Evidence and Quantification of the Vasopressin Arterial Pressure Control System in the Dog

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SUMMARY We determined quantitatively the importance of vasopressin (AVP) release in the regulation of arterial pressure during hemorrhagic hypotension in dogs. The recovery of arterial pressure after rapid hemorrhage was studied in 10 dogs with spinal cord destruction below the level of C-1 to remove efferent sympathetic nerve activity. Bilateral nephrectomy was used to remove the renin-angiotensin system. Results for this group were compared to those for another group of dogs in which the entire central nervous system, including the pituitary gland, were removed surgically. In all groups, arterial pressure was lowered rapidly from an average control value of 106 ± 2 (mean ± SE) to 51 ± 1 mm Hg by hemorrhage. In dogs with spinal cord destruction and bilateral nephrectomy, arterial pressure rose from 51 mm Hg to 89 ± 3 mm Hg in 3 minutes and stabilized at that level over the next 30 minutes, representing a 71% compensation of arterial pressure. Left atrial pressure fell from 3.3 to 0.8 mm Hg during hemorrhage and subsequently rose only 12% during the hemorrhage. Plasma AVP rose during hemorrhage from 19 ± 2 to 75 ± 10 μU/ml. Injection of the competitive AVP inhibitors, [1-deaminopenicillamine, 4-valine]-8-D-arginine-vasopressin (dPVDAVP), completely reversed the effects and returned the compensated pressure to 50 mm Hg. In the complete absence of the central nervous system, arterial pressure compensation averaged only 10 ± 3%. Plasma osmolality, sodium and potassium concentrations, hematocrit, and heart rate were unchanged in all experimental groups. The relationships involved in the AVP-arterial pressure control system were determined quantitatively and analyzed. A systems analysis using experimentally determined values for AVP secretion and metabolism, plasma AVP, and changes in arterial pressure closely predicted the changes observed during hemorrhage. It appears from this study that AVP has potent systemic vasoconstrictor actions enabling it to make a significant contribution in the restoration of arterial pressure during hemorrhage.


Nearly 84 years have elapsed since Oliver and Schäfer (1895) first described a vasoactive substance from posterior pituitary extracts later called vasopressin. Since that time, it has become clear that the primary function of vasopressin is to alter the permeability of the terminal portions of the renal tubule to water and urea. The vasoactive properties of this peptide on the other hand generally have been disregarded, since it appeared that an increase in arterial pressure could be elicited only by using pharmacological amounts.

Numerous investigators, however, have observed that vasopressin is released in amounts exceeding those producing maximum antidiuresis during both hypotensive and nonhypotensive hemorrhage and have suggested that the vasoconstrictor activity of this peptide might be sufficient to influence arterial pressure (Ginsburg and Heller, 1953; Weinstein et al., 1960; Rocha e Silva and Rosenberg, 1969; Cowley et al., 1974; Szczepanski-Sadowska, 1972; Arnauld et al., 1977; Pullan et al., 1978). Similar increases in plasma vasopressin have been observed during minor surgery and stress (Rocha e Silva and Rosenberg, 1969; Szczepanski-Sadowska, 1972). It also has been demonstrated that, in the absence of the opposing sino-aortic baroreceptor reflexes, physiological amounts of infused vasopressin could influence arterial pressure significantly both in the anesthetized (Rocha e Silva and Rosenberg, 1969) and conscious dog (Cowley et al., 1974). Despite these suggestions that vasopressin could participate in the control of arterial pressure, the quantitative importance of the mechanism has remained unclear.

The present study therefore was designed not only to measure the changes in plasma vasopressin during hemorrhage but, more importantly, to quantify the capability of these changes to compensate for a decrease in arterial pressure. To quantify the actions of only vasopressin release on arterial pressure, all of the other rapid-acting pressure control systems were abolished. The efferent sympathetic nervous system was eliminated by injecting alcohol and procaine retrograde in the spinal canal to the level of C-1, but not beyond. The renin-angiotensin system was eliminated by bilateral nephrectomy. The degree of pressure compensation (feedback...
Hemorrhage Experiments

In dogs that released vasopressin was compared to the compensation observed in decapitated dogs incapable of releasing vasopressin and to dogs in which the effect of vasopressin was blocked using the competitive peptide inhibitor [1-deamino-penicillamine,4-valine]-8-D-arginine-vasopressin (dPVDAVP). Plasma vasopressin concentration was measured using a radioimmunoassay procedure that is described elsewhere (Cowley and Switzer, 1978).

