Role of the Baroreceptor Reflex in Daily Control of Arterial Blood Pressure and Other Variables in Dogs

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ABSTRACT

Normal and sinoaortic baroreceptor-denervated dogs were monitored continuously (24 hours a day) to quantify the role of the baroreceptors in determining the average level and the variability of arterial blood pressure, heart rate, cardiac output, and total peripheral resistance. The frequency of occurrence over 24-hour periods was obtained for each variable using a fiber optic curve-scanning system to read the variables from continuously recorded charts and a digital computer system to plot curves. The results indicate that the degree of hypertension previously reported for this preparation has been highly exaggerated, presumably due to the methods of study. The average 24-hour mean arterial blood pressure was 101.6 mm Hg in normal dogs and only 112.7 mm Hg in baroreceptor-denervated dogs. The normal dogs exhibited narrowly distributed 24-hour frequency distribution curves for blood pressure; in contrast the denervated dogs exhibited curves with twice the 24-hour standard deviation. Similar analysis indicated that the baroreceptors exerted less influence on the daily stabilization of heart rate than they did on arterial blood pressure and that they had very little if any influence on the daily stabilization of cardiac output and total peripheral resistance. Hemodynamic variables during postural changes were studied along with diurnal rhythms. We concluded that the primary function of the baroreceptor reflex is not to set the chronic level of arterial blood pressure but, instead, to minimize variations in systemic arterial blood pressure, whether these variations are caused by postural changes of the animal, excitement, diurnal rhythm, or even spontaneous fluctuations of unknown origin.

KEY WORDS hypertension heart rate cardiac output total peripheral resistance computer data analysis heart rate curve tracer diurnal rhythms baroreceptor feedback gain

The original goal in this experiment was to study chronic neurogenic hypertension caused by sinoaortic denervation. This type of hypertension has been reported on in the past by many different investigators. However, our most noticeable immediate result following sinoaortic denervation in dogs was not that major amounts of hypertension appeared but that the arterial blood pressure varied greatly during the day, sometimes registering normal values, sometimes hypertensive values, and sometimes even hypotensive values. Furthermore, these dogs exhibited acute hypertensive episodes in response to very slight provocations, suggesting that the previously reported hypertension in sinoaortic baroreceptor-denervated animals might well have been the result of excitement of the animals when blood pressure was measured rather than the result of elevation of the basal level of arterial blood pressure. This supposition was reinforced by the recognition that many of the pressure measurements in early experiments were made in animals taught to endure artery puncture for pressure recording. The recorded pressure at the time of measurement could easily have been 30-100 mm Hg above the mean resting value (1-6).

Therefore, before any real judgment can be made about the causal role of sinoaortic denervation in neurogenic hypertension, it is necessary to reevaluate the effects of sinoaortic denervation on all the important hemodynamic variables such as arterial blood pressure, heart rate, cardiac output, and total peripheral resistance. Because of the marked variability in arterial blood pressure from one moment to another and from one time of day to another, 24-hour recordings of pressure followed by appropriate analysis are also necessary. Moreover, factors which disturb the animals need to be removed as completely as possible. With these requirements in mind, we employed some special techniques that were very laborious but necessary.
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These techniques enabled us to characterize the normal role of the sinoaortic baroreceptor reflexes in the regulation of arterial blood pressure and other cardiovascular variables.

Methods

Animal Preparation.—Twenty-seven young adult mongrel dogs were used for these studies; a normal control group (12 dogs) was compared with 15 sinoaortic baroreceptor-denervated dogs. Five dogs in the latter group were evaluated in the normal state and then again weeks later following the baroreceptor denervation procedures.

Baroreceptor denervation was performed by surgically stripping the nerves and the adventitia from the aortic arch and carotid sinus areas and applying a 5% phenol solution followed by isopropyl alcohol. In addition to the aortic stripping, the left cervicovagal trunk was severed by removing about 1.5 cm of its length, and the medial bundle of the right vagus, in which the aortic baroreceptor nerves run, was cut. These procedures were a combination of several previously described techniques (2, 3, 7). The areas of denervation corresponded to the major areas of baroreceptor activity in dogs as recently reported by Aumonier (8). A left thoracotomy was performed for denervation of the aortic arch and for implantation of an electromagnetic flow transducer (Biotronex BL-5000) on the ascending aorta in nine dogs. Rupture was prevented by first fitting the aorta with a coarse Dacron protective sleeve that became interwoven with fibrous connective tissue and thus yielded a good electrode contact approximately 1 week after surgery. Flow transducers were calibrated in vitro, both before implantation and after the dogs died, with calf aortas perfused with blood diluted with saline to a hematocrit of 40%. Calibration values were generally duplicated to within ±10% of the original value on recalibration.

A chronic indwelling polyvinyl-Tygon catheter was placed in the femoral artery at the beginning of surgery and tunneled subcutaneously to the cephalad portion of the back for protection. The catheters were maintained patent by flushing once a week with sterile saline and heparin/ml.

Plasma renin activity was measured using the radioimmunoassay technique for angiotensin I described by Haber et al. (9) with angiotensin 11-28 and antiserum from Schwarz-Mann Company. Plasma volumes were determined by the dye-dilution technique using Evans blue dye. Plasma sodium and potassium were determined with a flame spectrophotometer (Instrumentation Laboratory, model 143).

