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chemiluminescence significantly increased in the failing heart compared with the normal (Normal 17.0RLU/wt/min, HF 62.6RLU/wt/min, $P<0.01$). NADPH oxidase activity also significantly increased in the failing heart compared with the normal (Normal 629.8RLU/drywt/min, HF 3044.9RLU/wt/min, $P<0.01$), which was inhibited by apocynin, a NADPH oxidase inhibitor. Moreover, the expression of the NADPH oxidase subunits, p22phox, p47phox, p67phox and rac2 mRNA significantly increased in the failing heart compared with the normal. Those indexes were negatively correlated to LV ejection fraction and volume. In conclusion, the activity and expression of NADPH oxidase were increased in the failing heart, suggesting that NADPH oxidase may contribute to cardiac dysfunction by the increased oxidative stress in HF.

PJ-225

Tropomyosin as One of the Earliest Target of Apoptotic Proteolysis Facilitating Cytoskeletal Catastrophe in Cardiac Myocytes

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An apoptotic cell shows dynamic structural alterations, which are accompanied by disassembly of cytoskeletal and nuclear scaffold as the result of apoptotic proteolysis. The specialized proteases are well investigated, representatively caspases. In contrast, the target proteins of cellular components have been elucidated to the lesser extent. Adult cardiac myocytes, despite their extremely specialized structure in which well-developed cytoskeletons are tightly compacted, also undergo apoptosis within a short period. It is thus assumed that some exquisite mechanisms for efficient execution of apoptosis must be included, which degrade the stout structure of this cell type. Apoptosis was induced in isolated adult rat ventricular myocytes by activation of β-adrenergic pathway with isoproterenol (10^{-5} M). Apoptosis was evident, as documented by DNA fragmentation and the typical ultrastructure. It was shown that tropomyosin was one earliest (as early as 3 hours) target of proteolysis in this apoptosis by confocal microscopy and Western blot findings. Breakdown of tropomyosin, which is not only a constituent of the Z discs but also keeps actin filamentous form in the thin filament, accompanied breakdown of both the Z discs into pieces and myofibrilar striation. Such changes progressed from the edges towards the center of the cells. Thus, the early breakdown of tropomyosin seems an exquisite and efficient trigger to facilitate the subsequent catastrophe of cytoskeletons of cardiac myocytes.

PJ-226

Nicorandil promotes coronary capillary formation via VEGF and suppresses the transition to heart failure in Dahl salt-sensitive hypertensive rats

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Background: Impaired coronary microcirculation in hypertrophic myocardium contributes to myocardial ischemia and plays an important role in the transition to heart failure (HF). We hypothesized that nicorandil could promote coronary capillary formation and suppress the transition to HF. **Methods:** When fed a high-salt diet from 6 weeks of age, DS rats establish compensated LVH at 11 weeks followed by decompensated HF at 18 weeks. Nicorandil (6mg/kg/day) was orally given to DS rats from 11 to 18weeks. DS rats given a low-salt diet served as controls. At 18 weeks, all rats were killed, and the hearts were removed and subjected to further analysis. **Results:** Untreated DS rats showed significant increases in the ratio of LV weight to tibial length and the lung weight to tibial length compared with controls. ANP, BNP and β-MHC mRNAs were significantly increased in DS rats. Treatment with nicorandil significantly decreased these genes and suppressed the development of HF. Intramyocardial capillary density was similar between untreated DS rats and controls. However, this index was significantly increased by nicorandil. VEGF and eNOS mRNAs were markedly decreased in untreated DS rats. Nicorandil significantly increased these genes. **Conclusions:** Nicorandil promotes coronary capillary formation via VEGF and suppresses the transition to HF in DS rats. Nicorandil may be beneficial for the treatment of hypertensive HF as well as ischemic heart disease.

PJ-227

Different anti-ischemic heart failure effect of L-arginine or tetrahydrobiopterin and nitrate through their effects on ischemia-induced oxidative stress generation

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Nitric oxide (NO) supplementation relieves angina, but it is controversial whether it attenuates heart failure due to ischemia (IHF). To assess our hypothesis that the effects on reactive oxygen spieces (ROS) generation as well as on NO donation may be the key to alleviate IHF by NO supplementation, we administered vehicle (n=70), L-arginine (LA: n=58), tetrahydrobiopterin (BH4: n=38), isosorbide dinitrate (ISDN: n=98) or vitamin C (VC: n=41) (100, 10, 10-30, 100mg/kg/day, respectively) orally for 4 weeks in a rat coronary stenosis-induce IHF model by Yaoita (Circulation 2002). We assessed left ventricular (LV) function by echo, LV perfusion by microspheres, coronary endothelial NO function by the in vitro MVO2 method, urinary excretion of NOx, cGMP, serum ascorbyl free radical (AFR)/VC ratios by ESR, and myocardial O2- generation by fluorescent microscopy. At comparably increased urinary cGMP and NOx excretions, LA and BH4 ($p<0.01$) but not ISDN decreased AFR/VC (10.4 ± 2.9, 8.0 ± 0.5, 20.4 ± 2.3 vs 21.7 ± 4.3 in vehicle), improved NO function and perfusion, and attenuated IHF, and their LV ejection fractions were negatively correlated ($p<0.01$) with AFR/VC (LVEF=1.1-0.04 × AFR/VC, r=0.50). Among three therapies, only ISDN failed to reduce O2- generation. Coadministration of VC with ISDN (n=38) improved LV perfusion and function. Thus, NO supplementation with L-arginine or BH4 attenuates coronary stenosis-induced HF whereas ISDN alone does not partly through differential effects on ROS generation in ischemia.

PJ-228

Protein Phosphatase Dysregulation and Its Effect on Phosphorylation of Ca^{2+} Regulatory Proteins in Hamster Cardiomyopathy

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Although increase in protein phosphatase (PP) activity and subsequent dephosphorylation of Ca^{2+} regulatory proteins is proposed to depress cardiac function in heart failure, the pathophysiological role of PP has not been fully characterized. We investigated time courses of PP activity, protein kinase A (PKA) activity and phosphorylation levels of Ca^{2+} regulatory proteins with progression of hamster cardiomyopathy and aging. PP1, PP2A and PKA activity and phosphorylation of ryanodine receptor (p-RyR) and phospholamban (p-PLN) were assessed at 6, 10 and 28 weeks (wk) of age in cardiomyopathic (CMH) and age-matched normal hamsters (NH). PP1 and PKA activity were well-correlated and decreased with aging in NH, whereas PP1 progressively increased in CMH and maximized at 28 wks compared to relative decrease in PKA activity. Increase in PP1 activity may be partially explained by increased cytosolic PP1 β expression. Increased phosphorylation in PLN and RyR was paralleled in all ages of CMH but those changes were relatively smaller than its age-dependent alteration, suggesting hyper phosphorylation event is relatively minor in this model. Chronic administration of selective β 1-blocker metoprolol, futher increased phosphorylation of PLN and RyR together with increased PKA and PP1 activity. These data suggest that increased PP1 activity is a counter mechanism in compensating cardiomyopathy progression, whereas its dominance to PKA activity may be associated with heart failure decompensation.