The data indicate that vasopressin released in hemorrhage can function as a rapid and potent system to normalize arterial pressure.

Methods

Hemorrhage Experiments

Thirty mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv), and catheters were placed bilaterally into the femoral arteries for arterial pressure measurement and rapid withdrawal of blood for the hemorrhage procedure. Femoral vein catheters were used for all intravenous infusions. A saline drip (2 ml/min) was started immediately after catheterization and continued for 90 minutes to minimize vasopressin secretion. One of three procedures then was followed.

Procedure No. 1—Coagulation of Spinal Cord and Nephrectomy

In 10 dogs, the spinal cord was exposed in the area of the foramen magnum using an electrical cautering unit to minimize bleeding. This enabled opening of a drainage hole for the spinal fluid at C-1. A spinal needle then was inserted at L-3 and 10 ml of ethanol (80%) and 5 ml of procaine were injected retrograde up the spinal canal with the head elevated, and a suction apparatus was applied to the opening at the foramen magnum to prevent further ascent of the irreversible neural coagulation into the medullary regions. Neural afferent responses through the 9th and 10th cranial nerves were thereby left intact, so neural activity from cardiopulmonary and arterial pressure stretch receptors could initiate reflex release of vasopressin from the neurohypophysis. Artificial ventilation with a Harvard respirator (model 613) was begun immediately after alcohol destruction of the spinal cord. A slow infusion of norepinephrine with a Sage syringe pump (model 355) (0-0.6 µg/kg per min) was used to stabilize arterial pressure close to 100 mm Hg prior to and throughout the experimental manipulations. A bilateral nephrectomy then was performed using retroperitoneal flank incisions, after which the saline drip was discontinued. After a 90- to 120-minute stabilization period, the hemorrhagic experimental protocol was started.

Four dogs in this group had undergone thoracic surgery 2 weeks prior to the study for implantation of indwelling left atrial catheters which were inserted through the left atrial appendage, tunneled subcutaneously to the intrascapular region, and filled with a solution containing 1000 USP units of heparin.

Procedure No. 2—Coagulation of Spinal Cord, Cervical Transection, and Nephrectomy

Another eight dogs were treated in a manner identical to that just described but, in addition to the spinal injection of ethanol-procaine, a complete transection of the spinal cord was made at the level of C-1. Although total removal of efferent sympathetic activity was assured by this additional maneuver, these preparations were not as stable hemodynamically as those with spinal coagulation alone because of greater associated blood losses. All spinal cords were examined later to determine completeness of transection.

Procedure No. 3—Decapitation and Nephrectomy

Nine dogs were anesthetized lightly with sodium thiopental (30 mg/kg, iv) (Pentothal, Abbott) and then received a spinal injection of ethanol to coagulate the spinal cord and lower brain stem (no opening was made in the foramen magnum). Artificial ventilation was initiated together with infusion of norepinephrine (0-0.5 µg/kg per min) to maintain arterial pressure at 100 mm Hg. A hydraulic clamp then was closed rapidly (6 seconds) to compress the neck so that the head could be removed cephalad to the fixed clamp without loss of blood. This procedure, described previously (Cowley et al., 1971), ensured the complete absence of the central nervous system and any centrally released humoral factors. The preparation provided a hemodynamically stable preparation for periods exceeding 12 hours. An interval of 30-50 minutes generally was required after decapitation to stabilize arterial pressure at 100 mm Hg with a constant level of norepinephrine. After this period, these preparations were characteristically very stable and required no alterations in the amount of infused norepinephrine throughout the experimental procedure. Hemorrhage was performed 50-90 minutes after decapitation. In two of these dogs, left atrial catheters had been implanted previously as described above.

