Regulation of Arterial Blood Pressure by Aortic Baroreceptors in the Unanesthetized Dog

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With the technical assistance of Roger Scott, Dana Matthews, and Kregg Hoover

SUMMARY We studied the effect of section of both carotid sinus nerves on arterial blood pressure in nine unanesthetized dogs. Four to seven recording sessions were conducted on each dog before and after sinus nerve section (SNS). During each session, histograms of mean arterial pressure during each heart cycle and of heart rate were assembled over 75 minutes. Then, responses to rapid aortic injection of nitroglycerin and phenylephrine were studied. Mean blood pressure was 94.86 ± 11.37 mm Hg with arterial baroreceptors intact. After SNS, mean blood pressure was 92.55 ± 9.82 mm Hg. Mean heart rate was 88.64 ± 11.97 beats/min in the intact dog and 86.20 ± 10.24 beats/min after SNS. Differences in mean blood pressure and heart rate were not significant (P > 0.05). The standard deviation of beat-by-beat mean arterial pressure was slightly, but not significantly, greater following SNS. The standard deviation of heart rate was slightly and significantly smaller (P < 0.02) after SNS. Blood pressure decreases following nitroglycerin were identical before and after SNS. There was a greater rise in blood pressure following phenylephrine after SNS. Heart rate changes following phenylephrine and nitroglycerin were smaller after SNS, but significant (P < 0.05) only for nitroglycerin. The dog with carotid sinus nerves sectioned regulates its mean blood pressure at the same level as the intact dog. Aortic baroreceptors reflexly compensate for both increased and decreased arterial pressure.

THE BARORECEPTORS in the carotid sinus and in the aortic arch are usually exposed to the same arterial pressure. The baroreceptor reflex responses from each of these two sites have been compared in the anesthetized dog by changing pressure at one baroreceptor site while maintaining constant or eliminating baroreceptor activity from the other site. Although these responses from the two baroreceptor sites are qualitatively similar, several studies indicate that there are marked quantitative differences. These studies indicate that the most sensitive region (pressure at which the greatest reflex changes are seen), the threshold (lowest pressure at which reflex responses are seen), and the saturation level (pressure at which there is no further response to increased pressure) are higher when pressure changes are applied to the aortic receptors than for pressure changes to the carotid receptors. In most cases, the change in peripheral resistance for a given change in pressure at the baroreceptor site (resistance gain) is much greater for the carotid than for the aortic baroreceptors. In these studies, the pressure at the baroreceptors was nonpulsatile. However, several investigators concluded that these differences in response from the two baroreceptor sites are also present when the pressure at the baroreceptors is pulsatile.

If these differences in reflex response to pressure changes at the carotid sinus and the aortic arch persist in the awake dog, the aortic baroreceptors should be functionally important in contributing to reflex responses when arterial pressure is high and should be of little importance when arterial pressure is low. In addition, if these properties persist in the awake dog, after the sensory fibers from the carotid baroreceptors are cut, the mean arterial pressure should be higher than in the intact animal, since reflex responses to changes in pressure at the aortic receptors have a higher threshold and region of maximal sensitivity than do responses to changes at the carotid receptors. Even if mean pressure is not elevated following carotid baroreceptor nerve section, the variations of pressure around the mean should increase, since the aortic receptors apparently would produce smaller reflex responses to decreased pressure.

In the study reported here, the aortic blood pressure was examined before and after section of the carotid sinus nerves in the unanesthetized dog, and the responses of arterial pressure and heart rate to changes in arterial pressure induced by vasoactive drugs were compared before and after carotid sinus nerve section. In all studies, each dog served as its own control.

Methods

Using aseptic surgical procedures, 11 healthy mongrel dogs of both sexes, weighing between 17 and 26 kg, were prepared for chronic study. One carotid artery was placed in a skin tube; the other carotid artery was moved to a subcutaneous position in the neck. For other studies, not reported here, both vagosympathetic nerve trunks were also placed in skin tubes in the neck. While the dogs were recovering from surgery, they were trained to remain quietly in a Pavlov stand in the laboratory. Animals with carotid and vagal skin tubes will be designated as "intact" animals.

