Hypertension following Denervation of Aortic Baroreceptors in Unanesthetized Dogs

Cyril S. Ito and Allen M. Scher

SUMMARY After cervical aortic nerve section, mean arterial pressure in the unanesthetized dog increased by an average of 7.4 mm Hg. Following a more extensive denervation of aortic arch receptors by section of intrathoracic vagal branches, arterial pressure increased by 16.7 mm Hg. The above changes were seen in the stable state after the effects of surgery had disappeared. In both cases carotid baroreceptors were functional. After administration of nitroglycerin and phenylephrine subsequent to either denervation procedure, blood pressure changes were larger and heart rate responses were smaller than in the control state. The unanesthetized dog regulates mean arterial pressure at a higher-than-normal pressure after aortic baroreceptor denervation. Reflexes from the aortic baroreceptors continuously participate in the normal control of mean arterial pressure. Section of the cervical aortic nerves only partially denervates aortic baroreceptors. Our findings may be relevant to human essential hypertension.

BARORECEPTORS of the carotid sinus and aortic arch respond to changes in arterial blood pressure by initiating reflex vasomotor and cardiac responses, which tend to return pressure to normal (Heymans and Neil, 1958). This reflex control is generally considered operative for short- and long-term regulation. Recently, however, Guyton et al. (1974) have expressed the view that arterial baroreceptors are not important in long-term control of arterial pressure. They believe that the baroreceptor reflexes will act for only 1 or 2 days to correct alterations in arterial pressure, and they attribute long-term control of arterial pressure to nonneural mechanisms.

The view that arterial baroreceptors are unimportant in long-term control is related to studies of arterial baroreceptor denervation, to the concept of baroreceptor adaptation, and to the phenomenon of baroreceptor "resetting." Denervation of all arterial baroreceptor should, according to the traditional theory, produce sustained hypertension (Heymans and Neil, 1958). Hypertension has been seen in awake dogs after arterial baroreceptor denervation (Ferrario et al., 1969; Heymans and Neil, 1958; Nowak, 1940; Thomas, 1944). However, in other studies (Cowley et al., 1973; Cowley and Guyton, 1975; Cowley and DeClue, 1976; Heymans and Neil, 1958; Koch and Mattonet, 1934), little or no increase in mean arterial pressure followed baroreceptor nerve section. If baroreceptor denervation produces no sustained rise in mean arterial pressure, despite the decrease in input to the medulla from the baroreceptors, this implies an adaptation of the central nervous system and/or of peripheral motor mechanisms. Cowley et al. (1973) believed that some prior studies in which hypertension was produced were suspect because only brief recordings of pressure were taken and because emotional responses might have altered the pressure. In all of the above studies, pressure was more labile in the denervated than in the normal animal.

Baroreceptor resetting refers to the observation that receptors subjected to maintained high pressure lower their discharge rate over a few days, despite the increased pressure (Angell-James, 1973; McCubbin et al., 1956; Sleight et al., 1977). This implies that with time the reflex changes that counteract hypertension would be attenuated or would disappear. Resetting thus may have effects indistinguishable from those of adaptation. Resetting might explain the findings of Cowley et al. (Cowley and Guyton, 1975; Cowley and DeClue, 1976) that the maximal increase in pressure caused by volume loading or angiotensin infusion was not influenced by procedures considered to denervate arterial baroreceptors.

If the arterial baroreceptors are not important in long-term control of arterial pressure, then denervating either the carotid or the aortic baroreceptors, or both, should alter arterial pressure only transiently. In an earlier study on the unanesthetized dog, we found that carotid sinus nerve section caused no chronic increase in mean arterial pressure (Ito and Scher, 1978). In the present study, we measured the mean arterial blood pressure in dogs before and after section of either (1) the cervical aortic nerves, (2) the intrathoracic vagal branches,
which conduct impulses centrally from aortic baroreceptors, or (3) both (1) and (2). In some dogs, we combined section of the right cervical aortic nerve with section of vagal branches on the left side. In all cases the carotid sinuses were innervated. We also compared the responses of arterial pressure and heart rate to injection of vasoactive drugs and to carotid occlusion before and after the nerve sections.

