Baroreceptor Reflex Effects on Transient and Steady-State Hemodynamics of Salt-Loading Hypertension in Dogs

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ABSTRACT
Intact dogs were compared with baroreceptor-denervated dogs to determine the extent to which the baroreceptor reflexes delay the onset and offset transients and alter the final steady-state levels of salt-loading hypertension. Two months after their renal mass had been reduced to about one-third of normal, hypertension was produced in both groups of dogs by continuous intravenous infusion of isotonic saline (190 ml/kg day⁻¹). Major hemodynamic variables were recorded continuously 24 hours/day throughout the experimental period. Both groups of dogs had similar control 24-hour arterial blood pressure values: intact dogs averaged 112 ± 4.1 (SE) mm Hg, and denervated dogs averaged 110 ± 4.3 mm Hg. Both groups reached the same average plateau of elevated arterial blood pressure: intact dogs averaged 142 ± 4.8 mm Hg, and denervated dogs averaged 142 ± 8.7 mm Hg. After the start of salt loading, the denervated dogs reached their plateau level of arterial blood pressure in an average of 8 hours compared with nearly 24 hours for the intact dogs. Cardiac output also rose more rapidly in the denervated dogs and reached a maximum elevation of 26% above the control level in an average of 7.4 hours compared with a maximum elevation of 40% above control in the intact dogs in 18 hours. Total peripheral resistance fell below the control level during the entire first day of infusion in the intact dogs but was somewhat elevated in the denervated dogs. When the saline infusion was stopped, arterial blood pressure in both groups returned to control levels within 24 hours. The results indicate that the major action of the baroreceptor reflexes on the onset of salt-loading hypertension is to slow the development of hypertension by modifying the total peripheral resistance; the final steady-state level of hypertension is unaffected by the baroreceptor reflexes.

KEY WORDS baroreceptor denervation cardiac output total peripheral resistance arterial blood pressure continuous 24-hour hemodynamic monitoring autoregulation baroreceptor resetting reduced renal mass volume expansion

Arterial baroreceptor reflexes exert a powerful stabilizing influence on arterial blood pressure, and presumably they can influence hemodynamics during the development of hypertension (1). It is reasonable to believe that these reflexes also obscure events that are of primary importance in explaining the development and the maintenance of chronic long-term hypertension. The ability of these reflexes to compensate for a sustained elevation in arterial blood pressure gradually adapts with time; this process is referred to as resetting (2). Theoretically, the rate at which this resetting occurs is one of the major factors that determines how rapidly hypertension develops. Moreover, the degree to which the reflex system adapts probably influences the final steady-state level of hypertension. The extent to which the baroreceptor reflexes influence hemodynamic variables in different types of hypertension is poorly understood.

In a previous study on Goldblatt hypertension (3), we have found that the baroreceptor mechanisms considerably delay the onset of hypertension but do not alter the degree of hypertension. Since the apparent degree of influence of the reflex system on arterial blood pressure is theoretically determined by how rapidly the arterial pressure is being forced to change and perhaps by the nature of the stimulus driving the pressure change, a different model of hypertension was examined in the present study, salt-loading hypertension.

The present experiments quantified the extent to which the arterial baroreceptor reflexes delayed the rate of development of hypertension and their influence on the final steady-state level of hypertension induced by salt loading of dogs. It has been well documented that hypertension develops when...
an animal or a man with reduced functional renal mass is placed on a high salt intake (4–9).

To evaluate these parameters, procedures that permitted continuous 24-hour/day recording of major hemodynamic variables for periods of 1–3 weeks were used. The sequence of hemodynamic changes during salt loading was recorded in a group of reflex-intact dogs and compared with the sequence of changes that occurred in sinoaortic baroreceptor-denervated dogs. In both groups, renal mass had been reduced to nearly one-third of normal. The great variability of arterial blood pressure following denervation of the baroreceptors necessitated the use of special data collection and analytical techniques to enable quantitative evaluation of the hemodynamic variables in these labile dogs during the development of hypertension.