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Recording Procedures

After the dogs had recovered from surgery, the aortic blood pressure was measured in each dog through a 60-cm teflon catheter (0.7 mm i.d.) introduced through the externalized carotid artery and advanced to the aortic arch, using a modified Selinger technique.10 No local anesthetic was needed for catheterization; the dogs showed no sign of discomfort. The aortic catheter was connected to a P37B Statham pressure transducer and was continuously flushed with heparinized saline (6 ml/hr, 10 IU heparin/ml) through a Sorenson CFS Intraflo Unit. Heart rate was determined by a conventional analog cardiocochrometer triggered by the blood pressure signal. The chest circumference was monitored as an indication of respiration, using a flexible pneumogram tube placed around the dog's chest and connected to a Statham transducer. Respiration rate was similarly determined from the chest circumference signal with a pneumotachometer. The above signals were continuously displayed on a Beckman 8-channel Dynograph recorder at a paper speed of 10 mm/min.

A voltage proportional to the aortic blood pressure from the Beckman recorder and the trigger pulses from the cardiocochrometer and the pneumotachometer were passed to a digital minicomputer (LM²). The computer digitized the blood pressure signal (250 samples/sec) through an A-D converter with 12-bit resolution. This 12-bit range was equivalent to 250 mm Hg; i.e., the resolution was 0.0625 mm Hg/bit. We programmed the computer to compute the mean blood pressure during each heart beat by summing all digitized values of blood pressure during a beat and dividing the sum by the number of samples in that beat. We will refer to this mean pressure during each heart beat as the "beat mean arterial pressure." In addition, the program utilized the two trigger signals to compute heart rate and respiration rate. Some of these signals were (1) converted to analog form and displayed with other on-line data on the Beckman recorder (mean pressure, heart rate, respiration rate); (2) stored on digital tape (all); and (3) used to compute an on-line histogram for beat mean arterial pressure (histogram interval of 1 mm Hg), heart rate (interval of 1 beat/min), and respiration rate (interval of 0.5 breath/min). These histograms were available at the end of each experimental period, and the data were also stored on digital tape for later processing and analysis.

Experimental Protocol

Each dog was studied during 4-7 recording sessions, usually 3-7 days apart, starting approximately 14 days after the initial surgery, and during 4-5 sessions after bilateral section of the carotid sinus nerves. The procedure for carotid sinus nerve section has been described.19 The first recording session was usually 24 hours after sinus nerve section, and the next session was always 7 days after the nerve section. Figure 1 shows the number and distribution of recording sessions conducted on each dog.

To minimize possible diurnal variations in the measured variables, all recording sessions were started within one-half hour of 9 a.m. The laboratory was quiet and no visitors were allowed to enter during the recording session. During a recording session, the dog remained quietly in the Pavlov stand for 75 minutes while data were continuously collected. In each recording session, we then studied responses to occlusion of the carotid arteries and to rapid injection into the aortic arch of 0.8 mg of nitroglycerin and 0.8 mg of phenylephrine, both dissolved in normal saline.

Data Analysis

Statistical analysis of the data stored on digital tape was conducted with a Raytheon 440 computer. All computations utilized techniques described by Snedecor and Cochran. The following computations were made for the beat mean arterial pressure, heart rate and respiration rate. 1) The mean value and standard deviation were computed for each of the 75-minute recording sessions ("session mean"). 2) The mean values and mean of the standard deviations for each dog in the intact state were computed from all the session mean values and session standard deviations. The mean values and mean of the standard deviations for each dog after section of the carotid sinus nerves were similarly computed from the session mean values and session standard deviations. 3) Finally, the mean values and means of the standard deviations from each dog in the intact state and after sinus nerve section, as obtained in (2) above, were combined to give the mean values and mean standard deviations for the intact dogs as a group and for the dogs after sinus nerve section as a group. Note that all calculations utilize discrete rather than previously averaged values of the variables. When mean values and standard deviations of blood pressure are calculated in this fashion, the result is a more precise mean and standard deviation of blood pressure. The standard deviation so computed will tend to be larger than standard deviations calculated from resistance-capacitance averaged mean pressure records uniformly sampled.
The significance of the difference between measurements on the intact dogs and on the dogs after sinus nerve section was tested with the paired t-test. The significance of the difference in standard deviations between the two conditions was also assessed using the nonparametric Wilcoxon's signed rank test. The number of dogs studied and the number of recording sessions conducted on each dog were both too small to make the F-test sufficiently discriminating.