Methods

The procedures were similar to those described previously (Ito and Scher, 1978). Twenty-six mongrel dogs of both sexes, weighing between 18 and 27 kg, were prepared for study by placing one common carotid artery in a skin tube (Van Leersum, 1911) in the neck and moving the other common carotid artery to a subcutaneous position. The common carotid arteries were separated from the surrounding tissue to denervate any baroreceptors along their length. In most dogs, both vagal trunks were placed in separate skin tubes. During recovery from this preparatory surgery, the dogs were trained to remain quietly in a Pavlov stand for several hours. These dogs are considered intact or control animals.

Section of Aortic Baroreceptor Fibers

The aortic baroreceptors send fibers centrally both in the cervical aortic nerves and in the main cervical vagal trunk (Ito and Scher, 1973, 1974). Interruption of all aortic baroreceptor fibers thus requires denervation of aortic baroreceptors whose fibers course in the main cervical vagal trunk, in addition to interruption of those in the cervical aortic nerves. No surgical technique (except bilateral cervical vagotomy, which is fatal in the dog) interrupts all fibers from aortic baroreceptors.

Two surgical procedures were performed under aseptic conditions. In one procedure, the cervical aortic nerves were identified by recording their electrical activity and were then sectioned as in our earlier study (Ito and Scher, 1974). For more extensive denervation of aortic baroreceptors, a single-stage procedure was developed. The chest was entered through the left 3rd interspace. All intrathoracic branches of the left vagus were transected down to a point 1 cm below the caudal margin of the aortic arch. All branches of the inferior cervical ganglion, except the ansa subclavia and cervical sympathetic trunk, were cut. Trauma to the vagal trunk was avoided. On the right, the brachiocephalic artery was cleared of adventitia from its origin to 1 cm beyond the origins of the left and right common carotid and right subclavian arteries. The right vagal trunk was transected immediately caudal to its junction with the recurrent laryngeal nerve. The thoracic branches of the right recurrent laryngeal nerve and all branches of the right inferior cervical ganglion were sectioned except for the ansa subclavia and cervical sympathetic trunk. Derom (1958) has described a similar two-stage procedure.

With the exception of a small number of fibers that may join the left vagus more caudally (Coleridge et al., 1973; Ito and Scher, 1973), these procedures eliminate nerve fibers from most of the intrathoracic arterial baroreceptors and produce substantial sensory and motor denervation of the heart and other intrathoracic structures. If section of vagal branches on the left side is extended more caudally, the esophagus and stomach are denervated, leading to esophageal achalasia, intractable vomiting, and death.

Recording Procedures

During recording sessions the dogs were placed in a Pavlov stand. Aortic blood pressure was recorded from a Teflon catheter inserted into the carotid artery in the skin tube. The catheter tip was at the aortic arch. Heart rate was measured by a cardiotachometer triggered from the arterial pressure signal. Respiratory rate was measured with a flexible chest tube and a pneumotachometer. Mean blood pressure during each heart beat (beat mean arterial pressure) was determined by an on-line computer. Maximal rate of change of arterial pressure was determined by differentiation. Aortic pressure, beat mean arterial pressure, heart rate, and respiratory rate were continuously recorded on a Beckman recorder, and the values were stored simultaneously on magnetic tape by the computer. Histograms of beat mean arterial pressure, heart rate, and respiratory rate were assembled on-line. Mean values and standard deviations of these variables were calculated after each recording session. These procedures have been described (Ito and Scher, 1978).

To see whether pulse pressure or rate of change of arterial pressure was altered by the surgical procedure, we averaged aortic pulse pressure and maximal rate of change of aortic pressure over 30 seconds. We assumed that aortic pulse pressure and rate of change of aortic pressure would accurately reflect these variables in the carotid sinus region. In a brief investigation, we found a correlation of 0.91 between carotid and aortic pulse pressures.

Experimental Plan

Each dog was studied for four to eight recording sessions at intervals of 3–7 days, starting about 2 weeks after the preparatory surgery. All sessions were started within 0.5 hour of 9 a.m. During the first 75 minutes of each session, we took records of the variables noted above and compiled histograms while the dog remained quietly in the Pavlov stand. We then recorded the changes in blood pressure and heart rate following bilateral carotid occlusion and rapid intra-aortic administration of nitroglycerin and phenylephrine (0.8 mg each in normal saline).