Collection of Data.—Several special procedures facilitated the collection and the analysis of hemodynamic data in relatively undisturbed dogs. First, to minimize the large pressure fluctuations that occurred in the denervated dogs following minor laboratory disturbances, experiments were performed in a small, quiet, isolated room. Entrance to the room was not permitted except for routine checks of the dog and the equipment. The dog could be viewed through a peephole in the door window.

An arterial blood pressure transducer (Statham model 7-23AC) was built into a plaster-of-Paris jacket which fitted over the dog's back and was held in place by a canvas bib extending around the chest of the dog with openings for the front legs. The position of the transducer remained fixed at heart level on the dog's side so that postural changes such as lying and standing did not significantly alter the zero reference level for pressure. The cables from the pressure and electromagnetic flow transducers were brought to the top of the pen through a protective flexible tube attached to the top of the plaster jacket (swimming pool vacuum hose, Seabluo Corp., Dallas, Texas). This tube was maintained in a vertical position by a system of counterweights and pulleys above the pen. Springs were attached to three corners of the plaster jacket and extended to the upper part of each side of the pen, thus permitting relatively unrestricted movement of the dog about the pen but preventing more than a 360° rotation or rolling over of the dog onto his back. The pen was large enough (5 x 5 x 5 ft) to give the dog sufficient room for movement so that the dog never appeared cramped or disturbed by the confinement. Generally, after remaining in the recording pen about 1 day the dogs appeared quite relaxed in the apparatus. In some cases they were monitored continuously, except for the 1-hour exercise period every other day, for up to 3 weeks with no apparent discomfort.

A Grass polygraph (model 7) was used to record blood pressure, cardiac output, and heart rate. Since long, continuous records were desired, very slow paper speeds of 5 or 10 mm/min were used.

Six channels of data were continuously recorded, including heart rate, arterial pressure pulse, mean arterial blood pressure, cardiac output, aortic pulse flow, and position of the dog. The heart rate was obtained using a Grass tachygraph (model 7P4-C) triggered from the differential of the arterial pressure pulse. Cardiac output was obtained using a pulsed logic Biotronex blood flowmeter (model BL610). The vertical position of the dog was determined by attaching a small fluid-filled flexible tube to the counterweighted vertical tube connected to the dog's jacket and recording changes in the hydrostatic pressure with a Statham P23AC pressure transducer. In the dogs that did not have aortic flow transducers, two channels of arterial pressure pulse were recorded for analytical reasons explained below.

Analysis of Data.—The polygraph records were taken to the computer center for analysis. Experimental results were measured from the records using a Grass recorder (model 7) specially equipped with a four-channel analog curve-reading system which used fiber optic scanning pens that generated analog voltages from the recorded ink tracings (10, 11). The analog output voltages from the curve tracer were fed to an analog-to-digital converter which converted the analog voltages to numbers for analysis by a PDP-9 computer. The sinusoidal motion of the scanning pens permitted sampling of 30 points/sec so that an extremely large number of points could be sampled and stored for each record per unit time; the precise number was

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determined by the speed at which the data were recorded and played back.

Although four separate fiber optic scanning pens were used, each individual pen was only capable of reading one leading edge of any ink tracing. For example, if a pen was adjusted to trigger on the upper edge of a slowly recorded (10 mm/min) arterial pressure pulse, the voltage output would represent systolic pressure; if a pen was adjusted to trigger on the trailing or lower edge of an arterial pressure pulse, the diastolic pressure would be monitored. For a single narrow line as seen with an electrically meaned arterial pressure pulse, either the upper or the lower edge could be chosen. Therefore, for a simultaneous measurement of systolic, diastolic, and mean pressure, three channels of the Grass recorder were linked in parallel to obtain two identical recordings of the pressure pulse and one of the mean arterial pressure. This type of recording can be seen in Figure 1 (top), with the addition of heart rate in the uppermost channel. Also in Figure 1 (bottom) is a photograph of the oscillographic output of the curve scanner obtained from the record seen in the top. This figure is included to demonstrate that the curve scanner was quite capable of faithfully monitoring rapid changes in arterial blood pressure.

Similar scanning techniques monitored the electrically meaned cardiac output of the flowmeter, but special procedures enabling the computer to make instant corrections for zero-flow base-line shifts encountered over the 24-hour recording periods were used. The corrections were accomplished by recording cardiac output on two separate channels—one channel for mean aortic flow and another channel for pulsatile aortic flow (Fig. 3). The lower edge of the pulsatile aortic flow channel provided a continuous record of the approximate zero flow, which occurred near the end of the diastolic period. This lower edge was then monitored by one of the curve-scanning pens, and any deviations from the initial zero-flow base line were added to or subtracted from the mean cardiac output values (monitored simultaneously on another channel) by the digital computer.