Changes in beat mean arterial pressure and heart rate induced by rapid injection of nitroglycerin and of phenylephrine were measured from the Beckman chart records. For each drug, the differences in the changes elicited before and after section of the carotid sinus nerve were subjected to the paired t-test.

Results

The response to bilateral common carotid occlusion enabled us to assess the success of our carotid sinus nerve section during each recording session (and would have enabled us to detect reinnervation, which did not occur). Little or no response (5 mm Hg mean change in systemic pressure, largest response 9 mm Hg, no change in heart rate) was observed following carotid occlusion after carotid sinus nerve section in 9 of the 11 dogs. In the remaining two dogs, pressure increases of 20 and 34 mm Hg and a heart rate increase of 13 beats/min followed carotid occlusion after sinus nerve section; these responses persisted even after a subsequent attempt to denervate by stripping the adventitial layers from the carotid sinuses. Data from these two dogs are not included in the results below.

Variability of Mean Blood Pressure

The mean blood pressure (mean value of beat mean arterial pressure over a 75-minute recording session) showed some variation from one session to the next, both before and after bilateral section of the carotid sinus nerves. A typical example is presented in Figure 2, which shows histograms obtained before and after the sinus nerve section. Prior to the nerve section, there was no consistent trend in the mean blood pressure during successive recording sessions. Some dogs showed slightly increased mean blood pressure over the successive recording sessions, others showed decreases. Mean blood pressure became stable, i.e., it changed little from session to session, by the fourth recording session. Mean blood pressure rose abruptly following section of the carotid sinus nerves and remained substantially elevated 24 hours after the nerve section. Mean blood pressure continued to fall during the next several recording sessions. A stable mean blood pressure was generally seen 17 days after surgery. Most of the decrease in blood pressure occurred during the first week. Mean heart rate also showed a time-dependent decrease paralleling the mean blood pressure. (There was no rise in mean blood pressure 24 hours after the initial surgery in which the carotid artery was placed in a skin tube.)

Comparison of the mean blood pressure and mean heart rate for all animals before and after carotid sinus nerve section is presented in Figure 3A. The data presented are taken no earlier than 1 week after the surgical procedures because our intent is to compare stable values of mean blood pressure and mean heart rate.

In dogs with the aortic and carotid sinus nerves intact, the mean blood pressure was 94.86 ± 11.37 mm Hg; the heart rate was 88.64 ± 11.97 beats/min. After section of the sinus nerve, the mean blood pressure was 92.55 ± 9.82 mm Hg, 2.31 mm Hg less than in the intact dog. The mean heart rate after sinus nerve section was 87.96 ± 7.65 ± 0.82 mm Hg, 2.31 mm Hg less than in the intact dog. The mean heart rate after sinus nerve section was 87.96 ± 7.65 ± 0.82 mm Hg, 2.31 mm Hg less than in the intact state. Mean blood pressure and mean heart rate were lower in five of the nine dogs after sinus section and higher in four.

