ORAL CONTRIBUTIONS

869 Preserved Systolic Function: Heart Failure

Tuesday, March 19, 2002, 2:00 p.m.-3:30 p.m.
Georgia World Congress Center, Room 367W

2:00 p.m.

869-1 Heart Failure With Normal Ejection Fraction: Lack of Relationship Between Doppler Indices of Diastolic Function and LV Pressure Transients

Gerard P. Aurigemma, Michael R. Zile, William H. Gaasch, *University of Massachusetts Medical School, Worcester, Massachusetts, Lahey Clinic, Burlington, Massachusetts.*

Background: Doppler indices of diastolic function are thought to be useful in the assessment of the physiologic properties of the diastolic left ventricle, but few data validate their use in patients with heart failure (CHF) and normal ejection fraction (EF). Accordingly, the purpose of this study was to determine how Doppler indices perform in a series of patients with definite diastolic heart failure: CHF and EF exceeding 50%. **Methods:** Doppler indices: E, A, E/A ratio, E deceleration time (DT),and isovolumic relaxation time (IVRT) were recorded during cardiac catheterization (micromanometer: LV end diastolic pressure [LVEDP] and the time constant of isovolumic relaxation, tau) in 45 pts (mean age 57± 7) with clinical CHF, evidence of LV hypertrophy, and normal EF. **Results:** There was a significant positive correlation between tau and LVEDP, r=0.72, p<0.005. However, a relationship between tau and IVRT could only be discerned when patients were grouped separately by LVEDP. Despite the fact that one or more Doppler abnormalities was present in each patient, no simple relationship existed between Doppler parameters and LVEDP or tau (see Table). **Summary/Conclusion:** In CHF patients with normal EF (diastolic heart failure), Doppler indices of diastolic function do not correlate with either LVEDP or tau. Such limited sensitivity of these Doppler parameters is likely due to the multiplicity of factors (unstable hemodynamic loads, transmitral pressure gradients, etc.) influencing these indices.

r values relating Doppler and pressure indices of diastolic function

	E velocity	E/A ratio	DT	IVRT
tau	0.08	0.24	0.01	0.15
LVEDP	0.01	0.04	0.04	0.16

2:15 p.m.

869-2 Racial Paradox in Congestive Heart Failure Survival in Patients With Normal Left Ventricular Ejection Fraction

Padmini Varadarajan, Sanju Sharma, Ramdas G. Pai, *VA Medical Center, Loma Linda, California, Loma Linda University, Loma Linda, California.*

Background: It is generally believed that black and hispanic Americans fare poorly compared to Caucasians in a variety of cardiovascular disorders. This has been attributed to lack of health care access, compliance, and differences in biology. We examined the prognosis of patients with congestive heart failure by race at our VA medical center where access to care and medical management is likely to be similar independent of race.
Methods: We examined the survival of 2258 patients with a primary hospital discharge diagnosis of heart failure between 1990 and 1999. Over a mean follow-up of 786 days there were 1535 deaths. The racial composition was 80% caucasians, 10% black and 8% hispanic Americans. 963 (43%) patients had normal EF (≥55%). Mean age was 71 years and 97% were men. Computerized echo and ECG data were used. Survival analysis was performed using Kaplan-Meir method and proportional hazards model.
Results: Survival was similar among the 3 races in the whole cohort and those with reduced LVEF. However, in those with normal LVEF, survival was significantly better among the Hispanic and the black Americans compared to the caucasians, the 5 year probability of survival being 37%, 27% and 21% respectively (p=0.04). Compared to Caucasians, black and hispanic Americans were younger (p<0.0001and 0.01), had a lower prevalence of atrial fibrillation (p=0.03 and 0.04), but similar degrees of valvular dysfunction. In addition, the black Americans had greater degree of LVH (p<0.0001) and lesser prevalence of myocardial infarction on the ECG (p=0.01) compared to caucasians. The effect of race on survival persisted after correcting for the above confounders (p=0.03).
Conclusions: 1)Black Amercans with diastolic heart failure are younger and have greater degrees of LVH compared to caucasians. 2)Hispanic and black Americans have a better diastolic heart failure prognosis compared to caucasians after correcting for other confounders

2:30 p.m.

