Interaction of Vasopressin and the Baroreceptor Reflex System in the Regulation of Arterial Blood Pressure in the Dog

By Allen W. Cowley, Jr., Emil Monos, and Arthur C. Guyton

ABSTRACT

The hemodynamic effects of 1-hour intravenous infusions of vasopressin were evaluated in trained, unanesthetized dogs in the normal state and following sinoaortic baroreceptor denervation. Pressor sensitivity to vasopressin was greatly enhanced following baroreceptor denervation; threshold sensitivity was increased 11-fold and sensitivity at higher dose levels was increased 60-100-fold. Infusion of physiological levels of vasopressin caused an average increase in arterial blood pressure of 33 mm Hg in conscious, baroreceptor-denervated dogs compared with an increase of 5 mm Hg in normal dogs. In contrast, similar intravenous infusions of norepinephrine at physiological levels resulted in a 3-fold increase in pressor sensitivity with no change in threshold dose. Hypophysectomy of baroreceptor-denervated dogs did not significantly alter their pressor sensitivity to vasopressin in the conscious state. The arterial blood pressure response to intravenous vasopressin infusions was greatly depressed when a high background level of circulating vasopressin was present. Decapitated, spinal, anesthetized dogs maintained with a small continuous infusion of norepinephrine exhibited the greatest sensitivity to vasopressin; the threshold dose for a pressor response was similar to that in conscious baroreceptor-denervated dogs, but pressor sensitivity at physiological dose levels was increased nearly 8,000-fold. The elevations in arterial blood pressure resulting from vasopressin infusions of less than 1.0 munits/kg min⁻¹ were large enough to implicate the direct pressor effect of vasopressin in the normal control of arterial blood pressure.

KEY WORDS

dose-response curve  cardiac output  norepinephrine

diabetes insipidus  areflexic dog  continuous data collection

Contrary to generally held views, reports from several different laboratories have indicated that vasopressin participates in the normal daily regulation of arterial blood pressure. Szczepanska-Sadowska (1, 2) has recently reported that, following a mild nonhypotensive hemorrhage in normal conscious dogs, the elevation in plasma vasopressin is sufficient to be significant in the maintenance of arterial blood pressure and blood volume. Also, the increased plasma vasopressin concentrations observed during hypovolemia and mild water deprivation exceed those producing antidiuresis (3, 4). If these plasma levels of vasopressin have significant vasoactive properties, then the hypothalamic-hypophyseal antidiuretic system could function as a moderately rapid-acting mechanism for maintaining a normal level of arterial blood pressure. Support for this hypothesis is found in the results of Rocha E Silva and Rosenberg (5), who have shown that the amount of vasopressin secreted in response to mild hemorrhage in anesthetized dogs is sufficient to cause a pressor response when the reflex feedback control loops of the baroreceptor system are eliminated. Monos et al. (6) have observed that normal subpressor infusions of vasopressin result in an increase in arterial blood pressure following hypophysectomy; this observation suggests that endogenous vasopressin normally influences vascular tone. Further support for this idea comes from the report that dogs with diabetes insipidus are more susceptible than normal dogs to low arterial blood pressure following hemorrhage (7). It has also been shown that the pressor sensitivity to vasopressin can be greatly enhanced under certain conditions. For example, the pressor responses to catecholamines are potentiated by infusions of physiological concentrations of vasopressin (7), and persons with primary autonomc insufficiency exhibit marked pressor responses to vasopressin infusions within the normal physiological range (8).
The purpose of the present experiment was to examine the potential role of vasopressin in the regulation of arterial blood pressure, perhaps even under normal conditions. The experiments differed from those previously conducted in several important aspects. First, trained, unanesthetized dogs with chronically implanted arterial and venous catheters were used. In all previous studies except one (1), the pressor effects of vasopressin were evaluated in anesthetized animals, but anesthesia alters both the reflex responses to pressor agents and the plasma concentrations of vasopressin (9) and the plasma concentrations of vasopressin (10). Second, new techniques were used to precisely quantify the variable arterial blood pressures which occur in unanesthetized, baroreceptor-denervated dogs. Thus, the pressor effects of small doses of vasopressin were observed in the absence of the baroreceptor reflexes and without the depressant effects of anesthesia. Third, vasopressin responses were quantified for the first time in resting, unanesthetized, hypophysectomized, baroreceptor-denervated dogs. Fourth, vasopressin was administered to decapitated, areflexic dogs so that direct pressor effects could be studied without any interactions with the central nervous system or any endogenous release of vasopressin. Finally, a wide dose range of vasopressin was tested to generate a complete dose-response curve characterizing each type of dog preparation.

