

Abstract

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Title **Acute intravenous infusion of the beta-3 adrenergic receptor antagonist APD418 improves left ventricular function in dogs with heart failure: a dose escalation study**

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Background: Unlike β_1 and β_2 -adrenergic receptors (ARs), β_3 -AR stimulation inhibits cardiac contractility and relaxation through links to inhibitory G proteins. In the failing left ventricular (LV) myocardium, β_3 -ARs are upregulated, a maladaptation that can contribute to LV dysfunction. This study examined the effects of acute intravenous (i.v.) infusions of the β_3 -AR antagonist APD418 on LV systolic and diastolic function by conducting a dose-escalation study in dogs with chronic heart failure (HF) (LV ejection fraction, EF~35%).

Methods: Studies were performed in 7 dogs with coronary microembolizations-induced HF. After baseline measurements, 0.9% NaCl (vehicle) was administered as a continuous i.v. infusion for 30 min. This was followed by infusions of 3 escalating doses of APD418 (0.696, 1.407 and 2.814 mg/kg) with each dose maintained for 30 min. Heart rate (HR), mean aortic pressure (mAoP), LV end-diastolic (EDV) and end-systolic (ESV) volumes, EF, stroke volume (SV) cardiac output (CO), LV end-diastolic pressure (EDP) and systemic vascular resistance (SVR) as well as the diastolic function measures Ei/Ai and mitral inflow velocity deceleration time (DCT) were measured at end of each 30 min period.

Results: Infusion of APD418 had no effects on HR, mAoP, or EDV but significantly decreased ESV, LVEDP and SVR and significantly increased EF, SV, CO Ei/Ai and DCT in a dose-dependent manner (Table).

Conclusions: Acute i.v. infusions of APD418 in HF dogs elicit positive inotropic and lusitropic effects along with modest preload and afterload reductions. The findings support the development of APD418 for the in-hospital treatment of patients with exacerbation of chronic HF.

	Baseline	Vehicle	APD418 (0.696 mg/kg)	APD418 (1.407 mg/kg)	APD418 (2.814 mg/kg)
LV EDV (ml)	62±1	63±1	62±2	62±2	61±2
LV ESV (ml)	41±1	41±1	38±1*	38±1*	36±1*
LV EF (%)	34±1	35±1	38±1*	39±1*	41±1*
SV (ml)	21±1	22±1	23±1*	24±1*	25±1*
CO (L/min)	1.70±0.08	1.81±0.07	1.94±0.11	2.02±0.08*	2.14±0.08*
HR (beats/min)	81±2	83±1	83±1	84±1*	85±1*
mAoP (mmHg)	74±2	79±3	79±4	79±5	77±4
LVEDP (mmHg)	14±0.6	15±0.6	14±0.8	13±0.8	12±1.0*
SVR (dynes-sec-cm ⁻⁵)	3525±257	3537±152	3293±205	3118±183*	2895±153*
Ei/Ai	3.1±0.1	2.9±0.3	3.6±0.3*	3.7±0.3*	4.3±0.4*
DCT (msec)	98±6	99±9	119±14	117±11	133±16*

*=p<0.05 vs. Baseline