Experimental Protocol

After the appropriate postsurgical stabilization period, 5 ml of blood were removed for plasma analysis of sodium and potassium concentration, osmolality, vasopressin concentration, and hematocrit. Arterial pressure then was lowered to 50 mm Hg by the rapid withdrawal (60-70 seconds) of blood into several large heparinized syringes. Arterial pressure was monitored continuously for the next 30 minutes, at which time 5 ml of blood again were removed for analysis. Immediately after blood
sampling, the hemorrhaged blood was rein infused over a period of 2 minutes, and arterial pressure was monitored until it had returned to within ±5 mm Hg of the initial control value. Experiments in which pressure did not return to within this range were not included in the present analysis, except for those dogs with complete spinal transection for which a ±10 mm Hg limit was accepted. A blood sample was then taken again 30 minutes after infusion of blood.

In four spinal anesthetized, nephrectomized dogs, prepared as described in procedure 1, the synthetic vasopressin inhibitor dPVDAVP (Manning et al., 1977) was injected intravenously 15 minutes after hemorrhage to determine the extent to which pressure would return to its precompensated level.

**Calculation of Open-Loop Gain**

The open-loop gain (G_o) of the vasopressin pressure control system was calculated using linear control theory as follows: G_o = G_c / (1 - G_c), where G_c is the closed-loop gain and is equivalent to the fractional compensation (the amount of the pressure increase during the hypovolemic period divided by the decrease in arterial pressure caused by hemorrhage) (Milhorn, 1966).

**Relationship between Arginine Vasopressin (AVP) Secretion, Plasma AVP, and Arterial Pressure**

Intravenous infusions of AVP (USP Posterior Pituitary Reference Standard) at rates from 2.5 to 100 μU/kg per min were administered to two stabilized decapitated dogs (procedure 3) to determine the relationship between AVP secretion and plasma AVP concentration. Sixty-minute infusion periods were used except at doses that raised arterial pressure to over 180 mm Hg, where the infusion period was shortened to 20 minutes. In the complete absence of endogenous vasopressin secretion, the rate of infused vasopressin could be equated to secretion, and the relationships between measured plasma AVP and the accompanying changes in arterial pressure could be determined. Arterial pressure was recorded, and a sample was withdrawn for AVP analysis near the end of each infusion period.

**Vasopressin Half-Life Determination**

The biological half-life of circulating vasopressin was determined in three dogs by sequential sampling and measurement of plasma vasopressin concentration after decapitation. Blood samples were taken immediately before the 6-second decapitation procedure and at intervals of 5, 10, 15, 20, 30, 45, and 60 minutes.

**Radioimmunoassay of Vasopressin**

Plasma AVP was determined using a specific and highly sensitive radioimmunoassay procedure developed in our laboratory (Cowley and Switzer, 1978). Minimum sensitivity of the assay with 1-ml plasma samples ranged from 0.1 to 0.2 μU/ml depending on the freshness of the 125I-AVP. Intraassay coefficient of variation averaged ±4.0% over the range of standards used. Interassay variation determined from the confidence limits of the least squares fit curvilinear regression analysis of 12 plasma standard curves ranged from ±3 to ±7% over the range of standards used (0.1-20 μU). In the present study, all samples were analyzed in triplicate at two different dilutions which ranged from 1:1 to 1:24.

Blood samples were collected in Na₂ EDTA vacuum tubes (Becton-Dickinson), and plasma was stored at −20°C until the time of assay. Storage in this form resulted in no detectable loss of immunoreactive vasopressin over a period of 6 months as determined by a frozen plasma pool analyzed bimonthly, which exhibited no tendency toward change in either direction and averaged 5.5 ± 0.2 μU/ml over 10 analyses.

Plasma osmolalities were determined with a model 3R osmometer (Advanced Instruments, Inc.) and plasma electrolytes by flame photometry (Instrumentation Laboratory, IL 343). Arterial pressure was monitored with a Grass Instruments (model 7D) recorder.

All values presented are expressed as mean ± SE. Student’s t-test was used to determine statistical significance which was considered to be P < 0.05.

**Results**

**Arterial Pressure Compensation with Hemorrhage in Spinal-Areflexic-Nephrectomized Dogs**

Figure 1 is an experimental tracing illustrating a representative arterial pressure response following hemorrhage in a spinal-areflexic-nephrectomized dog. Arterial pressure was lowered from 108 to 50 mm Hg by the rapid withdrawal of 250 ml of blood (14 ml/kg) in 1 minute. The recovery of arterial pressure was rapid, and pressure returned to 90 mm Hg by the 3rd minute after completion of the hemorrhage. Pressure then settled gradually to a stable level of 85 mm Hg and remained there over the next 30 minutes. Left atrial pressure decreased from 4.0 to 0.0 mm Hg and recovered only to 1.0 mm Hg throughout the 30-minute hypovolemic period. Heart rate decreased from 82 to 74 beats/min in this dog which was not a constant finding. Upon replacement of blood, arterial pressure and left atrial pressure rose by 30 and 5 mm Hg, respectively, above their control values and gradually returned to control over the ensuing 40 minutes.

