1135-145 **Preoperative Diagnosis of Diabetes Affects Long-Term Outcome in Patients After Heart Transplantation**

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Background. To compare long-term outcome in patients with and without diabetes at the time of heart transplantation.
Methods. A retrospective analysis of 773 consecutive adult patients who underwent primary heart transplantation from 1986 through 2000 was conducted. The total population consisted of 633 patients without diabetes (male n=532; 84%) and 140 patients with diabetes (male n=115; 82%).
Results. Long-term survival rates of patients with diabetes mellitus were lower as compared with patients without (w/o) diabetes mellitus (survival at 10 years with diabetes: 40% vs. w/o diabetes: 58%; log-rank=0.025). Both patient groups showed the same incidence of angiographically documented transplant coronary artery disease-TxCAD (TxCAD at 10 years with diabetes: 28% vs. w/o diabetes: 22%; n.s.). Patients with diabetes were older as compared with patients w/o diabetes (with diabetes: 54.9±6.8 vs. w/o diabetes: 49.7±10.8a, p=0.0001) and showed a higher incidence of coronary artery disease as indication for transplantation as compared with patients w/o diabetes (with diabetes: 52% vs. w/o diabetes: 30%; p=0.0001). In multivariate regression analysis, the presence of diabetes at the time of transplantation (HR 1.594; 95%CI 1.009-2.518; p=0.045) as well as the use of thymoglobulin induction therapy (HR 0.476; 95%CI 0.319-0.710; p=0.0003) were independent predictors affecting long-term survival. Female gender (HR 0.075; 95%CI 0.010-0.538; p=0.012) as well as thymoglobuline antibody induction therapy (HR 0.586; 95%CI 0.359-0.957; p=0.033) were independent predictors affecting the development of TxCAD. Interestingly, diabetes did not exhibit any influence on the occurrence of TxCAD.
Conclusion. The diagnosis of diabetes at the time of transplantation adversely affects long-term survival but not the occurrence of transplant coronary artery disease. The major limitation for patients with diabetes seems to be advanced age and a higher incidence of coronary artery disease resulting in an impairment of global organ function and consecutively, in a diminished physiologic reserve.

FEATURED ORAL PRESENTATION

838FO Featured Oral Session...Ventricular Hypertrophy/Remodeling

Monday, March 18, 2002, 4:00 p.m.-5:30 p.m.
Georgia World Congress Center, Room 267W

4:15 p.m.

838FO-2 **Temporal Evolution of Molecular, Functional, and Structural Phenotypes in a Transgenic Rabbit Model of Human Hypertrophic Cardiomyopathy**

Sherif F. Nagueh, Natalia Tsyboulev, Rajnikant Patel, Helen A. Kopelen, Tripti Halder, Silvia Lutucuta, Lorraine Salek, William A. Zoghbi, Miguel A. Quinones, Mark Entman, Robert Roberts, Ali J. Marian, *Baylor College of Medicine, Houston, Texas.*

Hypertrophic cardiomyopathy (HCM) is a genetic disease with protean clinical and pathological phenotypes including left ventricular hypertrophy (LVH), myocyte disarray (MD), interstitial fibrosis (IF), heart failure, and sudden death. Slow evolution of phenotypes hampers determination of their temporal sequence in humans. We developed transgenic rabbits by cardiac-specific expression of βmyosin heavy chain-glutamine (MyHC-Q)403, known to cause HCM in humans. Transgenic rabbits exhibit LVH, MD, IF, and myocardial dysfunction. We determined temporal evolution of molecular, functional, and structural phenotypes in the βMyHC-Q403 rabbits by performing serial M-mode, 2-D, Doppler echocardiography and tissue Doppler imaging, histological staining of myocardial sections, and immunoblotting for hypertrophic signaling kinases in 36 β-MyHC-Q 403 and 35 non-transgenic rabbits at <6 (pre-puberty), 6-24 (adulthood), >24 (old) months of age. Compared to control rabbits, LV wall thickness increased progressively in the βMyHC-Q^{403} rabbits (septal thickness: 2.4±0.2, 2.8±0.5, and 3.1±0.4, respectively, p<0.001). End diastolic and end systolic diameters were increased and fractional shortening reduced progressively (p<0.05). Doppler indices of LV filling pressure and left atrial size were also increased progressively (<0.05). Myocardial contraction and relaxation velocities were decreased in βMyHC-Q403, compared to controls, in all three age groups. IF increased progressively with aging (2.7 ± 1.2, 7.6 ± 4.7, and 9.0 ± 1.7%, p=0.005). Myocyte disarray was present early and did not change with aging (9.0 ± 4.2, 11.8 ± 3.8, 10.6 ± 4.0%). Myocardial velocities were reduced even in the absence of IF and MD. Expression of active but not ERK1/2 was increased in 6-24 months old rabbits. Expression levels of active and total p38, JNKs, and GTP bound Ras, Rac1 and Rho1 were unchanged. Thus, myocardial dysfunction occurs early and in the absence IF and MD. Disarray precedes LVH and IF, which are progressive. Preserved global systolic function evolves into progressive systolic dysfunction with LV and left atrial enlargement and increased filling pressures.

4:30 p.m.