The digitized information from the analog-to-digital converter was used by the computer to calculate the average hourly arterial blood pressure, cardiac output, total peripheral resistance, and heart rate along with simultaneous calculations of standard statistical information. The frequency of occurrence at each level for the hemodynamic variables was tabulated by the computer in increments of 1.0 mm Hg for arterial blood pressure, 1.0 beat/min for heart rate, 20.0 ml/min for cardiac output, and 0.001 mm Hg/ml min⁻¹ for total peripheral resistance. Examples of these frequency distribution curves are seen in Figures 4-6. Each recorded circulatory variable was sampled by the curve scanner 30 times/sec, and the chart records were adjusted to run at a speed which yielded a data point for every 2 seconds of real recorded time. In this way 1,800 sample points of each variable were stored for each hour of recorded time; this procedure permitted very accurate determination of all recorded hemodynamic data as well as accurate graphing of frequency distribution curves for each parameter throughout any desired period of experimentation. A 24-hour record could be analyzed in about 20 minutes, including calculation of hourly statistics and frequency distributions permanently stored on magnetic DECtape, printed in tabular form on a line printer, and displayed on graphics devices linked to the computer.

Results

Figure 2 compares the arterial blood pressure of a normal dog with the extreme lability of pressure in an untrained dog following sinoaortic baroreceptor denervation. These recordings were made in two unanesthetized dogs over a 96-minute period during initial recording sessions. During these periods the dogs exhibited no overt signs of excitement but were quietly standing in the recording pen with no one present in the room. The arterial systolic and diastolic pressures of the denervated dog shown in

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Extreme lability of the arterial blood pressure in a baroreceptor-denervated dog (bottom) contrasted with the stable arterial blood pressure of a normal dog (top). Both of the dogs were unanesthetized and standing quietly in the isolated recording pen.

This record fluctuated between 220/180 mm Hg and 75/45 mm Hg. Lability of this magnitude was usually not observed after several days of training when the dog was undisturbed, but fluctuations of this type returned with only minimal excitement such as entrance of the investigator into the room. This hemodynamic pattern was generally observed when measurements were made under routine laboratory conditions. This behavior emphasized the need for new methods to quantify arterial blood pressure in the denervated dog.

Figure 3 (top to bottom) shows recordings of heart rate, arterial pressure pulse, mean arterial pressure, cardiac output, cardiac stroke volume, and vertical position of a trained, sinoaortic denervated dog during a continuous 24-hour recording session. These representative portions of the record illustrate events that most frequently occurred during an average day to alter the arterial blood pressure, such as postural changes, excitement, and spontaneous changes of unknown cause. Three postural changes from the supine to the upright position are indicated (Fig. 3, bottom). In each case the arterial blood pressure fell 30–50 mm Hg, and the cardiac output rose from 300 to 800 ml/minute. In the first instance (Fig. 3A), the increases in heart rate, blood pressure, and cardiac output preceded the postural movement. In the second instance (Fig. 3B), the heart rate increase corresponded to the fall in arterial blood pressure, and, in the third instance (Fig. 3C), the heart rate exhibited little change. Figure 3D shows the large elevations in heart rate, pressure, and cardiac output that frequently occurred when the investigator entered the room. Spontaneous changes in pressure with little alteration in cardiac output are also evident at different points throughout the record.

Arterial Blood Pressures in Normal and Denervated Dogs—24-Hour Frequency Distributions.—Figure 4 compares the 24-hour mean arterial blood pressure frequency distribution curves in normal and sinoaortic denervated dogs. Figure 4A represents a typical pattern of daily pressures before and after sinoaortic denervation in an individual dog. The abscissa indicates arterial blood pressures between 0 and 250 mm Hg, and the ordinate indicates the frequency of occurrence of each level of mean arterial blood pressure in percent of the total time that it occurred during a continuous 24-hour period. The arterial blood pressure of this dog, which was characteristic of other normal dogs, was...
distributed around a mean pressure of 98 mm Hg with a range of 75 to 125 mm Hg for the 24-hour period. In sharp contrast, baroreceptor denervation resulted in a wide distribution of pressures ranging from 45 to 175 mm Hg and in this case a mean level of mean arterial blood pressure of 104 mm Hg for the 24-hour period.

Figure 4B and C are composite overlays of 24-hour frequency curves recorded from 10 normal dogs and 12 denervated dogs, respectively. These curves were superimposed from the daily records of arterial blood pressure which were stored on magnetic DECTape and were drawn by the computer-linked plotting system. Both the intradog and the interdog daily pressure variations in the normal and denervated groups are immediately evident in these summary graphs.

Summarized hemodynamic data including all the dogs studied (12 normal and 15 denervated dogs) are presented in Table 1. Included with the average 24-hour hemodynamic mean data are the standard deviations obtained from averaging the individual 24-hour standard deviation values of each variable.

Several important features clearly emerge from inspection of both the composite graphs and the tabular data. First, the average 24-hour mean arterial blood pressure in the 12 normal dogs was 101.6 mm Hg compared with a pressure of 112.7 mm Hg in the 15 denervated dogs. The difference, although physiologically small, was statistically significant (P<0.001). Similar differences were observed for the systolic and the diastolic pressures. Figure 4B and C illustrates that the mean 24-hour pressure about which the minute-to-minute pressures fluctuated varied in normal dogs between 91 and 116 mm Hg compared with 85 to 139 mm Hg in denervated dogs. Second, the daily range of mean arterial blood pressures in individual normal dogs was about 50 mm Hg compared with 125 mm Hg in denervated dogs. The average 24-hour standard deviation of the mean pressure in normal dogs was ±10.9 mm Hg compared with ±20.6 in denervated dogs (Table 1). Third, the mean arterial blood pressure in most of the denervated dogs was elevated to high levels many times during the day, even though the average daily pressure was not elevated (Fig. 4C). Slight disturbances nearly always resulted in elevated pressures. Therefore, when pressures were measured for only short periods during any given day under normal laboratory conditions.