Methods

Animal Preparation.—Sixteen mongrel dogs weighing an average of 23.9 ± 1.2 kg, 10 male and 6 female, were used for 22 separate salt-loading experiments. All of the dogs initially underwent surgery to acutely reduce their total renal mass to approximately one-third of normal; the right kidney was completely removed and the poles of the remaining left kidney were excised. Efforts were made to maintain normal innervation to the left kidney. About 1 month following this procedure, a chronic indwelling polyvinyl-Tygon catheter was introduced through a femoral artery and placed in the abdominal aorta distal to the renal artery. Another catheter was made to maintain normal innervation to the left kidney. They were kept filled with 1,000 U.S.P. units of heparin when they were not in use.

In 10 of the 16 dogs, the baroreceptor area of the aortic arch was denervated via a left thoracotomy through the third intercostal space. Denervation was accomplished by surgically stripping the ascending aorta and the aortic arch past the bifurcation of the left subclavian artery. The adventitia was also removed 2–3 cm up the brachiocephalic and left subclavian arteries. Next, 5% phenol solution followed by isopropyl alcohol was applied to these same areas. Finally, to further ensure denervation of the thoracic baroreceptors, the left cervical vagus was completely cut, and the right sympathetic aortic nerve portion of the right vagus was dissected and removed. If the line of demarcation separating the vagus and the sympathetic aortic nerve bundle could not be visually identified (about 10% of the dogs), the entire medial third of the right cervical vagal trunk was dissected and cut. Bilateral denervation of the carotid sinus areas and the common carotid arteries was performed through a midline incision in the neck. The procedure consisted of surgically stripping the adventitia of the common carotid arteries for a distance of 3–4 cm and of the internal and external carotid arteries for a distance of nearly 1.5 cm beyond the bifurcation. Stripping was followed by application of 5% phenol and then application of isopropyl alcohol. The 10 dogs prepared in this manner were designated baroreceptor-denervated dogs. All surgical procedures were performed using sodium pentobarbital anesthesia (30 mg/kg, iv).

The procedures used to test for completeness of denervation have been previously reported (3). In brief, there was no evidence of reflex control of arterial blood pressure or heart rate as determined from intravenous injections and infusions of angiotensin II, vasopressin, and norepinephrine. All of the denervated dogs exhibited an average 24-hour standard deviation of arterial blood pressure at least twice that observed in intact dogs, clearly demonstrating their inability to stabilize arterial blood pressure.

In the remaining six dogs subjected to the reduction of renal mass and the implantation of arterial and venous catheters, the baroreceptors were not denervated; these dogs were designated intact dogs.

In five denervated and two intact dogs, electromagnetic flow transducers (Biotronics, series 400) were placed on the ascending aorta at the time of denervation or catheter implantation. Calibration of the flow transducers was performed in vitro before implantation and, if possible, after the end of the experiment as well by using calf aortas perfused with blood diluted with saline to a hematocrit of 40%. Recalibration values were within ±10% of the original calibration values.

Experimental Procedures.—All experiments were carried out in a quiet isolated room to minimize the large pressure variations that occur in denervated dogs subjected to minor disturbances. Dogs were placed in a large metabolic cage for water-balance measurements. Procedures used for the continuous 24-hour recording of arterial blood pressure, heart rate, and cardiac output have been previously reported (10). Data were recorded on model 7 Grass polygraph charts that were later analyzed using a fiber-optic curve-scanning system to convert the analog records to digital form for storage and analysis by a PDP-9 digital computer (11). Cardiac output was obtained using a Biotronics blood flowmeter (model BL-610). The analytical techniques permitted very accurate computation of the average hourly arterial blood pressure, cardiac output, total peripheral resistance, and heart rate. Records were digitized to about 1,500 data points/hour recorded time. Standard statistical information was simultaneously computed for each hour of collected data. Individual data points stored in the computer memory were used to generate frequency variables over any desired time period (see Fig. 2).

