Positive and Negative Inotropic Responses of the Atria and Ventricles to Vagosympathetic Stimulation in the Isovolumic Canine Heart

By Donald V. Priola, Ph.D., and Robert L. Fulton, M.D.

With the Technical Assistance of Constantine Anagnostelis

ABSTRACT

The responses of the paced, isovolumic atria and ventricles to cervical vagosympathetic stimulation were examined in eight normal and seven sympathectomized dogs under chloralose anesthesia. Before atropine, stimulation usually caused decreases in both atrial and ventricular contractility but with significant quantitative and qualitative variation from animal to animal. The right atrium showed the greatest average decrease (>30%), followed by the left atrium (12%), right ventricle (4% to 12%), and the left ventricle (1% to 10%). After atropine, 0.5 mg/kg, all chambers responded positively to stimulation. The right ventricle was most responsive (about 30%), and the other chambers showed increases of 10% to 20%. These positive inotropic responses were eliminated by propranolol, 0.5 mg/kg, or by pentolinium tartrate, 0.5 mg/kg. In the sympathectomized animals, negative inotropic responses were usually greater and positive responses were reduced or eliminated. The data demonstrate that fibers exist in the cervical vagosympathetic trunks which have both negative and positive inotropic effects on all chambers of the heart. The net effect of vagosympathetic stimulation on a chamber's contractility reflects the relative numbers of the two fiber types which supply it. The fibers mediating the positive effects are probably preganglionic with significant postganglionic stations in the caudal cervical and stellate ganglia and perhaps in the heart itself.

ADDITIONAL KEY WORDS

ventricular contractility
vagus nerve
sympathectomy
atrial contractility
nervous control of the heart

Preceding the demonstration by DeGeest et al. (1) that the isovolumic canine left ventricle is depressed by stimulation of the cervical vagus nerves, it was generally believed that the vagus exerted no influence on ventricular muscle. Subsequently, there have been many reports confirming and extending the observations of DeGeest and his co-workers (2-5). In addition, it has been suggested that these vagal inhibitory fibers may play a significant role in the reflex regulation of ventricular contractility (6-8). Recently, Pace et al. (9) and Randall and his co-workers (10) have demonstrated the existence of fibers within the cervical vagosympathetic trunks of the dog which exert a positive inotropic effect on ventricular contractility. These experiments have also suggested that the vagus nerves supply fibers to the atria which produce an increase in contractility after parasympathetic blockade with atropine. These data, although convincing, were obtained in a preparation that was uncontrolled except for rate. The source of these sympathetically-like vagal fibers is at present unknown.
The present experiments were performed (1) to examine the positive and negative inotropic influences of the vagosympathetic nerves on simultaneously recorded atrial and ventricular isovolumic pressures in a single preparation, (2) to examine the distribution of these two fiber types to the four cardiac chambers, and (3) to evaluate the possible sources of the sympathetic-like fibers using ganglionic blocking agents and preparations in which the classical cervicothoracic sources of the sympathetic cardiac innervation have been removed.

Methods

Fifteen mongrel dogs were employed in this study. Eight were unoperated controls, and seven were subjected to bilateral cervicothoracic sympathectomy 2 weeks earlier. The sympathectomy included removal of stellate, caudal cervical, and thoracic sympathetic ganglia (to T 5, inclusive) bilaterally along with the ansa subclavia and a section of the cervical sympathetic trunks extending about 2 cm rostral from the caudal cervical ganglionic blocking agents and preparations in which the classical cervicothoracic sources of the sympathetic cardiac innervation have been removed.

