at 10, 30 and 100 mcg/kg/d at all time points from 6h to Day 14. The largest effects were seen at 30 mcg/kg/d. Dyspnea improvement by VAS was 96% greater in the 30 mcg group than placebo at 6h. The VAS change from baseline over time was significant (P=0.03 for 30 mcg vs PBO, for 6h to Day 14). Time to first moderate or marked improvement by Likert was 2.7, 2.4, 1.8, 2.4 and 2.2 days in PBO, 10, 30, 100 and 250 dose groups (P<0.05, relaxin 30 vs PBO). Similar trends were seen in measures of HF including greater weight loss (up to 1 kg difference), lower IV loop diuretic use and lower incidence of in hospital worsening HF. Mean length of stay was shorter in the active arms by 1-2.5 days, most pronounced at 30 mcg/kg/d. There were no safety or tolerability issues, including the absence of symptomatic hypotension or worsening of renal function. Follow-up to Day 180 will be presented.
Conclusion: In patients with AHF and normal to high SBP (>75% of AHF patients), early IV relaxin administration for 48 hours may produce rapid and sustained improvement in dyspnea and other heart failure measures, without evidence of symptomatic hypotension or adverse effects on renal function. Larger studies are planned with relaxin to confirm these effects.

3:30 p.m.

1024-208 **Does Endothelial Dysfunction Contribute to Exercise Limitation in Heart Failure With Preserved Ejection Fraction?**

Barry A. Borlaug, Thomas P. Olson, Carolyn S.P. Lam, Kelly S. Flood, Bruce D. Johnson, Margaret M. Redfield, Amir Lerman, Mayo Clinic, Rochester, MN

Background Arterial stiffening and impaired vasodilation with exercise are frequently observed in Heart Failure (HF) with preserved Ejection Fraction (HFpEF). While endothelial dysfunction is common in systolic HF, its role in HFpEF remains uncertain.
Objectives To compare endothelial function and vascular stiffening in patients with HFpEF and hypertension (HTN) and determine relationships with exercise performance.
Methods Age/gender matched subjects with HFpEF (n=21) and HTN (n=19) underwent baseline assessment of peripheral reactive hyperemia index (RHI), a measure of endothelium-dependent vasodilation, and central aortic pulse pressure (PP), an index of vascular stiffness, followed by metabolic exercise testing (Ex). Systemic vascular resistance (SVR) was determined from echo-Doppler at rest and Ex.
Results RHI and PP were similar in HFpEF and HTN, while Ex capacity was reduced in HFpEF (*p<0.0001; Table). In combined analysis, ΔSVR with Ex was associated with peak VO2 (r= -0.55, p<0.05). ΔSVR was lower in HFpEF than HTN (†p=0.003). In HFpEF, peak VO2 was directly related to resting RHI (r= 0.50, p<0.05) and inversely to aortic PP (r= -0.51, p<0.05), but neither of the latter was associated with ΔSVR.
Conclusions While patients with HFpEF display abnormal vasodilation with exercise, resting indices of endothelial function are similar to HTN. Endothelial dysfunction and vascular stiffening contribute to exercise limitation in HFpEF and may serve as novel therapeutic targets.

	HTN (n=19)	HFpEF (n=21)
Aortic Systolic Blood pressure (mmHg)	130±12	125±19
Aortic Pulse Pressure (mmHg)	54±12	59±22
Reactive Hyperemia Index	2.31±0.66	2.18±0.69
Percent with Endothelial Dysfunction (RHI<2)	28	42
Peak VO_2 (ml/min*kg)	18.6±3.7	12.7±3.0*
Baseline SVR(DSC)	1780±400	1600±500
ΔSVR with Exercise(DSC)	-980±300	-620±350†

ACC.ORAL CONTRIBUTIONS

901

Ventricular Assist Devices: The Good, the Bad and the Ugly

Monday, March 30, 2009, 8:00 a.m.-9:30 a.m.
Orange County Convention Center, Room W308A

8:00 a.m.

0901-3 **Predictors of Stroke on Heartmate II Left Ventricular Assist Device**

Biswajit Kar, Sukhdeep S. Basra, Pranav Loyalka, Igor D. Gregoric, Reynolds Delgado, Andrew Civitello, Roberta Bogaev, William Cohn, Antonius Attallah, Rohan Wagle, O. H. Frazier, Texas Heart Institute, Houston, TX, University of Texas at Houston, Houston, TX

Background: The Heartmate II is an effective treatment alternative for patients with end stage heart failure refractory to medical therapy. However, a relatively large proportion of patients on Heartmate II develop stroke. We aimed to determine the predictors of stroke in this patient population.
Methods and Materials: All patients (n=71) implanted with Heartmate II at our institute were included in the study. Patients developing a stroke were classified as cases (n = 18) with the remaining as controls (n=53). We specifically assessed the following predictors of stroke: Non-Pulsatile flow, Anticoagulation, Mean Arterial Pressure (MAP) and Infections.
Results: The mean duration of support for cases and controls was 429.06 and 304.92 days respectively, with a median implant-stroke interval of 174 days. On statistical analysis, Non Pulsatile Flow (O.R: 4.68, 72.2% vs. 37.7% in cases and controls; p = 0.039) and Bacteremia (O.R: 9.59, 88.9% vs. 51% in cases and controls ; p = 0.045) were found to be significantly associated with an increased risk of developing stroke. This remained significant even after adjusting for potential confounders like duration of support, MAP, anticoagulation status, gender, and atrial fibrillation using logistic regression in a multivariate analysis. However, Anticoagulation (Median INR 1.3 vs. 1.55 in cases and controls, p = 0.181) and MAP (Median 85.5 vs. 78.6 mm Hg in cases and controls; p = 0.123) were not significantly associated with stroke. 53.8% of the cases suffered from acute peristroke infections (positive cultures 15 days before upto 5 days after stroke).
Conclusions: Traditional risk factors of stroke like Diabetes, Hypertension, Hyperlipidemia, Age, Smoking and Atrial Fibrillation are not associated with stroke in patients on Heartmate II LVAD. Instead, Non-pulsatile flow and Bacteremia are the important predictors of stroke in patients on Heartmate II.

8:15 a.m.

0901-4 **Validation of the Model for End-Stage Liver Disease in Predicting Left Ventricular Assist Device Mortality**

Jennifer Cowger Matthews, Todd F. Dardas, Jonathan W. Haft, Francis D. Pagani, Keith D. Aaronson, University of Michigan Health System, Ann Arbor, MI

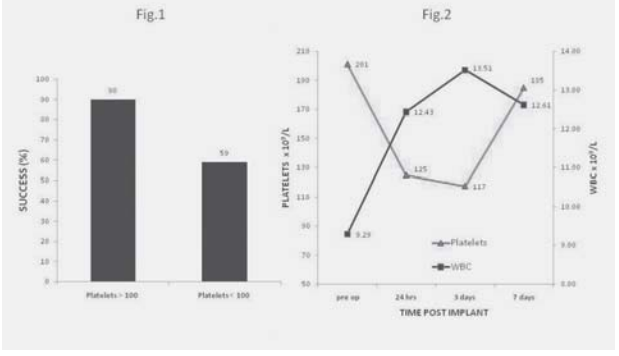
Background: Preoperative Model for End-Stage Liver Disease (MELD) scores have previously been shown to predict mortality in LVAD recipients at our center. Our aim was to validate the prior findings using a national LVAD database.
Methods: Preoperative MELD scores were calculated for subjects undergoing LVAD support enrolled into the INTERMACS registry between 2006-2008. MELD score= 9.57(logeCreatinine) + 3.78(logeBilirubin) + 11.2(logeINR) + 6.43, with minimums for all variables set at 1.0. Complete data for MELD score calculations were available on 324 (87%) of 372 subjects.
The primary outcome of interest was the relationship between preoperative MELD score and operative death (death within 30 days of LVAD operation). Student's t tests were used to compare mean MELD scores amongst operative deaths and survivors with odds ratios (OR, 95% CI) generated from logistic regression. MELD scores were dichotomized at the previously published threshold of 17. Secondary outcomes included survival and the hazard ratio for death at 6 months in high (MELD ≥17) versus low (MELD <17) strata, calculated with Kaplan-Meier and Cox regression analyses, respectively.
Results: The mean±standard deviation preoperative MELD score for the entire cohort was 15.2±5.8, with mean creatinine, bilirubin, and INRs of 1.6 ±0.9 mg/dL, 1.7±0.1 mg/dL, and 1.4±0.02 sec., respectively. Operative deaths (n=19, 6%) had higher mean (95% CI) MELD scores [17.9(14.2,21.6)] than survivors [15.0(14.4,15.7); p=0.036)], such that the odds of operative death increased 50% [OR 1.5(1.1,2.1)] for each 5-unit increase in MELD. At 6 months, survival for subjects with MELD scores ≥17 (n=120) was 67±5% compared with 82±3% in subjects with lower scores (p=0.032). At 6 months, the hazard ratio for death (n=56) in subjects with MELD scores ≥17 was 1.76 (1.04,2.98) times that of those with lower scores (p=0.035).
Conclusion: Preoperative MELD scores, a marker of multisystem dysfunction, are predictive of operative and 6-month LVAD mortality in INTERMACS and may serve as an important preoperative tool in assessing LVAD risk.

8:30 a.m.

0901-5 **Early Decrease in Platelet Counts Following Left Ventricular Assist Devices Implantation Is Part of the Systemic Inflammatory Response Syndrome and a Marker of Poor Long-Term Outcome.**

Andrea Mignatti, Daniel B. Sims, Nir Uriel, Basil Ramlawi, Steve Holleran, Yoshifumi Naka, Ulrich P. Jorde, Columbia University, New York, NY

Background: Alterations of platelet (plt) count have been described as part of the systemic inflammatory response syndrome (SIRS) following open heart surgery. Several studies suggest that SIRS can be modulated using perioperative steroid and/or statin therapy. Plt behavior has not been studied after implantation of left ventricular assist devices (LVADS).
Methods and results: Retrospective single center study of 114 consecutive HM I & II implants performed at our institution for BTT or DT since 04/2004. For the purposes of this study, success was defined as being alive and/or transplanted 180 days post-op. Mean plt count on day 3 (123 vs 91, p 0.009) and day 7 (196 vs 130 p 0.001) were significantly higher in success (n=87) compared to failure (n=27) pts. Overall success was 77 %. However, success rate was 59% in pts whose plt count averaged < 100 between day 3 and 7 and 90% in those who averaged > 100 (Fig 1).Decrease in plt was weakly correlated with pump time (R= 0.3 p 0.01) and pump time was not different between success and failure pts (105 vs 111 min P=NS). Decrease in platelet count was significantly correlated with increase in WBC (median correlation coeff = -0.45 p<0.01) (Fig. 2).
Conclusion: Early plt count decrease following LVAD implant at least in part reflects SIRS and the degree of plt decrease is a marker of long term outcome. Pharmacological modulation of SIRS occurring in the early postoperative period should be investigated and may improve long term outcomes of pts undergoing LVAD implantation.



8:45 a.m.

0901-6 **Predictors of Improvement in Right Ventricular Function After Placement of a Left Ventricular Assist Device**

Barry A. Boilson, John A. Schirger, Basar Sareyyupoglu, Sudhir S. Kushwaha, Irina Penev, Christopher GA McGregor, Richard C. Daly, Lucian A. Durham, III, Brooks S. Edwards, Soon J. Park, Mayo Clinic, Rochester, MN

Background: End stage heart failure is increasing in prevalence and left ventricular assist device (LVAD) technology being used increasingly as a bridge to transplantation and also as destination therapy. Although LVAD placement is followed by left ventricular offloading and increase in systemic cardiac output, persistent right ventricular (RV) dysfunction is common.The aim of this study was to investigate the baseline characteristics which contribute most to improvement in right ventricular dysfunction after LVAD placement.
Methods: All patients who underwent LVAD implantation at our institution between May 2003 and July 2008 were evaluated. The primary endpoint was improvement in RV function measured by echo. Secondary endpoints were improvement in measures of pulmonary hypertension by right heart catheterization and echo. Both bridge to transplant and destination therapy patients were included. Both continuous flow and pulsatile devices were included.
Results:A total of 57 patients were studied. Mean duration of followup was 230.5 days. Mean age was 58.4±12.3 years. Baseline mean peak VO2 was 10.3±2.1 ml/kg/min, mean serum creatinine 1.5±0.5 mg/dl, and mean BNP 1688±1195 pg/ml. The most powerful predictors of improvement in right ventricular function at last followup were baseline severity of mitral valve regurgitation (MR) (p=0.0006, R=-0.51), tricuspid valve regurgitation (TR) (p=0.01, R=0.39) and pulmonary vascular resistance (PVR) (p=0.006, R=0.42). Similarly, improvement in pulmonary hypertension was predicted by baseline MR (p=0.005, R=0.4), PCWP (p=0.002, R=0.44) and PVR (p<0.0001, R=0.53). Predictors of change in PVR were baseline PA pressure (p=0.0002, R=0.5), MR severity (p=0.05, R=0.28)and PVR at baseline (p<0.0001, R=0.9)
Conclusions: Improvement in RV function improves most after LVAD implantation when it occurs in the setting of severe MR. Dramatic offloading of the left ventricle and reduction in MR severity in these patients post LVAD placement results in a significant drop in RV afterload and PVR which facilitates recovery of RV function. RV dysfunction present at baseline in the absence of significant MR may not improve to the same degree post LVAD placement.

9:00 a.m.

0901-7 **Ventricular Assist Device Removal After Cardiac Recovery: Main Predictors for Long-Term Outcome Without Transplantation or Assist Device Re-Implantation**

Michael Dandel, Yuguo Weng, Henryk Siniawski, Hans B. Lehmkuhl, Thorsten Drews, Evgenij Potapov, Thomas Krabatsch, Christoph Knosalla, Roland Hetzer, Deutsches Herzzentrum Berlin, Berlin, Germany

Background: There is increasing evidence for cardiac recovery which allows ventricular assist device (VAD) removal. However, few chronic heart failure (HF) patients have been weaned from VADs, most of them only recently. Thus, long-term (> 5 years) outcome data after VAD removal are few. Now that our patient cohort with post-weaning stability for > 5 years has become larger, we focused on these patients, in order to obtain new information for future weaning decisions.
Methods: Among 84 patients weaned from VADs since 3/1995 we selected only patients (n = 36) who were weaned ≥ 5 years ago, before 9/2003. We evaluated echocardiogtaphic (ECHO) data recorded before VAD implantation and during pre-explantation "off-pump" trials, HF duration before VAD implantation, duration of mechanical support, and stability of unloading-induced recovery before and early after VAD removal.
Results: Of 36 evaluated patients, 33 (91.7%) had non-ischemic, and the other 3 ischemic cardiomyopathy. Only 2 had BVADs; the other 34 had LVADs. Post-weaning 5- and 10-year survival with native hearts was 76.5% and 70.6.%, respectively. Post-weaning survival for ≥ 13 years was reached by 3 patients. During the first 5 post-weaning years, HF recurred in 13 (36.1%) patients (9 underwent HTx, one received another LVAD and 3 died). Patients with ≥ 5 years stability were younger, their history of HF and recovery time during unloading were shorter and pre-weaning LV assessment revealed lower diameters, less altered geometry and higher LVEF. For LVEF ≥ 45% at end-diastolic diameter ≤ 55mm the predictive value for ≥ 5 year was 88.9%. Early post-wening time course of LVEF also appeared predictive for long-term stability. History of HF > 5 years and pre-weaning instability of unloading-induced recovery appeared predictive for HF recurrence.
Conclusions: Long-term successful weaning from VADs is possible even in patients with chronic HF and incomplete cardiac recovery. Pre-explantation off pump ECHO-data, stability of recovery, duration of HF before VAD insertion and duration of VAD support allow identification of patients with the potential to remain stable for > 5 years. LVEF time course early after-weaning facilitates prognostic assessment.

ACC.POSTER CONTRIBUTIONS

1033

Myocardial Function/Heart Failure--Clinical Pharmacological Treatment; Cardiomyopathies/Myocarditis/Pericardial Disease

Monday, March 30, 2009, 9:30 a.m.-12:30 p.m.
Orange County Convention Center, West Hall D

9:30 a.m.

1033-165 Intermittent Claudication as a New Predictor of Outcome in Heart Failure: Evidence From the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)

John J. V. McMurray, Peter Dunselman, John Wikstrand, Magnus Lindberg, Hans Wedel, Finn Waagstein, John Kjekshus, Ake Hjalmarson, University of Glasgow, Glasgow, United Kingdom

Background: Patients ≥60 years with NYHA class II-IV, low ejection fraction (EF) heart failure (HF) of ischemic etiology were enrolled in CORONA. Rosuvastatin did not reduce mortality. Intermittent claudication (IC) is an important predictor of clinical outcome in patients with coronary heart disease but its prognostic importance in HF has not been studied.
Methods: To determine whether IC is an independent predictor of mortality in ischemic, systolic, HF we built a multivariable model, first using demographic/clinical variables (step 1), then adding biochemical measures (step 2) and finally incorporating high-sensitivity C-reactive protein (hsCRP) and N-terminal pro B-type natriuretic-peptide (NT-BNP) - 3342 patients had all variables measured.
Results: 637 patients in CORONA had IC. 38% of patients with IC died compared to 28% of those without, p<0.00001 (934 deaths overall). The table shows the top ten predictors of death at step 1, ranked according to the Wald χ^2 (total model χ^2 343). Creatinine was most predictive at step 2 (χ^2 440). Log NT-BNP was the most powerful of the 14 independently predictive variables at step 3 (χ^2 600). IC remained an independent predictor of mortality at all three steps.
Conclusion: IC is a previously unrecognized independent predictor of outcome in HF.

Table: Multiple Cox regression: all-cause mortality

Variable	Hazard (95% CI)	χ^2	p-value
Age/10	1.44 (1.31,1.58)	56	<0.0001
Ejection fraction *100	0.97 (0.96,0.98)	44	<0.0001
BMI	0.95 (0.93,0.96)	42	<0.0001
Diabetes Mellitus	1.44 (1.25,1.66)	25	<0.0001
Sex	0.67 (0.57,0.80)	22	<0.0001
NYHA	1.40 (1.21,1.62)	20	<0.0001
Intermittent claudi.	1.40 (1.18,1.67)	14	0.0002
Heart rate/10	1.11 (1.05,1.17)	12	0.0005
SBP/10	0.94 (0.90,0.98)	10	0.0020

9:30 a.m.

1033-166 Continuous Infusion of Furosemide Combined With Low Dose Dopamine Compared to Intermittent Boluses in Acutely Decompensated Heart Failure Patients is Less Nephrotoxic and Carries a Lower Readmission at 30 Days

Emad F. Aziz, Eyal Herzog, Amjad Nader, Manpreet Singh Sabharwal, Dan Musat, Ajay Shah, Rishi Malhan, Divyajot Sandhu, Raja Singh, Sahil Jaiswal, Deborah Tormey, Suzanne Karl, Amanda Schneider, Marrick Kukin, St. Luke's-Roosevelt Hospital Center, New York City, NY

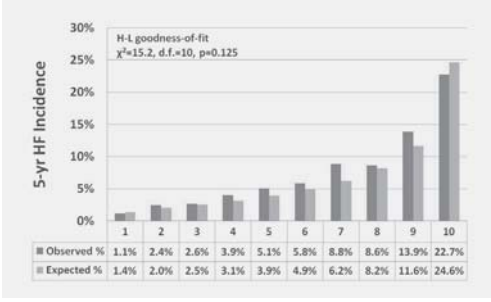
Background: Furosemide is a potent loop diuretic that is widely used in management of heart failure. Several reports have suggested that continuous intravenous administration of loop diuretics may be superior to intermittent administration. In addition the effect of low dose dopamine might be of benefit to this patient cohort.
Methods: To test this hypothesis we retrospectively evaluated 45 consecutive Cardiac Care unit patients, who admitted with acute decompensated heart failure (ADHF) and compared the effect of low dose dopamine and Continuous Furosemide infusion (Group A) to the standard of care with IV Furosemide boluses (Group B). Furosemide infusion was started at 0.2-0.4 mg/kg/hr and Dopamine infusion was at 1-2 mcg/kg/min; primarily used in 'sicker' patients with creatinine higher than 2.1. Group B was managed according to our novel heart failure pathway by which outpatient total oral daily Furosemide dose is converted into intravenous route. The effect on renal function and readmission rate was recorded.
Results: Among 45 patients (55% males, average age 74, range 46 - 96 years) 35% had ischemic cardiomyopathy, NYHA functional Class was 2.9 ± 1.2 and average EF was 27 ± 15%. Average admission Sodium was 138 ± 5.4 mEq/L, Potassium 4.6 ± 0.8mEq/L, Blood Urea Nitrogen (BUN) 39 ± 25 mg/dL, Creatinine (Cr) 1.9 ± 1 mg/dL and B-type Natriuretic Peptide (BNP) 1135 ± 894 pg/mL. Furosemide and dopamine infusions were used in 21 patients and IV Furosemide bolus was used in 24 patients. Patients in Group A had Cr 2.1 ± 0.6, BUN level of 47 ± 26 and BNP level of 1464 ± 1086 compared to group B patients with Cr 1.7 ± 0.8, BUN of 32 ± 21 and BNP of 846 ± 562. The average Furosemide infusion dose in group A was 6.9 mg/hr compared to 7.6 mg/hr for group B (P=NS). At the end of the study, patients in group A had lower Cr 1.5 ± 0.5 (p=0.0025), lower BUN 26.8 ± 16.4 (p=0.06), shorter stay in the CCU (p=0.06) and most importantly lower readmission rate at 30 days (p=0.028)
Conclusions: Continuous Infusion of Furosemide in addition to Low Dose Dopamine is safe, effective and less nephrotoxic than intermittent boluses in patients admitted with acute decompensated heart failure and carries shorter ccu stay and lower readmission at 30-days.

9:30 a.m.

1033-167 Prediction of Incident Heart Failure in the Elderly: Validation of the Health ABC HF Model in the Cardiovascular Health Study

Andreas P. Kalogeropoulos, Vasiliki V. Georgiopoulou, Tamara B. Harris, Ramachandran S. Vasan, Andrew L. Smith, Nicholas L. Smith, Stephen B. Kritchevsky, Anne Newman, Peter WF Wilson, Bruce M. Psaty, Javed Butler, Emory University, Atlanta, GA

Background: The published Health ABC Heart Failure (HF) model uses nine routinely available clinical variables (age, history of coronary heart disease, smoking, ECG left ventricular hypertrophy, blood pressure, heart rate, and plasma levels of glucose, creatinine, and albumin) to estimate 5-yr incident HF risk in the elderly. We evaluated the external validity of the model in the Cardiovascular Health Study (CHS).
Methods: Observed HF incidence rates in 5335 CHS participants (median age 71 yr, 57.6% female, 84.7% white) without baseline HF were compared with 5-yr HF risk estimates derived from the model. Goodness-of-fit, calibration, and discrimination of the model were evaluated.
Results: Over 5 years of follow-up, there were 400 (7.5%) new HF events (16.2/1000 person-years). Observed HF rates in CHS closely followed the model-predicted rates across deciles of risk (Fig. 1), suggesting adequate model fit. The weighted sum of risk factors of the model had a β=0.95 (95% CI, 0.85-1.05, p=0.316 vs. optimal β=1), suggesting adequate calibration. Results were consistent across gender and race. The C-index was 0.74 (95% CI 0.72-0.76) as compared to optimism-corrected 0.72 in the derivation cohort, indicating acceptable discrimination.
Conclusions: The Health ABC HF model predicted the 5-yr incident HF risk in the community-based CHS sample, supporting the model's external validity and suggesting that the model may be used to identify high-risk individuals in the community who could be targeted to prevent HF.

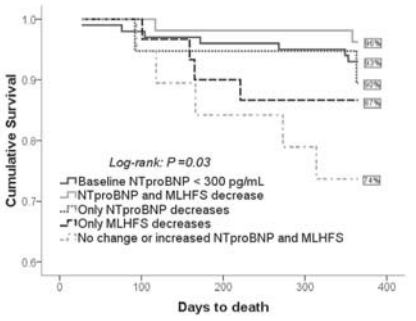


9:30 a.m.

1033-168 Interpreting the Follow-Up NT-ProBNP Concentration and Symptoms After Hospitalization for Acute Dyspnea

Keyur B. Shah, Willem J. Kop, Robert H. Christenson, Deborah B. Diercks, Dick Kuo, Sue Henderson, Christopher R. deFilippi, University of Maryland School of Medicine, Baltimore, MD, Baltimore Veterans Affairs Medical Center, Baltimore, MD

Background: Elevated NTproBNP levels in acute dyspnea patients (pts) identifies increased mortality irrespective of diagnosis. The significance of a change in level compared to symptoms on outpatient follow-up is uncertain.
Methods: 262 pts (58±14 yrs, 40% female) presenting with dyspnea were prospectively enrolled and had 30 day follow-up. Clinical data, Minnesota Living with Heart Failure Score (MLHFS), and NTproBNP levels were obtained. A change in NTproBNP and MLHFS was considered 25% and 5 points. The predictive value of changes in NTproBNP and MLHFS for 1-year mortality were evaluated by Cox proportional hazards and KM analysis.
Results: At 30 day follow-up, we observed significant decreases of NTproBNP levels (median [IQR]; 312 [37-2299] vs 289 [79-1439]; P=0.03, 109 (48%) decreasing by > 25%), and MLHFS (55±24 vs 43±29; P<0.001, 164(62%) decreasing > 5). 251 (96%) At 1 year, 23 (9%) had died. Compared to pts with baseline NTproBNP < 300 pg/mL (n=132): elevated NTproBNP pts that didn't decrease were at higher risk of death (RR=2.69, 95% CI=1.07-6.80) vs pts that did decrease (RR=0.75, 95% CI=0.23-2.44). When combining NTproBNP and symptoms, pts who had both no decrease in either NTproBNP and MLHFS at follow-up were at highest risk of death (RR=4.14, 95% CI=1.31-13.07). Decrease of either variable identified intermediate risk (figure).
Conclusions: Outpatient follow-up for change in both NTproBNP and symptoms in acute dyspnea pts with elevated NTproBNP is important for long-term risk stratification.



9:30 a.m.

1033-169 **Short-Term Treatment With Rosuvastatin Increases the Number of Endothelial Progenitor Cells in Patients With Heart Failure**

Dimitris Tousoulis, Ioannis Andreou, Meletios-Athanasios Dimopoulos, Nikos Papageorgiou, Panagiota Gounari, Charalambos Antoniades, Gerasimos Siasos, Costas Tentolouris, Christodoulos Stefanadis, 1st Cardiology Department, Hippokration Hospital, Athens Medical School, Athens, Greece

Background: Current evidence suggests that HMG-CoA reductase inhibitors (statins) modify the number of endothelial progenitor cells (EPCs) in patients with atherosclerosis. However their effect on EPC mobilization in patients with heart failure (HF) remains unknown. We evaluated the impact of rosuvastatin on EPC number in patients with HF.
Methods: Forty two clinically stable patients with systolic HF (NYHA II-III, mean age 65±11 years, mean LVEF 28±8%, 76% ischemic) who were already on optimal conventional cardiovascular treatment were randomized to receive rosuvastatin 10 mg/day (n=21), or placebo (n=21) and followed up for 4 weeks. The number of EPCs in whole blood was measured as CD34/KDR and CD34/AC133/KDR positive cells using fluorescence-activated cell sorting. Endothelial function was evaluated by estimating the brachial artery flow mediated dilation (FMD). All measurements were made before and after 4-week treatment.
Results: $CD34^+/KDR^+$ and $CD34^+/AC133^+/KDR^+$ cells were significantly increased after rosuvastatin treatment (from 0.023 (0.017-0.038) and 0.001 (0.0008-0.0024) to 0.039 (0.023-0.052) cells/100 peripheral blood mononuclear cells (PBMNCs) and 0.0019 (0.0008-0.0033) cells/100 PBMNCs respectively, p=0.004 and p=0.008), whereas they remained unchanged in the placebo group. FMD was significantly increased in the rosuvastatin group (from 2.9±1.5 to 3.5±1.6%, p<0.05), while it remained unchanged in the placebo group. There was no correlation between baseline EPC number and FMD (r=-0.09, p=0.87). Moreover, the change in EPC levels after rosuvastatin treatment was not correlated with the change in FMD (p=0.24).
Conclusions: Short-term treatment with rosuvastatin significantly increases endothelial progenitor cells number in patients with heart failure. This finding provides further insights into the role on the pleiotropic effects of statins in patients with chronic heart failure.

9:30 a.m.

1033-170 **Changes in Drug Utilization in Patients Referred to Outpatient Heart Failure Clinics in Canada Between 1999 and 2007**

J. Malcolm O. Arnold, Andrew Ignazweski, Jonathan Howlett, Marie-Helene LeBlanc, Peter Liu, Rosa Guiterrez, Gordon Marchiori, University of Western Ontario, London, ON, Canada

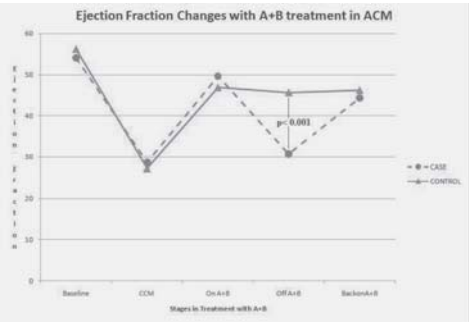
Background: The Canadian Heart Failure Network (CHFN) links 26 clinics across Canada which share a common longitudinal database and a common philosophy that a specialized heart failure physician(s) and nurse(s) can optimize care in patients referred from hospital or community physicians. The Network supports the Canadian Cardiovascular Society National Guidelines for the diagnosis and management of heart failure but allows each clinic to practice within those guidelines according to local resources which may differ across the country.
Methods: We describe here the referral patterns of heart failure drug use at the time of first referral for the years from January 1999 to December 2007 to determine if evidence based guidelines have resulted in an increase in the community use of guideline recommended drugs.
Results: Over that period of time 10,449 patients were referred to active CHFN clinics who recorded data at the first clinic visit. These data reflect selected heart failure and other medications used in the referral community at the time that referral to a specialized clinic was considered necessary or desirable. From January 1999 to December 2007, referral drug use of angiotensin receptor blockers, beta-blocker and statins remained unchanged (means 10.8%, 58.5%, 34.8%).. The use of angiotensin converting enzyme inhibitors decreased from a high of 86.6% in 1999 to low of 15.5% in 2005, spironolactone decreased from 38.0% in 2001 to 20.9% in 2007, frusemide decreased from 82,2% in 2000 to 38.9% in 2005, digoxin decreased from 49.5% in 1999 to 10,5% in 2006, coumadin from 38.3% in 2000 to 22.5% in 2007, and aspirin from 46.5% in 2001 to 22.% in 2007.
Conclusions: These data suggest that, between January 1999 and December 2007, physicians referred patients on fewer rather than more drugs related to their heart failure condition. This suggests that, over the last 9 years, patients are being referred earlier to outpatient heart failure clinics and prior to optimization of drug therapy. This may reflect the perceived benefit of early referral to heart failure clinics by these referring physicians.

9:30 a.m.

1033-171 **Deleterious Effects on Ejection Fraction Upon Withdrawal of ACE Inhibitors and Beta-Adrenergic Blockers in Patients With Anthracycline Associated Cardiomyopathy**

Ashish Shukla, Wamique Yusuf, Iyad Daher, Xiao Zhou, Cezar Illiescu, Daniel Lenihan, Jean-Bernard Durand, MD Anderson Cancer Center, Houston, TX, SUNY, Buffalo, NY

Background: Left ventricular (LV) function is the most common assessment of cardiac performance in cancer patients. Although Beta Adrenergic blockers and ACE inhibitors (A+B) are used for treatment of left ventricular (LV) dysfunction in patients with anthracycline-associated cardiomyopathy (ACM), the effect of their withdrawal after an improvement of LV function is unknown. We report a retrospective cohort study of patients with ACM on A+B who underwent withdrawal from these medications and their follow up LV ejection fraction (LVEF).
Methods: From a cohort of patients with ACM stabilized on A+B, sixteen patients were identified to have been withdrawn from therapy. These patients were restarted on A+B and LVEF changes compared using paired t test and t test using a matched control population.
Results: A total of 48 patients (case =16 and matched control =32) were studied. The mean LVEF of the sixteen patients at presentation with ACM was 28.68%, down from a mean EF of 54% at baseline (p<0.0001). Once on maximal doses of A+B, the patients' EF improved to a mean of 49.62% (p<0.0001). Upon withdrawal of the treatment with A+B, the mean EF decreased to 30.62% (p<0.0001). Upon reinstitution of A+B therapy, the patients' LVEF improved to a mean of 45% (p<0.0001).
Conclusions: The initial fall in LVEF with ACM is reversible and is then maintained on continuous treatment with A+B. Withdrawal of treatment is associated with a significant reduction in LVEF. We conclude that patients with ACM should remain on A+B indefinitely.



9:30 a.m.

1033-172 **Vitamin D Deficiency Is Common in Chronic Heart Failure Patients and Relates to the Severity of the Heart Failure**

Klaus K. Witte, Richard M. Cubbon, Christopher P. Gale, Lorraine C. Kearney, Rachel E. Klawiter, Mark T. Kearney, University of Leeds, Leeds, United Kingdom

Background: Chronic heart failure (CHF) is a syndrome of exercise intolerance in the presence of left ventricular dysfunction. A further feature is deficiency of essential micronutrients. Vitamin D deficiency leads to imapired skeletal and cardiac muscle and immune function, hence deficiency might also be an aetiological factor. We examined the prevalence of vitamin D deficiency in CHF patients and whether vitamin D levels were related to CHF severity.
Methods: Serum 25(OH)D_3 levels were measured in 55 stable CHF patients, (40 men) mean age 70 (11) years. CHF was defined as current or previous symptoms of fatigue or breathlessness and left ventricular ejection fraction <45%. Patients taking vitamin D supplementation were excluded from the analysis. Vitamin D levels were categorised as deficiency (serum level <25nmol/l), insufficiency (<50nmol/l), and hypovitaminosis D (<75nmol/l). Patients with levels ≥75nmol/l were classed as sufficient.
Results: Patients were taking appropriate medical therapy (80% on beta-blockers, 90% ACE inhibitors). Calcium levels were normal (2.32 (0.1)mmol/l). Only three patients had sufficient vitamin D. Patients with NYHA class II and III CHF had lower levels of vitamin D than those in class I (29.0 (16.2) v 45.2 (32.5); p=0.03). There was no difference in vitamin D levels between class II and III, although there was an interaction between NYHA class and vitamin D category (χ^2-value 15.0; p=0.02). There was an inverse relationship between furosemide dose and vitamin D (r=0.40; p=0.005). Patients taking spironolactone had lower levels than those not taking this agent (25.8 (13.8) v 43.1 (22.6); p=0.002). There was no relationship between vitamin D and age, left ventricular function, calcium or creatinine or CRP, and no differences between those patients taking and those not taking beta-blockers and angiotensin-converting enzyme inhibitors.
Conclusions: CHF patients are frequently deficient of vitamin D, related to the severity of the condition. Whether vitamin D deficiency contributes to CHF or is merely a result of lifestyle constraints in these patients requires further investigation with a randomised, placebo-controlled trial of high dose vitamin D supplementation.

9:30 a.m.

1033-173 Relationships of Late Enhancements in Myocardium by Multislice CT With Ventricular Late Potentials in Subjects With Hypertrophic Cardiomyopathy

Marehiko Ueda, Nobusada Funabashi, Masae Uehara, Hiroyuki Takaoka, Michiko Daimon, Yoko Mikami, Taichi Murayama, Issei Komuro, Chiba University, Chiba, Japan

Background: Late enhancement (LE) in the left ventricular myocardium (LVM) detected by magnetic resonance imaging (MRI) or multislice computed tomography (MSCT) is believed to identify non-ischemic cardiomyopathy patients at risk for sustained ventricular tachycardia and sudden death. Meanwhile, the usefulness and significance of ventricular late potentials by signal averaged electrocardiography is unconfirmed in subjects with hypertrophic cardiomyopathy (HCM). We evaluated the relationship of LE in the LVM by MRI or MSCT with ventricular late potentials in HCM.
Methods: 49 subjects with HCM (34 male, 15 female, mean age: 63±14 years) underwent signal averaged electrocardiography and enhanced MSCT (Light Speed Ultra 16, GE). According to the method by Simpson, three leads of signal-averaged electrocardiograms were obtained. An average of 250 beats was recorded after filtering with a band-pass filter between 40 and 250 Hz.
Results: LE in the LVM was detected in 32 of 49 subjects (65.3%) in whom the presence and distribution of LE in the LVM in MSCT. There were no significant differences in the duration of filtered QRS (132 ± 25 ms vs. 120 ± 21 ms), the root-mean-square voltage of the terminal 40 ms of the filtered QRS complex (54 ± 43 μV vs. 47 ± 34 μV), or duration of the terminal filtered QRS complex that remains <40 μV (29 ± 16 ms vs. 34 ±14 ms, p <0.05) between the groups. All 14 subjects with a QRS complex that remained <40 μV shorter than 22 ms had LE. Conversely only 15 of 35 subjects (43%) with a QRS complex that remained <40 μV equal or longer than 22 ms had LE.
Conclusions: In HCM subjects, interaction between fibrosis, represented by LE in the LVM by MRI or MSCT, and hypertrophy or heterogeneity of myocardial fibers, may prevent detection of slow conduction developing independently on signal averaged electrocardiography. The significance of ventricular late potentials by signal averaged electrocardiography in subjects with HCM may be influenced by the presence of LE in the LVM by MRI or MSCT.

9:30 a.m.

1033-174 Abnormal Response to Mental Stress in Patients With Takotsubo Cardiomyopathy Evaluated Using Gated Single-Photon Emission Computed Tomography

Guido Parodi, Roberto Sciagrà, Stefano Del Pace, Sabrina Genovese, Linda Zampini, Benedetta Bellandi, Nazario Carrabba, Gentian Memisha, Gian Franco Gensini, Alberto Pupi, David Antoniucci, Department of Cardiology, Careggi Hospital, Florence, Italy

Background: Beyond the acute phase, no persistent abnormality is detected in patients with Takotsubo cardiomyopathy (TTC). Since sympathetically-mediated myocardial damage has been proposed as the causative mechanism of TTC, we verified whether mental stress, which acts also through sympathetic activation, could evoke abnormalities in these patients.
Methods and results: At least one month after the acute event, 21 patients fulfilling all TTC diagnostic criteria (Mayo Clinic) underwent resting and mental stress gated single-photon emission computed tomography (SPECT). Perfusion and wall motion were blindly scored, and transient ischemic dilation (TID) and left ventricular (LV) ejection fraction (EF) measured using an automated program. In 3 patients (all with significantly higher enzyme release during acute event) resting perfusion defects suggested the diagnosis of prior myocardial infarction instead of TTC. In the remaining 18 subjects, mental stress evoked 3 patterns of response: 1) regional changes (perfusion defects and/or wall motion abnormality) in 12 cases; 2) global abnormalities (LVEF fall > 5% and/or TID > 1.10) in 11 patients; and 3) completely negative response in 2 patients. During 6-month follow up, 3 patients of those with normal resting gated SPECT and mental-stress-induced changes (1 regional and 2 global) experienced new cardiac events (angina and/or heart failure).
Conclusion: Mental stress is able to evoke regional and/or global abnormalities in most TTC patients; soft clinical event may occur during follow up in patients with abnormal response.

9:30 a.m.

1033-175 Analogies and Differences Between the Three Main Types of Systemic Cardiac Amyloidosis

Cristina C. Quarta, Letizia Riva, Paolo Ciliberti, Simone Longhi, Fabrizio Salvi, Francesca Pastorelli, Giuseppe Galati, Elena Biagini, Michele Cavo, Angelo Branzi, Claudio Rapezzi, University of Bologna and S.Orsola-Malpighi Hospital, Bologna, Italy, Bellaria Hospital, Bologna, Italy

Background: Most studies of amyloidotic cardiomyopathy consider as a single entity the three main systemic cardiac amyloidoses: 1) primary amyloidosis (AL), 2) hereditary, transthyretin-related amyloidosis (ATTR), 3) systemic "senile" amyloidosis (SSA). Our aim was to assess and compare the diagnostic and clinical profiles of the three main types of systemic cardiac amyloidosis.
Methods: We conducted a longitudinal study of 115 cardiac amyloidosis patients with clear-cut etiological diagnosis seen at our institutional network for diagnosis/treatment of systemic amyloidosis since 1994 (minimum follow-up, 6 months). In addition to diagnostic ECG and echocardiographic findings, hemodynamic data were available for most patients (n = 71).
Results: Average age at diagnosis was higher in AL than in ATTR; all but one of the SSA patients were elderly men. Table summarizes patients' baseline instrumental characteristics according to etiology.

	AL(n=64)	SSA(n=14)	ATTR(n=37)	p value
Low QRS voltage, n/N (%)	33/62 (53)	5/12 (42)	9/33 (27)	0.052
Left bundle branch block, n/N (%)	3/62 (5)	4/12 (33)	1/33 (3)	0.001
Voltage/mass ratio	0.9 ± 0.5	1.0 ± 0.5	1.2 ± 0.5	0.017
Diastolic interventricular septum thickness (mm)	15.8 ± 2.8	19.5 ± 4.2	16.2 ± 3.8	0.001
Left atrial diameter (mm)	46.0 ± 6.6	49.8 ± 6.7	41.1 ± 6.7	0.0001
LV ejection fraction (%)	50.6 ± 13.9	44.5 ± 15.9	59.5 ± 14.7	0.001
E-wave deceleration time (msec)	153.8 ± 40.7	168.2 ± 20.8	190.0 ± 70.6	0.004
Atrioventricular valve thickening, n (%)	25 (39)	7 (50)	25 (68)	0.022
Mean RA pressure (mm Hg)	9.4 ± 5.7 (n=38)	6 ± 4.5 (n=11)	5.0 ± 4.8 (n =22)	0.006
Mean PCWP (mm Hg)	17.9 ± 8.2 (n =38)	15.3 ± 6.1 (n =11)	11.2 ± 7.1 (n =22)	0.006
Cardiac index (L/min/m2)	2.4 ± 0.6 (n =38)	2.3 ± 0.4 (n =11)	2.8 ± 0.7 (n =22)	0.027

ATTR and SSA patients had better outcomes than AL patients in terms of both overall survival (at 2 yrs 48% for AL, 92% for ATTR, 69% for SSA; p <0.001) and freedom from major cardiac events (at 2 yrs 38.18% for AL, 83% for ATTR, 100% for SSA; p <0.001). At Cox proportional hazards analysis, ATTR was a strongly favorable predictor of survival, and SSA predicted freedom from major cardiac events.
Conclusions: AL, ATTR and SSA should be considered three different cardiac diseases, characterized by different pathophysiological substrates and courses.

9:30 a.m.

