Activating Cardiac Myosin, a Novel Inotropic Mechanism to Improve Cardiac Function in Conscious Dogs with Congestive Heart Failure

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INTRODUCTION

Many cardiotoxic agents are not useful in the chronic treatment of congestive heart failure (CHF), either because they increase myocardial CO consumption or undergo desensitization, such that their efficacy is actually reduced in CHF, compared to that under normal physiological conditions.

OBJECTIVE

To examine the effects of a novel agent, CK-452 (CK-452), which exerts inotropic action by activating cardiac myosin, in conscious chronically instrumented dogs in the presence and absence of CHF.

METHODS

Surgical Instrumentation & Model Preparation:

- Mongrel dogs (15–18 kg) of either sex were anesthetized and a left thoracotomy was performed. Catheters were placed in aorta, atrium and coronary sinus. A pressure transducer was implanted in the LV chamber. Ultrasonic dimension crystals were implanted on left ventricular wall. Transonic flow probes were placed around the left pulmonary and left coronary arteries and the ascending aorta. Pacing leads were attached to the right atrium and the left atrium.

- Heart failure was induced by combination of myocardial ischemia and ventricular pacing at a rate of 220–240/min. Coronary artery occlusion (LA) was performed during surgery (Fig 1).

- Experimental Measurements:
  - LV fractional shortening (%) was calculated as [(LV end-diastolic diameter (EDD) – end-systolic diameter (ESD)]/EDD*100.
  - Myocardial oxygen consumption (MVO2) was calculated as the product of the coronary blood flow and arterio-venous oxygen difference measured.
  - Total peripheral resistance was calculated as [mean arterial pressure – mean right atrial pressure]/cardiac output.
  - CK-452 was infused (0.5 mg/kg) in normal conscious dogs, i.e., before CHF, and in conscious dogs with CHF.

- Effects of bolus injection of CK-452 on mean arterial pressure (MAP), LV dP/dt, cardiac output (CO), coronary sinus oxygen content (A-O2), and decreases (p<0.001) in heart rate (HR) and left atrial pressure (LAP) in normal conscious dogs. This occurred by increasing LV systolic ejection time, LV fractional shortening, and stroke volume, without a change in MVO2. The unique profile of this myosin activator provides a novel therapeutic approach for patients with CHF.

CONCLUSION

The present results demonstrated that unlike existing inotropic agents, which generally induce desensitization and increase MVO2, chronic infusion of the myosin activator produced even a greater improvement in LV function in CHF without a change in MVO2. The unique profile of this myosin activator provides a new therapeutic approach for patients with CHF.