When the average values of all variables became
stable (after several recording sessions), we performed the denervation procedures described above and conducted five to nine additional recording sessions. Again, we were concerned with the stable values of the measured variables. Each dog thus served as its own control.

Data Analysis

The mean values and standard deviations were computed, and the paired t-test and Wilcoxon’s signed rank test were performed on the differences in the mean values and standard deviations of blood pressure, heart rate, and respiratory rate before and after section of the aortic nerves.

The maximal changes in beat mean arterial pressure and heart rate produced by nitroglycerin and phenylephrine were measured from the chart recordings. The ratio of the maximal change in heart rate to the maximal change in blood pressure also was computed as an indicator of the reflex “gain” in heart rate. The differences in these changes and in the ratios before and after aortic baroreceptor denervation were subjected to the paired t-test.

Test of Baroreceptor Denervation

The reflex increase in arterial pressure following bilateral occlusion of the common carotid arteries before and during block of the cervical vagosympathetic trunk with local anesthetic [according to the procedure devised by Phillipson et al. (1970) for respiratory studies] was used to test the completeness of our denervation. If some aortic baroreceptor fibers survived the denervation procedure, the carotid occlusion response should have been larger during the vagal block, because aortic baroreceptors no longer opposed the increase in arterial pressure.

Results

Number of Dogs Studied

The cervical aortic nerves were successfully identified by recording their electrical activity and were sectioned in 10 of 15 dogs. The average changes in blood pressure and heart rate in response to bilateral carotid artery occlusion were, respectively, 2.1 ± 1.1 and 4.7 ± 5.8 times as great as before the nerve section. In five dogs (not included in this study), at least one cervical aortic nerve could not be identified.

The thoracic vagal branches were successfully sectioned in six dogs. In three of these, the cervical aortic nerves had been sectioned earlier, as indicated. In three additional dogs, the left thoracic vagal branches and right cervical aortic nerve were sectioned. In these animals, the increase in blood pressure following carotid occlusion was 2.1 ± 0.9 times as great after section. While we were developing this denervation procedure, two dogs showed the same maximal aortic pressure rise following carotid occlusion before and after the denervation. We considered the denervation unsuccessful in these dogs, and they were not studied further.

Arterial Pressure Changes following Cervical Aortic Nerve Section

The average beat mean arterial pressure varied slightly between recording sessions in each dog both before and after section of aortic baroreceptor nerve fibers. Figure 1 shows histograms of beat mean arterial pressure for all recording sessions from one dog. The mean pressure for the seven control sessions was 92.5 ± 6.8 mm Hg, and the mean standard deviation was 8.6 ± 1.3 mm Hg. Twenty-four hours after section of the cervical aortic nerves, the blood pressure was 129 mm Hg. The pressure decreased to 111 mm Hg over the first 17 postoperative days and remained near that level thereafter (Fig. 1). The stable mean arterial pressure (2 weeks after the nerve section) and its variation were higher in nine of 10 dogs; for the group, the increases were 7.4 ± 8.4 and 1.3 ± 1.2 mm Hg, respectively.

Arterial Pressure Changes following Section of Intrathoracic Vagal Branches

Figure 2 shows histograms of beat mean arterial pressure from one dog for five sessions before and after 100, 200 mm Hg.
HYPERTENSION FOLLOWING AORTIC DENERVATION

INTACT NO DAYS MEAN STANDARD POST-SURGERY B.P. (mm Hg) DEVIATION

<table>
<thead>
<tr>
<th>Number</th>
<th>No. of</th>
<th>Mean B.P. (mm Hg)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>beats</td>
<td>POST-SURGERY</td>
<td>101.92</td>
<td>6.55</td>
</tr>
<tr>
<td>200</td>
<td>29</td>
<td>96.96</td>
<td>7.24</td>
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<tr>
<td>200</td>
<td>33</td>
<td>92.17</td>
<td>6.63</td>
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<td>200</td>
<td>38</td>
<td>96.84</td>
<td>8.29</td>
</tr>
<tr>
<td>200</td>
<td>40</td>
<td>96.95</td>
<td>8.29</td>
</tr>
</tbody>
</table>

