Effects of Left Ventricular Receptor Stimulation on Coronary Blood Flow in Conscious Dogs

Irving H. Zucker, Kurtis G. Cornish, Johnnie Hackley, and Kay Bliss

The present study was undertaken to determine the effects of intracoronary administration of the veratrum alkaloid veratridine on coronary blood flow and resistance in conscious, chronically instrumented intact and sinoaortic denervated dogs. Ten dogs were instrumented with a Doppler flow probe on the left anterior descending coronary artery. A chronic catheter was placed in the left circumflex coronary artery and in the aorta and left atrium. A Konigsberg pressure cell was placed in the left ventricle, and pacing leads were attached to the left atrium and ventricle. While heart rate was kept constant, bolus intracoronary injections of veratridine (0.1–0.4 μg/kg) were administered in the unblocked state after β1-receptor blockade, after α-receptor blockade, and after cholinergic blockade. In the unblocked state, late diastolic coronary resistance fell by 34.7±5.0%. The maximum response was achieved at a time when arterial pressure was not significantly different from control. After α-blockade, coronary resistance fell by 29.1±7.9%. After combined α- and β-blockade, coronary resistance fell by 25.4±6.5% in response to veratridine. The addition of atropine completely blocked the decrease in coronary resistance, changing it by an average of −0.10±2.5%. The responses in sinoaortic denervated dogs were similar to those in intact animals. The response was abolished by vagotomy. We conclude that cardiac receptor stimulation causes a reflex decrease in coronary resistance in the awake dog that is completely accountable by a cholinergic mechanism. (Circulation Research 1987;61(suppl II):II-54-II-60)

Baroreflex, chemoreflex, and cardiac receptor stimulation have been shown to modulate coronary blood flow in anesthetized dogs via a cholinergic mechanism. 1-4 Both baroreflex and chemoreflex stimulation have also been shown to alter coronary blood flow in conscious animals. 5-7 There have not been any studies, however, that have investigated the role of cardiac receptors (left ventricular receptors in particular) on coronary blood flow and resistance in the awake animal. In a study done by Feigl in the anesthetized dog, 8 it was determined that cardiac receptor stimulation resulted in a vasodilation that was cholinergic in origin. The role of other components of the autonomic innervation of the coronary blood vessels was not investigated in that study because the measurements were made after α- and β-blockade. Therefore, the present study was undertaken with three primary goals: to determine if stimulation of left ventricular receptors with intracoronary injections of veratridine in conscious, chronically instrumented dogs increases coronary blood flow and decreases coronary resistance, to determine the autonomic components of the observed change in resistance, and to determine if removal of the arterial baroreceptors altered the coronary response to ventricular receptor stimulation.

Materials and Methods

Ten mongrel dogs weighing 20–30 kg were used. Each dog was instrumented using techniques that have been described previously. 8,9 Briefly, under halothane anesthesia, a left thoracotomy was performed. A 20-MHz pulsed Doppler coronary flow transducer was placed around the left anterior descending coronary artery (LAD) as close to the bifurcation with the circumflex artery (CX) as possible. This transducer was similar in design to that described by Hayward et al. 10 A catheter was inserted into the left circumflex coronary artery using the technique of Herd and Barger. 11 Catheters were also placed in the descending thoracic aorta and in the left atrium. A Konigsberg pressure cell (P7) was placed in the left ventricle via a stab wound in the apex. Pacing electrodes were sutured to the left atrial appendage and to the left ventricle.

In 5 of the 10 dogs, the aortic arch was stripped during the initial thoracotomy to denervate the aortic baroreceptors. These 5 dogs subsequently underwent carotid sinus denervation to produce a condition of chronic sinoaortic denervation (SAD). Satisfactory SAD was confirmed by the lack of any heart rate response to large changes in blood pressure (30–40 mm Hg) induced by intravenous infusion of phenylephrine and nitroprusside. At the conclusion of all surgery, the animals were returned to the kennel and treated for at least 1 week with antibiotic therapy. All catheters were flushed daily with heparin sodium.

The dogs were allowed to recover for approximately 2 weeks before the experiment. During this time, they were brought to the laboratory periodically and trained to lie quietly on a padded table.

Hemodynamic Recording

All pressures with the exception of left ventricular pressure (LVP) were recorded using Millar catheter tipped pressure transducers, which were attached to each catheter. The signals were conditioned using
Honeywell bridge amplifiers (model 143, Denver, Colo.). Heart rate was recorded using a Honeywell cardiotachometer triggered by the left ventricular or aortic pressure pulse. Left ventricular (LV) dP/dt was determined with a differentiating circuit (model 622, Biotronex, Denver, Colo.). All parameters were recorded simultaneously on an eight-channel Hewlett-Packard recorder (model 7758A, Waltham, Mass.) and a Vetter FM tape recorder (model D, Rebersburg, Penn.).