The average results from 10 dogs bled of 14 ml/kg body weight (239 ± 29 ml blood for 16.9 ± 0.7 kg) are shown in Figure 2. Five major features were observed. First, the steady state fractional compensation of arterial pressure after hemorrhage aver-
-aged 71 ± 3%. Control arterial pressure averaged 105 ± 2 mm Hg, decreased to a minimum of 50 ± 0.9 mm Hg with hemorrhage, and averaged 89 ± 3 mm Hg during the compensated steady state period. The 71% compensation of arterial pressure greatly exceeded left atrial pressure compensation, which returned only 12% toward control levels throughout the period of hypovolemia. The average control left atrial pressure was 3.3 ± 1.2 mm Hg, which decreased to 0.8 ± 1.7 mm Hg with hemorrhage and recovered to 1.1 ± 1.0 mm Hg during the period of hypovolemia (n = 3). Second, an average interval of 3 minutes was required to achieve the maximum pressure compensation after final withdrawal of blood. Third, arterial pressure compensation was associated with a significant rise of plasma vasopressin from 19 ± 2 μU/ml to 75 ± 9 μU/ml as determined 25 minutes after hemorrhage. Fourth, after replacement of blood, arterial pressure rose to 135 ± 10 mm Hg, and left atrial pressure rose to 6.5 ± 2.0 mm Hg. All measured variables returned nearly to control levels in 60 minutes. Fifth, heart rate was not significantly changed during the hemorrhagic period and averaged 80 beats/min during the control and 81 beats/min during the period of hemorrhage.

Figure 1  Experimental tracing of the results of a hemorrhage performed in a spinal-areflexic-nephrectomized dog showing the compensatory changes in mean arterial pressure, left atrial pressure, and heart rate.

Figure 2  The average results of hemorrhage (14 ± 4 ml/kg) in spinal-areflexic-nephrectomized dogs (n = 10). The steady state fractional compensation of arterial pressure averaged 71 ± 3% and was associated with a 5-fold increase of plasma vasopressin concentration.
Hemorrhage of Spinal-Areflexic-Nephrectomized Cord-Transsected Dogs

Hemorrhage of eight dogs, in which the spinal cord was severed completely in addition to the spinal injection of alcohol-procaine, produced results qualitatively and quantitatively similar to those just described. This group averaged a 70 ± 5% steady state fractional compensation at the end of the 30-minute hypovolemic period. Plasma vasopressin was increased from a control of 15.5 ± 4.8 µU/ml to an average of 65.8 ± 10 µU/ml at the end of the hypovolemic period. These experiments were performed to provide assurance that efferent sympathetic nerve activity was abolished totally. The additional surgery associated with the complete cord transection sometimes resulted in spinal bleeding that was difficult to manage. Therefore, arterial pressure was less stable in these dogs, and a return of pressure to within ± 10 mm Hg of control values after replacement of the withdrawn blood was accepted for averaging in this group.

Hemorrhage of Decapitated-Nephrectomized Dogs

Figure 3 illustrates that arterial pressure compensation after hemorrhage was nearly abolished in areflexic dogs incapable of releasing any humoral substances from the central nervous system and in which renin release was prevented by nephrectomy. Arterial pressure was lowered to 50 mm Hg by rapid withdrawal of blood, 7 ml/kg body weight (122 ± 16 ml blood per 17.6 ± 1.0 kg). The average compensation of arterial pressure under these circumstances determined in nine dogs was 10 ± 3%. Left atrial pressure averaged 2.7 ± 0.6 during control, decreased to 1.0 ± 0.9 with hemorrhage, and was compensated to a similar extent (16%), as was observed in the dogs capable of releasing vasopressin. Heart rate was unchanged. No overshoot of either arterial or left atrial pressure was observed with replacement of blood. Plasma vasopressin concentrations were not significantly changed during the 30-minute period of hypotension, averaging 5.1 ±
1.0 μU/ml 50–90 minutes after decapitation and prior to hemorrhage, and 3.0 ± 0.8 μU/ml 15 minutes after hemorrhage.