THORACIC BRANCHES OF VAGI CUT

<table>
<thead>
<tr>
<th>Number</th>
<th>No. of</th>
<th>Mean B.P. (mm Hg)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>beats</td>
<td>POST-SURGERY</td>
<td>115.84</td>
<td>7.66</td>
</tr>
<tr>
<td>200</td>
<td>1</td>
<td>111.77</td>
<td>9.42</td>
</tr>
<tr>
<td>200</td>
<td>2</td>
<td>122.01</td>
<td>9.21</td>
</tr>
<tr>
<td>200</td>
<td>7</td>
<td>123.30</td>
<td>6.99</td>
</tr>
<tr>
<td>200</td>
<td>15</td>
<td>125.52</td>
<td>8.01</td>
</tr>
<tr>
<td>200</td>
<td>19</td>
<td>110.10</td>
<td>9.69</td>
</tr>
<tr>
<td>200</td>
<td>26</td>
<td>110.34</td>
<td>7.56</td>
</tr>
</tbody>
</table>

Thoracic denervation increased mean arterial pressure by 40.7 ± 7.2 beats/min and eliminated respiratory sinus arrhythmia, both effects due largely to cardiac denervation. Respiratory rate was significantly lower, probably due to section of pulmonary afferent fibers. Table 2 summarizes the changes in beat mean arterial pressure, heart rate, and respiratory rate in the six dogs before and after bilateral section of intrathoracic vagal branches. The decreased

\[ \text{Heart Rate, Respiratory Rate, and Pulse Pressure} \]

Heart rate increased and had a smaller standard deviation (higher in six dogs and lower in four) after cervical aortic nerve section. The differences were not significant \((P > 0.05)\). Respiratory rate was lower after cervical aortic nerve section in nine dogs and higher in one. The mean values and standard deviations of beat mean arterial pressure, heart rate, and respiratory rate for the 10 dogs before and after cervical aortic nerve section are shown in Table 1.

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\[ \text{FIGURE 2 Histograms of beat mean arterial pressure during 75-minute recording sessions from one dog before (upper half) and after (lower half) bilateral section of the thoracic branches of the vagus nerve trunk. Note the increase in pressure after the nerve section.} \]

\[ \text{FIGURE 3 Change of mean arterial pressure after bilateral section of the thoracic branches of the vagus trunks. Each unfilled circle represents the average value of the changes of mean arterial pressure in six dogs, and the bars show one standard deviation of the mean for each recording day. The filled circle on the left shows the average mean pressure with all baroreceptor nerves intact. The filled circle on the right shows the average mean pressure after the thoracic branches of the vagi had been sectioned.} \]
Cervical aortic nerves cut
Right cervical aortic nerves cut and left thoracic vagal branches cut
Thoracic vagal branches cut bilaterally

FIGURE 4 Comparison during 75-minute recording sessions of the average increases in the mean arterial pressure produced by section of the cervical aortic nerves in 10 dogs, section of the right cervical aortic nerve and left thoracic vagal branches in three dogs, and section of the thoracic branches of the vagi in six dogs (Table 1). Bars represent one standard deviation. Asterisks indicate statistically significant difference from intact: * P < 0.05, ** P < 0.02, *** P < 0.001.

standard deviation of beat mean arterial pressure may reflect the loss of respiratory sinus arrhythmia. Note that both Tables 1 and 2 concern dogs with an innervated carotid sinus.

Pulse Pressure

The average aortic pulse pressure and average dp/dt decreased in eight of 10 dogs after cervical aortic nerve section. The pulse pressure also decreased in all dogs after section of intrathoracic vagal branches. The decrease in aortic pulse pressure after aortic nerve section could either be a cause for the increase in mean arterial pressure (baroreceptors are sensitive to changes in pulse pressure) or an effect of the increase in heart rate following the denervation. The decrease in pulse pressure was positively correlated (r = 0.57) with mean arterial pressure change, i.e., mean arterial pressure increased least in those dogs in which pulse pressure was reduced the most by either denervation procedure. Thus it is unlikely that the increase in mean arterial pressure is a reflex response to the decrease in arterial pulse pressure.

