Regional Desensitization of β-Adrenergic Receptor Signaling in Swine With Chronic Hibernating Myocardium

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Background: Contractile reserve to submaximal β-adrenergic stimulation is attenuated in patients and swine with hibernating myocardium and the blunted contractile response is not related to metabolic evidence of ischemia. This study tested the hypothesis that there is an attenuation of β-adrenergic signaling arising as a regional adaptive response in hibernating myocardium.

Methods & Results – Pigs (n=8) with chronic hibernating myocardium were studied 3-months after instrumentation with a chronic LAD stenosis. At the time of study, resting subendoocardial flow (LAD 0.7±0.2 vs. 1.2±0.1 ml/min/g in normal, p<0.05) and regional LAD wall thickening (LAD 1.9±0.5 vs. 5.5±0.4 mm in normal, p<0.05) were reduced in the absence of infarction. We assessed regional β-adrenergic responsiveness in subendocardial membrane fractions from hibernating LAD vs. normally perfused remote region (shunt depilation in the border zone). TSP-1 +/- mice had significantly higher collagen (LAD 97±13 vs. 81±8 mlg/ml in normal) but there was shift from a 2-state (high and low-affinity) model (Ki: 775±288 pm and 0.9±0.6 µM) to a low-affinity β-adrenergic receptor state in hibernating myocardium (Ki: 0.5±0.4 µM). The proportion of β1 receptors was unchanged (LAD: 79±1 vs. 75±3 % in normal), Western analysis demonstrated normal levels of adenylyl cyclase and no alterations in G-protein receptor kinase 2 and 5. Interestingly, there were reciprocal changes in G-proteins with an increase in Gi and reduction in Gq in hibernating myocardium. These changes were associated with reduced isoproterenol and Gpp(NH)p stimulated cAMP accumulation while basal forskolin stimulated responses were unchanged.

Conclusion – These data support the notion that there is a regional attenuation of β-adrenergic receptor adenylyl cyclase coupling in hibernating myocardium that may lead to attenuated contractile reserve when myocardial viability is present. The observations support the notion that intrinsic adaptations in hibernating myocardium serve to protect the regional circulation from a myocardial supply/demand imbalance when external determinants of myocardial workload increase during sympathetic activation.

The Critical Role of Thrombospondin (TSP)-1 in Limiting Expansion of Fibrosis in Healing Myocardial Infarcts: Studies in Dogs and TSP-1 -/- Mice

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Background: Healing of a myocardial infarct depends on suppression of the inflammatory response after scar formation and prevention of its expansion to normal areas. We observed that expression of Thrombospondin (TSP)-1, a potent inhibitor of angiogenesis and activator of TGF-β, is localized in the border zone of healing canine infarcts and hypothesized that it may suppress the inflammatory response, inhibiting local angiogenesis and limiting expansion of fibrotic tissue to the non-infarcted area.

Methods: A canine and a murine model of reperfused myocardial infarction were used. Methods: Fifteen pigs were treated with FENO 50 mg/kg orally for 4 weeks; 15 untreated pigs served as controls (CON). Plasma FENO concentration was similar to that achieved in clinical use. At 4 wks, both groups underwent 90 min low flow regional myocardial ischemia followed by 120 min REP, resulting in myocardial stunning. Regional LV external work (sonomicroscopy), blood flow, substrate uptake, and cytokine mRNA expression (IL-1β, IL-6, IFN-γ) were measured. Results: PPAR-α mRNA expression in myocardium was confirmed by ribonuclease protection assay, fulfilling a necessary condition for the action of a PPAR-α agonist. Prior to ISC, regional LV function and substrate uptake did not differ between groups. During ISC, reductions in blood flow were similar in both groups. During both ISC and REP LV function was depressed in both groups but better preserved in FENO than CON (p<0.05, Table), with differences in myocardial substrate uptake or cytokine mRNA expression. Conclusion: Chronic treatment with FENO attenuates the severity of LV stunning in pigs. The mechanism of protection appears to be unrelated to substrate uptake or cytokine expression.

Regional LV ext work (fraction of baseline). Note: Baseline function did not differ between groups.

Angiotensin II Inhibition of Vascular Matrix Metalloproteinases in Heart Failure Is Nitric Oxide-Dependent

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Introduction: The role of angiotensin II (AngII) in promoting vascular remodeling is well established. However, the mechanisms of AngII-mediated remodeling in ischemic heart failure (IHF) are unclear. We hypothesized that AngII mediates vascular remodeling in IHF by modulating the balance of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs).

Methods: Segments of rat aortic segments were treated ex vivo with AngII (100 mM) and AT1 receptor blocker, candesartan (100 mM) for 24 hrs. MMP/TIMP activities were measured using gelatin zymography. In addition, aortic rings were treated with a nitric oxide inhibitor, L-NAME (200 µM) to determine if AngII effects are nitric oxide-dependent. Results: In both sham and IHF, AngII decreased MMP-2 and -9 activities compared to untreated controls. L-NAME reversed the effects of AngII on MMP-2 and -9 that were 100% in sham and 80% in IHF, compared to untreated controls. Similarly, candesartan reversed the effects of AngII on MMP-2 and -9 to 95% in sham and only to 5% in IHF compared untreated controls. Conclusion: AngII-mediated decrease in vascular MMP activities is NO-dependent, while the effects of candesartan on MMP-2 and -9 activation is mainly due to AT1 receptor blockade. This study suggests that AngII modulation of MMP-2 and -9 may be AT1 receptor mediated.

Age-Related Changes in Adaptation of the Heart to Ischemia-Reperfusion: A Possible Role for NADPH Oxidase-Induced Superoxide Production

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Background: Aging is associated with an increase in myocardial susceptibility to ischemia and a decrease in post-ischemic recovery. However, the mechanisms involved regarding age-related changes are still not clear. The aim of our study was to examine age-related differences in myocardial ischemia-reperfusion and to determine the possible relationship between oxidative stress and age.

Methods: Isolated perfused hearts from young (2 months) (Y), adults (6 months) (A) and old (21 months) (O) rats underwent 30 min of global total ischemia followed by 30 min of reperfusion. The spin-probe CP-H (0.1 µM) was perfused in order to evaluate (in coronary effluents) superoxide-associated oxidative stress during reperfusion using electron spin resonance spectroscopy (ESR). Studies concerning vascular NADPH oxidase were