1033-176 Impact of Renin-Angiotension System Polymorphisms on Occurrence of Atrial Fibrillation Associated With Heart Failure in Hypertrophic Cardiomyopathy: Results From Clinical and Gene Analyses of Genotyped Patients

Akira Funada, Hidekazu Ino, Noboru Fujino, Kenshi Hayashi, Katsuharu Uchiyama, Eiichi Masuta, Yuuichirou Sakamoto, Toshinari Tsubokawa, Akihiko Muramoto, Masakazu Yamagishi, Kanazawa University, Kanazawa, Japan

Background: Atrial fibrillation (AF) and heart failure due to systolic dysfunction are major complications of hypertrophic cardiomyopathy (HCM). Since HCM with identical sarcomere gene mutation show various clinical courses, other modifier genes such as renin-angiotensin system (RAS) may play important roles in clinical deterioration. However, few data exist regarding the relationship between RAS polymorphisms and these cardiac events. Therefore, we determined impact of RAS polymorphisms on clinical manifestations of genotyped HCM.
Methods and Results: In 134 carriers of HCM-causing sarcomere gene mutations such as MYH7, MYBPC3, TNNT2, and TNNI3 (age 50±21 years, 70 males), we examined relationship between RAS polymorphisms (angiotensin-converting enzyme insertion/deletion (ACE I/D) and angiotensin II type 1 receptor A/C1166 (AT1 A/C1166)), echocardiographic parameters and occurrence of AF. Thirty-two patients (24%) had AF which was closely related to dilated left ventricular end-diastolic dimension, decreased fractional shortening (FS) and dilated left atrial dimension (p<0.05, respectively). As for polymorphisms and AF, Kaplan-Meier analysis demonstrated that the first onset of AF was significantly earlier in carriers with AT1 C allele than in those with A/A homozygotes (log-rank test, p<0.05). As for polymorphisms and heart failure associated with decreased FS (<25%), ACE D allele (D/D and D/I) exhibited significantly lower FS than I/I homozygotes (p<0.05). Interestingly, simultaneous presence of AT1 C allele and ACE D allele was significant risk factor of occurrence of AF associated with heart failure (p<0.05).
Conclusion: These results demonstrate that in genotyped HCM, subjects with both AT1 C allele and ACE D allele may develop systolic dysfunction and show early onset of AF, and could be at high-risk compared with other groups. We suggest the usefulness of detecting RAS polymorphisms for risk stratification in genotyped HCM.

9:30 a.m.

1033-177 Pathologic Changes to the Heart Induced by Chronic Exposure to Air Pollutants Generated in Traffic and the Wildfires of Southern California in October 2007

Boris Z. Simkhovich, Glenn Gookin, Dianne Meacher, Paul Willert, Michael T. Kleinman, Robert A. Kloner, Good Samaritan Hospital, Los Angeles, CA, University of California - Irvine, Irvine, CA

Background: Air pollutants (AP) affect cardiovascular indices. We sought to characterize pathophysiological changes in the cardiovascular system using controlled exposure to particulate AP.
Methods: In the first experiment, Sprague Dawley rats were exposed for 9 months to filtered air (FA) vs. AP of different aerodynamic diameter (AD); i.e. coarse (CP, median AD 4.0 microns), fine (FP, median AD 0.7 micron) and ultrafine (UFP, median AD 0.06 micron) in a mobile trailer located near a busy Southern California freeway. In the second experiment, SHR and WKY rats were exposed for 3 months to UFP, including the period of October 2007 California wildfires. Animals in this set had implanted wireless sensors for continuous arterial blood pressure (ABP) monitoring.
Results: In the 9 month experiment, hearts exposed to UFP demonstrated significant degenerative changes within the cardiomyocytes including intracellular edema and intensive vacuolization. In addition, UFP caused myocardial inflammation and vascular congestion. CP caused a trend towards increased accumulation of collagen (assessed by picrosirius red staining, p=0.065). Bronchoalveolar lavage demonstrated 3.5 fold

increase in polymorphonuclear leukocytes in the UFP- vs. FA-exposed rats (p<0.05). In the 3 month experiment, SHR rats (both FA- and UFP-exposed) demonstrated increases in heart/body weight ratio (p<0.05 vs. WKY), wall thickness of blood vessels and amount of collagen in their hearts. Exposure to UFP caused inflammation in both SHR and WKY rat hearts including a characteristic linear stacking of mononuclear cells within intra-myocardial vessels. This phenomenon has not been seen in cardiac inflammation induced by traffic-generated AP and might be specific to fire-generated AP. In the SHR group UFP increased the mean ABP by ~26 mmHg as compared to the SHR group exposed to FA.
Conclusions: Our results indicate that chronic exposure to AP caused degenerative changes within the cardiomycytes and inflammation within the cardiac muscle and vasculature which had an unusual pattern in the fire-generated pollution group. Chronic exposure to AP exacerbated hypertension in SHR.

9:30 a.m.

1033-178 Relationship of Left Ventricular Non-compaction With Papillary Muscle Insertion Site and Partition

Mitra Sahebazamani, Ijaz Ahmad, Geetha Bhumireddy, Igor Klem, Joshua A. Socolow, Sorin J. Brener, Terrence Sacchi, John F. Heitner, New York Methodist Hosptial, Brooklyn, NY, Duke Univ Medical Center, Durham, NC

Background: Left ventricular non-compaction (LVNC) is a rare congenital morphogenetic abnormality and occurs as a result of an arrest in the compaction of the embryonic myocardium during development resulting in excessive trabeculations in the left ventricle (LV). The relationship of the papillary muscle (PM) development and LVNC has not been previously described.
Methods: We enrolled 297 consecutive patients referred to our cardiac magnetic resonance (CMR) center for cardiac evaluation. We assessed the non-compacted (trabecular region) and compacted myocardium by drawing diameters of each at the left ventricular apex and averaging from two long axis cine views. LVNC was defined as non-compacted to compacted ratio 2.3. The PM insertion site was determined by dividing the long axis of the LV into 3 equal regions and determining in which region (mid or apical) the papillary muscle inserted into the LV. The number of partitions of the PM was determined by counting the number of separate PM visualized 10mm apical from the mid plane of the LV on short axis cine view.
Results: The mean age of the patients was 58.1 years, 60% were males. The patients were referred to CMR for the following reasons: evaluation of left ventricular function (37%), viability (30%), valvular diseases (21%), and other (12%). The average LVEF was 51.2 ± 14.6%. The mean number of PM partition in the LVNC group was 5, and in the normal group was 6(p=0.41). The LVNC group had a significantly higher apical insertion of the PM compared to the normal group, 87% (67 of 77 patients) vs 67.3 % (148 of 220 patients, p<0.001).
Conclusions: Patients with LVNC have a higher incidence of apical insertion of the papillary muscle into the myocardium, without a higher number of partitions.

9:30 a.m.

1033-179 A Case-Control Study of Cellular and Humoral Autoimmunity to Cardiac Troponin-I in Patients With Idiopathic Dilated Cardiomyopathy

Jason M. Lappe, Clara M. Pelfrey, Anne Cotleur, WH Wilson Tang, Cleveland Clinic, Cleveland, OH

Background: The presence of autoantibodies (AAbs) specific to cardiac troponin I (cTnI) has been associated with deleterious outcomes in the post-infarction setting. However, the mechanistic role of active cellular autoimmunity in patients with idiopathic dilated cardiomyopathy (iDCM) remains unclear.
Methods: Serum samples and peripheral blood monocytes (PBMCs) were obtained from stable ambulatory iDCM patients and healthy controls. A cellular response was identified by staining PBMCs with CFSE dye and culturing for 7 days with 10 µg/mL of cTnI. Proliferation was measured using flow cytometry, and a positive response was defined as a ratio between the test and the background of >/= 2.0 and an absolute increase of at least 1.0%. AAbs against cTnI were detected by ELISA, and a positive response defined as a titer >/= 1:1000. Specificity of anti-cTnI AAbs binding was confirmed by competitive inhibition studies.
Results: Forty-four patients with iDCM (mean age 52±12 years, 46% male, LVEF 23±7%, 54% on statin) and 35 healthy controls (mean age 47±14years, 63% male) were enrolled. A positive cellular proliferative response to cTnI was identified in 21% (9/44) patients with iDCM and 6% (2/35) of healthy controls (p<0.05). Positive anti-cTnI AAbs were identified in 14% (6/44) of iDCM patients and 20% (7/35) of healthy controls (p = NS). The presence of anti-cTnI AAbs did not correlate with a positive cellular proliferative response to cTnI. Interestingly, iDCM patients who had an AAb response to cTnI were less likely to be taking a statin (p<0.05).
Conclusions: Active cellular autoimmune response to cTnI has been identified in one-fifth of patients with iDCM. The presence of a cellular response was not correlated with the presence of AAbs to the same antigen; however this may be confounded by statin use.

9:30 a.m.

1033-180 Hereditary Transthyretin-Related Amyloidosis With Predominant or Exclusive Cardiac Phenotype in a White Caucasian Population

Paolo Ciliberti, Candida Cristina Quarta, Letizia Riva, Simone Longhi, Fabrizio Salvi, Elena Biagini, Giuseppe Galati, Angelo Branzi, Claudio Rapezzi, University of Bologna and S.Orsola-Malpighi Hospital, Bologna, Italy

Background. In hereditary transthyretin-related amyloidosis (ATTR), cardiac involvement usually occurs after neurologic signs (except among Afro-Americans carrying Val122Ile). When neurological manifestations are mild or absent, diagnosis of amyloidotic cardiomyopathy may be delayed or missed. Since little is known about the frequency of cardiac phenotype in Caucasian ATTR patients, we assessed its prevalence and clinical features in an Italian setting.
Methods. Our institution provides a coordinated ATTR diagnosis/treatment network with a dedicated database (all patients receive echocardiography). We defined cardiac phenotype as echocardiographically diagnosed amyloidotic cardiomyopathy accompanied by subclinical (mild/absent) neurologic signs not constituting the *primum movens* for referral.
Results. 16/134 (12%) patients (all Caucasian) had cardiac phenotype (65/118 patients with predominantly neurologic phenotype also presented amyloidotic cardiomyopathy). Median value of follow-up was 30 months.
Table. Patients' characteristics according to cardiologic/neurologic phenotype.

	Cardiac (n=16)	Neurologic (n=118)	p value
Men, n (%)	14 (87%)	61 (51%)	0.02
Age at diagnosis, years (mean ± SD)	61±10	48±14	< 0.001
Diastolic interventricular septum thickness, mm (mean ± SD)	18 ± 3	16 ± 4 (n = 65)	0.06
Restrictive filling pattern, n (%)	8 (50%)	19/65 (29%)	0.2
Left ventricular ejection fraction, % (mean ± SD)	49 ± 11	59 ± 13 (n = 65)	<0.01
TTR mutation, n (%) - Val30Met - Ile68Leu - Glu89Gln - Other	0 (0%) 10 (62%) 1 (7%) 5 (31%)	41 (35%) 5 (4%) 24 (21%) 48 (40%)	 0.01 0.001 0.3 n.a.
Orthotopic liver transplantation, n (%)	1 (6%)	17 (14%)	0.6
Heart and liver transplantation, n (%)	2 (12%)	5 (4 %)	0.4
Annual mortality rate (100 pts/year)	0	15	0.01

Conclusion. Over 10% of our patients presented with cardiac phenotype, highlighting the need for cardiologists to consider the possibility of ATTR, even in the absence of overt neurologic manifestations. The majority of the patients with cardiac phenotype carried the Ile68Leu mutation (and tended to be elderly men); timely recognition of Ile68Leu could be relevant for clinical management.

9:30 a.m.

1033-181 Left Ventricular Rotational Mechanics: Differences Between Acute Myocardial Infarction and Chronic Ischemic and Nonischemic Heart Failure Patients

Matteo Bertini, Gaetano Nucifora, Nina Ajmone Marsan, Victoria Delgado, Rutger J. van Bommel, Giuseppe Boriani, Edward R. Holman, Ernst E. van der Wall, Martin J. Schalij, Jeroen J. Bax, Leiden University Medical Center, Leiden, The Netherlands

Background: Left ventricular (LV) twist and untwisting rate are emerging as global and thorough parameters for the assessment of LV function. Aim of the study was to assess the differences of LV twist and untwisting rate between acute myocardial infarction (AMI) patients and ischemic (IHF) and non-ischemic (NIHF) chronic heart failure patients.
Methods: A total of 50 AMI patients, 49 IHF and 38 NIHF patients were studied. As a control group, 28 normal subjects were included. Speckle tracking analysis was applied to LV short-axis images at basal and apical level. LV twist was defined as the net difference of apical and basal rotation at isochronal time points. The first time derivative of LV untwist was defined as LV untwisting rate.
Results: Peak LV twist was reduced in AMI patients and extremely reduced in IHF/NIHF patients. Furthermore, peak LV twist occurred earlier in patients with worse systolic function. In addition, LV untwisting rate was reduced in AMI patients and a trend towards a lower value was observed in IHF/NIHF as compared to AMI patients (Table). In the overall population, an excellent correlation between peak LV twist and LV ejection fraction (r = 0.85, p <0.001) was found and a good correlation between peak LV untwisting rate and grade of diastolic dysfunction (r = 0.56, p <0.001) was observed.
Conclusions: LV twist and untwisting rate are strongly related with LV function. An impairment of LV function is associated with a reduction of LV twist and untwisting rate and with an earlier peak of LV twist.

Table. Clinical, echocardiographic and rotational parameters of the different groups: normal controls, AMI patients, IHF patients and NIHF patients

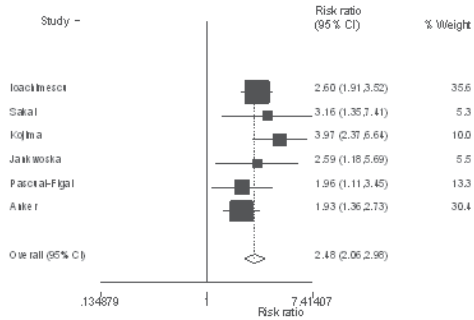
	Normal controls (n = 28)	AMI patients (n = 50)	IHF patients (n = 49)	NIHF patients (n = 38)	ANOVA p value
Age (years)	60±11	60±11	64±11	65±13	0.084
Gender male, n (%)	21 (75)	38 (76)	43 (88)	28 (74)	0.16
LVEDV (ml)	87±26	103±28	179±67	214±74	<0.001
LVESV (ml)	34±11	55±21	130±52	164±61	<0.001
LVEF (%)	63±7	47±10	28±5	24±6	<0.001
Diastolic function, n (%)					
Grade 0	28 (100)	7 (14)	0 (0)	0 (0)	<0.001
Grade 1	0 (0)	19 (38)	12 (24)	8 (21)	0.002
Grade 2	0 (0)	14 (28)	13 (26)	6 (16)	0.014
Grade 3-4	0 (0)	10 (20)	24 (49)	24 (63)	<0.001
Peak LV twist (°)	15.7±3.1	11.6±3.8	5.2±2.2	4.0±2.9	<0.001
Peak LV untwisting rate (°/s)	-108±30	-75±35	-58±34	-59±33	<0.001
Time peak LV twist (% systole)	98±8	83±14	83±19	75±27	<0.001
Time peak LV untwisting (% systole)	114±9	118±17	116±17	116±23	0.75

9:30 a.m.

1033-182 **Uric Acid as a Predictor of Mortality in Congestive Heart Failure: A Meta-Analysis**

Leonardo Tamariz, Arash Harzand, Sameer Verma, John Jones, Joshua Hare, University of Miami, Miami

Background: Serum uric acid (SUA) is a product of xanthine oxidase (XO). Apoptosis leads to increased purine catabolism increasing XO activity and SUA levels.The purpose of this study is to evaluate the evidence supporting SUA as a predictor of all cause mortality in patients with heart failure (HF) and to determine the SUA cut-off for the increase in risk. Methods: We selected all cohort studies in the English literature in which SUA was measured and mortality was reported in patients with HF. We calculated the pooled relative risk (RR) with the corresponding 95% confidence interval (CI) for all cause mortality using the fixed effects method. We evaluated the effects of SUA on all cause mortality at different cut-offs >6.5, 6.0-6.5 and 5.0-6.0 mg/dl. Results: Our search strategy yielded 333 studies; however, only 6 studies met our eligibility criteria. We found no heterogeneity (p=0.73). The studies included 4,996 patients with heart failure with a median age of 63 (range 18-67) and a median ejection fraction of 32% (range 11-37). The RR of all cause mortality was 2.48; 95% CI (2.06 - 2.98) for SUA >6.5 mg/dl compared with < 6.5 mg/dl SUA level (figure). The RR of all cause mortality for SUA of 6.0-6.5 mg/dl was 1.69; 95% CI (1.35 - 2.12) compared with SUA <6.0 mg/dl. The RR of all cause mortality was 1.42; 95% CI (1.05-1.93) for SUA of 5.0-6.0 mg/dl compared to SUA <5.0 mg/dl.
Conclusions: Uric acid is an important prognostic marker for all cause mortality in HF. SUA has a dose-dependent effect on all cause mortality.



9:30 a.m.

1033-183 **The Prevalence of Effusive Constrictive Pericarditis in Patients With Confirmed Tuberculous Pericarditis**

Mpiko Ntsekhe, Faisal S. Syed, James Russell, Phillip Usim, Bongani M. Mayosi, Department of Medicine, University of Capetown, Capetown, South Africa

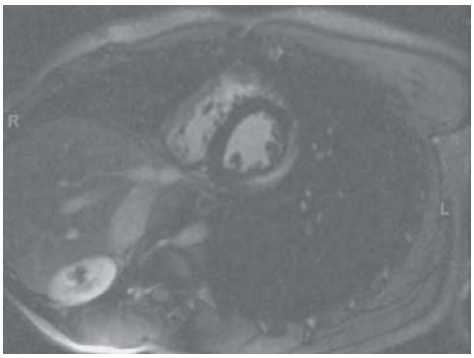
Background: Effusive constrictive pericarditis (ECP) occurs when pericardial effusion and visceral pericardial constriction coexist and is thought to be a precursor to constrictive pericarditis. In the largest study reported to date <10% of the 190 patients undergoing pericardiocentesis had evidence of ECP. A small minority in the study had tuberculosis pericarditis where ECP may be more common.Using the Initiative for the Investigation and Management of Pericarditis In Africa (IMPI Africa) registry we set out to determine the prevalence of ECP in patients with TB pericarditis.
Methods: Between Jan '06 and May '08 consecutive patients with symptomatic pericardial effusions referred for therapeutic or diagnostic pericardiocentesis were recruited. Simultaneous right atrial and intra-pericardial pressures were measured pre and post pericardiocentesis in all who met entry criteria. Tuberculosis was confirmed by pericardial fluid microbiology and or chemistry. ECP was defined as failure of the right atrial pressure to fall by 50% or to a new level of ≤12mmHg after the intra-pericardial pressure was normalized. Tamponade was defined as equalization of the intra-pericardial and mean right atrial pressure.
Results: In the period under review, of 148 consecutive patients referred with symptomatic pericardial effusions, 60 had a tuberculous etiology confirmed and had complete hemodynamic data for analysis. 38% met criteria for ECP. 52% met criteria for cardiac tamponade. By univariate analysis the hemodynamic predictors of ECP were RAP ≥ 20mmHg OR 24.08 [p=,006]) and pericardial pressure ≥ 20mmHg OR 10.93[p=.004]). Cardiac tamponade was not associated with ECP (OR 0.87)[p=.673] By multivariate analysis only RAP ≥ 20mmHg remained significantly [.001] associated with ECP (OR 18 [p=.001])
Conclusions: We show, in this first and largest study of its kind anywhere, that effusive constrictive pericarditis is relatively common (38% prevalence) in tuberculous pericardial effusions.

9:30 a.m.

1033-184 **MRI Characteristics of Acute Myocarditis in Pediatric Patients: Patterns and Predictors of Outcomes**

Sudhir Vashist, Pamela Woodard, Mark Grady, Gautam Singh, Washington University School of Medicine, St. Louis, MO

Background: Acute myocarditis (AMC) often presents a diagnostic dilemma. AMC in adults exhibits specific MRI characteristics, which have not been well described in children with AMC. The purpose of the study is to investigate MRI characteristics and predictors of outcome in children with AMC.
Methods: Study population consisted of 21 consecutive patients (pts) (age 18d-17y median 11 y) who underwent MRI for a clinical diagnosis of myocarditis. The cardiac MRI included cine-bright-blood True FISP and delayed contrast-enhanced T1-weighted inversion recovery (IR) segmented fast gradient recalled echo imaging. Outcomes measured by echo normalization of LV size (end diastolic dimension z score ≤ 2) and function (EF ≥ 50%) on follow up (1- 45m median 7m) divided the patients in complete, partial and no recovery groups defined as resolution of both, either or none respectively.
Results: Subepicardial enhancement (SEE) was present in 100% and transmural enhancement (TME) in 67% of pts. Only 50% of pts with TME had recovery compared to 100% of pts without TME. Pts who had SEE associated with normal wall motion, LV size and EF had complete recovery. However, pts with TME in combination with segmental akinesia, global hypokinesia and LV dilation had 0%, 43% and 22% recovery respectively.
Conclusions: AMC in children is characterized predominantly by subepicardial enhancement on cardiac MRI. MRI characteristics such as transmural enhancement, wall motion abnormality, LV dilation and EF may be predictors of outcomes.

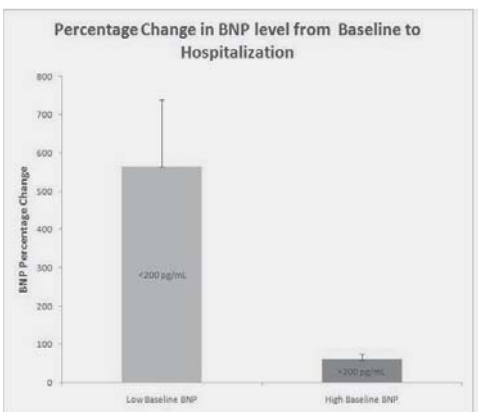


9:30 a.m.

1033-185 **Outpatients With Heart Failure and Low Baseline BNP Levels (<200 pg/mL) Have the Greatest Magnitude of Change When Undergoing Clinical Decompensation**

Pam R. Taub, Ellen Fitzpatrick, Kimberly Tran, Kevin Shaw, Kevin Jiang, Paul Clopton, Mitchell Saltzberg, Robert Fitzgerald, Alan Maisel, UCSD Medical Center, San Diego, CA

Background: B-type natriuretic peptide (BNP) has become mainstay in the diagnosis or exclusion of acute heart failure (HF). However, criteria for interpreting BNP changes in the outpatient setting and in detecting early subclinical congestion prior to clinical decompensation have not been established.
Methods: 194 patients with HF and at least 5 BNP measurements over 6 month to 2 year period were recruited and over 2000 clinical visits with BNP levels were reviewed. Clinical determination of decompensation was made by a cardiologist blinded to BNP levels and based on Framingham criteria. For this subanalysis, only patients with hospitalizations (n=75) were included and were divided into low (<200 pg/mL) and high baseline BNP (>200 pg/mL) groups. Baseline BNP was defined as the first BNP value upon study enrollment not corresponding to hospitalization.
Results: 16 patients in the low baseline BNP group and 59 patients in the high baseline BNP group had hospital admissions. Patients in the low baseline BNP group had 564% increase (SEM 175) while those in the high baseline BNP group had a 60% increase (SEM 16)) prior to hospitalization for decompensated HF (figure 1, p<.0001).
Conclusions: Patients with low baseline BNP have significantly larger changes in BNP levels prior to decompensation than those with higher baseline BNP levels. Understanding the clinical significance of changes in BNP levels prior to decompensation maybe useful in diagnosing subclinical congestion and preventing hospitalization.



9:30 a.m.

1033-186 **Echocardiographic Two-Dimensional Speckle Tracking Radial Strain for Detection of Severe Heart Iron Overload in Transfusion-Dependent Thalassemia Major: Validation With Magnetic Resonance Heart T2***

Thu-Thao Le, Yacui Gu, Ru-San Tan, National Heart Centre, Singapore, Singapore

Background. Siderotic cardiomyopathy in transfusion-dependent thalassemia major (TM) often exhibits normal echocardiographic findings. T2* magnetic resonance (MR) imaging allows early detection - heart T2*<10ms indicates severe heart iron overload with high risk of heart failure - but is not widely available. We studied echo radial strain in severe heart iron overload.
Methods. 24 beta TM patients underwent MR scans and were stratified by heart T2* results: <10ms (severe iron loading) and ≥10ms (no or mild iron loading). From same-day echo scans, we measured left ventricular (LV) ejection fraction, mitral E and A velocities, deceleration time, myocardial septal velocity E'. From 2D speckle tracking analysis of 12 segments in the mid and apical LV short-axis views, we determined average peak radial strain (S), average (t) and maximum time lag (t_{max}) between aortic valve closure and peak radial strain.
Results. See table. There was no significant difference in all variables except t (p=0.022) and t_{max} (p=0.008) at mid LV level. t_{max} has higher area under curve (AUC=0.82) compared to t (AUC=0.77) for diagnosis of T2*<10ms. Cutoff value t_{max} = 77ms predicts severe heart iron overload (NPV 76.5, PPV 83.3).
Conclusion. In TM, severe heart iron overload significantly delays peak radial strain development in the mid LV, without significant decrease in amplitude of myocardial radial strain. Prolonged t_{max} >77ms at mid LV may be used to triage TM patients for MR imaging and intensified iron chelation therapy.

Echocardiographic parameters by heart T2* status (values expressed as mean ± SD)

	T2*<10ms (n = 10)	T2*≥10ms (n = 14)	p value
Age (years)	19.6 ± 5.8	19.3 ± 8.6	ns
Gender (M:F)	8:2	10:4	ns
Mitral deceleration time (ms)	149 ± 20	142 ± 24	ns
Mitral E/A	2.31 ± 0.70	2.43 ± 0.57	ns
Mitral E/septal E'	10.21 ± 3.73	7.99 ± 1.27	ns
Ejection fraction (%)	59.2 ± 4.3	59.7 ± 5.3	ns
Mid S (%)	48.8 ± 14.9	57.4 ± 10.5	ns
Mid t (ms)	49 ± 34	22 ± 19	0.022
Mid t_max (ms)	77 ± 38	33 ± 34	0.008
Apical S (%)	31.9 ± 11.7	57.4 ± 10.5	ns
Apical t (ms)	59 ± 48	38 ± 36	ns
Apical t_max (ms)	68 ± 53	51 ± 49	ns

9:30 a.m.

1033-187 **Impact of Race on Prevalence of Hypertrophic Cardiomyopathy in Healthy Teenagers Undergoing Screening Echocardiography**

Mohammad Reza Movahed, Sudhakar Sattur, Sharon Bates, The Southern Arizona VA Health Care System and Sarver Heart Center, Tucson, AZ

Background: The prevalence of Hypertrophic Cardiomyopathy (HCM) in the population has been thought to be less than 1%. The goal of this study was to evaluate the prevalence of HCM in a population of teenage high school students who underwent screening echocardiography for the detection of HCM based on race across the United States
Method: The Anthony Bates Foundation has been performing screening echocardiography in high schools across the United States for the prevention of sudden death since 2002. A total of 2066 students were identified between the ages of 13 to 19 years who underwent screening echocardiography with documented wall thickness. Suspected HCM was defined as any wall thickness ≥ 15 mm.
Results: The total prevalence of suspected HCM, defined by a cut off value of 15 mm or more, was 1.3% (7/551). The incidence of suspected HCM was markedly higher in the African American teenagers [6% (3/50) of African American teenagers, vs. 0.8 % (4/501) of other races, OR 7.93, CI 1.72-36.49, p=0.002]. Using multivariate analysis adjusting for age, gender, BMI and HTN (systolic BP >140 and diastolic BP of > 90), African American race remained independently associated with suspected HCM (OR 4.89, CI 1.24-39.62, p= 0.02).
Conclusion: The prevalence of suspected HCM in young African American teenagers is markedly higher in comparison to other races. The cause of this difference is not known warranting further investigations.

9:30 a.m.

1033-188 **Arrhythmias and Implantable Cardioverter-Defibrillators in Fabry Cardiomyopathy**

Peter G. Robertson, G. Neal Kay, David Warnock, Leslie Jackson, Jose Tallaj, University of Alabama at Birmingham, Birmingham, AL

Background: Arrhythmias have been reported in patients with Fabry cardiomyopathy (FC).
Methods: Retrospective chart review and analysis of the ICD interrogation strip in patients with known FC to determine the observed arrhythmias.
Results: Fifteen patients (10 male, 5 female) with FC were followed in our clinic; all patients were on enzyme replacement therapy (ERT). Structural cardiac abnormalities included at least moderate valvular regurgitation in 53%, obstructive hypertrophy in 27% and severe CAD in 20%. In addition, clinically significant bradycardia was present in 33%, palpitations in 59%, atrial fibrillation in 20% and documented non-sustained VT in 13%. Forty-six percent (7/15) of patients had implanted devices; 6 were ICDs, and 1 was a dual chamber pacemaker. Indications for implantation were symptomatic bradycardia in 3 patients, NSVT in 1 patient, hypertrophic cardiomyopathy in 1 patient, syncope in 1 patient and palpitations in 1 patient. There was only one detected ventricular tachyarrhythmia over a mean follow-up of 30 ± 18 months (range:14-63 months). This episode occurred 63 months after placement in the setting of profound gastrointestinal bleed, hemorrhagic shock, lactic acidosis and hypoxemic respiratory failure as a terminal event during the attempted resuscitation.
Moreover, patients were paced in the atrium 84 +/- 23% of the time and in the ventricle 42 +/- 52% of the time. Three patients in the ICD group and the patient with the pacemaker were paced over 95% of the time and likely pacemaker-dependant. Patients with an ICD had lower heart rates prior to ICD implant (57+/- 11 BPM vs 81 +/- 12 BPM, p<0.01) than the group that did not have devices implanted. There was a trend towards higher LV mass in the patients with devices, especially in the subgroup of patients being paced over 95% of the time.
Conclusions: Ventricular arrhythmias are less common than previously described in patients with FC who are on ERT. However, utilization of pacing is high, and patients may become pacemaker dependent as the disease progresses. Sinus bradycardia may be an indicator of disease severity and should be considered for device therapy.

9:30 a.m.

1033-189 **Relapsing Pericarditis Is Not a Benign Disease in Terms of Complications**

Kye Hun Kim, Dali Feng, James Glockner, Matthew Martinez, Imran S Syed, Philip Aroaz, Paul R Julsurud, Jerome F Breen, Eric Williamson, Jae K Oh, Mayo Clinic, Rochester, MN

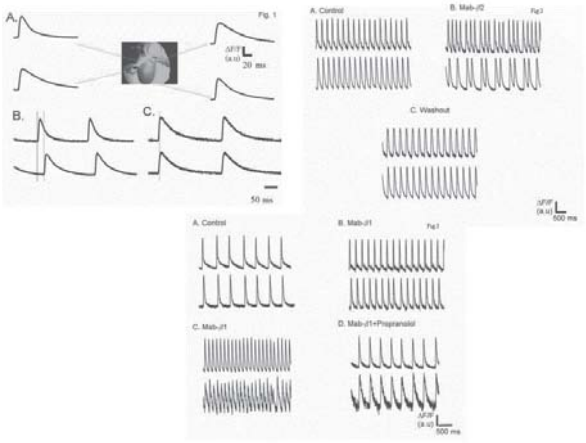
Background: Although the impairment of quality of life may be severe, it has been generally accepted that relapsing pericarditis has excellent life prognosis with exceedingly rare severe complications. The aim of this study was to investigate clinical outcomes according to the types of initial clinical presentation in patients with relapsing pericarditis.
Methods: A total of 52 patients with relapsing pericarditis were divided into two groups and analyzed the development of complications; intermittent type (group I, 36 patients, 40.0±13.6 years, 21 males), incessant type (group II, 46.5±23.0 years, 9 males).
Results: The frequency of the recurrence in group I was 5.0±2.4. Clinically significant ventricular dysfunction, arrhythmias, and valvular heart diseases were not developed. However, cardiac tamponade requiring pericardiocentesis in 20 patients (38.5%), pleural effusion requiring thoracentesis in 16 patients (30.8%), intractable symptoms requiring pericardiectomy in 13 patients (25.0%), constrictive pericarditis in 5 patients (1 persistent, 4 transient) (9.6%), treatment-related complications in 2 patients (1 iatrogenic Cushing, 1 renal failure) were developed during the clinical courses in patients with relapsing pericarditis. Among these complications, the development of cardiac tamponade was significantly higher in group II (11 patients, 68.8%) than in group I (9 patients, 25.0%) (p=0.003). Fourteen patients (38.9%) in group I had developed steroid dependency and thus changed into incessant type during clinical courses. Improvement of pericarditis without recurrence following pericardiectomy was observed in only 2 patients (15.4%) and the remainders were still symptomatic or showed recurrence of pericarditis. Conclusion: The present study demonstrated that relapsing pericarditis is not a benign disease in terms of complications. Clinically significant cardiac tamponade are not uncommon, especially in incessant type, and constrictive pericarditis either persistent or transient may be developed.

9:30 a.m.

1033-190 **Impact of Anti-B1 and Anti-B2 Antibodies on the Genesis of Ventricular Arrhythmias**

Juan A. Marques, Alfredo Mijares, Nancy Linares, Rodolfo Fernandez-Gomez, Johan Hoebeke, Ivan Mendoza, Ariel L. Escobar, Ivan Mendoza-Britto, IVIC, Caracas, Venezuela, Central University of Venezuela, Caracas, Venezuela

Background: Ventricular arrhythmias in ischaemic heart disease, congestive heart disease, idiopatic dilated cardiomiopathies and Chagas disease have been related with autoantibodies against beta-receptors
Objective: To evaluate the impact of autoantibodies against beta-receptors in a mouse whole heart Langendorff's preparation that allows the assessment of calcium currents and action potentials.
Methods: Hearts from 5-7 weeks old Balb/c mice were perfused in a whole heart Langendorff's preparation. Calcium currents were evaluated by local-field fluorescence microscopy. Action potentials were recorded through 2-mm electrodes. Monoclonal anti beta-2 antibodies against H19C peptide in the second extracellular loop of human beta-2 receptor and anti beta-1 against H26R peptide were used.
Results: Calcium currents in different heart areas were obtained (fig 1). Monoclonal beta-2 antibodies on calcium currents in right atrium and right ventricle produce AV conduction block (fig 2-B), that dissappers with the washout (fig 2-C).Anti-B1 antibodies produce produce a positive chronotropic effect (fig 3-B), disappearing with washout and propranolol (fig 3-C). **Conclusions:** Anti beta-1 antibodies show a positive chronotropic effect, while anti beta-2 antibodies affect AV conduction. The presence of both could contribute to the appearance of ventricular arrhythmias in whole hearts.



9:30 a.m.

1033-191 **Trastuzumab Cardiotoxicity: Not as Benign as It Looks?**

Christopher C. Reynolds, Gregory Hartlage, Vinod Patel, Ren Chen, Maya Guglin, University of South Florida, Tampa, FL, H. Lee Moffitt Cancer Center, Tampa, FL

Background: Trastuzumab (TZB) reduces mortality and recurrence in breast cancer. Cardiotoxicity (CTX) is a major side effect often resulting in early cessation of treatment (TX). The full extent of the problem in a "real life" situation is not well studied. Our objective is to determine the incidence of TZB-induced CTX and the rate of discontinuation of TZB in patients.
Methods: We retrospectively reviewed the records of 187 women with breast cancer who received TZB as an adjuvant (ADV) TX (118) or TX of metastatic (MET) cancer (69) between 2004 and 2006. CTX was defined as a decrease of ejection fraction (EF) to ≤50%, or ≥10% from the baseline, or symptoms of heart failure. Statistical analysis was done with Chi-square test and Fisher exact test.
Results: After excluding 25 patients with no follow-up EF, 161 patients, all women ranging from 29 to 86 years, mean 51.4±10.9, were analyzed. CTX developed in 56 patients (34.8%), including 33.1% of ADV patients and 39.5% of MET patients.
In the ADV group, 19.5% of patients discontinued TZB due to CTX. CTX accounted for 75.5% of premature discontinuation of TZB. In both groups, EF decreased in 3 months in patients with CTX and remained below baseline for the 12 months of TX. In 3 of 5 patients with follow-up beyond 12 months, EF remained <50%. In patients with either hypertension or diabetes, risk of CTX was higher (56.4% vs 32.9%, p<0.05).
Conclusions: CTX occurred in 1/3 of breast cancer patients treated with TZB and was the reason for premature discontinuation of TX in 20% of the ADV group.

Ejection Fraction in Patients With Breast Cancer Treated with Trastuzumab

	Baseline (%)	3 Months (%)	6 Months (%)	9-12 Months (%)
Adjuvant				
No Cardiotoxicity	59.2+4.9	59.9+5.3	59.2+5.0	59.2+4.7
Cardiotoxicity	61.3+7.0	54.4+7.6	54.2+7.9	53.1+6.5
Metastatic				
No Cardiotoxicity	59.3+7.2	59.1+7.3	59.8+6.8	59.6+6.7
Cardiotoxicity	59.4+6.8	56.7+5.7	55.6+5.0	54.2+7.0
Total				
No Cardiotoxicity	59.3+5.5	59.7+5.6	59.3+5.2	59.3+5.2
Cardiotoxicity	60.7+6.9	54.9+7.2	54.5+7.3	53.5+6.9

9:30 a.m.

1033-192 **Diagnosis of Post-surgical Constrictive Pericarditis: Demonstration of Left Heart-Dominant Pericardial Adhesion**

Teruo Noguchi, Sunao Kojima, Naoaki Yamada, Yoichi Goto, National Cardiovascular Center, Suita, Japan

Background: We sought to identify the distinctive clinical and hemodynamic features of post-surgical constrictive pericarditis (PSCP) in comparison with idiopathic CP (ICP) and to assess the utility of magnetic resonance imaging (MRI) in PSCP diagnosis.
Methods: High-fidelity intracardiac pressure waveforms from 51 consecutive patients with surgically proven CP (16 PSCP patients and 35 ICP patients) were examined. Tagged cine MRI was performed in 10 PSCP and 10 ICP patients using a 1.5T MR system.
Results: Only 6% and 25% of the 16 PSCP patients fulfilled the classic hemodynamic criteria or had dynamic respiratory variations, respectively, in contrast to 77% and 86% of the 35 ICP patients (both p<0.0001). In PSCP patients, pulmonary capillary wedge pressure (20±6 vs. 15±4 mmHg; p<0.01) and left ventricular end-diastolic pressure (22±4 vs. 17±4 mmHg; p<0.01) were significantly higher, and the difference between left ventricular end-diastolic pressure and right ventricular end-diastolic pressure (6.7±1.8 vs. 1.5±2.1 mmHg; p<0.0001) was significantly greater than in ICP patients, indicating a left heart-dominant constrictive physiology for PSCP. Tagged cine MRI distinguished the pericardial adhesions that predominantly covered the left heart in PSCP from those uniformly covering both the left and right heart in ICP.
Conclusions: The classic hemodynamic criteria and dynamic respiratory variations for CP, which are based on the assumption of uniform pericardial constriction, may not be applicable to PSCP patients who have left heart-dominant pericardial constriction. Tagged cine MRI is useful for detecting left heart-dominant pericardial adhesions in PSCP.

9:30 a.m.

1033-193 **Reversal of Heart Iron Overload Following Intensified Chelation Therapy in Tranfusion-Dependent Thalassemia Major: Assessment Using Magnetic Resonance Heart T2***

Thu-Thao Le, Ru-San Tan, National Heart Centre, Singapore, Singapore

Background. Siderotic cardiomyopathy is the commonest cause of premature death in thalassemia major (TM). The degree of heart iron overload is inversely proportional to the magnetic resonance (MR) relaxation parameter T2*. We studied the time course of heart iron load reversal, expressed as improvement in heart T2*, following iron chelation therapy.
Methods. We retrospectively analyzed the initial and serial MR T2* scans (performed every 6 to 12 months) in 19 beta TM patients, who had been detected to have heart iron overload on MR scans (T2*<20ms) and were treated thereafter with intensified iron chelation regimen.
Results. 14 patients had severe (T2*<10ms, Group A), and 5 had mild to moderate (T2* 10ms to 20ms, Group B) heart iron overload (table). On survival analysis, median durations for heart T2* values to increase by 10% were 20 and 12 months in Groups A and B, respectively.
Conclusion. Despite intensive chelation therapy, heart T2* improved very slowly, especially in severe heart iron overload. This implies that intensive chelation therapy must be prolonged in patients with heart iron overload. MR T2* scans should be performed to document resolution of heart iron deposition before withdrawal of intensive chelation.

Transfusion history and chelation treatment of patients in both groups

	Group A, T2*<10ms (n = 14)	Group B, T2* 10ms to 20ms (n = 5)	p value
Age (years)	23 ± 5	24 ± 8	ns
Transfusion duration (years)	23 ± 5	23 ± 8	ns
Transfusion units per transfusion	2.3 ± 0.6	2.4 ± 0.5	ns
Interval between transfusions (weeks)	3.6 ± 0.5	3.9 ± 0.5	ns
Chelation duration (years)	12 ± 5	15 ± 5	ns
Chelation therapy: deferoxamine : deferiprone : combination (%)	60:0:40	26.3:5.3:68.4	ns
Serum ferritin level (mg/dl)	5621 ± 5646	2400 ± 1920	ns

9:30 a.m.

1033-194 **Factors Determining Clinical Outcomes of Patients With Stress-Induced Cardiomyopathy in a Tertiary Referral Hospital**

Pil Hyung Lee, Byung Joo Sun, Hyung Oh Choi, Ji Hye Yim, Jong-Min Song, Duk-Hyun Kang, Jae-Kwan Song, Seong-Wook Park, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Stress-induced cardiomyopathy (SCMP) is an increasingly recognized disease entity and clinical features and outcomes of SCMP in a tertiary referral hospital are not known.
Methods: Inclusion criterion was newly developed wall motion abnormalities on echocardiography beyond a single epicardial coronary distribution without clinical evidence of coronary artery disease.
Results: A total of 60 patients (median 63 years) were enrolled from Jan 2000 to June 2008. Women comprised 78% of total patients. The triggering events were acute medical illness (sepsis, hypoxemia, bleeding, etc) in 31 patients (52%, group I), in-hospital surgery or procedure (endoscopy, bronchoscopy, elective surgery, etc) in 17 (29%, group II) and emotional stress in 12 (19%, group III). Chest pain was more frequently observed in group III, whereas dyspnea was more frequent in group I and II. Age and sex ratio were not different among groups. Median ejection fraction was 34% and peak troponin I level was only mildly elevated (median 3.2 ng/mL). QT prolongation was the most freqent ECG abnormality (88%) and T wave inversion was present in 73%. Typical apical ballooning was present in 45 patients (75%) and right ventricular involvement in 12 (20%). Tachyarrhythmia (atrial fibrillation [n=7], atrial flutter [n=2], and ventricular tachycardia [n=3]) was observed in 12 patients (20%). Laboratory findings were not significantly different among groups. Admission to the intensive care unit (ICU) was needed in 48 patients (81%), largely due to pulmonary edema (n = 30, 51%) or shock (n =21, 35%). Although the frequency of ICU admission was not different, endotracheal intubation was

more frequently needed in group I and II. Fifteen patients (25%) died and mortality was not different among groups. Multivariate analysis showed that APACHE II score, a clinical index representing the severity of systemic illness, (HR 1.233, 95% CI 1.116 - 1.362, p<0.001) and right ventricular involvement (HR 6.187, 95% CI 1.727 - 22.158, p = 0.005) were independently associated with death.
Conclusions: Clinical features of SCMP in a tertiary referral hospital are quite different with grave prognosis depending on the severity of underlying disease.