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Systolic pressure (mm Hg)</th>
<th>Diastolic pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac output (ml/min)</th>
<th>Total peripheral resistance (mm Hg/ml min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal dogs</td>
<td>101.6 ± 10.9</td>
<td>137.2 ± 23.0</td>
<td>80.0 ± 11.3</td>
<td>89.0 ± 15.0</td>
<td>2070 ± 414</td>
<td>0.032 ± 0.014</td>
</tr>
<tr>
<td>Denervated dogs</td>
<td>112.7 ± 20.6</td>
<td>149.8 ± 23.8</td>
<td>98.4 ± 21.6</td>
<td>105.0 ± 21.0</td>
<td>2025 ± 417</td>
<td>0.054 ± 0.015</td>
</tr>
</tbody>
</table>

The average pressure and heart rate values were obtained from 12 normal dogs recorded from for 440 continuous hours and from 15 sinoaortic baroreceptor–denervated dogs recorded from for 994 continuous hours. Cardiac output and total peripheral resistance averages were obtained from 4 normal dogs recorded from for 65 hours and from 5 denervated dogs recorded from for 268 continuous hours. Data were obtained after initial training sessions to accustom the dogs to the recording pen and were recorded between 1 and 52 weeks after surgery. All values are means ± SD.
conditions, these dogs appeared chronically hypertensive. Fourth, hypotensive episodes during which the mean arterial blood pressure remained at levels of 50-60 mm Hg for 15-20 minutes were as characteristic as the episodes of hypertension.

Heart Rates in Normal and Denervated Dogs—24 Hour Frequency Distributions.—Figure 5 shows the 24-hour frequency distributions of heart rates in normal and baroreceptor-denervated dogs. The pattern of heart rate distribution over a 24-hour period was generally similar to the pattern of arterial blood pressure (Fig. 4). The heart rates of normal dogs varied considerably less than the heart rates of denervated dogs during a 24-hour period as is illustrated by the narrower and more elevated distribution curves. This phenomenon can best be seen in the results from a single dog before and after baroreceptor denervation (Fig. 5A), and it is reinforced by the composite curves (Fig. 5B and C). In general, denervated dogs showed greater daily variability in heart rate, which is illustrated by the wider, lower curves (Fig. 5C) compared with the taller, narrower curves from normal dogs (Fig. 5B).

The summary data (Table 1) indicate that normal dogs had a mean heart rate of 89.0 beats/min compared with a significantly higher rate of 105.0 beats/min ($P < 0.05$) in baroreceptor-denervated dogs. Denervation did not, however, have as profound an effect on the variability of heart rate as it did on the variability of arterial blood pressure (Fig. 5 and Table 1). The average 24-hour standard deviation in normal dogs was ±15 beats/min compared with ±21 beats/min in denervated dogs.

Cardiac Output and Total Peripheral Resistance in Normal and Denervated Dogs—24-Hour Frequency Distributions.—The average cardiac output and the total peripheral resistance values obtained in four normal and five baroreceptor-denervated dogs are shown in Table 1. All of the denervated dogs were recorded from on a continuous 24-hour basis. Two of the normal dogs were recorded continuously for 24 hours; the other two were trained to lie quietly in the laboratory and were recorded from during six 1-hour sessions.

The results indicate that a similar 24-hour distribution of cardiac output and total peripheral resistance existed in normal and baroreceptor-denervated dogs. This finding is supported by the average 24-hour standard deviation of cardiac output which was ±414 ml/min in normal dogs and ±417 ml/min in denervated dogs; similarly, the 24-hour standard deviation of total peripheral resistance was ±0.014 mm Hg/ml min$^{-1}$ in normal dogs and ±0.015 mm Hg/ml min$^{-1}$ in denervated dogs. Although the 24-hour distribution of cardiac output was similar in normal and denervated dogs, characteristic differences were apparent in short-term variations between the two groups. For example, denervated dogs exhibited more abrupt changes in cardiac output during excitement and postural changes.

Finally, the average cardiac output in the four normal dogs (2079 ml/min) was not significantly different from that in the five denervated dogs (2025 ml/min); total peripheral resistance was also not significantly different. The average mean arterial blood pressure of these same normal dogs was 97 mm Hg and was not statistically different from the pressure in the five denervated dogs of 99 mm Hg.

Figure 6 graphically illustrates these conclusions with 24-hour frequency distribution curves of cardiac output and total peripheral resistance from one normal dog and one denervated dog. The mean
24-hour pressures were similar in the two dogs (Fig. 6A) with the characteristically wider distribution seen in the denervated dog. However, the cardiac output (Fig. 6B) and the total peripheral resistance (Fig. 6C) distributions were almost superimposed on one another in the normal and the denervated dogs. This striking similarity, contributed in part by selecting two dogs with nearly equal mean cardiac output values, illustrated that the daily variability in cardiac output and total peripheral resistance was not altered by the absence of the baroreceptor reflexes.

