The Bezold-Jarisch Reflex in the Conscious Dog

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SUMMARY The Bezold-Jarisch reflex was studied in 22 conscious, instrumented dogs. Specific left ventricular receptor stimulation was elicited by the circumflex coronary artery injection of veratridine in doses ranging from 0.01 to 0.40 µg/kg. None of these doses resulted in any hemodynamic effects when given intravenously. Heart rate, arterial blood pressure, left ventricular pressure, and cardiac output. With the heart paced to prevent bradycardia, the decrease in all the above parameters was significantly attenuated; however, a significant decrease in total peripheral resistance was still observed (−30.2 ± 3.7%). Cardiac pacing plus the administration of the α-adrenergic-blocking agent, phentolamine, blocked the decrease in total peripheral resistance when compared to pacing alone. The administration of atropine significantly attenuated the bradycardia, hypotension, decrease in dp/dt max, and decrease in total peripheral resistance in response to intracoronary veratridine. Atropine plus phentolamine abolished the decrease in total peripheral resistance that was evoked by intracoronary veratridine. The decrease in dp/dt max which resulted from veratridine administration was induced largely by the associated bradycardia, since both cardiac pacing and atropine significantly attenuated it. These experiments indicate that the chemical stimulation of left ventricular receptors in the conscious dog mediates a bradycardia, hypotension and decrease in total peripheral resistance which is produced by sympathetic withdrawal as well as cholinergic vasodilation. There is no significant inotropic effect elicited by the stimulation of these receptors. Circ Res 49: 940-948, 1981

IN 1867, von Bezold and Hirt described the cardiovascular response to the systemic administration of veratrum alkaloids. Subsequently, Jarisch and Richter (1939) further substantiated and elaborated upon the reflex nature of this response. There is good evidence that the afferent limb of this reflex resides within receptors located primarily in the left ventricular wall (Dawes, 1947). There has been growing interest concerning the role of this reflex in various acute and chronic pathological states such as coronary artery occlusion (Costantin, 1963; Hanley et al., 1971; Thorén, 1973, 1976; Thames et al., 1978) and aortic stenosis (Mark et al., 1973a). In addition, it has been postulated that these ventricular receptors increase their discharge during exercise and that they respond to increases in the ventricular contractile state (Thorén, 1979; Estrin et al., 1979). Several investigators have analyzed the peripheral components of this reflex using a variety of stimuli in anesthetized, acutely traumatized preparations. It is most commonly believed that the decrease in total peripheral resistance that results from the activation of ventricular receptors is due to the withdrawal of α-adrenergic tone (Mark et al., 1973b; Thorén, 1979). However, Feigl (1975) has demonstrated cholinergic vasodilation in the coronary bed of the anesthetized dog in response to the chemical stimulation of ventricular receptors.

There have been no studies, to our knowledge, which have investigated the peripheral and cardiac components of the Bezold-Jarisch reflex in conscious instrumented animals. Because ventricular receptor reflexes may play an important role in cardiovascular control, we chose to investigate the peripheral vascular and cardiac responses which result from the selective activation of left ventricular receptors in the conscious dog.

Methods

Twenty-two mongrel dogs of either sex averaging 21.4 ± 0.6 kg were used in the present study. Ten to 14 days prior to the first experiment, the dogs were instrumented as described below.

Surgical Instrumentation

After anesthesia had been induced with sodium thiopental (Pentothal, 17 mg/kg, Abbott), the animal was placed on halothane anesthesia (0.5–1.5%, Halocarbon Labs, Inc.), a left thoracotomy was performed through the 5th intercostal space, and the pericardium opened. A Silastic catheter was inserted into the chamber of the left ventricle through a stab wound in the apex. A circular dacron patch which was attached to the catheter and sutured to the apex kept the catheter in place. This
catheter was used as a guide catheter for the placement of a Millar micromonometer (for further details, see Cornish and Zucker, 1980). We placed a Silastic catheter in the left circumflex coronary artery after carefully dissecting the vessel from the surrounding connective tissue without visibly damaging any nerve fibers, using the technique of Herd and Barger (1964).

In 16 dogs, an electromagnetic flow probe (Biotronix Laboratory, Inc.) was placed around the root of the ascending aorta after first wrapping the aorta with dacron. Silver wire pacing electrodes were sutured to the left atrial appendage and a platinum pacing electrode (CPI, Inc.) was placed on the left ventricle. A Silastic catheter (0.040", i.d.) was inserted into the descending thoracic aorta with its end facing downstream for the measurement of arterial pressure. In five dogs, a single pair of 5 MHz piezoelectric crystals were implanted in the left ventricular myocardium approximately 1.5-2.0 cm apart for the measurement of segment length shortening velocity.

