# A Novel Inotropic Agent That Activates Cardiac Myosin and Increases Cardiac Contractility Without Increasing $MVO_2$ in Heart Failure with Left Ventricular Hypertrophy

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## INTRODUCTION

One reason for the failure of mechanisms explored for chronic inotropic therapy in heart failure is thought to be related to an increase in $MVO_2$ resulting in an imbalance between $O_2$ supply and demand, particularly evident in subendomyocardium of the hypertrophic dilated left ventricle. CK-1827452 (CK-452) is a novel inotropic agent that acts by directly activating the force generating protein cardiac myosin. As opposed to most $Ca^{++}$ dependent agents, this mechanism is downstream of second messenger signaling and calcium cycling, which should provide a different and perhaps better profile as compared to other agents.

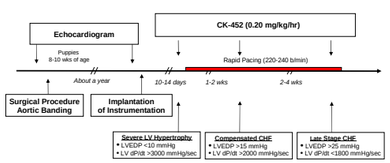
## OBJECTIVES

To examine the effects of CK-452 in conscious, chronically instrumented dogs with heart failure (HF) either with or without pre-existing left ventricular hypertrophy (LVH).

## METHODS AND PROTOCOL

Surgically implanted instrumentation included an LV pressure gauge, ascending aortic and coronary flow probes, ultrasonic crystals for cardiac dimensions, pacers and catheters in the aorta and coronary sinus. HF was induced by a combination of coronary artery occlusion and ventricular pacing (240 bpm) and LVH was induced by aortic banding.

**Experimental Protocol for LVH and Heart Failure Model**




## RESULTS

***Comparison of Baseline Hemodynamics in Conscious Dogs with LVH and CHF***

| | LVH (n=7) | Compensated CHF (n=6) | Late Stage CHF (n=5) |
|---|---|---|---|
| LV Systolic Pressure (mmHg) | 188±6.6 | 139±7.7* | 133±10.7* |
| LV dP/dt (mmHg/s) | 3705±281 | 2019±153* | 1780±93* |
| LV End Diastolic Pressure (mmHg) | 11.2±0.9 | 21.1±1.9* | 29.2±2.5* |
| Mean Arterial Pressure (mmHg) | 93±1.8 | 85±3.0 | 89±5.3 |
| Systolic Arterial Pressure (mmHg) | 112±2.6 | 98±3.4 | 103±7.4 |
| LV/Aortic Pressure Gradient (mmHg) | 76±7.4 | 41±6.7* | 30±5.1* |
| Mean Left Atrial Pressure (mmHg) | 4.6±0.5 | 13.2±1.8* | 22.3±2.1* |
| Systolic Wall thickening (mm) | 3.7±0.4 | 2.5±0.2* | 2.1±0.2 * |
| LV End Diastolic Diameter (mm) | 46.0±3.2 | 47.1±3.2 | 47.8±3.6 |
| Fraction Shortening (%) | 14.1±2.2 | 10.6±2.5* | 9.9±2.9* |
| Heart Rate (beat/min) | 123±3 | 130±6 | 142±7 |

p<0.05 vs. LVH alone

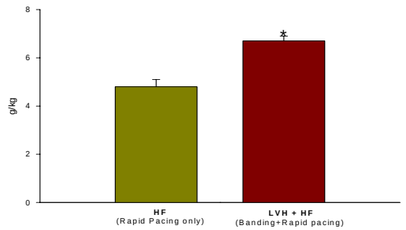



Fig 1. LV/Body weight ratio obtained at the end of study from dogs subjected to pacing and myocardial ischemia vs. one year banding then followed by rapid pacing and myocardial ischemia. LV/Body weight was significantly higher in the banded dogs as compared to dogs without banding. * p<0.05 vs. pacing only dogs (historical data).

**Effects of CK- 452 in Conscious Dogs with LVH, LVH+HF and HF**

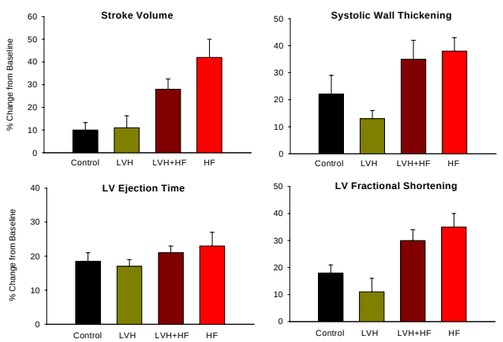



Fig 2. Stroke volume, systolic wall thickening, LV ejection time, and LV fractional shortening in control dogs, dogs with LVH only, LVH plus HF, and HF only after a bolus injection of CK-452 (0.5 mg/kg/hr) followed by infusion. Note that CK-452 induced greater effects in stroke volume, systolic wall thickening and LV fractional shortening in dogs with HF compared to control and LVH alone.

