Spinal Sympathetic Cardiocardiac Reflexes

By Alberto Malliani, D. Fred Peterson, Vernon S. Bishop, and Arthur M. Brown

ABSTRACT
We studied the reflex changes in myocardial contractility elicited by electrical stimulation of afferent cardiac sympathetic nerve fibers or chemical stimulation of their cardiac endings. Veratridine injected directly into the left coronary artery was the chemical stimulus. The maximum rate of rise of left ventricular pressure, dP/dt max, was used as an index of myocardial contractility. The stimuli evoked increases in dP/dt max in vagotomized cats with or without spinal transection (C1). Electrical stimulation provoked the same effect in vagotomized dogs. Increases in dP/dt max occurred which were independent of changes in heart rate, preload, or afterload. They were reflex in nature since they were abolished by section of the upper thoracic sympathetic rami or cardiac sympathetic nerves. These results are the first demonstration of a cardiocardiac reflex which can be mediated entirely by the spinal cord. Electrical stimulation in vagotomized cats and dogs also produced a reflex increase in arterial blood pressure partly due to sympathetic vasoconstriction.

KEY WORDS

dP/dt max
myocardial contractility
heart rate
spinal cardiac reflexes
preload
veratridine
cats
dogs

cardiac sympathetic nerves
afterload
coronary circulation

We have previously presented electrophysiological evidence that stimuli restricted to the heart, such as transient changes in coronary blood flow or pressure, produce sympathetic reflexes mediated solely by the spinal cord (1, 2). Even though the sympathetic nerves from which we recorded are known to contribute substantially to the efferent innervation of the heart (3, 4), reflex changes in heart rate or systemic arterial blood pressure were not identified. Despite this, it seemed possible that another index of cardiac performance which was not measured, namely myocardial contractility, might be reflexly altered. The purpose of the present experiments was to determine if such an alteration could occur. Changes in coronary flow or pressure were not used as stimuli since these events can directly affect myocardial contractility (5, 6). Instead, we resorted to electrical stimulation of afferent sympathetic fibers arising from the heart or to chemical stimulation of their endings in the heart. We found that such stimulation elicited a reflex increase in myocardial contractility due to a cardiocardiac reflex which could be integrated entirely by the spinal cord.

Methods

EXPERIMENTS IN CATS
Thirty cats were anesthetized by intraperitoneal injection of pentobarbital sodium, 35 mg/kg. The trachea was cannulated and positive pressure respiration was begun. The pump was set so as to provide an arterial PCO₂ of 30–35 mm Hg, which is normal for cats in Salt Lake City (elevation 4,200 feet) (2). The animals were paralyzed with gallamine triethiodide (Flaxedil), 2 mg/kg.1 Bilateral cervical vagoto-

1The guidelines of the American Physiological Society regarding anesthetized, curarized animals were adhered to.
Effects of stimulating afferent cardiac sympathetic nerve fibers in vagotomized cats. A: On the left at faster paper speed are, from top to bottom, control records of dP/dt (mm Hg/sec), left ventricular pressure measured simultaneously with the tip-transducer and the catheter-manometer systems (mm Hg, calibration for catheter-manometer system only), aortic pressure (mm Hg), and ECG. The tip-transducer trace has a faster rise time and, on the tape playback, more amplification than the catheter-manometer trace. See text for fuller discussion of the left ventricular pressure traces. On the right, at slower paper speed, the tip-transducer pressure has been omitted for simplification. Nerve stimulation is indicated by the artifact on the ECC record.

B: Same as A except the inferior cardiac nerve was cut. Nerve stimulation did not change dP/dt max.

Pressures and the ECG were recorded on a Honeywell 1508 Visicorder and an Ampex FR 1300 tape recorder.

Pressures and heart rates were measured for 10-20 cardiac cycles during control experiments, and maximum responses and average values were calculated.

Nerve Stimulation.—Small branches of nerves which arose from the heart and projected to the left stellate ganglion were dissected and cut, care being taken to preserve the inferior cardiac nerve (Fig. 1 of ref. 9). A Grass S4 stimulator was used to stimulate the central end of one of the cut nerves. The pulses were generally 5-10 v, 2-5 msec at a frequency of 15 Hz. The peripheral cut end of the nerve was also stimulated, and in all cases dP/dt max was increased, indicating that the nerve ran to the heart.

