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elderly (225±41 ms) than in younger patients (208±31 msec) (p<0.001). Increased atrial refractory period and age > 70 years were independent factors of decreased AF inducibility. Conclusion : AF inducibility is paradoxically decreased in elderly patients. The AF induction is facilitated by the presence of a short atrial refractory period in patients younger than 70 years and programmed atrial stimulation should be interpreted cautiously in these patients. In the opposite, the increase of atrial refractory period could protect the patients older than 70 years against AF induction.

ORAL CONTRIBUTIONS

839 Hypertrophic Cardiomyopathy: Basic and Clinical II

Tuesday, March 09, 2004, 10:30 a.m.-Noon
Morial Convention Center, Room 210

10:30 a.m.

839-1 The Long-Term Effect of Surgical Myectomy on Survival in Patients With Obstructive Hypertrophic Cardiomyopathy

Steve R. Ommen, Iacopo Olivotto, Martin S. Maron, Sandro Betocchi, Franco Cecchi, Michael J. Ackerman, Bernard J. Gersh, Joseph A. Dearani, Hartzell V. Schaff, Rick A. Nishimura, Barry J. Maron, Mayo Clinic, Rochester, MN

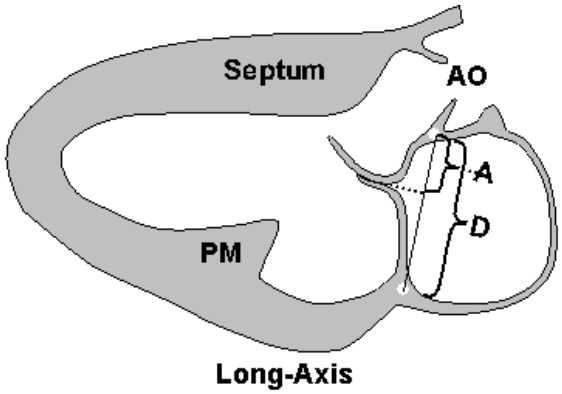
Background: Surgical septal myectomy is the definitive treatment for relief of drug-refractory symptoms in hypertrophic cardiomyopathy (HCM). Recent data document reduced survival when left ventricular outflow (LVOT) obstruction is present. However, the potential effects of myectomy on long-term survival are unresolved.
Methods: Overall mortality was assessed in 1337 HCM pts evaluated between 1983-2001: (1) 289 consecutive pts underwent isolated surgical myectomy at Mayo Clinic for advanced symptoms attributable to LVOT obstruction; (2) 228 other pts with LVOT obstruction were managed without surgery; (3) 820 pts had nonobstructive HCM. Survival after myectomy was compared to age and sex matched general population, nonoperated obstructive pts, and nonobstructive pts.
Results: Patients were 45 ± 20 years old, 58% were males, LV wall thickness was 22 ± 6 mm, the average resting gradient was 68 ± 37mmHg among the pts with LVOT obstruction. Including 4 operative deaths (procedural mortality, 1.4%), survival after myectomy at 1, 5, and 10 years was 98%, 96%, and 83%, respectively. This survival did not differ statistically from the age and sex matched general population, nor the pts with nonobstructive HCM (98%, 95%, 88%). Myectomy pts had more favorable survival than nonoperated obstructive pts (90%, 80%, and 67%, log-rank p <0.0001). Multivariate Cox modelling with all relevant co-variates showed that myectomy (hazard ratio 0.20, p<0.0001) was independently associated with more favorable long-term survival.
Conclusion: Surgical septal myectomy performed for the relief of LVOT obstruction and severe drug-refractory symptoms is associated with long-term survival equivalent to that of an age and sex matched general population. Although these data are retrospective and nonrandomized, they strongly suggest that myectomy reduces the excess mortality risk associated with the presence of LVOT obstruction.

10:45 a.m.