869-3 Are Racial Differences in the Long-Term Prognosis of Systolic Heart Failure Independent of Differences in Etiology?

Kevin L. Thomas, Mark East, Robert Tuttle, Linda Shaw, Judy Battle, Eric Peterson, Christopher O'Connor, *Duke University Medical Center, Durham, North Carolina.*

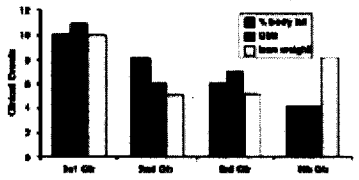
Background:
Prior studies have shown that African-Americans (AA) have worse long-term prognoses than whites with systolic heart failure. However, the reasons for these differences are unclear. We sought to determine if racial differences in the long-term mortality of patients with systolic heart failure could be explained by differences in ischemic etiology.
Methods:
Prospectively collected data on 1774 (28% black) patients with Class II-IV symptoms and systolic dysfunction (EF<40%) were identified in the Duke Databank of Cardiovascular Disease between 1986-1999. Adjusted survival comparisons were performed using Cox proportional hazards models.
Results:
AA patients with heart failure were younger (median age 56 vs. 63; p<0.01), more often female (49% vs. 33%; p<0.01), diabetic (37% vs. 31%; p=0.02), hypertensive (75% vs 56%; p<0.01), and had a S3 gallop (37% vs. 29%; p<0.01). AA patients were less likely to have significant coronary disease by angiography (41% vs. 69%; p<0.01), prior MI (21% vs. 41%; p<0.01), or prior revascularization with PTCA (6% vs. 14%; p<0.01) or CABG (4% vs. 16%; p<0.01). There were no significant differences in degree of symptoms based on NYHA class. Ischemic etiology was associated with a 50% increase in mortality risk (HR 1.50; 95% CI 1.28-1.75). However, after adjusting for age, gender, NYHA class, diabetes, hypertension, peripheral vascular disease, renal disease, S3 gallop and ischemia, race was not an independent predictor of mortality (p=0.31).
Conclusion:
Although previous studies report racial differences in the long-term mortality of patients with systolic heart failure, we found no racial differences in the long-term mortality risk of patients with systolic heart failure after adjusting for clinical differences and ischemia.

2:45 p.m.

869-4 Body Composition and Prognosis in Chronic Systolic Heart Failure: The Obesity Paradox

Carl J. Lavie, Ahmed F. Osman, Richard V. Milani, Mandeep R. Mehra, *Ochsner Medical Institutions, New Orleans, Louisiana.*

Introduction: Obesity impairs systolic and diastolic function and is associated with increased congestive heart failure (CHF) prevalence; yet low body weight has been associated with worse prognosis in chronic CHF patients (pts). We sought to determine the impact of body composition on clinical outcomes in chronic CHF pts.
Methods: We assessed the impact of body composition on major clinical events in 209 consecutive CHF pts (age 54±10, 81% male, NYHA class 2.4±0.6, ejection fraction 23±13%) followed for 18.5±11.5 months, by evaluating quartiles of body mass indices (BMI), % body fat as determined by the sum of the skinfold method, and lean body weight.
Results: There were 28 major events (13 deaths, 15 transplants). Pts in the lowest quartile had significantly greater clinical events than those in the highest quartile of BMI and % body fat (p=0.03 for both) (Figure). Pts with the lowest lean weights had significantly greater events (p=0.02) than those in the second and third quartiles (but not when compared with the fourth quartile). In fact, a high % body fat was associated with greater event-free survival in both univariate (p=0.02) and multivariate (p=0.03) analyses.
Conclusion: Obesity may be a CHF risk factor, but this study demonstrates a significant inverse relationship between indices of obesity, especially BMI and % body fat, with subsequent clinical outcomes. This paradox may be related to a heightened catabolic state often associated with lower lean body weight in chronic systolic heart failure.



3:00 p.m.