Response to Vasoactive Drugs

The changes in blood pressure and heart rate caused by vasoactive drugs varied from day to day and among different dogs. However, all animals showed similar changes when all runs were averaged. Greater changes in blood pressure and smaller changes in heart rate (compared to control dogs) generally were seen following injection of nitroglycerin and phenylephrine after cervical aortic nerve section. The responses to vasoactive drugs are summarized in Table 3. After cervical aortic nerve section, the ratio of the maximal change in heart rate to the maximal change in blood pressure following nitroglycerin was reduced by more than 40% (P < 0.005).

The rise in blood pressure due to phenylephrine was larger (P < 0.05) after cervical aortic nerve section, and both the change in heart rate and the ratio of change in heart rate to change in blood pressure were smaller after the nerve section than before, but only the difference in the heart rate-blood pressure ratio was significant (P < 0.05).

After bilateral section of intrathoracic vagal branches, much larger changes in blood pressure and much smaller reflex alterations in heart rate were produced by intra-aortic administration of vasoactive drugs. Following nitroglycerin, beat mean arterial pressure decreased more than twice as much as in control dogs (42.8 vs. 18.8 mm Hg), and the reflex increase in heart rate was only about one-third of the control responses (22.8 vs. 76.4

TABLE 1 Average Values of Mean Blood Pressure, Heart Rate, and Respiratory Rate during 75-Minute Recording Sessions from 10 Dogs with All Baroreceptor Nerves Intact and after Bilateral Section of Cervical Aortic Nerves

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Respiration rate (breaths/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (I)</td>
<td>95.73 ± 8.36</td>
<td>83.65 ± 12.51</td>
<td>46.05 ± 16.46</td>
</tr>
<tr>
<td>Cervical aortic nerves cut (C)</td>
<td>103.16 ± 6.29</td>
<td>89.44 ± 13.35</td>
<td>39.56 ± 20.42</td>
</tr>
<tr>
<td>Difference (C - I)</td>
<td>7.43 ± 8.16*</td>
<td>5.79 ± 10.99</td>
<td>-7.49 ± 8.76†</td>
</tr>
<tr>
<td>Standard deviations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (I)</td>
<td>8.42 ± 1.17</td>
<td>20.90 ± 3.38</td>
<td>22.75 ± 3.21</td>
</tr>
<tr>
<td>Cervical aortic nerves cut (C)</td>
<td>9.73 ± 1.43</td>
<td>19.78 ± 4.06</td>
<td>18.93 ± 6.93</td>
</tr>
<tr>
<td>Difference (C - I)</td>
<td>1.31 ± 1.22‡</td>
<td>-1.12 ± 3.83</td>
<td>-2.76 ± 4.37§</td>
</tr>
</tbody>
</table>

Significance of differences as determined by paired t-test (* P < 0.02; † P < 0.025).
Significance of differences as determined by paired t-test and Wilcoxon's signed rank test (‡ P < 0.01; § P < 0.005).
HYPERTENSION FOLLOWING AORTIC DENERVATION

TABLE 2 Average Values during 75-Minute Recording Sessions from Six Dogs with Arterial Baroreceptors Intact and after Bilateral Section of Intrathoracic Vagal Branches

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Respiration rate (breaths/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact (I)</td>
<td>95.50 ± 4.84</td>
<td>82.24 ± 13.54</td>
<td>44.02 ± 16.93</td>
</tr>
<tr>
<td>Intrathoracic vagal branches cut (TD)</td>
<td>112.22 ± 6.13</td>
<td>122.90 ± 6.99</td>
<td>35.74 ± 20.33</td>
</tr>
<tr>
<td>Difference (TD - I)</td>
<td>16.72 ± 4.43*</td>
<td>40.66 ± 7.16*</td>
<td>-8.28 ± 7.79†</td>
</tr>
</tbody>
</table>

| Standard deviations    |                        |                        |                               |
| Intact (I)             | 8.93 ± 2.73            | 19.81 ± 4.23           | 21.55 ± 3.47                  |
| Intrathoracic vagal branches cut (TD) | 7.41 ± 1.01         | 6.99 ± 2.10            | 17.66 ± 6.54                  |
| Difference (TD - I)    | -1.52 ± 3.62           | -12.82 ± 4.72*         | -3.89 ± 4.12                  |

