Report

Short-Term Treatment With Ranolazine Improves Mechanical Efficiency in Dogs With Chronic Heart Failure

Margaret P. Chandler, William C. Stanley, Hideaki Morita, George Suzuki, Bridgette A. Roth, Brent Blackburn, Andrew Wolff, Hani N. Sabbah

The present study assesses whether ranolazine increases left ventricular (LV) function without an increase in myocardial oxygen consumption (MV\(\dot{O}_2\)) and thus improves LV mechanical efficiency in dogs with heart failure (HF). Ranolazine did not change MV\(\dot{O}_2\) and LV mechanical efficiency increased (22.4±2.8% to 30.9±3.4% \(P<0.05\)). In contrast, dobutamine significantly increased MV\(\dot{O}_2\) and did not improve mechanical efficiency. Thus, short-term treatment with ranolazine improved LV function without an increase in MV\(\dot{O}_2\), resulting in an increased myocardial mechanical efficiency in dogs with HF.

Free fatty acids (FFAs) are the primary energy substrate of the myocardium; however, they are not as efficient as glucose and lactate. Studies in isolated rat hearts, dogs, pigs, and humans show that external power is reduced for a given myocardial oxygen consumption (MV\(\dot{O}_2\)) when the heart has elevated FFA oxidation. Abnormalities of energy metabolism may contribute to the poor left ventricular (LV) function that characterizes heart failure (HF). Patients with HF designated as New York Heart Association (NYHA) class II–III have greater myocardial FFA oxidation and lower carbohydrate oxidation compared with healthy individuals. Impaired carbohydrate oxidation may contribute to mechanical dysfunction in the failing heart, as suggested by improved contractile function and efficiency in HF patients when carbohydrate oxidation is stimulated with dichloroacetate or intracoronary pyruvate.

It has been suggested that pharmacological inhibition of myocardial FFA oxidation improves LV function without an increase in MV\(\dot{O}_2\), and thus increases LV mechanical efficiency. Ranolazine inhibits FFA \(\beta\)-oxidation and significantly improves treadmill time to onset of angina and 1-mm ST-segment depression in patients with chronic stable angina. The purpose of this investigation was to measure MV\(\dot{O}_2\), LV function, and mechanical efficiency during short-term treatment with ranolazine. We used dobutamine, a positive inotropic agent that should not improve the mechanical efficiency, as a comparator. In addition, the net myocardial uptake of FFAs, glucose, and lactate was assessed.

Materials and Methods

The canine model of chronic HF was previously described in detail. Chronic LV dysfunction and failure were produced by multiple sequential intracoronary embolizations, which results in loss of viable myocardium. Eight healthy dogs (Hodgins Kennel, Howell, Mich) underwent microembolizations to induce HF. This study was approved by the Henry Ford Health System Institutional Animal Care and Use Committee.

Dogs were anesthetized and catherized in the femoral vein, coronary sinus, and left ventricle under fluoroscopic guidance, and LV pressure was measured. Cardiac function and coronary flow measurements were made and arterial and coronary sinus (cs) blood samples drawn at baseline and after 30 minutes of treatment with either ranolazine (0.5 mg/kg bolus, followed by a constant infusion of 1.0 mg · kg \(^{-1}\) · h \(^{-1}\)) or dobutamine (initial infusion 1 μg · kg \(^{-1}\) · min \(^{-1}\) and up-titrated to 3 or 4 μg · kg \(^{-1}\) · min \(^{-1}\)). LV end-diastolic volume (LVEDV) and end-diastolic volume (LVEDV) were measured from angiographic silhouettes. Coronary artery blood velocity was measured with a Doppler flow velocity wire placed in the left circumflex or left anterior descending coronary artery. Blood samples were analyzed for glucose and lactate in blood and for plasma FFAs.