Figure 3B shows the standard deviations of arterial pressure and of heart rate before and after sinus nerve section for each dog. The standard deviation of beat mean arterial pressure for the entire group of dogs was 7.65 ± 0.82 mm Hg with the aortic and carotid sinus nerves intact, and 8.69 ± 1.89 mm Hg after section of the carotid sinus nerves. The corresponding standard deviations of heart rate were 15.58 ± 1.99 beats/min and 13.69 ± 2.89 beats/min. Standard deviations of blood pressure were higher in seven dogs and lower in two after sinus nerve section, while heart rate standard deviations were lower in eight and higher in only one dog after sinus nerve section.
The differences in mean blood pressure, mean heart rate, and standard deviation of beat mean arterial pressure indicated above were not statistically significant ($P > 0.05$). However, the decrease in standard deviation of heart rate after sinus nerve section (Fig. 3B) was statistically significant ($P < 0.02$). Table 1 summarizes data for beat mean arterial pressure, heart rate, and respiration rate in the control state and following section of the carotid sinus nerves.

The correlation coefficients between mean blood pressure and mean heart rate before and after section of the carotid sinus nerves are shown above the diagonal (upper right) in Table 2, those for the corresponding standard deviations are shown below the diagonal (lower left). The correlations show a noticeable interdependence of mean blood pressure and mean heart rate— the higher the blood pressure, the higher the heart rate (see Fig. 3A). The high correlation (0.929) of the standard deviation of heart rate before and after sinus nerve section indicates that those dogs with high variability in heart rate before the nerve section had a high variability after the nerve section, despite the decrease in variability produced by the nerve section.

**Response to Vasoactive Drugs**

The expected large changes in beat mean arterial pressure and in heart rate followed the rapid injection of nitroglycerin and phenylephrine, both before and after section of the carotid sinus nerves. A typical record is shown in Figure 4. The magnitude of these changes varied from dog to dog and varied for the same dog on different recording days. Figure 5 shows the peak changes in arterial pressure plotted against the corresponding peak changes in heart rate for each dog and for the mean values of the changes from all dogs before and after sinus nerve section. There was no difference in the change in arterial pressure caused by nitroglycerin before and after sinus nerve section. In each case, beat mean arterial pressure decreased by $29.0 \pm 8.6$ mm Hg. After sinus nerve section, the observed heart rate change was smaller (by $9.5 \pm 7.5$ beats/min). This difference was statistically significant ($P < 0.05$). On the other hand, the difference of $8.1 \pm 19.2$ beats/min in heart rate between the changes produced by phenylephrine before and after the nerve section was not statistically significant ($P > 0.05$), but the difference in the response of beat mean arterial pressure was significant ($P < 0.05$). The maximal change in beat mean arterial pressure in response to phenylephrine was $16.3 \pm 18.9$ mm Hg greater following sinus nerve section than before. Statistical data for the responses to both of these drugs are given in Table 3.

The blood pressure returned to normal more slowly following nitroglycerin injection after sinus nerve section. There was no difference in the time course of the response to phenylephrine before and after sinus nerve section.

**Discussion**

As Table 1 shows, the mean level of blood pressure is no higher after recovery from the transient effects of carotid sinus nerve section than before section. The variation (standard deviation) in beat mean arterial pressure during a 75-minute interval is unchanged or only slightly greater after the nerve section. Heart rate is also no higher after sinus nerve section, but the variation in heart rate is smaller after sinus nerve section. If the pressure required to activate reflexes from the aortic baroreceptors (aortic baroreflex) exceeds that required to activate re-
flexes from the carotid baroreceptors (carotid baroreflex), the mean blood pressure and the mean heart rate should be higher, or the standard deviation of arterial pressure should be greater after carotid sinus nerve section, or both.

In studies by others, the threshold of the aortic reflex in the anesthetized dog has been reported to range from 75 to 225 mm Hg, with a mean value of 90 to 163 mm Hg. In contrast, the carotid baroreflex has been reported to have a threshold ranging from 40 to 150 mm Hg, with a mean of 47 to 108 mm Hg. No such differences could be deduced from our results. Although the beat-by-beat variation of mean arterial pressure was slightly higher after sinus nerve section, the difference was not significant. The variation of heart rate was slightly but significantly smaller after sinus nerve section. From these data it appears that there is no threshold difference between the aortic and the carotid baroreflex in the unanesthetized dog 7 days after sinus nerve section and thereafter.