Other Measurements.—Plasma sodium and potassium concentrations were measured by flame photometry. Plasma renin activity was measured using a radioimmunoassay technique for angiotensin I (12). Blood urea nitrogen was measured in plasma using a Technicon autoanalyzer. Plasma volume was measured by spectrophotometry using three samples collected 20, 40, and 80 minutes after injection of Evans’ blue dye.

Experimental Protocol.—Two to 3 weeks following the final surgery, the dogs were placed in a metabolic recording pen with free access to drinking water and maintained on a fixed sodium intake of 40–50 mEq/day. During this control period, the fluid volume “balance” (the net 24-hour difference between water drunk and urine collected per kilogram body weight) was deter-
mined daily for at least 4 days prior to the salt-loading period. Two days prior to the saline infusion, blood samples were obtained for determination of plasma electrolytes, blood urea nitrogen, and plasma renin activity. Plasma volume was determined in eight dogs. Continuous recording of arterial blood pressure, heart rate, and cardiac output was initiated 24-48 hours before the start of salt loading. Salt loading was induced by continuous intravenous infusion of 0.9% saline at a fixed rate of 190 ml/kg day⁻¹ using a Sigmamotor pump (model TM 20). Hemodynamic variables were recorded continuously 24 hours/day throughout the course of the experiment. Drinking was permitted ad libitum throughout the experiment. All infusions were continued for at least 5 days, and in two intact and two denervated dogs salt loading was continued for a 10-day period.

During the third to fifth day of saline infusion, plasma volume was again determined, and blood samples were obtained for measurement of plasma renin activity, plasma electrolytes, and blood urea nitrogen. Following the end of the saline infusions, recording of the hemodynamic variables continued until they returned to control values. All values unless otherwise stated are expressed as means ± se.

Results

Contrasting Recordings of Saline Infusions in an Intact and a Denervated Dog.—Figure 1 illustrates portions of records obtained at four time periods during a representative salt-loading experiment in an intact dog and a denervated dog. Five-minute time slices are shown of the control period and portions of the sixth, twentieth, and sixtieth hour after the start of the saline infusion. Characteristically, by the sixth hour of the infusion, the intact dog had responded to the salt loading with a sizable increase in cardiac output, although the mean arterial blood pressure was only slightly elevated at this time. Values obtained from the complete averaged data from this dog showed that by this time the cardiac output had risen 21% (from 2,250 to 2,750 ml/min) and the mean aortic blood pressure had risen only 5% (from 100 to 105 mm Hg). These changes were associated with a decrease in calculated total peripheral resistance of nearly 14% (from 0.044 to 0.038 mm Hg/ml min⁻¹). Toward the end of the first day of the infusion (twentieth hour), the cardiac output reached a maximum value of 44% above the control value. By this time, the arterial blood pressure was elevated to a level 35% above the control value and the total peripheral resistance had returned to within slightly less than 5% below the control value. By the sixtieth hour of infusion, the cardiac output had fallen back to within 28% of the control value, and the mean arterial blood pressure had reached a stable plateau value of 140 mm Hg. At this time, the total peripheral resistance was elevated to 10% above the control value.

