APD418, A Selective Beta$_3$-Adrenergic Receptor Antagonist Enhances Cardiac Positive Inotropic and Lusitropic Responses to Dobutamine in Conscious, Chronically-Instrumented Dogs with Pacing-Induced Heart Failure: Assessment by Pressure-Volume Analysis

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Abstract:
Background. Attenuation of heart failure (HF) response to positive inotropic agents such as dobutamine (DOB) represents a major clinical problem. The regulation of cardiac function by catecholamine involves 3 populations of β-adrenergic receptors (AR). β_1-and β_2-AR stimulation produces an increase in contractility, and β_3-AR stimulation mediates a negative inotropic effect. In HF, β_3-AR-mediated negative action is increased due to β_3-AR upregulation. Since DOB is a non-selective β-AR agonist, the diminished response of DOB in HF patients may be caused by DOB-induced β_3-AR stimulation. Therefore, we tested the hypothesis that APD418, a novel, potent, selective, human β_3-AR antagonist (β_3-ANT), may restore cardiac positive responses to DOB in HF.

Methods. We compared the effect of APD418 treatment (1.9 mg/kg, i.v., 10 min) on left ventricular (LV) systolic and diastolic performance and LV contractile response to DOB (6 μg/kg/min, iv, 10 min) in 5 chronically-instrumented, conscious dogs after pacing-induced HF. LV contractile performance was measured by pressure (P)-volume (V) analysis.

Results. After HF, DOB caused a 25% increase in LV contractility (E_{ES}) (5.3±1.7 vs 4.2±1.3 mmHg/ml), a 13% increase in M_{SW} (58.7±3.8 vs 51.1±2.9 mmHg), and a 9% decrease in the time constant of LV relaxation (τ) (41.0±2.9 vs 45.2±4.1 ms). APD418 infusion resulted in APD418 plasma levels of ~2800 ng/ml. DOB followed by APD418 resulted in significantly greater effects with a 73% increase in E_{ES} (7.2±2.7 vs 4.2±1.3 mmHg/ml), a 47% increase in M_{SW} (75.0±4.8 vs 51.1±2.9 mmHg), and a 21% decrease in τ (35.9±3.4 vs 45.2±4.1 ms). Compared with DOB alone, DOB plus APD418 caused no significant changes in heart rate (128 vs 124 bpm) or LV end-systolic P (107 vs 105 mmHg), but significantly increased stroke volume (15.0±2.2 vs 11.4±1.9 ml). DOB plus APD418 significantly improved LV mechanical efficiency, measured as the ratio of stroke work to the total P-V area (0.61±0.18 vs 0.47±0.17).

Conclusion. In pacing-induced HF, APD418 enhanced LV positive inotropic and lusitropic responses to dobutamine. This suggests combination therapy with intravenous β_3-ANT and DOB may be appropriate in HF, providing a potential method of enhancing β-adrenergic responsiveness in the failing myocardium.

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