9:30 a.m.

1033-195 Patterns of Septal Hypertrophy in Hypertrophic Cardiomyopathy Are Associated With Differences in Clinical and Functional Characteristics by Echocardiography and Cardiac MRI

Aslan T. Turer, Zainab Samad, Anne M. Valente, Michele A. Parker, Brenda Hayes, Raymond J. Kim, Joseph Kisslo, Andrew Wang, Duke University, Durham, NC

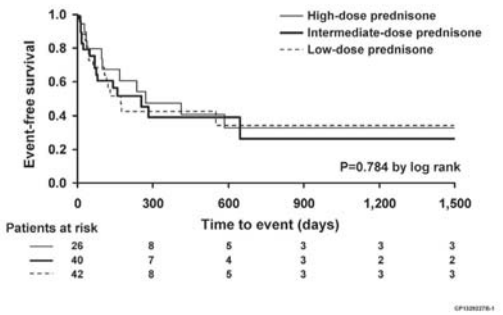
Background: Hypertrophic cardiomyopathy (HCM) has a wide spectrum of anatomic and clinical expression, yet septal hypertrophy is a typical finding.. Classification of septal morphology in HCM has been proposed, yet its clinical significance is undefined.
Methods: 75 patients with HCM were prospectively enrolled. Septal morphology was categorized based on the echocardiographic parasternal long-axis (LAX) and apical 4-chamber (Ap) views into 5 subtypes:
Simple sigmoid: maximal septal wall thickness at the basal septum in both LAX and Ap views. Complex sigmoid: maximal septal wall thickness at the basal septum in LAX view (i.e. subaortic) and an additional prominent mid-septal wall thickness ≥ basal septum in Ap view. Catenoid: maximal septal wall thickness at the mid-septum in Ap view. Neutral: uniformly thickened septum, with a ratio of each septal segment:maximal septal wall thickness ≥0.8 in Ap view. Apical: maximal septal wall thickness in the apical septum in Ap view. All patients underwent delayed-enhanced cardiac MRI (DE-CMR) imaging. Hyperenhancement (HE) was measured by 2 investigators blinded to the clinical and echocardiography results.
Results: Catenoid septum was the most common morphologic subtype (31/75, 41%), followed by simple sigmoid (22/75, 29%), complex sigmoid (15/75, 20%), neutral (4/75, 5%), and apical (3/75, 4%). The age at symptom onset was youngest among catenoid and complex sigmoid groups (p=0.008). Provocable LV outflow obstruction by Doppler velocity was highest among simple and complex sigmoid septal subtypes. Diastolic function differed between groups, with catenoid or complex sigmoid septal morphologies more strongly associated with restrictive filling pattern (grade 3) by tissue Doppler. By DE-CMR, the presence of HE also differed significantly between the subtypes [apical (100%), catenoid (77%), complex sigmoid (67%), simple sigmoid (27%), neutral (25%), p=0.002].
Conclusions: A simple classification of 5 septal hypertrophy patterns in HCM demonstrates significant differences in clinical and functional characteristics, as well as the amount of hyperenhancement by CMR, among the septal subtypes.

9:30 a.m.

1033-196 Effect of Corticosteroid Dose in Relapsing Pericarditis

Masud H. Khandaker, Raul E. Espinosa, Nandan S. Anavekar, Steven I. Robinson, Rowlens M. Melduni, Sharonne N. Hayes, Jae K. Oh, Mayo Clinic, Rochester, MN

Background: A recent retrospective study has suggested that high dose but not low dose corticosteroids are associated with a higher recurrence rate and morbidity in patients with relapsing pericarditis. The purpose of this study was to validate this concept further.
Methods: Retrospective review of 244 patients who presented to the Mayo Clinic, Rochester, between 1994 to 2005 with a diagnosis of relapsing pericarditis yielded 108 patients who were treated with prednisone. Patients were divided into high dose (≥ 40 mg; n = 26), intermediate dose (20 - 39 mg; n = 40) and low dose (< 20 mg; n = 42) prednisone groups. The primary endpoint was the time to recurrence, cardiac tamponade, constrictive pericarditis or pericardiectomy.
Results: No significant differences in mean age and gender were found in the high (48.7 ± 17.4 years, 58% female), intermediate (49.3 ± 14.4 years, 63% female) and low dose (45.6 ± 14.1 years, 64 % female) prednisone groups. In addition, baseline clinical and demographic characteristics were similar across the groups. Mean highest prednisone dose was 54 ± 22 mg/day vs 23 ± 4.4 mg/day vs 8.9 ± 3.6 mg/day for the high, intermediate and low dose groups respectively. Kaplan Meier analysis was used to analyze event free survival over 5 years (Figure) and revealed no differences in any corticosteroid group (p = 0.784).
Conclusion: While this study is limited by sample size and its retrospective design, corticosteroid dosage does not appear to affect outcome in patients with multiple relapses of pericarditis.



9:30 a.m.

1033-197 Immunological Correlates of Tuberculous Effusive Constrictive Pericarditis

Bongani M. Mayosi, Kerryn van Veen, Faisal Syed, James Russell, Kemilembe Tibazarwa, Okechukwu Usim, Mpiko Ntsekhe, Robert J. Wilkinson, Katalin A. Wilkinson, University of Cape Town, Cape town, South Africa

Background: Effusive constrictive pericarditis is present when there is evidence of clinical and haemodynamic constriction following pericardiocentesis in a patient with a pericardial effusion. It is not known whether effusive constrictive physiology is associated with specific immunological changes compared to pure effusive disease in tuberculous pericarditis.
Methods: The expression of inflammatory, anti-inflammatory, and fibrotic response genes were analysed using quantitative RT-PCR of RNA extracted from pericardial fluid and blood of 23 patients with tuberculous pericardial effusion. Gene expression was normalized to human beta-actin in the same sample. Blood and pericardial fluid was compared in all patients, after which patients were stratified according to disease outcomes of either pure effusive or effusive-constrictive pericarditis according to invasive haemodynamic monitoring of the pericardium and right side of the heart..
Results: There was abundant expression of the profibrotic TGF-beta, inflammatory IL-1 beta, SPARC (a fibrotic response gene with a regulatory role) and Timp1 (the natural inhibitor of matrix metalloproteinase 2 and 9) in both blood and pericardial fluid. There was clear evidence of compartmentalized gene expression as RNA levels of genes associated with fibrosis Col1a1, Col1a2, Col4a1 and Col4a2 (encoding procollagen molecules) and regulatory FOXP3 were significantly upregulated in the pericardial fluid compared to the blood. We next stratified the data according to disease status and found that TGF-beta (p=0.016) and IFN-gamma (p=0.014) were significantly down regulated in the pericardial fluid of patients with effusive constrictive pericarditis compared to those with purely effusive pericardial disease.
Conclusion: We show for the first time that effusive constrictive pericarditis is associated with a specific pattern of cytokine expression in tuberculosis. These findings may assist in the development of predictive biomarkers for fibrosis in pericardial tuberculosis.

9:30 a.m.

1033-198 Sudden Death Due to Concentric Left Ventricular Hypertrophy in the Absence of Myofibrillary Disarray in African-Americans

Laudino M. Castillo-Rojas, David A. Appel, Jennifer A. McNear, Lena Avedissian, John E. Atwood, Lisa A. Pearse, Robert N. Potter, Allen P. Burke, Ladd Tremaine, Eric A. Shry, Philip J. Gentlesk, Stephen S. Reich, Robert E. Eckart, Department of Defense Cardiovascular Death Registry Group, Brooke Army Medical Center, San Antonio, TX, Armed Forces Institute of Pathology, Washington, DC

Background: Sudden death in young African-Americans is frequently under-reported and limited to case series of athletes. We sought to describe a cohort of patients to define differences in cause of death as a function of race.
Methods: Clinical and pathologic records from the Office of the Armed Forces Medical Examiner from 1998 to 2008 were reviewed.
Results: There were 838 deaths identified that serve as the basis for the cohort (mean age 38±11 years). Reported race included Caucasian (n=589, 70.3%), African-American (n=213, 25.4%), Pacific Islander (n=19, 2.3%), and Asian (n=17, 2.0%). There was no difference in finding of idiopathic sudden death as a function of race (Caucasians - 20.2%, African-Americans - 22.5%, p=0.54). Fatal coronary disease was most common in Caucasians (n=381, 64.7%), while significantly lower in African-Americans (n=97, 45.5%, p<0.001). Concentric left ventricular hypertrophy without myofibrillary disarray was more common in African-Americans than Caucasians (16.9% vs. 3.7%, p<0.001), but there was no difference in hypertrophic CM (3.7% vs. 2.0%, p=0.17) as a function of race. There was no clinical difference in LV thickness or cardiac mass between African-Americans and Caucasians (1.7±0.4cm vs. 1.6±0.4cm, p=0.022; and 454±88gm vs. 451±86gm, p=0.69).
Conclusion: Idiopathic concentric left ventricular hypertrophy without myofibrillary disarray, but not hypertrophic cardiomyopathy, is more commonly noted in African-Americans than Caucasians and represents a common cause of sudden cardiac death.

9:30 a.m.

1033-199 Clinical Significance of Plasma Brain Natriuretic Peptide Level in Cardiac Sarcoidosis Patients Treated With Corticosteroids

Yoshikazu Yazaki, Mitsuaki Horigome, Ayako Takahashi, Uichi Ikeda, Noriyuki Sekimura, Division of Cardiology, Matsumoto Medical Center, Matsumoto, Japan, Department of Cardiovascular Medicine, Shinshu University, Matsumoto, Japan

Background: Corticosteroid treatment is generally indicated in patients with cardiac sarcoidosis (CS). A reliable heart-specific marker for the monitoring of steroid treatment remains to be established in CS. Although plasma brain natriuretic peptide (BNP) level is related to the severity of heart failure, clinical utility of BNP measurement on the follow-up of CS patients treated with corticosteroids is unknown.
Methods: We studied 30 CS patients who measured plasma BNP levels, and compared the values to clinical findings and outcome. Serial measurements were also performed before and during steroid treatment.
Results: At the time of BNP measurement, 8 patients showed abnormal gallium-67 uptake in the myocardium. BNP levels of the 8 patients were significantly higher than those of the other patients with negative results (549±515pg/ml versus 104±122pg/ml, p<0.05), although left ventricular ejection fraction was similar between the two groups.

Plasma BNP levels of 16 patients requiring device therapies were significantly higher than those of the other 14 patients (342±459pg/ml versus 43±35pg/ml, p<0.05). All patients received oral prednisone with an initial dose of 30mg/day and a maintenance dose of 5 to 10mg/day. Plasma BNP concentrations were unchanged within 6 months after starting corticosteroids (221±144pg/ml to 188±124pg/ml, not significant), but significantly decreased until 12 months (221±144pg/ml to 118±136pg/ml, p<0.05). During a mean follow-up of 3 years, we clinically detected relapse of cardiac lesions in 8 patients presenting with recurrence of abnormal myocardial gallium-67 uptake, conduction disturbance or arrhythmias, or rapid worsening left ventricular ejection fraction (LVEF) after the long-term stable clinical course. The 8 showed a significantly increased BNP level when the relapse occurred (58±53pg/ml to 125±116pg/ml, p<0.05). After an increase in corticosteroid dose or addition of methotrexate, the BNP levels were significantly decreased (125±116pg/ml to 58±68pg/ml, p<0.05).
Conclusions: Plasma BNP levels may be related to the disease activity in CS. Serial measurements of BNP are helpful for the management of CS patients treated with corticosteroids.

9:30 a.m.

1033-200 Early Diastolic Myocardial Tissue Doppler Velocities Are Not Reduced in Asymptomatic Carriers of MYBPC3 Gene Mutation for Hypertrophic Cardiomyopathy

Sabe De, Heng Wang, Leah Nye, Baozhong Xin, W.H. Wilson Tang, Cleveland Clinic Foundation, Cleveland, OH, Das Deutsch Center (DDC) Clinic for Special Needs Children, Middlefield, OH

Background: Prior studies have suggested that early diastolic myocardial tissue Doppler (TD) velocities (Ea) may be reduced in mutation positive patients without left ventricular hypertrophy (LVH). We examined echocardiographic characteristics of asymptomatic carriers for a known *MYBPC3* gene mutation for hypertrophic cardiomyopathy (HCM)
Methods: We prospectively evaluated 15 consecutive subjects with a known myosin binding protein C 3 (*MYBPC3*) mutation (c.3330+2T>G) identified by familial screening. All subjects underwent anthropometric measurements, electrocardiogram, and transthoracic echocardiography.
Results: In our study cohort (mean age 33±12 years, 47% male), 26% had evidence of LVH, and one had asymmetric septal hypertrophy without evidence of obstruction. All patients had preserved left ventricular ejection fraction with no evidence of significant valvular diseases. Of the 14 phenotype-negative patients, 3 (27%) had evidence of diastolic dysfunction (all with Stage 1). Mean Ea were 11.1 ±3.2 cm/s
for the septal annulus and 16.4 ±5.3 cm/s for the lateral annulus, both higher
than expected (from normal controls or prior reports).
Conclusions: In our cohort of symptomatic, phenotype-negative carriers of *MYBPC3* gene mutation for HCM, TD-derived Ea levels were not reduced as previously reported. These results challenge the ability of TD imaging for early screening in HCM gene mutation carriers.

9:30 a.m.

1033-201 Cardiac MRI Findings in Patients With Relapsing Pericarditis: Comparison With Acute Idiopathic Pericarditis

Kye Hun Kim, Dali Feng, James Glockner, Matthew Martinez, Imran S Syed, Philip Aroaz, Paul R Julsrud, Jerome F Breen, Eric Williamson, Jae K Oh, Mayo Clinic, Rochester, MN

Background: Cardiac MRI (CMR) is a useful imaging method for identifying inflammation of the pericardium, using delayed enhancement (DE) of Gadolinium. However, CMR's findings of relapsing pericarditis are not well known.
Methods: Fifty two patients with relapsing pericarditis (group I), 11 patients with acute pericarditis (group II), and 10 controls (group III) who had CMR were analyzed.
Results: Pericardial, myocardial, or pleural DE, thickened pericardium, pericardial or pleural effusion, dilation of IVC (inferior vena cava), septal bouncing motion were not found in control group. The findings of CMR between group I and II were summarized in table. The prevalence of DE of the pericardium and pleura were not different, but DE of the myocardium was significantly prevalent in group II than in group I (p<0.001). Pericardial thickness measured by pre-enhancement CMR was significantly thicker in group I than in group II (p<0.001), but the pericardial thickness measured by fast imaging employing steady state acquisition (FIESTA) sequence and DE CMR were not different. Septal bouncing motion was observed in 12 patients and constrictive physiology was observed in 5 patients (1 persistent, 4 transient) in group I, but not in group II.
Conclusions: CMR in this study demonstrated that the pericardial thickening and pleuropericarditis are not uncommon, the development of constrictive pericarditis may be seen, and the myocardial involvement is not a feature in patients with relapsing pericarditis.

CMR findings of the patients

	Group I (n=52)	Group II (n=11)	P value
DE of pericardium (%)	42 (80.8)	11 (100.0)	0.119
DE of pleura (%)	10 (19.2)	2 (18.2)	0.936
DE of myocardium (%)	0 (0.0)	5 (45.5)	<0.001
Pericardial thickness by pre-enhance CMR (mm)	2.66±1.15	1.88±0.31	<0.001
Pericardial thickness by FIESTA (mm)	2.32±2.01	2.01±0.47	0.193
Pericardial thickness by DE CMR (mm)	2.55±1.49	2.18±1.26	0.458
Septal bouncing motion (%)	12 (23.1)	0 (0.0)	0.077
Constrictive physiology (%)	5 (9.6)	0 (0.0)	0.284
Dilation of IVC (%)	4 (7.7)	0 (0.0)	0.342

9:30 a.m.

1033-202 Left Ventricular Dysfunction in Patients Receiving Cardiotoxic Cancer Therapies: Are Clinicians Responding Appropriately?

Geoffrey Yoon, Melinda Telli, David Kao, Kelly Matsuda, Ronald Witteles, Stanford University, Stanford, CA

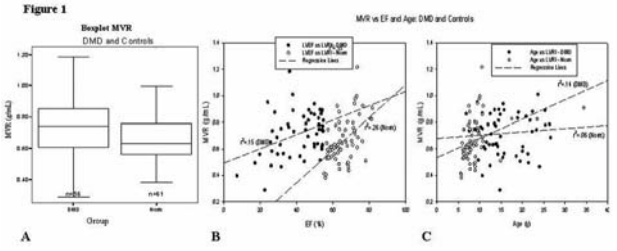
Background: Cancer survivors treated with anthracyclines and/or trastuzumab are at risk for cardiotoxicity. Left ventricular (LV) systolic dysfunction, symptomatic or asymptomatic, represents a Class I indication for therapy with beta-blockers and angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) according to ACC/AHA guidelines. We designed this study to examine treatment practices for patients with cancer therapy-associated LV dysfunction, and the real-world adoption of treatment guidelines.
Methods: After IRB approval, we reviewed all patients who received anthracycline and/or trastuzumab cancer therapy at Stanford University from October 1, 2005 to October 31, 2007. Out of 6,530 total cycles of chemotherapy administered, we identified all unique patients who had at least one echocardiogram performed before and after the start of chemotherapy. Detailed chart review was then conducted for these patients, examining chemotherapy regimens, cardiac risk factors, cardiac imaging results, concomitant medications, and patient referrals/consultations.
Results: A total of 88 patients met inclusion criteria. Ninety-two percent were treated with anthracyclines, 25% with trastuzumab in combination with anthracyclines, and 8% with trastuzumab alone. Mean baseline EF was 60%, with 13% of patients having a baseline EF below normal. A total of 41% had LV dysfunction (EF less than 55%) during or after cancer therapy. Of these patients, 56% received beta-blocker therapy, 47% received ACE-I or ARB therapy, and 50% received Cardiology consultation. Of the patients with asymptomatic LV dysfunction (75% of the LV dysfunction cohort), 41% received beta-blocker therapy, 33% received ACE-I or ARB therapy, and 37% received Cardiology consultation.
Conclusions: In real-world clinical practice, many cancer survivors with cardiotoxicity are not adequately evaluated and treated from a cardiovascular standpoint. Multidisciplinary collaboration between oncologists and cardiologists is vitally needed to improve the quality of care for these patients.

9:30 a.m.

1033-203 Cardiac MRI Study of Duchenne Cardiac Dysfunction: Is It a Dilated Cardiomyopathy?

William M. Gottliebson, Joshua T. Germann, Robert J. Fleck, Linda H. Cripe, Wojciech Mazur, Janaka P. Wansapura, Erik C. Michelfelder, D. Woodrow Benson, Kan N. Hor, Cincinnati Childrens Hospital Medical Center, Cincinnati, OH

Background: The cardiac findings in Duchenne muscular dystrophy (DMD) are considered a progressive dilated cardiomyopathy. Our experience with cardiac MRI (CMR) surveillance of DMD patients, however, has not shown consistent elevation of LV volume. We hypothesized that DMD cardiomyopathy has geometric features distinguishing it from the classic dilated cardiomyopathies.
Methods: Clinical and research CMR data was reviewed from DMD patients with cardiac dysfunction (LV EF < 55%), and from normal controls. Age, LV EF, and indexed LV mass (LVMi) and LV end-diastolic volume (EDVi) were tabulated for each individual. LV geometry was quantified by the Mass/Volume Ratio (MVR). MVR between groups was compared via Student's t-test.
Results: LVMi and EDVi were normal in both the controls (n=61, age 6.87 - 34.2 years) and DMD patients (n=56, age 5.57 - 34.4 years). EF ranged from 7 - 54% in DMD patients; EF was normal (> 55%) in all controls. Mean MVR values for controls (0.67 ± 0.17) and DMD patients (0.72 ±0.17) were not statistically different (p=0.092).Figure 1a (boxplot) demonstrates the similarity in the MVR values, while Figures 1b-c confirm the absence of a significant relationship between MVR and either age or EF.
Conclusion: MVR of DMD patients is normal, in distinction to published MVR values of classic dilated cardiomyopathies. This suggests that DMD LV myocardium responds with a unique pattern of remodeling, and thus requires consideration of alternative therapeutic strategies for this disease.



9:30 a.m.

1033-204 Variable Wall Motion Abnormalities Seen With Stress Mediated Cardiomyopathy

Khadija Siddiqui, Matthew Weinberg, Ronald Siegel, Medical College of Wisconsin, Milwaukee, WI

Background: Takotsubos cardiomyopathy (TC) has been reported as an apical ballooning ("typical") or midventricular ("atypical") dysfunction. However, transient global wall motion abnormality in the absence of obstructive epicardial disease has not been described.

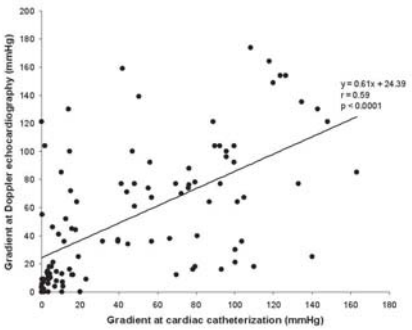
In addition, information regarding recurrent ventricular dysfunction also appears to be limited.
Methods: 38 cases of cardiac catheterization confirmed TC were reviewed. Assessment of patient population included demographic, clinical, serial echocardiographic, and angiographic data. Also reviewed, were the variable presentations in this group; these were then categorized by apical, midventricular, or global wall motion abnormalities. Clinical management and outcomes was assessed, and subsequent recurrent presentations were recorded.
Results: Of the 38 patients, 32 (84%) were females, and 6 (16%) were males. 11 (29%) patients had evidence of apical ballooning, 20 (53%) had midventricular dysfunction, and 3 (8%) were found to have global hypokinesis. Of the patient population, 4 (11%) had recurrent episodes. Specifically, in the patients with recurrences, 2 (50%) of the 4 had similar midventricular wall motion abnormality on both occasions. 1 (25%) of the 4 initially presented with apical ballooning, and then subsequently with midventricular involvement; while the other patient (25%) had midventricular dysfunction on initial presentation, but global hypokinesis with the recurrent episode. All recurrences occurred within 1 month to a year of initial presentation.
Conclusions: While most literature notes only the apical ballooning form of TC, recent reports also recognize the midventricular dysfunction as a less frequent presentation of this syndrome. However, based on our data, we suggest midventricular ballooning as a more common abnormality of stress induced cardiomyopathy than has been reported. Furthermore, we also propose global hypokinesis as another variable presentation of TC. Finally, it is also important to note, that patients with recurrences may not have the same wall motion abnormalities as seen on the initial presentation.

9:30 a.m.

1033-205 Variability of the Left Ventricular Outflow Tract Gradient in Hypertrophic Cardiomyopathy: A Cardiac Catheterization-Echocardiographic Study

Jeffrey B. Geske, Paul Sorajja, Rick A. Nishimura, Steve R. Ommen, Mayo Clinic College of Medicine, Rochester, MN

Background: The presence of severe left ventricular outflow tract (LVOT) obstruction directs the management algorithm in patients with hypertrophic cardiomyopathy (HCM). There are few data on the variability of the LVOT gradient and the potential impact of this variability on clinical practice.
Methods: One hundred HCM patients (age 58±13 years, 47% male) underwent comprehensive two-dimensional and Doppler transthoracic echocardiography and cardiac catheterization with transseptal measurement of left-sided pressures. All studies were performed within 48 hours of one another.
Results: LVOT gradients from both methods correlated (r=0.59, p<0.0001, see figure); however, wide scatter was present with 95% confidence limits of agreement ±84 mmHg. For classifying patients as having severe LVOT obstruction on the basis of either method (<30 vs. ≥30 mmHg), discrepant results occurred in 21% of patients. Eighteen studies were performed with simultaneous measurement of the LVOT gradient, in whom there was a very strong correlation (r=0.99, p<0.0001) with 95% confidence limits of agreement ±11 mmHg.
Conclusions: In patients with HCM, LVOT gradient measurements are routinely obtained to characterize the severity of obstruction. These data demonstrate the marked variability of the LVOT obstruction, which must be considered when determining both appropriate therapy and their efficacy.



9:30 a.m.

1033-206 Diagnostic Accuracy of Differential ^{99}Tc-DPD Myocardial Uptake in Transthyretin-Related and Primary Systemic Cardiac Amyloidosis

Cristina C. Quarta, Paolo Ciliberti, Simone Longhi, Letizia Riva, Elena Biagini, Pier Luigi Guidalotti, Cinzia Pettinato, Giuseppe Galati, Angelo Branzi, Claudio Rapezzi, University of Bologna and S.Orsola-Malpighi Hospital, Bologna, Italy

Background. We previously reported that ^{99}Tc-DPD scintigraphy tests positive in transtyretin-related (TTR) but not primary (AL) cardiac amyloidosis (CA). We reassessed diagnostic accuracy of DPD scintigraphy for distinguishing TTR from AL in an extended population of CA patients.
Methods. We evaluated 35 TTR (23 mutant; 12 wild-type) and 28 AL patients, all with echocardiographically diagnosed CA. Myocardial uptake of DPD was semiquantitatively/visually assessed by experts 3 h (and 5 min) after ^{99}Tc-DPD (740 MBq iv).
Results. Semiquantitative measures of late (3 h) DPD uptake were ~2-fold higher in TTR (table). Heart/body retention ratio correlated with LV mass in TTR (R=0.37; P=0.04 at linear regression analysis) but not in AL (P=0.9). In a multivariate model (adjusting for age, sex, LV mass/vol, LV mean wall thickness and renal failure), TTR predicted increasing DPD uptake (COEF -3.5998; 95%CI, -4.898 to -2.301; P=0.0001). Sensitivity of visual score 0-1 for diagnosis of AL was 93% (95%CI, 83%-100%), specificity 100% [reference standard: immunohistochemistry/DNA analysis].

	TTR-related (n=35)	AL (n=28)	p value
Age, yr	62±14	61±9	0.7
Left Ventricular Mass, g	423±167	297±101	0.0001
Heart tracer retention: median (iqr)	7.9% (6.5%-8.9%)	3.5% (3.2%-5.9%)	0.0001
Heart/body retention ratio: median (iqr)	10.3 (8.2-11.6)	5.2 (4.5-6.6)	0.0001
Visual cardiac score:			0.0001
0 (no uptake)	0 (0%)	20 (72%)	
1 (mild uptake)	0 (0%)	6 (21%)	
2 (moderate uptake)	12 (34%)	2 (7%)	
3 (strong uptake)	23 (66%)	0 (0%)	

Conclusions. In TTR CA, myocardial DPD uptake is strong and correlates with LV mass, whereas in AL CA it is weak and not correlated with LV mass. The visual score may be a useful non-invasive tool for etiologic diagnosis of AL vs TTR, particularly when the score is clear-cut (ie “no” or “strong” uptake).

9:30 a.m.

1033-207 Clinical and Pathologic Characteristics of Myocarditis as a Cause of Sudden Death

Lena Avedissian, Jennifer A. McNear, David A. Appel, Laudino M. Castillo-Rojas, John E. Atwood, Lisa A. Pearse, Robert N. Potter, Allen P. Burke, Ladd Tremaine, Philip J. Gentlesk, Eric A. Shry, Stephen S. Reich, Robert E. Eckart, Department of Defense Cardiovascular Death Registry Group, Brooke Army Medical Center, San Antonio, TX, Armed Forces Institute of Pathology, Washington, DC

Background: Myocarditis has been a significant cause of death in prior studies of young military personnel.
Methods: Clinical and pathologic records from the Office of the Armed Forces Medical Examiner from 1998 to 2008 were reviewed.
Results: We identified 739 patients with an autopsy with sudden cardiac or idiopathic death. There were 30 cases (4.1%) of pathology-defined myocarditis on autopsy that serve as the basis for the cohort. The mean age was 31±10 years (range 18-45 years, 86.7% male). In contrast to other cardiac causes of death, most cases were non-exertional (80.0%). A clinical prodrome was reported in 69.6% of cases where information was available. The most common antemortem symptoms were a constellation of fever, myalgias, nausea and vomiting in 52.2% of cases. Chest pain was less common, reported in only 3 (10%) cases. Out of hospital arrest, with survival to hospital admission was seen in 22.2% of cases. Of those cases in which there was discrimination as to location of fibrosis and/or necrosis, the findings were most commonly biventricular (43.8%), and isolated right ventricular (31.3%). While the finding of atherosclerosis was noted in 27.6%, there was disease with >70% occlusion in only 3.5%, and there was no evidence of plaque rupture or coronary thrombosis in any of the cases identified.
Conclusion: Myocarditis represents a unique cause of sudden death with characteristic prodrome in some that may allow for earlier recognition before the fatal event and improved treatment.

9:30 a.m.

1033-208 Mortality due to Cardiomyopathy and Heart Failure in a Population of 41 654,020 Habitants

Edimar A. Bocchi, Guilherme Guimarães, Sandrigo Mangini, Heart Institute (InCor) of the São Paulo University Medical School, São Paulo, Brazil

Background: Continued assessment of temporal trends in mortality and epidemiology of specific cardiovascular diseases is needed to provide a scientific basis for rational allocation of the limited health care resources, and strategies to reduce risk and predict the future burden of cardiovascular disease. Specific data about specific cardiomyopathies (CMP) and heart failure (HF) is not well reported.
Methods: Causes of deaths due to CMP, HF or etiologies associated with HF based on the SEADE data Foundation from São Paulo State (Brazil) during 2006 according International Classification of Diseases (ICD)-10 in an estimated 41 654,020 habitants
Results: From 242,832 deaths 15336 (6.3%) were due to CMP or HF. Chagas´disease (acute or chronic with heart involvement were responsible by 1197 deaths (7.8% of HF deaths) being acute in one case and chronic in 1196; amyloidosis by 23 deaths (0.15%); hypertensive diseases by 2128 (13.88%); ischemic cardiomyopathy by 1404 (9.16%); chronic constrictive pericarditis by 7 (0.046%); dilated cardiomyopathy by 2638 (17.2%); endomyocardial disease (endomyocardial fibrosis, Löffler´s endocarditis) by 6 (0.039%); endocardial fibroelastose by 24 (0.16%); other restrictive cardiomyopathy by 3 (0.02%); alcoholic cardiomyopathy by 69 (0.45%); drugs and other external agents 2 (0.013%); other cardiomyopathies by 8 (0.052%); unspecified cardiomyopathy by 821 (5.3%); HF by 6468 (42.18%); cardiomegaly by 458 (2.99%) ; and cardiogenic shock as main manifestation 79 (0.52%) .
Conclusion: Restrictive CMP, pericarditis,drugs, and alcoholic were rare causes of HF. Chagas´disease, hypertensive, and ischemic etiologies remain as important preventable causes of HF deaths. These findings have important public health implications because the allocation of health care resources, and strategies to reduce risk of HF, CMP and Chagas´disease.

ACC.POSTER CONTRIBUTIONS

1042

Cardiomyopathies/Myocarditis/Pericardial Disease; Cardiac Transplantation/Assist Devices--Basic and Clinical ;Myocardial Function/Heart Failure--Clinical Nonpharmacological Treatment

Monday, March 30, 2009, 1:30 p.m.-4:30 p.m.
Orange County Convention Center, West Hall D

3:30 p.m.

1042-165 Incidence of Adequate ICD Interventions in Patients With Hypertrophic Cardiomyopathy Supposed to Be at High-Risk for Sudden Cardiac Death

Christian Prinz, Juergen Vogt, Bogdan G. Muntean, Johannes Heintze, Detlef Hering, Dieter Horstkotte, Lothar Faber, Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany

Background: In patients (pts.) with hypertrophic cardiomyopathy (HCM) risk assessment for sudden cardiac death (SD) is currently based on presence or absence of risk markers (RM) like non-sustained ventricular tachycardia (nsVT) on Holter ECG, excessive left ventricular hypertrophy (LVH) of >30 mm on imaging, abnormal blood pressure response (aBPR) during exercise, family history of SD, and recurrent syncope. Recently, detection of myocardial fibrosis by gadolinium-enhanced magnetic resonance imaging (GE-MRI) has been suggested as an additional RM.
Methods: In a cohort of 1291 clinically characterized HCM-pts. 50 individuals (33 men, 17 women; mean age: 44±13 years, NYHA class: 2.0±0.9) were identified who had more than 1 (2-4) RM and a GE-MRI before their ICD implantation. ICD implantation was performed for secondary SD prophylaxis in 2, and for primary prophylaxis in 48 pts.. Outflow obstruction was present in 25 pts., the other 25, including 1 pt. after septal ablation and 1 pt. after myectomy, were non-obstructive. With GE-MRI maximum wall thickness and LV mass were measured, and the presence of fibrosis was scored semiquantitatively (from 0=absent, 1=point-shaped, 2=limited to 1 LV segment, 3=involving ≥2 segments). During follow-up device-related problems were noted, and the ICD memories were analyzed for adequate ICD interventions or other arrhythmic events.
Results: The number of RM per pt. was 1.7±0.8. Evidence of myocardial fibrosis ≥2 was present in 39 pts. with a mean score of 2.2±0.9. During follow up (1.5±1.5 [0.2-6.0]) years, adequate ICD interventions (9 episodes) were documented in 3 pts., 11 pts. had at least 1 episode of atrial fibrillation. Inadequate ICD interventions were noted in 3 cases. The only difference among pts. without vs. with event was a longer follow-up duration (2.3±2.0 vs. 1.2±2.3 years, p=0.03) in the latter group.
Conclusions: The incidence of appropriate ICD discharges in our cohort of 50 pts. with HCM who received ICD implantation for SD prevention was 4%/pt.-year, supporting the proposed risk stratification. However, no single RM nor additional GE-MRI was predictive for future arrhythmic events.

3:30 p.m.

1042-166 Association Between Circulating Neuregulin-1β and Clinical Outcomes in Heart Failure

Bonnie Ky, Stephen E. Kimmel, Radwan Safa, Mary E. Putt, Nancy K. Sweitzer, James C. Fang, Douglas B. Sawyer, Thomas P. Cappola, University of Pennsylvania School of Medicine, Philadelphia, PA, Vanderbilt University Medical Center, Nashville, TN

Background: Basic research has demonstrated that the neuregulin/ErbB pathway is necessary for fetal cardiac development and cardioprotection in the adult heart. Cardiac stress leads to increased NRG-1/ErbB signaling, and loss of this pathway results in decreased survival in animal models. However, whether these findings translate to humans is unknown. Our objective was to establish the relationship between circulating NRG-1β levels and incident adverse clinical outcomes in a diverse heart failure cohort.
Methods: Serum NRG-1β was quantified in 899 outpatients in the Penn Heart Failure Study, a prospective cohort of patients with primarily systolic heart failure. At time of study entry, detailed clinical data regarding cardiac history were obtained and two-dimensional transthoracic echocardiography was performed. The primary outcomes were all-cause mortality and cardiac transplantation. Univariate and multivariable associations between NRG-1β and the combined endpoint death or transplant were determined using Cox proportional hazards models.
Results: The mean±sd ejection fraction in this cohort was 31.6±16.5%, and 72.9% had NYHA Class II/III heart failure. Over a median follow-up time of 2.4 years, 195 patients reached the composite endpoint. In univariate models, higher circulating NRG-1β was associated with an increased risk of death or transplant [HR 1.20 per log increase (1.008-1.433, p=0.04)]. After multivariable adjustment, this remained significant [HR 1.24 (1.03-1.49, p=0.02)]. This relationship was modified by cardiomyopathy etiology, with higher NRG-1β levels associated with worse outcomes in ischemics, but a decreased risk in hypertensive cardiomyopathy patients (interaction p=0.003).
Conclusions: This study demonstrates an independent association between NRG-1β levels and risk of all-cause death or cardiac transplant, supporting a role for NRG-1/ErbB signaling in human heart failure. Our data suggest that NRG-1β is a marker of heart failure severity and provide insight into the differing functions of NRG-1β in various cardiomyopathy etiologies. Further study of NRG-1β will help define its utility as a novel prognostic biomarker in heart failure.

3:30 p.m.

1042-167 Plasma Natriuretic Peptide Levels Between Asymptomatic Carriers and Non-carriers of MYBPC3 Gene Mutation for Hypertrophic Cardiomyopathy

Wai Hong Wilson Tang, Baozhong Xin, Leah Nye, Stanley L. Hazen, Heng Wang, Cleveland Clinic, Cleveland, OH, Das Deutsch Center (DDC) Clinic for Special Needs Children, Middlefield, OH

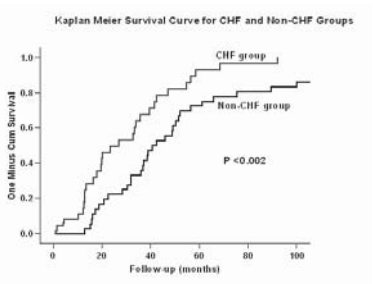
Background: Several sarcomeric gene mutations have been identified in the pathogenesis of hypertrophic cardiomyopathy (HCM). The potential for cardiac biomarker screening such as B-type natriuretic peptide (BNP) to identify carriers for such mutations has not been examined in a prospective manner.
Methods: From a large cohort of families with a specific *MYBPC3* gene mutation (c.3330+2T>G), we measured plasma BNP levels (Abbott Architect) and compared levels between asymptomatic carriers and non-carriers.
Results: A total of 125 consecutive subjects were enrolled and genotyped, including 3 homozygous carriers (all phenotype-positive), 54 heterozygous carriers, and 68 non-carriers. Overall, homozygous carriers have significantly higher BNP levels than asymptomatic individuals (median BNP 2,994 pg/mL vs 15.8 pg/dL, respectively), but the mean and median levels were similar between asymptomatic carriers and non-carriers (mean BNP 27 ±40 vs 19 ±17 pg/mL, p=0.17; median 15.8 vs 15.8 pg/mL, p=0.96).
Conclusion: Plasma BNP levels were similar between asymptomatic carriers versus non-carriers of *MYBPC3* mutation, challenging the utility of BNP testing in asymptomatic non-carriers of sarcomeric gene mutations.

3:30 p.m.

1042-168 Predictors of Survival for More Than OneYear in Primary Cardiac Amyloidosis

Ahmad M. Alqaqa'a, Hussam Suradi, Kamran Asl Hamidi, Mithilesh K. Das, Merrill Benson, Krannert Institute of Cardiology, Indiana University, Indianapolis, IN

Background: Cardiac involvement in 1º amyloidosis (AL) is associated with poor prognosis. We postulated that prognosis of 1º cardiac amyloidosis (CA) is better than reported.
Methods: Clinical, ECG,echo and mortality data of 172 patients with histologically proven 1º amyloidosis were studied.
Results: 121 patients (age: 60±13.7 yrs; male, 66%) had CA (57 patients had positive cardiac biopsy or autopsy, and 64 patients had CA by clinical criteria [CHF with LVH or low voltage ECG]). The median survival was 15.9±3.2 months and 55% patients survived >1 year. CHF was present in 81(72%) patients. Low voltage ECG, Q wave, and LVH were present in 39.9%, 43%, and 13% respectively. Echo showed LVH, mitral regurgitation (MR), left atrial enlargement and speckled appearance in 85%, 13%, 14% and 14.5% patients, respectively. Univariate predictors of survival for >1year were absence of CHF (class II-IV), MR and pericardial effusion, as well as presence of interventricular septum <1.5 cm (all p <0.05). Absence of CHF (p=0.028, RR 1.86[95% CI: 1.1-3.25]) was the only multivariate predictor of survival. Multiorgan involvement, low voltage ECG, speckled appearance, LVEF and pulmonary HTN were not predictors for survival. Median survival with CHF was 8.9 ±2.1months compared to 31±6.3 months without CHF (P<0.001).
Conclusion: 1-Contrary to previous reports, the median survival of patients with 1º CA is 15.6 months and 55% patients survive >12 months. 2-CHF is the only multivariate predictor of mortality in these patients.



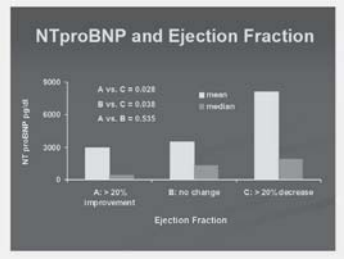
3:30 p.m.

1042-169 Amino-Terminal Pro-B-Type Natriuretic Peptide (NTproBNP) Levels Predict Deterioration of Left Ventricular Function in Chronic Heart Failure

Leandro Perez, Denise Petersen, Jun Chiong, Loma Linda University Medical Center, Loma Linda, CA

Background: Left ventricular (LV) remodeling leads to loss of myocytes, increased interstitial fibrosis; its negative impact in chronic heart failure (HF) is evidenced by chamber enlargement, contractile dysfunction and dyssynchrony. Response to HF therapy is largely defined in terms of changes on LV size, shape and contractility. Natriuretic peptides are prognostic markers in patients with HF and are useful in their risk stratification; it is unknown whether they correlate with LV remodeling.
Methods: NTproBNP levels and ejection fraction (EF) were measured in 515 ambulatory

HF patients before and during optimal medical therapy. The initial and final EF were compared and subjects were subdivided into 3 groups based on EF changes: Group A, EF > 20% improvement; Group B, EF ≤ 20% change; Group C, EF >20% reduction.
Results: The mean NTproBNP levels among the 3 groups were: Group A, 2987pg/dL; Group B, 3536pg/dL and Group C, 8101pg/dL. Patients in group C had significantly higher NTproBNP (figure) when compared to Groups A (p=0.028) and B (p=0.038).
Conclusions: Elevated plasma NTproBNP levels predict deterioration of ejection fraction in heart failure individuals; they are helpful in the identification of high-risk patients who warrant closer outpatient follow-up.



3:30 p.m.

1042-170 **Renal Dysfunction in Heart Failure Results From Congestion but Not Poor Perfusion**

Maya E. Guglin, Marcos Garcia, Abel Rivero, Fadi Matar, University of South Florida, Tampa, FL

Background: Renal dysfunction in heart failure is thought to be due to poor perfusion of the kidney. We tested the hypothesis that passive congestion is more important than poor perfusion.
Methods: We retrospectively studied 223 sequential patients who underwent right heart catheterization. In 178 of them, serum creatinine was checked before the procedure. In 156, echocardiograms were performed within six months of the procedure. We divided the subset based on cardiac index (CI≤2.4L/min/m2 and >2.4 L/min/m2), based on wedge pressure (wedge≤12 mm Hg and >12 mm Hg), and based on ejection fraction (EF≥50% and <50%). Student's t test and Pearson's correlation coefficient were used for analysis.
Results: There was a progressing increase in serum creatinine with increase in wedge pressure, from 0.99±0.3 mg/dL in wedge pressure 0-12 mm Hg, to 1.04±0.4 mg/dL (p=NS) in wedge pressure 13-21 mm Hg, and to 1.17 ±0.5 mg/dL (p2.4 L/min/m2) creatinine even was worse (1.13±0.5 mg/dL) than in patients with CI ≤2.4 L/min/m2 (1±0.3 mg/dL, p<0.05). In the whole dataset, serum creatinine correlated with invasively measured pulmonary artery systolic and diastolic pressure (r=0.29, p<0.01, and r=0.17, p<0.05, respectively), and with the end diastolic velocity of pulmonary regurgitation and tricuspid regurgitation velocity by echo (r=0.46, p<0.0001, and r=0.17, p<0.05) and with the wedge pressure (r=0.19, p<0.05), but not with cardiac index, cardiac output, or EF.
Conclusions: Renal dysfunction in heart failure is determined more by passive congestion than by low perfusion.