Nerve Recording.—Efferent nervous discharge was recorded from single units in filaments dissected out of the third left thoracic ramus communicans. The methods of recording have been described (2).
Effects of Stimulating Afferent Cardiac Sympathetic Fibers and Their Cardiac Endings in the Cat

<table>
<thead>
<tr>
<th>Group</th>
<th>No. cats</th>
<th>No. trials</th>
<th>Control</th>
<th>Stimulated</th>
<th>Mean difference</th>
<th>AoSP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>9</td>
<td>1602 ± 54</td>
<td>1935 ± 84</td>
<td>243 ± 72*</td>
<td>163 ± 11</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>5</td>
<td>1530 ± 28</td>
<td>1580 ± 41</td>
<td>50 ± 16</td>
<td>159 ± 14</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>7</td>
<td>2182 ± 87</td>
<td>2401 ± 131</td>
<td>219 ± 66*</td>
<td>123 ± 8</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>3</td>
<td>2030 ± 238</td>
<td>2032 ± 291</td>
<td>2 ± 3</td>
<td>113 ± 3</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>6</td>
<td>1586 ± 209</td>
<td>2008 ± 253</td>
<td>422 ± 94*</td>
<td>90 ± 7</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>5</td>
<td>1170 ± 248</td>
<td>1180 ± 251</td>
<td>10 ± 6</td>
<td>76 ± 8</td>
</tr>
</tbody>
</table>

Group 1 = electrical stimulation of afferent cardiac sympathetic fibers in vagotomized cats; group 3 = electrical stimulation of afferent cardiac sympathetic fibers in spinal vagotomized cats; group 5 = intracoronary injection of veratridine (1-\(\mu g\)) in spinal vagotomized cats; groups 2, 4, and 6 are repetitions of groups 1, 3, and 5, respectively, but in group 2 the left inferior cardiac nerve was sectioned and in groups 4 and 6 TI-T4 left rami were cut. AoSP = aortic systolic pressure; Aol = aortic diastolic pressure; LVP = left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; dP/dt max = maximum rate of rise of left ventricular pressure. Values are means ± SE. Measurements in the columns labeled Stimulate were made when dP/dt max was clearly increased.

*P < 0.005.

Coronary Perfusion.—The main left coronary artery was perfused according to the method of Brown (10). Veratridine, 1-10 \(\mu g\) in 0.1-0.2 ml of saline, was injected into the perfusion tubing using a calibrated Hamilton microsyringe (eight experiments). Similar injections were made into the root of the aorta and femoral vein.

EXPERIMENTS IN DOGS

Thoracotomies were performed on 12 mongrel dogs, weighing 18-27 kg, anesthetized with sodium pentobarbital, 30 mg/kg. Bilateral cervical vagotomies were performed in each experiment. A stab incision was made through the anterior wall of the left ventricle and a sonomicrometer was implanted across the greatest internal transverse diameter of the left ventricle. The sonomicrometer has a theoretical resolution of 0.25 wavelengths which corresponds to 0.07 mm at 5 X 10^6 Hz. The frequency response of these two catheter-manometer systems was better than 30 Hz.

Aortic flow was measured with an electromagnetic flow probe (Zepeda Instruments) placed around the ascending aorta. The late diastolic level of aortic flow was used as the zero-flow reference point. Flow probes were calibrated in vitro prior to implantation, and subsequently the calibration was verified at autopsy; in all cases the two calibrations varied by less than 5%.

Results

The control values of dP/dt max were generally lower in the cat than the dog (compare Tables 1 and 2). The measurements in the dog experiments are in agreement with those of others (14). We have disregarded the maximum rate of fall in left ventricular pressure since its meaning cannot be interpreted.

In two experiments, we passed the tip transducer from the femoral artery to the root of the aorta as well as from the left atrium into the left ventricle. We measured the time interval between the initial deflection of the QRS complex of the ECG and the upstroke of aortic systolic pressure, which indicated opening of the aortic valve. This latter point corresponded to the point at which the rapid upstroke of ventricular pressure measured with the transducer became abruptly more rounded (Figs. 1 and 2). Using this latter reference point, we were able to record the time interval between the initial deflection of the QRS complex of the ECG and the upstroke of aortic systolic pressure.
criterion, dP/dt max was always attained before the aortic valve opened in the present experiments.