The pericardium was closed, the lungs momentarily hyperinflated to eliminate atelectasis, and the thoracotomy closed. Before approximating the ribs, liberal amounts of aqueous penicillin G (Squibb) were introduced into the chest. All wires, cables, and catheters were tunneled beneath the skin and exited at the back of the animal. The catheters and wires were protected by fitting the dogs with a jacket of stocking gauze. The dogs were treated with 600,000 units of penicillin and 0.5 g streptomycin per day for 7 days postoperatively.

Recording Procedures

Left ventricular and aortic pressure were measured using Millar catheter-tipped micromonometers (model PC 350). The left ventricular transducer was passed through the guide catheter as previously described. Honeywell model 143 bridge amplifiers were used as signal conditioners. The frequency response of the micromanometer system was flat to 200 Hz as measured with a sine wave from a multifunction pressure generator (Millar, model WGA 200). Left ventricular dp/dt max was recorded by differentiating the left ventricular pressure signal (Biotronix 622) and calibrated by applying triangular pressure waves of known amplitude and frequency to the Millar transducers. Alternatively, an equivalent triangular waveform equal in voltage to 100 mm Hg and of known frequency was applied to the differentiator. Heart rate was continuously recorded using a Honeywell cardiocachometer (model 133) which was triggered by the left ventricular pressure signal. Aortic flow was used as an index of cardiac output. Flow was measured using a Biotronix Laboratory, Inc., flowmeter (model BL613). Zero aortic flow was taken in late diastole just prior to aortic ejection. The flow probes were calibrated at the factory and checked in the laboratory using bovine aorta and normal saline prior to implanta-

tion. Segment length was measured using an ultrasonic dimension system (Scheussler and Assoc., model 401).

All parameters were recorded on a Hewlett-Packard 8-channel recorder (model 7758A) and simultaneously on an 8-channel FM tape recorder (Vetter, model D).

Drugs Used

Veratridine (kindly supplied by Dr. Otto Krayer, University of Arizona) was made up in a stock solution of 100 μg/ml in 0.1 N HCl. Just prior to injection, the final concentration of the injectate was adjusted with a phosphate buffer (0.10 M) resulting in a final pH of 7.38. Atropine sulfate or atropine methylbromide (Sigma) was given to achieve vagal efferent blockade. Atropine was made up in isotonic saline and given as an iv injection at a dose of 0.1-0.2 mg/kg. The adequacy of the blockade was assessed by the bradycardia evoked by a 50-μg bolus of acetylcholine (Calbiochem) given into the coronary artery before and after atropine administration. β-Adrenergic blockade was achieved with dl-propranolol (Sigma) made up in isotonic saline and given as an iv injection at a dose of 1 mg/kg. Adequate propranolol blockade was assessed by observing the lack of a chronotropic response to a 1-μg bolus of isoproterenol (Isuprel, Winthrop) injected into the coronary artery. α-Adrenergic receptors were blocked by the administration of phentolamine (Regatine HCl, Ciba-Geigy) made up in isotonic saline and given as a 1 mg/kg iv bolus followed by a continuous infusion of 1 mg/kg per min for 20-30 minutes. The effectiveness of the phentolamine blockade was assessed by the magnitude of the hypertensive response to a 20-μg iv bolus of phenylephrine (Neo-Synephrine, Winthrop) before and after blockade. Five dogs were studied after combined α-adrenergic and cholinergic blockade.

Experimental Protocol

During the postoperative recovery period, the dogs were trained to lie quietly on a table or stand in a Pavlov sling in a dimly lit, quiet room. The dogs were brought into the laboratory on the morning of the experiment and an intracath was placed in a forelimb vein. A sterile ventricular transducer was calibrated and inserted into the left ventricle. After all instrumentation was functional, the dog was allowed to stand or lie quietly for approximately 30 minutes before the experiment began. The responses to varying doses of veratridine (0.01-0.40 μg/kg) given as an intracoronary bolus injection of 0.5 ml was assessed and compared to the parameters recorded during the control period (which was a 1-minute recording taken just prior to the injection). The injection was given over approximately 1 second. Control injections of 0.5 ml of vehicle were given intracoronary to each animal. In addition, each animal was given an intravenous injection of
0.4 μg/kg of veratridine as a control for the selectivity of the intracoronary veratridine injections. Because of possible tachyphylaxis to veratridine, injections were made 20-30 minutes apart, with varying doses being given in random order.