3:30 p.m.

1042-171 **Detection of Constrictive Pericarditis: A Single-Centre Experience of 523 Surgically Confirmed Cases**

Lieng H. Ling, Hartzell V. Schaff, Jacob dal-Bianco, Marion E. Barnes, Brian D. Lahr, Thoralf M. Sundt, III, Jae K. Oh, Mayo Clinic, Rochester, MN, National University of Singapore, Singapore, Singapore

Background: Constrictive pericarditis (CP) often eludes detection because presentation is nonspecific. We aimed to determine the means by which CP was detected over a 2-decade period.
Methods: We reviewed clinical data and use of diagnostic tests in 523 pts (mean age±SD 57±15 yrs; 70% male) with a surgically confirmed diagnosis of CP at Mayo Clinic Rochester from 1985-2006. Data were tested for a temporal trend using χ^2 tests.
Results: Etiologies of CP were prior cardiac surgery (n=154, 29%), idiopathic (n=117, 22%), acute pericarditis (n=89, 17%), mediastinal irradiation (n=64, 12%), arthritides (n=29, 6%), non-viral infection (n=22, 4%), neoplasm (n=7, 1%) and miscellaneous (n=41, 8%). Procedures done elsewhere while investigating CP symptoms included liver biopsy (n=28, 5%), pleurodesis (n=17, 3%), thoracoscopy/mediastinoscopy (n=16, 3%), gastrointestinal endoscopy (n=16, 3%), bronchoscopy (n=15, 3%), pleural biopsy (n=10, 2%), laparotomy (n=5, 1%), cholecystectomy (n=5, 1%), lung biopsy (n=6, 1%) and bone marrow biopsy (n=3, 1%). Two pts had unneeded valve replacement. Among 292 pts undiagnosed at presentation, CP was diagnosed preoperatively in 279 pts - clinically in 174 pts (60% of undiagnosed cases), by echocardiography in 81 (28%) and by radiologic or hemodynamic studies in 24 (8%). Echocardiography performed in 496 pts was initially diagnostic in 72% of cases. Compared to 1985-1995, there was a 2.4 fold increase (n=156 vs 367) in pericardiectomies for CP from 1996-2006. During this period, the only significant trend in attributable causes was an increase in postoperative CP (19% vs 34%, P=0.001). Between the 2 decades, no significant differences in utilization of diagnostic tests or clinical or echocardiographic detection of CP were observed; however pts more frequently had an outside diagnosis of CP (33% vs 49%, P<0.001) from 1996-2006.
Conclusions: Cardiac surgery is the contemporary leading cause of CP and accounts partly for the increasing volume of pericardiectomies. While the increase in referred cases suggests a growing recognition of CP, the frequency of noncardiac procedures conducted before diagnosis indicates that its detection remains challenging.

3:30 p.m.

1042-172 **Cytokine Gene Polymorphisms Are Associated With Disease Severity and Prognosis in Patients With Idiopathic Dilated Cardiomyopathy**

Stamatis Adamopoulos, Fotis Kolokathis, Angeliki Gkouziouta, Panagiota Georgiadou, Antigoni Chaidaroglou, Alexandros Kouloubinis, George Karavolias, Dimitrios Degiannis, Vassilis Voudris, Dimitrios Th Kremastinos, Onassis Cardiac Surgery Center, Athens, Greece

Background: Specific genes coding for cytokines involved in the pathophysiological process of heart failure may promote the progression and contribute to the severity of idiopathic dilated cardiomyopathy (IDC). We investigated the potential associations of 6 gene polymorphisms with markers of disease severity and prognosis in patients (pts) with IDC.
Methods: Polymorphisms investigated in 80 clinically stable pts with IDC were the T10C and C25G of the transforming growth factor beta1 (TGF-β1) gene, the G-174C of the interleukin-6 (IL-6) gene, the A-592C of the inteleukin-10 (IL-10) gene, the G-308A of the tumor necrosis factor-alpha (TNF-α) gene and the T874A of the interferon-gamma (IFN-γ) gene. Potential associations were sought between genotypes and the disease severity as expressed by symptoms, measures of exercise capacity, echocardiographic indices and specific biomarkers. Pts were stratified during their first admission according to the disease severity and followed-up for 79±21 months.
Results: A positive correlation was observed between T carriers of the T10C polymorphism of the TGF-β1 gene and the peak oxygen consumption (p=0.04), which remained significant only for pts younger than 39 years old after adjusting for age and sex (p=0.009). C carriers for C25G TGF-β1 were 4.2 times more likely to present worse symptoms of heart failure than non C carriers (OR: 4.2, 95%CI 1.43- 12.34, p=0.009). Pts GG homozygous for G-174C IL-6 polymorphism presented with greater left ventricle end-systolic (p=0.002) and end-diastolic (p=0.02) diameters in comparison to the CC homozygous. A carriers of the G-308A TNF-α polymorphism were associated with higher levels of IP-10 (p=0.05) whereas T carriers of the T874A IFN-γ polymorphism were associated with lower levels of MCP-1 (p=0.06). C carriers of the C25G TGF-β1 polymorphism were associated with worse prognosis (p=0.0423) whereas T carriers of the T874A IFN-γ polymorphism were associated with better survival (p=0.0163).
Conclusions: Polymorphisms in genes coding for cytokines seem to be associated with measures of disease severity and prognosis in IDC. These associations may identify genes in pathways important for IDC pathogenesis and therapy.

3:30 p.m.

1042-173 **Left Atrial Remodeling Is Common and Associated With High Risk Markers in Patients With Cardiac AL Amyloidosis**

Jennifer E. Liu, Teimuraz Apridonidze, Richard Steingart, Ray Comenzo, James Hoffman, Yuliya Goldsmith, Memorial Sloan Kettering Cancer Center, New York, NY

Background: AL amyloidosis is known to affect all cardiac chambers. Although changes in LV structure and function are well known, the effect of amyloidosis on the left atrium is less well defined.
Methods: We examined eight-six patients with cardiac AL amyloidosis who had an echocardiogram at the time of diagnosis between March 1997 - May 2008. The patients were divided into Group I: left atrial volume indexed to body surface area (LAVI) ≤ 32 ml/m^2 (n= 38) or Group II: LAVI >32 ml/m^2 (n=48)
Results: Fifty-six percent of the patients had LAVI>32 ml/m^2. The two groups were similar in age, gender and body surface area (BSA). Group II had a significantly higher BNP than Group I with no significant difference in creatinine clearance or troponin. Higher prevalence of clinical congestive heart failure (CHF) at baseline was noted in Group II than Group I. Group II had higher interventricular septal thickness, LV mass and mitral E/A ratio with lower ejection fraction and stroke volume than Group I. Left atrial systolic force (LASF), an index of left atrial systolic function was significantly lower in Group II than Group I.

	Group I	Group II	P
Age (y)	59	60	0.3
Gender, male	17 (35%)	31 (65%)	0.5
BSA m2	1.82	1.86	0.5
BNP	809	1291	0.0004*
Creatinine Clearance (ml/min)	65	54	0.1
troponin	0.128	0.184	0.14 *
Clinical CHF	7 (32%)	15 (68%)	0.04*
Interventricular septum (cm)	1.40	1.50	0.002*
Ejection fraction %	61	69	0.045*
LV mass (gm)	201	227	0.0014*
LASF (kdynes)	14.02	9.14	0.007*
Stroke volume (ml)	65	52	0.008*
E/A ratio	1.42	2.39	0.006*

*adjusted for age,gender and creatinine clearance
Conclusion:
Left atrial remodeling is common in patients with cardiac AL amyloidosis and is associated with worse LV structure, systolic and diastolic function and atrial function. Left atrial volume is highly correlated with BNP level and provides an index of overall cardiovascular disease burden in the amyloid heart.

3:30 p.m.

1042-174 Primitive Microorganisms (Archaea) in Idiopathic Dilated Cardiomyopathy: A New Etiological Frontier

Maria L. Higuchi, Marcia M. Reis, Nadia V. Sambiase, Renata N. Ikegami, Sandrigo Mangini, Victor S. Issa, Alfredo Fiorelli, Edimar A. Bocchi, Noedir Stolf, São Paulo, Brazil

Background: The occurrence of DNA and antigens from viruses in the myocardium of patients with idiopathic dilated cardiomyopathy (IDCM) has been reported. However the presence of primitive microorganisms as archaea has not been well demonstrated.
Objective : The primary objective was to test endomyocardial biopsies (EMB) samples for the presence of archeal forms. Additionally we sought for the presence of *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and viruses.
Material and Methods: EMB fragments from four patients with myocarditis (acute and subacute) and from four patients with IDCM were studied by *in situ* hybridization (ISH), immunohistochemistry and electron microscopy (EM)techniques.
Results: Generic archaeal DNA was present in all cases, as well as *M. pneumoniae* antigens. Antigens for Hepatitis B viral surface were present in 3 myocarditis cases; antigens for Parvovirus B19 were present in four IDCM cases and in one myocarditis case, with negative ISH. EM of positive cases for Epstein-Barr virus revealed viral-like particles in regions of myocytolysis, with 30-35 nm diameter in complete virus or 16nm when only nucleocapsides. The Parvovirus B19 cases revealed icosahedric particles with less than 16 nm, non-encapsulated. These viral particles have lower diameters than those found in human viruses, were in round vesicles with double lipidic envoltory membrane containing clear thin cytoplasm and intracellular vacuole, compatible with archaea. There were also other procaryont forms at the interstitium or inside macrophages. Viral-like tailed particles were present in macrophages or among the fibrosis.*C. pneumoniae* bodies were found inside macrophages in two positive cases for Parvovirus B19.
Conclusion : Archeal forms are frequent findings in patients with myocardial diseases. To the extent of our knowledge this is the first report to suggest that archaea forms are present in the myocardium in association with bacteria and viruses. Our findings open new frontiers for the diagnosis and treatment of patients in this setting.

3:30 p.m.

1042-175 Neurohormonal Features of Stress Cardiomyopathy Triggered by Acute Central Neurologic Injury

Jacob Abraham, Hunter C. Champion, Navin K. Kapur, James O. Mudd, Ilan S. Wittstein, Johns Hopkins University School of Medicine, Baltimore, MD, Tufts Medical Center, Boston, MA

Background: Stress cardiomyopathy (SCM) is triggered by acute emotional and physiologic stressors, but the clinical and neurohormonal features of SCM following neurologic injury remain poorly defined.
Methods: We identified 30 patients who developed left ventricular (LV) ballooning following central neurologic injury. Serial electrocardiography and echocardiography were performed in all patients, and 18 patients underwent coronary angiography. Plasma catecholamine (CA) and neuropeptide (NP) levels were measured in 27 SCM patients and compared to 32 patients with acute myocardial infarction (AMI) and 9 healthy controls.
Results: The mean age of SCM patients was 63 ± 16 years and 83% were women. Neurologic triggers included intracranial hemorrhage, seizure, migraine, carotid thrombosis, and brain contusion. Hypotension, heart failure, and shock were common. Troponin-I levels were elevated on admission (4.7± 6.2 ng/ml), and no patients undergoing angiography had obstructive coronary disease. LV function was severely reduced on admission (EF 25 ± 12%) and significantly improved (EF 52 ± 9%, p<0.0001) at follow-up (mean 16 ± 7 days). All 3 patterns of LV ballooning (apical, mid-ventricular, basal) previously described in SCM were observed. Plasma CA and NP levels were significantly elevated in SCM compared to both AMI and controls (Table).
Conclusions: SCM can be precipitated by diverse central neurologic insults. Excessive sympathetic stimulation is strongly implicated in its pathogenesis.

Plasma Catecholamines and Neuropeptides in SCM Following Neurologic Injury

	SCM	AMI	Control
Dihydroxyphenylalanine	1857 ± 240 *	1376 ± 252	1229 ± 243
Epinephrine	676 ± 149 *	231 ± 144	92 ± 30
Norepinephrine	1952 ± 458 *	563 ± 392	213 ± 44
Dopamine	94 ± 15 *	45 ± 16 †	21 ± 7
Dihydroxyphenylglycol	2183 ± 448 *	1225 ± 299	914 ± 172
Dihyroxyphenlacetic acid	2164 ± 399 *	1528 ± 190 †	984 ± 360
Metanephrine	156 ± 19 *	94 ± 19	79 ± 24
Normetanephrine	162 ± 22 *	116 ± 32 †	75 ± 29
Neuropeptide Y	108 ± 51 *	61 ± 18	65 ± 22
Brain natriuretic peptide	1012 ± 242 *	160 ± 177	22 ± 9
5-Hydroxytryptamine	1994 ± 359 *	1094 ± 247	1092 ± 434

All values are expressed as mean ± standard deviation.
All units are pg/ml.
* P<0.001 versus AMI and Control.
† P<0.001 versus SCM and Control.

3:30 p.m.

1042-176 Adiponectin Serum Levels, Hemodynamics and Inflammatory Markers in Patients With Inflammatory Cardiomyopathy

Peter Bobbert, Uwe Kuehl, Ursula Rauch, Carmen Scheibenbogen, Heinz Peter Schultheiss, Carsten Skurk, Department of Cardiology and Pneumology, Charite Universitätsmedizin, Campus Benjamin Franklin, Berlin, Germany

Background: Adiponectin (APN) is an adipocytokine present in the systemic circulation in different isoforms exerting anti-inflammatory, anti-apoptotic and pro-angiogenic effects. The adipocytokine has recently been shown to prevent remodeling after cardiac injury. Adiponectin is also synthesized within the heart and cardiac expression is downregulated in patients with inflammatory cardiomyopathy (DCMi) indicating the cytokine as a potential new therapeutic target. However, systemic expression of the cytokine, i.e. plasma levels of APN and its isoforms, have not been studied in DCMi. Therefore, we determined the systemic expression and its correlation with hemodynamic and inflammatory parameters in patients with DCMi.
Results: Plasma APN concentrations (total, high, medium, low molecular weight) were significantly higher in patients with DCMi (n=140, EF<50%, LVEDD>55mm, positive inflammatory score) when compared with controls (n=30, EF>65%, LVEDD<55mm, no inflammation), i.e. 4.8±0.4 vs 6.0±0.4 µg/ml for APN (p<0.02). Furthermore, plasma levels of the cytokine in DCMi were not significantly different from patients with dilative cardiomyopathy (DCM) (n=52, EF<50%, LVEDD>55mm, negative inflammatory score). APN concentrations in patients with DCMi but not DCM strongly correlated with LV-EF (r= -0.44, p<0.01), LVEDP (r=0.51, p<0.001), mean PAP (r=0.39, p<0.002), and PCPW (r=0.39, p<0.002) after normalization for BMI. Similar correlations were found with HMW-adiponectin, while MMW and LMW isoforms did not correlate with hemodynamic parameters. For further analysis, serum inflammatory cytokine concentrations were measured. However, only IL-8 serum concentrations significantly correlated with APN concentrations (r=0.37, p<0.015). During follow-up, DCMi patients in the upper quartile of APN basal levels showed increased LVEF and decreased LVEDD, that was significant after 6-12 months (p<0.05).
Conclusion: Our results indicate a dissociation of systemic and local cardiac APN expression in DCMi that is associated with increased IL-8 expression. High serum HMW/APN levels might be beneficial in the progression of DCMi.

3:30 p.m.

1042-177 Septal Morphology and Late Gadolinium Enhancement Predict Genetic Test Status in Patients With Hypertrophic Cardiomyopathy

J. Martijn Bos, Ronen Rubinshtein, Melissa L. Will, Uma Valeti, James Glockner, Phillip A. Araoz, A. Jamil Tajik, Rick A. Nishimura, Bernard J. Gersh, Steve R. Ommen, Michael J. Ackerman, Mayo Clinic, Rochester, MN

Background: Contrast enhanced cardiac magnetic resonance imaging (CE-MRI) is a useful tool to define cardiac morphology and the presence of late gadolinium enhancement (LGE) indicating myocardial fibrosis. Previous studies have shown a strong correlation between reverse-curve hypertrophic cardiomyopathy (HCM) and a positive HCM genetic test, but fibrosis cannot be assessed. We therefore sought to evaluate MRI-derived septal contour and LGE in a large cohort of patients who also had genetic testing for sarcomeric HCM.
Methods: A genotype-phenotype subset analysis of 230 HCM patients (148 male, mean age 56 ± 17yrs) who underwent both CE-MRI and genetic testing for mutations in 9 myofilament-encoding, HCM-susceptibility genes was performed. Patients with prior history of septal ablation/myectomy were excluded. Septal shape was assessed from a 3-chamber standard steady state free precession pulse sequence. The presence of LGE was traced from a dynamic post contrast inversion recovery pulse sequence.
Results: Overall, only 44/230 patients (19%) had a positive HCM genetic test. Among the mutation positive subset, 47% had mutations in myosin binding protein C, 39% had thick myofilament mutations, and 9% had mutations involving the thin myofilaments. By MRI, the distribution of septal morphologies were sigmoidal in 144 (63%), reverse curve in 37 (16%), and apical in 15 (7%). Over half of the patients with reverse curve-HCM by MRI had a positive genetic test compared to only 15% for sigmoidal-HCM and 13% for apical-HCM (p < 0.001). There were no significant differences between the particular HCM gene involved and septal morphology. LGE was present in 75% of patients with a positive genetic test compared to 53% with a negative genetic test (p < 0.001). In a multivariate analysis, adjusting for age, gender, LV morphology and function, and presence of LGE, reverse curve morphology was the only independent predictor of a positive genetic test (p<0.001).
Conclusion: Comparable to echocardiography, reverse septal curvature on CE-MRI is a strong and independent indicator of myofilament-HCM. Furthermore, fibrosis as indicated by LGE is more common in patients with a positive genetic test.

3:30 p.m.

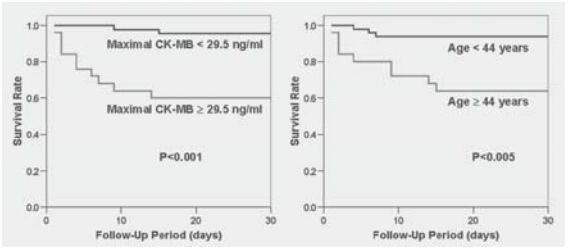
1042-178 In-Hospital Prognostic Factors in Patients With Acute Myocarditis

Jong Pil Park, Jong-Min Song, Sung-Hwan Kim, Sung Sik Kim, Jae-Joong Kim, Duk-Hyun Kang, Jae-Kwan Song, Asan Medical Center, Seoul, South Korea

Background: The initial prognostic predictors of acute or fulminant myocarditis remain to be clearly established.
Methods: In a total of 73 consecutive patients diagnosed as acute myocarditis, initial presentations and short-term outcomes were analyzed.
Results: Of 73 patients, mechanical ventilation, extracorporeal membrane oxygenation

and continuous renal replacement therapy were required in 16 (22%), 8 (11%), 5 (7%) patients, respectively. Twenty-five patients presented with fulminant myocarditis. In-hospital mortality occurred in 12 patients (16%). All of them presented with fuminant myocarditis and showed significantly older age (46 ± 11 vs. 36 ± 15 years, p<0.05), lower body mass index (21 ± 2 vs. 23 ± 3 kg/m^2, p<0.05), higher initial creatinine level (2.0 ± 1.7 vs. 1.2 ± 0.7 mg/dl, p<0.05) and higher maximal CK-MB level (95 ± 128 vs. 30 ± 42 ng/ml, p<0.05) than the patients who survived by univariate logistic regression analyses. Multivariate logistic regression analysis revealed that maximum CK-MB level (p=0.026, OR; 0.018, 95% CI; 0.002 - 0.034) and age (p=0.028, OR; 1.073, 95% CI; 1.008 - 1.143) are independent predictors for in-hospital mortality. The maximum CK-MB level ≥ 29.5 ng/ml predicted in-hospital mortality with a sensitivity of 83% and a specificity of 73%, and age ≥ 44 years did with a sensitivity of 75% and a specificity of 74% (Figure).

Conclusion: Old age and high maximal CK-MB level are short-term poor prognostic factors in patients with acute myocarditis.



3:30 p.m.

1042-179 **A High Prevalence of Brugada Syndrome Among Patients With Steinert's Disease: A New Insight Into the Pathophysiology of the Brugada Syndrome**

Karim Wahbi, Véronique Fressart, Henri Marc Bécane, Christophe Meune, Arnaud Lazarus, Nawal Benamar, Pascale Richard, Bruno Eymard, Denis Duboc, Pitié Salpétrière Hospital, Paris, France, Cochin Hospital, Paris, France

Background: *SCN5A* is the principal gene currently known to be associated with Brugada syndrome, but a mutation is identified in only 15 to 20% of families, suggesting that other genes have to be identified. Cardiac manifestations in Steinert's disease - an autosomal dominant systemic disease caused by a mutation in the *DMPK* gene - and in patients with *SCN5A* mutations are very similar, including ventricular and supraventricular arrhythmias, atrioventricular block and sudden death. However, Brugada syndrome was never reported in patients with Steinert's disease. We aimed at determining whether it could have been previously overlooked.

Methods: The electrocardiograms of 500 patients with genetically proven Steinert's disease were independently reviewed by two electrophysiologists. Patients with a type 1 Brugada ECG pattern were screened for mutations in the *SCN5A* gene and underwent resting and 24-hours ambulatory electrocardiogram, echocardiography and electrophysiological study.

Results: A type 1 Brugada ECG pattern was identified in 7 patients (6 males, 37-60 year old), representing a prevalence of 1.4%. It was previously unknown in 5 patients and paroxysmal in 3. No confounding factor such as fever or medication was identified. The genetic analysis of *SCN5A* gene was normal in all patients. One patient died suddenly of ventricular fibrillation and 4 had severe ventricular arrhythmias.

Conclusion: The 80-fold higher than expected (1.4% vs 5/10.000) prevalence of Brugada syndrome in our patients with Steinert's disease suggests a link between both diseases. In addition, *SCN5A* gene sequencing was normal in all our patients and Steinert's disease's systemic complications are known to be caused by alterations of the splicing of multiple gene mRNAs. This suggests that Steinert's disease could be the first cause of Brugada syndrome related to post transcriptional abnormalities of cardiac ion channels.

3:30 p.m.

1042-180 **Increased Left Ventricular Torsion in Hypertrophic Cardiomyopathy Mutation Carriers With Normal Wall Thickness**

Iris Rüssel, Wessel Brouwer, Tjeerd Germans, Tim Marcus, Marco Götte, Albert van Rossum, VU University Medical Center, Amsterdam, The Netherlands

Objective: To determine the amount of left ventricular (LV) torsion in hypertrophic cardiomyopathy (HCM) mutation carriers (carriers) with normal wall thickness.

Background: Increased LV torsion has been observed in HCM and is thought to be caused by wall thickening (1). However, structural abnormalities that precede the development of hypertrophy in HCM may also cause alterations in LV torsion in carriers with normal wall thickness (2).

Methods: Ten carriers with an LV wall thickness <10 mm, and ten age and gender matched controls underwent CMR cine imaging and tissue tagging. LV volumes were calculated from the cine images. Basal and apical rotations and LV torsion, defined as the circumferential-longitudinal shear angle (3), were determined from tissue tagging. Counterclockwise rotation as seen from the apex was considered positive. LV volumes, peak rotation and torsion were compared between both groups using Student's T-test. A p-value <0.05 was considered significant.

Results: LV end-diastolic and end-systolic volumes were not significantly different between both groups (p=0.79 and p=0.36, resp.), whereas EF was significantly larger in the carriers (63.2±3.2% vs. 59.7±2.8%, p=0.02). Peak apical rotation and peak torsion were significantly larger in the carriers (14.6±3.2 º vs. 10.3±3.3º, p=0.01, and 10.2±2.3 º vs. 7.1±1.0 º, p=0.001, resp.), while peak basal rotation was significantly smaller (-2.5±2.2 º vs. -4.6±1.7 º, p=0.03).

Conclusion: HCM mutation carriers with normal wall thickness demonstrate increased LV torsion. Underlying altered myocardial architecture might be responsible for this finding.

References:
1. Circ 90, 854-867(1994).
2. Circ115, e610-1(2007).
3. J Cardiovasc Magn Reson 10, 26(2008).

3:30 p.m.

1042-181 **Differential Cardiac Autonomic Modulation in Transient Left Ventricular Apical and Midventricular Ballooning**

Hendrik Bonnemeier, Robert Amschler, Wanda Mäuser, Timothy Krauss, Michael Reppel, Heribert Schunkert, Medizinische Klinik II, Universität zu Lübeck, Lübeck, Germany

Background: Recently, a new variant of the transient left ventricular apical ballooning (AB) syndrome with only midventricular affection was described, suggestive for a shared pathophysiologic etiology. As in midventricular ballooning (MB) the apical segment is spared, only etiologies not related to an epicardial coronary artery distribution can be supported. Thus we hypothesized that differences in regional autonomic modulation may play a role in the genesis of these syndromes.

Methods: We prospectively enrolled 37 consecutive patients with transient left ventricular dysfunction syndrome. AB was diagnosed in 27 (73%), MB in 10 (27%) patients. Non-linear indices of heart rate dynamics [Detrended fluctuation analysis (DFA); power-law-slope (PLS)], traditional time and frequency parameters of heart rate variability (HRV), as well as deceleration capacity (DC) were determined from 24-hour-Holter-ECGs, recorded on the third day after hospital admission.

Results: There were no significant differences in baseline clinical characteristics. Mean RR-interval was higher in AB patients (908±118 vs. 835±104ms, p<0.05). There were no differences regarding parameters of time domain HRV, except higher values of SDNNi in AB patients (46.6±22 vs. 40.8±12ms; p<0.05). In frequency domain, LF and LF/HF-ratio were higher in MB patients (LF/HF-ratio 1.28±0.6 vs. 1.69±0.9, p<0.01). MB patients exhibited lower values for DC (5.98±1.4 vs. 4.55±1.4, p<0.01) and PLS (-1.13±0.15 vs. -1.27±0.18, p<0.01), and higher values for DFA-α1 (0.991±0.12 vs. 1.094±0.07) compared to AB patients.

Conclusions: This is the first study to show that there are significant differences in cardiac autonomic modulation and fractal organization of heart rate dynamics between AB and MB syndromes. Patients with MB exhibit stronger fractal correlations of short- and long-term heart rate dynamics, and lower levels of tonic parasympathetic nervous activity. Thus, the interplay between right and left cardiac autonomic nervous modulation and differences in bilateral sympathetic co-activation may be an underlying pathophysiological mechanism for AB and MB syndromes.

3:30 p.m.

1042-182 **Progressive Left Ventricular Remodeling and Adverse Cardiac Events in Hypertrophic Cardiomyopathy Associated With Mutations in Cardiac Troponin Genes:Longitudinal Ten-Year Follow-Up**

Toshinari Tsubokawa, Noboru Fujino, Hidekazu Ino, Kenshi Hayashi, Kastuharu Uchiyama, Eiichi Masuta, Yuichiro Sakamoto, Akira Funada, Akihiko Muramoto, Masakazu Yamagishi, Kanazawa University Graduate School of Medicine, kanazawa, Japan

Background: Although mutations in cardiac troponin T (TNNT2) and troponin I (TNNI3) genes cause hypertrophic cardiomyopathy (HCM), little is known about differences in long term clinical course and changes in left ventricular (LV) morphologies .To elucidate differences in clinical manifestations between carriers with TNNT2 and TNNI3 genes mutations by a 10 years longitudinal evaluation.

Methods: Total 7 carriers with the TNNT2 mutations (Arg92Trp, Val85Leu and Phe110Ile) and 7 carriers with the TNNI3 mutation (Lys183del) were examined by longitudinal evaluations.

Results: At the initial, there were no differences in echocardiographic parameters between 2 groups. During a mean follow-up period of 10±3.2 years, 3/7(43%) carriers in both groups and suffered from congestive heart failure (CHF). Interestingly, carriers of end-stage HCM in TNNT2 group showed larger LV end-diastolic dimension (74±8.7 mm v.s. 53±2.9 mm, p<0.05) compared with those in TNNI3 group at the time of follow-up. In addition to the occurrence of CHF, ventricular and/or supraventricular arrhythmias which required hospitalization occurred in 5/7 (71%) in TNNT2 group while 3/7 (43%) in TNNI3 group. Cardiac death occurred in 2/7 (29%) in TNNT2 group while none in TNNI3 group.

Conclusions: There data demonstrate that HCM with TNNT2 rather than TNNI3 mutation may have unfavorable clinical course during 10 years follow-up periods, probably due to enhanced extent of LV remodeling in TNNT2 mutation.

3:30 p.m.

1042-183 **Utility of ECG-Gated MDCT to Differentiate Arrhythmogenic Right Ventricular Cardiomyopathy Patients From the Ventricular Tachyarrhythmia Patients**

Takatomo Nakajima, Fumiko Kimura, Katsuya Kajimoto, Tsuyoshi Sihga, Morio Shouda, Hiroshi Kasanuki, Nobuhisa Hagiwara, Tokyo Women's Medical University, Tokyo, Japan, International Medical Center of Saitama Medical University, Saitama, Japan

Background: Cardiac MRI is accepted as a noninvasive method in diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC). The utility of CT is not assured because CT is difficult in evaluating functional abnormality. We propose a comprehensive

CT scoring system for diagnosing ARVC and clarify CT's diagnostic ability using the Task Force (TF) criteria as a gold standard.
Methods: Forty patients (pts) (mean age: 41.5 years, 24 men) previously diagnosed with or suspected of ARVC because of ventricular tachyarrhythmia underwent pre- and post-contrast enhanced scanning using ECG-gated MDCT to evaluate listed CT criteria (table). We measured the maximum AP diameter of RV to evaluate RV enlargement using normal diameter in Japanese as 33.7 +/- 4.1mm. Locations of the fatty tissue contain RV outflow, RV free wall, trabeculation, and modulator band. We assessed minor (1 point) and major (2 points) aspects of each criterion and diagnosed ARVC in pts with more than 4 points.
Results: We diagnosed 14 pts with ARVC according to the TF criteria (table). Each CT finding listed was more significantly observed in patients with ARVC (P < 0.0001, Fisher's exact probability test) but also seen in those without ARVC and, so, might cause false positive diagnosis. Sensitivity and specificity for diagnosis of ARVC were 100% using the scoring system.
Conclusions: Our CT scoring system is optimal in classifying patients with tachyarrhythmia and diagnosing ARVC.

CT findings	ARVC (n = 14)	non-ARVC (n = 26)
1. RV enlargement	14 (100%)	8 (30.8%)
Major: > 3 SD of normal range	13 (92.9%)	2 (7.6%)
Minor: 2 to 3 SD of normal range	1 (7.1%)	6 (23.1%)
2. Scalloped appearance of RV free wall	13 (92.9%)	2 (7.7%)
Major: definite presence	10 (71.4%)	0 (0%)
Minor: probable presence	3 (21.4%)	2 (7.7%)
3. Presence of fatty tissue in RV and/or ventricular septum	14 (100%)	6 (23.1%)
Major: obvious or minor presence in > 2 locations	13 (92.9%)	4 (15.4%)
Minor: minor presence in one location or remarkable thinning of free wall	1 (7.1%)	2 (7.7%)

3:30 p.m.

1042-184 **Withdrawn**

3:30 p.m.

1042-185 **The Immunomodulatory Properties of Brain Natriuretic Peptide After Cardiac Transplantation**

Steven M. Shaw, Mohammed KH Shah, Nizar Yonan, James E. Fildes, Simon G. Williams, University Hospital of South Manchester NHS Trust, Manchester, United Kingdom

Background: Several observations about Brain Natriuretic Peptide (BNP) remain unexplained and could highlight gaps in our understanding of its physiology. It is currently accepted that ventricular myocytes secrete BNP in response to stretch stimuli or increased transmural pressure. However, after cardiac transplantation levels remain elevated despite replacement of the failing ventricle and restoration of intracardiac hemodynamics. Peaks in serum BNP also occur during acute rejection episodes and bacterial sepsis. In addition, experimental studies have shown that BNP is released not only from ventricular myocytes, but cells of the immune system such as T cells and macrophages. We therefore hypothesized that BNP has a discrete role within the immune system and devised a series of *in vitro* cell cultures to explore this.
Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from the whole blood of 60 cardiac transplant recipients. Cells were co-cultured for 72 hours in the presence or absence of BNP. Cultures were then immunophenotyped using flow cytometry. The supernatants from 20 patients were also analysed in duplicate using a multiplex bead immunoassay kit.
Results: Co-culture of PBMCs with BNP dose dependently reduced the standard cell count of Monocytes, T helper, T memory, NK, cytotoxic T, B and myeloid dendritic cells (all p<0.05). BNP also impaired functional aspects of several immune cells, including the reduction of cytotoxicity in NK cells and reduced adhesion of non-classical monocytes (via down-regulation of CD11c).
Supernatant analysis showed that BNP reduced the expression of several inflammatory cytokines including TNF-α (p=0.016), IL- 1α (p=0.017), IL-6 (p=0.038), IL-7 (p=0.033) and IL-12 (p=0.001). Interestingly there was preservation of anti-inflammatory and regulatory cytokines including IL-4, 5, 10 and 13.
Conclusions: Our findings suggest that BNP immunoregulates multifarious elements of the immune system after cardiac transplantation. This may impart significant consequences on immune mediated disease processes, such as allograft rejection. Further investigation is ongoing to see if similar effects are seen in a non transplant setting.

3:30 p.m.

1042-186 **Altered Left Ventricular Mechanics in Cardiac Allografts: Novel Insights From 2-Dimensional Speckle Strain Echocardiography**

Eun Joo Cho, Robert L. Scott, D. Eric Steidley, Francisco Arabia, Krishnaswamy Chandrasekaran, Marek Belohlavek, Bijoy K. Khandheria, Partho P. Sengupta, Mayo Clinic Arizona, Scottsdale, AZ

Background: Transplanted hearts (TXH) show gradual decline in left ventricular (LV) compliance and diastolic function, while global LV ejection fraction (EF) typically remains preserved. We hypothesized that chronic biomechanical changes in TXH would produce unique alterations in LV deformation patterns that are independent of injuries related to transplant rejection.
Methods: 30 patients with TXH (314±110 days old): 23 with no previous rejection (58±11 yrs, 18 male), 7 with previous rejection (57±9 yrs, 4 male) and 18 healthy controls (46±18 yrs, 8 male) underwent transthoracic echocardiography. Peak longitudinal, circumferential and radial strains (LS, CS and RS), and rotation were averaged from LV apical, mid and basal segments using 2D speckle tracking.
Results: Despite a normal LV EF (57±10 %), LS and CS in TXH were significantly reduced with a loss of the apex-to-base gradient of LV shortening (Table 1). RS was spared in mid segment and exaggerated in the apical segments although rotation of LV apical segments was reduced. Transplanted hearts with previous rejection showed only reduction of the LS at LV apex (Table 1).
Conclusion: Global LV EF in TXH is preserved despite reduction in longitudinal and circumferential shortening due to a compensatory increase in radial deformation. Knowledge of unique cumulative alterations in myocardial mechanics that evolve independent of changes due to transplant rejection may impact clinical assessment of long term prognosis in heart transplant recipients..

Table 1. Left Ventricular Deformation in Normal and Transplanted Hearts

		Control	Cardiac Transplantation	
	Deformation Parameter	(n=18)	No rejection (n=23)	Rejection (n=7)
Base	Longitudinal strain (%)	-14.9±5.1	-13.8±3.4	-11.0±7.0
	Circumferential strain (%)	-18.3±5.2	-12.0±5.5*	-14.5±5.8
	Radial strain (%)	50.3±20.5	25.0±16.4*	33.7±9.9
	Rotation (degree)	-3.2±2.3	-3.0±2.0	-2.8±1.2
Mid	Longitudinal strain (%)	-18.0±3.2‡	-14.8±3.8	-10.6±8.1*
	Circumferential strain (%)	-21.4±6.0	-14.3±3.9*	-10.3±7.3*
	Radial strain (%)	38.5±12.5	36.6±18.5‡	40.0±16.4
	Rotation (degree)	3.0±1.1‡	-1.3±0.8*	-1.7±0.8*
Apex	Longitudinal strain (%)	-20.0±3.3‡, ‡‡	-14.8±5.2*	-9.8±5.6*,†
	Circumferential strain (%)	-28.1±11.1‡, ‡‡	-16.8±5.7*,‡	-18.4±6.5
	Radial strain (%)	13.4±10.1‡, ‡‡	27.3±11.5	24.5±13.1
	Rotation (degree)	18.5±1.8‡, ‡‡	4.2±1.3*,‡, ‡‡	7.1±1.8*
Net twist angle (degree)		23.2±7.5	8.5±3.7*	7.3±4.5*

*, P <0.05 vs. control; †, P<0.05 vs. non-rejection; ‡, P <0.05 vs. basal level; ‡‡, P <0.05 vs. mid level

3:30 p.m.

1042-187 **Sirolimus Based Immunosuppression Improves Coronary Endothelial and Vasomotor Function Compared to Calcineurin-Inhibitors in Stable Cardiac Transplant Recipients**

Eugenia Raichlin, Abhiram Prasad, Walter K. Kremers, Brooks S. S Edwarads, Rihal S. Charanjit, Amir Lerman, Sudhir S. Kushwaha, Mayo Clinic, Rochester, MN

Background: The aim of the study was to evaluate and compare coronary endothelial and vasomotor function in heart transplant recipients maintained on sirolimus (SRL) or cyclosporin (CyA) based immunosuppression.
Methods: Endothelium dependent response to incremental intracoronary acetylcholine (Ach) infusion and endothelium independent response to intracoronary nitroglycerin and adenosine were assessed in 15 SRL- and 21 CyA- treated cardiac transplant recipients with angiographically normal coronary arteries. Three dimensional intravascular ultrasound (3D IVUS) was also performed.
Results: Baseline mean aortic blood pressure was significantly lower in the SRL group (93.6 10.2 mm.Hg vs. 105.2 8.7 mm Hg, p=0.002). Although adenosine administration resulted in reduced coronary flow reserve (CFR) during SRL treatment compared to CyA treatment univariately (2.67 0.64 vs. 3.53 0.72, p=0.0006), after multivariate analysis there was no difference between the groups (p=0.34). In 13 SRL treated subjects without angiographic and 3-D IVUS evidence of coronary allograft vasculopathy (CAV), Ach administration resulted in less epicardial vasoconstriction compared to CyA treated subjects (2.7 17.7% vs.-15.6 17.2%, p=0.005). However, two SRL treated subjects with significant CAV on 3 D IVUS (despite normal coronary angiogram) developed coronary spasm in response to Ach 10^{-4}. Microvascular endothelial function did not differ between the groups. Nitroglycerin administration resulted in significant increase in coronary artery diameter (Cad) in the SRL group compared to the CyA group (2.79 0.54 vs. 2.57 0.61, p=0.0036).
Conclusions:SRL immunosuppression is associated with less pronounced coronary epicardial endothelial dysfunction compared to CyA immunosuppression. Improvement of coronary vasomotor function during SRL immunosuppression may be an important mechanism for the prevention of CAV.

3:30 p.m.

1042-188 **Comparisons of the Acute Effects of Intra-Aortic Balloon Counterpulsation Therapy and Continuous Aortic Flow Therapy on Plasma Biomarkers in Dogs With Chronic Heart Failure**

Ramesh C. Gupta, Menjung Wang, Itamar Ilsar, Alice Jiang, Michael S. Sabbah, Hani N. Sabbah, Henry Ford Hospital, Detroit, MI

Background: We previously showed that acute aortic flow therapy (AFT) with the Cancion system (Orqis Medical, Inc.) is superior to intra-aortic balloon counterpulsation (IABP) in unloading the failing canine left ventricle (LV). This study compared the effects of acute AFT and IABP on circulating plasma levels of biomarkers of enhanced neurohormonal and pro-inflammatory activity in dogs with chronic heart failure (HF).
Methods: Seven dogs with coronary microembolization-induced HF were studied one week

apart with both AFT and IABP. The AFT Cancion system was positioned using a dual femoral approach with constant pump flow of 250 ml/min. Blood samples obtained at baseline and at 4 hours after each therapy were used to measure atrial natriuretic peptide (ANP), nt-pro brain natriuretic peptide (BNP), norepinephrine (PNE), endothelin-1 (ENDO-1), angiotensin-II (A-II), tumor-necrosis factor-alpha (TNF), interlukin-6 (IL-6) and C-reactive protein (CRP).
Results: IABP had no significant benefits on any of the biomarkers (Table). In contrast, AFT elicited significant reductions in ANP, BNP, PNE, ENDO-1, TNF, IL-6 and CRP but did not affect A-II (Table).
Conclusions: In dogs with chronic HF, AFT is superior to IABP in attenuating plasma markers of enhanced neurohumoral and pro-inflammatory activity. The results support our earlier findings that AFT is superior to IABP in unloading the failing canine LV.

***=p<0.05 Baseline vs. 4 Hours**

	AFT		IABP	
	Baseline	4 Hours	Baseline	4 Hours
ANP (pmol/ml)	0.56 ± 0.05	0.45 ± 0.04*	0.58 ± 0.03	0.52 ± .02
BNP (fmol/ml)	123 ± 14	95 ± 8*	135 ± 15	138 ± 17
PNE (pg/ml)	663 ± 50	454 ± 23*	699 ± 50	721 ± 45
ENDO-1 (pg/ml)	1.31 ± 0.09	1.06 ± 0.06*	1.31 ± 0.05	1.95 ± 0.12*
A-II (pg/ml)	141 ± 59	141 ± 58	107 ± 135	111 ± 33
TNF (pg/ml)	4.1 ± 0.5	2.9 ± 0.3*	4.1 ± 0.5	4.6 ± 0.6
IL-6 (pg/ml)	34.9 ± 6.8	22.3 ± 5.9*	30.9 ± 5.0	29.2 ± 5.8
CRP (ng/ml)	214 ± 10	151 ± 10*	218 ± 10	202 ± 15

3:30 p.m.

1042-189 **Withdrawn**

3:30 p.m.

