

Moderated Posters

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Chronic Treatment with GLP-1 Improves Cardiac Function, Delays Cardiac Remodeling and Enhances Exercise Performance in Rats with Congestive Heart Failure

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Failing heart is characterized by inefficient substrate utilization. Glucagon-like peptide-1 (GLP-1) is a gut peptide with insulinotropic and insulinomimetic properties that stimulates glucose uptake and improves the efficiency of energy production. Acute treatment with GLP-1 exerts cardioprotective effects in patients with myocardial infarction (MI). We hypothesized that long-term treatment with GLP-1 could improve cardiac function and exercise capacity (EC) in rats with MI-induced congestive heart failure (CHF). **Methods:** SD rats underwent left coronary artery ligation to induce MI and subsequently CHF. Some rats underwent sham surgery. Starting 2 weeks (wk) after coronary ligation, rats were treated with GLP-1 (2.5 or 25 pmol/kg/min) or vehicle for 11 wk via subcutaneous infusion. Cardiac function and remodeling were assessed by echocardiography. At the end of study, rats underwent treadmill testing and hemodynamic measurements. **Results:** Compared with sham surgery group, peak velocity ratio of the E wave and A wave was increased by 116% ($p < 0.001$) in vehicle group at 13 wk after MI. GLP-1 at each dose prevented such increase during the progression of CHF. At 13 wk after MI, left ventricular end diastolic pressure (LVEDP) in vehicle group increased by 97% ($p < 0.001$) compared with sham group. GLP-1 eliminated the LVEDP elevation. Cardiac output and $+dp/dt_{max}$ in vehicle group dropped by 19% ($p < 0.01$) and 24% ($p < 0.05$), respectively, compared with sham group. GLP-1 at each dose normalized cardiac output and contractility. LV end diastolic dimension and systolic dimension were significantly enlarged during the progression of CHF. GLP-1 significantly attenuated such remodeling. At 25 pmol/kg/min, GLP-1 significantly reduced LV mass, infarct size dropped by 30% ($p < 0.05$) compared with vehicle group. Compared with sham group, baseline plasma lactate level was significantly higher in vehicle group (2.67 ± 0.2 vs 1.72 ± 0.17 mM, $p < 0.001$). GLP-1 at each dose significantly reduced baseline lactate level compared with vehicle group. Although peak metabolic rate, oxygen uptake (VO_2) and lactate level were comparable compared with vehicle group during treadmill test, GLP-1 dose-dependently improved EC and exercise efficiency (EC/VO_2). **Conclusion:** Long-term treatment with GLP-1 improved cardiac function, attenuated remodeling, and enhanced exercise performance in a rat model of CHF. Development of GLP-1 receptor agonists may represent a novel approach for the treatment of CHF.

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Direct Activation of Cardiac Myosin by CK-1827452 Improves Cardiac Function in a Dog Heart Failure ModelF. Malik¹, K. A. Elias¹, J. T. Finer¹, B. P. Morgan¹, R. Sakowicz¹, R. Anderson¹, R. Baliga¹, L. Conn¹, D. Cox¹, M. Garard¹, J. Hartman¹, J. Irvine¹, R. Kawas¹, E. Kraynack¹, A. Kuklov¹, K. H. Lee¹, P. Lu¹, A. Muci¹, D. W. Pierce¹, H. Rodriguez¹, I. Suehiro¹, S. H. Sueoka¹, S. Sylvester¹, T. Tochimoto¹, C. Valdez¹, W. Wang¹, T. Katori¹, D. A. Kass¹, Y. T. Shen¹, S. F. Vatner¹, D. J. Morgans²; ¹Div. Cardiology, Johns Hopkins, Baltimore, MD; ²CVRI, UMDNJ, Newark, NJ; ³Cytokinetics, SSF, CA