We have already reported that electrical stimulation of afferent cardiac sympathetic fibers in cats elicits substantial and prompt increases in arterial pressure which are due to sympathetic vasoconstriction and are abolished by blocking doses of phenoxybenzamine (9). These increases in arterial pressure would have complicated the interpretation of changes in dP/dt max. Therefore, in the present experiments, they were reduced and delayed in onset by doses of phenoxybenzamine hydrochloride, 0.5 mg/kg, that partially blocked alpha-receptors. In spinal (C1) vagotomized cats and in vagotomized dogs, the changes in arterial pressure were smaller and more delayed in onset; hence in these experiments phenoxybenzamine was not required.

Effects of Electrical Stimulation of Afferent Cardiac Sympathetic Fibers in Vagotomized Cats.—When a substantial increase in dP/dt max was clearly attained, there were slight increases in aortic systolic and peak left ventricular pressures, but there were no changes in aortic diastolic and left ventricular end-diastolic pressures and heart rate (Table 1, group 1, and Fig. 1A). At this time, increases in dP/dt max were almost completely independent of changes in afterload, preload, or heart rate. Stimulation was stopped as the rising dP/dt max approached its plateau; aortic pressures continued to rise for some 20 seconds thereafter (Fig. 1A, right).

The tip-transducer trace represented the left ventricular pressure pulse more accurately than the catheter-manometer record. Hence, it was essential for the derivation of dP/dt. The end-diastolic pressures on both records were the same when there was no drift on the tip-transducer record, and the peak left ventricular pressure measured with the catheter-manometer system equaled the aortic systolic pressure. Thus, the catheter-manometer system accurately described the range of left ventricular pressures. The tip-transducer measurements were readily calibrated from the catheter-manometer measurements.

Section of the left inferior cardiac nerve, which was the main efferent limb of the reflex, did not significantly alter control measurements, but the increase in dP/dt max during stimulation was greatly reduced (Table 1, group 2, and Fig. 1B). A smaller increase in aortic pressure persisted, and its onset was delayed. The increase in dP/dt max was subsequently abolished by right stellectomy although the increase in aortic pressure was reduced but still present. This increase was eliminated in two cats following the intravenous injection of full blocking doses of phenoxybenzamine, 5 mg/kg (9).

Effects of Electrical Stimulation of Afferent Cardiac Sympathetic Fibers in Spinal Vagotomized Cats.—When the increase in dP/dt max due to stimulation reached its plateau, aortic systolic and peak left ventricular pressures were only slightly elevated. There were no changes in aortic diastolic and left ventricular end-diastolic pressures or heart rate (Table 1, group 3, and Fig. 2). Section of the first four left thoracic rami (T1-T4) abolished the response (Table 1, group 4). This ruled out the existence of functional

---

**Table 1**

<table>
<thead>
<tr>
<th>AoDP (mm Hg)</th>
<th>LVP/max (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Stimulated</td>
<td>Control</td>
<td>Stimulated</td>
</tr>
<tr>
<td>AoDP (mm Hg)</td>
<td>LVP/max (mm Hg)</td>
<td>LVEDP (mm Hg)</td>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Control</td>
<td>Stimulated</td>
<td>Control</td>
<td>Stimulated</td>
</tr>
<tr>
<td>14 ± 11</td>
<td>124 ± 10</td>
<td>165 ± 12</td>
<td>171 ± 11</td>
</tr>
<tr>
<td>30 ± 12</td>
<td>123 ± 10</td>
<td>160 ± 14</td>
<td>163 ± 14</td>
</tr>
<tr>
<td>6 ± 7</td>
<td>74 ± 7</td>
<td>126 ± 8</td>
<td>130 ± 9</td>
</tr>
<tr>
<td>10 ± 2</td>
<td>60 ± 3</td>
<td>114 ± 3</td>
<td>114 ± 2</td>
</tr>
<tr>
<td>6 ± 6</td>
<td>56 ± 13</td>
<td>92 ± 8</td>
<td>97 ± 8</td>
</tr>
<tr>
<td>39 ± 2</td>
<td>39 ± 2</td>
<td>80 ± 14</td>
<td>83 ± 7</td>
</tr>
</tbody>
</table>
connections, either direct or synaptically mediated by the stellate ganglion, between the nerve being stimulated and the efferent cardiac sympathetic nerves. The effects were therefore reflex in nature.