For the acute experiment, the animals were anesthetized with alpha-chloralose, 80 to 150 mg/kg, and the chests opened by transsternal thoracotomy. Respiration was maintained with a Harvard positive-pressure respirator. The external jugular and femoral veins were cannulated bilaterally, and after ligation of the venae cavae, the systemic venous blood was diverted by gravity into a Kay-Cross disk oxygenator. The venous blood was oxygenated in an atmosphere of 100% O2, passed through a heat exchanger where it was warmed to 37 ± 0.2°C, and returned to the animal through a femoral artery. Drain tubes were inserted into both ventricles, and this blood was returned to the oxygenator by continuous suction. During each experiment, the arterial flow rate was maintained constant at 75 to 100 ml/kg/min. This was usually sufficient to produce a mean arterial pressure of 80 to 120 mm Hg.

Saline-filled balloons were inserted into each of the cardiac chambers through small puncture wounds and secured with purse-string sutures. The balloons were filled with enough saline to bring the chamber's diastolic pressure to normal levels for the anesthetized, open-chest dog; i.e., right atrium, 0 to 3 mm Hg; left atrium, 2 to 5 mm Hg; right ventricle, 0 to 4 mm Hg; left ventricle, 0 to 5 mm Hg. Pacing electrodes were attached to the epicardial surfaces of the ventromedial right atrium and the right ventricular inflow tract. Atrioventricular pacing of the heart was maintained throughout the experiment at 10 to 20 beats/min above the unpaced heart rate, and the As-Vs interval (interval between atrial and ventricular systole) was maintained constant by setting the delay between the triggering of the right ventricular stimulator by the right atrial stimulator.

The cervical vagosympathetic trunks were isolated bilaterally and divided, and the distal ends were stimulated at 20 Hz, 5-msec duration, and supramaximal voltage (usually between 1 and 5 v) to give a maximum negative inotropic response. Thereafter, the voltage was left unchanged. Recordings of isovolumic chamber pressures were made on a Beckman Type SII Dynograph using Statham P23Db pressure transducers. Recordings of the effects of vagal stimulation were obtained before and after atropine, before and after pentolinium tartrate, and before and after propranolol. All of these drugs were administered in a dose of 0.5 mg/kg into the oxygenator chamber.

Results

Responses to Vagosympathetic Stimulation Before Muscarinic Blockade

The results of vagosympathetic stimulation before muscarinic blockade with atropine are shown in Table 1 for the eight normal dogs. On the average, stimulation of either vagosympathetic trunk induced decreases in the isovolumic pulse pressures of all four heart chambers. In addition, the maximum systolic dP/dt of both the right and left ventricles was similarly depressed. Ventricular contractility was less strongly affected than atrial contractility, and the rate of decrease of atrial pressures after the onset of stimulation was invariably greater than the rate of decrease in the ventricular pressures (Figs. 1 to 3). Although it cannot be seen in the average values, responses to stimulation followed two apparent patterns. One type of response is illustrated in Figures 1 and 2. As shown in Figure 1, stimulation of the right vagosympathetic trunk produced a decrease in the isovolumic pressure of each chamber. The decreases in ventricular pulse pressures and dP/dt developed more slowly than the atrial...

1DL-Propranolol (Inderal), kindly supplied by Ayerst Laboratories.
TABLE I

Individual Chamber Responses to Vagal Stimulation in Eight Animals without Cervicothoracic Sympathectomy

<table>
<thead>
<tr>
<th>Chamber</th>
<th>Vagus</th>
<th>Before atropine</th>
<th>After atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average %A ± SE</td>
<td>P₁</td>
</tr>
<tr>
<td>Right atrial pulse pressure</td>
<td>Right</td>
<td>21</td>
<td>-33 ± 10</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>17</td>
<td>-38 ± 13</td>
</tr>
<tr>
<td>Right ventricular pulse pressure</td>
<td>Right</td>
<td>21</td>
<td>-3 ± 6</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>17</td>
<td>0 ± 11</td>
</tr>
<tr>
<td>Right ventricular dP/dt</td>
<td>Right</td>
<td>17</td>
<td>-4 ± 9</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>15</td>
<td>-12 ± 11</td>
</tr>
<tr>
<td>Left atrial pulse pressure</td>
<td>Right</td>
<td>21</td>
<td>-11 ± 9</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>17</td>
<td>-12 ± 16</td>
</tr>
<tr>
<td>Left ventricular pulse pressure</td>
<td>Right</td>
<td>20</td>
<td>-1 ± 8</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>16</td>
<td>-1 ± 13</td>
</tr>
<tr>
<td>Left ventricular dP/dt</td>
<td>Right</td>
<td>17</td>
<td>0 ± 10</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>15</td>
<td>-10 ± 12</td>
</tr>
</tbody>
</table>

