**A NOVEL SELECTIVE HUMAN BETA3-ADRENERGIC RECEPTOR ANTAGONIST OF APD418 IMPROVED LEFT VENTRICULAR AND CARDIOMYOCYTE FUNCTIONAL PERFORMANCE IN CONSCIOUS, CHRONICALLY-INSTRUMENTED DOGS WITH PACING-INDUCED HEART FAILURE**

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**Objective.** To evaluate the hypothesize that APD418, a novel β3-AR antagonist with high affinity and selectivity for the human β3-AR may improve LV and myocyte function in heart failure (HF).

**Background.** In HF, the cardiac β3-AR-mediated inhibitory pathway is up-regulated, suggesting a contributing role of β3-AR activation on HF progression. However, its precise role is still unclear due to lack of β3-AR-selective antagonists (β3-ANT).

**Method.** We measured LV functional responses after APD418 treatment (1.9 mg/kg, i.v. for 10 min) in 7 conscious dogs before and after pacing-induced HF, and compared HF myocyte contractile responses to β3-AR stimulation with or without APD418.

**Results.**In both normal (N) and HF, similar plasma APD418 levels were achieved after termination APD418 infusion, at 0 (N: 3908 vs HF: 3806 ng/ml) and 10 min (2719 vs 2755 ng/ml), which paralleled the increased LV contractility (EES) (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 EESwhich were significantly greater and accompanied by improved LV-arterial coupling and mechanical efficiency (ratio: 0.55 vs 0.46 ). In myocytes isolated from HF dogs, stimulation with β3-AR agonist BRL-37344 (BRL, 10-8 M) significantly decreased cell contraction (dL/dtmax: 49.7 vs 67.2 μm/s) and relengthening (dR/dtmax: 40.5 vs 53.3 μm/s). Versus HF baseline, perfusion of nadolol (NAD, 10-5 M, a β1- and β2-ANT) caused 12% and 10% reductions in dL/dtmax and dR/dtmax. Addition of isoproterenol (10-8 M) caused further decreases in dL/dtmax(23%) and dR/dtmax(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, β3-AR activation exacerbated LV and myocyte systolic and diastolic dysfunction; whereas, β3-ANT with APD418 caused beneficial actions supporting the usefulness of selective β3-ANT as a new therapeutic option for HF.