1042-190 The Allomap Test Fails to Distinguish Between Quilty Lesions and Acute Allograft Rejection in Heart Transplant Patients

Rajesh M. Kabadi, Colleen Flanagan, Barbara Ebert, John L. Farber, Paul J. Mather, Thomas Jefferson University Hospital, Philadelphia, PA

Purpose: The Allomap test is a non-invasive alternative to biopsy as a screen for acute cellular rejection (AR) in cardiac transplantation patients. Using the polymerase chain reaction (PCR), the test measures the expression of 20 genes in peripheral blood lymphoctyes. The PCR values are used to generate a 0-40 score that reflects immune activation and leukocyte trafficking pathways related to AR. A score greater than 30 indicates a high probability of AR.
Quilty lesions (QL) are nodular endomyocardial aggregates of inflammatory cells found only in cardiac allografts of patients treated with a calcineurin inhibitor (CNI). QL represent ectopic lymphoid tissue formed by an anti-cardiac allograft immune response that has been modified by the CNI. QL are not associated with AR, viral infection, or the development of vasculopathy and, as such, are not treated.
Thus, it is of importance to know if the Allomap test distinguishes QL from AR.
Methods and Materials: From 2/1/08 to 9/26/08, 45 heart transplant patients underwent endomyocardial biopsy (total of 170 biopsies). Of these, 36 patients were at least 55 days post transplantation and, thus, eligible for Allomap testing.
Results: Five of the 36 patients had an Allomap score greater than 30 (32, 34, 34, 35, and 37) and a biopsy that showed QL (invasive or non-invasive) without significant acute rejection (3 with ISHLT grade 0 and 2 with grade IR). Two patients are African American females (age 53 and 64), who were 11 and 16 months post transplantation. The other 3 patients are Caucasian males (age 29, 65, and 67), who were 32, 24, and 13 months post transplantation, respectively. None of the 5 patients received any additional treatment and were maintained on their current immunosuppressive regimen. Follow-up has been uneventful in all 5 patients.
Conclusions: Over a 34 week period, nearly 15 percent of our eligible patients had QL and no significant AR, despite an Allomap score greater than 30. Thus, the Allomap test fails to distinguish between Quilty lesions and acute cellular rejection.

3:30 p.m.

1042-191 Sildenafil or Bosentan in Patients Considered Inelegible for Heart Transplantation Because of Severe Pulmonary Hypertension

Marta Farrero, Felix Perez Villa, Adrian Arias, Maria Angeles Castel, Alessandro Sionis, Eulalia Roig, Hospital Clinic Barcelona, Barcelona, Spain

Background: Elevated pulmonary vascular resistance (PVR) is associated to an increase in mortality in the early post-heart transplant period, mainly due to right ventricle dysfunction. This study aims to asses the effectiveness of both sildenafil and bosentan in decreasing the PVR in a group of patients initially considered ineligible for heart transplantation because of severe pulmonary hypertension.
Methods: Sixteen patients with end-stage congestive heart failure and severe pulmonary hypertension were prospectively included. These were randomly assigned to receive either bosentan 125mg bid (n=8) or sildenafil 80mg tid (n=8). A second right heart catheterization was performed after 16 weeks of therapy.
Results: No significant differences were observed in the two group's basal characteristics. The bosentan group had a basal transpulmonary gradient (TPG) of 21 +6mmHg that was reduced to 10 + 7 (p=0.005) during the treatment. Also the pulmonary vascular resistance decreased from 5.6 +2.4 Wood Units to 2.2 + 1.5 (p=0.003).
The sildenafil group showed a non significative trend towards RVP reduction (4.8 +1.5 vs. 3.29 +1.1; p=0,053) and TPG decrease (21 +4 vs. 19 +6; p=NS). TPG reduction was greater with bosentan (10.5 +5 vs. 4.5 +2mmHg, bosentan vs sildenafil; p=0.04).
Treatment was stopped in 1 patient of each group due to intolerance. After treatment, 8 patients (5 bosentan, 3 sildenafil) were listed for heart transplantation and 6 of them (4 bosentan, 2 sildenafil) have already been transplanted successfully.
Conclusions: Bosentan and sildenafil reduce PVR in patients considered ineligible for heart transplantation due to pulmonary hypertension, allowing them to be transplanted with good results. In our study, bosentan showed to be more effective than sildenafil in decreasing TPG and PVR.

3:30 p.m.

1042-192 An Analysis of Single Institution Data for a Maximum BMI for Heart Transplantation: Comparison With UNOS Data

Mohammed A. Kashem, James T. Fitzpatrick, Lazaros Nikolaidis, James B. McClurken, Satoshi Furukawa, Alfred A. Bove, Temple University School of Medicine, Philadelphia, PA

Background: In heart transplantation, body mass index (BMI) is traditionally considered a risk factor for orthotopic heart transplantation (OHT). We report results from 10 years of OHT and compare them with the United Network for Organ Sharing (UNOS) database, which provides more extensive BMI data from all US heart transplanted patients.
Methods: We reviewed our single institute data (T-n=430 total patients between 1992-2002) and of UNOS data to identify 23,113 initial OHT recipients (U) between years 1996 and 2006. Primary stratification was by BMI at time of transplant. Demographic and clinical factors including wait list (WL) times were recorded. Primary endpoint was all cause mortality during the study period. Secondary outcomes included length of hospital stay (LOS), need for reoperation and postoperative infection. Post transplant survival was estimated by Kaplan-Meier methodology and compared using Cox proportional hazard regression.
Results: Of 23,113 patients with available data, the distribution of BMI was as follows: BMI ≤ 25; 9,983 (43.2%), 26-30; 8,480 (36.7%), 31-35; 3,556 (15.4%), 36-40; 891 (3.9%) and > 40; 203 (0.9%). BMI was not an independent risk factor for mortality in the study (Hz ratio = 0.98, p = 0.17) and no level of BMI led to significantly worse survival. Age, donor age, female gender, ischemic time, creatinine, hypertension, and diabetes emerged as independent predictors of mortality on multivariable analysis. BMI was not associated with increases in LOS (r = 0.01, p = 0.4), postoperative infections, or reoperation rate (OR ratio = 0.99, p = 0.6 for each) BMI correlated strongly with WL times (p = 0.01). Our single institute results were similar (BMI<30; 80%; 31-35;16.5%; and >35;3.5%; p=0.892) and there was no significant between the groups in K-M survival curve.
Conclusions: The present study is the largest reported series focusing on obesity in OHT. We found BMI to not be a significant predictor of mortality, reoperation, or infection even to a BMI of 40. Obesity by itself should not be a contraindication to OHT.

3:30 p.m.

1042-193 Effects of the HeartMate II Continuous-Flow Left Ventricular Assist Device on RV Function

Sangjin Lee, Forum Kamdar, Richard Madlon-Kay, Ranjit John, University of Minnesota, Minneapolis, MN

Background: The effects of the HeartMate II (HMII) Left Ventricular Assist Device (LVAD) on RV function and tricuspid regurgitation (TR) have not been evaluated in detail. The goal of this study was to assess for the incidence of RV failure, alterations in RV function, TR and cardiac hemodynamics in the unloaded heart following HMII implantation.
Methods: Echocardiograms (n=23) and right heart catheterizations (n=40) were performed prior to and following 4-6 months of HMII support in 40 bridge-to-transplant patients. Right heart failure was defined as the requirement for inotropes post-LVAD implantation for > 14 days or the need for right-sided mechanical circulatory support.
Results: The overall incidence of RV failure after HMII implantation was 5% (2/40). As shown in the table, there was a significant improvement in the cardiac index with reductions in right atrial pressure, RV Stroke Work Index (RVSWI), mean pulmonary artery pressure and pulmonary vascular resistance following HMII LVAD support. There was a trend towards reduction in TR following LVAD support (p=0.075).
Conclusions: The incidence of RV failure following HMII implantation is low. The favorable effects of the HMII on cardiac hemodynamics results in improved RV function, improved right and left-sided hemodynamic profiles and reduction in TR. These findings may have important implications for patients with bi-ventricular failure needing longer-term support.

Parameter	Pre-LVAD	Post-LVAD	p- value
TR (n=23)	2.5±1.1 (Mild-Mod)	2.0±1.1 (Mild)	0.075
RAP (n=40)*	13.7±5.3	7.71±5.6	<0.001
RVSW (n=40)*	15.1±8.5	12.5±6.6	0.03
RVSWI (n=40)*	7.5±3.9	6.3±3.3	0.04
MPAP (n=40)*	37.4±8.0	23.3±7.1	<0.001
PVR (n=40)*	3.7±1.8	2.1±0.8	<0.001
PCWP (n=40)*	24.5±5.7	12.9±6.23	<0.001
CO (n=40)*	3.8±1.24	4.9±1.3	<0.001
CI (n=40)*	1.9±0.5	2.5±0.5	<0.001

3:30 p.m.

1042-194 **A Recombinant Human Neuregulin-1 Peptide Added to Celsior Solution Further Improves Preservation of the Transplanted Rat Heart After Prolonged Hypothermic Storage**

Andrew Jabbour, Ling Gao, Jair Kwan, Alasdair Watson, Xifu Liu, MinDong Zhou, Robert M. Graham, Mark Hicks, Peter S. Macdonald, Victor Chang Cardiac Research Institute, Sydney, Australia

Background: Maintenance of nitric oxide flux and the minimization of intracellular calcium levels are important for donor heart preservation. We have shown that modulating these processes by supplementing a cardiac storage solution (Celsior; C) with glyceryl trinitrate (GTN) and cariporide, improves cardiac preservation after 6 hrs of hypothermic storage. Neuregulin-1 also plays a critical role in the adaptation of the heart to injury, promoting cell survival via activation of ErbB2/4 receptors. We hypothesized that the addition of a recombinant human neuregulin-1 (β_{2a} isoform) (rhNRG-1) to C, in combination with GTN and cariporide, would further improve cardiac preservation after prolonged storage (10 hrs).
Methods: Pre-arrest indices of cardiac function were measured in isolated working rat hearts. Hearts were arrested and stored for 10 hrs at 4° Celsius in C supplemented with either: 1) GTN (0.1mg/ml); 2) cariporide (10μM); 3) rhNRG-1 (14μM) alone or in combination (see table). Hearts were remounted on the perfusion apparatus after storage and cardiac function reassessed. Hearts were then frozen for western blotting or prepared for immunohistochemical analysis.
Results: Functional improvements were accompanied by significant activation of Akt, ERK 1/2 and GSK-3β.
Conclusions: Polypharmaceutical activation of multiple pro-survival pathways further improves preservation of the rat heart and shows promise for increasing the cold ischemic 'shelf life' of donor hearts in transplantation.

Post-storage recovery as percentage of pre-arrest function (mean+-SEM). *p<0.02 vs all groups

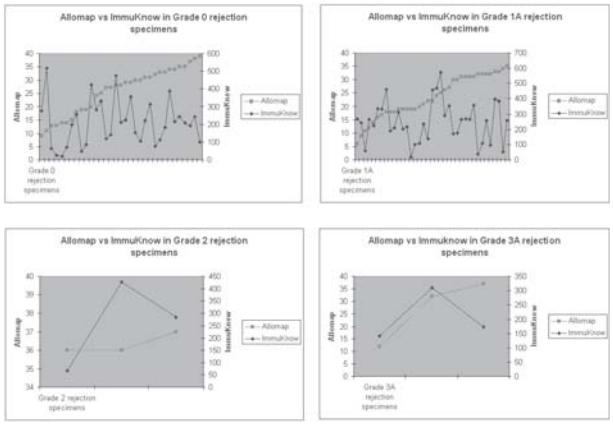
Supplement	Number	Heart Rate (beats/min)	Coronary Flow (ml/min)	Cardiac Output (ml/min)
GTN	5	9.9±9	8.0±1.7	3.0±0.7
Cariporide	6	17.4±10.2	21.0±4.3	5.8±1.2
rhNRG-1	6	47.5±6.3	5.9±3.9	3.8±0.8
GTN + Cariporide	6	54.5±14.7	48.6±12	25.7±10.6
GTN + Cariporide + rhNRG-1*	6	84.3±2.4	79.7±4.7	49.2±5.9

3:30 p.m.

1042-195 **Allomap and ImmuKnow - Can They Partner for Post Cardiac Transplant Management?**

Moses Mathur, Colleen P. Flanagan, Barbara A. Ebert, Paul J. Mather, Thomas Jefferson University Hospital, Philadelphia, PA, Jefferson Medical College, Philadelphia, PA

We studied the relationship between Allomap(AL), ImmuKnow(IK) and outcomes in post-cardiac transplant (OHT) patients.
We studied 42 OHT patients from a single center between 3/08 and 8/08. 79 visits were recorded. The AL score measures the expression of 20 genes and reflects immune activation and leukocyte trafficking pathways, whereas IK measures the ATP production by activated T-cells. For each visit, the serum AL and IK levels, and biopsy grades were collected. The data was sorted by ISHLT grades, and corresponding AL and IK values.
14 out of 79 specimens (18%) had AL>34. Of these 14, 1 patient had grade 2 rejection, and 1 had 3A rejection. The IK levels for these patients were 44 and 175 respectively. There were 3 grade 3A rejections, and 3 grade 2 rejections. For grade 2 rejections, the AL-IK pairings were (28,254), (29,257) and (37,44) respectively. The pairings for 3A rejections were (12, 142), (32, 311) and (37, 175). Pearson correlation scores between AL, IK, and rejection values 0, 1A, 2 and 3A were found to be 0.069, 0.015, -0.993 and 0.496 respectively. 4 patients had infections (3 had CMV, 1 had Staphylococcus pneumonia). Their corresponding (AL, IK) levels were (39,101), (9,243), (32, 77) and (37,175) respectively.
We found discordance between AL and IK values, whether in the setting of cardiac allograph rejection or infections. Given this, further advances are needed before the clinician may feel comfortable using AL and IK values as non-invasive surrogates for the gold standard: endomyocardial biopsy.



3:30 p.m.

1042-196 **Extremes of Body Mass Index Do Not Affect Short- and Long-Term Survival Outcomes Following Cardiac Transplantation**

Sangjin Lee, John Connett, Monica Colvin-Adams, University of Minnesota, Minneapolis, MN

Background: The association of recipient body mass index (BMI) with heart transplant (HTx) outcomes is unclear, though it is generally accepted that BMI extremes negatively affect outcome. The goal of this study is to determine the impact of recipient BMI on survival and post HTx infections in all transplants performed in the United States.
Methods: From 1/2000 to 4/2008, 15,359 heart transplants were performed in the United States. Using data provided by the Organ Procurement and Transplantation Network (OPTN), we evaluated 1 month and 1 year survival stratified by BMI. In addition, we assessed infection at one month and one year.
Results: The mean age was 51.7±12.3 years. 76% were male recipients. Survival was comparable between the BMI groups at 30 days and 1 year. The highest survival rate at 1 year was in the morbidly obese group with BMI>40 at 88.2%. The infections rates requiring hospitalization for all BMI categories were comparable within 1 year post-transplant.
Conclusions: Recipient BMI extremes at the time of cardiac transplantation have acceptable peri-operative mortality, long-term mortality and infection rates requiring hospitalization. These findings may have important implications for the selection of heart transplant recipients.

Recipient BMI	Number of transplants	1 month post-transplant survival rate (%) and 95% Conf. Limits	12 month post-transplant survival rate (%) and 95% Conf. Limits	1 year post-transplant infection rate (%)
<20	1099	94.8 [93.3,96.2]	86.4 [84.2,88.5]	14.8
20-30	10759	94.5 [94.0,94.9]	87.5 [86.8,88.1]	15.7
30-35	2762	93.7 [92.8,94.7]	85.6 [84.3,87.0]	17.3
35-40	575	93.2 [90.9,95.4]	86.4 [83.4,89.4]	18.8
>40	140	93.5 [88.5,98.5]	88.2 [82.0,94.5]	15.3

3:30 p.m.

1042-197 **Reduced Left Ventricular Torsion With Two-Dimensional Speckle Tracking Echocardiography Would Predict Acute Rejection in Heart Transplant Recipients**

Takahiro Sato, Tomoko S. Kato, Shuji Hashimoto, Noboru Oda, Masanobu Yanase, Hideaki Kanzaki, Kazuhiko Hshimura, Hatsue Ueda, Kazuo Komamura, Toshiaki Shishido, Takeshi Nakatani, Masafumi Kitakaze, National Cardiocascular Center, Suita, Japan

Background: Invasive screenings for acute rejection (AR) by endomyocardial biopsy (EBM) in heart transplant (HTx) recipients are standard procedures. Abnormal ventricular systolic torsion has been reported to associate with AR. Speckle tracking echocardiography (STE) provides a powerful means of assessing left ventricular (LV) torsion (LVtor).
Objectives. We investigated the utility of LVtor derived from STE in HTx recipients.
Methods: In 32 HTx recipients, 301 EMBs and hemodynamic studies were obtained between 6 month and 7.2 years post-transplant. The echocardiograms were recorded within 3 hours from EMB performed. The apical and basal short-axis rotations were assessed by STE.The LVtor was defined as the net difference between rotation angles in the two short-axis planes normalized for LV longitudinal length. Echocardiographic and hemodynamic parameters were compared with EMB results. According to the conventional International Society for Heart and Lung Transplantation criteria, EMBs of grade 0 to 1b were defined as group AR- and those of grade 2 or higher were difined as group AR+. Additionally, we assessed the utility of diachronic observation of changes in LVtor in each patient. Baseline LVtor in each patients was defined as mean values of 3 serial LVtors obtained during initial phase after HTx without evidence of AR.
Results: The LVtor was significantly reduced in group AR+ than that in group AR-(9.3 ± 0.7 vs. 12.2 ±0.2 degree, p<0.001). Conventional echocardiographic parameters were not different between the groups. Pulmonary artery wedge pressure and right atrial pressure

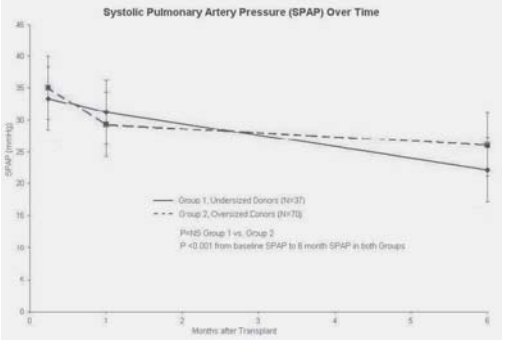
tended to be higher in group AR+ than those in group AR- (7.84±0.18 vs. 8.93 ± 0.54 mmHg, p=0.054, 3.80±0.15 vs. 4.7±0.46 p=0.058, respectively). In a diachronic analysis in each patient, a cut-off value of 25% reduction of LVtor could discriminate grade 2 or higher rejection with a sensitivity of 73%, specificity of 94%, and predictive accuracy of 92%. Conclusions: The LVtor derived from STE could be of clinical value in non-invasive evaluation for AR. We might be able to optimize the timing of routine EMBs by the use of STE.

3:30 p.m.

1042-198 Cardiac Allograft Sizing in Heart Transplant Candidates With Pulmonary Hypertension

Murray Kwon, Allison Ankrom, Abbas Ardehali, Matt Kawano, Michelle Kittleson, Jignesh Patel, Krista Kiyosaki, Jon Kobashigawa, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: Oversized donor hearts are favored for candidates with mild-moderate pulmonary hypertension (PH). This selection bias may exacerbate the donor organ shortage by bypassing suitable smaller donor hearts. We hypothesize that undersized and oversized donor hearts fare equally well in the setting of perioperative PH.
Methods: 107 patients from 2003-2008 were reviewed and divided into 2 groups: those receiving organs from undersized donors (Donor/Recipient Weight0.90, n=37) and those receiving organs from oversized donors (Donor/Recipient Weight >/=1.2, n=70). PH was defined as systolic pulmonary arterial pressures (PAP) >/=40 mmHg. Hemodynamic data and 1-year survival were examined.
Results: Perioperative PH was seen in 49% of undersized and 57% of oversized donors (p=NS). 1-month and 1-year survival for undersized donors was 94.7% and 89.5% and for oversized donors was 100% and 90%, respectively (p=NS). Left and right ventricular ejection fractions were normal in all patients at 6 months after transplant. There was no difference between groups in PAP one week-6 months post-transplant. Both groups showed reductions in PAP over 6 months after transplant (p<0.001; Figure).
Conclusions: Hearts from undersized and oversized donors did equally well with respect to short and long term survival as well as hemodynamic recovery and normalization of PAP over time. The selection bias favoring oversized donor hearts for patients with PH may be unwarranted and unjustifiably decreases the donor pool.



3:30 p.m.

1042-199 Microvascular Dysfunction and Suboptimal Glycemic Control Predicts Poor Outcome Following Heart Transplantation

Prateeti Khazanie, Francois Haddad, Anna M. Simos, Michael Pham, Dana M. Weisshaar, Sapna V. Desai, Maulik G. Shah, Tracey L. McLaughlin, Sharon A. Hunt, Hannah A. Valantine, William Fearon, Stanford University Hospital & Clinics, Stanford, CA, Kaiser Permanente- Santa Clara, Santa Clara, CA

Background: Microvascular dysfunction is increasingly recognized as a risk factor for adverse outcomes following heart transplantation. The objective was to determine whether early microvascular dysfunction at one year predicted hemodynamically compromising rejection (HCR) or allograft vasculopathy at three years.
Methods: Forty-eight consecutive heart transplant patients who underwent coronary physiology measurements at one year at Stanford University were included in the study. Microcirculation was assessed invasively at one year using a coronary pressure sensor/thermistor-tipped guidewire, measuring coronary flow reserve (CFR) and the index of microcirculation resistance (IMR) in the left anterior descending artery. Diabetes mellitus (DM) was defined as fasting blood glucose > 126 mg/dL or random glucose > 200 mg/dL. Suboptimal glycemic control was defined as HbA1C > 7.0%. The combined endpoint at three years consisted of HCR or early allograft vasculopathy defined as > 50% angiographic stenosis or severe diffuse disease. Predictors of outcome were analyzed using univariate regression analysis; the three strongest predictors were then entered into a multivariate logistic regression analysis to identify independent predictors of poor outcome.
Results: The study population consisted of 8 women (17%) and 40 men (83%). The mean age at transplantation was 53 ± 11 years. The majority of patients were transplanted for non-ischemic cardiomyopathy (56%). DM was present in 23 patients (48%); seven patients had suboptimal glycemic control. Combined outcome occurred in 17 patients (35%). Multivariate analysis identified both evidence of microvascular dysfunction (CFR < 2) at one year (O.R. 5.55, 95% CI: 1.07-28.88) and suboptimal diabetes control (O.R. 8.55, 95% CI: 1.39-52.65) as predictors of adverse outcome.
Conclusions: Early microvascular dysfunction and suboptimal glycemic control is associated with an increased risk of HCR and early allograft vasculopathy at three years.

3:30 p.m.

1042-200 UNOS Status Escalation and Adverse Clinical Events Among Patients Initially Listed as UNOS Status 2

Todd F. Dardas, Jennifer C. Matthews, Keith D. Aaronson, Francis D. Pagani, University of Michigan, Ann Arbor, MI

Background: Previous publications have suggested that patients initially listed as UNOS status 2 have an event-free survival of 89% at 1 year. However, some patients initially listed as UNOS 2 will deteriorate and may transition to a higher UNOS status. Initial UNOS status 2 listing may not be an indicator of future survival and may oversimplify the transitions that take place during the listing experience. The result may be an overestimation of survival for patients initially listed as UNOS status 2.
Methods: The SRTR database was used to identify 7176 unique patients, of which 3647 (51%) were initially listed as UNOS status 2 from 2004 to 2007. One-year survival estimates were created using the Kaplan-Meier method. Different definitions of events and censoring variables were used to estimate the frequency of adverse clinical outcomes and transitions to a higher urgency UNOS status.
Results: Of patients initially listed as UNOS status 2 who received a transplant, 48%, received a transplant as UNOS status 2, while 52% received a UNOS status 1a or 1b transplant. Freedom from death or being too ill to remain listed was 0.87 (95% CI; 0.85, 0.89), which agrees with previously published estimates. The freedom from death, being too ill to remain listed or having a first transition to status 1a or 1b was 0.25 (95% CI; 0.23, 0.27), which demonstrates a high cumulative probability of status escalation within 1 year of initial listing. Freedom from death or being too ill to remain listed, with censoring of those who transition to UNOS status 1a/b, was 0.86 (95% CI; 0.84, 0.88), suggesting a reasonable survival among those who remain UNOS status 2 throughout their listing experience.
Conclusions: Patients initially listed as UNOS status 2 have a high probability of transition to UNOS status 1a or 1b and subsequent transplantation from that higher urgency status, while those who remain status 2 appreciate relatively low risk of death in the subsequent year. This relatively favorable prognosis for status 2 patients is dependent upon physician identification of clinical deterioration and upgrade to higher UNOS status. The perception that UNOS 2 status has a favorable prognosis is misleading.

3:30 p.m.

1042-201 Inflammatory Burden of Cardiac Allograft Coronary Atherosclerotic Plaque Is Associated With Recurrent Acute Cellular Rejections and Predicts a Higher Risk of Vasculopathy Progression

Eugenia Raichlin, Bae Jung-Ho, Sudhir S. Kushwaha, Ryan J. Lennon, Abhiram Prasad, Charanjit S. Rihal, Amir Lerman, Mayo Clinic, Rochester, MN

Background: We investigated tissue characterization of the coronary allograft atherosclerotic plaque with virtual histology intravascular ultrasound (VH-IVUS) imaging to assess the presence and predictors of vessel wall inflammation and its significance in CAV progression.
Methods: Eighty six patients with coronary allograft vaculopathy underwent VH-IVUS examination of the left anterior descending coronary artery 3.61 3.04 years following cardiac transplantation. Based on the VH-IVUS plaque characteristics coronary allograft plaque was divided on inflammatory (IP necrotic core and dense calcium 30%) and non-inflammatory plaque (NIP, necrotic core and dense calcium < 30%). Total rejection scores (TRS) was calculated based on ISHLT R 2004 grading.
Results: In the whole study population, the mean percentage of fibrous, fibrofatty, dense calcified and necrotic core plaques in a mean length of 62.3 17.4 mm of the LAD were 50 17%, 16 11%, 15 11%, 18 9%. Patients with 6 month TRS > 0.3 had significantly higher incidence of IP as compared to those with TRS 0.3 (69% vs. 33%, p=0.011). The presence of IP at baseline was associated with a significant increase in plaque volume (2.42 1.78 mm^3/mm vs. -0.11 1.65 mm^3/mm, p=0.010), plaque index (7 9% vs. 0 8%, p=0.04) and remodeling index (1.24 0.44 vs. 1.09 0.36, p=0.030) during 12 months follow up as compared to NIP.
Conclusions: The presence of IP as assessed by VH-IVUS is associated with early recurrent rejections and with higher subsequent progression of CAV.
VH-IVUS assessment may add important information in the evaluation of transplant recipients.

3:30 p.m.

1042-202 Pretreatment of Human Marrow-Derived Mesenchymal Stem Cells With Pioglitazone Improved the Efficacy of Transplantation on Cardiac Function In Vivo

Daisuke Shinmura, Shinichiro Miyoshi, Hiroko Tsuji, Nobuhiro Nishiyama, Naoko Hida, Hikaru Nakamizo, Ikuko Togashi, Kaoru Segawa, Yuiko Tsukada, Akaru Ishida, Makoto Handa, Akihiro Umezawa, Satoshi Ogawa, Keio University School of Medicine, Tokyo, Japan, National Research Institute for Child Health and Development, Tokyo, Japan

Background: Transplantation of human marrow-derived mesenchymal stem cell (MSC) slightly improved the impaired cardiac function but the effect was insufficient. We found that the pretreatment of the cells with pioglitazone (PO) dramatically improved the cardiomyogenic transdifferentiation efficiency of MSCs via peroxisome proliferators-activated receptor-g (PPAR-g) activation in vitro. The effect on cardiac function of engrafted PO-treated MSCs in vivo has not been elucidated.
Methods & Results: LAD was ligated in open-chest anesthetized nude rats to produce myocardial infarction (MI). MSCs were cultured with medium containing 1μM of PO for 2 weeks. Two weeks after MI, MSCs pretreated with PO (P; n=30) or without PO (C; n=17) were isolated, and injected into the MI area (1x106 cells). In 15 rats, the culture medium was injected (MI). In 14 rats, sham operation was done (SHAM). Four weeks after the initial operation, we compared the rate of LV fractional shortening (%LVFS) measured by echocardiogram and systolic LV pressure (LVSP) with the rate of MI volume (%MIVOL)

measured by histological analysis. Data was shown in a table. Pretreatment with PO significantly improved %LVFS, LVSP, and %MIVOL (*p<0.05 vs C).
Conclusions: Transplantation of PO-pretreated MSCs decreased fibrosis area and restored the LV systolic function in the MI-model in vivo. PO-induced PPAR-g activation of MSCs can restore the efficacy of present cardiac stem cell therapy in clinical practice.

Improved cardiac function by PPAR-g pretreated hMSC

	% LVFS	LVSP (mmHg)	%MIVOL	
SHAM (n=14)	52.4 ± 1.6	116.9 ± 5.9	0.8 ± 0.4	
MI (n=15)	29.2 ± 2.0	104.2 ± 4.8	15.7 ± 1.4	
C (n=17)	30.3 ± 2.1	108.6 ± 4.3	15.7 ± 1.5	
P (n=30)	39.8 ± 1.6 *	124.8 ± 2.3 *	9.4 ± 1.3 *	*p<0.05 vs C

3:30 p.m.

1042-203 **Tandem Heart pVAD Outcomes Based on the Intention to Treat: A Single Institution Experience**

Biswajit Kar, Sukhdeep S. Basra, Reynolds Delgado, Andrew Civitello, Igor D. Gregoric, Pranav Loyalka, Texas Heart Institute, Houston, TX

Background : The Tandem Heart percutaneous Ventricular Assist Device (pVAD) is a novel short term mechanical circulatory device. Though primarily intended as a Bridge to Recovery for patients with Severe Refractory Cardiogenic Shock (SRCS), the Tandem Heart is now also being used as a Bridge to LVAD, Bridge to Surgery and Bridge to Transplant. We aim to review the survival outcomes for each of these indications.
Methods and Materials: A total of 143 patients implanted with the Tandem Heart at our institute were included in the study. These included Bridge to Recovery (n=74), Bridge to LVAD (n=32), Bridge to Surgery (n=34) and Bridge to Transplant (n=5).
Results: The mean duration of support was 5.174.6 days. Severe Refractory Cardiogenic Shock(SRCS) was observed in 74.8% patients. The overall mortality rate for Tandem Heart pVAD was 40.6%. This included an overall mortality rate of 56.8% for Bridge to Recovery, 12.5% for Bridge to LVAD, 42.6% for Bridge to Surgery and 0% for Bridge to Transplant. The mortality rate while on Tandem Heart support and immediately after weaning off was 21.7% and 18.9% respectively (overall), 36.5%and 20.3% (Bridge to Recovery), 0% and 12.5% (Bridge to LVAD), 25% and 16.7% (Bridge to Surgery)
Conclusions: Tandem Heart pVAD is an effective tool to reverse SRCS in a subset of high risk patients who can the be transitioned to recovery, LVAd, surgery , or transplant

	Total	Bridge to Recovery	Bridge to LVAD	Bridge to Surgery	Bridge to Transplant
Number	143	72	34	34	5
Age(years)	57.5±15.93	58.11±5.07	46.22± 15.78	67.41± 11.33	55.6 ±9.01
Duration of support(days)	5.17 ±4.6	5.57± 4.65	6.44± 5.33	3.03± 3.27	6.4±3.36
Overall mortality rate	40%	56.8%	12.5%	42.6%	0%
Mortality rate during Tandem Heart Support	21.7%	36.5%	0%	25%	0%
Mortality rate after removing Tandem Heart support	18.9%	20.3%	12.5%	16.7%	0%
Cardiogenic Shock	74.8%	98.6%	90.6%	94.4%	80%

3:30 p.m.

1042-204 **Sustained Improvement in Left Ventricular Strain Two Years Following Gastric Bypass Surgery in Severely Obese Patients**

Ronny S. Jiji, Theophilus E. Owan, Kimberly Morley, Zachary Williams, Nathaniel Hall, Richard Gress, Steven Hunt, Sheldon E. Litwin, University of Utah, Salt Lake City, UT

Background: Strain imaging can detect subclinical left ventricular (LV) dysfunction in obese patients. It is unclear whether surgically-induced weight loss can produce sustained reversal of this abnormality.
Methods: We prospectively studied 62 severely obese patients at baseline and 2 years after Roux-en-Y gastric bypass surgery (GBS). Longitudinal strain was measured from a four chamber echocardiographic view using Siemens VVI TM software. Peak systolic strain and strain rate were taken as the average value from the 6 standard LV segments. We investigated the association of various clinical parameters with average strain using linear regression models.
Results: Mean body-mass index (BMI) was 45.8±7.4 at baseline and 30±7.3 at 2 year follow up after GBS in this selected cohort of 55 females and 7 males. There was a significant increase in average LV strain from baseline (-18.7±3.8) to 2 year follow up (-21.7±4.1; p <0.001). Although there was an increase in average strain rate from baseline (-1.15±0.28) to 2 years (-1.25±0.3), this was not statistically significant (p=0.07). Midwall fractional shortening was an independent predictor of change in LV strain over 2 years (ΔLV strain), (t statistic=2.22, p=0.031). There was a positive correlation between ΔLV strain and the difference in BMI over 2 years (t statistic=2.17, p=0.034). This correlation between strain and BMI was independent of LV mass, systolic blood pressure, and age.
Conclusion: In this prospective, longitudinal study of severely obese patients, we found evidence that GBS produces long term improvement in myocardial function. Although there is a significant correlation between LV strain and both BMI and mid-wall fractional shortening, we were unable to attribute the improved LV function to alterations in traditional hemodynamic or metabolic parameters. Nevertheless, we demonstrate the utility of echocardiographic strain imaging in the evaluation of LV function in patients at high risk of cardiovascular disease, but who pose major challenges to most imaging modalities.

3:30 p.m.

1042-205 **Unrecognized Severe Left Ventricular Dysfunction in Patients With Anemia and Chronic Kidney Disease and Future Risk of Death and Heart Failure Hospitalization**

Sabha Bhatti, Abdul Hakeem, Jeffrey R. Cook, Kathryn S. Dillie, Su Min Chang, University of Cincinnati College of Medicine, Cincinnati, OH, Methodist DeBakey Heart and Vascular Center, Houston, TX

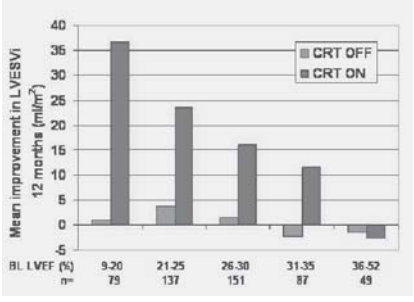
Background: While anemia and chronic kidney disease (CKD) portend a worse prognosis in patients with heart failure, the prevalence and outcomes of unrecognized severe left ventricular dysfunction (ULVSD) in patients with anemia and CKD is not known.
Objectives
The objective of this study was to determine whether anemia (Hemoglobin <13 g/l) and CKD (glomerular filtration rate < 60 ml/min/1.73 Kg/m2 as measured by MDRD equation) are risk factors for severe ULVSD (defined as EF<35%;no known history of heart failure) and to determine its impact on clinical outcomes .
Methods: 1358 patients (65±10 years,97%male; 40% with history of CAD;35% diabetic) without history of HF undergoing gated myocardial perfusion SPECT for evaluation of suspected CAD were followed for a mean duration of 2.15+/- 0.8 years. End points were death and heart failure hospitalization (HFH).Patients were divided into 4 groups (I: No Anemia/No CKD n=752, II: CKD/No anemia n=285, III: Anemia/ No CKD n=153, IV: Anemia+CKD n=168)
Results: Compared to the group I, severe ULVSD was significantly more common in those with anemia and CKD. [(11.3% vs. 4%; p=0.0009) Odds ratio = 2.77 (95% CI ;1.53-5.0;P=0.0007)]. The annualized death rate and HFH rates were significantly higher in patients with the anemia+CKD group compared to the normal group (Death Rate= group I :3.5%/yr vs group IV :12%/yr; p<0.0001) (HFH Rate= group I:1.5%/yr vs group IV: 8%/yr P<0.0001) translating into a relative risk (RR) of 3.45 (95% CI 2.38-5.01) for death (P<0.0001) and 5.02 (95%CI 3.05-8.1) for HFH (P<0.0001) compared to the normal group. Among patients with EF <35%, presence of anemia+CKD was associated with a RR of 2.48 (95% CI 1.13-5.4;p=0.02) for death compared to normal group.
Conclusions: In patients with suspected CAD and no known history of heart failure, unrecognized severe LVSD was almost 3 times more common in patients with Anemia+CKD compared to those with no CKD nor anemia , and was associated with a significantly higher risk of future death and HFH .Based on these results it may be beneficial to screen high risk patients with anemia and CKD for unrecognized LVSD as early therapy for LVSD including ICD therapy may improve outcomes in this high risk cohort.

3:30 p.m.

1042-206 **The Influence of Left Ventricular Ejection Fraction on the Extent of Reverse Remodeling by Cardiac Resynchronization Therapy in Mild Heart Failure: Results From the REsynchronization reVErses Remodeling in Systolic left vEntricular Dysfunction (REVERSE) Study**

Cecilia Linde, Claude Daubert, William T. Abraham, Michael R. Gold, Christian Hassager, John M. Herre, Stefano Ghio, Martin St. John Sutton, Genevieve Derumeaux, Karolinska University Hospital, Stockholm, Sweden

Background: The REVERSE trial is the first prospective randomized double blind parallel trial that demonstrated that CRT plus optimal medical therapy (CRT ON) compared to CRT OFF could slow disease progression and reverse left ventricular (LV) remodeling in patients (pts) with NYHA I-II HF, QRS ≥ 120 ms and LV ejection fraction (LVEF) ≤ 40%. We investigated if the extent of reverse remodeling was related to baseline LVEF.
Methods: 610 pts with NYHA II (82%) or I (18%) were randomized in 73 centres in the US, Canada and Europe. The mean LVEF at baseline was 27.0 ±6.6 and the mean QRS width 153 ± 22 ms. Echocardiograms were obtained in each patient at baseline and at 12 month post enrollment to measure LVEF and LV end systolic volume index (LVESVi) by a core lab.
Results: The mean change in LVESVi over 12 months was -1.3 ± 23.4 ml/m² in the CRT OFF group and -18.4 ± 29.1 ml/m² in the CRT ON group. The relationship between change in LVESVi and baseline LVEF is shown in the graph. CRT ON patients with lower baseline LVEF obtained greater improvements in LVESVi over 12 months than patients with higher baseline LVEF. An ANOVA concluded that baseline LVEF and randomization assignment (CRT ON vs CRT OFF) were significant factors (p<0.0001) in the magnitude of reverse remodeling.
Conclusions: REVERSE demonstrates that the extent of reverse remodeling after 12 months of CRT was related to magnitude to LVEF at baseline. No improvement was noted in subjects with a baseline LVEF above 36%.

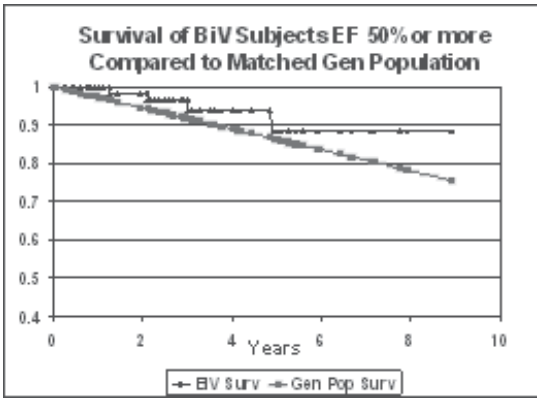


3:30 p.m.

1042-207 **Responders to Biventricular Pacing Who Normalize Their Left Ventricular Ejection Fraction Survive as Well as the Normal Population**

Mahesh Manne, Mina Chung, David Martin, Patrick Tchou, Cleveland Clinic, Cleveland, OH

Background: Patients with reduced Left Ventricular Ejection Fraction (LVEF) of 35% or less have reduced survival. We examined the survival of those who responded well to Biventricular (BiV) pacing by normalizing their LVEF to 50% or better and compared their survival to an age and sex matched set derived from the general population life table.
Methods: Over a nine year period, 750 patients underwent implantation of BiV pacing device at the Cleveland Clinic. 88 pts had follow up echocardiograms that showed LVEF of 50% or greater (test group). For each patient, an age and sex matched example was selected from the Social Security Life Tables. An expected survival plot derived from the matched population was then compared to the actual survival of our test group BiV pacing population.
Results: In the test group, there were 40 males. Mean age was 65.8±10.5. Pre-implant LVEF was 23.8±7.2. Follow up LVEF was 53.6 ± 4.0. The chart shows the survival plot comparison. There is no statistically significant difference in the survival curves.
Conclusions: Patients with reduced LVEF who respond well to BiV pacing have survivals comparable to the general population. This observation favors the concept of a cardiomyopathy generated by the conduction abnormality that is mostly reversed by BiV pacing.

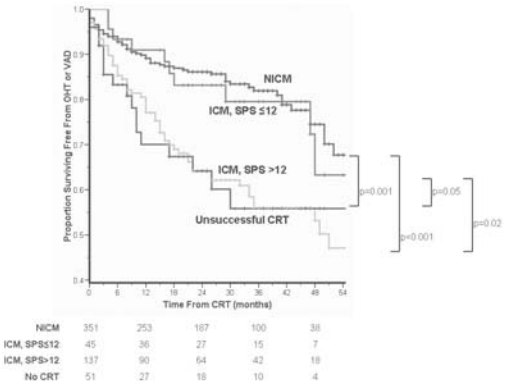


3:30 p.m.

1042-208 **Scar Burden From Prior Infarction, Not Heart Failure Etiology, Predicts Outcomes After Cardiac Resynchronization**

Evan C. Adelstein, Samir Saba, University of Pittsburgh, Pittsburgh, PA

Background: Pts with ischemic cardiomyopathy (ICM) may derive less benefit from cardiac resynchronization (CRT) than non-ischemic cardiomyopathy (NICM) pts.
Methods: 196 CRT pts with ICM (defined as angiographic >70% stenosis or prior revascularization) who underwent myocardial perfusion imaging (MPI) were compared to 349 NICM CRT pts and 53 pts with unsuccessful LV lead implants. Survival free from transplant (OHT) or ventricular assist device (VAD) and echo response were studied. MPI studies were read quantitatively, assigning each a summed perfusion score (SPS) from 0-68. ICM pts were divided into SPS quartiles (≤12, 13-21, 22-32, and >32); the highest 3 quartiles were combined.
Results: Pts with NICM or SPS≤12 had significantly better OHT- and VAD-free survival than those without CRT or SPS>12 (p<0.01; Figure). Survival was similar among pts with SPS>12 and those without CRT. Echo benefit followed a similar pattern; among pts with NICM, SPS≤12, SPS>12, and no CRT, the relative LVEF change was +59, +49, +17, and -2.8% (p<0.01) and the relative LVESD change was -9.4, -7.3, -3.6, and +1.4% (p=0.05), respectively. Controlling for age, gender, atrial fibrillation, diabetes, baseline bundle-branch block pattern and renal function, and spironolactone use corroborated these findings (p<0.01).
Conclusions: Pts with ICM and significant scar do not benefit from CRT compared to those with ICM and low scar burden or NICM, and their survival and echo response are similar to pts with unsuccessful LV lead implants.