These experiments indicated that vasopressin, infused so as to approximate physiological secretion rates, could significantly affect systemic resistance vessels and, under certain conditions, contribute to both short- and long-term regulation of arterial blood pressure.

Methods

CHRONIC EXPERIMENTS

The hemodynamic effects of intravenously infused vasopressin (0.05–100.0 munits/kg min⁻¹) were evaluated in 11 trained, unanesthetized dogs. Over a period of 1 year these dogs were evaluated in several different physiological states.

Normal, Unanesthetized Dogs.—At least 2 weeks prior to the experiment, catheters were chronically implanted in the femoral artery and vein of 11 dogs, tunneled subcutaneously to the back for protection, and kept patent by filling with 1,000 USP units of heparin solution. Seven of the dogs were studied without anesthesia to compare the hemodynamic effects of vasopressin infusions with those of norepinephrine infusions. Three of the dogs were used to compare the hemodynamic effects of Parke-Davis Pitressin (a mixture of lysine and arginine vasopressin) with those of pure synthetic arginine vasopressin,¹ the naturally occurring neurohypophyseal vasopressin produced by dogs.

Unanesthetized, Sinoaortic Baroreceptor-Denervated Dogs.—In six of the dogs, the sinoaortic baroreceptors were successfully denervated; the details of the surgery have been previously described (11). Several weeks after denervation, similar vasopressin and norepinephrine infusion studies were repeated in the unanesthetized dogs. Electromagnetic flow transducers (Biotronex 5000 series) had been placed on the ascending aortas of two of these dogs before the time of baroreceptor denervation for determination of cardiac output.

Unanesthetized, Hypophysectomized, Sinoaortic Baroreceptor-Denervated Dogs.—Three of the original 11 normal dogs were successfully subjected to baroreceptor denervation and hypophysectomy. The pituitary gland was approached transphyryngeally, and the dura was opened at the midline for the removal of the entire hypophysis as has been previously described (6). These dogs were then chronically maintained with intramuscular injections of adrenocortiotrophic hormone three times weekly. Within 48 hours after the surgery, the effects of vasopressin (Pitressin) infusions were studied in these dogs in the unanesthetized state. At this time all 3 dogs showed the classic signs of diabetes insipidus.

EXPERIMENTAL PROTOCOL AND ANALYSIS OF DATA

The experimental protocol consisted of a 1-hour control period of continuous collection of hemodynamic data followed by a 1-hour period of drug infusion. When the pressure had returned to control levels, control data were collected for another 1-hour period and then another randomly selected dose of drug was infused. At least five different doses of vasopressin and norepinephrine were studied in each dog. The dogs were assumed to be normally hydrated, since drinking water was freely available before and throughout the experimental procedures.

The dogs were fitted with a backpack housing a Statham P23DC pressure transducer at heart level. The infusion tubes and wires from the pressure and flow transducers were protected, brought out of the top of the pen housing the dog, and connected to a Grass model 7 recorder. Since the arterial blood pressure of the baroreceptor-denervated dogs is extremely labile and greatly influenced by surroundings, as is the endogenous secretion of vasopressin, the experiments were performed in a quiet, isolated room with no one present except to start and stop the infusion pump. The dogs were put in a large pen in which they had a high degree of freedom of movement. Heart rates were monitored using a Grass model 7P44A tachograph triggered from the first derivative of the arterial pulse wave. Cardiac outputs were obtained using a Biotronex model BL-610 blood flowmeter.

The data collection and analysis system has been described recently in detail (11). This system permitted arterial blood pressures, heart rates, and cardiac outputs recorded on polygraph records to be converted to

¹Supplied by Dr. Roderich Walter, Mount Sinai School of Medicine, New York.