The denervated dog also exhibited a rapid rise in cardiac output; by the sixth hour, cardiac output had increased from 1,800 to a maximum of 2,000 ml/min, a 25% rise. In contrast to the intact dog, this change was associated with a rapid rise in mean arterial blood pressure; in this denervated dog, the pressure rose to 35% above the control value (from 100 to 135 mm Hg) by the sixth hour. Thus, in the absence of the baroreceptors, there was no decrease in calculated total peripheral resistance but rather a mild increase of 8% above the control value (from 0.063 to 0.068 mm Hg/ml min⁻¹). By the twentieth hour of infusion, the cardiac output had fallen to within 9% of the control value, and the arterial blood pressure had risen to an even higher level of 140 mm Hg. Total peripheral resistance at this time was 27% above the control value. Arterial blood pressure stabilized in this dog at a maximum level of 143 mm Hg.
Onset Transients of Hypertension: Frequency Distribution Analysis of Mean Arterial Blood Pressure.—Figure 2 shows the progressive changes in the distribution curves of mean arterial blood pressure in an intact and a denervated dog during the developmental stages of salt-loading hypertension. The frequency of occurrence of mean arterial blood pressures over the 24-hour control period is shown by the computer-drawn curves on the far left of each graph. The distribution of pressures over succeeding 8-hour periods (numbered 1-3) during each graph. The distribution of pressures over the 24-hour control period is shown by the three curves displaced to the right of the control curve. It is clear that in the intact dog the shift of the distribution curves occurred gradually; with each succeeding 8-hour period, the curve was displaced slightly more to the right. In contrast, the distribution of arterial blood pressure for the denervated dog exhibited an immediate rightward shift during the first 8 hours of salt loading; blood pressure was maintained at this elevated level during the succeeding two 8-hour periods.

This figure also demonstrates why it was necessary to perform continuous data collection and employ the analytical procedures that were used. Specifically, the control arterial blood pressures of the denervated dog were distributed between 45 and 150 mm Hg. Since the plateau level of mean arterial blood pressure during the hypertensive phase averaged 155 mm Hg in this dog with pressures distributed between 90 and 180 mm Hg, it would have been very difficult to quantify accurately the degree of change if only a few intermittent pressure measurements had been made. Such measurements could have fallen anywhere on the broad distribution curve of mean arterial blood pressure.

Average Changes in Mean Arterial Blood Pressure during Salt Loading.—Figure 3 summarizes the average changes in mean arterial blood pressure (plotted hourly) that occurred during 6 saline infusions in six intact dogs and 16 infusions in ten baroreceptor-denervated dogs. Four significant features can be seen in these summary graphs. (1) Both groups had similar control values: the intact dogs averaged $112 \pm 4.1$ mm Hg, and the denervated dogs averaged $110 \pm 4.3$ mm Hg. (2) Both groups reached nearly the same average plateau level of elevated arterial blood pressure: the intact dogs averaged $142 \pm 4.8$ mm Hg, and the denervated dogs averaged $142 \pm 8.7$ mm Hg. (3) Although in both groups of dogs arterial blood pressure rose to its plateau level by the end of the first day, the denervated dogs showed a much more rapid onset of hypertension. (4) Arterial blood pressure returned to nearly normal in both groups over a period of 24 hours after cessation of the saline infusion. Thus, the principal difference between the two groups was the rate of onset of hypertension. The transient onset and offset phases of the arterial blood pressure responses can be seen better in Figures 4 and 5.

On-Transients of Arterial Blood Pressure during Salt Loading.—In Figure 4, an expanded time scale is used to plot the average mean arterial blood pressure data seen in Figure 3 so that the transient responses during the first day of saline infusion can be seen. Intact dogs required nearly 24 hours to reach a plateau level of arterial blood pressure. In contrast, denervated dogs reached a pressure plateau in an average of 8 hours after the start of saline infusion. The average time difference required to

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reach two-thirds of the plateau value was significantly different \((P < 0.001)\) between the two groups of dogs (5 vs. 15 hours). In dogs with intact baroreceptors, the time period for the full development of hypertension was three times as long as that in denervated dogs.

**Off-Transients of Arterial Blood Pressure at the End of Salt Loading.**—Figure 5 plots on an expanded time scale the average mean arterial blood pressure off-transient responses seen in Figure 3. The time required to return to control levels was nearly 24 hours in both groups. The only observable difference between the groups was an immediate abrupt fall of about 15 mm Hg in the denervated group during the first hour after the infusion was stopped. Thus, except during the very initial stages, the baroreceptors appear to have only a slight influence on the normalization of arterial blood pressure when the saline infusion is ended.