Protocol

After the dog was placed on the table and all catheters were appropriately attached and calibrated, the experiment began. When all hemodynamic variables were stable, a control recording was taken. With the heart paced, a bolus injection of veratridine was given at a dose of 0.1–0.4 μg/kg. These doses had no hemodynamic effects when given intravenously. The dose depended on the animal’s sensitivity to veratridine. The veratridine was given as a 0.5-ml bolus followed by a saline flush of an equal amount. Intracoronary vehicle (isotonic saline) had no effect on any hemodynamic parameter measured. Continuous recordings were made of all hemodynamic parameters for the following 60 seconds. Injections of veratridine were made with the heart paced during each of the following conditions: metoprolol (1 mg/kg), metoprolol + phentolamine (1 mg/kg), metoprolol + atropine methylbromide (0.1 mg/kg), and metoprolol + phentolamine + atropine. We waited at least 20 minutes between injections of veratridine to minimize tachyphylaxis.

Data Analysis

Mean arterial pressure and mean coronary flow velocity were sampled every 2 seconds beginning at 10 seconds before the injection of veratridine and ending approximately 60 seconds after the injection. Sampling was done with an IBM PC XT computer and a Tecmar (Labmaster, Solon, Okla.) analog-to-digital converter. Late diastolic flow velocity, systolic and late diastolic arterial pressure, LVP, left ventricular end-diastolic pressure (LVEDP), and LV dP/dt were quantified using a digitizing tablet directly from the strip chart records.

Since it has been shown that the Doppler shift is proportional to the flow velocity and absolute volume flow if diameter remains constant, we chose to express the coronary flow data in kHz Doppler shift. In these experiments, the flow probe had grown in during the recovery period, and it was presumed that the diameter was well fixed. Coronary resistance was expressed as both mean resistance and late diastolic resistance and was calculated as the ratio of the appropriate pressure to the appropriate Doppler shift; the units of resistance were mm Hg/kHz.

Baseline parameters were compared under each condition using a one-way analysis of variance and Duncan’s new multiple range test. A two-way analysis of variance was used to determine statistical significance for each parameter under each condition and across time. Statistical significance was assumed at p<0.05.

Results

Figure 1 shows a recording of the response to an intracoronary injection of veratridine in an intact dog without autonomic blockade. In this particular record, the heart was not paced. However, as can be seen, the injection did not evoke much of a decrease in arterial pressure or heart rate, but increased mean and pulsatile coronary blood flow velocity. The latency of the response was approximately 5 seconds from the start of the injection, and the response reached a peak at 8 seconds. There was little, if any, change in LVP or LV dP/dt. Table 1 shows the average baseline values under each condition for each parameter in the intact dogs. As can be seen, the addition of the β1-blocker metoprolol did not alter the resting parameters from the control or unblocked state. The addition of phentolamine caused a significant decrease in mean arterial pressure (LVP) and left ventricular end-diastolic pressure (LVEDP), and LV dP/dt.
Table 1. Control Hemodynamic Values for Each Intervention in Intact Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Metoprolol</th>
<th>Metoprolol + phenolamine</th>
<th>Metoprolol + phenolamine + atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP (mm Hg)</td>
<td>97.1 ± 2.2</td>
<td>99.0 ± 2.4</td>
<td>86.3 ± 4.2*</td>
<td>89.7 ± 4.0*</td>
</tr>
<tr>
<td>MCBF (kHz)</td>
<td>2.18 ± 0.25</td>
<td>1.96 ± 0.15</td>
<td>1.64 ± 0.23*</td>
<td>1.40 ± 0.18*</td>
</tr>
<tr>
<td>MCR (mm Hg/kHz)</td>
<td>58.4 ± 5.1</td>
<td>62.2 ± 5.8</td>
<td>73.5 ± 12.8</td>
<td>72.2 ± 8.5</td>
</tr>
<tr>
<td>LDP (mm Hg)</td>
<td>92.0 ± 2.5</td>
<td>95.8 ± 2.7</td>
<td>81.7 ± 3.7</td>
<td>82.3 ± 4.1</td>
</tr>
<tr>
<td>LDF (kHz)</td>
<td>2.37 ± 0.20</td>
<td>2.21 ± 0.21</td>
<td>1.98 ± 0.30*</td>
<td>1.67 ± 0.19*</td>
</tr>
<tr>
<td>LDR (mm Hg/kHz)</td>
<td>53.6 ± 5.9</td>
<td>58.6 ± 7.2</td>
<td>57.7 ± 10.5</td>
<td>64.2 ± 9.6</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>157.5 ± 5.8</td>
<td>151.5 ± 2.7</td>
<td>147.3 ± 3.2*</td>
<td>136.0 ± 6.6*</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>133.5 ± 3.6</td>
<td>133.7 ± 4.2</td>
<td>118.5 ± 7.1</td>
<td>119.7 ± 7.0</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>6.4 ± 1.3</td>
<td>9.6 ± 1.4</td>
<td>9.0 ± 2.3</td>
<td>7.0 ± 1.3</td>
</tr>
<tr>
<td>dP/dt (mm Hg/sec)</td>
<td>2,273.6 ± 78.1</td>
<td>2,097.7 ± 109.8</td>
<td>1,880.3 ± 141.1*</td>
<td>2,067.3 ± 164.2</td>
</tr>
</tbody>
</table>