Figure 4 contrasts the response of arterial pressure to hemorrhage of dogs capable of releasing vasopressin to that of decapitated dogs.

Vasopressin Blockade during Hemorrhage

Figure 5 summarizes the effects on arterial pressure of injecting the vasopressin inhibitor dPVDAVP at a time when arterial pressure had reached a compensated level of 88 mm Hg following hemorrhage. Injection of 5 ml of the 0.02 M sodium phosphate dilution buffer ("carrier") had no significant effect on arterial pressure. The bolus intravenous injection of the analog inhibitor resulted in an abrupt fall of arterial pressure to precompensated hemorrhagic pressure levels (40–50 mm Hg) within 1 minute after injection (n = 4 dogs).

The average dose of the blocker used in these studies was 60 μg/kg with similar effects observed with doses ranging from 32 to 98 μg/kg. The only difference that was noted between these doses was a more rapid fall of arterial pressure with the higher doses (1 minute vs. 2 minutes). This dose was sufficient to block the 30–40 mm Hg rise of pressure associated with a bolus injection of 100 μU vasopressin.

With replacement of blood, arterial pressure returned to 90 mm Hg with no overshoot and remained at that level for the next 30 minutes. A second hemorrhage at 90 minutes after replacement of blood resulted in less than a 2% fractional compensation of arterial pressure, whereas second hemorrhages at this time generally resulted in nearly a 50% compensation of pressure in the absence of blockade.

Open-Loop Gain of the Vasopressin Pressure Control System

The average calculated open-loop feedback gain was −2.5 ± 0.4 in dogs that released vasopressin and −0.3 ± 0.1 for decapitated and/or pharmacologically blocked dogs. It can be demonstrated using principals of linear control theory that, when two linear systems operate simultaneously on the same parameter, the gain for the system is equal to the sum of the gains of each of the systems. The portion of the gain which therefore may be attributed solely to vasopressin release was −2.2 as determined by the difference between the two preparations. This indicates that vasopressin per se was responsible for at least a 70% compensation of arterial pressure.

Plasma Osmolality, Electrolytes, and Hematocrit

No significant changes were observed in plasma osmolality or serum sodium or potassium concentration, which averaged 300 ± 7.7 mOsmol/kg, 143.1 ± 0.5 mEq/liter, and 3.8 ± 0.2 mEq/liter before hemorrhage and 298 ± 7.3 mOsmol/kg, 142.8 ± 0.5 mEq/liter, and 3.7 ± 0.2 mEq/liter at the end of the 30-minute hypovolemic period. Also, no significant change in hematocrit was observed, which averaged 40% prior to and after hemorrhage.

Influence of Norepinephrine Infusion Rate on Arterial Pressure Compensation

A wide range of norepinephrine infusion rates were required to maintain the control of arterial pressure close to 100 mm Hg after spinal anesthesia (0–600 ng/kg per min). A significant correlation was not observed (r = 0.193, P = 0.5) between the norepinephrine infusion rate and fractional compensation of arterial pressure.

Relationship between AVP Secretion, Plasma AVP, and Arterial Pressure

Figure 6 (top) shows the changes in plasma AVP associated with 1-hour intravenous infusions of the USP Posterior Pituitary Reference Standard. Two separate samples at each infusion rate were determined in triplicate at two dilutions. The average of each triplicate analysis is represented by a single point on the graph. The AVP infusion rate can be equated to secretion rate since absence of the head precluded endogenous secretion or pituitary reuptake. The calculated line of best fit determined by standard regression analysis was log Y = 1.139 log X − 1.705, r = 0.964.

Figure 6 (center) summarizes the relationship obtained between AVP infusion ("secretion"), shown on the upper abscissa, and the change in mean arterial pressure. In addition to the two dogs used to determine the change in plasma AVP concentrations (unfilled circles), data from a previous study also were included (filled circles) in the regression analysis (Y = 54.9 log X − 99.8, r = 0.94), since similar results were obtained. The lower scale of the abscissa again relates AVP infusion rate to plasma AVP concentration. The total metabolic clearance determined by the quotient of the appro-

![Figure 5](https://i.imgur.com/5jZj.png)
priate infusion rate and the plasma concentration averaged 16 ml/kg per min.

