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INCREASED GI-2 AND DECREASED GS-S LEVELS IN A MICROINFARCTION MODEL OF HEART FAILURE

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Introduction: Chronic heart failure (CHF) is associated with altered signal transduction. The guanine-nucleotide binding proteins (G proteins) Gs and Gi-2 regulate cardiac inotropy via receptor-mediated stimulation and inhibition of adenylyl cyclase, respectively. In humans with ischemic, end-stage CHF, Gs levels remain relatively unchanged. In contrast, Gi-2 is significantly increased and may play a role in -adrenergic receptor desensitization and cardiac dysfunction. We examine the effects of coronary microembolization-induced CHF on Gs and Gi-2 protein levels in an ovine model to determine if alterations comparable to those in humans occur.

Methods: Left ventricular (LV) myocardial tissue was obtained from four control (nonfailing) and four CHF sheep (LV ejection fraction <35% for 1-2 years) created via coronary microembolization technique (Monreal et al, J Card Fail, in press, 2/2004). Membrane proteins (~25ug/lane) were solubilized and separated with 12% SDS-PAGE. Western blots were performed with antisera specific for either Gs or Gi-2, with visualization by enhanced chemiluminescence. Densitometry was performed on the resulting autoradiographs to quantify band intensity.

Results: In the CHF sheep, the Gs 45-kDa splice variant (Gs-s) decreased 2.2-fold (-54%) and trended towards significance (p=0.12) while the Gs 52-kDa splice variant (Gs-l) remained relatively unchanged (1.2-fold increase) as compared to controls. In contrast, Gi-2 was significantly increased in the CHF sheep 6.4-fold relative to the controls (p=0.0004).

Conclusion: In agreement with clinical findings of humans in CHF, our animal model of microinfarction-induced CHF exhibited decreased ejection fraction and cardiac function. Gs-l levels were unchanged, whereas Gs-s was decreased along with significantly increased Gi-2 levels. Depressed adenylyl cyclase function due to increased Gi-2 and the lack of a compensatory increase in stimulatory Gs to counterbalance Gi-2 may play a role in the pathophysiological processes of receptor desensitization in CHF. This model serves as a platform for further understanding the molecular alterations associated with ischemic heart disease.

This study is supported by a FAER/SCA Research Starter Grant.