Changes in isovolumic pulse pressure and maximum systolic rate of pressure change (dP/dt) are expressed as the percent change from the control value ± the standard error of the mean. \( P₁ \) is the range of probability that the differences between the averages of the responses before and after atropine occurred by chance.

Changes and were not as great. Figure 2 illustrates a similar response in the same animal to stimulation of the left vagosympathetic trunk. Again, all four chambers were depressed, atria more than ventricles. The pattern of pressure changes in the atria and ventricles was also quite similar to those seen in response to right vagosympathetic stimulation. However, there was another pattern of response to stimulation that was observed quite frequently. This is typified by the control panels of Figure 3. As in Figures 1 and 2, stimulation of the right vagosympathetic trunk evoked prompt decreases in the isovolumic pressures of both atria, virtually obliterating pulsation. There was also a slight, but definite, decrease in left ventricular contractility which developed quite slowly. The right ventricle, however, exhibited an increase in isovolumic pressure of 25%. This would indicate, then, that the right vagosympathetic trunk, in this animal, supplied few inhibitory fibers to the ventricles and a significant number to the atria. The pattern of response to stimulation of the left vagosympathetic trunk in this animal differed markedly from that of the right. Right atrial contractility was suppressed, but not as rapidly or as profoundly as with right vagosympathetic stimulation. The left atrium, on the other hand, displayed a biphasic response, first negative and then positive. The negative inotropic left atrial response was much less and developed much more slowly with left vagosympathetic stimulation in this animal. The right ventricle again displayed a positive inotropic response, but it was considerably more striking than that seen with right stimulation, i.e., 71% above control. In contrast to the slight inhibition seen with right vagosympathetic stimulation, the left ventricle now exhibited a positive inotropic response with left stimulation, i.e., 20% above control. In this animal, then, the contribution of inhibitory fibers to the ventricles from the vagosympathetic trunk would appear to be minor, only being derived from the right side. By the same token, the atria appeared to receive a large number of inhibitory fibers from the right side as judged by the prompt and profound depression of contractility in response to stimulation. The left side, on the other hand, appeared to contribute a significant number of inhibitory fibers to the right atrium while supplying a lesser number to the left atrium. When the responses of the type illustrated in Figures 1 and 2 are compared with

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the preatropine responses of Figure 3, it is clear that the pattern of distribution of inhibitory fibers to the heart varies from animal to animal, ranging from a general distribution to all four chambers to a rather discrete distribution, more or less fibers being supplied to a given chamber from one side or the other.

RESPONSES TO VAGOSYMPATHETIC STIMULATION AFTER MUSCARINIC BLOCKADE

After muscarinic blockade with atropine (Fig. 3) right vagosympathetic stimulation no longer produced negative inotropy in any chamber. On the contrary, the right ventricle, which exhibited a moderate positive inotropic response before atropine, now showed an even greater increase in contractility after blockade, i.e., 25% and 50%, respectively. Stimulation of the left vagosympathetic trunk, which produced generally small inhibitory effects before blockade, now produced a positive inotropic response in every chamber. These could be seen as small increases in the isovolumic pressures of the right atrium (+17%) and the left atrium (+20%). The ventricles, which showed increases in contractility in response to left stimulation before atropine, now exhibited even greater positive inotropic responses; i.e., right ventricle, +84%; left ventricle, +36%.