ACC.ORAL CONTRIBUTIONS

907

Innovative Biomarkers: Boon or Bane?

Monday, March 30, 2009, 2:00 p.m.-3:30 p.m.
Orange County Convention Center, Room W308A

2:00 p.m.

0907-3 **Prognostic Utility of Natriuretic Peptides in Preserved Ejection Fraction: An Exploratory Analysis of the Biomarkers in Acute Heart Failure (BACH) Trial**

Kabir J. Singh, Niraj Parekh, Garrett Terracciano, Paul Clopton, Inder Anand, Robert Christenson, Lori B. Daniels, Salvatore DiSomma, Gerasimos Filippatos, Christopher Hogan, James McCord, Martin Möckel, Christian Müller, Sean-Xavier Neath, Leong Ng, Richard Nowak, W. Franklin Peacock, Piotr Ponikowski, Mihael Potocki, Alan Wu, A. Mark Richards, Stefan D. Anker, Alan Maisel, Veterans Affairs San Diego Health Care System, San Diego, CA, University of California San Diego, San Diego, CA

Background: Natriuretic peptides (NPs) are well-validated in the diagnosis and prognosis of acute heart failure (HF). In this study, we compared the prognostic utility of NPs in acute systolic versus preserved ejection fraction (EF) HF.
Methods: The study was an exploratory analysis of results from the Biomarkers in ACute Heart Failure trial, a multi-center study assessing novel biomarkers in dyspneic patients presenting to the emergency department. Of patients diagnosed with acute HF, discharge plasma levels of NPs including B-type natriuretic peptide, mid-region pro-A-type natriuretic peptide (MRproANP), and amino-terminal pro-BNP were measured. Patients were monitored for 90 days post-discharge for readmission for HF or other cardiac admission and all-cause mortality. Relationships between log-transformed NP levels and outcomes were assessed by Cox regression and receiver-operator curve analysis.
Results: Of 1641 patients, 429 had a primary diagnosis of HF and EF data, and of these patients 104 had an event. 162 had an EF ≥ 50%. There were 23 events amongst preserved EF patients, and 81 events amongst patients with EF <50%. Amongst all patients with acute HF, the NPs were prognostic. This predictive capacity of NPs was more robust amongst patients with preserved EF (see table).
Conclusions: Among decompensated HF patients, discharge NP levels, carry prognostic information. Importantly, this phenomenon is significant and far more pronounced in patients with exacerbation of preserved EF HF.

	Cox Regression			Receiver-Operator Curve Analysis		
	All HF HR per log	EF < 50% HR per log	EF ≥ 50% HR per log	All HF AUC	EF < 50% AUC	EF ≥ 50% AUC
BNP	3.306 (p<.001)	2.036 (p=.020)	8.026 (p<.001)	0.657	0.567	0.814
NTproBNP	1.997 (p=.002)	1.445 (p=.148)	4.627 (p=.006)	0.611	0.554	0.736
MRproANP	4.748 (p<.001)	2.379 (p=.062)	20.554 (p<.001)	0.631	0.566	0.792

EF = Ejection Fraction HR= Hazard Ratio AUC = Area under the curve
All p values for Receiver-Operator Curve Analysis were <.001

2:15 p.m.

0907-4 Hyporesponsiveness to Endogenous Erythropoietin Predicts Mortality in a Large Cohort of Heart Failure Patients

Anne M.S. Belonje, Adriaan A. Voors, Peter van der Meer, Tiny Jaarsma, Dirk J. van Veldhuisen, University Medical Center Groningen, Groningen, The Netherlands

Background In a small cohort of heart failure (HF) patients, we recently demonstrated that elevated erythropoietin (Epo) levels, in particular when related to their haemoglobin (Hb) levels, were related to an increased mortality. In the present study we investigated the prognostic role of serial measurements of Epo, related to Hb, on mortality in a large cohort of HF patients.
Methods In a cohort of 1023 patients hospitalized for HF, who were studied for 18 months, Epo levels were measured at discharge and after 6 months. Of the anemic patients the adequateness of Epo levels according to their Hb levels was determined by calculating the observed/predicted (O/P) ratio of Epo levels.
Results Mean age of patients was 71±11 years, 63% was male, and mean LVEF was 34±14%. Median Epo levels at baseline were 9.6 U/L and at 6 months 10.6 U/L. Higher Epo levels at baseline were independently related to an increased mortality (hazard ratio (HR) 2.01 per U/L; P<0.01). In addition, Kaplan Meier survival analysis showed that patients with persistently high Epo levels (>median) both at baseline and during follow-up were at higher risk, compared to patients with low Epo levels either at baseline or during follow-up (Log Rank P=0.01). The O/P ratio could be assessed in 135 anemic patients, of which 12 patients (9%) had Epo levels higher than expected. Multivariate Cox regression analysis revealed that patients with Epo levels that were higher than predicted on the basis of Hb levels, had an increased mortality risk (HR 3.52 per U/L; P=0.003).
Conclusion Epo levels predict mortality in HF patients, even when measured serially. In addition, anemic HF patients with Epo levels higher than expected have an impaired prognosis compared to patients with normal or lower than expected Epo levels. These elevated Epo levels might be an indication of hyporesponsiveness of the bone marrow to the effects of endogenous Epo.

2:30 p.m.

0907-5 The Novel Interleukin Receptor Family Member ST2 Correlates With Cardiac Structure, Function, and Prognosis: Results From the PRIDE Echocardiographic Substudy

Ravi V. Shah, Roland RJ van Kimmenade, Annabel Chen-Tournoux, James L. Januzzi, Massachusetts General Hospital, Boston, MA

Background: ST2, a novel biomarker of myocyte stretch, is a powerful marker of poor outcomes in patients with acute dyspnea, including those with heart failure. Nothing is known regarding the relationship between ST2 and cardiac structure and function, and it remains unclear if ST2 is prognostically relevant in patients with echocardiographic data.
Methods: 139 patients admitted with acute dyspnea (age 69±14 years, mean left ventricular [LV] ejection fraction 49±15, 49% male), had echocardiography during index admission and were followed for vital status at 4 years. ST2 at presentation was correlated with echo, clinical and biochemical variables by Spearman regression. Cox proportional hazards analyses identified independent predictors of death at 4 years.
Results: ST2 correlated with several echocardiographic variables, including LV end-systolic volume (= 0.19, *P* =.03) and LV ejection fraction (= -0.37, *P* <.001) as well as tissue Doppler Ea wave peak velocity (= -0.26, *P* =.01). In addition, ST2 was associated with right ventricular (RV) fractional area change (=-0.18, *P* =.05), RV systolic pressure (= 0.26, *P* =.005) and tricuspid regurgitation severity (= 0.28; *P* =.001). In multivariate linear regression, independent predictors of ST2 included LV ejection fraction (t = 2.2, *P* = .05), LV end-diastolic (t = 3.0, *P* = .005) and LV end-systolic (t = 2.6, *P* = .01) dimension, transmitral E to tissue Doppler Ea wave velocity ratio (t = -2.1, *P* = .03), tissue Doppler A wave velocity (t = 2.1, *P* = .05), RV systolic pressure (t = 2.3, *P* = .002), NT-proBNP (t = 3.3, *P* = .009), heart rate (t = 2.6, *P* = .01), and presence of jugular venous distension (t = 2.0, *P* = .05). ST2 was an independent predictor of 4-year mortality (hazard ratio, HR = 2.7; *P* =.003), even after echocardiographic, biomarker, or clinical variables were included in the model.
Conclusions: In patients with acute dyspnea, ST2 levels are independently associated with prevalent cardiac structure and functional abnormalities, and yet are strongly predictive of long-term mortality independent of these variables. Higher ST2 level on presentation is a marker of poor hemodynamics and prognosis independent of traditional clinical or serologic biomarkers of risk.

2:45 p.m.

0907-6 Neutrophil Gelatinase-Associated Lipocalin (NGAL) Levels Predict the Development of Worsening Renal Function in Patients Admitted With Acute Decompensated Heart Failure (ADHF)

Arash Aghel, Kevin Shrestha, W.H. Wilson Tang, Cleveland Clinic Foundation, Cleveland, OH

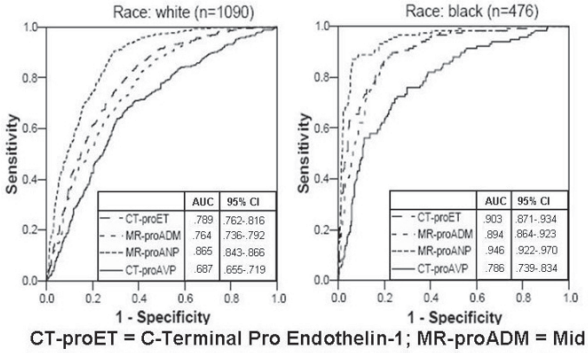
Background: The development of worsening renal function (WRF, defined as creatinine rise >0.3 mg/dl) occurs frequently in the setting of ADHF and strongly predicts adverse clinical outcomes. NGAL is produced by the nephron in response to tubular epithelial damage and serves as an early marker for acute kidney injury. We sought to assess the predictive value of NGAL for the development of WRF in the setting of acute heart failure.
Methods: We measured serum NGAL (BioPorto diagnostic, Gentofte Denmark) in 90 patients admitted to the hospital with ADHF. Patients were adjudicated by independent physician into those that did or did not develop WRF over the ensuing 5 days of in-hospital treatment.
Results: In our study cohort (57% male, mean age 60±15 years, mean LVEF 30±15%), mean and median serum NGAL were 178 ± 85 and 164 [108 - 229] ng/ml, respectively. Thirty-four patients (37%) developed WRF within the 5-day follow-up. Patients who developed WRF versus those without WRF had significantly higher baseline serum NGAL levels (210 ± 77 versus 159 ± 84 ng/ml, p=0.0019). In logistic regression analysis, high serum NGAL levels were associated with greater likelihood of developing WRF (Odds Ratio [OR]: 1.9, 95%CI: 1.2-3.1, p=0.0047). NGAL >140 ng/ml (defined by Receiver Operator Characteristic curve analysis) had a sensitivity and specificity of 88% and 54% respectively to predict the development of WRF. The OR for development of WRF in patients with NGAL >140 ng/ml compared those <140 ng/ml was 8.7 (95%CI= 2.9-32.1, p-value <0.0001).
Conclusions: High NGAL levels predict the development of worsening renal function in patients admitted with ADHF.

3:00 p.m.

0907-7 Effect of Race on the Diagnostic Performance of Novel Cardiovascular Biomarkers in Patients With Dyspnea: Results From the BACH Multinational Study

Lori B. Daniels, Sonal Sakariya, Paul Clopton, Stefan D. Anker, Inder Anand, Robert Christenson, Salvatore DiSomma, Gerasimos Filippatos, Christopher Hogan, Michael Hudson, James McCord, Martin Möckel, Christian Müller, Sean-Xavier Neath, Leong Ng, Richard Nowak, W. Franklin Peacock, Piotr Ponikowski, Mihael Potocki, A. Mark Richards, Alan Wu, Alan S. Maisel, University of California, San Diego, San Diego, CA, Veterans Affairs San Diego Healthcare System, La Jolla, CA

Background: The **Bi**omarkers in **Ac**ute **H**eart Failure (BACH) study examined the utility of a panel of novel prohormone cardiovascular biomarkers in diagnosing heart failure (HF), but little is known about how levels of these markers vary between racial groups.
Methods: 1641 patients presenting to the ED with acute dyspnea were enrolled in the prospective, multinational, 15-center BACH trial, and plasma levels of several prohormone biomarker fragments were measured. The diagnosis of HF was determined by 2 independent cardiologists, blinded to the ED physicians' diagnoses and to the biomarker levels being examined in the trial. Race was determined by self-report.
Results: Of the 1626 patients of known race, 67% were white and 29% were black. White patients were more likely to have a final diagnosis of HF than black patients (40% vs. 25%, p <0.001). Median levels of all BACH markers except CT-proAVP were lower in blacks than in whites among patients with a final diagnosis other than acute HF; in those with acute HF, levels differed by race only for MR-proANP, which was higher in blacks (519 pmol/L vs. 395 pmol/L, p=0.002). All BACH markers were stronger predictors of HF in blacks than in whites, with MR-proANP emerging as an especially powerful predictor in blacks (AUC=0.946, Figure). Adjusting for age did not materially alter the results.
Conclusions: Novel prohormone biomarkers performed better in blacks than in whites for diagnosing acute HF. MR-proANP proved an especially accurate predictor in black patients.



CT-proET = C-Terminal Pro Endothelin-1; MR-proADM = Mid Region pro Adrenomedullin; MR-proANP = Mid Region pro A-type Natriuretic Peptide; CT-proAVP = C-Terminal pro Arginine Vasopressin

ACC.ORAL CONTRIBUTIONS

913

Myocardial Repair, Regeneration and Beyond

Tuesday, March 31, 2009, 8:00 a.m.-9:30 a.m.
Orange County Convention Center, Room W308A

8:00 a.m.

0913-3 Pravastatin Followed by Intracoronary Fibroblast Growth Factor (FGF-5) Synergistically Amplifies Endogenous Cardiac Repair in Swine With Hibernating Myocardium

Gen Suzuki, Vijay S. Iyer, Arsalan Q. Shabbir, David Zisa, Beth A. Palka, Thomas Cimato, Te-chung Lee, John M. Canty, Jr., UNIVERSITY AT BUFFALO, Buffalo, NY

Background: Individually, pravastatin and AdvFGF-5 increase myocyte regeneration in swine with hibernating myocardium by increasing CD117$^+$ cells in the circulation and myocardium. We hypothesized that administrating both would synergistically amplify cardiac repair.
Methods: Swine with a chronic LAD occlusion and hibernating myocardium received pravastatin (160mg/day, p.o.) followed by 2x10^{12} vp of intracoronary AdvFGF-5 (n=6, Statin+FGF-5 combined therapy). We assessed regional perfusion (microspheres) and function at baseline and 4-weeks after treatment. Myocyte size and nuclear density were compared to pravastatin (n=12), FGF-5(n=5), untreated hibernating myocardium (n=7) and sham (n=5). We quantified myocytes in the cell cycle with Ki-67 and phospho-Histone H3 (pHH3) nuclear staining. Myocardial CD117$^+$ cells colocalizing cardiac lineage markers were quantified using GATA4 and TnI staining.
Results: After combined therapy, LAD wall thickening increased from 3.0 ± 0.3 mm to 5.9 ± 0.6 mm (p<0.01) with no change in flow. Immunohistochemistry (Table) demonstrated that combined therapy increased CD117$^+$ cells and both Ki-67 and pHH3 positive myocytes significantly more than pravastatin or FGF-5 alone. Myocardial CD117$^+$ cells expressing cardiac lineage markers increased along with increases in myocyte nuclear density and a reduction in myocyte diameter.
Conclusion: Combined therapy with statins and AdvFGF-5 synergistically amplifies endogenous cardiac repair.

Quantitative Histology / Immunohistochemistry

	Hibernating LAD				Sham LAD
	Untreated (n=7)	Statin(n=12)	FGF-5(n=5)	Statin+FGF5(n=6)	Sham(n=6)
Myocyte Nuclear Density (number/mm2)	926±52	1054±19*	1057±50*	1217±44*†‡	1212±42*
Ki67+ Myocytes (/106 myocytes)	447±212	1605±278*	1477±394*	4052±870*†‡	284±69
pHH3+ Myocytes (/106 myocytes)	9±5	43±7*	27±4*	398±129*†‡	2±2
CD117+cells (/106 myocytes)	223±49	953±123*	1133±104*	1576±282*†‡	20±11*
CD117+GATA4+ (%)	4±4	8.8±3.5	6.9±1.3	14.3±2.6*†‡	0±0
CD117+cTnI+ (%)	0±0	2.2±0.7*	2.7±1.3*	9.3±1.7*†‡	0±0
Myocyte Diameter (μm)	16.2±0.3	13.2±0.6*	14.5±0.5*	11.0±0.5*†‡	13.8±0.4*
Mean ± SEM, *p<0.05 vs. Untreated, †p<0.05 Statin+FGF5 vs. Statin, ‡p<0.05 Statin+FGF5 vs. FGF5					

8:15 a.m.

0913-4 Adult Human Bone Marrow-Derived Mesenchymal Progenitor Cells Secrete Proangiogenic Factors Which Promote Mobilization and Recruitment of Circulating EPCs to the Infarcted Heart

Fiona See, Tetsunori Seki, Hugo Sondermeijer, Henry Krum, Darren Kelly, Silviu Itescu, Columbia University, New York, NY, University of Melbourne, Melbourne, Australia

Background: We have previously shown that the benefits of mesenchymal progenitor cell (MPC) therapy post-MI occur in part via release of paracrine factors which augment myocardial neovascularization. We further sought to determine whether the proangiogenic effects of MPC-derived soluble factors might involve promotion of EPC mobilization and homing to the infarcted heart.
Methods & Results: Nude rats underwent LAD ligation. Baseline echocardiography was performed at 24h post-MI and rats received serum-free control medium (CON, n=6) or MPC (10^6) conditioned medium (CM, n=6) via intramyocardial (IM) injection at 48h post-MI. Echocardiography was repeated on day 6 and on day 7 PBMNCs were collected prior to tissue harvest. In comparison to CON treatment, CM injection post-MI attenuated LV dilatation (% change LVIDd, CON: +10.1±4.1 vs CM: +4.3±1.3, p<0.05) and dysfunction (% change FS, CON: -11.9±5.2 vs CM: -4.8±2.6, p<0.05). PBMNCs were cultured and the number of acLDL+lectin+ EPCs was higher after CM treatment cf. CON (cells/mm2, CON: 21.9±9.2 vs CM: 52.5±8.3, p<0.05). To determine whether CM injection promotes EPC homing to the MI heart, additional rats received 2.5x10^6 DiI-labeled human CD34+ MNCs by intra-ventricular delivery, followed by IM injection of CON (n=4) or CM (n=4), at 48h post-MI. At 7d post-MI, Cells+CM attenuated LV dilatation and dysfunction cf. Cells+CON (% change LVIDd, Cells+CM: +1.6±1.0 vs Cells+CON: +6.8±2.0%, p<0.05; % change FS, Cells+CM: +2.0±1.3 vs Cells+CON: -6.6±2.5%, p<0.05). Cells+CM also increased myocardial counts of DiI+ cells per HPF (Cells+CM: 40.9±10.8 vs Cells+CON: 17.3±9.7, p<0.05) and augmented peri-infarct neovascularization (vWF+ vessels/HPF, Cells+CM: 27.9±4.8 vs Cells+CON: 15±5.7, p<0.05). In vitro, anti-VEGF MAb mitigated EPC migration in response to CM (migration index, CM: 1.9±0.2 vs VEGF MAb+CM: 1.3±0.1, p<0.05).
Conclusion: The beneficial effects of MPC therapy on LV dysfunction and remodeling post-MI are due, at least in part, to release of proangiogenic factors which enhance EPC mobilization and homing to the infarcted heart. These data may provide insight for the development of novel strategies to optimize cell therapy post-MI.

8:30 a.m.

0913-5 Stem Cell Therapy Affects Paracrine Signalling Pathway in Ischemic Myocardium

Kai Jaquet, Korff T. Krause, Martin Bergmann, Sigrid Boczor, Karl-Heinz Kuck, Asklepios Klinik St. Georg, Hamburg, Germany

Background: Bone marrow is a major reservoir of adult autologous stem cells distal from the heart. Adequate regulation of signalling between bone marrow, peripheral circulation and infarcted myocardium is important in orchestrating the process of myocardial regeneration. In this respect, we analyzed the mRNA expression of inflammatory, angiogenic, cell mobilizing/chemoattractant as well as cell adhesion genes. Especially, SDF-1 which is differentially expressed in ischemic myocardium pre- and post cell therapy seems to be crucial to stem cell mobilization.
Methods: Myocardial ischemia was generated in 15 pigs by implanting an ameroid constrictor around the LCX artery. Fourteen days later the animals were devided into 4 groups: unselected BM was transplanted into 4 animals, 7 animals received mesenchymal stem cells (MSC), and 4 pigs got saline injections. Another 4 healthy animals (no ischemia, no cell therapy) served as negative controls. After a follow-up time of 28d the animals were sacrificed and hearts excised. mRNA analysis via Realtime-PCR was done on heart tissue specimen derived from ischemic and remote areas.
Results: On day 28 post cell therapy the mRNA expression levels of most inflammatory, angiogenic, cell mobilizing and/or chemoattractant as well as cell adhesion genes turned out to be normal. In contrast the mRNA of SDF-1 was highly overexpressed in placebo-treated ischemic pig myocardium (p<0.05). In contrast, when pigs received a cell therapy either with bone marrow mononuclear cells (BMNC) or mesenchymal stem cells (MSC) the SDF-1 expression decreased to normal values comparable to healthy controls. BMNC- vs. MSC-group show no difference in SDF-1 expression levels. The corresponding receptor CXCR4 is not differentially regulated, since corresponding target cells are supposed to be located within BM.
Conclusion: 1. As a result of myocardial ischemia the SDF-1 expression rises dramatically indicating, that the paracrine SDF-1/CXCR4 signalling pathway is switched on. 2. An intramyocardial stem cell therapy switches the SDF-1 expression off again". 3. These findings might be first evidence that paracrine mechanisms play a role in stem cell action and recruitment in the heart.

8:45 a.m.

0913-6 Intravenous Injections of Hypoxia-Conditioned Bone Marrow-Derived Stem Cell Medium Improve Left Ventricular Function in Dogs With Heart Failure

Sharad Rastogi, Victor G. Sharov, Michael S. Sabbah, Hani N. Sabbah, Henry Ford Hospital, Detroit, MI

Background: Transplantation of bone marrow-derived stem cells (BMSC) into infarcted or failing myocardium can improve LV function by inducing angiogenesis through the release of growth factors rather than cell incorporation. This suggests that mechanisms other than BMSC incorporation, contribute to the hemodynamic improvement. We examined the in-vitro expression of growth factors and cytokines in BMSC hypoxia-conditioned medium (BMSC-hcm) and the in-vivo effects of intravenous administration of BMSC-hcm (no cells) in dogs with microembolization-induced heart failure (HF).
Methods: BMSCs were obtained from adult dogs and cultured using Iscoves modified Dulbecco medium. Cultured BMSCs were exposed to hypoxia (95% Nitrogen, 5% Carbon Dioxide) in an incubator for 72 hours or to normoxia (95% room air and 5% Carbon Dioxide). RNA was extracted from the medium only and mRNA expression of growth factors was measured using real time PCR. In a pilot study, HF dogs were treated with intravenous injections (20 ml) of BMCS-hcm daily for 5 days.
Results: Compared to BMSC-nm, BMSC-hcm showed a 1.8 to 33 fold increase in the expression of growth factors and cytokines (Table). In HF dogs, LV ejection fraction increased from ~35% to ~46% at 6 weeks after treatment with BMSC-hcm.
Conclusions: An increase in mRNA expression of key growth factors and cytokines was observed in BMSC-hcm. In HF dogs, treatment with BMSC-hcm improved LV function. The observations support a novel concept of BMSC-hcm alone as a therapy for HF.

mRNA Expression of Growth Factors

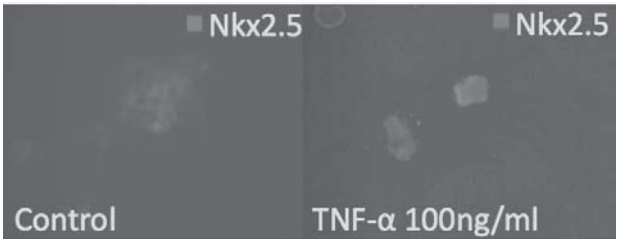
Growth Factors	Fold Increase with Hypoxia
Angiopoetin	8.73
Vascular endothelial growth factor	13.47
Fibroblast growth factor	33.31
Platelet derived growth factor	5.81
Transformin growth factor-beta	8.51
Tumor necrosis factor-alpha	1.79
Interleukin-6	5.82
Granulocyte-colony stimulating factor	19.16
Hepatocyte growth factor	14.54

9:00 a.m.

0913-7 **Transformation of Bone Marrow Stem Cells Into Cardiomyocytes by Tumor Necrosis Factor Alpha**

Mayra Guerrero, Sharad Rastogi, Hani N. Sabbah, Henry Ford Hospital, Detroit, MI

Background: Tumor necrosis factor-alpha (TNF-alpha) can induce cardiogenic transformation of normal adult human mesenchymal stem cells. This directed differentiation of stem cells into cardiomyocytes represents a therapeutic strategy for treating heart failure (HF). This study tested whether bone marrow mesenchymal stem cells (BMMSC) harvested from dogs with HF and exposed to TNF-alpha also undergo cardiogenic transformation.
Methods: Bone marrow was extracted from dogs with coronary microembolization-induced HF. BMMSC were obtained using the Ficoll method and cultured in Iscove's Modified Dulbecco's Medium (IMDM). BMMSC were then incubated in IMDM alone (untreated control) or IMDM with TNF-alpha for 4 or 7 days at concentrations of 30, 50, 75 and 100 ng/ml. Cardiogenic transformation was evaluated in paraformaldehyde-fixed cells by measuring expression of cardiac transcription factors Nkx2.5 and myocyte-specific enhancer binding factor (MEF2C) using immunocytochemistry.
Results: Expression of MEF2C and Nkx2.5 was observed in BMMSC cultured with TNF-alpha at all doses and for both 4 and 7 days. BMMSC cultured in control IMDM did not express either factor (Figure).
Conclusions: TNF-alpha induces cardiogenic transformation of BMMSC obtained from dogs with chronic HF. To the extent that TNF-alpha mediated cardiogenic transformation of BMMSC represents a therapeutic pathway in HF, our observation confirms that an autologous approach is possible, thus avoiding the need for a BMMSC donor pool.



ACC.POSTER CONTRIBUTIONS

1051

Myocardial Function/Heart Failure--Clinical Nonpharmacological Treatment

Tuesday, March 31, 2009, 9:30 a.m.-12:30 p.m.
Orange County Convention Center, West Hall D

9:30 a.m.

1051-165 **Effect of Waon Therapy on Oxidative Stress in Patients With Chronic Heart Failure**

Shoji Fujita, Masaaki Miyata, Takashi Kihara, Tsuyoshi Fukudome, Takuro Shinsato, Takuro Kubozono, So Kuwahata, Tsuyoshi Yamaguchi, Shuichi Hamasaki, Hiroyuki Torii, Chuwa Tei, Department of Cardiovascular, Respiratory and Metabolic Medicine, Kagoshima University, Kagoshima, Japan, Kagoshima city medical association hospital, kagoshima, Japan

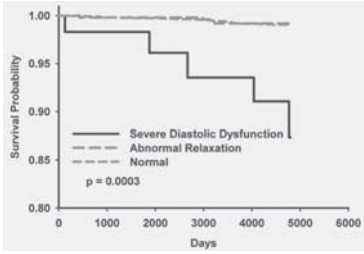
Background: We developed a form of thermal therapy, namely Waon therapy, that differs from the traditional sauna. We have reported that Waon therapy improves cardiac function, vascular endothelial function, neurohormonal factors, and clinical symptoms in patients with chronic heart failure (CHF). Furthermore, we demonstrated that Waon therapy upregulated the expression of endothelial nitric oxide synthase in aorta of hamsters. The purpose of this study is to clarify the effect of Waon therapy on oxidative stress in patients with CHF.
Methods: We enrolled 40 patients with CHF in NYHA functional class II or III, who were admitted to our hospitals and divided into Control (n=20) and Waon therapy (n=20) groups. All patients received standard medications for CHF. Waon therapy group were treated with a far infrared-ray dry sauna at 60 degrees centigrade for 15 minutes and then kept on bed rest with a blanket for 30 minutes, once a day, for 4 weeks. Consentrations of hydoroxyperoxide as a marker of oxidative stress, stable metabolitis of nitric oxide (NO), and brain natriuretic peptide (BNP) were measured before and 4 weeks after treatment. Chest radiography and echocardiography were also performed before and 4 weeks after treatment.
Results: In Waon therapy group, chest radiography demonstrated that cardiothoracic ratio (CTR) significantly decreased after 4-week Waon therapy (56.3±6.2 to 53.0±5.6%, P<0.001). Echocardiography also showed the significant increase of ejection fraction (EF) after 4-week Waon therapy (31.8±11.3 to 35.8±13.1%, P<0.01). Concentrations of hydoroxyperoxide and BNP significantly decreased after 4-week Waon therapy (hydoroxyperoxide: 422±116 to 327±88 U.CARR, P<0.01; BNP: 438±293 to 212±141 pg/ml, P<0.01). In addition, 4-week Waon therapy increased NO levels (71.2±35.4 to 92.0±40.5 μmol/l, P<0.05). In contrast, none of the variables changed at the 4-week interval in Control group. In all patients, there was a positive correlation between the changes in hydoroxyperoxide and BNP levels before and 4 weeks after treatment (r=0.36, P<0.05).
Conclusions: Waon therapy decreased oxidative stress, increased NO, and improved cardiac function in patients with CHF.

9:30 a.m.

1051-166 **Long-Term Prognostic Value of Diastolic Dysfunction in Young Adults- The Coronary Artery Risk Development in Young Adults (CARDIA) Study**

Kofoworola O. Ogunyankin, Laura Colangelo, Donald M. Lloyd-Jones, Kiang Liu, Northwestern University, Chicago, IL

Background: The prevalence and consequences of diastolic dysfunction in young adults are unknown. **Methods:** Asymptomatic adults aged 23-35 yrs (n= 3402) enrolled in the NHLBI's CARDIA study were classified into groups ('Normal', 'Abnormal relaxation' (AR) or 'Severe diastolic dysfunction' (SDD)), based on 2-D and Doppler echocardiographic data obtained in 1990-1991. The hazards of all-cause death, myocardial infarction (MI), stroke, and heart failure (composite endpoint) and of CVD death and all CVD events (CHF, stroke, MI) were determined in the subjects at year 15 follow-up. **Results:** Abnormal diastolic function was present in 9.6% (SDD 0.94%, AR 8.61%). Compared to Normal, the relative risk among those with SDD for the composite endpoint was 7.01 (95% CI 3.16 - 15.55; p<0.0001) and for those with AR was 1.49 (0.82-2.70; p=0.19), after adjustment for age, sex, race, systolic blood pressure, body mass index, total and HDL cholesterol, smoking and diabetes. Hazards ratios for all CVD events were 15.03 (5.31-42.50; p<0.0001) for SDD, and 0.87 (0.29-2.63; p=0.80) for AR respectively. The Cox proportional hazard model showed a significant risk associated with diastolic dysfunction (X^2 = 16.35, df=2 p- for likelihood ratio test = 0.0003). Figure 1 shows the risk factor adjusted survival plots for the 3 groups.
Conclusion: Despite a low prevalence in young adults, SDD is independently associated with substantially elevated risks for death and cardiovascular events.



9:30 a.m.

1051-167 **Cardiac Resynchronization Therapy Induces Major Structural and Functional Reverse Remodeling in Mild Heart Failure. Results From the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) Trial**

Martin G. St. John Sutton, Stefano Ghio, Ted Plappert, Luigi Tavazzi, Laura Scelsi, Claude Daubert, William T. Abraham, Michael R. Gold, Christian Hassager, John M. Herre, Genevieve Derumeaux, Cecilia Linde, University of Pennsylvania Medical Center, Philadelphia, PA

Background: Cardiac resynchronization therapy (CRT) improves left ventricular (LV) structure and function and clinical outcomes in New York Heart Association (NYHA) Class III and IV heart failure (HF) with prolonged QRS. It has not been firmly established whether NYHA Class I/II systolic HF patients exhibit LV reverse remodeling with CRT and whether reverse remodeling is modified by the etiology of HF. The specific aims of this prospective study were to determine whether patients with NYHA Class I/II systolic HF exhibited LV reverse remodeling with CRT at one year, and if so, whether this reverse remodeling was modified by the etiology of HF.
Methods: Six hundred ten patients with NYHA Class I or II HF with a QRS ≥ 120 ms, LV end-diastolic dimension ≥ 55mm, and LV ejection fraction (LVEF) ≤ 40% received a CRT device (± defibrillator) and were randomly assigned to active CRT (CRT ON; n=419) or control (CRT OFF; n=191) for 12 months. Doppler echocardiograms were recorded at baseline, pre-hospital discharge, 6 and 12 months in all patients. LV volume indices, EF, LV mass and diastolic function were quantified at all time points by a Core Echo lab.
Results: LV end-diastolic and end-systolic volume indices decreased progressively (both p<0.0001) while LVEF increased (p<0.0001) from baseline through 12 months in CRT ON compared to CRT OFF. LV mass (calculated at end-diastole as: [5/6 x LV short axis myocardial area x LV length x 1.055]) and echo measures of LV diastolic function did not change significantly in either group by 12 months. In the CRT ON group, there was a 3-fold greater reduction in LVEDVi and LVESVi and a 3-fold greater increase in LVEF in patients with HF of a non-ischemic etiology.
Conclusions: CRT in patients with NYHA II or NYHA I HF resulted in major progressive LV reverse remodeling at 1 year with the greatest changes in patients with HF of a non-ischemic etiology. Therefore, CRT may delay the natural disease progression and might play a new and important therapeutic role in NYHA class I/II HF patients, especially in those patients with HF of a non-ischemic etiology.

9:30 a.m.

1051-168 **Improved Cardiac Structure and Diastolic Flow Velocities in Early-Stage Heart Failure with Chronic Treatment Using an Implantable Device: Results From European and United States Trials of the Rheos® System**

John D. Bisognano, Peter W. de Leeuw, David S. Bach, Christopher L. Kaufman, Eric G. Lovett, University of Rochester, Rochester, NY, University Hospital of Maastricht, Maastricht, The Netherlands

Background: Early stage heart failure (HF) is associated with abnormalities in cardiac structure and function. Rheos Therapy reduces blood pressure (BP) in patients with hypertension (HTN) and improves left ventricular (LV) structure and systolic function in a canine HF model. It is unknown if Rheos Therapy improves cardiac structure and function in patients.
Methods: Stage A-B HF (stage II HTN) patients (systolic BP ≥160 mmHg) taking ≥3 anti-HTN drugs were implanted with the Rheos System. Baseline data were acquired before implant. The Rheos System was activated 1 month after implant. Follow-up occurred after 3 and 12 months of therapy. Echocardiograms were reviewed at a blinded core lab. Changes at follow-up versus baseline were analyzed with paired t-tests.
Results: 33 subjects (18 M/15 F, Age 52.4±10.4 yr, BMI 33.0±7.3 kg/m^2) were implanted at 5 centers. The Rheos System improved cardiac structure and function while reducing BP. Reduced mitral A wave velocity coupled with decreased left atrial dimension and LV mass index suggests that the therapy reduces LV diastolic filling pressure. No unanticipated adverse events occurred.
Conclusions: In addition to sustained BP reduction, chronic Rheos Therapy in early-stage HF patients remodels left atrial and ventricular chambers and improves systolic function. Benefits are incremental to those achieved with aggressive medical therapy. A feasibility study is now underway to assess the potential benefit of Rheos Therapy in patients with more advanced HF.

Values: mean±SD °p<0.05 *p≤0.01 †p≤0.005 ‡p<0.001

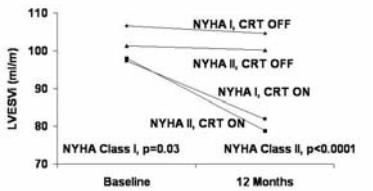
	Baseline (N = 33)	Δ 3 Months (N = 33)	Δ 12 Months (N = 20)
LV Mass Index (g/m2)	138.8 ± 35.4	-17.8 ± 16.0‡	-25.0 ± 18.3‡
Left Atrial Dimension (mm)	44.9 ± 6.5	-1.0 ± 2.7°	-2.3 ± 3.5*
Mitral E Wave Velocity (cm/s)	78 ± 20	-1 ± 13	-5 ± 14
Mitral A Wave Velocity (cm/s)	83 ± 19	-2 ± 12	-11 ± 14†
Septal Wall Thickness (mm)	14.5 ± 3.0	-1.2 ± 1.3‡	-1.6 ± 1.9‡
LV Posterior Wall Thickness (mm)	14.0 ± 2.3	-0.9 ± 0.8‡	-1.5 ± 1.1‡
Midwall Fractional Shortening (%)	13.8 ± 2.8	+0.9 ± 2.2°	+1.7 ± 2.7*
Office Cuff Systolic BP (mmHg)	178.9 ± 25.1	-22.0 ± 30.3‡	-28.0 ± 24.4‡
Office Cuff Diastolic BP (mmHg)	104.4 ± 17.4	-11.0 ± 19.6†	-13.8 ± 19.9*

9:30 a.m.

1051-169 **Cardiac Resynchronization Therapy in Mild Heart Failure: Is There Is Difference in Outcome Between NYHA Class I Versus II? Results From the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) Trial**

Cecilia Linde, Robert Leman, Claude Daubert, William T. Abraham, Michael R. Gold, Karolinska University Hospital, Stockholm, Sweden

Background: The REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial is the first prospective randomized double-blind parallel trial that demonstrated that CRT plus optimal medical therapy (CRT ON) compared to CRT OFF could slow disease progression and reverse LV remodeling in patients (pts) with NYHA I-II HF, QRS ≥ 120 ms and LV ejection fraction ≤ 40%. The results over 12 months in relation to baseline NYHA class are reported here.
Methods: 610 pts randomized in 73 centres in the US, Canada and Europe. At baseline, the mean LVEF was 27.0 ± 6.6%, LVESVi was 100.0 ± 37.7, and QRS width was 153 ±22 ms.
Results: Of 610 pts, 503 were in NYHA class II (82%, 159 CRT OFF, 344 CRT ON) and 107 pts in NYHA I (18%, 32 CRT OFF, 75 CRT ON). NYHA I patients had better quality of life by the KCCQ and Minnesota scores than NYHA class II patients at 12 months. 5.8% of NYHA class I pts in CRT ON pts were hospitalized for heart failure compared to 6.3% in CRT OFF (p=0.80). In NYHA II pts 3.3% in CRT ON pts were hospitalized for heart failure vs. 8.2% in CRT OFF (p=0.02). The mean LVEF improved significantly by CRT only in NYHA II (p<0.0001).The results with respect to LVESVi are shown in the figure. While randomization was a strong factor (p<0.0001), neither NYHA (p=0.68) nor the interaction of NYHA and randomization (p=0.49) were factors in the change in LVESVi.
Conclusions: The effects of CRT on remodeling appear to be similar in NYHA class I and II patients.



9:30 a.m.

1051-170 **Efficacy of Adaptive Servo Ventilation in Patients With Heart Failure and Central Sleep Apnea That Is Not Sufficiently Treated with Continuous Positive Airway Pressure**

Takatoshi Kasai, Koji Narui, Ryo Naito, Ken-ichi Maeno, Mitsue Kato, Fusae Kawana, Sugao Ishiwata, Minoru Ohno, Tetsu Yamaguchi, Shin-ichi Momomura, Sleep Center, Toranomon Hospital, Tokyo, Japan

Background: In heart failure (HF) patients, the presence of central sleep apnea (CSA) is associated with a poor prognosis. There are several studies showed the efficacy of continuous positive airway pressure (CPAP) for such patients. However, a large-scale trial showed that CPAP did not improve survival. In this trial, CSA were not sufficiently treated with CPAP in nearly forty percent of patients and this might affect the results. Recently it was reported that adaptive-servo ventilation (ASV) can treat CSA very efficiently. However, there are no specific data which showed the efficacy of ASV in patients with HF and CSA that is not sufficiently treated with CPAP.
Methods: Patients with HF due to depressed LVEF <50% complicated with CSA defined as an apnea-hypopnea index ≥15 /h, of which ≥50% were central events, were enrolled if they met the following inclusion criteria: 1) having been treated with CPAP for ≥3 months, but their AHI was not suppressed below 15 /h; 2) remaining their LVEF <50% and NYHA functional class ≥II. Then, CPAP was switched to ASV with appropriate settings in each case. The LVEF, plasma BNP, urine norepinephrine level, and 6 minute walk distance (6MWD) were compared between baseline (at the time of enrollment) and after 3 months. In addition, the compliance with the ASV for 3 months was compared to that with CPAP for prior 3 months.
Results: Ten males (mean age: 63.3, BMI: 28.1) were enrolled. In all cases, ASV reduced their apnea-hypopnea index appropriately (21.7±5.7 to 1.5±0.8, P<0.05). Three months later, LVEF and 6MWD significantly increased from 33.6±13.0 to 41.2±11.1 % (P<0.05), from 375.8±56.0 to 405.6±46.7 m (P<0.05), respectively. As well, plasma BNP and urine norepinephrine significantly decreased from 156.7±68.2 to 118.4±77.4 pg/ml (P<0.05), from 266.5±138.9 to 161.5±35.0μg/L (P<0.05), respectively. Furthermore, the compliance with the device significantly improved on ASV (4.4±1.6 to 5.3±1.2 h/night, p<0.01).
Conclusions: ASV efficiently treats CSA and improves compliance with the device in patients with HF and CSA that is not sufficiently treated with CPAP. ASV is promising as an effective alternative in these patients.

9:30 a.m.

1051-171 **Cardiac Dyssybchrony Quantitiated by Time-to-Peak, Temporal Uniformity or Cross-Correlation of Strain Curves: Implications for Resynchronization Therapy**

Paolo N. Marino, Chiara Cavallino, Elisa Rondano, Gabriele Dell'Era, Eraldo Occhetta, Miriam Bortnik, Giuliano Marti, Eastern Piedmont University Clinical Cardiology, Novara, Italy, Azienda Ospedaliero Universitaria "Maggiore della Carità", Novara, Italy

Background: Time-to-peak standard deviation (TP-SD) of echographic strain has been proposed as index of dyssynchrony (DYS) in CHF pts who undergo CRT. Other indices like temporal uniformity (TUS) or cross-correlation of strain curves (CCSC), less conceptually limited, have been suggested. Aim of our study is to assess which of these 3 methods tracks the response in terms of LV remodeling and changes in ejection fraction (EF) in pts submitted to CRT. **Methods:** DYS was quantified in 75 pts computing longitudinal and transversal strain using speckle-tracking 2D analysis from 2 apical views (12 segments) pre- vs. 3 months post-CRT. Optimal LV lead position was defined as concordance or immediate neighbouring of the segment with latest systolic strain prior-CRT and segment with assumed LV lead position, defined as the segment with maximal temporal difference of peak strain before-to-on CRT. 3D apical LV volumes were computed. **Results:** 3 groups were identified according to LV lead position and systolic volume (ESV) reduction ≥15%: group 0, non optimal lead position plus ESV reduction <15%; group 2, optimal lead position plus ESV reduction ≥15%; group 1, if only one criterion was met. Although there were no baseline differences, grouping exerted an interaction effect in terms of remodeling and pump performance, with only CCSC, among the asynchrony indexes, mirroring LV volume and EF changes pre/post-CRT (table).

pre/post-CRT	Group 0 (n=15)	Group 1 (n=36)	Group 2 (n=24)	ANOVA
EDV (%)	+4.2+9.8	-6.1+19.5	-22.8+16.2	<.001
EF (%)	+1.3+10.7	+11.9+15.0	+23.2+17.2	<.001
TP-SD (%)	-0.64+4.7	-1.83+5.6	-3.64+5.45	NS
TUS	+0.02+0.13	+0.02+0.13	+0.06+0.13	NS
CCSC	-0.03+0.09	+0.006+0.06	+0.03+0.05	.007

Conclusion: DYS indexed by CCSC yields greater quantitative results and CRT benefits than TP-SD and TUS.