Pattern of Arterial Blood Pressure up to One Year after Denervation.—The mean arterial pressure rose greatly during surgery immediately following denervation of the final baroreceptor area. Mean arterial blood pressures obtained at this time under sodium pentobarbital anesthesia were elevated from an average of 120 mm Hg to 175–225 mm Hg, a level which was associated with increased heart rates to over 180 beats/min. Mean pressures measured 6 hours after surgery in three dogs had fallen to an average of 135 mm Hg. This apparent progressive postoperative fall in arterial blood pressure was confirmed in seven dogs whose pressure averaged 103 ± 8.0 mm Hg the day after surgery. A gradual rise was observed in several dogs over the next 7 days; after this time the 24-hour mean arterial blood pressure exhibited no further consistent pattern of change. Three dogs were followed for 6 months and a fourth dog for 15 months, and no progressive pressure changes were seen.

Daily Pattern of Pressure Behavior—Diurnal Rhythm.—Figure 7 compares the normalized daily arterial blood pressure pattern based on 40 days of 24-hour pressure recordings in 15 denervated dogs with the pattern based on 18 days of 24-hour recordings in 12 normal dogs. Pressure deviations from the 24-hour mean pressure of the individual dogs were calculated at each hour in each dog. Each hour's deviation was then averaged from all the dogs in each group and added to or subtracted from the mean 24-hour pressure value in each group (i.e., normal 101.6 mm Hg and denervated 112.7 mm Hg).

The top curve in Figure 7 represents the pattern of behavior in baroreceptor-denervated dogs. A
diurnal variation in arterial blood pressure was evident in the denervated dogs with a fundamental frequency of twice per day. Peak pressures occurred in the periods from 7 to 9 AM and 9 to 10 PM, and minimum pressures occurred from 1 to 2 AM and 2 to 4 PM. These maximum and minimum pressure values were all statistically different from the 24-hour mean ($P < 0.05$).

The 24-hour results from normal dogs (Fig. 7, bottom curve) exhibited only a slight decrease in pressure in the early morning (2-5 AM), which corresponded to the time that the denervated dogs were showing a steady increase in pressure.

Therefore, two types of lability occur following baroreceptor denervation. The first is the rapid random variations seen in Figure 2, and the second is the slow, two-cycle diurnal oscillations. The summation of these variations determines the mean 24-hour pressure value and the frequency distribution pattern of pressures shown in Figure 4.

Hemodynamics during Postural Changes in Normal and Denervated Dogs.—The continuous recording of postural changes permitted analysis of the hemodynamic changes that occurred in normal and denervated dogs going directly from a supine to a standing position. The wide variety of intermediate postural positions was not included in this analysis. The records were hand analyzed during 170 such postural changes in three normal dogs and during 570 changes in five baroreceptor-denervated dogs (Table 2). Mean arterial blood pressure decreased in both groups 98% of the time on standing up, but the fall was twice as great in denervated dogs. In normal dogs the average decrease was $15.5 \pm 0.8$ (SE) mm Hg, and in denervated dogs it was $30.4 \pm 0.8$ mm Hg. The hypotension in denervated dogs was proportional to the preexisting arterial blood pressure level. At levels of 170-180 mm Hg, a fall of 100 mm Hg was often seen on rising; however, a fall of only 10 mm Hg resulted when the preexisting pressure was 70-80 mm Hg. Arterial blood pressure often decreased to 50 mm Hg but seldom fell below this level.

In nearly half of the cases, the dogs exhibited an elevation in heart rate and arterial blood pressure 5-10 seconds before standing. Immediately after standing, there was frequently a brief 5-10-second decrease in heart rate in denervated dogs. This decrease was then followed by an increase in heart rate in both normal and denervated dogs. Heart rate in normal dogs showed a greater increase ($34.5 \pm 4.1$ beats/min) than did heart rate in denervated dogs ($23.9 \pm 1.2$ beats/min).

Cardiac output on standing increased 94% of the time in normal dogs and 97% in denervated dogs, but the average increase of $17.9 \pm 1.5$ ml/kg min$^{-1}$ in normal dogs was only half that observed in denervated dogs, $37.3 \pm 1.7$ ml/kg min$^{-1}$. The calculated total peripheral resistance before standing averaged 0.050 mm Hg/ml min$^{-1}$ in normal dogs and decreased to 0.036 mm Hg/ml min$^{-1}$ immediately on standing, at a time corresponding to the maximum pressure decrease. The decrease was much greater in denervated dogs: total peripheral resistance averaged 0.053 mm Hg/ml min$^{-1}$ before standing and fell to 0.027 mm Hg/ml min$^{-1}$ on standing. Denervated dogs thus showed a 48% decrease in calculated total peripheral resistance on standing compared with a 27% decrease in normal dogs. Therefore, despite the greater increase

### Table 2

| Hemodynamic Changes during Postural Changes in Normal and Sinoaortic Denervated Dogs |
|-----------------------------------------|-----------------------------------------|-----------------|
|                                         | Normal                                  | Sinoaortic denervated |
| ABP (mm Hg)                            | $-15.5 \pm 0.8$ (n = 118)               | $-30.4 \pm 0.8$ (n = 500) |
| Recovery time (sec)                     | 21.0 (n = 100)                          | 81.0 (n = 110) |
| ΔHR (beats/min)                        | $+34.5 \pm 4.1$ (n = 111)               | $+23.9 \pm 1.2$ (n = 168) |
| ΔCO (ml/kg min$^{-1}$)                  | $+17.9 \pm 1.5$ (n = 52)                | $+37.3 \pm 1.7$ (n = 168) |
| ΔTPR (mm Hg/ml min$^{-1}$)              | $-0.014$ (n = 52)                       | $-0.025$ (n = 168) |
| Average weight (kg)                     | 20.5                                    | 23.5 |

ΔBP = the immediate decrease in mean arterial blood pressure when the dog stood up, ΔCO = the change in cardiac output which occurred over the period indicated by the recovery time, ΔTPR = the change in total peripheral resistance corresponding to the time of maximum pressure decrease, ΔHR = the change in heart rate, recovery time = the time required for the arterial blood pressure to return to 67% of the prestanding level, and n = number of measured postural changes. All values are means ± SD.
in cardiac output in denervated dogs, they were still unable to compensate for the large decrease in arterial blood pressure with an increase in arterial resistance as did the normal dogs.