The responses of a different animal to vagosympathetic stimulation following muscarinic blockade are illustrated in the two

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FIGURE 3

Responses of an animal to vagosympathetic trunk stimulation that illustrate a different pattern of reaction than those shown in Figures 1 and 2. The two left-hand panels are control and show the responses to stimulation of the right and left trunks before the administration of atropine. The two right-hand panels show the responses following muscarinic blockade with atropine. Heavy lines between the second and third channels down denote the periods of stimulation. RA = right atrium; RV = right ventricle; LA = left atrium; LV = left ventricle; AP = aortic pressure; ECG II = lead II of the limb lead electrocardiogram. Heart paced at 180 beats/min.

left-hand panels of Figure 4. In this experiment, right stimulation produced positive inotropic responses in all four chambers of the heart, particularly the right atrium and right ventricle. Stimulation of the left vagosympathetic trunk also produced an increase in contractility in all chambers (except the right atrium) and caused greater positive inotropy of the left atrium and left ventricle than did right stimulation.

The data obtained from vagosympathetic stimulations following atropine are summarized in Table 1. Whereas no positive inotropic responses were shown in the averages before atropine, all the averages are positive following atropine. The differences between the averages for the right atrium and right ventricle are significant at the 0.05 level or less. In general, both the positive and negative inotropic responses of the right heart to stimulation tended to be greater. Although the differences between the average responses of the left atrium and left ventricle are apparent, they were of marginal statistical significance. The changes exhibited by these chambers tended to be less than those seen on the right side.

The positive inotropic responses to vagosympathetic stimulation following atropine could be completely eliminated by the administration of propranolol, 0.5 mg/kg.

RESPONSES TO VAGOSYMPATHETIC STIMULATION FOLLOWING GANGLIONIC BLOCKADE

Figure 4 shows the results of an experiment in which the ganglionic blocking agent, pentolinium tartrate, was administered to an animal that had been previously atropinized. In the two left-hand panels, the positive inotropic responses to stimulation following atropine are apparent (vide supra). Following
FIGURE 4

Responses of a different intact animal illustrating the effect of ganglionic blockade on the cardiac augmentation produced by stimulation of the vago sympathetic trunks after blockade of the inhibitory effects with atropine. The two left-hand panels show the control responses to stimulation after atropine and the two right-hand panels show the responses to identical stimulation shortly after injection of the ganglionic blocking agent, pentolinium. Heavy lines in the third channel down denote the periods of stimulation.

these stimulations, pentolinium was administered and the records in the two right-hand panels of Figure 4 were obtained a few minutes later. Ganglionic blockade resulted in a decrease in the contractility of all chambers of the heart presumably because of the blockade of existing sympathetic tone. Right vagosympathetic stimulation no longer produced any change in any cardiac chamber. The positive inotropic responses to stimulation of the left vagosympathetic trunk were also largely eliminated. Upon close examination, some small degree of positive inotropy can be detected in the right ventricle and the left atrium. However, these changes are certainly insignificant when compared to those produced by left vagosympathetic stimulation prior to pentolinium.

RESPONSES OF SYMPATHECTOMIZED ANIMALS PRIOR TO MUSCARINIC BLOCKADE

The responses of the sympathectomized animals to vagosympathetic stimulation before muscarinic blockade with atropine are summarized in Table 2. The average values reflect accurately the typical experimental results. Not only were positive inotropic responses not seen, but the negative inotropic responses were generally exaggerated over those seen in the intact animals before atropine (Table 1). This was especially apparent in the left heart, but only statistically significant for the left atrium ($P_a$ in Table 2). However, there was a clear trend that suggested that the inhibitory effects of stimulation were unaffected, and even made more apparent, by removal of the cervicothoracic sympathetic nerves.