In studying the effect of cardiac pacing and autonomic blockade on the Bezold-Jarisch reflex, a standard dose of 0.4 μg/kg of veratridine was used. The heart was paced using both atrial and ventricular pacing electrodes. A square wave stimulus was delivered from a Grass S88 stimulator and Grass stimulus isolation unit to the atrial and ventricular leads separated by a delay of 100 msec. Pacing rates were adjusted to slightly greater than the dogs' resting heart rate. Following the establishment of an adequate pace, intracoronary veratridine was administered as described above. In those experiments in which phentolamine blockade was employed, heart rate was also held constant by pacing. Each experiment on an individual dog was separated by several days.

### Data Analysis

Not all parameters were measured on each dog. Because of instrumentation failure, some dogs had nonfunctional aortic flow probes, some had nonfunctional pacing electrodes, etc. In those dogs that had functional aortic flow probes, the total peripheral resistance (TPR) was calculated using the ratio of mean aortic pressure to mean aortic flow and expressed as mm Hg/(ml/min). The mean data are expressed as the percent change from control ± SEM. The data of duplicate injections in each animal were averaged and used as a single data point. A paired two-tailed t-test was used to determine the level of significance for a given parameter within a group. A one-way analysis of variance and Duncan's new multiple range test were used to determine the level of significance between groups. A P value of less than 0.05 was used to determine significance.

### Results

#### Responses to Intracoronary Injection of Vehicle and to Intravenous Injection of Veratridine

Tables 1 and 2 show some of the baseline hemodynamic parameters as well as the lack of effect to the intracoronary injection of 0.5 ml of vehicle (Table 1) and to the iv injection of 0.4 μg/kg of veratridine. Therefore, the intracoronary injection of veratridine was specific to the stimulation of left ventricular receptors.

#### Dose-response Relationships to Intracoronary Veratridine

The basic response and dose dependency of the intracoronary injection of veratridine is shown in Figures 1 and 2. Following the injection, there was a decrease in left ventricular pressure, arterial pressure, heart rate and left ventricular dp/dt max (Fig. 1). The latency for the onset of the hypotensive response averaged 3.74 ± 0.30 seconds. The maximum hypotensive response that was observed was seen 12.38 ± 0.85 seconds from the onset of the injection. The bradycardia, hypotension, and decrease in left ventricular pressure all were dose-dependent when varying doses were given no less than 20 minutes apart in random order. Figure 2 indicates the mean dose-response relationships for the doses of veratridine used on the percent change from control of MABP and heart rate.

### The Effects of Cardiac Pacing on the Responses to Intracoronary Veratridine

To assess the effect of the bradycardia in mediating the hypotension and the decrease in dp/dt max, we injected 0.4 μg/kg of veratridine into the coronary in cardiac paced dogs. During cardiac

### Table 1  Effects of 0.5 ml of Vehicle Given into the Left Circumflex Artery of Conscious Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Maximum response</th>
<th>Δ (%)</th>
<th>Δ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP (mm Hg)</td>
<td>90.3</td>
<td>89.9</td>
<td>-0.36</td>
<td>-0.60</td>
</tr>
<tr>
<td></td>
<td>±2.50</td>
<td>±3.0</td>
<td>±1.0</td>
<td>±1.1</td>
</tr>
<tr>
<td>(11)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>111.3</td>
<td>117.1</td>
<td>±5.8</td>
<td>±5.5</td>
</tr>
<tr>
<td></td>
<td>±6.6</td>
<td>±7.0</td>
<td>±2.5</td>
<td>±2.5</td>
</tr>
<tr>
<td>(11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>119.2</td>
<td>120.9</td>
<td>±1.7</td>
<td>±1.5</td>
</tr>
<tr>
<td></td>
<td>±7.1</td>
<td>±7.1</td>
<td>±1.8</td>
<td>±1.6</td>
</tr>
<tr>
<td>(8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>1.86</td>
<td>1.81</td>
<td>-0.5</td>
<td>±3.5</td>
</tr>
<tr>
<td></td>
<td>±0.18</td>
<td>±0.20</td>
<td>±0.03</td>
<td>±2.7</td>
</tr>
<tr>
<td>(8)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Numbers in parentheses denote the number of dogs that the mean data is based upon. MABP = mean arterial blood pressure; HR = heart rate; LVSP = left ventricular systolic pressure; CO = cardiac output.