869-5 Acute Subcutaneous BNP Administration in Human Heart Failure Enhances Diastolic Function and Filling Pressures as Assessed by Doppler Echocardiography and Plasma ANP

Horng H. Chen, John C. Burnett, Jr., Lynda J. Nordstrom, Margaret M. Redfield, *Mayo Clinic and Foundation, Rochester, Minnesota.*

Background: In experimental heart failure (HF), brain natriuretic peptide (BNP) reduces preload and has direct lusitropic properties while increasing cardiac output (CO). The need for intravenous therapy has limited the use of BNP in humans with chronic HF. The objective of the current study was to assess the effects of subcutaneous (SQ) administration of BNP (Scios,CA) on diastolic function and filling pressures as assessed by Doppler echocardiography and plasma ANP in humans with NYHA class II-III HF (n=8).
Methods: The dose of SQ BNP was 10 μg/Kg. CO was measured by Echo Doppler. Diastolic assessment included mitral early to late filling velocity ratio (E/A) and deceleration time before and with Valsalva and the pulmonary venous systolic to diastolic flow velocity ratio and Doppler tissue imaging. Diastolic function was classified according to increasing severity and filling pressures as: *Abnormal relaxation* (Grade I); *Pseudonormal* (Grade II) or *Restrictive* (Grade III). Doppler and plasma ANP were measured before and after SQ BNP. Doppler diastolic assessment was possible in 5 of the 8 patients (atrial fibrillation in other 3).
Results: (* p<0.05 vs before BNP). With SQ BNP, CO increased (4.8± 0.4 to 6.4± 0.5 l/min*) and systolic blood pressure decreased (125± 5 to 104± 3 mmHg*) without a change in heart rate. Plasma BNP (167± 115 to 830± 470 pg/ml*) and cGMP (4± 2 to 14± 4 pmol/ml*) increased. Plasma ANP decreased (261± 90 to 161± 60 pg/ml*). The changes in the Doppler patterns were consistent with decreases in filling pressures (restrictive or pseudonormal to abnormal relaxation, n=3) and improvement in relaxation (shortening of deceleration time without increased E/A ratio in patients with abnormal

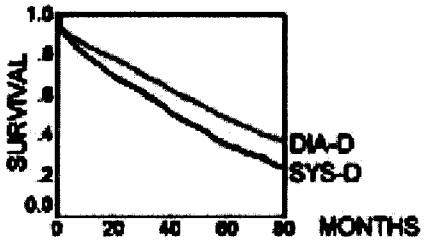
relaxation prior to SQ BNP, n=2).
Conclusion: Acute SQ BNP reduced cardiac filling pressures and improved lusitropic function as evidenced by the changes in the Doppler patterns and the decrease in plasma ANP. This investigation supports the conclusion that SQ BNP is an effective treatment strategy for this lusitropic hormone and that plasma ANP may serve as a serum marker for cardiac filling pressures during the administration of BNP.

3:15 p.m.

869-6 Epidemiology of Systolic and Diastolic Dysfunction Heart Failure In 3,471 Urban Patients

Akshay K. Khandelwal, John E. McKinnon, Heather J. Shenkman, Vijayamalini Pampati, David Nori, Scott Kaatz, Keisha R. Sandberg, Peter A. McCullough, *Henry Ford Hospital, Detroit, Michigan, University of Missouri-Kansas City School of Medicine, Truman Medical Center, Kansas City, Missouri.*

BACKGROUND: We sought to describe congestive heart failure (CHF) in an urban setting with respect systolic dysfunction (SYS-D) and diastolic dysfunction (DIA-D) in terms of age, sex, race, and echo parameters, and survival.
METHODS: Data were abstracted from the Resource Utilization Among Congestive Heart Failure Study, which identified 29,686 CHF patients from a large urban mixed-model managed care organization from 1989 to 1999. A target population of 3,471 had clinical data taken from automated sources during the first year of diagnosis. We defined DIA-D as the presence of CHF with an ejection fraction (EF) of ≥ 45%. Survival was analyzed by Cox regression methods.
RESULTS: Among the CHF population, 52.2% had DIA-D. A total of 751 men (43.6%) and 1,060 women (60.6%), p<0.001, 773 whites (54.1%) and 986 blacks (51.2%), p > 0.05, had DIA-D. Prevalence of DIA-D trended with age, from 46.4% <45 years to 58.7% 85+ years (p<0.001 for trend). Mean EF was 55.66 vs. 27.96, left ventricular end systolic diameter was 3.11 vs. 4.74 cm, and left atrial/aortic outlet ratio was 1.28 vs. 1.38 for DIA-D and SYS-D, respectively (p<0.001 for both). Annual age-adjusted mortality was 11.2% and 13.0% for DIA-D and SYS-D, respectively (see figure) (p<0.001).
CONCLUSIONS: A majority of urban CHF patients including equal proportions of blacks and whites have DIA-D and enjoy a slightly better age-adjusted survival than their counterparts with SYS-D.