Significance by paired t-test: * P < 0.001; † P < 0.05.

beats/min). Both changes were statistically significant (P < 0.01). The change in blood pressure due to phenylephrine increased more than 50% (76.8 vs. 47.0 mm Hg), and the reflex decrease in heart rate was less than half as large as in the control state (20.2 vs. 46.6 beats/min); both changes were significant (P < 0.02). The ratio of the peak changes in heart rate to peak changes in blood pressure was 17% of the control response after nitroglycerin and 30% of control after phenylephrine following section of thoracic vagal branches. Changes in response to vasoactive drugs undoubtedly are influenced by cardiac motor denervation.

Completeness of Denervation; Sham Surgery

In six of the 10 dogs with cervical aortic nerve section, we tested the aortic denervation by noting the response to carotid occlusion before and after vagal block. Increased responses were found in three of the six dogs, and this indicated that some baroreceptor fibers were still intact. In addition, in two of the three dogs in which the cervical aortic nerves were sectioned first, the reflex increase in blood pressure following carotid occlusion was 5-10 mm Hg greater after the intrathoracic vagal branches were sectioned. The third dog showed no change in the response.

Vagal block produced no increase in response to carotid occlusion in five of six dogs after section of intrathoracic vagal branches. This indicated that, within the limitations of this test, aortic denervation was complete.

Several dogs in this study and others were subjected to identical surgical procedures, except that denervation was unsuccessful, as indicated above. These dogs showed little or no change in arterial pressure and may be considered sham controls.

TABLE 3 Effects of Rapid Intra-aortic Injections of Nitroglycerin (800 μg) and Phenylephrine (800 μg) on Blood Pressure and Heart Rate in 10 Dogs

<table>
<thead>
<tr>
<th></th>
<th>Nitroglycerin</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (I)</td>
<td>-23.40 ± 8.19</td>
<td>56.20 ± 13.97</td>
</tr>
<tr>
<td>Cervical aortic nerves cut (C)</td>
<td>-30.50 ± 7.43</td>
<td>66.70 ± 13.29</td>
</tr>
<tr>
<td>Difference (C - I)</td>
<td>7.10 ± 7.00*</td>
<td>10.50 ± 12.66†</td>
</tr>
<tr>
<td>Change in heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (I)</td>
<td>67.40 ± 27.11</td>
<td>-45.80 ± 14.57</td>
</tr>
<tr>
<td>Cervical aortic nerves cut (C)</td>
<td>49.70 ± 24.87</td>
<td>-39.90 ± 9.19</td>
</tr>
<tr>
<td>Difference (C - I)</td>
<td>17.70 ± 27.29†</td>
<td>5.90 ± 15.90</td>
</tr>
<tr>
<td>Ratio of change in heart rate to change in blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (I)</td>
<td>-3.06 ± 1.14</td>
<td>-0.83 ± 0.27</td>
</tr>
<tr>
<td>Cervical aortic nerves cut (C)</td>
<td>-1.78 ± 0.92</td>
<td>-0.90 ± 0.20</td>
</tr>
<tr>
<td>Difference (C - I)</td>
<td>1.36 ± 1.10‡</td>
<td>0.23 ± 0.32†</td>
</tr>
</tbody>
</table>

Significance by paired t-test: * P < 0.02; † P < 0.05; ‡ P < 0.006.

Discussion

Denervation of Intrathoracic Structures

The mean arterial blood pressure increases 16.7 mm Hg after bilateral section of the intrathoracic vagal branches, even with the carotid sinus nerves intact. Our thoracic surgery denervated other intrathoracic structures as well as the aortic receptors. We will consider the possibility that denervation of these structures might have contributed to the increase in arterial pressure.