### Table 2  The Effects of Intravenous Injection of 0.4 μg/kg of Veratridine in Conscious Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Maximum response</th>
<th>Δ (%)</th>
<th>Δ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP (mm Hg)</td>
<td>91.9</td>
<td>90.6</td>
<td>-1.36</td>
<td>-1.31</td>
</tr>
<tr>
<td></td>
<td>±3.0</td>
<td>±2.7</td>
<td>±0.87</td>
<td>±1.04</td>
</tr>
<tr>
<td>(9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>108.9</td>
<td>104.1</td>
<td>±4.9</td>
<td>±4.2</td>
</tr>
<tr>
<td></td>
<td>±5.2</td>
<td>±5.5</td>
<td>±2.9</td>
<td>±2.5</td>
</tr>
<tr>
<td>(9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>119.4</td>
<td>120.1</td>
<td>±0.6</td>
<td>±0.4</td>
</tr>
<tr>
<td></td>
<td>±7.8</td>
<td>±8.2</td>
<td>±1.2</td>
<td>±1.1</td>
</tr>
<tr>
<td>(7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>2.09</td>
<td>2.10</td>
<td>±0.1</td>
<td>±0.7</td>
</tr>
<tr>
<td></td>
<td>±0.43</td>
<td>±0.41</td>
<td>±0.03</td>
<td>±1.2</td>
</tr>
<tr>
<td>(5)</td>
<td></td>
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Abbreviations as defined in footnote, Table 1.
pacing, heart rate averaged 147.6 ± 4.4 beats/min and did not change significantly following the injection of veratridine (146.8 ± 4.4 beats/min). Figure 3 shows a representative response to the intracoronary injection of veratridine before (3A) and after cardiac pacing (3B). Note that the hypotension seen in response to veratridine was attenuated during pacing. In addition, the decrease in dp/dt max also was attenuated during cardiac pacing. The mean changes from control with the heart paced and unpaced for MABP, left ventricular pressure, dp/dt max, and cardiac output are shown in Figure 3. Cardiac pacing caused significant attenuation of the decrease in mean arterial blood pressure (P < 0.01) as well as left ventricular pressure (P < 0.01), cardiac output (P < 0.01), and dp/dt max (P < 0.01). In addition, in three dogs the velocity of left ventricular segment length shortening was mea-
The dose-response relation of intracoronary veratridine vs. the percent change of mean arterial blood pressure (*) and heart rate (O). The vertical bars are ± 1 SEM (n = 19).

Figure 2

Measured during cardiac pacing after the intracoronary injection of veratridine. Control shortening velocity averaged 20.3 ± 3.9 mm/sec. The maximum change in shortening velocity after veratridine administration was −2.3 ± 2.1 mm/sec.

The change in TPR that was seen following veratridine administration in paced dogs is shown in Figure 5. With the heart paced, veratridine evoked a 30.2 ± 3.7% decrease in TPR, which was highly significant (P < 0.001).

The Effects of α-Adrenergic Blockade on the Responses to Intracoronary Veratridine

To assess the role of peripheral α-adrenergic tone in the mediation of the hypotension to intracoronary veratridine, 0.4 μg/kg of veratridine was administered into the coronary during cardiac pacing combined with α-adrenergic blockade. Figure 3C shows a representative response to this intervention. The hypotension (reflected both in the MABP and left ventricular pressure tracings) was attenuated when compared to pacing without phentolamine (Fig. 3B). However, a significant hypotension (P < 0.001, Fig. 4) was still observed. Although there was still a significant decrease in left ventricular pressure after pacing plus phentolamine (P < 0.001), this parameter was not significantly different from the decrease observed with pacing alone. The change in TPR that was seen following veratridine in paced plus phentolamine treated dogs is shown in Figure 5. After pretreatment with phentolamine, there was a 9.6 ± 3.3% decrease in TPR in response to veratridine, a value significantly different from zero. There was a significantly greater percent change in TPR with pacing alone compared to pacing plus phentolamine (P < 0.01).