A shortcoming of the experiments was that in addition to afferent cardiac sympathetic fibers (2) other noncardiac afferent fibers were probably being stimulated. To restrict the stimulus to nerve endings within the heart, we injected veratridine directly into the left coronary artery.

Effects of the Intracoronary Injection of Veratridine in Spinal Vagotomized Cats.—When the increase in dP/dt max following the intracoronary injection of veratridine was at its plateau, slight elevations of aortic systolic and peak left ventricular pressures also occurred (Table 1, group 5, and Fig. 3A). Aortic diastolic and left ventricular end-diastolic pressures and heart rate were unaffected. Section of left T1-T4 rami prevented the response in these cats (Table 1, group 6, and Fig. 3B). When the dose of veratridine was subsequently doubled, a smaller rise in dP/dt max was evoked. This was then abolished by right stellectomy.

Control injections of similar doses of veratridine into the femoral vein or root of the aorta were without effect. Likewise, intracoronary injection of equivalent volumes of saline were ineffective.

Effects of the Intracoronary Injection of Veratridine on Afferent and Efferent Nervous Discharge in T3.—We have previously reported an increased discharge in afferent cardiac sympathetic fibers following the intracoronary injection of veratridine (2). A reflex increase in the neural discharge of two preganglionic units in one cat was noted at this time (2). We have confirmed and extended this finding in four additional cats (Fig. 4) and now have recorded increased efferent discharge in six units in five cats. The
FIGURE 3
Effects of injection of 2 μg of veratridine into the coronary perfusion circuit (at brief interruption in bottom traces) in spinal vagotomized cats. A = before and B = after section of left T1–T4 rami. Traces from top to bottom are dP/dt (mm Hg/sec), left ventricular pressure (mm Hg), coronary arterial pressure (mm Hg), and aortic pressure (mm Hg). Calibration values are the same in A and B. Coronary flow was 7 ml/min making coronary arterial pressure higher than aortic pressure. The time required for the drug to circulate from the injection site to the tip of the cannula was about 15 seconds. The rise in dP/dt max was much greater than the rise in aortic pressure in A.

FIGURE 4
Effects of the injection of 1 μg of veratridine into the coronary perfusion circuit (signal, bottom trace) on the discharge of a single efferent preganglionic fiber dissected from the white ramus of T3. Record from top to bottom shows the electroneurogram (smaller deflections are ECG artifacts), coronary arterial pressure (mm Hg), aortic pressure (mm Hg), and signal mark. The time that elapsed between drug injection and its appearance at the end of the coronary cannula was about 10 seconds. Spinal vagotomized cat.

Circulation Research, Vol. XXX, February 1972
response was abolished by prior section of both ansa subclaviae and inferior cardiac nerves.

**Effects of Electrical Stimulation of Afferent Cardiac Sympathetic Fibers in Vagotomized Dogs.**—In the dog, \( dP/dt \) max has been shown to be a reliable index of myocardial contractility when changes in heart rate, preload, or afterload are minimized (14). Its usefulness in the cat has not been so clearly established, although it seems reasonable to assume that the same considerations apply in this species as in the dog. Therefore, we repeated the experiments in dogs. In addition, we were able to measure aortic flow and left ventricular internal diameter.

Stimulation elicited a significant increase in \( dP/dt \) max, peak left ventricular pressure, and arterial systolic and diastolic pressures (Table 2, Fig. 5). Mean cardiac output and stroke volume increased slightly, but left ventricular end-diastolic pressure and heart rate were unchanged. Neither end-systolic nor end-diastolic internal left ventricular diameters were altered significantly. However, the rate of change of internal diameter increased significantly \( (P < 0.01) \) from an average of \( 30.8 \pm 1.1 \) to \( 33.6 \pm 1.0 \) (SD) mm/sec.

