INTRAVENTOUS RANOLAZINE RELIEVES ISCHEMIA BY INCREASING MYOCARDIAL ADENOSINE LEVELS

Moderated Poster Contributions
Stable Ischemic Heart Disease Moderated Poster Theater, Poster Hall B1
Saturday, March 14, 2015, 10:45 a.m.-10:55 a.m.

Session Title: Stable Ischemic Heart Disease: Highlighted Research
Abstract Category: 25. Stable Ischemic Heart Disease: Basic
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Authors: Dai-Trang Elizabeth Le, Kevin Wei, Yan Zhao, Matthew Nugent, Luiz Belardinelli, Sanjiv Kaul, Portland VA Medical Center, Portland, OR, USA, Knight Cardiovascular Institute-Oregon Health and Science University, Portland, OR, USA

Background: The mechanism of action by which ranolazine (RAN) reduces stress-induced myocardial ischemia is not fully understood. We hypothesized that RAN relieves ischemia through the cardioprotective effects of adenosine (ADEN).

Methods: Non-flow limiting stenosis was created in the LAD artery in 17 open-chest dogs. We compared hemodynamic changes, global (peak LV dP/dt) and regional (radial strain) myocardial function, myocardial perfusion, and regional ADEN level in the absence and presence of intravenous RAN at rest and during dobutamine (DOB) stress.

Results: With stenosis, RAN significantly reduced the rate-pressure product, LAD pressure without changing pressure gradient, peak LV dP/dt without changing left atrial pressure, and radial strain. It had no effect on LAD blood flow. DOB produced the opposite effects, which were not altered with the addition of RAN. Blood flow improved and ADEN increased at rest and with DOB in the presence of RAN. Arterial blood volume also increased without change in myocardial blood volume, implying dilatation of intramyocardial vessels.

Conclusion: RAN increased myocardial ADEN levels, which likely is cardioprotective during exercise-induced ischemia. The mechanism of increased ADEN levels induced by RAN is unknown but may be related to increased availability in association with resistance vessel dilatation. This is the first observation of this novel mechanism of action of RAN during intravenous administration.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Rest+RAN</th>
<th>Rest+DOB</th>
<th>DOB+RAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (beats/min)</td>
<td>105±2</td>
<td>99±2</td>
<td>158±4</td>
<td>159±4</td>
</tr>
<tr>
<td>Mean Aortic Pressure(mmHg)</td>
<td>98±3</td>
<td>83±2</td>
<td>153±9</td>
<td>151±7</td>
</tr>
<tr>
<td>RPP (mmHg x mmHg)</td>
<td>12,070±621</td>
<td>10,589±481 *</td>
<td>39,015±1,909</td>
<td>24,513±1,908</td>
</tr>
<tr>
<td>LAD Aortic Pressure(mmHg)</td>
<td>81±3</td>
<td>65±3</td>
<td>101±6</td>
<td>76±5</td>
</tr>
<tr>
<td>Aortic-LAD Pressure Gradient(mmHg)</td>
<td>17±3</td>
<td>13±1</td>
<td>50±6</td>
<td>42±6</td>
</tr>
<tr>
<td>LAD Blood Flow (mL/min)</td>
<td>20±1</td>
<td>17±1</td>
<td>44±4</td>
<td>36±3</td>
</tr>
</tbody>
</table>

**Hemodynamics**

**Myocardial Function**

**Myocardial Blood Flow**

**Arterial Blood Volume (ml/kg)**

**MYOCARDIAL BLOOD FLOW**

**LAD Endocardial/Epicardial Ratio**

**Arterial Blood Volume (ml/kg)**

**LAD Myocardial Blood Volume (ml)**

**METABOLIC DATA**

LAD Regional Adenosine (ng/ml): 10.6±2 21.7±8 3 * 20.5±3 2 * 43±13 3

Ran=ranolazine, Dob=dobutamine, RPP=rate pressure product, LAD=left anterior descending, SD=standard deviation
* p<0.05 vs. rest, † p<0.01 vs. stenosis.