Introduction and Hypothesis: Current inotropes increase intracellular calcium and secondarily increase cardiac contractility. In addition, they increase heart rate, oxygen consumption, the incidence of arrhythmias, and reduce blood pressure. A more direct approach to improving cardiac contractility that may address these liabilities is activation of cardiac myosin itself. We sought to demonstrate our therapeutic hypothesis with a small molecule activator of cardiac myosin, CK-1827452. **Methods:** Using a reconstituted cardiac sarcomere, we screened a small molecule library and identified several chemical classes that activate the cardiac myosin ATPase. One class has been optimized extensively using an iterative process guided by biochemical and cellular activity; CK-1827452 is the most advanced exemplar of this class. We investigated its pharmacology in isolated adult rat cardiac myocytes, anesthetized rats, and a chronically instrumented canine model of heart failure induced by myocardial infarction combined with rapid ventricular pacing. **Results:** CK-1827452 increased cardiac myocyte contractility ($EC_{20} = 0.2 \mu M$) but did not increase the magnitude or change the kinetics of the calcium transient at concentrations up to $10 \mu M$ in Fura-2 loaded myocytes. CK-1827452 ($30 \mu M$) did not inhibit phosphodiesterase type 3. In anesthetized rats, CK-1827452 increased echocardiographic fractional shortening from $45 \pm 5.1\%$ to $56 \pm 4.6\%$ after a 30 minute infusion at 1.5 mg/kg/hr ($n = 6$, $p < 0.01$). In conscious dogs with heart failure, CK-1827452 (0.5 mg/kg bolus , then $0.5 \text{ mg/kg/hr i.v.}$ for 6–8 hours) increased fractional shortening by $74 \pm 7\%$, cardiac output by $45 \pm 9\%$, and stroke volume by $101 \pm 19\%$. Heart rate decreased by $27 \pm 4\%$ and left atrial pressure fell from $22 \pm 2 \text{ mmHg}$ to $10 \pm 2 \text{ mmHg}$ ($p < 0.05$ for all). In addition, neither mean arterial pressure nor coronary blood flow changed significantly and diastolic function was not impaired. There were no significant changes in a vehicle treated group. **Conclusions:** CK-1827452 improves cardiac function in a manner consistent with our therapeutic hypothesis. This approach may prove beneficial in patients with heart failure.

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Intravenous Istaroxime Improves Left Ventricular Systolic Function in Dogs with Advanced Heart Failure without Increasing Myocardial Oxygen Consumption Makoto Imai¹, Mihai Gheorghide², Doug Cowart³, Dan Zhang³, Antonino Amato³, Paolo Carminati⁴, Hani N. Sabbah¹; ¹Medicine, Henry Ford Health System, Detroit, MI; ²Medicine, Northwestern University, Chicago, IL; ³Sigma-Tau Research, Inc., Gaithersburg, MD; ⁴Sigma-Tau S.p.A., Pomezia (RM), Italy

Background: Istaroxime (ISTA) is a novel inotropic agent that increases sarcoplasmic reticulum Ca^{2+} -ATPase activity and inhibits the Na^+ - K^+ ATPase pump. We tested the effects of intravenous ISTA on LV systolic function in dogs with coronary microembolization-induced heart failure (HF). **Methods:** Studies were performed in 7 dogs with HF (LV ejection fraction, EF $25 \pm 1\%$). Each dog received intravenous ISTA or saline in random order one week apart in equal volume/volume escalating doses with each dose maintained for one hour. Escalating ISTA doses of 0.5, 1.0, 2.0, 3.0 and $5.0 \mu g/kg/min$ were used. Hemodynamic and ventriculographic measurements were made at baseline and at the end of each hour of each dose of ISTA or saline used. Measurements included heart rate (HR), mean aortic pressure (mAoP), LV end-diastolic (EDV) and end-systolic (ESV) volumes, LV EF and myocardial oxygen consumption (MVO₂). The latter measured as the product of total LV coronary blood flow and the difference in O₂ content between arterial and coronary sinus blood. **Results:** Saline had no effect on HR, mAoP or on any measures of LV systolic function. ISTA data are shown in Table I. Compared to baseline, ISTA had no effect on HR with only a modest but significant reduction of mAoP at doses of 3.0 and $5.0 \mu g/kg/min$. ISTA decreased EDV and ESV and significantly increased EF in a dose-dependent manner. This improvement in LV function was not associated with increased MVO₂ or the development of ventricular arrhythmias. **Conclusions:** In dogs with advanced HF, intravenous ISTA elicits potent positive inotropic effects. Unlike classic c-AMP-dependent positive inotropic agents, ISTA elicits its benefits without increasing MVO₂ and without chronotropic or pro-arrhythmic activity. The results suggest that ISTA may be useful in the treatment of patients with advanced decompensated HF.