839-2 Mechanism of Systolic Anterior Motion and Regurgitation Post Septal Ablation in Hypertrophic Cardiomyopathy

Francesca Nesta, Danita M. Yoerger, Michael H. Picard, Michael A. Fifer, Igor F. Palacios, Gus J. Vlahakes, Robert A. Levine, Judy Hung, Massachusetts General Hospital, Boston, MA

Background: Systolic anterior motion of the mitral valve (SAM) in hypertrophic cardiomyopathy (HCM) is secondary to both outflow tract narrowing and primary structural abnormalities of the mitral apparatus: the papillary muscles (PM) and leaflets are shifted anteriorly into the LV outflow path, causing SAM with regurgitation (MR). Clinical observations suggest that relief of obstruction by septal ablation (SAb) does not always cause resolution of SAM and MR. We tested the hypothesis that persistent SAM relates to malposition of the mitral apparatus, and that this finding can predict persistence of SAM. **Methods:** We reviewed echoes of 30 patients with HCM before and 3 months post SAb. We assessed anterior leaflet malposition by the antero-posterior projection of the coaptation point onto the mitral annular diameter (A/D ratio) in early systole. MR was assessed by proximal jet in the LAX view. **Results:** Most patients (22/30=73%) had SAM at 3 months despite successful SAb (gradient reduction > 50%), and had more anterior malposition and less MR reduction than those without SAM: A/D 0.44 vs 0.57, MR proximal jet reduction by 7% vs 51%, p < 0.0001. Anterior malposition was also present prior to SAb, with A/D < 0.4 being predictive of SAM post SAb (p<0.007). **Conclusions:** SAM and its related MR are not always eliminated by SAb. MV malposition is a strong determinant and predictor of SAM and MR reduction post SAb and may represent a new therapeutic target during ablation procedures.



11:00 a.m.

839-3 Frequency, Spectrum, and Phenotype of Hypertrophic Cardiomyopathy Patients With Multiple Sarcomeric Mutations

Sara L. Van Driest, Steve R. Ommen, Melissa L. Will, Vlad C. Vasile, Susan Chung, A. Jamil Tajik, Bernard J. Gersh, Michael J. Ackerman, Mayo Clinic, Rochester, MN

Background: Hypertrophic cardiomyopathy (HCM) is caused by pathogenic mutations involving 8 genes that encode critical proteins comprising the sarcomere. Here, we determine the frequency, spectrum, and phenotype associated with complex genetic status (i.e. > 1 sarcomeric mutation) in a cohort of unrelated patients (pts) evaluated at a tertiary outpatient HCM clinic.
Methods: DNA was obtained from 389 unrelated HCM pts and analyzed for mutations in myosin binding protein C encoded by *MYBPC3*, β -myosin heavy chain (*MYH7*), regulatory and essential light chains (*MYL2* and *MYL3*), troponin T (*TNNT2*), troponin I (*TNNI3*), α -tropomyosin (*TPM1*), and actin (*ACTC*) using polymerase chain reaction, denaturing high performance liquid chromatography, and DNA sequencing. Clinical data were extracted from pt records blinded to pt genotype.
Results: Of the 389 HCM pts, 151 (38.8%) harbored at least one putative pathogenic mutation. Eleven pts (2.8% of total and 7.2% of genotyped subset) had 2 putative sarcomeric mutations: compound *MYBPC3* in 2 pts, *MYBPC3* and *MYH7* (3), *MYBPC3* and *TNNT2* (2), *MYBPC3* and *TNNI3* (1), *MYBPC3* and *TPM1* (1), compound *MYH7* (1), and *MYH7* and *TNNT2* (1). When compared to pts with single sarcomeric mutations, or no sarcomeric mutations, pts with multiple mutations were younger at diagnosis (21.7 ± 11 years vs 36.4 ± 17 vs 45.1 ± 19, p <0.005, had greater hypertrophy (maximum left ventricular wall thickness = 24.6 ± 12 mm vs 22.8 ± 6 vs 20.7 ± 6, p <0.05), and more frequently received an ICD (36% vs 24% vs 10%, p = 0.0002). However, those with multiple mutations were not more likely to have had a surgical myectomy than those with a single mutation or no identifiable sarcomeric mutation.
Conclusion: This study represents a comprehensive mutational analysis searching for multiple genetic defects in a large HCM cohort from a single tertiary referral center. Complex genetic status was found in nearly 3% of HCM pts. On average, pts with multiple sarcomeric mutations were diagnosed 20 years earlier and displayed the greatest degree of hypertrophy. The possibility of multiple mutations involving the sarcomere adds further complexity to the development and implementation of clinical molecular genetic testing for HCM.