Figure 6 (lower) shows the change in endogenous AVP measured after rapid decapitation. Vasopressin half-life calculated over the first 5 minutes in two individual dogs averaged 3.5 minutes. The half-life of circulating AVP determined from an analysis of regression over the first 30 minutes after decapitation yielded $T_1/2 = 6.5$ minutes ($\log Y = -0.037X + 1.66, r = -0.9$). The data also suggested a third and slower component with a half-life of 45 minutes ($\log Y = -0.007X + 0.48, r = -0.4$). The relationships between these data and the results of the hemorrhage experiments will be treated in the Discussion section.

**Discussion**

It is well known that release of vasopressin is enhanced greatly during hypovolemic states in both animals and man (Ginsburg and Heller, 1953; Weinstein et al., 1960; Rocha e Silva and Rosenberg, 1969; Szczepanski-Sadowska, 1973; Arnauld et al., 1977; Goetz et al., 1974). However, the physiological significance of vasopressin release under these conditions has remained unclear. It has been observed that plasma levels of vasopressin could rise as much as 10-fold above normal with hemorrhage, but even those changes were considered by many to be insufficient to achieve significant pressor activity. The present study measured the change of plasma vasopressin with hemorrhage and determined the relative potency of this pressure control system compared to other known rapid-acting systems, such as the sinoaortic baroreceptor reflexes and the renin-angiotensin system.

**Evidence in Support of a Vasopressin Pressure Control System.**

The results of the present study support the conclusion that the endogenous release of vasopressin during hemorrhage can serve as a potent and rapid-acting controller of arterial pressure. In the absence of all of the other known fast-acting pressure-regulating systems, lowering of arterial pressure to 50 mm Hg with hemorrhage resulted in a 5-fold increase of plasma vasopressin concentration. This was associated with a 71% compensation of arterial pressure. Reinfusion of blood after 30 minutes of hypotension, at a time when vasopressin was found to be elevated, resulted in a rise of arterial pressure to nearly 30 mm Hg above control, which then returned to normal levels commensurate with the fall of plasma vasopressin. Since only a 10% compensation of arterial pressure was observed in the absence of the head, it can be concluded that the circulating pressor agent was released from the brain. Blockade and reversal of the compensatory pressure response after hemorrhage by injection of the competitive antagonist to AVP.
confirmed the role of AVP in the control of arterial pressure. Total inhibition of the efferent sympathetic nervous system in the ethanol-injected spinal cords was confirmed when similar results were obtained during hemorrhage with the cord completely transected at C-1. Total nephrectomy assured that no part of the compensatory response was a result of the renin-angiotensin system or a decrease in activity of a renal depressor system. The return of arterial pressure to ±5 mm Hg of control pressure attested to the hemodynamic stability of the preparation during the period of hypovolemia and infusion. Other data also lend support to the conclusion that endogenous release of AVP can participate in the control of arterial pressure. The dose-response relationship seen in Figure 6 illustrates that the minimum secretion rates of vasopressin which are associated with maximum concentration of the urine can cause as much as a 25 mm Hg rise of arterial pressure in the absence of the buffer reflexes. Vascular sensitivity of this magnitude has been observed previously in our laboratory (Cowley et al., 1974). Altura et al. (1977) have reported that, on a molar basis, vasopressin exerts a greater pressure activity than angiotensin when studied in isolated aortic and arteriolar vascular strips.

The influence of vasopressin on arterial pressure has also been demonstrated in hypertensive states. Möhring et al. (1977, 1978) used a vasopressin-specific antiserum to demonstrate significant pressor activity of this peptide, especially in the malignant phase of DOC-salt hypertension and malignant two-kidney Goldblatt hypertension in rats.