As indicated in our results, the arterial pressure rises immediately after sinus nerve section and is elevated 1 day later. The pressure then falls over several days. It might be argued that section of the carotid sinus nerves shifted the reflex control of arterial pressure to the aortic baroreflex, which might initially maintain the pressure at the high operating levels found in some acute studies. Over the next several days, the aortic baroreflex might be "reset" so that the threshold and region of maximal sensitivity ultimately lie at the level where the carotid baroreflex previously maintained the pressure. Resetting of baroreceptors has been demonstrated in dogs by Mc- Cubbin et al. and by Kezdi et al. and in rats by Krieger. In their experiments, the receptors exposed to chronic high pressures in renal hypertensive animals show increased threshold and decreased sensitivity. With resetting, afferent nerve activity decreases to a normal level even though the receptors are exposed to a high pressure. Similar changes were seen in the reflex responses in the experiments of Kezdi et al.

To deal with the question of resetting, we must consider two points: (1) How strong is the evidence that resetting of baroreflexes to lower pressures occurs? (2) How strong is the evidence that the aortic baroreflex normally has such a high threshold and region of maximal sensitivity.
that it is inactive or unimportant at normal arterial pressures?

The return of arterial pressure to normal in human or experimental renal hypertension after removal of an abnormal kidney\(^19,20\) might be evidence that resetting to lower pressures can occur. Resetting of baroreceptors or of baroreceptor reflexes to a lower pressure has not been clearly demonstrated experimentally. Kezdi et al.\(^17\) studied two groups of chronic renal hypertensive dogs. In the first group, the baroreceptors were exposed to lower than normal pressures (45 mm Hg) before and during the hypertension. No resetting was seen. In the second group, the receptors were exposed to hypertensive pressure levels (90 mm Hg) before and during the hypertension. A return to the receptors were exposed to hypertensive pressure levels and presumably reset. These receptors were then exposed to the same lower than normal pressures. A return to near normal operating characteristics ("re-resetting" to lower pressures) was seen in only one of five dogs. Thus, the available data do not indicate clearly that resetting to a lower pressure can occur, but the possibility cannot be ruled out. Resetting of baroreceptors to a high pressure, which does seem clearly demonstrated, occurs after pressure has been raised (as by renal hypertension).

Concerning the second point, we do not believe that the aortic baroreflex is inactive at normal pressures for three reasons. First, many studies demonstrate that there is sensory discharge in aortic nerve fibers at normal arterial pressures.\(^21\)\(^-\)\(^23\) Second, severing the carotid nerves in awake rabbits in the studies of Alexander and DeCuir\(^24\) produced a large sustained increase in heart rate and a decrease in overall baroreflex sensitivity. Finally, in ongoing studies, we find that mean arterial pressure rises when the vagosympathetic trunk is blocked with a local anesthetic in intact dogs. This seems to us to indicate that the aortic baroreceptors are operative at normal arterial pressures. Although we believe that the aortic baroreflex is operative in the intact animal, we do not know the reflex threshold or region of maximal sensitivity.

A more likely reason for the differences in reflex sensitivity noted in the earlier studies\(^1\)\(^-\)\(^4\) is suggested by the experiments of Angell James and Daly.\(^3\) When the baroreceptors were exposed to pulsatile pressures, the sensitivity of the aortic and carotid baroreflexes was nearly identical over the pressure ranges of 75–200 mm Hg. The nearly perfect match between the sensitivities of the aortic and carotid baroreflexes with pulsatile pressures can also be found in studies of renal nerve activity.\(^25\) Pulsations appear to make the carotid baroreflex less sensitive to mean pressure.\(^5\) This effect may be due to the anatomical differences in the two receptor sites—the aortic arch is large, thick-walled, and relatively rigid, while the carotid sinus is smaller, thin-walled, and more elastic.