11:15 a.m.

839-4 Treatment With Antioxidant N-Acetylcysteine Reverses Interstitial Fibrosis in a Mouse Model of Human Hypertrophic Cardiomyopathy Mutation

Natalia Tsybouleva, Tripti Halder, Rajnikant Patel, Silvia Lutucuta, Gilberto De Freitas, Masakuni Ishiyama, Blase Carabello, Ali J. Marian, Baylor College of Medicine, Houston, TX

The genetic basis of human hypertrophic cardiomyopathy (HCM) is known but the pathogenesis of its phenotypes is unknown. We have generated transgenic mice by cardiac-restricted expressing mutant cardiac troponin T (cTnT)-Q92 protein, known to cause HCM in humans; which exhibits enhanced systolic function, interstitial fibrosis (IF) and myocyte disarray. Since oxidative stress is implicated in the pathogenesis of fibrosis, we tested whether treatment with anti-oxidant N-acetyl cysteine (NAC) could reverse or attenuate IF in the cTnT-Q92 mice. We performed a placebo-controlled study and randomized 24 mice to placebo or NAC (1g/Kg/d) and include 12 non-transgenic (NTG) mice as controls. We performed echocardiography prior to and after 16 weeks of therapy followed by histological and molecular characterization. Transgenic mice had higher left ventricular (LV) ejection fraction and smaller LV end systolic diameter and smaller heart weight/body weight (HW/BW) as compared to NTG mice at the baseline. No significant differences in the body weight, male/female ratio, mean age, and heart rates were present among the three groups. Treatment with NAC reduced concentrations of alondialdehyde and 4-hydroxy-2(E)-nonenal, indices of oxidative stress, in the left ventricular tissue (NTG: 3.0 ± 0.6; Placebo: 3.5 ± 0.4; NAC: 2.3 ± 0.3, p=0.01). Similarly, collagen volume fraction (CVF) was normalized (NTG: 3.4% ± 0.9; Placebo: 7.8 ± 1.7; NAC: 3.8 ±

1.4, respectively, p=0.003). HW/BW, LV wall thickness and myocyte disarray were unchanged with therapy. Levels of oxidized nuclear but not mitochondrial DNA was increased in the cTnT-Q92 mice and reduced to normal in the NAC group. Similarly, expression levels of signaling kinases p-ERK1/2 were increased in the cTnT-Q92 and normalized with NAC. Thus, treatment with anti-oxidant NAC reduces myocardial oxidative stress and normalizes IF in a mouse model of hypertrophic cardiomyopathy. The results in a genetic animal model of HCM, show the potential salutary effects of NAC in reversal of interstitial fibrosis, implicated in arrhythmogenesis, in HCM, which is the most common cause of sudden cardiac death in the young and a major cause of mortality and morbidity in elderly.

11:30 a.m.

839-5 Two Transgenic Animal Models Expressing Human Troponin T Gene Mutations: One Exhibiting Dilated Cardiomyopathy (W141) and the Other Exhibiting Hypertrophic Cardiomyopathy (Q92)

Jasvinder Sidhu, Duanxiang Li, Zhinong Wang, A.J. Marian, Francesco J. DeMayo, George E. Taffet, Robert Roberts, Baylor College of Medicine, Houston, TX