Circulation Research, Vol. XXXIV, April 1974
electrical signals for computer analysis. A four-channel analog curve-reading system with fiber optic scanning sensors generated analog voltages from the recorded ink traces. The analog voltages in turn were fed into an analog-to-digital converter that changed them to digital signals for analysis by a PDP-9 computer. The information was used by the computer to calculate average hourly arterial blood pressure, heart rate, cardiac output, and standard statistical information. Such procedures enabled the frequency of occurrence of different mean arterial blood pressures to be tabulated by the computer (Fig. 1). Nearly 1,800 sample points for each variable were stored for each hour of recorded time. This procedure permitted very accurate measurement of all recorded hemodynamic data. Moreover, the method allowed the variable pressures of baroreceptor-denervated dogs to be presented by graphing frequency distribution curves throughout the desired period of experimentation.

ACUTE EXPERIMENTS

Dogs used for acute studies were anesthetized with a short-acting barbiturate (Suratal, 30 mg/kg); a rachectomy was performed and catheters were placed in the femoral artery and vein. A 12-ml spinal injection of 80% ethanol was then administered followed by a rapid decapitation procedure requiring less than 12 seconds. These dogs were then maintained with positive-pressure ventilation, and arterial blood pressure was stabilized at 100 mm Hg by infusing norepinephrine at a constant rate between 0.01 and 0.1 µg/kg min⁻¹. The details of this preparation have been described previously (12).

One hour after decapitation, when arterial blood pressure had been stabilized at 100 ± 5 mm Hg for 15 minutes, a vasopressin-pressure dose-response curve was obtained by infusing vasopressin intravenously at randomly selected rates between 0.05 and 100 munits/kg min⁻¹. In these acute studies, each rate of infusion was maintained for 10 minutes, which was sufficient to establish the plateau of the pressure response. Following each infusion, pressure was permitted to return to control values; within 10 minutes after the infusion, pressure was generally within ±5 mm Hg of control, indicating a stable preparation.

Results

Typical Response to Low Rates of Vasopressin Infusion before and after Baroreceptor Denervation.—The results of 1 hour of vasopressin infusion at 1.6 munits/kg min⁻¹ in an unanesthetized dog before and after sinoaortic baroreceptor denervation are illustrated in Figure 1; the frequency distribution curves for mean arterial blood pressure before and during infusions are shown. In the normal state, the infusion of vasopressin did not have a significant effect on arterial blood pressure (P > 0.5). Following denervation of the sinoaortic baroreceptors, however, the same dose of vasopressin resulted in an average pressure rise of 32 mm Hg during the 1-hour period. This rise is clearly demonstrated by the shift in the pressure-frequency distribution curve.

![Figure 1](http://circres.ahajournals.org/)[1024x1024]

**Figure 1**

Frequency of occurrence of different mean arterial blood pressures for 1 hour before and 1 hour during intravenous vasopressin infusions (1.6 munits/kg min⁻¹) in a single unanesthetized normal dog before (left) and several weeks after (right) sinoaortic baroreceptor denervation.
All infusions in baroreceptor-denervated dogs and in most of the normal dogs were analyzed in this manner, and a statistical comparison was made between each control period and its corresponding infusion period (Student's t-test). Since each distribution period contained 1,800 sample data points, the technique permitted fine discrimination between the results during control and infusion periods, even with the randomly fluctuating pressure of baroreceptor-denervated dogs.

