Adverse Functional Significance of Cardiac Beta\textsubscript{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\textsubscript{3}-adrenergic receptor (AR)-mediated inhibitory pathway is up-regulated, suggesting a contributing role of β\textsubscript{3}-AR activation on HF progression. However, its precise role is still unclear due to lack of β\textsubscript{3}-AR-selective antagonists (β\textsubscript{3}-ANT). APD418 is a novel β\textsubscript{3}-ANT with high affinity and selectivity for human β\textsubscript{3}-AR. We hypothesize that up-regulation of β\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{3}-AR agonist BRL-37344 (BRL, 10\textsuperscript{-8} M) significantly decreased cell contraction (dL/dt\textsuperscript{max}: 49.7 vs 67.2 μm/s) and relengthening (dR/dt\textsuperscript{max}: 40.5 vs 53.3 μm/s). Versus HF baseline, perfusion of nadolol (NAD, 10\textsuperscript{-5} M, a β\textsubscript{1}- and β\textsubscript{2}-ANT) caused 12% and 10% reductions in dL/dt\textsuperscript{max} and dR/dt\textsuperscript{max}. Addition of isoproterenol (10\textsuperscript{-8} M) caused further decreases in dL/dt\textsuperscript{max} (23%) and dR/dt\textsuperscript{max} (20%) (p<0.05). The BRL and isoproterenol induced negative inotropic responses were abolished by pre-treatment with APD418 (5x10\textsuperscript{-6} M).

**Conclusions:** This study demonstrated that in pacing-induced HF, β\textsubscript{3}-AR activation exacerbated LV and myocyte systolic and diastolic dysfunction; whereas, β\textsubscript{3}-ANT with APD418 caused beneficial actions supporting the usefulness of selective β\textsubscript{3}-ANT as a new therapeutic option for HF.

**Author Disclosure Information:**

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