The latency before onset of the increase in \( dP/dt \) max was \( 12.5 \pm 3.8 \) seconds, whereas \( 23.6 \pm 10.5 \) seconds elapsed before arterial pressure began to rise \( (P < 0.05, 50 \) trials, six dogs). In one experiment, phenoxybenzamine, \( 5 \) mg/kg, did not affect the latency or magnitude of the response of \( dP/dt \) max but delayed the onset and reduced the magnitude of the increase in arterial pressure.

The response was abolished in four experiments by cutting T1-T4 left rami. In two experiments, section of the left major cardiac nerves prevented the rise in \( dP/dt \) max and had only a small effect on the increase in arterial pressure. The aorta was constricted in these animals to increase arterial pressure to levels generally attained during nerve stimulation. In all cases, left ventricular end-systolic and end-diastolic internal diameters and peak left ventricular and left ventricular end-diastolic pressures increased significantly as the arterial pressure was elevated. In contrast to the nerve stimulation experiments, a very small increase in \( dP/dt \) max \( (4\%) \) was noted.

**Discussion**

The increase in left ventricular \( dP/dt \) max that we have described either represents a neurally mediated increase in myocardial contractility or is the consequence of a change...
Effects of stimulating afferent cardiac sympathetic fibers in the vagotomized dog. Left: Control record taken at fast paper speed. Right: Peak effect of nerve stimulation at fast paper speed. Middle: Response to nerve stimulation at slow paper speed. The record from top to bottom shows the greatest left ventricular internal transverse diameter (mm), left ventricular pressure (mm Hg), dP/dt (mm Hg/sec), aortic pressure (mm Hg), and ECG.

in heart rate, preload, or afterload (14-17). Since in our experiments neither heart rate nor preload changed, we need only consider the possible contribution of an increase in afterload, i.e., arterial pressure. The following findings may be used to support the idea that this contribution was negligible and that the rise in dP/dt max represented a true augmentation of myocardial contractility due to a spinal sympathetic reflex. (1) In spinal cats, electrical and chemical stimuli produced no change in arterial diastolic pressure, and the small increase in arterial systolic pressure which occurred was detectable only when dP/dt max had already reached its peak value. (2) In vagotomized dogs, the increase in dP/dt max began with a latency that was about half of that for the increase in arterial pressure. In vagotomized cats, the increase was clearly established when the changes in arterial pressure were still small. (3) In these experiments, section of the left inferior cardiac nerve greatly reduced or prevented the increase in dP/dt max, but the rise in arterial pressure, although smaller and further delayed in onset, nevertheless persisted. (4) In the dog, equivalent increases in arterial pressure produced mechanically had very little effect on dP/dt max (14).

The increases in myocardial contractility and arterial pressure were reflexly evoked since there were no direct connections among...
the afferent fibers which were stimulated and the efferent limbs of the nervous pathway. We consider this reflex to have at least two components: (1) an increase in myocardial contractility due to increased cardiac sympathetic drive and (2) an increase in arterial pressure due to sympathetic vasoconstriction and to the reflex increase in myocardial contractility. The reflex sympathetic vasoconstriction is probably similar to that already reported (9). However, we do not interpret these results to indicate that spinal sympathetic reflexes are excitatory only. In this regard, we were limited by the artificial nature of the stimuli we used. It is possible that more physiological stimulation of the cardiac endings might also reflexly inhibit the sympathetic outflow in spinal vagotomized cats (18).

We have already reported that physiological and pathophysiological alterations in the activity of cardiac receptors initiate spinal sympathetic reflexes which may participate in the neural control of circulation. However, since the evidence was electrophysiological, the target organs to which the reflexly modulated sympathetic activity was directed were not identified. Therefore, the argument in favor of spinal sympathetic myocardial reflexes was not conclusive (1, 2, 18). Now, by establishing the heart as a target organ, we have definitely proved the existence of a spinal neural circuit mediating cardiocardiac reflexes which subserve changes in myocardial contractility.

References


Circulation Research, Vol. XXX, February 1972
Spinal Sympathetic Cardiocardiac Reflexes
ALBERTO MALLIANI, D. Fred PETERSON, VERNON S. BISHOP and ARTHUR M. BROWN

*Circ Res.* 1972;30:158-166
doi: 10.1161/01.RES.30.2.158
*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1972 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/30/2/158

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org/subscriptions/