**870-1**

**Title:** Chronic beta-3-Adrenergic Receptor Blockade Causes Regression of Cardiac Dysfunction in a Rat Model of Progressive Heart Failure

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**Background:** The negative inotrope and upregulation of beta-3-adrenergic receptors (AR) in failing human and animal hearts suggest a direct and contributing role of cardiac beta-3-AR activation on heart failure (HF) progression. Therefore, we tested the hypothesis that chronic beta-3-AR blockade may limit or prevent the progression of HF.

**Methods:** Left ventricular (LV) and myocyte functional response and beta-1 and beta-3-AR expression were compared in 3 groups of rats (6 each) for a period of 4 months: 1) ISO-proterenol (ISO)-treated, 4 months after receiving ISO (340 mg/kg, sc, for 2 days); 2) ISO/beta-3-ANT, one month after receiving ISO, L-748,337, a selective beta-3-AR antagonist (beta-3-AR blockade); and 3) sham controls (sham-ISO/proterenol). The progression of disease was assessed by monitoring indices of cardiac structure and function.

**Results:** Compared with controls, ISO-treated rats had HF onset at one month after ISO and progressed to severe CHF at 4 months. Plasma norepinephrine (NE, 1482 ± 247 pg/ml) increased 6-fold. Both stroke volume (SV) and ejection fraction (EF, 34 vs 62%) decreased more than 45%, and LV end-diastolic pressure (PDE) (16.3 ± 6.4 mmHg) doubled, parallel with 49% reductions in cell contraction (dL/dtmax, 95 vs 189 µm/s) and relaxation (dP/dtmin, 75 vs 158 µm/s) and a much less increase in dL/dtmax (32 vs 74%) in response to superfusion of ISO (10-4 M). These changes were associated with significantly decreased beta-3-AR mRNA (62%, 0.30 ± 0.62), but increased beta-3-AR mRNA (119%, 1.25 ± 0.57) expression. Treatment with beta-3-ANT significantly decreased PDE and plasma NE (197 pg/ml). Both SV and EF (59%) increased to more than 75% from ISO-treated values. The signal ratios of beta-3-AR mRNA (0.59) and beta-3-AR mRNA (0.66) remained close to control levels. ISO-induced increase in dL/dtmax (75%) was also significantly augmented.

**Conclusion:** Chronic beta-3-AR antagonists normalize beta-1 and beta-3-AR gene expression, reduce myocardial responsiveness of myocyte to beta-AR stimulation, and leads to regression of LV and myocyte dysfunction in a rat model of progressive CHF. Thus, beta-3-AR blockade may provide a new therapeutic strategy for the treatment of CHF.

**870-2**

**Title:** In Vivo Evidence of Isolated Impaired Myocardial Relaxation in Mice Overexpressing the Transcription Factor TREF-1

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**Background:** TREF-1 mediates transcriptional responses to alpha-thrombin signaling in cardiac myocytes. Mice with cardiac-specific overexpression of TREF-1 develop atrial dilation and atrial arrhythmias. To assess whether mechanical abnormalities contribute to these observations, we performed thoracoscopic echocardiography and pressure-volume conductance catheterization (closed chest via right carotid artery) in TREF-1 and WT (WT) mice (Avertin anesthesia). Conductance catheter data (mean ± SD) are summarized in the table. Acute LV volume loading (200 μl NS) revealed no difference between groups in the slopes of the end-diastolic pressure-volume relation (0.54 vs. 0.68 mmHg/μl; p<NS), indicating normal passive compliance. This is in keeping with the absence of myocardial fibrosis seen on pathology. Echocardiography revealed no difference in LV mass (confirmed by ex vivo heart weights) or dimensions. Doppler interrogation of LV filling revealed an increase in the E/A ratio in TREF-1 mice (1.59 ± 0.15 vs. 1.26 ± 0.23; p<0.05), mediated by trends toward an increase in the E wave velocity (60 ± 18 vs. 55 ± 8 cm/s; p=N.S) and a decrease in the A wave velocity (38 ± 10 vs. 44 ± 7 cm/s; p<NS).

**Conclusions:** Mice overexpressing TREF-1 exhibit preserved LV systolic function with impaired relaxation, resulting in elevated filling pressures. While the mechanisms by which TREF-1 overexpression impairs LV relaxation are unknown, this may serve as a useful model of diastolic dysfunction in the absence of LV hypertrophy.