887 Cellular and Molecular Modifications in Cardiomyopathy: Ischemic and Nonischemic

Wednesday, April 1, 1998, 10:30 a.m.–Noon
Georgia World Congress Center, Room 257W

10:30

887-1 Different Cellular Mechanisms Account for Ventricular Dilatation in Ischemic and Idiopathic Dilated (DCM) Human Heart Failure

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Background: Controversy exists as to the contribution of increase in myocyte length and relative slippage of myocytes in left ventricular (LV) chamber dilatation and wall thinning in end-stage human heart failure. A mechanism purely involving increase in cell length would potentially preserve normal myocyte topography and permit reversibility of ventricular dilatation.

Methods: Human LV myocardium from control (n = 4) and explanted end-stage failing hearts of patients with ischemic heart disease (n = 5) or DCM (n = 8) were compared. Confocal microscopy of transversely sectioned tissue immuno-labeled for connexin43 was used to identify intercalated discs and cell profiles. The proportion of total myocyte profiles with identifiable discs is inversely proportional to cell length, and thus provided an indirect measure of corresponding cell length. Values were expressed relative to control tissue. Cell length was correlated with corresponding echocardiographic measurements of LV diameter (LVEDD).

Results: There was a significant increase of 59% in *cell length* in DCM, although there was no change in the long dimension in myocytes in the corresponding tissue from ischaemic dilated hearts (3% increase in cell length); Kruskall-Wallis Test $p < 0.01$. Regression analysis of the paired data of cell length and corresponding LVEDD showed a strong correlation in the case of DCM, with a sample regression coefficient (r) of 82.3%, $p = 0.002$, $n = 11$. There was no significant correlation in the ischemic cardiomyopathic tissue; $r = 33.6$, $p = 0.377$ (ns), $n = 8$.

Conclusions: These results indicate that a high proportion of ventricular dilatation in DCM can be accounted for by increased myocyte length with minimal cell slippage. In contrast, ischemic hearts failure occurs with minimal changes in myocyte length suggesting myocyte slippage as the predominant mechanism.

10:45

887-2 The Cardiac Troponin T Phe110Ile Mutation Shows Phenotypic Heterogeneity and Benign Prognosis

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Background: Familial hypertrophic cardiomyopathy (FHC) can be caused by a mutation in the cardiac troponin T (cTnT) gene. Six mutations in the cTnT gene (Ile79Asn, Arg92Gln, Arg92Trp, Ala104Val, ΔGlu160, Intron15$G_1 \rightarrow A$) were characterized by high incidence of sudden death. However, clinical characteristics and prognosis of the Phe110Ile mutation are not known. We studied 6 families with the Phe110Ile mutation in the cTnT gene.

Methods: Forty-six probands (24 males, 22 females, mean age 58 ± 17 yrs) with FHC were screened for mutations in the cTnT gene. The Phe110Ile missense mutation was found in 6 probands. The 6 families were analyzed genetically and clinically. According to classification of Maron et al., distribution of left ventricular hypertrophy was classified into type I, II, III and IV. Kaplan-Meire survival curve was constructed and compared with those of other mutations.

Results: Sixteen (5 males, 11 females, mean age 48 ± 17 yrs) were affected with the Phe110Ile mutation. Distributions of hypertrophy were type II in 4, type III in 6 (1 with left ventricular outflow obstruction), type IV in 3, and nonpenetrance in 3. The distributions of hypertrophy varied within each family, and among families. Disease related death was seen in 2 individuals. The product-limit survival curve showed a benign prognosis with a survival significantly longer than the reported malignant cTnT mutations ($P < 0.01$).

Conclusions: The Phe110Ile mutation in the cTnT gene shows phenotypic heterogeneity and benign prognosis.