**Average Arterial Blood Pressure Responses to Vasopressin in Normal, Baroreceptor-Denervated, and Decapitated Dogs.**—Figure 2 illustrates three dose-response curves comparing the increases in arterial blood pressure during 1-hour vasopressin infusions in normal dogs, baroreceptor-denervated dogs, and decapitated, areflexic dogs. Responses were obtained from 34 vasopressin infusions in seven normal dogs, 27 infusions in six baroreceptor-denervated dogs, and 32 infusions in five decapitated dogs. Comparison of the respective regression equations shows that the unanesthetized, baroreceptor-denervated dogs were considerably more sensitive to vasopressin than were the normal dogs. The regression equation for normal dogs was $Y = 12.8 \log X + 7.6$ with a coefficient of correlation ($r$) $= 0.75$; for baroreceptor-denervated dogs it was $Y = 23.0 \log X + 29.9$, $r = 0.64$. There was an 11-fold difference in threshold sensitivity between the two groups. Pressor sensitivity was 60-100-fold higher in the baroreceptor-denervated dogs at higher dose levels, which is apparent from the significant difference between the slopes of the regression equations ($P < 0.01$). For example, the regression equations show that vasopressin infused at 0.42 munits/kg min$^{-1}$ in a baroreceptor-denervated dog will result in a 25-mm Hg rise in arterial pressure, although 30.0 munits/kg min$^{-1}$ is required to obtain the same response in normal dogs; thus, 70-fold sensitivity difference exists.

The average arterial blood pressure elevation in baroreceptor-denervated dogs at infusion rates between 0.2 and 2.0 munits/kg min$^{-1}$ was +33 mm Hg. This dose range was examined specifically, since it represents secretion rates which are observed in number of different physiological conditions. In comparison, Figure 2 shows that normal dogs generally responded with less than a 5.0-mm Hg rise in mean blood pressure at this dose range.

Decapitated, spinal, anesthetized dogs exhibited the greatest sensitivity to vasopressin infusions, as illustrated by the steep regression line in Figure 2 ($Y = 51.7 \log X + 64.5$, $r = 0.94$). Although the threshold dose was similar to that for baroreceptor-denervated dogs, the dose of vasopressin required to achieve a 25-mm Hg pressure rise in the normal dogs was 188-fold greater than in the decapitated preparation. To achieve a 50-mm Hg arterial blood pressure rise, 8,000 times more vasopressin was required in a normal dog than was needed in an areflexic dog.

The average mean arterial blood pressure during the control periods in the normal dogs infused with vasopressin was $110.5 \pm 5.7$ (SE) mm Hg, in the baroreceptor-denervated dogs it was $105.0 \pm 6.0$ mm Hg, and in the decapitated dogs was $100.2 \pm 0.2$ mm Hg. Each point plotted above zero on the Y axis in these regression equations was statistically different ($P < 0.05$) from its own control value according to the total sampled points used in the calculation of the frequency distribution curves for the control and infusion periods (Student's t-test).

The transient responses of arterial blood pressure at the beginning of a vasopressin infusion were nearly the same in all three preparations; the plateau of the pressure response was reached within 4-8 minutes. The transient pressure responses at the end of the infusions were quite variable in both the normal and the baroreceptor-denervated dog return of arterial blood pressure to control level.
took from 10 minutes to 2 hours. However, in
decapitated dogs the pressures consistently re-
turned to control levels in an average of about 10
minutes.

Heart Rate Responses to Vasopressin.—In
normal dogs heart rate generally decreased at
progressively higher levels of vasopressin
\( Y = -13.2 \log X - 8.7, \ r = 0.45 \), but in barorecep-
tor-denervated dogs heart rate was not affected in
any consistent manner by the increasing infusion
rates \( \ r = 0.001 \), as shown in Figure 3. A similar
lack of correlation between the dose of infused
vasopressin and heart rate occurred in decapitated
dogs. In normal intact dogs the progressive
decrease in heart rate was associated with a rise in
mean arterial blood pressure and yielded a correla-
tion coefficient of \( r = -0.7 \). When baroreceptors
were removed, the correlation between arterial
blood pressure and heart rate was very low
\( r = +0.15 \). The average control heart rate in nor-
mal dogs was 90.4 ± 5.9 (SE) beats/min, and it was
102.4 ± 3.1 beats/min in baroreceptor-denervated
dogs.

Cardiac Output Responses to Vasopressin.—
Cardiac output responses to vasopressin were
determined in two dogs before and after denerva-
tion. Four dose levels of vasopressin between 1.0
and 20 munits/kg min\(^{-1}\) were tested in each dog.
There was a consistent decrease in cardiac output
in both the normal and the baroreceptor-denerv-
ated dogs ranging between 5.0% at low infusion
rates (less than 2.0 munits/kg min\(^{-1}\)) and 30.0% at
higher infusion rates (greater than 10 munits/kg
min\(^{-1}\)). The responses were too variable to detect
any statistically significant difference between the
normal and the baroreceptor-denervated dogs.

