Japanese Circulation Society

Heart Failure- Basic: Role of Extracellular Matrix (M)

FRS23

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Room 8
(Fukuoka International Congress Center/4F/404～406)

13:30—16:00

Keynote Lecture

Heart Failure Basic: Role of Extracellular Matrix and Myocyte Degeneration

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The mode of progression from compensated hypertrophy to heart failure (HF) is still a matter of debate. We investigated patients with isolated valvular aortic stenosis (AS) and differing degrees of LV systolic dysfunction to test the hypothesis that structural remodeling as well as cell death contribute to the transition to heart failure (HF). Morphological changes were studied in LV myectomies from 3 groups of patients (I: EF>50% II: EF 30-50%, III: EF< 30%) undergoing aortic valve replacement (AVR) and compared to normal human LV tissue. An increase in the degree of fibrosis (2.3, 2.2 and 3.2-fold over control in the 3 groups) was the earliest sign of structural remodeling. ACE positive capillaries were threefold increased in all groups and TGF-β in fibroblasts was 2-3 times elevated indicating participation in the pathogenetic mechanism of fibrosis. Low-grade inflammation was present. Myocyte hypertrophy was evident and myocyte degeneration (MD) increased significantly over control, but occurred later than fibrosis. Cell death by ubiquitin-related autophagy and by oncosis were the decisive mechanisms for myocyte loss. Apoptosis was barely detectable. Mitosis was absent. An excellent correlation exists between EF or LVEDP and MD or fibrosis and the degree of postoperative recovery. **Conclusions:** These structure-function-correlations confirm the hypothesis that transition to HF occurs first by fibrosis and later by myocyte degeneration. Therefore, the decision for surgical intervention should take into account that complete postoperative recovery after AVR is dependent on the degree of preoperative structural alterations.

FRS-222

NRSF Is Involved in Molecular Pathways for Sudden Death Associated with Heart Failure

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Introduction: Recently we showed that a transcriptional repressor, NRSF, represses expression of multiple fetal cardiac genes including ANP, BNP and α-skeletal actin, and attenuation of NRSF-mediated repression contributes to their induction during cardiac hypertrophy. In this study, we examined the role of NRSF in vivo using transgenic (Tg) mice carrying a dominant-negative mutant NRSF (dnNRSF) in the heart. **Method:** A construct containing dnNRSF fused to α-MHC promoter was used for the generation of Tg mice. **Results:** The dnNRSF Tg hearts showed increased expression of ANP, BNP and α-skeletal actin genes and displayed dilated cardiomyopathy and sudden death. Continuous ECG monitoring revealed that dnNRSF Tg mice exhibit a variety of arrhythmias that are observed in the human cardiomyopathic hearts; second degree AV block and ventricular ectopies including ventricular tachycardia (VT). In addition, sustained VT and ventricular fibrillation followed by asystole were recorded at the time of death in dnNRSF Tg mice. In vivo intracardiac electrophysiological study showed dnNRSF Tg to be more vulnerable to VT than non-Tg. We found that the expression of several ion channel genes encoding fetal ionic currents are under control of NRSF and are activated in dnNRSF Tg ventricle. **Conculusion:** NRSF, a transcriptional regulator of cardiac fetal gene program, may play a key role in common molecular pathways leading to heart failure and sudden cardiac death.

FRS-223

Cardiac Nuclear Hyper-Acetylation by Inhibiting Histone Deacetylase Facilitates Left Ventricular Remodeling Following Myocardial Infarction in Adult Mice *in Vivo*

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Histone acetyltransferase (HATs) and histone deacetylases (HDACs) govern gene expression patterns by being recruited to target genes through association with specific transcription factors. While HDACs in cardiac myocytes act as signal-responsive suppressors of transcriptional program governing hypertrophy and heart failure, HATs, such as p300, act as coactivators of hypertrophy-responsive transcriptional factors such as MEF-2 and GATA-4. Our recent study shows that p300-mediated acetylation plays a role in myocyte growth in response to hypertrophic stimuli. However, it is unknown whether cardiac nuclear acetylation might be involved in left ventricular (LV) remodeling following myocardial infarction (MI) *in vivo*. To solve this problem, following MI or sham operation, 12-week-old mice were subjected to daily intraperitoneal injection of 1mg/kg of trichostatin A (TSA), a specific HDAC inhibitor, or 10%DEMSO for 4 weeks. Echocardiography showed that TSA-treatment altered neither LV size nor function in the sham-operated group. In contrast, in the MI-operated group, TSA-treatment induced more progressive LV remodeling, exemplified by lower LV ejection fraction and larger LV dimension. Immunohistochemistry revealed that MI induced cardiac nuclear hyper-acetylation and up-regulation of cardiac β-myosin heavy chain, both of which were further potentiated by TSA-administration. These findings demonstrate that cardiac nuclear hyper-acetylation plays a role in LV remodeling following MI, which is further exaggerated by inhibition of HDACs in adult mice *in vivo*.

FRS-224

Final Common Pathway of Dystrophin Disruption in Advanced Heart Failure of Both Hereditary and Acquired Origins

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Background: Dystrophin(Dys) in collaboration with Dys-related proteom (DRP) stabilizes sarcolemma(SL) with inhibitingexcessive expansion during the repeated systole. We evaluated degradation process of Dys, using hereditary DCM hamsters (TO-2)with δ-SG gene mutation or catecholamine toxicity secondary to isoproterenol (ISP) overdose in rats. **Methods and Results:** After confirming LV failure by cardiac catherization of TO-2 hamsters at 20-40 weeks old, the heart was fixed. Immunostaining revealed that, in TO-2 hamsters, Dys was translocated from SL to myoplasm, while Dys in normal hamsters were homogeneously preserved on SL. The)*i.v.* preinjection of membrane-inpermeable fluorescent Evans blue showed intracellular deposit of the dye, indicating the increment of SL permeability. Double fluorescence microscopy revealed that Dys-disrupted cells completely matched with Evans blue-positive cells. Western blot analysis indicated the increment of multiple bands of Dys in TO-2 hamsters around 150, 97 and 45KDa at 20 and 40 weeks old. Furthermore, over administration of Isp (10mg/kg, *i.p.*) torats caused cell degradation at 4-24 hours in subendocardial myocardium, showing the similar features of translocation and fragmentation of Dys to TO-2 hearts. Double fluorescence microscopy of Dys and Evans blue also denoted the coincidence of bothcardiomyocytes. **Conclusions:** These results suggest that Dys disruption is a final common in advanced heart

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