MABP, mean arterial pressure; MCBF, mean coronary flow velocity; MCR, mean coronary resistance; LDP, late diastolic pressure; LDF, late diastolic flow velocity; LDR, late diastolic resistance; HR, heart rate; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end diastolic pressure; dP/dt, maximum first derivative of left ventricular pressure.

* significantly different from control; n = 10.

Discussion

It is well documented that veratridine stimulates cardiac receptors with vagal afferents. This agent most likely stimulates both mechanically and chemically sensitive endings. The site of administration of veratridine in the present study makes it highly likely that receptors in the posterior wall of the left ventricle were stimulated. Stimulation of left ventricular receptors in conscious dogs has been shown to cause a slight but statistically significant decrease in total peripheral and iliac resistances. Similar results were reported by Barron and Bishop. It could be demonstrated in studies that reflex cholinergic vasodilation was a small component of the decrease in resistance. As recently reviewed by Feigl, cholinergically mediated coronary vasodilation in anesthetized animals has been demonstrated by a number of investigators and in conscious animals by a lesser number of investigators. To our knowledge, there has been no study that has investigated the effects of left ventricular receptor stimulation on coronary blood flow in conscious dogs.

The primary determinants of coronary blood flow are perfusion pressure, myocardial oxygen consumption, myocardial compressive forces, and neural influences. We have tried to demonstrate that the results of the present study were primarily attributable to a neural reflex mediating cholinergic vasodilation. Since the primary determinants of myocardial oxygen consumption are inotropic state, heart rate, and wall tension, the
present experiments were done around a background of constant heart rate, $\beta_1$-blockade, and few, if any, changes in LVEDP to minimize metabolically related changes in coronary blood flow and resistance. Furthermore, the changes in coronary resistance in response to intracoronary veratridine were assessed in late diastole, a time when myocardial compressive forces are at a minimum. Although stimulation of ventricular receptors caused a decrease in arterial pressure, the time course of this response was such that the peak coronary flow velocity and resistance changes occurred at a time (approximately 8 seconds) when arterial pressure was not significantly reduced. By the time arterial pressure had reached its minimum value (approximately 15 seconds), coronary blood flow and resistance were returning to control levels. In addition, following the administration of phentolamine + atropine, there was still a fall in arterial pressure, which was similar to that seen following metoprolol; however, coronary flow velocity and resistance did not change (Figures 3 and 4). The efferent mechanism of this reflex was attributable primarily to activation of cholinergic fibers, most probably in the vagi. The withdrawal of $\alpha$-adrenergic tone to the coronary vasculature is an unlikely mechanism because the reduction in coronary resistance following phentolamine in response to veratridine was similar to that following metoprolol before phentolamine was given. Because the

**Figure 2.** Time course of mean coronary blood flow velocity (A) and mean coronary resistance (B) expressed as percent change from control for each intervention tested. Standard error bars have been left off for clarity.
administration of atropine abolished the coronary vasodilation, it is unprobable that it was caused by the activation of $\beta_2$-receptors. It is also not probable that the tachycardia induced by atropine prevented the coronary vasodilation because there was a similar abolition of the response following combined phenolamine and atropine when the heart rate was paced at a significantly lower rate than with atropine alone.