POSTER SESSION

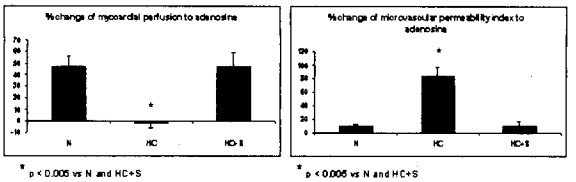
1204 Novel Approaches to Improve Ventricular Function

Tuesday, March 19, 2002, 3:00 p.m.-5:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: 3:00 p.m.-4:00 p.m.

1204-141 Simvastatin Preserves Myocardial Perfusion and Permeability in Experimental Hypercholesterolemia Independent of Lipid Lowering

Piero O. Bonetti, Stephanie H. Wilson, Martin Rodriguez-Porcel, David R. Holmes, Jr., Lilach O. Lerman, Amir Lerman, *Division of Cardiovascular Diseases and Division of Hypertension, Mayo Clinic, Rochester, Minnesota.*

Background: Experimental Hypercholesterolemia (HC) leads to endothelial dysfunction, which is characterized by impaired endothelium dependent vasorelaxation and increased vascular permeability. Statins have been shown to preserve endothelial function in HC not only by cholesterol lowering but also by direct lipid-lowering-independent mechanisms. However, the impact of these effects upon myocardial perfusion (MP) and vascular permeability is still unknown.
Methods: Pigs were randomized to 3 experimental groups: normal diet (N; n=6), high cholesterol diet (HC; n=6) and HC diet plus simvastatin (HC+S; n=6) for 12 weeks. Electron beam computed tomography studies of the heart were performed before and during intravenous infusion of adenosine, and MP and microvascular permeability index (PI) were measured in vivo.
Results: Total and LDL-cholesterol were similarly and significantly increased in the HC and HC+S group compared to N. Basal MP was similar in all groups, as was basal PI. The changes of MP and PI in response to adenosine are shown in the figure below.
Conclusion: The current study demonstrates that the impairment of MP and the increase in PI in response to cardiac stress associated with experimental HC are prevented by simvastatin therapy in the absence of any lipid-lowering effect. This study suggests a role for statins for preservation of myocardial perfusion in pathophysiological states associated with coronary endothelial dysfunction.



1204-142 Effect of Drug-Induced Hypothyroidism on Cardiac Function of Mice Expressing a Troponin T Mutation Associated With Familial Hypertrophic Cardiomyopathy

Bjoern C. Knollmann, Todd E. Miller, Fatima DeFreitas, Neil J. Weissman, James D. Potter, *Georgetown University School of Medicine, Washington, Dist. of Columbia, University of Miami School of Medicine, Miami, Florida.*