The Effects of Cholinergic Blockade on the Responses to Intracoronary Veratridine

To determine whether a cholinergic mechanism was responsible for any of the changes seen follow-
ing veratridine administration, we observed these responses following the administration of atropine. A typical response to a 0.4 µg/kg injection of veratridine is shown in Figure 6 before (A) and after (B) atropine. Atropine increased resting heart rate and substantially depressed the bradycardia that was elicited by veratridine. In addition, the hypotension was also attenuated as was the decrease in dp/dt max (Fig. 4). The mean heart rate responses are shown in Figure 7. In the unpaced animals, there was a 62.5 ± 3.7% decrease in heart rate after the 0.4 µg/kg dose of veratridine. After the administration of atropine, there was a 4.9 ± 1.8% decrease in heart rate. Although small, this decrease was significant at the 0.02 level. To see whether this small bradycardia after cholinergic blockade was due to withdrawal of cardiac sympathetic tone, we repeated the veratridine injection after combined cholinergic and β-adrenergic blockade with propranolol. There was still a slight (4.6 ± 1.6%) but significant (P < 0.02) decrease in heart rate following combined atropine and propranolol blockade. After atropine, there was no significant change in cardiac output. In those animals in which both cardiac output and mean arterial pressure were simultaneously determined, a significant decrease in calculated TPR was noted following veratridine administration after atropine (Fig. 5). Although the decrease in TPR following atropine was significantly different from zero (P < 0.01), it was not statistically different from the decrease observed following phentolamine plus pacing. In five dogs combined a-adrenergic receptor blockade and cholinergic blockade was achieved. As can be seen in Figure 5, the change in TPR was abolished by atropine plus phentolamine administration.
FIGURE 5  Mean ± 1 SEM percent change from control of total peripheral resistance to the intracoronary injection of 0.4 μg/kg of veratridine with the heart paced (closed bar), with the heart paced plus phentolamine (hatched line) and with atropine plus phentolamine (open bar). * = significantly different from control. Mean values above each bar are control values before each injection was made. Numbers in parentheses denote the number of dogs that the data are based upon.

Discussion

The reflex effects which occur from the chemical activation of left ventricular receptors have been observed and reported by a variety of investigators over the years (Jarisch and Richter, 1939; Dawes, 1947; Öberg and Thoren, 1972). However, to our knowledge, there have been only two reports of the demonstration of the Bezold-Jarisch reflex in the conscious animal (Sleight, 1964; Barron and Bishop, 1980) and these have concentrated on either the chronotropic and hypotensive effects alone, or on contractility effects alone. In the present study, we have demonstrated the hemodynamic effects of chemical stimulation (veratridine) of left ventricular receptors in the conscious, instrumented dog. We believe that the left circumflex injection of veratridine as it was carried out in the present experiments stimulated only left ventricular receptors for two reasons. First, Dawes (1947) has shown...
the bradycardia and hypotension to local coronary injection of veratrum alkaloids is abolished by vagotomy. It has been well documented that the majority of ventricular afferents traverse the vagi (Dawes and Widdicombe, 1953; Frink and James, 1971). In addition, Thames et al. (1978) have shown that the hypotensive response to intracoronary veratridine is more effective when injected into the circumflex circulation as compared to the left anterior descending circulation, even in far smaller doses. This indicates that the majority of the receptors are located in the posterior wall of the left ventricle. Second, the maximal dose of veratridine (0.4 \mu g/kg) that was used for intracoronary injections failed to produce any hemodynamic response when given intravenously.

Intracoronary veratridine evoked a dose-related decrease in mean arterial pressure and heart rate. Although not shown here, dose response relationships were also noted for the decrease in ventricular pressure and dp/dt max.

The data from the present experiments indicate that the hypotension evoked by intracoronary veratridine is due in large part to the associated bradycardia, since it was significantly attenuated after both cardiac pacing and atropine (Figs 3B and 4). Interestingly, following atropine there was still a small but statistically significant decrease in heart rate. This bradycardia was not blocked by propranolol (Fig. 7) so sympathetic withdrawal probably was not mediating it. We feel confident that the dose of atropine we used (0.1-0.2 mg/kg) was an adequate blocking dose, since a 50-\mu g bolus of acetylcholine given intracoronary following atropine did not cause bradycardia, and we have used this dose of atropine to completely prevent the reflex bradycardia elicited by a hypertensive dose of noradrenaline or phenylephrine. Likewise, the dose of propranolol used (1 mg/kg) completely blocked the response to 1 \mu g of isoproterenol given intracoronary. It is possible that veratridine has a direct negative chronotropic effect as a result of its action on SA and AV nodal tissue (Krayen et al., 1955; Benforado et al., 1961), although it is improbable that any of the injected veratridine could get to these areas from the left circumflex coronary artery, since we were injecting distal to the atrial branch of the left circumflex (James, 1977). However, it is not inconceivable that veratridine may have reached SA nodal tissue through some collateral branches.