The time required for arterial blood pressure to return to prestanding levels also reflected a difference in the homeostatic mechanisms involved in maintaining normal pressure during postural changes. The mean pressure returned 67% toward the prestanding level in 21 seconds in normal dogs, but 81 seconds were required in denervated dogs. This observation was based on 210 postural changes in two normal and three denervated dogs. The slow compensation seen in denervated dogs was associated with a slow rate of change in cardiac output.

Because a precise analysis of the transient responses was not possible at recording paper speeds of 10 mm/min, rapid recordings of postural changes in two denervated dogs were obtained at a paper speed of 50 mm/sec. Heart rate increased from 80 to 120 beats/min in the 6 seconds preceding the actual change in posture. During the 3 seconds that were required for the dog to stand fully, there was a 25% reduction in stroke volume and a 10% reduction in arterial blood pressure with essentially no further change in heart rate. By the fifth second following the initiation of the postural change, the heart rate was still 30 beats/min above the control value and the stroke volume remained 25% reduced. By the twentieth second, stroke volume had increased to 30% above the control level, the heart rate had nearly returned to normal, and the arterial blood pressure was reduced to 40% below the control level.

In about 5% of all postural changes examined, a decrease in stroke volume predominated throughout the period of postural change and resulted in a sustained decrease in cardiac output. In these cases arterial blood pressure returned to control levels very slowly.

Blood Volumes, Plasma Electrolytes, and Arterial Renin Activities.—The average blood volume for seven normal dogs was 80.9 ± 8.7 (sn) ml/kg, and for nine denervated dogs it was 81.7 ± 15.7 ml/kg; the difference was not statistically significant (P > 0.5). The plasma electrolyte values for normal dogs were Na+ 142.3 ± 4.4 mEq/liter and K+ 4.05 ± 0.49 mEq/liter; the values for denervated dogs were Na+ 142.9 ± 5.7 mEq/liter and K+ 3.98 ± 0.59 mEq/liter. None of the values were statistically different (P > 0.2). No significant differences were observed in arterial renin activity (0.84 ± 0.49 ng angiotensin/ml hour⁻¹ in normal dogs compared with 1.37 ± 1.7 ng angiotensin/ml hour⁻¹ in denervated dogs, P > 0.2).

Discussion

The results of these studies enabled us to characterize better the role of the baroreceptor reflex system in the regulation of arterial blood pressure and other cardiovascular variables. This study, originally designed to investigate neurogenic hypertension yielded results which are much more useful for understanding the normal control of cardiovascular variables than they are for understanding baroreceptor-denervation hypertension. In fact, the term neurogenic hypertension in baroreceptor-denervated dogs is a large extent a misnomer. When the dogs were undisturbed, the resulting mean 24-hour pressure was rarely far from normal. The most prominent feature following removal of the baroreceptor system was the marked variability in arterial blood pressure rather than the alteration of the basal level of pressure. The frequency distribution curves of arterial blood pressure showed that the major role of the baroreceptor system was to maintain the arterial blood pressure within a narrow range throughout the day. This role included pressure stabilization during various influences such as postural changes, diverse psychic stimuli which occurred from moment to moment, and slow diurnal rhythms of unexplained origin.

The baroreceptor reflex system did not appear to be important in setting the mean level of arterial blood pressure over prolonged periods. The marked hypertension observed after sinoaortic sectioning indicated that the reflex normally suppressed the inherent tone of the cardiovascular neural control. However, the elevated pressure resulting from increased sympathetic tone was compensated for by other mechanisms more influential in determining the mean level of arterial blood pressure, since the pressure returned to nearly normal values within a day. These changes could be brought about by central nervous system influences. However, long-term autoregulation of flow to the peripheral tissues (12) and adjustments by the renal-fluid volume mechanisms (13) possibly resulted in a return of total peripheral resistance to near normal levels. These mechanisms would act too slowly to suppress rapid variations in arterial blood pressure.

Some daily stabilization of heart rate by the baroreceptors existed, but it was not so marked an influence as that exerted on the control of arterial blood pressure. This finding was supported by the

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difference in the heart rate frequency distribution curves in the two groups, which was not so great as the difference in the curves for mean arterial blood pressures.

The circulatory variables least influenced by the removal of the baroreceptors were cardiac output and total peripheral resistance. The 24-hour frequency distribution curves for these variables were hardly affected by the removal of the baroreceptors, which indicated that the reflex system exerted little influence on the stabilization of these hemodynamic factors.