9:30 a.m.

1051-172 **The Paracor HeartNet™ Ventricular Elastic Support Therapy Feasibility Study: Two-Year Follow-Up**

Barry K. Rayburn, Juan M. Aranda, Jr., John P. Boehmer, Inder Anand, Helmut Klein, Russell J. Ivanhoe, William T. Abraham, University of Alabama, Birmingham, AL, University of Florida, Gainesville, FL

Introduction: The HeartNet System (Paracor Medical, Inc,
Sunnyvale CA) is a nitinol mesh device designed to improve clinical outcomes in patients with symptomatic heart failure (HF) and LV systolic dysfunction. The device is implanted via mini-thoracotomy using a custom designed delivery system and provides gentle

elastic restraint throughout the cardiac cycle to reduce wall stress and to induce reverse myocardial remodeling.
Methods: Pts with EF <= 35% and Class II/III HF on conventional medical and device therapy exhibiting progression of disease were enrolled. Pts with severe MR, coronary artery bypass grafts or recent cardiac procedure or event were excluded.
Results: Successful implantation was accomplished in 51/52 patients. Two year results:

	Baseline	Change at 24 months
Age (yrs)	52	
Male (%)	92	
Nonischemic (%)	79	
Biventricular pacing (%)	37	
EF (%) n=28	24±6.1	0.5±0.9
LVEDD (cm) n=29	7±1	-0.8±0.8*
LVEDV (cm3) n=28	333±81	-33±59***
LVESD (cm) n=29	6±1	0.5±0.9**
LVESV (cm3) n=28	257±75	-24±64
MR n=25	1.3±0.9	-0.4±0.9****
6 Minute Walk Test (m) n=28	384±96	34±82****
MLWHF n=22	55±19	-13±18***
NYHA (I/II/III/IV) n=33	0/18/34/0	7/16/9/1*

n=52; *p<.001** p < .005; ***p<.01; **** p < .05;
Of the 27 patients with follow up data for PVO2, 30% improved at least 1 ml/kg/min. There were two perioperative deaths and three deaths of non cardiac cause in long term follow up. One patient had successful emergency reoperation for an avulsed phrenic artery and four patients had either LVAD, transplant or both.
Conclusions: Implantation of the HeartNetTM bears high success rates. Early data suggest improvement in clinical parameters and significant reverse remodeling for up to 2 years post implant. PEERLESS-HF, a randomized controlled trial of the HeartNet™ in the management of HF due to LV systolic dysfunction is underway.

9:30 a.m.

1051-173 Relationship Between Right and Left Ventricular Function in Patients Selected for Surgical Ventricular Restoration

Marisa Di Donato, Serenella Castelvecchio, Marco Ranucci, Vincenzo Montericcio, Lorenzo Menicanti, IRCCS, Policlinico San Donato, Milan, Italy

Background: The prognostic value of right ventricular (RV) function in patients with chronic heart failure (CHF) is well established, but the data on patients undergoing Surgical Ventricular Restoration (SVR) are lacking.
Aim of the present study was to investigate the preoperative RV function, its correlations with left ventricular (LV) function parameters and prognostic implications in predicting the outcome in patients with CHF undergoing SVR.
Methods: 264 consecutive patients (65±9years, 50F) with previous anterior myocardial infarction and submitted to SVR at our Institution represent our study group. Indications for surgery were heart failure, angina and/or a combination of two. Baseline clinical and echocardiographic evaluation were obtained in all patients. Specifically, RV function was assessed by TAPSE (Tricuspid Annulus Plane Systolic Excursion) and patients were divided in three groups: N (n=103 with normal RV function, TAPSE > 20 mm), M (n=141 with moderate RV dysfunction, TAPSE ≥ 15 and ≤ 20 mm) and S (n=20 with severe RV dysfunction, TAPSE ≤14 mm).
Results: At baseline patients with impaired, either moderately or severely, RV function showed higher NYHA class (p 0.000), larger end-diastolic and end-systolic volumes (p 0.004 and 0.000, respectively), lower EF (p 0.000) and more severe diastolic dysfunction (p 0.001), as defined by diastolic pattern.
30-day cardiac mortality was 6.8% (18/264) and was significantly higher in patients with severe RV dysfunction (20% vs 5.6% and 5.8% in group M and N, respectively, p 0.0009). Average FUP was 31±18 months; survival for all cause mortality was significantly lower in patients with severe RV dysfunction (at Kaplan-Maier survival function Log Rank p 0.03).
Conclusions: Before surgery RV dysfunction correlates with baseline LV systolic and diastolic dysfunction and it is an important predictor of early and mid-term outcome in patients with CHF undergoing to SVR.

9:30 a.m.

1051-174 Adaptive Servoventilation Improves Cardiac Function in Heart Failure Patients With Cheyne-Stokes Respiration

Olaf Oldenburg, Thomas Bitter, Roman Lehmann, Stefan Korte, Anke Schmidt, Lothar Faber, Christian Prinz, Christoph Langer, Dieter Horstkotte, Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany, Cardiac Research Unit, Bad Oeynhausen, Germany

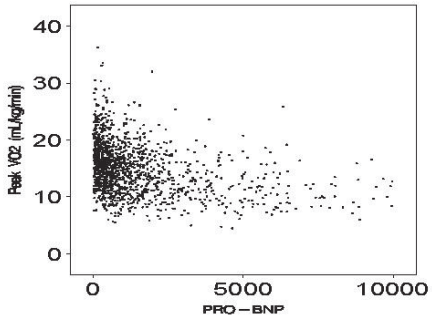
Background: Cheyne - Stokes respiration (CSR) is common in patients (pts) with chronic heart failure (CHF) and accompanied by an impaired prognosis. Nocturnal adaptive servoventilation (ASV) was recently introduced to treat CSR in CHF. Aim of this study was the investigation of ASV effects on CHF parameters after 3 months in compliant pts versus controls.
Methods: In a 98 pts with CHF treated according to current guidelines (NYHA ≥ II, LV-EF ≤ 40%) moderate to severe nocturnal CSR (apnea-hypopnea-index [AHI] ≥ 15/h) was documented by cardiorespiratory polygraphy (PG). All patients were informed about their PG results and ASV treatment was offered.
Results: 43 pts (control group: 63.7±13years; AHI 38±13/h) rejected ASV therapy, were intolerant to positive airway pressure ventilation or non-compliant (usage in <50% of possible nights and/or <4hrs/night); 55 pts (ASV group: 65.2±10years; AHI: 35±12/h) were compliant (80±23% nights possible, 6:23±1:23 h:min per night). NYHA class improved in ASV (2.5±0.7 to 2.0±0.8; p<0.001) as well as in controls (2.7±0.7 to 2.3±0.8, p<0.05). NT-proBNP significantly decreased in the ASV group only (2826±4123pg/ml to 1494±1852pg/ml, p<0.05 vs. 3113±3186 to 2258±2160pg/ml, ns). Left ventricular ejection fraction improved in ASV pts from 28.9±6% to 34.1±10% (p<0.001) and remained unchanged in controls (26.8±7% to 28.2±7%, ns). Predicted oxygen uptake during cardiopulmonary exercise testing increased in the ASV group (63±18% to 72±19%, p<0.01) and remained unchanged in controls (57±16% to 59±14%, ns). In addition, walking distance in 6 min exclusively increased in the ASV group (400±84m to 433±93m, p<0.05 vs. 336±150 to 359±135m, ns).
Conclusions: ASV is able to improve cardiac function in selected and compliant pts with CHF and CSR. Whether this improvement is long-lasting and accompanied by an improved prognosis needs to be determined.

9:30 a.m.

1051-175 Relationship Between NTproBNP and Exercise Capacity in Chronic Heart Failure: Baseline Data from the HF-ACTION Study

Gary Michael Felker, Faiez Zannad, Mark Donahue, Kirkwood F. Adams, Robert McKelvie, Robert Claire, William E. Kraus, David Whellan, Ileana Pina, Christopher M. O'Connor, for the HF-ACTION Investigators, Duke Clinical Research Institute, Durham, NC

Background: Natriuretic peptides such as NTproBNP are released in response to ventricular wall stress, and have been shown to be powerful diagnostic and prognostic biomarkers in chronic heart failure (HF). The relationship between NTproBNP and other measures of functional status such as exercise capacity has not been well studied.
Methods: We analyzed the relationship between baseline NTproBNP and maximal (peak V02) and sub-maximal (6 minute walk) exercise capacity in subjects enrolled in HF-ACTION, a randomized clinical trial of exercise training in chronic HF. NTproBNP (Roche Diagnostics) was analyzed at a core laboratory. Pearson correlation coefficients were used to analyze the relationship between NTproBNP and peak V02 and 6 minute walk distance.
Results: 1445 patients enrolled in HF-ACTION had baseline NTproBNP data available for analysis. Mean age was 59 years, and mean ejection fraction was 25%. Mean KCCQ summary score was 67. The median NTproBNP level was 782 pg/mL. The mean peak VO2 was 14.8 ml/kg/min, and the mean 6 minute walk distance was 364 meters. NTproBNP was moderately correlated with both peak V02 (r= -0.30, p<0.001, see figure) and 6 minute walk distance (r=-0.22, p<0.001).
Conclusions: In this analysis of a large cohort of HF patients from the HF-ACTION study, baseline NTproBNP was moderately correlated with both maximal and sub-maximal exercise tolerance. These data suggest that hemodynamic factors are important but are not the sole determinants of exercise capacity in chronic HF.



9:30 a.m.

1051-176 Acute Bi-Ventricular Pacing Reduces Dyssynchrony in Diastolic Heart Failure Patients With a Narrow QRS

Yi-Chih Wang, Chih-Chieh Yu, Kathryn Hilpisch, Vincent Splett, Rodolphe P. Katra, Chia-Ti Tsai, Juey-Jen Hwang, Ling-Ping Lai, Jiunn-Lee Lin, Natl Taiwan University Hosp, Taipei, Taiwan,ROC, Medtronic Inc, Mounds View, MN

Background: Diastolic heart failure (DHF) is a highly prevalent cause of mortality and morbidity that remains poorly understood with little therapeutic advancements made for its management. Recent evidence suggests that DHF has comparable dyssynchrony to that of systolic HF. This study examines the acute effects of Bi-V pacing in DHF patients with significant ventricular systolic dyssynchrony.
Methods: DHF patients with EF >50% (n=15) and mechanical dyssynchrony (using Tissue Doppler) were studied while undergoing cardiac catheterization studies. Patients were instrumented with temporary pacing catheters in the RA, LV and RV. Dyssynchrony and ECG were assessed at baseline and during a brief period of Bi-V pacing (5min). Patients were paced in VDD mode with AV timing selected to optimize transmitral flow and simultaneous RV-LV timing. Dyssynchrony metrics assessed were: Basal and 12 segment septal to free wall (S-FW) delay; time to peak systolic velocity in 12 segments (mean Ts); dispersion of Ts; and 12 segment standard deviation of Ts.
Results: DHF patients were 69±10years old, non-ischemic (100%), with female majority (73%), NYHA functional class of 2.5±0.5, high body mass index (27±4Kg/m^2), EF of 65±10% and narrow QRS (93±9ms). Cardiac dimensions were not dilated (LVEDD: 42±6mm and LVESD: 25±4mm). Bi-V pacing significantly improved synchrony compared

to baseline (basal S-FW: 104±36.3 vs 68±49ms; Ts Disp: 110±49 vs 87±37ms; 12seg Ts-SD: 50±16 vs 40±13ms, p<0.04), despite a significant increase in mean QRS width with pacing (92±10 vs 131±17ms, p<0.01). Regional analysis of intra-ventricular electromechanical delay revealed a significant contraction delay between septal and lateral regions (max delay=99ms). Interestingly, Bi-V pacing significantly reduced this delay (max delay=78ms, p<0.04). Significant improvement in E/E' was also observed (16.9±8.6 to 11.6±4.4, p<0.01).

Conclusion: These data suggest that acute Bi-V pacing may improve ventricular dyssynchrony in a DHF population with baseline dyssynchrony and narrow QRS. Whether acute improvements in cardiac performance with Bi-V pacing translate to chronic therapeutic benefit in this population will require further study.

9:30 a.m.

1051-177 Cardiac Resynchronization Therapy Increases Ejection Fraction In Right Bundle Branch Block With a Left Hemiblock

Ramesh Chandra, Ronald Zolty, Timothy J. Vittorio, Eugen C. Palma, Albert Einstein College Of Medicine, Bronx, NY, Montefiore Medical Center, Bronx, NY

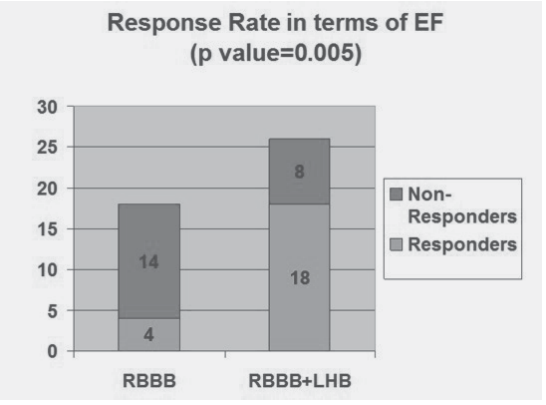
Background: The current recommendation for Cardiac Resynchronization Therapy (CRT) in Chronic Heart Failure (CHF) patients is based on QRS duration, not on QRS morphology. It is not known whether patients with Right Bundle Branch Block (RBBB) respond to CRT.

Methods and Patient Population: 271 consecutive patients who underwent CRT at Montefiore Medical Center were analyzed. Baseline EKGs were analyzed by two reviewers for a RBBB and further classified into those with a co-existing Left Hemi-Block (LHB) and pure RBBB. Response to CRT was defined to be an improvement in ejection fraction (EF) of at least 5% by a repeat echocardiogram 6 months after CRT.

44 patients with RBBB were identified: 18 had pure RBBB and 26 had a co-existing LHB. The two groups were similar in respect to baseline characteristics (p > 0.05): age, gender, body mass index, type of cardiomyopathy, QRS duration, co-morbidities (Diabetes, Hypertension, Chronic Renal Failure), and medications (ACE-Inhibitors/ Angiotensin Receptor Blockers, Beta Blockers, Spironolactone, Digitalis).

Results: Only 4 out of 18 patients with pure RBBB compared to 18 out of 26 with a LHB (p=0.005) had an improvement in EF > 5%. The mean delta EF was -1% in the RBBB group but +5.4% in those with LHB (p=0.0031)

Conclusion: Patients with a RBBB may respond to CRT if a co-existing LHB is present.



9:30 a.m.

1051-178 Underutilization of Device Therapy in Patients With Advanced Heart Failure

Daniel B. Sims, Luis I. Garcia, Andrea Mignatti, Paolo C. Colombo, Margaret Jones, Donna M. Mancini, Ulrich P. Jorde, Division of Cardiology, Columbia University Medical Center, New York, NY

Background: Internal cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) reduce mortality in advanced heart failure (HF). These modalities may be underutilized.

Methods: Retrospective chart review of 274 consecutive patients who underwent cardiopulmonary exercise testing after referral for heart failure/transplant evaluation at our center. Ejection fraction (EF), QRS width, and presence of ICDs and CRT were recorded to determine if patients who have an indication for device therapy based on current guidelines were appropriately treated.

Results: 202 of 274 patients had systolic dysfunction (LVEF ≤ 35%) with an average EF of 22±7%. Patients were 54±13 years old and had a mean peak VO_2 of 12.5±4.5 ml/kg/min. 71 patients (35%) had ischemic cardiomyopathy and 131 patients (65%) had nonischemic cardiomyopathy. 97 of the 202 patients had QRS <120 ms and were thus eligible for ICD therapy, however, 42 (43%) did not have an ICD. Eligible female patients were more likely to be without an ICD than men (65% vs. 35%, p <0.009). Of 105 patients with QRS >120 ms who met criteria for CRT therapy, 48 (46%) did not have CRT.

Conclusions: At the time of evaluation at an advanced heart failure center, both ICD and CRT devices are underutilized. This may be due to under appreciation of ICD/CRT benefits or the perception that ICD/CRT therapy should be initiated at specialized centers only despite nearly a decade experience. Female patients are disproportionately affected by this underutilization.

	Number of Patients Eligible for ICD	Number of Patients Without ICD (% total)
All Patients	97	42 (43%)
Female	26	17 (65%)
Male	71	25 (35%)

9:30 a.m.

1051-179 Decreased Global Longitudinal Strain in Diabetics With Preserved Ejection Fraction Post-Myocardial Infarction: A VALIANT Echo Sub-study

Amil M. Shah, Chung-Lieh Hung, Sung Hee Shin, Anil Verma, Lars Kober, Eric Velazquez, John J. V. McMurray, Frans Van de Werf, Marc A. Pfeffer, Scott D. Solomon, Brigham and Women's Hospital, Boston, MA

Background: Diabetes is associated with an increased risk of death and heart failure (HF) following myocardial infarction (MI). Recent studies suggest that the risk of heart failure attributable to diabetes may be particularly high in patients with preserved left ventricular (LV) ejection fraction (EF). Mechanisms of heart failure in this subgroup of patients may differ between diabetics and non-diabetics, and from patients with reduced EF.

Methods: 603 post-MI patients with LV systolic dysfunction or HF were enrolled in the Valsartan in Acute Myocardial Infarction Trial Echo sub-study. 138 had a history of diabetes. Mean follow-up was 24.7 months. We analyzed baseline parameters of LV deformation (strain and strain rate) among diabetics and non-diabetics with preserved (EF ≥ 40%, n = 299, mean EF 43.9%) and reduced (EF< 40%, n = 304, mean EF 34.7%) systolic function at baseline. Myocardial strain and strain rate were measured using 2D speckle tracking software (Siemens) in 380 subjects with adequate images (296 diabetics, 84 non-diabetics).

Results: Among subjects with EF ≥ 40%, diabetics had significantly higher risk of death or HF hospitalization compared to non-diabetics (33.8% vs 14.7%, adjusted OR 2.91, 95% CI 1.31-6.46). There was no significant difference in EF between diabetics and non-diabetics, although diabetics had significantly higher diastolic and systolic volumes (110.8 vs 103.7, p = 0.005; 66.2 vs 60.1, p = 0.005 respectively). Diabetics had significantly lower global longitudinal strain compared to non-diabetics even adjusting for ejection fraction and differences in 12 baseline demographic characteristics (-8.06 vs -8.92, p=0.041). This difference in longitudinal strain between diabetics and non-diabetics was not observed in patients with EF < 40% (-6.5 vs -7.10, p=0.185).

Conclusions: Altered longitudinal strain, a more sensitive measure of myocardial contractility than ejection fraction, may partly account for the higher risk of heart failure in diabetics with preserved EF post-MI.

9:30 a.m.

1051-180 Early Experience With Percutaneous Left Ventricular Partitioning Device in Patients With Ischemic Cardiomyopathy

Farshad Raissi Shabari, Biswajit Kar, Pranav Loyalka, Kathy Vershave, Igor Gregoric, Reynolds M. Delgado, Texas Heart Institute, Houston, TX

Background: Percutaneous Ventricular Partitioning Device (VPD) implantation is a novel modality to isolate the dysfunctional segments of left ventricle (LV) in patients with symptomatic heart failure (HF) and anteroapical aneurysm. It is postulated that this may help restore the ventricular geometry, increase ventricular function and improve patients' symptoms.

Methods: We report the preliminary results of the first 2 VPD implants performed at our center. The patients with ischemic HF for at least 6 months and apical aneurysm with New York Heart Association (NYHA) Class III or IV were screened for this study. All patients had cardiac CT to ensure appropriate LV anatomy.

Results: The first patient is a 52 year-old man with anterior myocardial infarction status post coronary intervention 10 years prior to study. He had NYHA Class III symptoms. Echocardiogram revealed EF of 25% with anteroapical wall motion abnormality. The device was successfully implanted through standard LV retrograde access from femoral artery. At one month, the patient's symptoms improved to NYHA Class I and echocardiogram revealed a well-seated device at LV apex with LVEF 28%. Postimplant course was complicated with groin wound infection which has now resolved. The second patient is a 64 year-old man with myocardial infarction and coronary artery bypass grafting 8 months prior to study. The patient had experienced worsening HF symptoms. A nuclear perfusion study revealed scar in left anterior descending and obtuse marginal artery territories. The echocardiogram showed LVEF of 23% and apical wall motion abnormality. The patient underwent the VPD implant with no complications. At one-month follow-up, his symptoms improved to NYHA Class I. The echocardiogram showed the VPD at the apex and LVEF 30%.

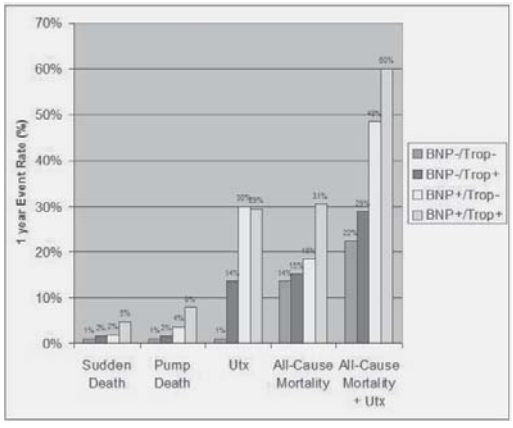
Conclusion:Our very early experience shows possible feasibility and safety of VPD implantation. The patients' symptoms improved after the device implantation. This device may help restore LV geometry in this particular group of patients. Long-term follow up of these patients and inclusion of subsequent patients in this ongoing study will elucidate the value of this device in treating selected patients with ischemic cardiomyopathy.

9:30 a.m.

1051-181 **BNP and Cardiac Troponin I as Predictors of Mode of Death in Patients With Advanced Heart Failure**

Vamsi Krishna, Tamara B. Horwich, Gregg C. Fonarow, Ahmanson-UCLA Cardiomyopathy Center, University of California at Los Angeles Medical Center, Los Angeles, CA

Background: Prognosis and mode of death in heart failure (HF) patients vary. Predicting risk may facilitate more informed treatment decisions. B-type natriuretic peptide (BNP) and Troponin I (TnI) are predictive of mortality in HF patients, but their value for mode of death and urgent transplantation (UTx) is unclear.
Methods: We followed 1103 advanced HF patients (EF $\leq$ 35%) from 1/1/00 to 7/7/08; 684 had baseline BNP and TnI I determined. Patients were categorized into 4 groups: -BNP/-TnI (n=206), -BNP/+TnI (n=125), +BNP/-TnI (n=163), +BNP/+TnI (n=190). BNP was considered positive if $\geq$ 602 pg/mL, based on ROC curves for all-cause mortality. TnI was considered to be positive if detectable ($\geq$ 0.04 ng/mL).
Results: Mean age was 53 $\pm$ 13, mean EF 23% $\pm$ 7, and 74% were male. During a mean of 2 years of follow up, 43 (6%) died from pump failure; 32 (5%) died from sudden death (SD); 172 (25%) of any cause; and 177 (26%) required UTx. A detectable TnI and BNP $\geq$ 602 were predictive of 5 year outcomes for pump death (OR 2.4, 95% CI 1.3-4.5), SD (2.4, 1.2 - 4.9), UTx (1.8, 1.3-2.6) and all-cause death (4.5, 3.1-6.6). On multivariate analysis, BNP and TnI were strong predictors of SD, UTx, and all-cause mortality; BNP but not TnI predicted pump death. BNP < 602 and non-detectable TnI were independent predictors for SD free survival.
Conclusions: BNP and TnI are strong predictors for all-cause mortality, SD, pump death and UTx in advanced HF. Prospective studies are needed to test if TnI and BNP can be used to accurately guide treatment decisions.



9:30 a.m.

1051-182 **Impaired Left Ventricular Rotation and Rotational Dyssynchrony in Heart Failure**

Yu-Ting Tan, Eveline Lee, Frauke W.G. Wenzelburger, Grant Heatlie, Francisco Leyva, Michael P. Frenneaux, John E. Sanderson, University of Birmingham, Birmingham, United Kingdom, University Hospital of North Staffordshire, Stoke-on-Trent, United Kingdom

Background: Left ventricular (LV) rotation contributes significantly to global LV function in normal subjects but the effect on heart failure is not clearly understood. We assessed LV rotation and rotational dyssynchrony in patients with a range of heart failure with reduced or normal LV ejection fraction (EF).
Methods: 36 patients with systolic heart failure (SHF): 28 female, age 69±7years, EF26±10%; 47 patients with heart failure with normal ejection fraction (HFNEF): 32 female, age 73±6years, EF 60±7%; and 25 controls: 17 female, age 70±8years, EF 64±8% were recruited. Standard echocardiography was performed and images were analysed offline. Apical rotation was examined using 2-dimensional (2D) speckle tracking. Peak apical rotation and time to peak rotation were recorded in 6 segments. Average peak rotation and standard deviation of the time to peak rotation (TrotSD) were calculated. At least 3 consecutive beats were analysed and read by two independent observers.
Results: The average apical rotation were 2.7±5.9º, 10.5±4.2º, 14.1±3.1º in SHF, HFNEF and controls respectively (one way ANOVA, p=0.000). TrotSD was 27.7±26.3ms, 11.3±7.3ms, 9.9±8.6ms in SHF, HFNEF and controls respectively. SHF had significantly more rotational dyssynchrony compared to HFNEF and controls (p<0.05). There was no difference in TrotSD between HFNEF and controls (p=0.48).
Conclusions: LV rotation is impaired and progresses through a spectrum of severity in heart failure. 2D speckle tracking detected regional systolic dysfunction which is unidentified with conventional echocardiography. SHF patients have rotational dyssynchrony in addition to known longitudinal and radial dyssynchrony.

9:30 a.m.

1051-183 **Systolic Ventricular Deformation and Rotation Are Reduced at Rest and on Exercise in Patients With Heart Failure and Normal Ejection Fraction**

Yu-Ting Tan, Frauke W.G. Wenzelburger, Eveline Lee, Grant Heatlie, Francisco Leyva, Michael P. Frenneaux, John E. Sanderson, University of Birmingham, Birmingham, United Kingdom, University Hospital of North Staffordshire, Stoke-on-Trent, United Kingdom

Background: Many patients presenting with symptoms of heart failure are found to have normal ejection fraction using standard 2D echocardiography and are labelled as having Diastolic Heart Failure or heart failure and normal ejection fraction (HFNEF). We used speckle tracking to study the overall systolic function by assessing longitudinal, radial and rotational function in this group of patients.
Methods: 27 aged-matched healthy controls and 56 patients with symptoms or signs of heart failure and documented normal left ventricular ejection fraction (LVEF) were recruited. All subjects underwent cardiopulmonary exercise test to determine their VO2max. Full echocardiographic assessment was performed at rest and on supine bicycle exercise. Speckle tracking analysis were performed offline on apical 4 and 2 chamber views for longitudinal strain, midventricular parasternal short axis view for radial strain and apical short axis view for apical rotation. All images were analysed by two independent observers and results were averaged.
Results: 48 subjects (BMI 30.1±4.6kg/m^2, biplane LVEF 61±7%, 35 female, age 72±8 years) clinically diagnosed with HFNEF with reduced VO2max (17.6±3.8ml/min/kg vs 30.9±4.6ml/min/kg, p= 0.000) and 24 age-matched controls (BMI 24.2±3.9kg/m^2, biplane LVEF 63±8%, 16 female, age 70±8 years) had suitable images for analysis. Patients were found to have significantly lower systolic longitudinal, radial strain and apical rotation at rest compared to controls (longitudinal strain: -18.9±3.5% vs -20.9±3.0%, p=0.018; radial strain : 41.8±13.5% vs 49.0±12.9%, p=0.003; apical rotation: 10.4±4.0 º vs 13.0±2.8º, p=0.015). On exercise the difference became more significant between the two groups (longitudinal strain: -20.1±4.1% vs -23.8±2.5%, p=0.000; radial strain: 49.1±15.4% vs 61.9±12.8%, p=0.002; apical rotation: 13.5±4.2º vs 17.7±3.6º, p=0.005).
Conclusions: Left ventricular strain and rotation are reduced in systole in patients with HFNEF. Abnormalities of ventricular function in HFNEF are more widespread than in diastole alone.

9:30 a.m.

1051-184 **Rapid In Vitro and In Vivo Phosphorylation of Phospholamban by Cardiac Contractility Modulation Electrical Signals**

Hani N. Sabbah, Sudhish Mishra, Ramesh C. Gupta, Sharad Rastogi, Benny Rousso, Yuval Mika, Henry Ford Hospital, Detroit, MI, Impulse Dynamics USA, Inc., Orangeburg, NY

Background: Therapy with non-excitatory cardiac contractility modulation (CCM) electrical signals improves LV ejection fraction and increases phosphorylation of phospholamban (P-PLB) in dogs with heart failure (HF). In patients and dogs with HF, CCM signals increase peak LV dP/dt within 1-5 min of application. We tested the hypothesis that the rapid increase in contractility by CCM signals is associated with a rapid increase in P-PLB.
Methods: CCM signals were delivered to the LV anterior wall from epicardial leads in open-chest HF dogs. Anterior wall biopsies were taken at baseline and at 1, 5, and 10 min after CCM application. Identical CCM signals were also applied in-vitro for 10, 20, and 30 sec to suspensions of isolated HF dog cardiomyocytes. P-PLB at serine-16 (S-16) and threonine-17 (T-17) normalized to calsequestrin (CSQ), was measured from all biopsies and cardiomyocyte samples using Western blots.
Results: CSQ expression was unchanged in both experiments. In-vivo P-PLB at S-16 and T-17 increased within one minute of CCM signal application and was associated with an increase of LV peak dP/dt (Table). Application of CCM signals in-vitro for as little as 10 sec increased P-PLB in isolated cardiomyocytes at both S-16 and T-17 (Table).
Conclusions: CCM signals rapidly increase P-PLB in-vitro and in-vivo. The exact mechanism remains unknown. The observed increase in P-PLB observed can explain the rapid increase in LV contractility seen with initiation of therapeutic CCM signal delivery.

In-Vivo Studies				
Time	0 min	1 min	5 min	10 min
P-PLB at S-16/CSQ	0.23	0.47	0.46	0.56
P-PLB at T-17/CSQ	0.23	0.54	0.55	0.57
LV dP/dt (mmHg/sec)	1270	1640	1590	1490
In-Vitro Studies				
Time	0 sec	10 sec	20 sec	30 sec
P-PLB at S-16/CSQ	0.35	0.85	0.96	1.04
P-PLB at T-17/CSQ	0.76	0.96	0.99	1.16

9:30 a.m.

1051-185 **Improvement in Tissue Doppler Derived Isovolumic Contraction Velocities, but Not Ejection Phase Velocities Underlie Reversal of Remodeling Following Cardiac Resynchronization Therapy in Both Ischemic and Nonischemic Heart Failure**

Michael H. Arredondo, Luka Lipar, Eun Joo Cho, Daniel Ng, Komandoor Srivathsan, Gregory T. Altemose, Susan Wilansky, Steven J. Lester, Krishnaswamy Chandrasekaran, Bijoy K. Khandheria, Luis R. Scott, Partho P. Sengupta, Mayo Clinic Arizona, Scottsdale, AZ

Background: Results from PROSPECT trial highlighted the limitations of tissue Doppler (TD) based ejection-phase indices in characterizing cardiac dyssynchrony. Electro-mechanical coupling and myocardial shortening during isovolumic contraction (IVC) stretch-activates the left ventricle (LV) for optimal ejection. We therefore hypothesized that assessment of LV mechanics during IVC will yield superior insights about the mechanism of LV function improvement following cardiac resynchronization therapy (CRT).
Methods: Total 59 heart failure patients (74±10 yrs., 42 men, etiology: 31 nonischemic and 28 ischemic) underwent CRT on the basis of four criteria: New York Heart Association (NYHA) class III and IV; QRS > 120 ms with a left bundle branch block pattern, and LV ejection fraction ≤ 35% under optimal medical treatment. Pulsed-wave TD velocities and durations were measured from the LV lateral and septal annulus during IVC, ejection, isovolumic relaxation, early and late diastolic phases before and 263±125 days after CRT. LV reverse remodeling, defined as improvement in end-systolic volume ≥ 15%, was observed in 43 patients (73%).
Results: Following CRT, the lateral wall of the LV in responders showed a significant increase in the IVC velocities (4.8±2.1 vs. 7.0±3.0 cm/s, P= 0.001) but not in ejection velocities. TD velocities averaged from the septum and lateral wall showed smaller improvement for ejection velocities, however, were significantly lower than percent improvement seen for IVC velocities (12% vs. 48%, P=0.005). Subgroup analysis of ischemic and nonischemic responders showed consistent improvements in only IVC velocities (4.3±1.4 vs. 6.1±2.3 cm/s, P=0.02 and 5.4±2.4 vs. 7.6±3.3 cm/s, P = 0.02, respectively). LV prestretch velocities from the lateral wall of LV during IVC correlated with post-systolic shortening velocities in responders (r=0.78, P<0.001).
Conclusions: Variations in tissue Doppler derived IVC and stretch velocities in the late activated regions of LV, rather than systolic ejection velocities correlate with reversal of LV remodeling following CRT. Understanding LV mechanics during IVC phase may impact future algorithms for assessing the effects of CRT.

9:30 a.m.

1051-186 **Adaptive Servoventilation as a Novel Therapeutic Approach for Patients With Diastolic Heart Failure and Cheyne-Stokes Respiration**

Thomas Bitter, Lothar Faber, Detlef Hering, Christian Prinz, Dieter Horstkotte, Olaf Oldenburg, Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany

Background: A high prevalence of nocturnal Cheyne-Stokes respiration (CSR) has been documented in patients (pts) with diastolic heart failure (DHF). It is supposed that an increase in left ventricular filling pressures leads to disordered breathing with CSR. CSR itself may worsen heart failure and initiate a vicious cycle. Therefore, aim of the present study was to investigate the effects of adaptive servoventilation (ASV) for treatment of CSR on DHF.
Methods: In a total of 60 pts DHF was diagnosed clinically (NYHA class ≥ II), by invasive (LVEDP≥20mmHg) and non-invasive (echocardiography: EF>55%; E/e'>15) measurements. CSR was documented by cardiorespiratory polygraphy (apnea-hypopnea-index (AHI) >15/h). ASV treatment was offered to all pts. Twenty-one pts rejected nocturnal ASV treatment (controls: 70±8years, 18men) whereas ASV therapy was initiated in 39 pts (ASV group: 67±8years, 33men). Echocardiography, cardiopulmonary exercise testing (CPX) and measurement of NT-proBNP were performed at baseline and at follow-up (10 to 12 months).
Results: Exclusively in the ASV-group there was an improvement in NYHA-class (2.5±0.7 to 2.0±0.8, p<0.05; controls: 2.5±0.5 to 2.4±0.4, n.s.), NT-proBNP concentration (1240±1634pg/ml to 740±1110pg/ml, p>0.01, controls: 1620±1080mg/ml to 1480±890pg/ml, n.s) as well as in peak oxygen uptake (14.6±4.5ml/min/kg to 17.6±5.5ml/min/kg, p<0.001; controls: 16.3±4.1m1ml/min/kg to 15.9ml/min/kg, n.s.). In addition, diameter of the left atrium 52.0± 5.5mm to 50.0±7.3, p<0.05 (controls: 48.2±6.0mm to 51.1±5.7mm, n.s.) and early diastolic mitral annular lengthening velocity (e´; 3.8±1.7m/s to 4.4±1.3m/s, p<0.05; controls: 4.6±1.1m/s to 4.3±1.6m/s, n.s.) improved in ASV, but not in the controls. In both groups, there was no significant change in ratio of early (E) Doppler mitral flow velocity to e´ (ASV: 17.2±7.2 to 17.9±5.8, n.s.; controls: 19.5±6.4 to 20.4±7.8, n.s.).
Conclusions: ASV-therapy seems to improve clinical and functional parameters in pts with DHF and CSR. Whether this is of prognostic value remains unclear and needs further investigations.

9:30 a.m.

1051-187 **Inflammation and Albuminuria Are Associated With the Risk of Incident Heart Failure: The Strong Heart Study**

Ana Barac, Washington Hospital Center, Washington, DC, Medstar Research Institute, Washington, DC

Background: Systemic inflammation and albuminuria may play a role in the pathophysiogy of heart failure (HF). The aim if this study was to assess the associations of markers of inflammation and albuminuria with incident HF, as well as their relationship with obesity and diabetes in American Indian population with high prevalence of obesity and diabetes.
Methods: Cases and controls were selected from the Strong Heart Study (SHS) cohort Participants with prevalent cardiovascular disease, prevalent HF, on dialysis and with creatinine >2.5mg/dl were excluded. Of eligible participants at baseline, 115 had incident HF in subsequent follow-up and had available stored serum specimens. Controls were matched for sex, age and center. CRP, fibrinogen and myeloperoxidase (MPO) were measured by commercial assays. Albuminuria was defined as urinary albumin-creatinine ratio >30 mg/g. Obesity was defined as body mass index BMI≥30.
Results: The 115 cases and matched controls had similar BMI (controls: 30.7±6.7 kg/m^2 and cases: 32.2±7.5kg/m^2, P=0.09). Diabetes and hypertension were more prevalent in the cases (73.9% vs. 41.7%, P<0.01 for diabetes, and 64.4% vs. 47%, P<0.001 for hypertension). Cases had higher baseline fibrinogen (392.5±89 mg/dl vs. 351.8±70 mg/dl, P<0.01), higher CRP (8.7±11.2 mg/dl vs. 4.9±4.8 mg/dl, P=0.04) and more albuminuria (33% vs.15%, P<0.01). MPO levels were not significantly different. Fibrinogen and albuminuria were associated with increased risk for HF even afer the adjustements for age, BMI, hypertension, diabetes and total/HDL cholesterol (OR 2.19 (C.I. 1.07-4.49) for fibrinogen and OR 2.67 (C.I. 1.22-5.82) for albuminuria).
Conclusion: In a population with high prevalence of obesity and diabetes fibrinogen and albuminuria are strongly and independently associated with incident HF.

9:30 a.m.

1051-188 **Impact of an Enhanced Heart Failure Monitoring System on Emergency Room Visits and Hospitalizations in Older Patients With Heart Failure Who Were not on Optimal Medical Treatment**

Ozlem Z. Soran, Faith Selzer, Gervasio A. Lamas, Ileana L. Piña, Sheryl F. Kelsey, John Pilotte, Arthur M. Feldman, University of Pittsburgh, Pittsburgh, PA

Background: Angiotensin converting enzyme inhibitors (ACE) and beta blockers (BB) are recommended by professional society guidelines for patients with systolic heart failure. However, almost 30% of the elderly population with heart failure is intolerant to these drugs. Prior studies suggest that disease management programs may be effective in improving clinical outcomes in patients with heart failure. Whether these types of programs can provide additional benefit to the care of elderly patients with heart failure who are ACE or BB intolerant is unknown. In this study we assessed the impact of a Computer Based Telephonic Monitoring System (CBMS) on emergency room visits and hospitalizations in elderly patients with heart failure who were ACE or BB intolerant and could not be on optimal medical treatment.
Methods: This was a multicenter, randomized, controlled trial of enhanced CBMS vs standard heart failure care (SC) in patients with heart failure and systolic dysfunction. All patients received patient one on one education, education to clinicians and an effort to use optimal medical care. CBMS patients received an electronic scale and an individualized symptom response system linked to a computerized data base operated by trained nurses. Six month follow -up data from patients who were intolerant to ACE inhibitors or BB were analyzed to assess the impact of the CBMS on clinical outcomes.
Results: There were 55 patients in each treatment arm. The mean age was 77 years and all baseline characteristics and laboratory evaluations were equivalent in both treatment groups. The 6-month cumulative rate for all-cause emergency room visits were 48% in the SC arm and 53% in the CBMS (p=0.84). All cause hospitalization rates were 49% vs 56%, respectively (p=0.48).
Conclusions: In this sub-set of patients, we were unable to identify any benefits of the CBMS over a period of 6 months of follow-up when comparing all-cause emergency room visits and hospitalization rates in elderly patients intolerant to optimal medical therapy and randomized to CBMS or SC.

9:30 a.m.

1051-189 **Effects of Reverse Remodeling With Cardiac Resynchronization Therapy in Mild Heart Failure on Left Ventricular Volume and Shape: Results From the REsynchronization reVErses Remodeling in Systolic left vEntricular Dysfunction (REVERSE) Trial.**

Martin G. St. John Sutton, Stefano Ghio, Ted Plappert, Luigi Tavazzi, Laura Scelsi, Claude Daubert, William T. Abraham, Michael R. Gold, Christian Hassager, John M. Herre, Genevieve Derumeaux, Cecilia Linde, University of Pennsylvania Medical Center, Philadelphia, PA

Background. Cardiac Resynchronization Therapy (CRT) improves survival, symptoms and exercise capacity in heart failure (HF) and induces reverse remodeling that consists primarily of reduction in left ventricular (LV) volume. Little is known about the effects of volume reduction on LV shape. We hypothesized that reduction in LV volume would restore LV shape towards normal with CRT, that change in shape would correlate with the change in volume during remodeling and be associated with increase in LV ejection fraction (LVEF).
Methods. Patients in the REVERSE study had an EF ≤40%, a QRS ≥120ms and received optimal HF therapy for at least 1 month prior to enrollment. Echocardiograms recorded at baseline and 1 year were digitized to obtain LV volume indices, EF and LV shape. LV shape was computed as the ratio of LV volume to the volume of a sphere with a diameter equal to LV cavity length at end-diastole.
Results: Of 610 patients, 82% had NYHA class II and 18% had class I HF. Patients were randomized 2:1 to CRT ON (n=419) or CRT OFF (n=191). LV volume indices at end-diastole (EDV) and end-systole (ESV) decreased, LV shape became less spherical (by -0.044 ± 0.115 for CRT ON and -0.007 ± 0.099 for CRT OFF) and EF increased significantly from baseline to 1 year in CRT ON compared to CRT OFF. The reduction in LVEDVi at 1 year in CRT ON correlated closely with change in LV shape (r=0.63, p<0.0001). Change in LV shape correlated with increased LVEF (r=0.23; p<0.001).