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Individual Chamber Responses to Vagal Stimulation in Seven Animals Two Weeks after Cervicothoracic Sympathectomy

Table 2

<table>
<thead>
<tr>
<th>Chamber</th>
<th>Vagus</th>
<th>No. of observations</th>
<th>Average %Δ ± SE</th>
<th>P&lt;sub&gt;v&lt;/sub&gt;</th>
<th>After atropine</th>
<th>No. of observations</th>
<th>Average %Δ ± SE</th>
<th>P&lt;sub&gt;v&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pulse pressure</td>
<td>Right</td>
<td>13</td>
<td>-31 ± 16</td>
<td>0.05-0.10</td>
<td>19</td>
<td>4 ± 8</td>
<td>0.05-0.10</td>
<td>0.20-0.30</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>10</td>
<td>-65 ± 13</td>
<td>&lt;0.001</td>
<td>15</td>
<td>-4 ± 8</td>
<td>0.10-0.20</td>
<td>0.20-0.30</td>
</tr>
<tr>
<td>Right ventricular pulse pressure</td>
<td>Right</td>
<td>13</td>
<td>-11 ± 4</td>
<td>&lt;0.001</td>
<td>19</td>
<td>9 ± 3</td>
<td>0.30-0.40</td>
<td>0.02-0.05</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>11</td>
<td>-7 ± 7</td>
<td>0.10-0.20</td>
<td>17</td>
<td>4 ± 3</td>
<td>0.60-0.70</td>
<td>0.01-0.001</td>
</tr>
<tr>
<td>Right ventricular dP/dt</td>
<td>Right</td>
<td>13</td>
<td>-20 ± 5</td>
<td>&lt;0.001</td>
<td>19</td>
<td>6 ± 2</td>
<td>0.10-0.20</td>
<td>0.02-0.05</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>11</td>
<td>-15 ± 5</td>
<td>0.05-0.10</td>
<td>17</td>
<td>3 ± 8</td>
<td>0.80-0.90</td>
<td>0.05-0.10</td>
</tr>
<tr>
<td>Left atrial pulse pressure</td>
<td>Right</td>
<td>12</td>
<td>-37 ± 10</td>
<td>&lt;0.001</td>
<td>19</td>
<td>4 ± 3</td>
<td>0.02-0.05</td>
<td>0.80-0.90</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>9</td>
<td>-64 ± 19</td>
<td>0.01-0.001</td>
<td>17</td>
<td>-1 ± 3</td>
<td>0.02-0.05</td>
<td>0.01-0.02</td>
</tr>
<tr>
<td>Left ventricular pulse pressure</td>
<td>Right</td>
<td>13</td>
<td>-12 ± 3</td>
<td>&lt;0.001</td>
<td>19</td>
<td>5 ± 3</td>
<td>0.20-0.30</td>
<td>0.50-0.60</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>11</td>
<td>-12 ± 11</td>
<td>0.10-0.20</td>
<td>17</td>
<td>6 ± 3</td>
<td>0.50-0.60</td>
<td>0.20-0.30</td>
</tr>
<tr>
<td>Left ventricular dP/dt</td>
<td>Right</td>
<td>13</td>
<td>-11 ± 6</td>
<td>0.02-0.05</td>
<td>19</td>
<td>8 ± 6</td>
<td>0.30-0.40</td>
<td>0.50-0.60</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>11</td>
<td>-13 ± 5</td>
<td>0.02-0.05</td>
<td>17</td>
<td>2 ± 4</td>
<td>0.80-0.90</td>
<td>0.20-0.30</td>
</tr>
</tbody>
</table>

The ranges of probability that the differences between means could have occurred by chance are indicated for the following groups: sympathectomized animals, before versus after atropine (P<sub>v</sub>); responses before atropine of the intact versus the sympathectomized animals (P<sub>x</sub>); and responses after atropine of the intact versus the sympathectomized animals (P<sub>x</sub>).