McRitchie and co-workers\(^25\) found that arterial blood pressure was 15 mm Hg higher after carotid sinus nerve section in the unsedated dog. Our results indicate that such an increase in pressure will be found if pressure is measured within a few days after the carotid sinus nerve section. Studies in the dog\(^6\)\(^-\)\(^8\) and in man\(^9\)\(^-\)\(^11\) indicate that there is little or no difference in the mean blood pressure several weeks after bilateral carotid sinus nerve section. Moderate hypertension was seen in only one study.\(^12\)

The slightly larger beat-by-beat variation in mean arterial pressure and the slightly smaller variation in heart rate after sinus nerve section can be explained by the hypothesis that the gain is lower when the aortic baroreflex operates alone than when both the aortic and carotid baroreflexes operate. This is compatible with the response to nitroglycerin and phenylephrine shown in Table 3. This assumption also is consistent with the smaller changes in heart rate following injection of either drug after sinus nerve section and with the greater increase in blood pressure following injection of phenylephrine after sinus nerve section. It might also account for the slower return of blood pressure to normal following injection of nitroglycerin after sinus nerve section. However, since the same decrease in pressure was seen in response to nitro-

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Nitroglycerin (mean)</th>
<th>Phenylephrine (mean)</th>
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</thead>
<tbody>
<tr>
<td>Change in blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intact (I)</td>
<td>29.13 ± 8.56</td>
<td>56.25 ± 6.41</td>
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<tr>
<td>Sinus nerves cut (A)</td>
<td>29.38 ± 8.63</td>
<td>72.50 ± 19.82</td>
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<tr>
<td>Difference (I-A)</td>
<td>-0.28 ± 7.87</td>
<td>-16.25 ± 18.85*</td>
</tr>
<tr>
<td>Change in heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intact (I)</td>
<td>55.00 ± 13.09</td>
<td>38.25 ± 27.90</td>
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<tr>
<td>Sinus nerves cut (A)</td>
<td>45.50 ± 9.72</td>
<td>30.13 ± 15.03</td>
</tr>
<tr>
<td>Difference (I-A)</td>
<td>9.50 ± 7.54*</td>
<td>8.13 ± 19.22</td>
</tr>
</tbody>
</table>

* Significant at 0.05 level.
Other values not significant at 0.05 level.
glycerin with or without the carotid baroreflex, our results suggest that the aortic baroreflex was about as powerful as the carotid and aortic baroreflexes acting together during the initial stages of nitroglycerin-induced hypotension.

The observed responses to phenylephrine are similar to those reported for methoxamine by McRitchie et al.\textsuperscript{33}\textsuperscript{35} Our findings also agree with theirs in that there was a smaller heart rate response to nitroglycerin after sinus nerve section. However, we do not agree with their finding that the blood pressure fell more in response to nitroglycerin after carotid sinus nerve section. This disagreement may result from the fact that our injections were intra-aortic, whereas theirs were intravenous, although it is not clear why this should happen.

The responses to vasoactive drugs after sinus nerve section indicate that the aortic baroreflex can respond to both hypotension and hypertension. The response to nitroglycerin-induced hypotension after carotid sinus nerve section is only slightly smaller than the response seen in intact animals. The reflex response to phenylephrine-induced hypertension, however, is significantly smaller without the carotid baroreceptors. This finding would lead us to predict that, in an animal with both aortic and carotid sinus baroreceptors functioning, an increase in carotid sinus pressure (alone) would produce smaller reflex changes in heart rate and systemic blood pressure than would a decrease in carotid sinus pressure by the same amount. This prediction is supported by the observation that, in man, a decrease in transmural carotid sinus pressure elicits nearly twice as large a reflex change in arterial pressure\textsuperscript{33}\textsuperscript{35} and over twice as large a reflex change in heart rate\textsuperscript{33}\textsuperscript{35} as that elicited by an increase in transmural pressure of the same magnitude.

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