Cardiac denervation, which leaves most aortic
baroreceptor sites undisturbed, produces no significant change in mean arterial pressure in the dog (Glick et al., 1964; Gregg et al., 1972; Noble et al., 1972). In anesthetized dogs, block or section of the vagus after section of the cervical aortic nerves and denervation of the carotid sinus baroreceptors (or with carotid pressure held constant) produces a rise in arterial pressure (Mancia et al., 1975; Shepherd, 1974). The rise in pressure has been considered to be due to interruption of vagal fibers from cardiac and cardiopulmonary receptors. The latter studies are not comparable to those reported here, since the animals were anesthetized and the carotid sinus reflexes were inoperative. Our findings do not rule out the possibility that denervation of structures other than aortic baroreceptors contributes to the rise in arterial pressure following section of intra-thoracic vagal branches.

Section of the cervical aortic nerves alone produced an increase of 7.4 mm Hg in mean arterial pressure (Table 1), even though some aortic baroreceptors were functional (Ito and Scher, 1973, 1974). We believe that the larger rise in pressure following more extensive intra-thoracic denervation occurs at least in major part because more aortic baroreceptors are denervated.

Both of our procedures probably denervated the aortic bodies but left the carotid chemoreceptors intact. Denervation of aortic bodies probably did not contribute to the rise in arterial pressure, since chemoreceptor stimulation (not denervation) increases arterial pressure and since the carotid chemoreceptors were intact. Blood O₂ and CO₂ were normal.

The sustained increase in arterial pressure apparently is due mainly to denervation of aortic baroreceptors. It is possible that the cardiac denervation together with aortic baroreceptor denervation might have as-yet-undescribed synergistic effects that should be investigated. No such effect would appear to account for the hypertension following cervical aortic nerve section alone.

Comparison of Cervical Aortic Nerve Section with Section of Vagal Branches

Section of the cervical aortic nerves produces a small but significant increase in mean arterial pressure. However, many aortic baroreceptor fibers apparently remain intact in both the left and right vagal trunks, since blood pressure increases more after thoracic vagal branches are cut than after cervical aortic nerves are sectioned. Also, in two of three dogs whose vagal branches were cut after the cervical aortic nerves had been sectioned, the increase in arterial pressure following carotid occlusion was 5–10 mm Hg larger after the section of vagal branches. An even larger reflex increase in blood pressure following carotid occlusion might have been seen if the cardiac motor innervation had been intact (heart rate and cardiac output would have increased.)

Aortic and Carotid Baroreceptors and Blood Pressure Control

Reflexes from the aortic baroreceptors have been considered to have a higher threshold than reflexes from carotid sinus baroreceptors, and to contribute appreciably to the control of arterial pressure only when arterial pressure is high (Allison et al., 1969; Donald and Edis, 1971).

In the present study, mean arterial pressure was increased by cervical aortic nerve section. In addition, the standard deviation of beat mean arterial pressure was larger, indicating that there was less efficient pressure regulation. Also, larger increases in blood pressure and smaller heart rate changes were seen following administration of vasoactive drugs. Furthermore, these heart rate responses were reduced more when pressure decreased (nitroglycerin) than when it increased (phenylephrine). These changes are opposite to those expected if the thresholds were as postulated above. These findings, together with the fact that mean arterial pressure is even higher following section of intrathoracic vagal branches, indicate that in the intact, unanesthetized dog the reflexes from aortic baroreceptors participate continuously in the control of mean arterial pressure. This is in contrast to our finding that carotid sinus nerve section alone did not produce a chronic rise in mean arterial pressure (Ito and Scher, 1978). McRitchie et al. (1976) have also concluded that reflexes from aortic baroreceptors control arterial pressure in the unsedated dog.

There appear to be functional differences between the reflexes from carotid and aortic baroreceptors. Both carotid and aortic baroreceptors appear to regulate pressure in the normal dog (there are obvious responses to carotid occlusion). Sustained hypertension follows aortic baroreceptor denervation in dogs with functioning carotid sinus baroreceptor reflexes that regulate pressure well, but no significant lasting change in mean arterial pressure occurs following section of the carotid sinus nerves with functioning aortic baroreceptor reflexes (Ito and Scher, 1978; Kezdi and Nomura, 1967). If the mean level of arterial pressure is set preferentially by either carotid or aortic receptors, the latter appear more effective.