**Average Changes in Heart Rate.**—The average changes in heart rate for intact and denervated dogs are summarized in Figure 6. Three features are immediately evident. (1) The average heart rate of the intact dogs during the control period was lower \((80 \pm 6 \text{ beats/min})\) than that of the denervated dogs \((100 \pm 15 \text{ beats/min})\). (2) There was no consistent change in heart rate in either group of dogs during the period of salt loading. (3) There was a slight increase in the average heart rate of the intact dogs during the 24 hours following the end of saline infusion, but no changes were observed in the denervated group.

**Average Changes in Cardiac Output and Total Peripheral Resistance.**—Continuous recording of cardiac output was carried out in two intact dogs for periods lasting nearly 100 hours after the start of saline infusion and in five denervated dogs (three of which yielded reliable results for 48 hours and two others which lasted 120 hours after the start of saline infusion). The mean cardiac output data were digitized by the fiber-optic curve scanner to nearly 5,000 points/hour recording time; from these points the computer calculated the hourly averages and statistics. As has been previously described in detail in an earlier publication \((10)\), the computer was programed to correct for any base-line shift of the aortic flowmeter recording system. These procedures permitted precise analysis of continuously collected data and evaluation of the transient responses of cardiac output and total peripheral resistance during the development of hypertension.

Both intact and denervated dogs exhibited cardiac output oscillations during the first day of salt loading. Since these oscillations occurred at slightly different times in different dogs, they were nearly obscured when the data were averaged at identical time intervals. Therefore, the cardiac output data of each dog were recalculated and averaged.
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expressed in terms of the percent change from the maximum hourly cardiac output value obtained during the first 24 hours of infusion. The average time required for the intact group to reach a maximum hourly cardiac output elevation was 18 hours compared with 7.4 hours for the denervated group. The times of the peak cardiac outputs were superimposed, and the remainder of the hourly data (before and following this peak value) was plotted around this point in time. These average percent changes in cardiac output and the accompanying arterial blood pressures and total peripheral resistances for the two groups are shown in Figure 7.

Certain qualitative similarities are apparent between the intact and the denervated dogs. In both groups, long-term steady-state hypertension was initially associated with a rise in cardiac output, and total peripheral resistance played an increasingly important role in maintaining hypertension.
After several days, cardiac output tended toward normal in both groups. Despite these general similarities, there were significant quantitative differences in the transient responses of intact and denervated dogs. First, total peripheral resistance of intact dogs fell below control levels during the entire first day of saline infusion. At its lowest point, reached during the eighteenth hour of infusion, resistance averaged 25% below the control value. At this time the cardiac output was elevated 40%, the maximum increase for the entire experimental period. In contrast, denervated dogs exhibited increased resistance during the first day of infusion which was characterized by two early oscillations occurring at about 7-hour intervals. The cardiac output of denervated dogs rose rapidly to a maximum value, 26% above control, by the seventh hour of infusion. It then decreased to within less than 10% of the control value over the next 5 hours before rising once again to a maximum level by the twentieth hour of infusion. These oscillations of cardiac output were significantly different from zero (P < 0.05) (defined as the maximum cardiac output change). The changes in arterial blood pressure in these subgroups in which cardiac output was recorded corresponded to those obtained in the larger groups of intact and denervated dogs as seen in Figure 3. These data indicate that the baroreceptors dampen the oscillations as well as attenuate the development of hypertension.