Although the results are consistent with those of Feigl, there are some differences in the two studies. First, the role of $\alpha$-adrenergic mechanisms in this reflex was not assessed in Feigl's study because the control injections were done after $\alpha$-blockade. Second, veratridine was administered into the LAD while flow was measured in the Cx. Since it has been shown that the injection of agents that stimulate ventricular

Table 2. Control Hemodynamic Values for Chronic Sinusoidal Denervation (SAD) Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Metoprolol</th>
<th>Metoprolol + phentolamine</th>
<th>Metoprolol + atropine</th>
<th>Metoprolol + atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP (mm Hg)</td>
<td>103.1 ± 5.9</td>
<td>108.2 ± 5.3</td>
<td>73.4 ± 3.7*</td>
<td>79.1 ± 3.4*</td>
<td>115.9 ± 8.7</td>
</tr>
<tr>
<td>MCBF (kHz)</td>
<td>1.77 ± 0.14</td>
<td>1.45 ± 0.14</td>
<td>1.26 ± 0.11</td>
<td>1.18 ± 0.12*</td>
<td>1.35 ± 0.26</td>
</tr>
<tr>
<td>MCR (mm Hg/kHz)</td>
<td>65.7 ± 5.1</td>
<td>97.7 ± 15.7</td>
<td>64.5 ± 3.4</td>
<td>79.3 ± 13.2</td>
<td>98.2 ± 14.8</td>
</tr>
<tr>
<td>LDP (mm Hg)</td>
<td>102.3 ± 6.4</td>
<td>102.9 ± 5.5</td>
<td>61.7 ± 3.4*</td>
<td>74.4 ± 3.6*</td>
<td>109.5 ± 7.4</td>
</tr>
<tr>
<td>LDF (kHz)</td>
<td>2.32 ± 0.31</td>
<td>1.82 ± 0.27</td>
<td>1.57 ± 0.23*</td>
<td>1.30 ± 0.18*</td>
<td>1.25 ± 0.22*</td>
</tr>
<tr>
<td>LDR (mm Hg/kHz)</td>
<td>56.2 ± 12.5</td>
<td>69.0 ± 16.0</td>
<td>51.5 ± 13.8</td>
<td>67.7 ± 18.5</td>
<td>80.2 ± 5.9*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>166.2 ± 4.0</td>
<td>156.2 ± 4.9</td>
<td>152.4 ± 7.8</td>
<td>115.5 ± 4.2*</td>
<td>124.6 ± 8.3*</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>147.4 ± 6.2</td>
<td>144.7 ± 7.0</td>
<td>103.0 ± 7.0*</td>
<td>106.3 ± 7.2*</td>
<td>161.3 ± 4.4</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>11.1 ± 1.5</td>
<td>12.9 ± 1.8</td>
<td>8.5 ± 2.0</td>
<td>12.0 ± 1.3</td>
<td>14.5 ± 1.6</td>
</tr>
<tr>
<td>dP/dt (mm Hg/sec)</td>
<td>2.705 ± 129.6</td>
<td>2.349 ± 75.8*</td>
<td>1.613 ± 138.2*</td>
<td>2.009 ± 190.7*</td>
<td>2.239 ± 109.4*</td>
</tr>
</tbody>
</table>

* significantly different from control; n = 5.

Abbreviations are the same as in Table 1.
receptors, such as veratridine or PGI₂, into the Cx bed evoke more pronounced reflex effects than injection into the LAD, which a more pronounced stimulation (compared with that of Feigl) of ventricular receptors would probably have been evoked in the present study. Third, the study of Feigl analyzed only intact dogs, while the present study determined if SAD dogs showed augmented coronary flow responses to intracoronary veratridine when compared with intact dogs. Finally, and perhaps most important, our experiments were carried out in conscious dogs that had not been subjected to the trauma of recent surgery.

At first glance, the fact that the SAD dogs did not show an augmentation of the coronary response to veratridine may be surprising. However, in intact dogs, the decrease in coronary resistance generally occurs before systemic blood pressure falls significantly. Therefore, the arterial baroreceptors would probably not be unloaded and would not inhibit the veratridine response. The fact that the arterial pressure responses were potentiated in the SAD dogs indicates that unloading of these receptors competes with the stimulation of ventricular receptors. This is in agreement with earlier work from this laboratory. The reason the coronary vasodilator response is faster than the arterial pressure response is not precisely known; however, it may be speculated that 1) vagal mechanisms are more rapid than sympathetic mechanisms and 2) the coronary response is vagal and the peripheral response is attributable to a combination of withdrawal of α-adrenergic tone and activation of a sympathetic cholinergic vasodilator mechanism.

In summary, it would appear that elicitation of the Bezold-Jarisch reflex in conscious dogs results in rapid, cholinergically mediated coronary vasodilation that is not potentiated by removal of the arterial baroreceptors and has little, if any, adrenergic component.

**References**


KEY WORDS • cardiac receptors • vagus • coronary blood flow
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