838FO-3 **Volume Overload-Induced Cardiac Remodeling Is Exaggerated in Mice With Homozygous Deletion of the Atrial Natriuretic Peptide Gene**

Ji An Feng, Gilbert J. Perry, Suzanne Oparil, Yiu-Fai Chen, Tatsuhiko Mori, Tetsuya Hayashi, Yasushi Kitaura, *University of Alabama at Birmingham, Birmingham, Alabama, Osaka Medical College, Japan.*

Previous studies of the pathogenesis of cardiac enlargement in mice with homozygous deletion of atrial natriuretic peptide (ANP-/-) or the type-A natriuretic peptide receptor gene (Npr1-/-) have been confounded by concomitant elevations in blood pressure (BP) in ANP-/- and Npr1-/- animals when fed standard diets. To test the hypothesis that deletion of the ANP gene alters cardiac structure at baseline and in response to volume overload stress independent of BP, male ANP-/- mice and control wild type ANP+/+ mice were fed a low (0.05%) NaCl diet beginning at weaning. Mean arterial pressure (MAP) measure in conscious mice was not significantly different between genotypes (100.3±2.7 mmHg, n=9, in ANP-/-; 94.4±3.7 mmHg, n=10, in ANP+/+). After 5 weeks on the low NaCl diet, mice underwent placement of an aorto-caval fistula (ACF) or sham surgery (Sham) and were subjected to echocardiographic examination at 2 wks. ACF shunting assessed by a microsphere technique was similar in ANP-/- and ANP+/+ mice. Hearts were weighed and subjected to electron microscopic examination. Results (means±SEM, n=4-5) were shown in Table. These findings indicated that ANP deletion results in biventricular enlargement and an exaggerated response to volume overload (ventricular enlargement, increased myocyte diameter and myofibrillar lysis) independent of BP. This supports the hypothesis that ANP has direct antihypertrophic and cardioprotective actions in heart.

	Sham		ACF		
	ANP-/-	ANP+/+	ANP-/-	ANP+/+	
WH (mg)	136.3±12.4*	72.5±3.9	267.0±16.6#*	152.0±14.2 #	<0.01
LVEDD(mm)	3.0±0.1	3.1±0.1	4.8±0.2#*	4.2±0.2#	0.04
LVESD (mm)	1.5±0.1	1.7±0.1	2.6±0.2#*	2.1±0.2#	0.07
WT(mm)	1.2±0.0	1.1±0.1	1.7±0.2 #*	1.3±0.1	0.09
MD (mm)	19.3±0.1*	16.0±0.8	26.9±0.6#*	21.2±1.5#	0.21
ML	1+	0	4+	1+	

WH - whole heart weight, LVEDD - left ventricular (LV) end diastolic dimension, LVESD - LV end systolic dimension, WT - LV wall thickness, MD - myocyte diameter, ML - myofibrillar lysis. # p<0.05 vs. respective Sham groups. * p<0.05 vs. respective ANP+/+ groups, AxG - p value, interaction between ACF x Genotype by 2 way ANOVA

4:45 p.m.

838FO-4 **Disruption of Leptin Signaling Contributes to Cardiac Hypertrophy Independently of Body Weight**

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Introduction: Left ventricular hypertrophy (LVH), which is common in obesity, likely results from increased mechanical load, although neurohormonal signaling may participate as well. Abnormal regulation of leptin, a neurohormone essential to energy homeostasis, is implicated in the pathogenesis of obesity. Because leptin also has cardiovascular bioactivity, we tested the hypothesis that it may protect the heart from LVH.
Methods: We measured left ventricular (LV) wall thickness (VWT) and LV mass (LVM) with echocardiography in transgenic mice lacking leptin (*Ob/Ob*, *n*=15) or its receptor (*Db/Db*, *n*=10), and littermate controls at 2, 4, and 6 months of age and after 4-6 weeks of weight loss.
Results: All mice had similar VWT and LVM at 2 months. Obesity developed by 6 months in both *Ob/Ob* (67±3 *vs.* 36±3 g, *P*<0.0001) and *Db/Db* (62±7 *vs.* 37±5 g, *P*<0.0001) mice *vs.* controls. At 6 months, LVH developed in both *Ob/Ob* (VWT 0.75±0.02 *vs.* 0.56±0.01 mm, *P*<0.0001; LVM 91±4 *vs.* 64±3 mg, *P*<0.0001) and *Db/Db* (VWT 0.80±0.03 *vs.* 0.58±0.01 mm, *P*<0.0001; LVM 105±9 *vs.* 77±4 mg, *P*<0.01) *vs.* controls. To separate the direct contribution of leptin deficiency from the mechanical effects of excess body weight, we induced weight loss in 6-month-old *Ob/Ob* mice either by exogenous leptin infusion (0.3 mcg/g/day via subcutaneous osmotic pump, *n*=5) or caloric restriction (*n*=5). Mice in both leptin and diet groups (33±3 g *vs.* 37±1 g, respectively, *P*=NS) lost similar weight compared to control (placebo infusion and food *ad libitum*, *n*=5; 75±2 g, *P*<0.0001 *vs.* both weight loss groups). Leptin infusion completely reversed LVH (VWT 0.58±0.01 *vs.* 0.81±0.02 mm, *P*<0.001; LVM 70±4 *vs.* 96±3 mg, *P*<0.005) *vs.* control. In marked contrast, calorie-restricted mice had no regression of LVH (VWT 0.78±0.01 mm; LVM 104±13 mg, *P*=NS *vs.* control for both) despite similar weight loss.
Conclusion: Together these data show the effect of leptin on LV architecture is not due to weight loss alone, and suggest that leptin has direct anti-hypertrophic effects on the heart. Disruption of leptin signaling may represent a novel mechanism in the development of LVH and related cardiovascular disorders.