11:00

887-3 Association of Polymorphisms of Manganese Superoxide Dismutase and Plasma Platelet-activating Factor Acetylhydrolase Genes With Genetic Susceptibility to Non-familial Dilated Cardiomyopathy

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Background: Although several genes or genetic loci that are responsible for, or confer susceptibility to, familial dilated cardiomyopathy (DCM) have been identified, genetic defects that underlie non-familial DCM remain to be characterized. Mice lacking manganese superoxide dismutase (MnSOD) exhibit DCM, suggesting that impairment of the defense mechanisms against the oxidative stress is an important susceptibility factor for DCM.

Method: We studied 158 healthy individuals and 93 patients with non-familial DCM. The association of alleles of the MnSOD and plasma platelet-activating factor (PAF) acetylhydrolase genes with non-familial DCM has now been investigated.

Results: The frequencies of the mutant *T* allele of the MnSOD gene ($p = 0.041$; odds ratio, 1.9) and the mutant *m* allele of the plasma PAF acetylhydrolase gene ($p = 0.006$; odds ratio, 1.9) were significantly higher in Japanese individuals with non-familial DCM than in healthy controls. Combined genotype analysis revealed that the association of the MnSOD *TT* and plasma PAF acetylhydrolase *mm* or *Mm* genotypes with DCM was highly significant ($p = 0.0002$, odds ratio, 3.1).

Conclusion: The polymorphisms of the MnSOD and plasma PAF acetylhydrolase genes are associated with non-familial DCM in Japanese and that these polymorphisms may contribute to genetic susceptibility to this condition.

11:15

887-4 Marked Acceleration of Cardiac Endothelin-1 (ET-1) Expression Is Involved in Myocardial Growth in Bio 14.6 Syrian Cardiomyopathic Hamster

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Background: ET-1 is a potent vasoconstrictive and growth-promoting peptide and may be involved in the development of secondary cardiac hypertrophy. We have previously reported that the plasma ET-1 levels in hypertrophic cardiomyopathy patients with normal pulmonary hypertension are elevated and closely associated with myocyte diameter in endomyocardial biopsy specimens. This study was aimed to further clarify a role of ET-1 in primary myocardial disease.

Methods: We investigated the tissue level of ET-1 using specific enzyme linked immnosorvant assay (ELISA) in Bio 14.6 Syrian hamsters (Bio). In this ELISA, cross-reactivity with big ET-1 was less than 0.1%. In addition, we examined the effect of chronic treatment with oral ET-1 type A receptor antagonist, T0201 on myocardial growth in this animal model.

Results: ET-1 levels in left ventricles were not increased in 5 week-old (wo) Bio compared with control F1B hamster (F1B). However, the levels were 1.8-fold higher ($p < 0.05$) in 20 wo Bio and 6.4-fold higher ($p < 0.0001$) in 35 wo Bio than in F1B. Immunohistochemistry demonstrated that the elevated levels of ET-1 is localized to cardiac myocytes. T0201 inhibited the increase of the heart weight (HW) in Bio (Bio + vehicle: 502 ± 17 mg, Bio + T0201: 424 + 8 mg, $p < 0.05$). However, T0201 did not affect HW increase in F1B. Myocytes diameter was significantly smaller in T0201-treated Bio (16.5 ± 1.3 μm) than in vehicle-treated Bio (19.1 ± 2.0 μm)($p < 0.005$).

Conclusion: Marked acceleration of cardiac ET-1 expression may be involved in myocardial growth in this animal model.

11:30

887-5 Do Isolated Myocytes From the Remodeled Rat Infarct Heart Demonstrate Diminished Contractile Response?

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We have recently shown that unloaded cardiac myocytes, from the remote non-infarcted, hypocontractile regions of remodeled rat hearts, contract normally. Since load is an important determinant of contractile response, we investigated the effects of viscous loading on the contractile function (video edge detection) of 268 myocytes isolated from the remodeled myocardium of infarcted (MI) rat hearts, (n = 7, 6 weeks Post-MI) and compared them with 288 cells from age matched sham operated hearts (Sham; n = 7). Viscosity of the myocyte suspension buffer was varied by adding inert methyl cellulose [4 mM Ca2+; 1, 15, 200 & 300 centipoise (cp)]. Buffer perfused MI hearts had