Arterial Blood Pressure Responses to
Vasopressin Infusions in Baroreceptor-Denervated
Dogs Compared with Those in Hypophysectomized,
Baroreceptor-Denervated Dogs.—The
changes in mean arterial blood pressure during 15
infusions in three hypophysectomized, baroreceptor-
denervated dogs are indicated by the circled
crosses on the dose-response diagram in Figure 4.
The open circles are the same responses obtained
in the six baroreceptor-denervated dogs consi-
dered in Figure 2. There was little difference be-
tween the results obtained in the two groups of

Circulation Research, Vol. XXXIV, April 1974
dogs, although the regression equation for the baroreceptor-denervated dogs was slightly lower when it was recalculated to include the hypophysectomized dogs (upper solid line, Fig. 4 [\( Y = 26.8\log X + 28.1, r = 0.73 \)]). Thus, hypophysectomy resulted in little change in the response of baroreceptor-denervated dogs to vasopressin.

**Depression of Vasopressin Sensitivity by Prior Intramuscular Vasopressin Injections.**—Twenty days after hypophysectomy and baroreceptor denervation, three dogs were given an intramuscular injection of 10 units of vasopressin (Pitressin); 30 minutes was allowed for absorption into the circulatory system. Then a 30-minute control record was obtained followed by a 1-hour infusion of vasopressin in doses ranging from 0.5 to 15.0 munits/kg min\(^{-1}\). The effects of vasopressin preinjection are summarized in Figure 5. For rapid visual comparison, the results from the normal, baroreceptor-denervated, and decapitated dogs are also summarized in this figure by grouping them into the different indicated dose ranges. The last two columns in each dose range are the results from the unanesthetized, hypophysectomized, baroreceptor-denervated dogs (\( N = 3 \)) and the vasopressin-preinjected dogs (\( N = 3 \)). ADH = antidiuretic hormone.

**Sensitivity to Pitressin Compared with That to Pure Synthetic Arginine Vasopressin.**—The arterial blood pressure response to intravenous infusion of Pitressin was compared with that to pure synthetic arginine vasopressin in three normal dogs and in two hypophysectomized, baroreceptor-denervated dogs for 2 days following surgery. The results from 12 infusions of arginine vasopressin were compared with those from 12 identical infusions of Pitressin ranging between 0.4 and 5.0 munits/kg min\(^{-1}\). A paired variance statistical analysis for the same infusion rate in each individual dog established no statistical difference between the pressure changes resulting from the two drugs (\( P > 0.2 \)).

**Hemodynamic Responses to Norepinephrine in Normal and Baroreceptor-Denervated Dogs.**—Norepinephrine was infused to determine whether the increased sensitivity to vasopressin observed in baroreceptor-denervated dogs was a specific or a nonspecific response. Figure 6 compares the mean arterial blood pressure changes resulting from 19 norepinephrine infusions in five unanesthetized, normal dogs with those resulting from 20 infusions in five unanesthetized, baroreceptor-denervated dogs. This regression analysis shows that the sensitivity difference to norepinephrine between the normal and the baroreceptor-denervated dogs was considerably less than that to vasopressin. In nor-
Discussion

The physiological importance of the pressor activity of vasopressin has remained an unanswered question in the mind of many investigators. It has been generally concluded that the concentrations of circulating vasopressin required to produce a significant pressor response are rarely achieved under physiological conditions (13). Reexamination of the earlier studies on which this conclusion is based shows that the pressor effects were studied primarily in acute experiments using animals anesthetized with sodium pentobarbital—a situation in which both central nervous system reflexes and vascular reactivity are altered (9). Furthermore, it is well known now that the stress of surgery, as well as the effects of anesthesia, can increase the concentration of endogenous vasopressin (10). Since the vasopressin-pressure dose-response relationship is an exponential function (Fig. 2), many of the previous investigators probably determined pressor activity when the animals were already close to the plateau level of the dose-response curve because of endogenous vasopressin. For this reason, very large doses of vasopressin appeared to have no pressor effect (14, 15), but cardiac depressant effects were commonly observed, possibly due to constriction of the coronary vasculature. However, a few recent reports by other investigators, as well as the present study, indicate that the pressor activity of normally released vasopressin is greater than was previously suspected. In particular, Szczepanska-Sadowska (1, 2), using a femoral artery puncture technique for measurements in conscious dogs, concluded that vasopressin could be important in normal pressure regulation, and even in his experiments the dogs were subjected to abnormal stress which perhaps elevated endogenous vasopressin release.