Table I. Istaroxime in Dogs with Advanced HF

Istaroxime	Baseline	0.5 $\mu g/kg/min$	1.0 $\mu g/kg/min$	2.0 $\mu g/kg/min$	3.0 $\mu g/kg/min$	5.0 $\mu g/kg/min$
LV EDV (ml)	74 \pm 2	75 \pm 2	72 \pm 2	69 \pm 2*	67 \pm 2*	66 \pm 1*
LV ESV (ml)	56 \pm 2	55 \pm 2	52 \pm 2*	46 \pm 2*	41 \pm 2*	40 \pm 3*
LV EF (%)	25 \pm 1	26 \pm 1	29 \pm 1*	33 \pm 2*	38 \pm 1*	42 \pm 2*
MMVO ₂ (μ moles/min)	194 \pm 21	198 \pm 15	189 \pm 15	210 \pm 24	159 \pm 23	144 \pm 20

* = $p < 0.05$ vs. Baseline

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D-Ribose Improves Ventilatory Efficiency in Congestive Heart Failure Patients (NYHA Classes II-IV)Nampalli Vijay¹, Dean MacCarter¹, Melinda Washam¹, Mark Munger², John St.Cyr³; ¹Cardiology, Aurora Denver Cardiology Associates, Denver, CO; ²College of Pharmacy, University of Utah, Salt Lake City, UT; ³Clinical Research, Bioenergy, Inc., Minneapolis, MN

Energy is essential to maintain cellular integrity and function. Congestive heart failure (CHF) patients have decreased levels of myocardial high energy compounds, contributing to myocardial dysfunction. Advanced class CHF pts have compromised ventilatory efficiency (Veff), limiting their exercise reserve even during sub-maximal exertion. Ribose (R), a natural occurring pentose carbohydrate, has repeatedly shown to enhance high energy phosphates and improve diastolic dysfunction following myocardial ischemia. A two center study investigated the effect of R on Veff in CHF pts (NYHA classes II-IV). Twenty-three pts consumed oral R for 8 weeks (5 gm, tid). Repeat cardiopulmonary exercise tests¹ using a 4-minute sub-maximal step protocol was completed and a retrospective analysis was performed after the 8 week routine clinical visit. Ventilatory efficiency was assessed up to the anaerobic threshold at baseline and at 8 weeks of R. Ribose significantly improved Veff (VE to VCO₂ linear slope) in classes III and IV, with a trend towards improvement in class II pts (table, mean \pm SD). Oxygen uptake efficiency (linear regression slope of VO₂ to log VE) demonstrated a strong trend in classes III and IV (data not shown).

	Ventilatory Efficiency	
	Pre-R	Post-R
Class II, n = 8	29.4 \pm 5.0	28.8 \pm 4.9
Class III, n = 9	43.9 \pm 4.8	38.5 \pm 3.9*
Class IV, n = 6	60.4 \pm 5.8	46.1 \pm 6.8**

(* $p < 0.05$, ** $p < 0.005$)

Besides the consistently reported benefits of R in improving myocardial function, this study demonstrated a significant improvement in Veff (classes III and IV), the most powerful predictor of survival in CHF pts. Oral R as an adjunctive therapy utilizes a unique metabolic approach not provided by conventional guidelines.