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

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[281] ABSTRACT

Many cardiotonic agents are not useful in the chronic treatment of heart failure (HF), either because they increase myocardial O2 consumption (MVO2) or undergo desensitization, such that their efficacy is actually reduced in HF, compared to that under normal physiological conditions. We examined the effects of a novel agent, CK-1827452 (CK-452), which exerts its inotropic action by activating cardiac myosin, in conscious chronically instrumented dogs in the presence and absence of HF. Dogs were instrumented with a left ventricular (LV) pressure gauge, ascending aortic flow probe, coronary flow probe, LV dimension crystals and catheters in the aorta, left atrium, and coronary sinus. HF, induced by a combination of left anterior descending coronary artery occlusion and ventricular pacing (240 bpm), was characterized by an increase ($p<0.01$) in LV end diastolic pressure (from 7±1 to 26±2 mmHg), and decreases ($p<0.01$) in LV dP/dt (from 3065±138 to 1730±109 mmHg/s), fractional shortening (from 14±2 to 7±1%), stroke volume (from 30±4 to 13±2 ml), and cardiac output (from 2.8±0.4 to 1.7±0.2 L/min). In conscious normal dogs, infusion of CK-452 (0.5 mg/kg/hr, iv) increased ($p<0.05$) LV fractional shortening (21±2%) and stroke volume (11±4%) and modestly decreased heart rate (HR 8±2%), while cardiac output and total peripheral resistance (TPR) did not change significantly. After HF developed, infusion of CK-452 for 3 days induced sustained increases ($p<0.05$) in LV fractional shortening (34±7%), stroke volume (34±8%) and cardiac output (22±3%), and decreases ($p<0.02$) in HR (15±3%) and TPR (15±1%). Importantly, MVO2 (3.4±0.3 mlO2/min) was not significantly altered during CK-452 infusion. Interestingly, CK-452 did not increase LV dP/dt, but rather increased LV systolic ejection time by 33±2%. These results demonstrate that unlike existing inotropic agents, which generally increase LV dP/dt, induce desensitization and increase MVO2, chronic infusion of the cardiac myosin activator did not induce desensitization but actually produced a greater improvement in LV function in HF than in normal 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 may provide a new therapeutic approach for patients with HF.

INTRODUCTION

Many cardiotonic agents are not useful in the chronic treatment of congestive heart failure (CHF), either because they increase myocardial O2 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-1827452 (CK-452), which exerts its inotropic action by activating cardiac myosin, in conscious chronically instrumented dogs in the presence and absence of CHF.

METHODS

Surgical Instrumentation & Model Preparation:

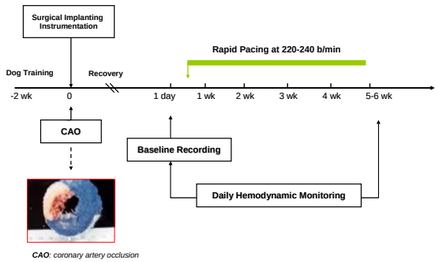
- Mongrel dogs (15–18 kg) of either sex were anesthetized and a left thoracotomy was performed. Catheters were placed in aorta, atrium and coronary sinus. A pressure transducer was implanted in the LV chamber. Ultrasonic dimension crystals were implanted on LV myocardium. Transonic flow probes were placed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

- Heart failure was induced by combination of myocardial ischemia and ventricular pacing at a rate of 220-240 b/min. Coronary artery occlusion (LAD) 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 (MVO_2) 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 (i.v.) in normal conscious dogs, i.e., before CHF and in conscious dogs with CHF.

Congestive Heart Failure Conscious Dog Model (Fig1)



***CAO**: coronary artery occlusion*

Baseline Values in Conscious Dogs with CHF

Hemodynamic Indices	Control (n=5)	CHF (n=6)
Mean Arterial Pressure (mmHg)	**93±8**	**87±5**
Heart Rate (beat/min)	**94±9**	**143±7***
Mean Left Atrial Pressure (mmHg)	**3±1**	**25±1***
LV End-Diastolic Pressure (mmHg)	**7±1**	**28±2***
LV dP/dt max (mmHg/s)	**3065±138**	**1663±111***
Systolic Wall Thickening (mm)	**2.1±0.4**	**1.5±0.2***
Cardiac Output (L/min)	**2.8±0.4**	**1.5±0.2***
Coronary Blood Flow (ml/min)	**23±5**	**34±5**

*p<0.05 vs. control

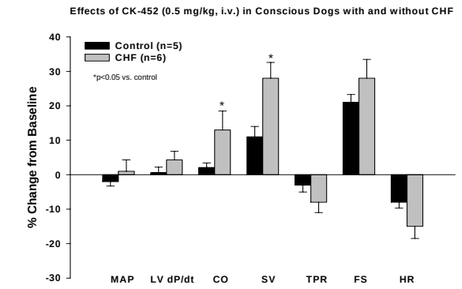


Fig 2: Effects of bolus injection of CK-452 on mean arterial pressure (MAP), LV dP/dt, cardiac output (CO), stroke volume (SV), total l peripheral resistance (TPR), LV fractional shortening (FS) and heart rate (HR) in control dogs and dogs with congestive heart failure (CHF). Note that CK-452 significantly increased CO and SV more in control dogs compared to dogs with CHF.