Background: The usual response of the heart is hypertrophy. Decompensation and subsequent heart failure often occurs after transition from hypertrophy to dilatation but appears to reflect an inhibition of growth. Troponin T (cTnT) mutations have been identified to cause familial hypertrophic cardiomyopathy (HCM) and others familial dilated cardiomyopathy (DCM). Thus, different mutations of the same gene induce different growth patterns. HCM is induced by cTnT Q92 and DCM by cTnT W141 mutations.
Methods: We generated a transgenic mouse (TM) expressing the cTnT Q92 mutation with a phenotype of HCM and a TM expressing the cTnT W141 with a phenotype of DCM using alpha MHC as the cardiac specific promotor.
Results: The HCM phenotype (cTnT Q92) has normal heart size with sarcomere disarray, fibrosis and an increased cardiac ejection rate 73.9 ± 9.4. In contrast, the DCM phenotype cTnT W141 has a large dilated heart without fibrosis but with decreased contractility. Echo analysis was normal at 4 weeks but at 12 weeks showed: Diastolic left ventricular dimension (LVD) in non-transgene (NT) was 3.68 ± .06 versus 4.77 ± .20 (p< .05) in TM; systolic LVD of 2.32 ± .09 in NT versus 4.01 ± .20 in TM; fractional shortening rate of NT was 0.37 ± .01 versus 0.16 ± .009 in TM; and peak ejection rate of 113 ± 5 in NT versus 84 ± 4 in TM. Gene microarray and northern analysis of myocardial gene expression in HCM and DCM were performed for markers associated with a hypertrophic growth response: Expression of IGF and ANP was normal in HCM and DCM. In contrast, skeletal alpha actin was decreased in HCM but increased in DCM. BNP normal in HCM was increased in DCM. GP130, increased in HCM was decreased 1 to 2 fold in DCM. Conclusion: GP130 a cytokine receptor claimed to be necessary for the hypertrophic growth response was down regulated in our DCM model and thus, may play a pivotal role in the lack of a hypertrophic growth response. Differential analysis of the GP130 pathway in the two models should determine whether this pathway is responsible for lack of the growth response in DCM.

11:45 a.m.

839-6 Role of Left Atrial Contractile Function in Functional Capacity of Patients With Hypertrophic Nonobstructive Cardiomyopathy

Yukitaka Shizukuda, Vandana Sachdev, Cynthia L. Brenneman, Charles W. Birdsall, Lameh Fananapazir, Jonathan F. Plehn, National Heart, Lung, and Blood Institute, Bethesda, MD

Background: Left atrial (LA) dilatation and reduced atrial contractile function have been demonstrated in symptomatic patients with hypertrophic, non-obstructive cardiomyopathy (HNCM), suggesting the presence of a primary atrial myopathy. Since LA contractile function partially governs left ventricular (LV) preload reserve and maintenance of the Frank-Starling mechanism, LA systolic dysfunction could provide a mechanism for exercise intolerance in HNCM. We, therefore, evaluated LA contractile function in 50 patients with HNCM (mean age=37±10 years, 29 men/21 women) with normal LVEF (mean=69±6%) who were stratified for symptoms of congestive heart failure. Methods: We analyzed LA volume normalized to body surface area, active atrial ejection fraction (LAEF), ejection force (LAF), and kinetic energy (LAKE), in asymptomatic (Group 1, n=19) and symptomatic (Group 2, n=31) subjects and compared these parameters to symptom-limited metabolic stress testing performed within one week of echocardiographic examination. Results: MRI-derived LV mass was similar between Groups 1 and 2 (mean=229 ±68 vs. 223 ± 78 gms, respectively, p=NS) and there were no differences in LAEF, LAF or LAKE in symptomatic versus asymptomatic subjects [59.8 ±19.9% vs. 60.6±22.8%, 14.7±8.7 vs. 15.6±11.2 (kdyne), 16.6±19.7 vs. 10.4±13.0 (kerg), respectively]. While resting LAEF correlated weakly with exercise time (r=0.319, p<0.05), it did not predict MVO2 or anaerobic threshold (p=NS for both). Neither were LAF nor LAKE associated with any objective exercise parameter. Maximum LA volume, an index of LA volumetric remodeling, was inversely correlated with peak MVO2 (r=-0.32, p<0.05). Conclusion: These data suggest that resting atrial contractile function is not a determinant of functional capcity in patients with HNCM. Possibly, atrial contractile reserve associated with exercise might be a more important factor for limitation of functional capacity in these patients.

ORAL CONTRIBUTIONS

842 Heart Failure and Anemia

Tuesday, March 09, 2004, 10:30 a.m.-Noon
Morial Convention Center, Room 257

10:30 a.m.