The hypotension which was exhibited during cardiac pacing following veratridine administration was reflected by a significant decrease in TPR (Fig. 5). This peripheral vasodilation was mediated by both sympathetic withdrawal and cholinergic vasodilation. Both \alpha-adrenergic and cholinergic blockade inhibited the decrease in TPR that was evoked by intracoronary veratridine (Figs. 3 and 5). The combination of \alpha-adrenergic and cholinergic blockade abolished the decrease in TPR in response to veratridine. Although most investigators generally agree that sympathetic withdrawal is a prime determinant of the decrease in TPR when ventricular receptors are stimulated, more controversy exists concerning the contribution of cholinergic vasodilatation. Oberg and Thoren (1973), and Mark et al. (1973a) as well as Voigt et al. (1975) could not find any evidence of cholinergic vasodilation in anesthetized cats and dogs when left ventricular receptors were stimulated chemically and mechanically. In contrast, Bergel and Makin (1967) did show evidence for cholinergic vasodilation after topical application of nicotine to the dog’s heart. Feigl (1975) has demonstrated cholinergic vasodilation in the coronary circulation after stimulation of ventricular receptors with veratridine. Recently, Abboud et al. (1979) reported increases in forearm blood flow in humans undergoing coronary arteriography. This increase in blood flow occurred even when heart rate was maintained by pacing. The increase in forearm blood flow was reduced significantly after intravenous atropine, implicating a cholinergic vasodilatory mechanism. The discrepancy in demonstrating cholinergic vasodilation as a result of stimulation of ventricular receptors may be related to the state of consciousness of the preparation. Most of the anesthetized preparations have been unable to show cholinergic vasodilation, whereas Abboud et al. (1979) and the present data were collected in conscious humans and dogs, respectively. Recently, Stock et al. (1978) have shown that stimulation of the amygdaloid complex in conscious cats increased aortic blood flow which could be blocked by atropine. This cholinergic vasodilation could not be observed after anesthetizing the cats with pentobarbital in doses greater than 25 mg/kg. From the above studies it seems reasonable to speculate that the hypotension after veratridine stimulation of left ventricular receptors in conscious dogs is, in part, due to cholinergic vasodilation.

Although many reflex effects have been ascribed to the stimulation of ventricular receptors (Thoren, 1979), little attention has been focused upon their role as reflex modulators of ventricular contractility. Intracoronary veratridine decreased dp/dt max significantly. This decrease could be abolished completely by cardiac pacing (Figs. 3 and 4), indicating that the decrease in dp/dt max was related to the concomitant bradycardia. Likewise, atropine prevented the decrease in dp/dt max in response to veratridine probably due to the significant depression of the bradycardia as indicated above. The insignificant change in dp/dt max as well as in maximum segment length shortening velocity following veratridine administration during cardiac pacing suggests that eliciting the Bezold-Jarisch reflex by intracoronary veratridine is not associated with a potent ventricular inotropic component which is independent from its chronotropic effects. In isolated heart preparations, veratridine has been shown to possess a direct positive ventricular inotropic effect (Vick and Kahn, 1957; Morales and
Atcheson, 1961; Gilmore and Miller, 1976) in a fashion similar to that of the structurally related cardiac glycosides. The results of the present experiments clearly show that in the intact, conscious dog veratridine does not exhibit a positive inotropic effect, if anything, a slight negative inotropic effect can be seen under certain circumstances.

In summary, this study constitutes the first demonstration of the Bezold-Jarisch reflex in the conscious dog in which both cardiac and peripheral components have been analyzed. The major components of this reflex are characterized by a decrease in heart rate that is primarily vagal in origin, a decrease in blood pressure that has both adrenergic and cholinergic components, and an insignificant change in left ventricular myocardial contractility.

Acknowledgments

We appreciate the expert technical assistance of Johnnie Hackley. We would also like to thank Dr. Joseph P. Gilmore for constructively criticizing the manuscript and offering helpful suggestions and Ruth Cozette for typing the manuscript. Phenolamine was generously supplied by the Ciba-Geigy Company.

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The Bezold-Jarisch in the conscious dog.
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doi: 10.1161/01.RES.49.4.940

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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