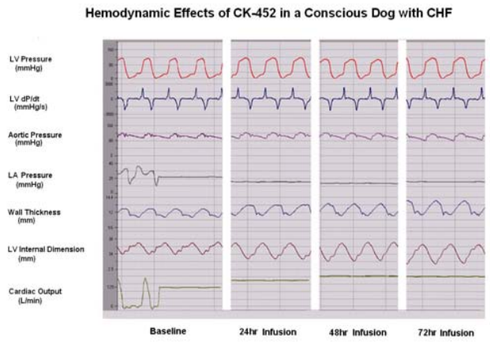


Fig 3: Representative waveforms of LV pressure, LV dP/dt, aortic pressure (AOP), mean left atrial pressure (LA), wall thickness, LV internal diameter and mean cardiac output in a conscious dog with CHF at baseline, 1, 2 and 3 days during infusion of CK-452. Note that CK-452 clearly increased wall thickening, fractional shortening and cardiac output and decreased mean LA pressure .

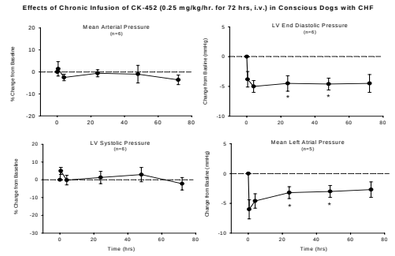


Fig 4: Effects of chronic infusion of CK-452 on mean arterial pressure, LV systolic pressure, LV end diastolic pressure, and mean left atrial pressure in dogs with congestive heart failure (CHF). Note that CK-452 significantly decreased LV end-diastolic pressure and mean left atrial pressure. * p<0.05 vs. baseline

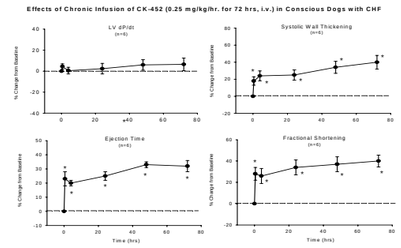


Fig 5: Effects of infusion of CK-452 on LV dP/dt, ejection time, systolic wall thickening and LV fractional shortening in dogs with congestive heart failure (CHF). Note that CK-452 significantly increased ejection time, systolic wall thickening and LV fractional shortening, while LV dP/dt was not altered. * p<0.05 vs. baseline

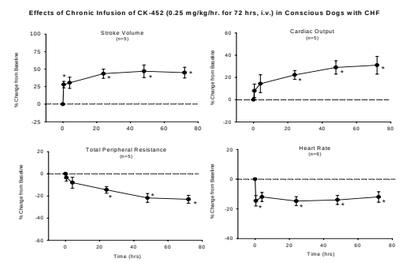


Fig 6: Effects of infusion of CK-452 on stroke volume, cardiac output, total peripheral resistance and heart rate in dogs with congestive heart failure (CHF). Note that CK-452 significantly increased stroke volume, cardiac output and heart rate, while total peripheral resistance was decreased. * p<0.05 vs. baseline.

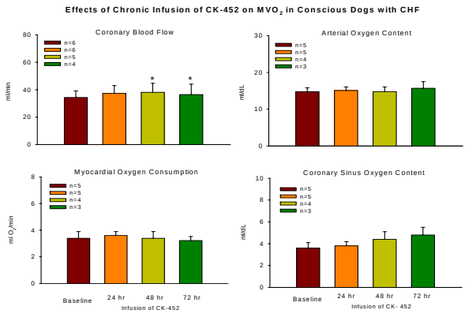


Fig 7: Effects of infusion of CK-452 on mean coronary blood flow, myocardial oxygen consumption, arterial and coronary sinus oxygen content in dogs with congestive heart failure (CHF). Note that coronary blood flow was slightly, but significantly increased during the infusion of CK-452 at 48 and 72 hrs. All other indices were not significantly different from baseline levels. * p<0.05 vs. baseline.

SUMMARY

- In conscious normal dogs, administration of CK-452 (0.5 mg/kg, i.v.) increased stroke volume and LV fractional shortening, and modestly decreased heart rate, while cardiac output and total peripheral resistance were only slightly changed.
- In conscious dogs with CHF, administration of CK-452 at the same dose used in the normal dogs increased cardiac output, stroke volume and LV fractional shortening, and decreased afterload and heart rate. Interestingly, the effects induced by CK-452 in CHF was greater compared to those observed in normal condition.
- Chronic infusion of CK-452 (0.25 mg/kg/hr., i.v.) for 3 days induced a sustained improvement of LV performance, along with decreases in preload, i.e., LV end-diastolic pressure, and afterload. Importantly, these effects were not associated with any changes in MVO_2.

CONCLUSION

The present results demonstrated that unlike existing inotropic agents, which generally induce desensitization and increase MVO_2, chronic infusion of the myosin activator produced even a greater improvement in LV function in CHF without a change in MVO_2. The unique profile of this myosin activator provides a new therapeutic approach for patients with CHF.