Mean Arterial Blood Pressure in Denervated Dogs.—The present study suggests that the high levels of arterial blood pressure reported in classic studies by Kock and Mies (1) and Heymans and Bouchaert (3) described as neurogenic hypertension were to a great extent caused by psychic stimuli resulting from the techniques required to measure arterial blood pressure (2, 4, 5).

When the denervated dogs were monitored in the conscious state under routine laboratory conditions, pressure levels of 150 mm Hg were routinely observed and were similar to the levels reported by earlier investigators (1-5). Ferrario et al. (7) recognized the hazards of pressure monitoring in trained denervated dogs and recorded arterial blood pressure daily for 60-90 minutes at the same time each day. Even this type of recording, based on the results of the present study, is probably inadequate because of the wide range of daily pressures and because even slight manipulation of baroreceptor-denervated dogs significantly elevates their pressures. These effects probably account for the 31-mm Hg difference that Ferrario et al. (7) reported between normal and denervated dogs compared with the 11-mm Hg difference in the present study. Figure 7 illustrates that the diurnal variation alone could alter the mean pressure nearly 15 mm Hg depending on the time of measurement. Also, the system for restraining the dog during pressure measurement, even if it was training of the dog, could easily elevate the pressure excessively in baroreceptor-denervated dogs. In brief, there has been a progressive trend toward more nearly normal arterial blood pressures reported in denervated animals as monitoring techniques have improved. Alexander et al. (14) reported that baroreceptor-denervated rabbits frequently did not exhibit hypertension yet showed good signs of being well denervated.

Chronic hypertension is characteristically accompanied by alterations in the physical structure of the vascular wall; the most prominent alteration is an increase in the ratio of wall to lumen (15-17). Since the chronic long-term arterial blood pressure in the baroreceptor-denervated dog is only slightly elevated, one would not expect to see vascular changes in these dogs unless such damage was caused by short transient pressure elevations. In fact, there have been indications that neurogenic hypertension might not result in the morphological changes that are apparent in other types of hypertension (18-21), although contradictory evidence has also been reported (22, 23).

In addition to monitoring techniques, other factors might help to explain the high levels of arterial blood pressure observed in earlier studies on baroreceptor-denervated animals. For example, some descriptions of denervation techniques indicate that to obtain a prolonged, marked elevation of pressure, it is necessary to excise the entire area of the common carotid bifurcations (4). This procedure suggests that a cerebral ischemic response (24-26) might also be involved in the determination of the pressure. Although bilateral ligation of the common carotids does not decrease cerebral blood flow in dogs (27), with the simultaneous removal of the carotid sinus, lack of other reflex compensations during ligation could possibly result in cerebral ischemic damage and the production of lasting effects.

Evidence for Complete Denervations.—Although complete surgical deafferentiation of all the reported sites of baroreceptor activity is probably not possible, numerous observations in our study suggest that the dogs lacked permanently all of the major afferent reflex pathways for pressure control.

First, we observed a consistent and permanent loss of the inverse pressure-heart rate relationship during both rapid injections and intravenous infusions of angiotensin, norepinephrine, and vasopressin, procedures carried out in nearly all of the dogs for other purposes. Infusions of these agents indicated that an arterial blood pressure elevation of about 30 mm Hg in normal dogs resulted in a significant decrease in heart rate averaging 18 beats/min ($P < 0.001$). A similar pressure elevation in denervated dogs was accompanied by a small but significant heart rate elevation of 7 beats/min ($P < 0.05$). Second, all of the denervated dogs consistently showed very characteristic, wide 24-hour arterial blood pressure frequency distribution curves which were never observed in normal dogs. Furthermore, this finding persisted without change.
throughout all of the experiments. Third, pressure changes observed when the dogs changed from the supine to the upright position demonstrated an obvious lack of rapidly acting pressure control mechanisms. Fourth, the denervated dogs, when only mildly excited, exhibited elevated arterial blood pressure. Finally, arterial blood pressures monitored during operative procedures exhibited an average increase of about 85 mm Hg following baroreceptor denervation; when these dogs were subjected to bilateral carotid occlusions, they responded with almost no rise in peripheral arterial blood pressure or heart rate.

**Diurnal Variation of Arterial Blood Pressure.**—The slow rhythm in mean arterial blood pressure that occurred twice a day in denervated dogs cannot be easily explained. This observation contrasts with the daily decrease seen in normal dogs in the early morning, which has also been reported in normal man (28, 29). The daily routines such as feeding, cage cleaning, and dog and equipment checks were staggered so that they could not have caused the changes. The changes also did not appear to be associated with surrounding noise levels, since one of the minimum pressure periods was between 2 and 4 P.M., a normally very active time. Also, there was no natural light source in the recording room, and there was no artificial day-night cycle. There is contradictory data concerning the effects of sleep on arterial blood pressure in baroreceptor-denervated animals. Most investigators have reported a decrease during deep sleep (30, 31), which indicates that the normally decreased sympathetic tone in sleep is not compensated for in debuffered dogs and, thus, the pressure falls to a deeper level in denervated dogs than in normal dogs.

Ferrario et al. (7) found elevations of pressures during sleep due to increased peripheral resistance. Visual observations of pressure in our dogs during what appeared to be sleep were inconclusive. However, in the early morning hours when the dogs were probably sleeping, the arterial blood pressure reached its lowest level (Fig. 7).