842-1 Anemia in Diastolic Heart Failure Is Frequent and Associated With Worse Outcome

Steffen Brucks, William C. Little, Tania Chao, Ronald L. Rideman, Bharathi Upadhya, Deborah Wesley-Farrington, David C. Sane, Wake Forest University School of Medicine, Winston-Salem, NC

Background: Many patients with heart failure (HF) and a reduced ejection fraction (EF) have anemia. The prevalence and importance of anemia in patients with HF and a normal EF (diastolic HF) are not known. Thus, we hypothesize that anemia is common in diastolic HF and associated with a worse outcome.
Methods: We evaluated 137 patients with clinical evidence of HF and a normal EF (> 0.50).
Results: The age was 65±15 (mean ± SD) years, and 58% were women. Anemia (hemoglobin, Hb, < 12 gm/dl in women; < 13 gm/dl in men) was common, occurring in 45% of patients. Patients with and without anemia had similar ages (65±15 vs 65±14), EF (0.62±0.08 vs 0.61±0.07), LV mass (213±77 vs 193±85 gms), and systolic mitral annular velocity (6.8±1.5 vs 6.9±2.1 cm/sec). Patients with anemia had a higher brain natriuretic peptide (BNP) (322±330 vs 160±240 pg/ml, p<0.001), worse diastolic dysfunction grade by mitral Doppler (1.3±8 vs 0.8±7, p<0.001), and a higher ratio of peak mitral inflow velocity to mitral annular velocity (E/E_M) (13.5±6.5 vs 9.7±4.2, p<0.001) compared to patients without anemia. Reduced Hb concentration correlated with both elevated BNP (r^2=0.15, p<0.0001) and E/E_M (r^2=0.15, p<0.0001). Patients with anemia had a reduced two-year cardiac hospitalization-free survival (hazard ratio 2.0, p<0.05)
Conclusion: Anemia is common in pts with HF and a normal EF (diastolic HF) and is associated with greater elevations in BNP, more severe diastolic dysfunction, and a worse prognosis.

10:45 a.m.

842-2 Hemoglobin Level Is Associated With Mortality and Hospitalization in Patients With Severe Chronic Heart Failure: Results From the COPERNICUS Study

Stefan D. Anker, Andrew JS Coats, Ellen B. Roecker, Paul Mohacsi, Jean Rouleau, Henry Krum, Armin Scherhag, Milton Packer, for the COPERNICUS study group, National Heart and Lung Institute, London, United Kingdom, Applied Cachexia Research, Charite, Berlin, Germany

Background: Anemia has been shown to be a risk factor for mortality in mild to moderate chronic heart failure (CHF), but its importance in severe CHF and its ability to predict hospitalization has not been defined.
Methods: We evaluated the relationship between hemoglobin level and mortality and hospitalization in 2286 patients (1822 men, 464 women) with severe CHF enrolled in the COPERNICUS study. All enrolled patients had dyspnea or fatigue at rest or on minimal exertion for at least 2 months and a left ventricular ejection fraction <25%.
Results: There was a highly significant (P<0.0001) but small (r = -0.089) inverse relationship between baseline hemoglobin and creatinine levels. Patients with low hemoglobin were at significantly higher risk of a major clinical events, the magnitude of risk decreasing with increasing hemoglobin, both in univariate analyses (all P<0.001) and in multivariate analyses which adjusted for sex and other predictors of risk, including age, left ventricular ejection fraction, creatinine, body mass index, systolic blood pressure, CHF etiology and treatment with carvedilol (all P<0.01). Mean creatinine levels and one-year Kaplan-Meier event rates are shown below:
Conclusion: Low hemoglobin is an independent risk factor for adverse outcomes in patients with severe HF. Whether correction of anemia improves outcomes in CHF warrants further study.

Table

Hemoglobin(g/dL)	N	Creatinine (µmol/L)	All-Cause Mortality (%)	Death or HF Hospitalization (%)	Death or Any Hospitalization (%)
<11.0	115	151.5	23.2	46.6	64.1
11.0 - <12.5	315	135.8	16.7	36.1	51.0
12.5 - <13.5	432	133.2	13.5	30.5	48.3
13.5 - <15.0	834	132.7	15.6	31.9	45.5
15.0 - 16.5	463	131.2	13.1	26.5	42.9
>16.5	127	131.5	9.0	25.5	38.0