Some of the major problems of previous studies were overcome in the present experiment in which the arterial blood pressure responses were quantified in totally undisturbed, conscious, normally hydrated dogs. The results in these dogs showed that vasopressin infusions at very low doses could result in mild pressor responses. But, even more important, greatly enhanced pressor responses were observed when the sinoaortic baroreceptors were removed and the sensitivity to vasopressin was tested in the same undisturbed conscious state. And, finally, when all central nervous system influences were removed by decapitating the dogs, which also completely eliminated the endogenous source of vasopressin secretion, the pressor
responses to physiological doses of vasopressin were dramatic. These findings are of particular interest, since they imply that the direct pressor effects of vasopressin could be of considerable physiological significance for three reasons.

First, the plasma levels of vasopressin in the present experiments were still within the physiological range when the infusion rates were less than 2.0 munits/kg min\(^{-1}\). As seen in Figures 2, 4, and 5, infusion rates in this range induced significant pressor responses in both baroreceptor-denervated and decapitated dogs. Tagawa et al. (16) have shown that under normal steady-state conditions the plasma concentration of vasopressin can be estimated from the rate of infusion. They infused vasopressin into dogs at rates of 0.5, 1.0, and 2.0 munits/min and reported increases in vasopressin concentrations of 1.0, 1.2, and 4.0 munits/ml plasma, respectively, from an average control level of 1.2 munits/ml, as measured by bioassay procedures. These results are very close to those that can be calculated using the reported 4-5-minute half-life of vasopressin and a volume distribution equal to 10% of body weight (17). For example, an infusion of 2.0 munits/min into a 20-kg dog would result in a calculated vasopressin plasma elevation of 4.0 munits/ml, the same rise that was found by Tagawa et al. (16) by their bioassay procedures. Similarly, infusion of 0.1–2.0 munits/kg min\(^{-1}\) (2.0–40.0 munits/min in a 20-kg dog), as was done in our unanesthetized dogs (Fig. 2), should have resulted in calculated plasma elevations of 4.0–80.0 munits/ml plasma. These infusion levels are the same as those that resulted in arterial blood pressure elevations of 10–35 mm Hg (Fig. 2) in baroreceptor-denervated dogs and 15–70 mm Hg in decapitated dogs, even though normal dogs showed less than a 5-mm Hg pressure elevation at this dose range. This dose range of vasopressin should yield the same plasma vasopressin concentrations that have been demonstrated to occur during mild surgical stress, 24-hour water deprivation, and nonhypotensive hemorrhage. For example, Bonjour and Malvin (10) have reported that normally hydrated, conscious dogs have a vasopressin concentration of 0.9 munits/ml plasma which is elevated to 1.7 munits/ml after 24 hours of water deprivation, 3.9 munits/ml during minor surgery, and 34.5 munits/ml during major surgery. In another study, mild hypotension induced by sodium pentobarbital anesthesia (decrease in diastolic pressure ranging from 21 to 30 mm Hg) produced an average fourfold increase in the concentration of vasopressin in blood (5). Also, a nonhypotensive 15% decrease in total blood volume elevated plasma vasopressin levels from an average of about 1.5 munits/ml to nearly 20 munits/ml within 50 minutes after hemorrhage (1). Maximum renal concentrating power has been reported to be obtained at intravenous vasopressin infusion rates of 0.004 munits/kg min\(^{-1}\) (18). It, therefore, appears that many of the lower doses infused in the present study were within physiological secretion ranges; yet, these doses caused large elevations of arterial blood pressure in both baroreceptor-denervated dogs and decapitated dogs.