Ischemic patients (n=236) did not reverse remodel as much as non-ischemic patients (n=183) with CRT ON with regard to LVEDVi (p<0.0001) or LV shape (p=0.008). However, there were strong correlations between change in LV shape and changes in LVEDVi and LVESVi, in both non-ischemic (r=0.54; r=0.51 respectively) and ischemic patients (r=0.68; r=0.64) with CRT ON.

Conclusions: LV reverse remodeling with CRT results in reduction in LV volumes and restoration of LV shape towards normal. Despite major differences in the extent of reverse remodeling between non-ischemic and ischemic patients, the strong correlation between reduction in LV volume and LV shape were conserved in both groups, emphasizing the importance of LV shape in reverse remodeling.

9:30 a.m.

1051-190 Attenuation of Left Ventricular Adverse Remodeling With Epicardial Patching After Myocardial Infarction

Hung-Fat Tse, Chung-Wah Siu, Song-Yan Liao, Wing-Sze Chan, Ed X. Wu, Yin Wu, John M. Nicholls, Ronald Li, Michael E. Benser, Stuart P. Rosenberg, Euljoon Park, Chu-Pak Lau, Cardiology Division, Department of Medicine, Queen Mary Hospital, Hong Kong, Hong Kong

Background: Experimental studies suggested that regional epicardial patch can prevent left ventricular (LV) remodeling early after myocardial infarction (MI); however, its effects in chronic phase of LV remodeling is unclear.

Methods: We compared the effects of passive dual-layer epicardial patch (polypropylene mesh and expanded polytetrafluoroethylene, Patch gp, n=12) implantation vs sham surgery (Control gp, n=12) in pigs with impaired LV ejection fraction (LVEF <50%) at 8 wks post-MI. Serial measurement of LV function and dimensions using invasive assessment and cardiac MRI were performed at 8 and 20 wks post-MI.

Results: In control gp, there were no differences in +dP/dt, and LV end-diastolic pressure (LVEDP) at 20 wks vs. 8 wks (*P>0.05*). In contrast, +dP/dt increased and LVEDP decreased in patch gp at 20 wks vs 8 wks (*P<0.05*). In both groups, LV end-diastolic and end-systolic volumes increased at 20 wks vs 8 wks (Fig A & B). However, the increase in LV end-diastolic volume was greater in control gp vs patch gp (Fig D*)*. Furthermore, LVEF significantly increased at 20 wks vs 8 wks in patch gp but decreased in control gp (Fig C & D). Histological examination showed that LV wall thickness at infarct and adjacent peri-infarct regions were significant greater in patch gp vs. control gp (*P<0.05*).

Conclusions: Regional application of a simple, passive synthetic epicardial patch increased LV wall thickness at the infarct region, attenuated LV dilatation and improved LVEF and +dP/dt in a large animal model of chronic MI.

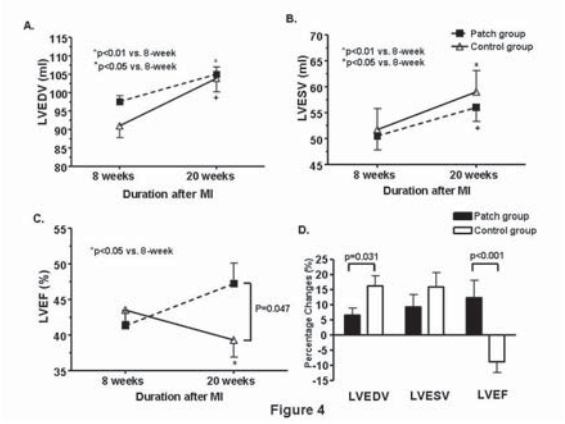


Figure 4

9:30 a.m.

1051-191 FOCUS-HF: The First US Randomized Blinded Controlled Trial of Transendocardial Injection of Bone Marrow Mononuclear Cells in Chronic Severe Ischemic Heart Failure Patients

Emerson C. Perin, Guilherme V. Silva, Marlos R. Fernandes, Timothy Henry, Warren Moore, Stephanie Coulter, James Patrick Herlihy, Ben Cheong, Scott Flamm, Sandi Shaw, Lynette Westbrook, Deirdre Smith, Yi Zheng, Cristiano Cardoso, John Canales, Rachel Olson, Jay Traverse, William Vaughn, Maria G. Cabreira, James T. Willerson, Texas Heart Institute, Houston, TX

Background: We described the initial experience of transendocardial (TE) bone-marrow derived mononuclear cell (BMMNC) injection in ischemic heart failure(IHF) pts. In the present study we evaluated BMMNC TE injection in severe IHF pts in a randomized blinded fashion.

Methods:30 pts with IHF (NYHA/CCS III/IV) with no option for revascularization were randomized (2:1) into treatment (TE injection of $30x10^6$ BMMNC) or controls (C) (mock injection). Cell function analyses were perfomed. Primary endpoint of safety, and efficacy endpoints (NOGA, Echo,SPECT, perfusion MRI, MVO2) were evaluated at baseline, 3 and 6 mo f/u. Comparisons were made by repeated measures ANOVA or Mann-Whitney U test.

Results: There were no major peri-procedural complications. At 3 mos 1 treated pt had a NSTEMI. Overall treated (T) pts had functionally compromised BMMNC progenitor compartments. T pts had a mean of 18±14 mesenchymal colony forming units (CFU-F) per 10^6BMMNC (nl>30). T pts <60 y had significantly higher CFU-F than older pts (27±17 vs 12±8 respectively; p=0.04). T pts had preserved contractility by NOGA compared to C (delta LLS -0.06±0.4% vs -2±0.6%; p=0.003). There was no difference in MVO2 from baseline to 3 and 6 mo f/u in T vs. C. T Pts <60 y had a significant improvement in MVO2 when compared to the correspondent C (Fig 1).

Conclusions: Patients <60 y had more preserved MSC function and may have a functional benefit from cell therapy. TE injections of BMMNC in pts with severe IHF were safe.

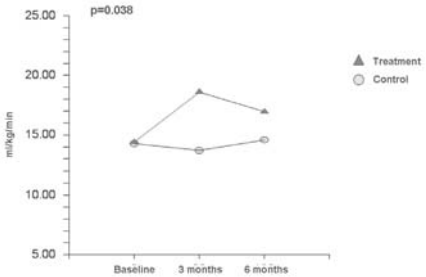


Figure 1: Results of MVO2 during the study for patients with less than 60 years.

9:30 a.m.

1051-192 Right Ventricular Dysfunction Does not Improve More With LVAD Than With Inotropic Support

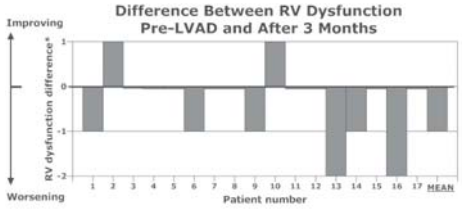
Maryse Palardy, Neal Lakdawala, Garrick C. Stewart, Mahoto Kato, Patricia M. Campbell, Christopher W. May, Waleed A. Alhabeeb, Gregory S. Couper, Prem S. Shekar, Leslie M. Griffin, Colleen M. Smith, Gilbert H. Mudge, Michael M. Givertz, Lynne W. Stevenson, Brigham and Women's Hospital, Boston, MA

Background: LVAD therapy reduces left-sided filling pressures and right ventricular (RV) afterload, and should improve RV stroke volume. We sought to determine how RV dilation and function seen on inotropic therapy improve after 3 months of LVAD support.

Method: Patients inotrope dependent at Brigham and Women's Hospital after 01/2007 were identified for implant of isolated LVAD. Echocardiograms recording quantifiable parameters of RV function were obtained before surgery and after 3 months of follow up. Paired t-test and Wilcoxon signed-rank tests were used to analyze continuous and categorical variables.

Results: Before LVAD, 17 patients were receiving inotropic therapy, 5 also on IABP support. Mean age was 54±15 yrs, LVEF 18±7%, RAP 11±5 mm Hg, PCWP 23±9 mm Hg, and cardiac index 2.0±0.6 L/min/m^2. RV diameter was 3.1±0.4 cm at the base and 3.5 ±0.6 cm at mid-RV, and global RV dysfunction was at least moderate in 53% of patients. Inotropes were discontinued within 3 weeks postoperatively. After 3 months of LVAD support, RV dilation remained unchanged at the base and slightly larger at mid-RV, and global RV function did not appear better (Figure 1)(NS).

Conclusions: RV dysfunction should not be expected to improve within 3 months after continuous inotropic support has been replaced by LVAD support. Until reverse RV remodeling can be demonstrated with different medical or device strategies, only patients in whom pre-operative RV function is adequate for rehabilitation should be selected for long-term LVAD.



9:30 a.m.

1051-193 The Impact of Right Ventricular Dysfunction on In-Hospital and Long Term Mortality in Patients With Acute Myocardial Infarction

Robert Dragu, Michael Kapeliovich, Yoram Agmon, Diab Mutlak, Jonathan Lessick, Doron Aronson, Salim Dabah, Shimon Reisner, Haim Hammerman, Rambam Health Care Campus, Haifa, Israel

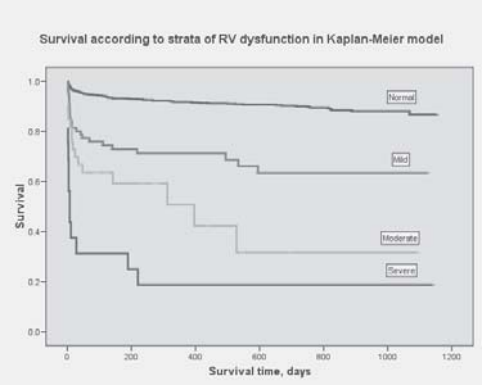
Background: To assess the impact of right ventricular (RV) dysfunction on in-hospital and long-term mortality in patients with acute myocardial infarction.

Methods: We prospectively studied 1217 consecutive patients with AMI and RV function assessed by echocardiography in the first 24 hours from admission. They were followed-up for a mean of 17 months.

Results: Mild RV dysfunction was detected in 6.2%, moderate in 2.7% and severe in 1.3% of the patients. In hospital mortality was 21.7%, 34.9% and 70.6% respectively, with only 4.5% in normal RV function group (p<0.0001). The long term mortality was 32.0%, 45.2% and 81.3% in mild, moderate and severe reduced RV function, and only 9.3% in the normal RV function group (p<0.0001). After adjusting for age, gender, Killip class, on-admission blood pressure, diabetes mellitus, inferior wall involvement, ST-elevation AMI,

creatinine clearance and left ventricular systolic function, the odds ratio for mortality were 3.07 (95% confidence interval [CI], 1.25-7.53, p<0.01), 3.89 (95%CI, 1.22-12.34, p<0.02) and 21.66 (95%CI, 3.12-150.0, p<0.002) for mild, moderate and severe RV dysfunction respectively, as compared to normal RV function group. Figure 1 depicts the Kaplan-Meier cumulative probability for mortality curves for each group.

Conclusions: There is a graded independent association between the severity of RV dysfunction after AMI and long-term mortality. Even a mild dysfunction is associated with an increase in risk of death.



9:30 a.m.

1051-194 **Chronotropic Incompetence Is an Independent Predictor of Mortality in Patients With Advanced CHF**

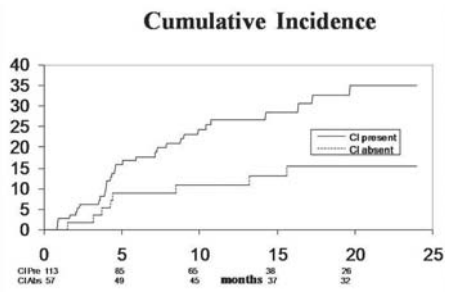
Luis I. Garcia, Daniel B. Sims, Andrea Mignatti, Paolo C. Colombo, Paula Karlin, Steve Holleran, Ayumi Goda, Donna M. Mancini, Ulrich P. Jorde, Columbia University Medical Center, New York, NY

Background: Chronotropic Incompetence (CI) is an emerging therapeutic target in CHF. Whether this inability to reach age adjusted maximal predicted heart rate (MPHR) is a maladaptive or protective mechanism in CHF remains unknown. Accordingly, we prospectively enrolled patients presenting to our center for CHF/transplant evaluation to determine if CI is an independent predictor of outcome.

Methods: Data for 274 consecutive pts, mean age 53.6±13yrs, LVEF 27.7 ±12% and peak oxygen consumption (pVO2) 12.7 ± 4.7 ml/kg/min were analyzed. Severe CI was defined as MPHR <70%. The primary composite endpoint was time to one of the following events: Death, HTX, LVAD.

Results: Mean f/u time was 509 days. 25 HTX, 8 LVAD, and 11Death occurred. In univariate analysis MPHR, pVO2, Hgb, BNP,serum sodium and LVEF predicted time to event (p < 0.05). In multivariate analysis, only MPHR, LVEF and pVO2 remained significant (p <0.05). Furthermore, using Kaplan-Meier analysis, the presence of severe CI conferred a 2.5 times increased proportional hazard ratio in the 170 patients with peak VO2 < 14 (95% Confidence Interval 1.12 - 5.17, p 0.02; Fig 1).

Conclusions: In subjects with advanced HF, severe CI is an independent predictor of death and/or the need for advanced surgical therapy. Severe CI does not appear to be a protective mechanism and its presence may be useful to further risk stratify subjects with pVO2 < 14. The prognostic impact of pacer-based CI modulation in subjects with advanced CHF and severe CI remains to be investigated.



9:30 a.m.

1051-195 **Long-Term Results of the ACORN CorCap: Five-Year Follow-Up From the CSD Only Stratum of the ACORN Trial**

Douglas L. Mann, Randall C. Starling, Hani N. Sabbah, Mariell Jessup, Michael A. Acker, Jae Oh, Spencer H. Kubo, Baylor College of Medicine, Houston, TX

Background: The Acorn CorCap Cardiac Support Device (CSD) is a polyester mesh that is fitted around the heart to reduce wall stress and promote reverse remodeling in patients (pts) with heart failure (HF). We previously reported the Acorn Randomized Trial with follow-up of ~22 months. We now report the results of 5 year follow-up from the CSD only stratum.

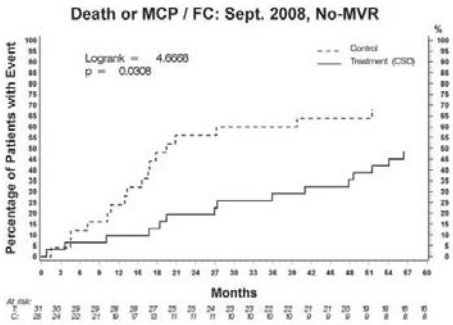
Methods: The CSD only stratum enrolled 107 pts with HF (NYHA Class III - 99%; mean LVEF 21%; mean LVEDV 282 ml) on optimal medical therapy (OMT). Pts were randomized to CorCap CSD + OMT or OMT only. Survival status, need for major cardiac procedures (MCP) and echocardiograms (Mayo Clinic Echo Core Lab) were followed for 5 years.

Results: At 5 years, the Kaplan-Meier estimate of overall mortality was 37% in the CSD group and 38% in the OMT group (p=0.92), confirming that the CorCap is safe.

The CSD group had greater reductions in LVEDV (31.3 vs. 2.8 ml; p=0.03) and a trend for greater increases in sphericity index (0.107 vs. 0.071; p=0.29). There continues to be no clinical cases of pericardial constriction during long term follow up.

We previously reported a subset analysis which excluded pts who were “too well” (LVEDDi <30 mm/m2) or “too sick” (LVEDDi >40 mm/m2) to focus on pts who had an optimal response to CorCap. In this subset (Fig 1), CSD pts had a significantly (p=0.03) lower rate of death or MCPs, including transplant (7% vs. 20%), LVAD (3% vs. 8%) and CRT (13% vs. 20%).

Conclusions: These results suggest that the benefits of the Acorn CorCap CSD are durable to 5 years**.**



9:30 a.m.

1051-196 **Allogeneic Mesenchymal Stem Cells Promote Recovery of Cardiac Function in Chronic Ischemic Cardiomyopathy Through Trilineage Differentiating Capacity**

Henry C. Quevedo, Konstantinos E. Hatzistergos, Behzad N. Oskouei, Gary S. Feigenbaum, Jose E. Rodriguez, David Valdes, Pradip M. Pattany, Karl H. Schuleri, Qinghua Hu, Juan P. Zambrano, Ian McNiece, Alan W. Heldman, Albert C. Lardo, Joshua M. Hare, Interdisciplinary Stem Cell Institute, Miller School of Medicine, University of Miami, Miami, FL, Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Background: Although allogeneic mesenchymal stem cells (aMSC) improve cardiac function after acute myocardial infarction (MI), whether this occurs in chronic infarcted myocardium remains uncertain. Here, we tested the hypothesis that aMSCs are effective at reducing infarct size and improving cardiac function in ischemic cardiomyopathy and that differentiation to cardiomyocytes and blood vessels contributes to this effect.

Methods: Three months after MI, ten female swine received transendocardial injections of 200 million male aMSC (n=6) or placebo (n=4) followed by serial cardiac magnetic resonance imaging. Twelve weeks later, in situ hybridization for the Y chromosome (Y ^{pos}) cells was assessed in infarct (IZ), border (BZ) and remote myocardium followed by characterization for cardiac (GATA-4/ a-sarcomeric actinin / connexin-43), vascular muscle (smooth muscle actinin) and endothelial (factor viii) lineages.

Results: MI reduced ejection fraction (from 47.7± 2.0% to 33.4± 1.0%; p<0.05, p=NS between groups) with similar scar size in both groups (aMSC= 18.3 ± 1.3%; placebo= 18.4 ± 2.5%). Twelve weeks later, aMSC therapy but not placebo increased ejection fraction (16.5 ± 8.0%; p<0.01) and reduced scar size (29.0 ± 5.1%, p<0.01). Myocardial strain analysis of aMSC-treated hearts displayed an improved regional function in IZ (aMSC = -14.5 ± 1.7%; placebo = -6.8 ± 2.2 %, p<0.001) and BZ (aMSC = -15.6 ±1.8%; placebo = -6.4 ± 2.2%, p=0.001). Confocal imaging of IZ and BZ showed that 14.0 ± 4.0% of engrafted Y ^{pos} aMSC also co-stained for GATA-4 ^{pos} /a-sarcomeric actinin ^{pos} as well as connexin-43. In addition, Y ^{pos} cells co-localized with smooth muscle actinin ^{pos} (5.9 ± 2.1%) and factor viii ^{pos} (3.9 ± 1.7%) and were incorporated into large and small vessels. Importantly, the degree of aMSC engraftment correlated with the recovery in regional wall motion (r= -0.82, p<0.05).

Conclusions: Together these findings demonstrate that aMSCs transplantation improves left ventricular function and decreases infarct size by clinically meaningful amounts in chronic cardiomyopathy, in a manner that correlates to definitive evidence of cell engraftment and differentiation into myocytes and vascular elements.

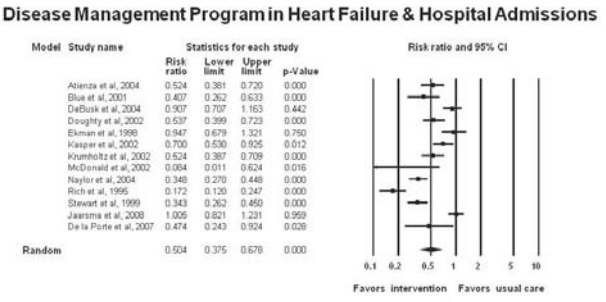
9:30 a.m.

1051-197 **Effectiveness of Nurse led or Multidisciplinary Disease Management Programs in Improving Clinical Outcomes in Heart Failure Patients: A Meta-Analysis**

Rohit Bhuriya, Navdeep Gupta, Updesh Bedi, Janos Molnar, Ahmad Khraisat, Param Puneet Singh, Amol Bahekar, Rohit Arora, The Chicago Medical School, North Chicago, IL

Background: Controversy persists regarding the effectiveness of nurse-led or multidisciplinary disease management programmes (DMP) to improve long term outcomes of heart failure (HF) patients. We performed a meta-analysis of randomized controlled trials (RCTs) comparing the effectiveness of nurse led or multidisciplinary DMP versus usual care in HF patients.

Methods: We performed a systemic literature search for RCTs, enrolling HF patients, and allocating them to usual care or nurse-led/multidisciplinary DMP. HF-related hospitalizations and all-cause mortality were assessed for clinical outcomes. Heterogeneity of the studies was analyzed by Cochran's Q statistic. Mantel-Haenszel random-effect model for HF-related hospitalizations, and fixed-effect model for all-cause mortality, was used to calculate the relative risk (RR). A two-sided alpha error of less than 0.05 was considered to be statistically significant (p<0.05).
Results: Thirteen RCTs provided data on HF-related hospitalizations (N=3,348) and 16 RCTs provided data on all-cause mortality (N=3,783). The RR for HF-related hospitalizations was 0.504 (95% CI, 0.375 to 0.678; p = 0.000) in the intervention group compared to usual care group (figure below). The RR for all-cause mortality was 0.808 (95% CI, 0.708 to 0.922; p = 0.002).
Conclusion: Nurse-led or multidisciplinary DMP significantly reduce heart failure-related hospitalizations and all-cause mortality, in patients with heart failure, when compared to usual care.



9:30 a.m.

1051-198 **Stroke Volume/End Systolic Volume Ratio Provides a Good Measure of Cardiac Function Following Surgical Ventricular Reconstruction**

Marisa Di Donato, Giuseppe Barletta, Serenella Castelvecchio, Fabio Fantini, Lorenzo Menicanti, IRCCS, San Donato Hospital, San Donato Milanese, Italy, Careggi Hospital, University of Florence, Florence, Italy

Background: Ejection fraction (EF) is not considered a good measure of cardiac function following surgical ventricular reconstruction (SVR) being the ratio Stroke Volume (SV) to End diastolic volume (EDV) heavily modified by volume reduction induced by surgery. The arterial coupling (the ratio between arterial and ventricular elastance) reflects the ventricular energetic being the optimal ratio (about 2) related to the best mechanical efficiency (about 80%). The mathematical relationship between ventricular elastance, that may be accurately measured as End systolic pressure (ESP)/ESV in a single beat evaluation, and arterial elastance (SV/ESP) allows to approximate arterial coupling as SV/ESV. Aim of the present study was to analyze changes in SV/ESV induced by SVR and to compare them to EF changes.
Methods: Four-hundred-sixty-six patients (65±10 yrs, 89 F) undergoing SVR at our Center between July 2001 and July 2008 for ischemic dilated cardiomyopathy. LV EDV, end systolic volumes (ESV), LVEF and the SV/ESV ratio were measured by transthoracic echocardiogram before surgery and at discharge in all survivors and in 190 patients at FUP. SVR was conducted on arrested heart.
Results: All patients had SVR**;** CABG was associated in 93% and mitral repair in 25%. LV EDV and ESV decreased (-32 and -40%, respectively), SV decreased (- 20%); LV EF improved (+18%) and SV/ESV increased (+35%) at discharge. All changes were significant at p 0.0001 and were maintained at follow-up. Interestingly, while SV at discharge was significantly reduced, SV/ESV was significantly increased to a greater extent than the improvement in EF. Such improvement was maintained at FUP.
Conclusions: The SV/ESV ratio may be more informative than LVEF following a surgical procedure that strongly changes loading conditions. The improvement in SV/ESV indicates an improvement in cardiac energetics, thus overcoming the limitation of EF in this cohort of patients.

9:30 a.m.

1051-199 **Acute Bi-ventricular Pacing Improves Cardiac Function in a Heart Failure Population With a Moderately Reduced Ejection Fraction**

Yi-Chih Wang, Chih-Chieh Yu, Kathryn Hilpisch, Vincent Splett, Rodolphe P. Katra, Chia-Ti Tsai, Juey-Jen Hwang, Ling-Ping Lai, Jiunn-Lee Lin, Natl Taiwan University Hosp, Taipei, Taiwan,ROC, Medtronic Inc, Mounds View, MN

Background: Cardiac resynchronization therapy (CRT) is an effective therapy for patients with a reduced ejection fraction (EF). However, the therapeutic benefit of CRT in a heart failure (HF) population with a mildly reduced EF remains under-explored. This study examines the acute effects of Bi-V pacing in a HF population with a mildly reduced EF.
Methods: Thirteen patients with EF between 35 and 50% undergoing cardiac catheterization were studied. Temporary pacing catheters were placed in the RA, LV and RV. LV systolic dyssynchrony by Tissue Doppler Echocardiography (TDI) and ECG were measured at baseline and during acute Bi-V pacing (5min). Patients were paced in VDD mode with AV timing selected to optimize transmitral flow and with simultaneous RV-LV timing. The dyssynchrony metrics assessed were: Basal and 12-segment septal to free wall delay; times to peak systolic and diastolic velocities in 12 segments (mean Ts and Te); dispersion of Ts; and 12 segment standard deviation of times to peak systolic and diastolic velocities.
Results: Patients were 66±14 years old, male (77%), ischemic (54%) with NYHA class of 2.2±0.7, a body mass index of 26±4Kg/m², a mean EF of 42±4% and a predominantly narrow QRS (110±26ms). Cardiac dimensions were mildly dilated (LVEDD: 56±10mm and LVESD: 43±10mm). Bi-V pacing did not significantly alter dyssynchrony measures, but increased mean Ts and Te (Ts: 207±29 vs 247±42ms, p<0.01; Te: 615±43 vs. 651±51ms, p<0.01) compared to baseline. This increase was paralleled by a significant increase in mean QRS width (111±26 vs. 142±19ms, p<0.01). There was a significant increase in LVOT onset and end time (125±27 vs. 167±33, p<0.01 and 416±32 vs. 456±34, p<0.01, respectively), a significant reduction in E/E' (16±9 vs. 11±4, p=0.03), and a significant reduction of LVESD and LVEDD (43±10 vs. 41±9mm, p=0.01, and 56±10 vs. 54±10, p=0.03).
Conclusion: These data suggest that acute Bi-V pacing may improve cardiac dimensions and echo indices of hemodynamics in a HF population with a moderately reduced EF and mildly dilated hearts, despite the marked QRS prolongation. Whether these acute changes with Bi-V pacing are chronically therapeutic requires additional investigation.

9:30 a.m.

1051-200 **Exercise Training in Diastolic Heart Failure: A Prospective, Randomized, Controlled, Multicenter Trial (ISRCTN 42524037)**

Frank Edelmann, Hans-Dirk Duengen, Rolf Wachter, Götz Gelbrich, Silja Schwarz, Martin Halle, Christoph Hermann-Lingen, Gerd Hasenfuss, Burkert M. Pieske, University of Göttingen, Göttingen, Germany

Background: This trial was designed to tests the hypothesis that exercise training improves exercise capacity, quality of life, and diastolic function in patients with diastolic heart failure.
Methods: n=67 with symptomatic heart failure, proven diastolic dysfunction, LVEF≥50%. Randomization (2:1) to supervised, combined endurance/resistance training on top on usual care (n=46/T) or usual care alone (n=21/C; control group). Spiroergometry (primary endpoint: peak VO2), diastolic function (echocardiography), quality of life, collagen turnover were recorded at baseline and after three months. Data analysis was by intention-to-treat principle.
Results: Patients were 65±7 years old (56% female, NYHA class II/III (84 vs. 16%), LVEF 67±7%. 64 patients completed the study (T n=44, C n=20). Peak VO2 (mL/min/kg) increased significantly (p<0.001) from 16.1±4.9 to 18.7±5.4 in the training group (T), but did not change (16.7±4.7 vs. 16.0±6.0; p=0.34) in the control group (C). The mean increase in peak VO2 with training was 3.3 mL/min/kg (95% CI, 1.8 to 4.8, P<0.001). The NNT to achieve an increase of peak VO2 by 3 mL/kg/min at an individual level was 3.5 (p=0.006). ATVO2 increased in T (p<0.001) and remained unchanged in C (p=0.79; T vs. C p<0.001). Diastolic function was analysed in a blinded fashion: E/e' ratio decreased from 12.8±3.2 to 10.5±2.5 (p<0.001) in T and remained unchanged (13.5±4.6 vs. 14.1±3.9; p=0.26) in C (mean difference of changes -3.2, C.I. -4.3 to -2.1, P<0.001); é medial (cm/s) increased (p<0.001) in T and remained unchanged in C. LAVI (mL/m2) decreased from 27.9+/-7.6 to 24.3±6.5 (p<0.001) in T and did not change (28.2±8.8 vs. 28.6±9.2; p=0.53) in C. Quality of life (MLWHFQ, SF-36) improved in T (p<0.001) and was unchanged in C. Median pro-collagen I (µg/L) decreased from 38 (25-51) to 34 (25- 42) in T (p=0.01) and remained stable in C (p=0.55).
Conclusions: A supervised 3 months exercise training program effectively improves exercise capacity, quality of life, diastolic function, and structural remodeling in patients with diastolic heart failure. Controlled lifestyle modification with physical activity may emerge as a major therapeutic approach in this yet poorly treatable condition.

9:30 a.m.

1051-201 **Does Exercise Systolic Tissue Velocity Predict Exercise Ability Compared to Other Resting Systolic and Diastolic Parameters? An Analysis Across Various Populations**

Robert A. McIntosh, John C. Silberbauer, Louisa Beale, Gary Brickley, Rick Veasey, Paul Hong, Nik Patel, Stephen Furniss, Neil Sulke, Guy Lloyd, Eastbourne General Hospital, Eastbourne, United Kingdom

Background: A poor relationship between resting parameters of systolic and diastolic heart function and exercise ability has been previously observed, less is known about cardiac parameters during exercise. This study evaluated both resting and stress echocardiography (SE) parameters in a number of clinical settings and compared them with VO_2 peak during cardiopulmonary exercise testing (CPET). **Methods:** 40 patients enrolled in various clinical trials were studied. Normal fit adults (n=10, mean age 27) patients with AF awaiting AV node ablation (n=10, mean age 73) patients with mild to moderate heart failure (n=14, mean age 74) and age matched older controls (n=6, mean age 67). All underwent CPET using a bicycle ergometer and had simultaneous SE (peak readings taken after anaerobic threshold during exercise). 2D, spectral Doppler and tissue Doppler (TDI) parameters were recorded. **Results:** Linear regression demonstrated a strong relationship between VO_2 peak and mean left ventricular peak TDI velocity (r^2 = 0.74 p<0.001), TDI judged contractile reserve (r^2 = 0.74 p<0.001) and change in ejection fraction (r^2 =0.2 p = 0.01). There was no relationship between resting heart parameters, including ejection fraction, E' velocity or E/E' ratio. Diastolic parameters on exertion were not related to VO2 max. When the population was dichotomised for 'diastolic dysfunction' (E/E' > 12 taken from the lateral wall) the relationship between peak TDI velocities remained high despite the small numbers (r^2 = 0.71 p =0.03). **Conclusions**: In the

absence of other extracardiac disease processes there is a strong relationship between contractile reserve judged by TDI and exercise ability during CPET. The relationship is robust in different groups of heart function and especially when diastole is abnormal. Heart failure with normal ejection fraction may be a failure of systole rather than of diastole as conventionally understood.

9:30 a.m.

1051-202 Mechanisms of Improvement of Mitral Regurgitation After Cardiac Resynchronization Therapy in Patients With Congestive Heart Failure

Katsuomi Iwakura, Hiroshi Ito, Atsunori Okamura, Yasushi Koyama, Motoo Date, Yoshiharu Higuchi, Koichi Inoue, Ryusuke Kimura, Hiroyuki Nagai, Yuko Toyoshima, Michio Imai, Makito Ozawa, Norihisa Ito, Yukinori Okazaki, Masahiko Shibuya, Hidetaka Suenaga, Asuka Kubota, Kenshi Fujii, Sakurabashi Watanabe Hospital, Osaka, Japan

Background: CARE-HF trial demonstrated that the severity of mitral regurgitation (MR) is one of the strongest predictor for mortality of patients with congestive heart failure (CHF) who receive cardiac resynchronization therapy (CRT) (J Am Coll Cardiol 2008; 52:438). Tethering of mitral valve leaflets associated with left ventricular remodeling is the major mechanism of functional MR. We investigated the effects of CRT on the tethering of mitral valve and on severity of MR.
Methods: We enrolled consecutive 32 patients with CHF eligible for CRT who had moderate to severe MR. They underwent echocardiography study before and 10±5 months after the CRT. We assessed severity of MR as jet area of MR to left atrial area ratio on color-Doppler image, and defined ≥20% reduction of the MR ratio as an improvement of MR. We measured midsystolic mitral annular area and mitral valve tenting height to estimate severity of tethering of mitral leaflet. We also assessed changes in left ventricular ejection fraction, end-diastolic and end-systolic volume (LVEDV and LVESV) after CRT.
Results: Among the 32 study patients, 15 patients (46.9%) showed the reduction of MR. There were no significant differences in MR ratio, mitral annular area and tenting height before CRT between those with and without MR reduction. Patients showing improvement had significant reduction of mitral annular area (2.3±0.5 cm^2 to 1.1±0.4 cm^2, p<.0001) and tenting height (1.1±0.2 to 0.6±0.1 cm, p<.001) after CRT, whereas those without improvement showed no significant differences in these values (1.9±0.9 cm^2 to 2.0±0.9 cm^2, p=.82 and 1.0±0.3 to 1.0±0.3 cm, p=.61). On the other hand, both groups showed significant reduction in LVEDV (179±67 mL to 139±58 mL, p=.02, and 201±100 mL to 174±104 mL, p=.03) and in LVESV (133±58 mL to 85±53 mL, p=.001, and 151±100 mL to 118±95 mL, p=.001), and improvement in ejection fraction (28±10% to 43±16%, p<.001, and 29±12% to 38±16%, p=.006).
Conclusions: Improvement of functional MR by CRT is mediated through the correction of tethering of mitral valve leaflet, however, reduction of left ventricular volumes could not be the sole mechanism of these improvements.

9:30 a.m.

1051-203 Red Cell Distribution Width: A Novel Prognostic Marker in Pulmonary Hypertension

Chetan V. Hampole, Amit K. Mehrotra, Thenappan Thenappan, Mardi Gomberg-Maitland, Sanjiv S. Shah, University of Chicago, Chicago, IL, Northwestern University, Chicago, IL

Background: Red cell distribution width (RDW), a widely available biomarker which independently predicts outcome in left-sided heart failure, has never been studied in pulmonary hypertension (PH). Based on our anecdotal experience that increased RDW is associated with severe PH, we hypothesized that RDW would be independently associated with increased mortality in PH.
Methods: In a prospective study of 187 consecutive patients with PH (mean PA pressure > 25 mmHg), we recorded RDW at time of right heart catheterization. Patients were then followed for 2.1±1.0 years and mortality was ascertained on all patients. We first used linear regression with RDW as the dependent variable to determine which clinical, demographic, laboratory, and hemodynamic variables were associated with RDW. We then used univariate and multivariate Cox proportional hazards models to determine whether RDW was independently associated with death.
Results: Of the 187 study patients, 78% were female, 62% had pulmonary arterial hypertension (PAH), and mean age was 55±14 years. Overall, patients in this cohort had severe PH (right atrial pressure [RAP] 11±7 mmHg, mean PA pressure 48±13 mmHg, cardiac index 2.5±1.0, and pulmonary vascular resistance 9.6±6.2) and poor functional status (87% had functional class III-IV symptoms). Increased RDW was associated with decreased hemoglobin (Hgb), decreased serum sodium (Na), increased blood urea nitrogen (BUN), and increased serum creatinine (SCr). Of the hemodynamic variables, only RAP was associated with RDW. During follow-up, 26/187 (14%) of the patients died. On Cox regression analysis, the highest tertile of RDW predicted death (univariate HR 3.2, 95% CI 1.1-9.1, p=0.030; multivariate HR 4.2, 95% CI 1.1-16.4, p=0.041, after adjusting for age, sex, etiology of PH, RAP, Na, BUN, SCr, and Hgb). These associations were also present in the subgroup of patients with PAH.
Conclusions: RDW is an independent predictor of death in PH. RDW seems to be a marker of the overall heart failure syndrome, since it is associated with anemia, worse renal function, hyponatremia, and elevated RAP. Further study of abnormalities in RDW may provide insight into the pathogenesis and prognosis of PH.

9:30 a.m.

1051-204 Chronic Therapy With Vagus Nerve Stimulation Is Associated With Reduced Levels of Circulating Plasma Biomarkers of Heart Failure

Ramesh C. Gupta, Itamar Ilsar, Mengjun Wang, Alice Jiang, Asaph Zaretsky, Michael S. Sabbah, Hani N. Sabbah, Henry Ford Hospital, Detroit, MI, Technion, Haifa, Israel

Background: Plasma levels of the soluble intracellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL-6), and atrial (ANP) and brain (BNP) natriuretic peptides are increased in heart failure (HF). We previously showed that chronic therapy with Vagus nerve stimulation (VNS) using the CardioFit system (BioControl Medical, Ltd.), when combined with beta-blockade (BB), significantly increases LV ejection fraction (EF) in dogs with coronary microembolization-induced HF compared to BB alone. This study examined whether VNS therapy in combination with BB is associated with a greater reduction of plasma levels of these biomarkers.
Methods: Blood samples were obtained from HF dogs treated for 3 months with BB alone (n=6), BB + VNS (n=6), untreated HF dogs (n=6) and normal (NL) dogs (n=6). Plasma level of sICAM-1, IL-6, nt-pro-BNP and nt-pro-ANP were measured using specific ELISA kits.
Results: sICAM-1, IL-6, ANP, and BNP levels in plasma increased significantly in untreated HF dogs compared to NL dogs (Table). Therapy with BB alone significantly lowered plasma levels of all markers compared to untreated HF dogs. Compared to BB alone, combined VNS + BB therapy significantly lowered all biomarkers tested except BNP.
Conclusions: In dogs with HF, combined VNS and BB therapy is associated with reduced plasma levels of biomarkers of worsening HF. This finding is consistent with our earlier observation of a greater improvement of LV EF in HF dogs treat with combined VNS and BB compared to BB alone.

	NL	HF-Control	HF + BB	HF + BB + VNS
sICAM-1 (μg/ml)	1.96 ± 0.30	10.82 ± 0.44*	5.66 ± 0.55†	2.66 ± 0.46‡
IL-6 (pg/ml)	145 ± 29	595 ± 92*	190 ± 29†	148 ± 12‡
nt-proBNP (fmol/ml)	587 ± 32	1038 ± 113*	633 ± 47†	580 ± 50
nt-proANP (nmol/ml)	13 ± 2	85 ± 7*	41 ± 3†	24 ± 2‡
*=p<0.05 vs. NL; †=p<0.05 vs. HF-Control; ‡=p<0.05 vs. BB				

9:30 a.m.

1051-205 Prognostic Value of Anemia in Elderly Patients With Diastolic Heart Failure

Faramarz Tehrani, Anita Phan, Ryan Morrissey, Christopher Chien, Asim Rafique, Ernst R. Schwarz, Cedars Sinai Medical Center, Los Angeles, CA

Background: Anemia is prevalent in patients with heart failure and has been associated with increased mortality. There is a lack of consensus regarding the effect of anemia in elderly (> 75 years) patients with heart failure and preserved ejection fraction. The current study assessed the effects of anemia on long term survival in patients with pure diastolic heart failure.
Methods: Patients with heart failure and preserved systolic function, EF≥50% (diastolic heart failure) were evaluated. Patients were separated into those anemic (group 1) and those non-anemic (group 2) at baseline (anemia defined as Hgb<12g/dL females or Hgb<13g/dL males). A multivariate Cox proportional hazards regression was conducted to test whether hemoglobin levels are an independent predictor of 5-year hospitalization rate and mortality in patients with diastolic heart failure.
Results: Two hundred and ninety four patients were evaluated (group 1, n=162; group 2, n=132). Anemic patients had a shorter mean survival (37.8±1.8 versus 44.9±1.8, p=0.010) but no significant difference in hospitalization rate (7.2±7.1 versus 7.5±6.3, p=0.677 for groups 1 and 2). In a subgroup analysis, anemia was a significant predictor of higher mortality in the elderly patients (>75 years old) with diastolic heart failure (p=0.018).
Conclusions: Anemia is associated with increased long term mortality in patients with diastolic heart failure, and appears to be an independent predictor of worse outcomes in elderly patients with heart failure.

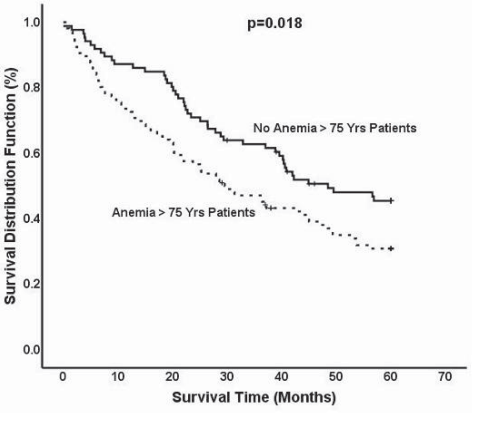


FIGURE 1: Survival and Anemia in Diastolic Heart Failure Patients Older than 75 years of Age

9:30 a.m.

1051-206 **Long-Term Effects of Intracoronary CD34+ Stem Cell Transplantation in Patients With Dilated Cardiomyopathy**

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Background: Stem cell therapy appears to have beneficial short-term effects in patients with dilated cardiomyopathy (DCM). We sought to investigate whether the early benefits of intracoronary stem cell transplantation are sustained over time.

Methods: We performed intracoronary autologous CD34+ stem cell transplantation in 17 DCM patients (15 male, 2 female; mean age: 55±7 years). Peripheral blood stem cells were mobilised by daily subcutaneous injections of filgrastim; CD34+ cells were collected via apheresis and labelled with technetium. Patients underwent myocardial perfusion scintigraphy for myocardial viability assessment and CD34+ cells were injected intracoronary in the artery supplying the segments of reduced tracer accumulation. Patients were reassessed at 1 and 12 months after the procedure.

Results: At 1 month we found a significant improvement in LVEF (from 24.1±6.3% to 31.3±6.2%; *P*=0.001) and 6-minute walk test distance (from 361±114 m to 426±84 m; *P*=0.02), but no changes in LVEDD (from 6.9±0.9 cm to 6.8±0.7 cm; *P*=0.42), target wall thickness (from 1.1±0.2 cm to 1.3±0.2 cm; *P*=0.16), and plasma levels of TNF-alpha (from 4.4±2.8 pg/ml to 3.0±1.9 pg/ml; *P*=0.07). The improvement in LVEF persisted throughout the 12-month period (-0.1±7.2%; *P*=0.96), and correlated with the numbers of the cells found at the site of intracoronary delivery (r^2=0.71, *P*=0.01). Similarly, we found no additional changes in 6-minute walk test distance (+52±74 m; *P*=0.35), LVEDD (-0.2±0.2 cm; *P*=0.40), or TNF-alpha (+0.8±2.0 pg/ml; P=0.14) between the 1st and 12th month. In contrast, a further increment in target ventricular wall thickness was found at 12 months after the procedure (+0.3±0.2 cm, P=0.02).

Conclusions: In DCM patients, the early benefits of intracoronary stem cell transplantation evident at 1 month following the procedure appear to be sustained up to 12 months.