Calculations

The following calculations were made:

- Stroke volume (SV) = LVEDV–LVEDV/LVEDV
- Cardiac output (CO) = (flow velocity × arterial cross-sectional area) \(\times\) heart rate (HR)
- LV ejection fraction = (LVEDV–LVEDV)/LVEDV \times 100

Total LV blood flow = (flow velocity × arterial cross-sectional area) \(\times\) heart rate

- MV\(\dot{O}_2\) = (LV blood flow × arterial–cs O\(_2\) difference)
- LV power (watts) = (CO) \(\times\) (10 \(^{-7}\) m \(^{3}\)/L) (peak LVP) (133.3 Pa/ mm Hg)/(60 s/min)
- LV energy expenditure was calculated from MV\(\dot{O}_2\) assuming 20.2 J/μmol of O\(_2\)
- LV mechanical efficiency = LV power/MV\(\dot{O}_2\)

Pretreatment values were compared with posttreatment values using a two-tailed paired Student’s \(t\) test with significance set at \(P<0.05\).

Results

Ranolazine and dobutamine increased SV, CO, peak +dP/dt, ejection fraction, and power, without affecting HR or peak LVP. The improvement in LV function with ranolazine was not accompanied by an increase in coronary blood flow or MV\(\dot{O}_2\) but did result in a significant increase in LV mechanical efficiency (22.4±2.8% to 30.9±3.4%; \(P<0.05\)) (Table 1, Figure). In contrast, the improvement in LV function with dobutamine was accompanied by increases in LV power, coronary blood flow, and MV\(\dot{O}_2\) (33±13% increase in MV\(\dot{O}_2\)), resulting in no change in LV mechanical efficiency (Figure).

To determine whether the improvements in cardiac function with ranolazine were specific to the HF state, the effects of ranolazine were assessed in 8 healthy dogs; there were no significant effects on any metabolic or functional measures.
except a small but uniform increase in SV from 33±2 to 35±2 mL (P<0.05).

The net rate of myocardial uptake of FFAs, glucose, and lactate was not affected by treatment with ranolazine in HF. However, dobutamine significantly increased FFA uptake (Table 2).

Discussion

Short-term treatment with ranolazine resulted in greater LV power, no increase in energy expenditure, and greater LV mechanical efficiency in dogs with chronic HF. In comparison, dobutamine increased LV power and energy expenditure and thus did not affect LV mechanical efficiency. Although recent human and animal studies demonstrate that LV mechanical efficiency can be increased in HF by reducing oxidative stress with allopurinol15,16 or biventricular pacing, 17 there are currently no HF therapies aimed specifically at optimizing myocardial energy metabolism. Studies in HF patients suggest that long-term treatment with β-blockers results in decreased FFA oxidation and enhanced carbohydrate oxidation.18 Treatment with metoprolol in HF patients improved LV efficiency by decreasing energy expenditure without a change in LV power.19 The short-term improvement in LV power and efficiency seen with ranolazine suggests a novel approach for treating HF with drugs designed to improve myocardial efficiency by optimizing energy metabolism.

Ranolazine did not affect the uptake of FFAs, glucose, or lactate, yet dobutamine significantly increased FFA uptake (Table 2), which suggests the increase in MVO₂ was supported by greater FFA uptake. Because of turnover of intracellular triglyceride and glycogen stores, the net uptake of FFAs and glucose does not necessarily reflect the rate of oxidation of exogenous FFAs and glucose. In future studies, the rate of substrate oxidation should be measured using radioisotopes.

Our results do not provide a mechanism for the greater mechanical efficiency observed with ranolazine in HF. Ranolazine is a partial FFA oxidation inhibitor,10 and there is evidence that suppressing FFA oxidation improves LV mechanical efficiency. Theoretically, FFA oxidation requires 11% more oxygen consumption for a given ATP synthesis than glucose or lactate.5 FFAs have been shown to uncouple oxidative phosphorylation,20 cause wasting of O₂ by mitochondria,21 and increase the MVO₂ for a given LV power. Previously shown in this HF model were severe abnormalities in mitochondrial structure, hyperplasia with a reduction of mitochondrial size,22 and depressed substrate and ADP-stimulated mitochondrial respiration compared with healthy dogs.5 Thus, the improved efficiency with ranolazine is likely attributable to either greater ATP synthesis per O₂ consumed and/or more effective ATP use by cardiac cells.