Responses of Sympathectomized Animals Following Muscarinic Blockade

In the animals subjected 2 weeks earlier to cervicothoracic sympathectomy, positive inotropic responses to vagosympathetic stimulation following atropine were sharply reduced or completely eliminated (Fig. 5). The average values for the responses of this group are shown in Table 2. Administration of atropine virtually eliminated the negative inotropic responses observed in these animals in response to stimulation of either vagosympathetic trunk. In most cases the differences between the means were significant at the 0.05 level, or less (P<sub>v</sub> in Table 2). After atropine, stimulation often failed to elicit any positive inotropic responses from the heart as illustrated in Figure 5. In other animals, some positive inotropy could be produced by vagosympathetic stimulation, especially in the ventricles where the responses were reduced as compared to the intact animals, but still discernible (Table 2). On the average, the positive inotropic responses of the right ventricle and left atrium (to left stimulation) were statistically different following sympathectomy. While the average responses of the right atrium and left ventricle after atropine were considerably lower than those of the intact animals, they were not statistically different. Of the seven sympathectomized animals studied, five displayed an absence of positive inotropic responses to stimulation of the right vagosympathetic trunk while four showed no significant positive responses to stimulation of the left trunk. The other animals showed various degrees of positive inotropic responses, but less than were normally observed in the intact animals after atropine.

Discussion

DeGeest et al. (1, 2), Levy et al. (3), and Daggett et al. (4) demonstrated that in both the isovolumic left ventricle and in the heart on right-heart bypass with controlled inflow, stimulation of the cervical vagosympathetic trunks causes a decrease in left ventricular contractility. These studies were only definitive for the left ventricle, and no information was obtained on the possible negative ino-
FIGURE 5

Recordings illustrating the complete elimination of positive inotropic responses after atropine to vagal stimulation in an animal subjected to cervicothoracic sympathectomy 2 weeks earlier. Periods of stimulation are indicated by the heavy lines in the bottom channel. The lack of responsiveness illustrated in this figure was typical of the majority, but not all, of the sympathectomized animals. (See text.)

In our studies, with all chambers of the heart beating isovolumically and with systemic arterial flow, heart rate, and As-Vs interval constant, it is clear that the negative inotropic influence of the vagosympathetic trunk extends to all four chambers of the heart. According to the average data obtained from the eight intact preparations, the right atrium is the chamber most powerfully inhibited by stimulation while the other three chambers show lesser degrees of negative inotropy. Right ventricular contractility appears to be depressed at least as much if not more than left ventricular contractility. In some animals, vagosympathetic stimulation uniformly depressed all heart chambers while, in others, some chambers exhibited positive inotropic responses while negative inotropic changes were simultaneously occurring in different chambers. These qualitative differences in the responses of different chambers of the same heart cannot be explained simply on the basis of differences in the distribution and density of one functional fiber type (vagal inhibitory fibers).

The positive chronotropic effects of the vagus nerve are well documented (12-14). In addition, Middleton and his co-workers (14) have demonstrated that stimulation of the vagus nerves in the isolated, atropinized cat heart can produce increases in the isotonic contractions of the atria and ventricles. More recently, Levy et al. (3) have observed a biphasic response of the isovolumic left ventricle during and after vagosympathetic stimulation. They suggested that the positive overshoot following cessation of stimulation might be due to the presence of sympathetic-like fibers in the cervical vagosympathetic trunk which are simultaneously activated with the inhibitory fibers. Randall et al. (10) measured simultaneous pressures from the four chambers of the uncontrolled canine heart and reported that, after muscarinic blockade with atropine, vagosympathetic stimulation produced changes suggestive of positive inotropy, notably in the ventricles.
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(10). Their work strongly suggested that stimulation of the dog's cervical vagosympathetic trunk simultaneously activated both inhibitory and augmentor fibers. The positive inotropic effects of the latter's activation could be abolished by the beta-receptor blocking agent, propranolol. Although these workers could not eliminate the possibility that changes in pulmonary vascular resistance, end-diastolic pressure, chamber pressure-volume characteristics, afterload, and As-Vs interval could be contributing to the changes they observed, the positive inotropic responses were still demonstrable after cross-clamping of the heart at the A-V junction. In the present study, these variables are eliminated so that alterations in chamber pressure almost certainly reflect changing levels of contractility. The results of stimulation following atropine administration confirm the observations of Randall et al. in the uncontrolled preparation. In addition, they established that two different fiber types are activated when the cervical vagosympathetic trunk is stimulated which simultaneously produce both positive and negative inotropic actions. The net response of any given chamber therefore depends on the relative numbers of the two fiber types present in that chamber and activated by stimulation. A study of Figure 3 strongly supports this contention. Before the administration of atropine, right vagosympathetic stimulation promptly and powerfully depressed the contractility of both atria while it produced a lesser depression of the left ventricle and a slight positive inotropic effect in the right ventricle. If the net chamber response was due to a summation of both negative and positive inotropic effects, then one would expect that the right vagosympathetic trunk of this animal supplied few, if any, augmentor fibers to the atria and left ventricle while supplying a relatively greater number to the right ventricle. After atropinization, the prediction is confirmed. There is slight right atrial augmentation, greater left atrial augmentation, and a strong positive inotropic response in the ventricles. The average data (Table 1) also support this hypothesis. After cervicothoracic sympathectomy, the general heightening of the inhibitory effects of stimulation before atropine (Table 2) can be explained by the surgical elimination of many of the simultaneously activated augmentor fibers.