The cardiac phenotype of transgenic mice expressing the FHC-linked Troponin T (TnT-I79N) mutation is characterized by increased myofilament Ca^{2+}-sensitivity, left-ventricular hypercontractility, PR prolongation on ECG, and cardiac dysfunction in response to inotropic stimulation. Here we examine the effect of drug-induced hypothyroidism in this model. **Methods:** I79N transgenic mice and non-transgenic littermates (Non-Tg) were fed a diet containing 0.15% 5-propyl-2-thiouracil (PTU) to induce hypothyroidism, which causes an isoform switch from α- to β-myosin heavy chain (MHC). This strategy is predicted to suppress the transgene expression driven by the α-MHC promoter. **Results:** After 8 weeks PTU treatment, all mice had clear evidence for hypothyroidism (hair loss, bradycardia (275 b/min vs. 400 b/min, p<.01), PR prolongation on ECG (47ms vs. 40 ms, p<.05), prolonged isovolumic relaxation time on Doppler (26ms vs. 18ms, p<.05). β-MHC mRNA was significantly increased, and transgenic TnT-I79N mRNA was barely detectable by RT-PCR. Endogenous mouse TnT mRNA and protein was not affected. Transgenic TnT-I79N protein was undetectable. Myofilament Ca-sensitivity of PTU-treated I79N mice was not significantly different from non-transgenic littermates. PTU treatment also abolished all differences in contractile parameters between I79N mice and non-transgenic littermates measured by echocardiography, Doppler, and isovolumic heart experiments (LV fractional shortening of I79N vs. Non-Tg: Control diet: 42±2% vs. 31±1%, n= 11, p<0.001; PTU diet: 31±2% vs. 32±2%, n=11, p=0.86). Although PTU treatment itself prolonged the PR interval, the PR interval remained significantly longer in I79N mice, both in surface ECG and isolated heart experiments. **Conclusion:** PTU treatment resulted in transcriptional downregulation of transgene expression and reversed most, but not all effects of cardiac-targeted transgenic protein expression.

1204-143 Mesenchymal Stem Cell Transplantation in the Reperfused or Nonreperfused Myocardial Infarction Scar Tissues

Tae-Jin Youn, Bo-Ra Sohn, Hainan Piao, Jin-Sook Kwon, So-Young Choi, Dong-Woon Kim, Young-Gyu Kim, Myeong-Chan Cho, *College of Medicine, Chungbuk National University, Cheongju, South Korea.*

Background: Mesenchymal stem cells (marrow stromal cells, MSCs) have myogenic potentials and transplantation of MSCs is considered to be a novel therapeutic approach for post-myocardial infarction (MI) heart failure. We tested whether transplanted MSCs could be implanted and subsequently survived in the reperfused or non-reperfused MI scar tissues in rats.
Methods and Results: Female Sprague-Dawley rats were randomly assigned to one of three groups: group 1, 45-minute left coronary artery ligation followed by reperfusion (early reperfusion with myocardial salvage); group 2, 4-hour left coronary artery ligation followed by reperfusion (late reperfusion without myocardial salvage); and group 3, permanent left coronary artery ligation (non-reperfused MI). MSCs from adult rats were cultured, treated with 5-azacytidine (5-aza, 10 μmol/L) or not and labeled with 4',6-diamidino-2-phenylindole (DAPI) for 60 minutes before transplantation. At 1 week after MI, cultured MSCs ($1x10^6$ cells), 5-aza-treated MSCs ($1x10^6$ cells), and medium (control) were autologously transplanted into the early- and late-reperfused and non-reperfused MI scar tissues (n=5, each). At 1 week after transplantation, numerous scattered DAPI-labeled cells were detected in early-reperfused infarct tissues irrespective of 5-aza treatment. However, in late-reperfused and non-reperfused infarct tissues, only scanty DAPI-positive cells were identified.
Conclusion: Both 5-aza untreated and treated MSCs could be transplanted successfully and viable until 1 week in early-reperfused infarct tissues. However, in late-reperfused and non-reperfused infarct tissues, transplanted MSCs could not survive. Our results implicate that early restoration of blood flow and salvage of myocardium is crucial for the fate of transplanted MSCs after MI.

1204-144 Requirements for Transplanted Skeletal Cells to Function Electrically Within Ventricular Myocardium

Robin M. Shaw, Randall J. Lee, *UCSF, San Francisco, California.*

BACKGROUND: Skeletal myocyte transplantation into diseased ventricle is suggested as a future therapy for patients with infarcted, non-regenerating myocardium. However despite initial clinical success, there is little evidence that implanted skeletal cells can communicate electrically with each other, or with surrounding myocardium. We assessed the electrical requirements for skeletal cells to communicate with each other and with ventricular myocytes.
METHODS: Theoretical strands were developed composed of sophisticated mathemati-