Adverse Functional Significance of Cardiac Beta$_3$-Adrenergic Receptor Activation on Left Ventricular Contractile Performance in Conscious, Chronically-Instrumented Dogs with Pacing-Induced Heart Failure

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Abstract:

Background. In heart failure (HF), the cardiac β_3-adrenergic receptor (AR)-mediated inhibitory pathway is up-regulated, suggesting a contributing role of β_3-AR activation on HF progression. However, its precise role is still unclear due to lack of β_3-AR-selective antagonists (β_3-ANT). APD418 is a novel β_3-ANT with high affinity and selectivity for human β_3-AR. We hypothesize that up-regulation of β_3-AR is detrimental and APD418 will improve left ventricular (LV) and myocyte function in HF.

Method. We measured LV functional responses immediately (0 min) and 10 min after termination APD418 infusion (1.9 mg/kg, i.v. for 10 min) in 7 conscious dogs before and after pacing-induced HF, and compared isolated HF myocyte contractile responses to β_3-AR stimulation with or without APD418 treatment.

Results. In both normal (N) and HF, similar plasma APD418 levels were achieved at 0 (N: 3908 vs HF: 3806 ng/ml) and 10 min (2719 vs 2755 ng/ml) with the treatment, which paralleled the increased LV contractility (E_{ES}) [N: from 6.6 (baseline) to 7.8 and 7.4; HF: from 4.3 to 6.2 and 5.5 mmHg/ml], and decreased time constant of LV relaxation (N: from 28.2 to 26.0 and 27.3; HF: from 45.9 to 36.6 and 39.8 ms) (P<0.05). Heart rate, LV end-systolic pressure, and end-diastolic volume were unchanged. In HF, APD418 caused increases in E_{ES} which were significantly greater and accompanied by improved LV-arterial coupling and mechanical efficiency (0.55 vs 0.46). In isolated HF LV myocytes, stimulation with β_3-AR agonist BRL-37344 (BRL, 10^{-8} M) significantly decreased cell contraction (dL/dt_{max}: 49.7 vs 67.2 μm/s) and relengthening (dR/dt_{max}: 40.5 vs 53.3 μm/s). Versus HF baseline, perfusion of nadolol (NAD, 10^{-5} M, a β_1- and β_2-ANT) caused 12% and 10% reductions in dL/dt_{max} and dR/dt_{max}. Addition of isoproterenol (10^{-8} M) caused further decreases in dL/dt_{max} (23%) and dR/dt_{max} (20%) (p<0.05). The BRL and isoproterenol induced negative inotropic responses were abolished by pre-treatment with APD418 ($5x10^{-6}$ M).

Conclusions: This study demonstrated that in pacing-induced HF, β_3-AR activation exacerbated LV and myocyte systolic and diastolic dysfunction; whereas, β_3-ANT with APD418 caused beneficial actions supporting the usefulness of selective β_3-ANT as a new therapeutic option for HF.

Author Disclosure Information:

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