Fluid Volume Balance Studies.—The difference between the 24-hour fluid volume intake and the urine volume (net fluid volume balance) was measured in five intact and five denervated dogs; each dog served as its own control. Both the intact and the denervated dogs were in a state of positive fluid balance during the first 24 hours of salt loading (averaging 77 ± 8 ml/kg 24 hours−1 of fluid retention) (P < 0.05). By the second day, both groups of dogs appeared to be nearly in a state of fluid balance, although the inherent difficulties in the collection of these fluid volumes would not distinguish small changes. Throughout the period of salt loading both intact and denervated dogs averaged a fluid intake of five times normal (187 compared with 37 ml/kg 24 hours−1), but during the first 24 hours of saline infusion the urinary excretion averaged only four times normal (97 compared with 24 ml/kg 24 hours−1), accounting for the initial fluid retention. When the saline infusion was stopped, a significant negative fluid balance (P < 0.05) occurred in both groups of dogs over the first 24-hour period, after which time balance was again achieved.

Denervated dogs showed a great tendency toward generalized peripheral edema. For example, one extraordinary denervated dog initially weighing 40 kg gained nearly 10 kg during 5 days of saline infusion. Another denervated dog (not included in the data) died during the third day of infusion from pulmonary edema. Denervation of the thoracic aortic arch baroreceptors may have resulted in significant denervation of cardiac sympathetic fibers in these particular dogs. In contrast, only slight or no edema was observed in the intact dogs during the experimental period.

Blood Volume and Hematocrit.—Blood volumes (Fig. 8) were determined before infusion and during the third to fifth day of saline infusion. Intact dogs averaged 80.6 ± 10.7 ml/kg during the control period and significantly increased to 112.1 ± 13.3
ml/kg during saline infusion ($P < 0.05$ by paired variance analysis). The denervated dogs averaged 75.9 ± 7.4 ml/kg during the control period and expanded to 92.4 ± 6.2 ml/kg during salt loading ($P < 0.05$). The rise in blood volume in the two groups did not differ statistically ($P > 0.05$).

Hematocrits averaged 31 ± 0.01% during the control period in both intact and denervated dogs and were not significantly changed (33% and 32%, respectively) during saline infusion.

Serum Sodium and Potassium, Plasma Renin Activity, and Blood Urea Nitrogen.—Serum sodium content (Fig. 8) of intact dogs determined between the third and fifth day of saline infusion was increased from an average control value of 145.5 ± 0.83 to 151.7 ± 4.8 mEq/liter ($P > 0.1$). Serum sodium concentration in denervated dogs averaged 142.1 ± 1.2 mEq/liter during control periods and rose to 147.8 ± 3.2 mEq/liter ($P < 0.05$).

Serum potassium concentration (Fig. 8) of intact dogs averaged 4.34 ± 0.07 mEq/liter during the control period and 4.33 ± 0.2 mEq/liter during the third to fifth day of infusion ($P > 0.2$). Denervated dogs, however, showed a significant decrease in serum potassium concentration during the saline infusion from 4.43 to 4.14 mEq/liter ($P < 0.05$).

The average control plasma renin activity (Fig. 8) of intact dogs was 1.04 ± 0.05 ng Al/ml hour$^{-1}$; it was 1.43 ± 0.45 ng Al/ml hour$^{-1}$ in the denervated dogs. Arterial renin activity in both groups was significantly depressed ($P < 0.05$) during saline infusion to a level that was below the sensitivity of the radioimmunoassay procedure. It remained depressed for 2 days after the saline infusion had been stopped and averaged 0.42 ± 0.08 ng Al/ml hour$^{-1}$ in seven dogs tested 24 hours ($N = 4$) and 48 hours ($N = 3$) after the saline infusion had been terminated.

Blood urea nitrogen (Fig. 8) averaged 26 ± 6.4 mg/100 in the intact dogs and 50.6 ± 7.4 mg/100 ml in the denervated dogs during the control period ($P < 0.05$). By the third to fifth day of saline infusion, both intact and denervated dogs showed a significant decrease to 15 ± 3.3 and 35 ± 7.0 mg/100 ml, respectively ($P < 0.05$).