In conclusion, ranolazine improved LV mechanical power without affecting MVO₂ and thus resulted in a greater LV mechanical efficiency in dogs with HF. Future studies need to address the effect of long-term treatment with ranolazine on cardiac function, LV remodeling, and clinical outcome.

### TABLE 1. Hemodynamic Responses to Short-Term Treatment With Ranolazine and Dobutamine in Dogs With HF

<table>
<thead>
<tr>
<th></th>
<th>Ranolazine Before Treatment</th>
<th>Ranolazine After Treatment</th>
<th>Dobutamine Before Treatment</th>
<th>Dobutamine After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak LVP, mm Hg</td>
<td>102±8</td>
<td>106±8</td>
<td>105±6</td>
<td>114±8</td>
</tr>
<tr>
<td>Peak LV +dP/dt, mm Hg · sec⁻¹</td>
<td>1733±158</td>
<td>1983±177*</td>
<td>1766±105</td>
<td>2243±141*</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>14±2</td>
<td>10±2</td>
<td>15±2</td>
<td>14±3</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>51±3</td>
<td>44±3</td>
<td>50±3</td>
<td>43±3*</td>
</tr>
<tr>
<td>Mean aortic pressure, mm Hg</td>
<td>80±5</td>
<td>83±5*</td>
<td>83±7</td>
<td>90±7</td>
</tr>
<tr>
<td>SV, mL</td>
<td>20±2</td>
<td>26±2*</td>
<td>20±2</td>
<td>28±3*</td>
</tr>
<tr>
<td>CO₂, L · min⁻¹</td>
<td>1.7±0.2</td>
<td>2.3±0.2*</td>
<td>1.9±0.3</td>
<td>2.6±0.4*</td>
</tr>
<tr>
<td>Coronary blood flow, mL · min⁻¹</td>
<td>56±12</td>
<td>53±9</td>
<td>60±12</td>
<td>83±17*</td>
</tr>
<tr>
<td>MVO₂, watts</td>
<td>1.89±0.37</td>
<td>1.90±0.34</td>
<td>1.50±0.21</td>
<td>2.06±0.41*</td>
</tr>
<tr>
<td>LV power, watts</td>
<td>0.40±0.07</td>
<td>0.54±0.08*</td>
<td>0.45±0.08</td>
<td>0.65±0.12*</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>28±2</td>
<td>37±2*</td>
<td>28±3</td>
<td>40±5*</td>
</tr>
</tbody>
</table>

*P<0.05, before vs after treatment.
TABLE 2. Myocardial Glucose, Lactate, and FFA Uptake Before and After Short-Term Treatment With Dobutamine and Ranolazine in Dogs With HF

<table>
<thead>
<tr>
<th></th>
<th>Ranolazine</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Glucose uptake, ( \mu \text{mol \cdot min}^{-1} )</td>
<td>10.0±2.4</td>
<td>10.7±2.7</td>
</tr>
<tr>
<td>Lactate uptake, ( \mu \text{mol \cdot min}^{-1} )</td>
<td>33.5±7.5</td>
<td>39.8±9.7</td>
</tr>
<tr>
<td>FFA uptake, ( \mu \text{mol \cdot min}^{-1} )</td>
<td>3.3±0.8</td>
<td>3.1±0.9</td>
</tr>
</tbody>
</table>

*P<0.05, before vs after treatment.

Acknowledgments
This study was supported by National Heart, Lung, and Blood Institute grants HL 49090 (Dr Sabbah) and HL 64848 (Dr Stanley) and a grant from CV Therapeutics, Inc.

References

Key Words: heart failure ■ mechanical efficiency ■ myocardial metabolism ■ fatty acids
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