The experiments in which the augmentor responses were blocked by pentolinium and reduced or abolished by prior sympathectomy offer some clues as to the source of the augmentor fibers within the cervical vagosympathetic trunk. Firstly, the fibers appear to be mainly preganglionic because their effects are eliminated by the ganglionic blocking agent, pentolinium. This must mean that they are either descending preganglionic fibers or ascending preganglionic fibers with their corresponding descending postganglionic elements in some area other than the vagosympathetic trunk. In the animals in which positive inotropic responses were abolished by prior sympathectomy, it was likely that the postganglionic cell stations were removed. This information would mean the effective elimination of the superior cervical ganglion as the source of the postganglionic fibers since it was left intact. It is conceivable that, in these animals, the stellate, the caudal cervical ganglion, or both served as the source of the postganglionic elements. In the other animals in which the augmentor responses were
diminished, but not abolished, by sympathectomy, it is possible that (1) the superior cervical ganglion could have served as a postganglionic source with the postganglionic fibers reaching the heart by some pathway which does not involve the cervical trunk; (2) the vagal preganglionic made synaptic connections within the vagal trunk itself, in one of the cardiac plexi, or with adrenergic cells within the myocardium; or (3) that the positive inotropic effects were, in part, the result of the release of catecholamine via acetylcholine from vagal postganglionic fibers, as suggested by the hypothesis of Burn and Rand (15). In the last instance, pentolinium would be expected to abolish this response since it would block transmission between the pre- and postganglionic vagal elements.

Middleton and his associates (14) observed that, in the cat, the cardio-stimulation that accompanies vagal stimulation following muscarinic blockade was not affected by prior superior cervical ganglionectomy but could be abolished by ganglionic blockade with nicotine. A more recent study by Smith (16) has demonstrated that, in the dog, ganglionic blocking agents abolish the cardioaccelerator responses to vagal stimulation and abolish or reduce the accelerator response to stimulation of the cervical sympathetic trunk. He suggests that the vagal preganglionics produce the positive chronotropic effect by activating intracardiac adrenergic neurons. His studies implicate the stellate ganglion as the source of the postganglionic fibers activated by stimulation of the cervical sympathetic trunk. He suggests that a greater or lesser proportion of these two types of augmentor fibers in any individual animal might explain the ability of sympathectomy to abolish the positive inotropic responses in many, but not all, animals.

Speculation on the source of the preganglionic fibers in the vagosympathetic trunk which mediate cardiac augmentation might include the possibilities that (1) they arise from the thoracic cord, ascend in the vagosympathetic trunk, loop back down (without synapsing), and descend in the vagosympathetic trunk or (2) they may arise in the brainstem itself.

We have been unable to find any information in the literature on the latter, very interesting possibility, although Kabat (13) has suggested an intracranial source for the vagal cardioaccelerator fibers.

References


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