Discussion

Hypertension was produced by the combined effects of increased salt and water intake and a reduced ability of the kidneys to excrete salt and water. Intact dogs with reduced renal mass were treated identically to denervated dogs so that the difference in the rate of transition from normotension to hypertension was presumed to be solely attributable to the baroreceptor reflex mechanism. Three significant points clearly emerged from this study. (1) There was no significant difference between the average 24-hour control mean arterial blood pressures of the intact and denervated groups. (2) Baroreceptor reflex activity slowed the rate of development of hypertension by a factor of nearly three. (3) By the twenty-fourth hour of saline infusion, both groups had reached the same steady-state level of mean arterial blood pressure. The degree of hypertension obtained after the first day of infusion was not influenced by the presence or the absence of the baroreceptor reflexes. Similar conclusions were reached from data obtained in our laboratory from comparative studies between intact and denervated dogs during the development of Goldblatt hypertension (3). These data lend support to the concept that the baroreceptor reflexes are important for moment-to-moment, rapid stabilization of arterial blood pressure but are not essential in determining the long-term mean level of arterial blood pressure, which is set by other mechanisms (8, 13).

Mechanism of Baroreceptor Action on Hemodynamic Transients during the First 24 Hours of Salt Loading.—Use of a continuous method for recording and analyzing the circulatory transients in the presence and the absence of baroreceptor reflexes has provided a greater insight into the early sequence of events leading to the development of the fixed state of hypertension. Based on the present studies and others, the probable sequence of hemodynamic events during salt loading is as follows: First, the fivefold increase in salt and water intake initially exceeds the excretory ability of the kidneys, resulting in fluid expansion of both the extracellular space and the blood volume by about 23% and 27%, respectively (see Results; 5, 14). Blood volume expansion results in the elevation of mean systemic filling pressure; this change is to some extent compensated for by stress relaxation of the vessel walls (14, 15). Cardiac output is thereby increased, resulting in the elevation of arterial blood pressure (see Results; 5, 6, 14). The rise in arterial blood pressure increases vascular wall stress and stimulates baroreceptor activity (1, 16, 17).

The present study indicates that reflex activity alters the course of the developing hypertension principally by acting on the peripheral vasculature. This effect was clearly demonstrated by the 22% decrease in total peripheral resistance by the eighteenth hour of infusion. This peripheral vasodilatation most certainly contributes to slowing the rate of rise of the arterial blood pressure. Although

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cardiac output was monitored continuously in only two control dogs, similar hemodynamic changes during salt loading of intact control dogs have previously been reported from our laboratory (6). Recently, Manning(14) determined the daily cardiac output using dye-dilution techniques during 12 saline infusion experiments identical to the present study.

The decreased vascular resistance observed in the intact dogs during the onset of the hypertension could theoretically have resulted from active reflex dilatation of the arterioles, passive distention of the vessels caused by increasing arterial blood pressure, or both. The first of these mechanisms, the reflex arteriolar vasodilatation, is probably the one most involved, since in the absence of the reflex there was actually an increase in peripheral resistance during the first day of saline infusion, despite the increasing pressure.

The peripheral vasculature is probably also altered by a change in vascular capacity as well as arteriolar resistance (18). Changes in sympathetic nerve activity initiated by the baroreceptor reflexes have been shown to alter the mean systemic filling pressure, a value which is determined mostly by changes in venous capacity (14, 19, 20).

Maintenance of Steady-State Levels of Hypertension.—Both intact and denervated dogs attained similar levels of arterial blood pressure which were associated with an initially large increase in cardiac output by the second day of saline infusion. After the second day of infusion, the total peripheral resistance played a progressively more important role in the maintenance of hypertension in both intact and denervated dogs. The volume expansion which occurred mainly during the first 24 hours of infusion continued to maintain elevated levels of cardiac output but, nevertheless, to a progressively lesser extent (Fig. 7). This study implies that the increased peripheral resistance was a secondary result of the excess cardiac output which elicited an autoregulatory effect. The phenomenon of autoregulation, although poorly understood, has been shown by others to occur in a situation of overperfusion of blood to the peripheral tissues in various types of hypertension (4, 21-23).