**Effects of Infusion of CK- 452 (0.20 mg/kg/hr) in Consicous Dogs with LVH and CHF**

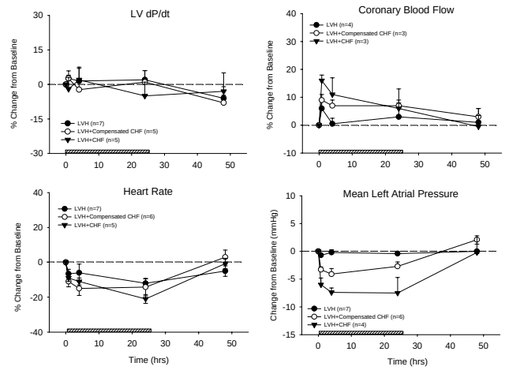



Fig 3. Effects of CK-452 on LV dP/dt, heart rate, mean coronary blood flow and left atrial pressure in dogs with LVH, LVH and CHF. Note that the decreases in mean left atrial pressure were more in CHF setting, compared to LVH alone. Heart rate was reduced similarly in all groups, and coronary blood flow was slightly increased shortly after administration of CK-452.

**Effects of Infusion of CK- 452 (0.20 mg/kg/hr) in Consicous Dogs with LVH and CHF**

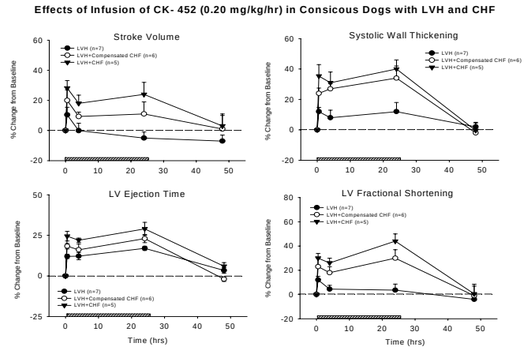



Fig 4. Effects of CK- 452 on stroke volume, LV ejection time, systolic wall thickening, and LV fractional shortening in dogs with LVH, LVH and compensated CHF, and LVH and late stage CHF. Note that the increases in LV function, as expressed by stroke volume, wall thickening and fractional shortening, appear more pronounced in late stage CHF as compared to LVH alone.

**Regional Myocardial Blood Flow**

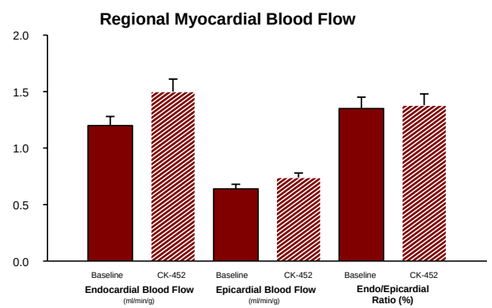



Fig 5. Effects of CK- 452 on regional myocardial blood flow in conscious dogs with CHF/LVH. Note that blood flow in the endo and epi myocardium was increased somewhat following bolus administration of CK- 452 (0.25 mg/kg, i.v), but there were no significant changes in the ratio of endocardial and epicardial blood flow.

Myocardial Oxygen Consumption

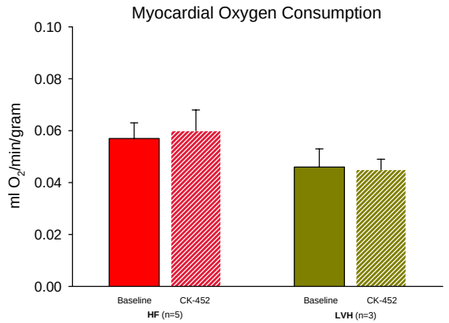



Fig 6. Effects of infusion of CK- 452 on myocardial oxygen consumption calculated from coronary blood flow, arterial and coronary sinus oxygen content in dogs with CHF and LVH. There were no significant changes in all indices.

## SUMMARY

- In conscious dogs with severe LVH but not heart failure, administration of CK- 452 produced a sustained and significant increase in ejection time and systolic wall thickening with only transient effects on fractional shortening and stroke volume. These actions were augmented in CHF with or without accompanying LVH.
- In conscious dogs with CHF or with CHF in the presence of severe LVH, CK- 452 produced a sustained increase in ejection time, systolic wall thickening, fractional shortening and stroke volume. These changes were accompanied by decreases in LV end-diastolic pressure, mean left atrial pressure, and heart rate.
- Most importantly, the endo/epi myocardial blood flow ratio and both arterial and coronary sinus oxygen content were unchanged. Thus, unlike most inotropic agents, overall myocardial oxygen consumption was unaffected even as overall systolic function improved.

## CONCLUSION

The novel cardiac myosin activator, CK-1827452, increased LV function and reduced filling pressures, but in contrast to conventional inotropic agents, it did not increase MVO2 or reduce subendocardial blood flow in the setting of heart failure or in heart failure with severe LV hypertrophy. These findings distinguish CK-1827452 from other inotropic mechanisms and suggest it may be beneficial for the long-term treatment of patients with heart failure.