Second, vasopressin could serve as another efferent limb of both the low-pressure atrial stretch receptors and the high-pressure baroreceptors for short term control of arterial blood pressure. Distention of the left atrium has been shown to inhibit vasopressin release (19), although enhanced release in response to decreasing atrial pressures remains to be clearly demonstrated. Similarly, both chemoreceptors and carotid sinus baroreceptors can significantly influence vasopressin secretion (20, 21). In the event of decreased circulating blood volume, the afferent limb of these reflex arcs would stimulate both increased peripheral sympathetic activity and increased release of vasopressin. Since the present experiment demonstrated that vasopressin has considerable pressor activity in the absence of the baroreceptors, its simultaneous release could contribute to an enhanced pressor response. Furthermore, it has been reported that the pressor effect of circulating norepinephrine can be considerably enhanced by vasopressin (7).

Third, adaptation of the baroreceptors has been shown to occur when the vascular system is subjected to prolonged stress such as Goldblatt hypertension (22, 23). The acute pressure responses obtained in the unanesthetized, baroreceptor-denervated dogs should thus represent the pressor response obtainable with prolonged elevations of plasma vasopressin, provided that other mechanisms such as alteration of thirst by the central nervous system and fluid volume regulation by the kidneys do not override the pressor responses.

**Possible Reasons for Enhanced Sensitivity.**—The reasons for the enhanced sensitivity to vasopressin are not entirely clear from the results of this experiment. Certainly some of the increased pressor sensitivity resulted from loss of reflex compensation by the baroreceptors. However, merely opening the reflex feedback loop should produce an in-
crease in sensitivity only as great as that caused by the norepinephrine infusions in baroreceptor-denervated dogs (Fig. 6) or that caused by angiotensin (24). Since the change in pressor responsiveness at similar doses of norepinephrine following baroreceptor denervation was less than a seventh of that obtained with vasopressin following baroreceptor denervation (at physiological doses), it appears that less than 15% of the enhanced sensitivity to vasopressin can be accounted for by the specific lack of reflex compensation.

Circulating plasma levels of vasopressin appear to determine, to some extent, the pressor sensitivity to infused vasopressin (Figs. 2 and 5). Chronically baroreceptor-denervated dogs may have depressed levels of plasma vasopressin; indeed, this possibility is supported by the observation that only slight differences in pressor sensitivity occur between baroreceptor-denervated dogs and hypophysectomized, baroreceptor-denervated dogs.

Another mechanism possibly contributing to enhanced sensitivity could be the interaction of catecholamines with infused vasopressin. This mechanism would have been of special significance in the decapitated, areflexic dogs, since their arterial blood pressure was maintained by constant intravenous infusion of norepinephrine, which probably resulted in somewhat elevated levels of circulating catecholamines. Therefore, the tremendous additional sensitivity to vasopressin in decapitated dogs compared with that in both normal and baroreceptor-denervated, unanesthetized dogs could have resulted from the reported potentiation of the pressor effect of norepinephrine by vasopressin (7).

**Significance of the Study.**—The elevations of arterial blood pressure which resulted from vasopressin infusions of less than 1.0 munits/kg min⁻¹ were of sufficient magnitude to suggest that the direct pressor effect of vasopressin must be considered to be yet another mechanism which can significantly contribute to the control of arterial blood pressure. The release of vasopressin in response to afferent signals from various receptor sites such as atrial stretch receptors and baroreceptors could serve as another efferent limb in the reflex control of arterial blood pressure. The rapidly acting pressor effects of vasopressin seen in the present study along with the possible potentiation of the pressor activity of the catecholamines indicate that this system deserves further study and additional quantification to determine the relative importance of these mechanisms in the overall daily regulation of arterial blood pressure.

**References**

Interaction of Vasopressin and the Baroreceptor Reflex System in the Regulation of Arterial Blood Pressure in the Dog

ALLEN W. COWLEY, Jr., EMIL MONOS and ARTHUR C. GUYTON

Circ Res. 1974;34:505-514
doi: 10.1161/01.RES.34.4.505

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/34/4/505

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/