**Cardiac Output and Total Peripheral Resistance in Normal and Denervated Dogs.**—Continuous recordings of cardiac output in denervated dogs over 24-hour periods (Fig. 6) have not been previously reported. This procedure was difficult, and the degree of error was greater than that encountered during continuous pressure monitoring. However, based on frequent checks of electrical base-line drift and electrical calibrations of the Grass and flowmeter recorders, we concluded that the system was capable of providing reliable cardiac outputs within ± 5% over a 24-hour period. An additional possible ± 5% error existed in the curve-scanning and correctional techniques used in the analysis of the records; therefore, a probable overall accuracy of ± 10% resulted.

It is difficult to conclude that the long-term average cardiac output was altered at all by the denervation procedures because of the natural variability in cardiac output and the very similar values in the two groups of dogs. Kreiger (32) reported little alteration in mean cardiac output in rats following denervation, but variable results were found in dogs (7).

Our data also indicated that little difference in the 24-hour variability of cardiac output or total peripheral resistance between normal and denervated dogs existed. This observation was demonstrated by the 24-hour frequency distribution curves (Fig. 6) and the average 24-hour standard deviations (Table 1).

The similarity of the 24-hour frequency distributions of total peripheral resistance in both groups of dogs despite the greater variability of arterial blood pressure in denervated dogs can be readily explained. In normal dogs, a primary change in the cardiac output resulted in a secondary, directionally opposite change in the total peripheral resistance through the baroreceptor reflex. The converse of this phenomenon occurred for primary changes in total peripheral resistance. Hence, the mean arterial blood pressure was stabilized even with large increases or decreases in the flow or resistance. When this reflex adjustment was removed by sinoaortic denervation, primary variations of flow or resistance or both caused proportional or even multiplicative variations in mean arterial blood pressure, except when the flow and the resistance incidentally varied to about the same extent but in opposite directions.

It has been a confusing issue whether the arterial blood pressure changes following denervation are caused by changes in total peripheral resistance or by changes in cardiac output. Ferrario et al. (7) found that in some dogs the alterations in mean arterial blood pressure following denervation were determined by peripheral resistance changes and in others by cardiac output changes. The results we obtained from continuous recording indicated that both situations existed in the same dog in various situations. In certain situations such as excitement, flow seemed to be the predominant cause of
ROLE OF BARORECEPTOR REFLEX

pressure changes. However, during diurnal changes of pressure or during random spontaneous fluctuations, the peripheral resistance changes predominated.

Hemodynamic Effects of Postural Changes.—The analysis of hemodynamic changes that occurred during postural changes from a supine to a standing position showed that the blood pressure fell nearly two times as much in denervated dogs as it did in normal dogs. Denervated dogs differed from normal dogs in their compensation for the decreased pressure. Normal dogs, after a brief transient decrease in resistance, maintained total peripheral resistance rather well and slightly increased their cardiac output (33). Denervated dogs appeared to be unable to increase rapidly their total peripheral resistance, which decreased to nearly half of the control value and returned to normal only after several minutes. The pressure homeostasis that did occur soon after a postural change was accomplished largely by an increase in cardiac output in denervated dogs. Contraction of leg and abdominal muscles associated with standing up might have acted as an important mechanism for increasing venous return in these dogs. The increased venous return, combined with the elevations in heart rate, slowly returned the arterial blood pressure to normal despite the inability to alter rapidly the total peripheral resistance. The slow increase in resistance could be explained by the rapid component of peripheral autoregulation that occurs to a considerable extent in less than 60 seconds (34, 35). The rapid compensation provided by the baroreceptor reflex was obviously lost in the denervated dogs; this phenomenon is illustrated by the fourfold increase in the time required for the pressure to return to control levels.

Gain of the Baroreceptor System in the Unanesthetized Dog.—The ability of the baroreceptors to stabilize the arterial blood pressure can be expressed as the overall gain of the feedback system. Since the 24-hour pressure distribution curves of denervated dogs showed twice the variability of curves from normal dogs, as reflected by the standard deviation, it was determined mathematically that this system had an approximate, algebraically averaged feedback gain of \(-1.0\). This gain of \(-1.0\) represented the average activity of the system throughout the day and over a broad range of pressures and pulse frequencies. Because of previously demonstrated nonlinearities of the baroreceptor system (36–38), the average gain calculated for the present study was expected to be less than the gains obtained under optimum conditions by Scher and Young (39) and Sagawa and Watanabe (40). Both the present value of daily overall gain and the values of optimum gain contribute to the understanding of the baroreceptor system, but there should not be confusion of the two values.

The continuous measurement of hemodynamic variables provides a powerful tool for precise quantification of physiological data in labile, unanesthetized dogs. Only by such methods is it possible to use the labile, unanesthetized, baroreceptor-denervated dog preparation in precise quantitative studies which clarify the role of the baroreceptor reflex system in the normal regulation of arterial blood pressure.

The results obtained from monitoring the sinoaortic baroreceptor-denervated dogs indicated that the degree of hypertension previously reported for this type of preparation has been highly exaggerated, presumably due to the methods of study. But, even more important, the results demonstrated vividly that the major function of the baroreceptor mechanism probably is to minimize systemic arterial blood pressure variations, rather than to set the chronic level of pressure, whether these variations be caused by postural changes of the dog, excitement, diurnal rhythm, or even spontaneous fluctuations of unknown origin.

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