The elevated mean arterial pressure after aortic baroreceptor denervation might indicate that aortic receptors are more sensitive than carotid receptors at normal arterial pressures, but in studies of receptor firing the opposite appears to be true (Irisawa and Ninomiya, 1967; Pelletier et al., 1972). Alternatively, the baroreceptors from these two sites (carotid and aortic) may have different central connections and/or motor effects. It would be surprising if any two sets of receptor fibers made identical central connections or could elicit identical motor responses. Although both carotid and aortic receptors are normally functional, denervation of the latter (but not the former) produces sustained hypertension.
Resetting, Adaptation, and Other Studies

Baroreceptors have been observed to reset or to lower their firing rate when exposed to high pressures for half a day or more (Krieger, 1970; McCubbin et al., 1956; Sleight et al., 1977). We cannot comment on resetting in our dogs, since we have not examined receptor firing as a function of pressure. Since the pressure was highest about 2 days after our thoracic denervation procedure and then decreased over the next 2 weeks, baroreceptors from the carotid sinus and other structures were not reset to maintain the highest pressure produced by denervation.

The hypothesis that the control of arterial blood pressure shows adaptation implies that maintained changes in baroreceptor activity lead to transient reflex effects. According to this hypothesis, loss of input from aortic baroreceptors to the medullary control centers following aortic baroreceptor denervation should produce a transient increase in pressure. Since the pressure remains elevated after aortic baroreceptor denervation, adaptation (if it occurs) does not return pressure to normal.

In some older studies (Nowak, 1940; Thomas, 1944) and in many of the animals studied by Cowley et al. (1973), denervation produced pressures higher than were seen in our dogs. Taken with our findings, these results argue against the importance of the nonneural "infinite gain" mechanisms that Guyton et al. (1974) have emphasized. Differences between our results and those of Cowley and DeClue (1976) and Cowley and Guyton (1975), who found very little average increase in blood pressure after attempts at complete (aortic and carotid sinus) baroreceptor denervation, probably reflect differences in denervation procedures. As described, their procedures would not denervate the baroreceptors at the root of the aorta described by Coleridge et al. (1973).

Essential Hypertension

The development of hypertension after section of aortic baroreceptor fibers leads us to consider the possibility that loss of aortic baroreceptor sensitivity may produce hypertension in humans. Human essential hypertensives show smaller reflex responses to vasoactive drugs than do normotensives (Bristow et al., 1969; Korner et al., 1974; Takeshita et al., 1975). Since the reflex response to changes of carotid transmural pressure in hypertensives is the same or nearly the same as that of normotensives (Mancia et al., 1976; Wagner et al., 1968), the sensitivity of both the aortic and carotid baroreceptors must be reduced in human hypertensives. (If only aortic baroreceptor sensitivity were reduced, the response to carotid pressure changes would be increased.)

It is speculative that impairment of baroreceptor function causes or contributes to hypertension in humans. In rabbits with renal hypertension, reduction in baroreceptor reflex sensitivity is believed to result from long-term exposure to high arterial pressure (Angell-James and George, 1976). Similar loss of sensitivity might also result from resetting or adaptation. If our findings in the dog can be extended to the human, then loss of aortic baroreceptor function (and, by implication, both aortic and carotid receptor function) will produce hypertension.

Our studies demonstrate, we believe for the first time, that it is possible to produce hypertension in dogs by aortic baroreceptor denervation.

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References

Derom FG (1956) Methode d'hypertension chronique neurogene chez le chien. Arch Int Pharmacodyn Ther 114: 237-244
Ito CS, Scher AM (1973) Arterial baroreceptor fibers from the aortic region of the dog in the cervical vagus nerve. Am J Physiol 213: 504-510
Ito CS, Scher AM (1973) Arterial baroreceptors // to


Thomas CB (1944) Experimental hypertension from section of moderator nerves. Johns Hopkins Hosp Bull 74: 335-377


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