Renal diuresis was already considerably increased by the end of the first day of saline infusion, probably as a result of the elevated level of arterial blood pressure (24) and perhaps aided by a reflex suppression of antidiuretic hormone (25, 26), by depressed circulating levels of renin, and by slightly depressed levels of aldosterone (14). These renal adjustments permitted the dogs to remain in a state of normal fluid balance throughout the remainder of the experiment despite the infusion of saline.

Resetting of the Sinoaortic Baroreceptors.—Interpretation of the present experiments was based largely on the assumption that the phenomenon of resetting of the baroreceptors occurs. There is general agreement that a shift in the operational set point of the baroreceptor reflex occurs in various types of hypertension. Studies indicate that when the arterial walls are subjected to a prolonged elevation of arterial blood pressure the initially increased afferent nerve activity from the baroreceptor zones gradually subsides back to a normal level (2, 27-31).

The present experiments were not designed to study the mechanisms involved in resetting, but the results do provide insight into some important aspects of this phenomenon which should be emphasized. First, it appears that a gradual resetting mechanism was indeed responsible for the more gradual rise in arterial blood pressure observed in intact dogs relative to that in the baroreceptor-denervated dogs. Second, resetting in these experiments appeared to occur very rapidly, within a 24-hour period. Third, if the phenomenon of resetting is to be explained by physical alterations in the vascular wall receptor areas, as has been suggested by some investigators (29, 31), these changes must occur quickly and be capable of rapid reversal, as shown by the return of arterial blood pressure to normal within 24 hours after the infusion was stopped.

Finally, it should be emphasized that the time differential in the attainment of a steady-state level of hypertension between intact and denervated dogs cannot be attributed solely to the time constant for baroreceptor resetting. It is rather a complex nonlinear relationship involving both the adaptive process and the rate of application of the forcing function, specifically the rate of salt loading. It is perhaps for this reason that arterial blood pressure returned to normal in a period of 24 hours after the saline infusion was stopped in both intact and denervated dogs. In addition, reversal of the resetting process may occur faster than the initial resetting (32).

Effects of Baroreceptors on Heart Rate.—Heart rate was not changed to any great extent in either the intact or the denervated dogs during the onset transients of the hypertension. This result was of course expected in the denervated dogs. Intact dogs, however, have been reported to exhibit a reflex bradycardia at the onset of salt-loading
hypertension (6). The failure to observe bradycardia in intact dogs might be explained by the slightly greater rate of fluid volume infusion used in the present studies. The resulting elevations of right atrial pressure could have elicited a Bainbridge reflex which would tend to increase the heart rate, counterbalancing the slowing effects of the baroreceptor stimuli (33, 34).

Effect of Baroreceptor Denervation on Control Level Arterial Blood Pressure: Evidence of Denervation.—During the past several years in which we have used the method of continuous collection and data analysis of hemodynamic variables in baroreceptor-denervated dogs, it has been apparent that the previously reported elevation of arterial blood pressure levels for such dogs has been greatly exaggerated. In a previous publication, we have reported that denervated dog preparations are very susceptible to transient elevations of arterial blood pressure during even very mild perturbations (10).

However, the results demonstrate that the most characteristic feature of these dogs is the variability of pressure rather than a significant elevation of the basal level of mean arterial blood pressure. From 24-hour frequency distribution analysis of the hemodynamic variables used to quantify the mean level and the variability of pressure, it can be concluded that the average 24-hour mean value is nearly normal. This initial study (10), the present experiments, and studies on a different group of intact and denervated dogs used to investigate Goldblatt hypertension have all yielded results that show no significant difference between the mean 24-hour control arterial blood pressures of intact and denervated dogs prior to the initiation of hypertension.

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