Relative Strength and Time Response of the Vasopressin System

Calculation of the open-loop feedback gain enables one to compare quantitatively the relative strengths of the various pressure control systems. The gain of the vasopressin control system determined from the fractional compensation of arterial pressure in the present study, and corrected for the fractional compensation of the passive system, averaged —2.2. This indicates that, within the range of pressures studied, the release of vasopressin can return a fall in pressure about 70% back toward prehemorrhage control levels. By comparison, the renin-angiotensin system and even the sinoaortic baroreceptor reflex system. The vasopressin system responds somewhat more slowly than the efferent sympathetic nervous system, which appears to exert its major actions in 20 seconds (Scher and Young, 1963), but considerably faster than the renin-angiotensin system, which requires at least 15 minutes to reach peak pressor activity (Cowley et al., 1971). It should be emphasized, however, that the results of the present study can be applied only to short-term pressure regulation and cannot be extrapolated to the chronic long-term state. The renal tubular interactions of this hormone, which influence significantly the status of the body fluid volumes and electrolytes, introduce an added dimension of complexity to the analysis of long-term arterial pressure regulation.

Simplified Analysis of Vasopressin Pressure Control System

Determination of the individual relationships between AVP secretion, plasma AVP concentration, and arterial pressure, as reported in this study, enabled a simplified quantitative analysis of the major aspects of the feedback pressure control system (Fig. 7). All calculations assume linearity of the system, which undoubtedly is an oversimplification, but nevertheless has provided a useful framework within which to view the operation of this control system. Although curvilinear relationships undoubtedly exist in the clearance of AVP, in the kinetics of distribution, and in the vascular effects of AVP, a nonlinear analysis was felt to exceed the limits of the present data. Using the changes in plasma AVP observed during hemorrhage, one can calculate the secretion rate that would be required to achieve those plasma concentrations by using the data from Figure 6. The relationship between arterial pressure and secretion rate (dAVP/dt) then can be represented as seen in block 1 of Figure 7 (Exp—solid upper line). Subtracted from the rate of secretion (the output of block 1) is the rate of AVP removal from the system, determined by multiplying the total amount of secreted AVP (the integrated secretion rate) by the measured rate constant (the reciprocal of the half-life, K = 0.143). Integration of the net rate of change of AVP yields the total amount in the system at any instant which is distributed into some undetermined volume. The volume into which AVP is distributed is calculated from the total amount of AVP and the experimentally observed plasma concentration. In the present study, this volume is estimated to be 1853 ml. Based on commonly reported values for dogs and the average 18-kg dog weight in the present study, this represents about
10% of the total body weight, or about 50% of an extracellular fluid space of 225 ml/kg, or 280% of a plasma volume of 38 ml/kg (Gamble and Robertson, 1952; Gaudino et al., 1948).

Arterial pressure is influenced by the plasma AVP concentration as indicated by the relationship in block 4. The changes of arterial pressure are added to the level of arterial pressure that initiated the release of AVP.

When used to simulate the results of the present study, this simplified model shows that a decrease in arterial pressure at block 5 from 100 to 50 mm Hg initiates an increase in AVP secretion in block 1 from 5,000 to 25,000 μU/min, which raises plasma AVP concentration to 95 μU/ml. This results in nearly a 32 mm Hg rise of arterial pressure seen in block 4, returning arterial pressure to 82 mm Hg. It is interesting that, if secretion rates in block 1 are used that represent those observed in conscious resting dogs (Normal—broken line), the resulting pressure compensation with hemorrhage is nearly the same. This is due to the exponential nature of the dose-response curve. Thus, an increase in plasma concentration from 1.9 to 9.5 μU/ml still results in nearly a 32 mm Hg rise of arterial pressure, the same degree of compensation. Despite the simplifications of this model, relatively accurate predictions of the behavior of this system in the regulation of arterial pressure are obtained.

Nature of Stimulus for Vasopressin Release and Hemodynamic Actions

The present study did not determine the precise nature of the stimulus for vasopressin release. Some of the known factors, however, can be eliminated. For instance, plasma osmolality or plasma sodium or potassium concentration did not change during the 30-minute period of hypovolemia. At the present time, it appears that the stimulus is probably reflex in origin, presumably initiated from cardio-pulmonary and/or arterial baroreceptors. As seen in Figures 1 and 2, it is clear that the arterial pressure is being regulated with vasopressin release, not the left atrial pressure, which exhibited less than 15% compensation throughout the period of hypovolemia. Further studies presently are being conducted to determine the location and the nature of the receptors initiating release of vasopressin during hemorrhage.

The mechanisms whereby vasopressin increased arterial blood pressure during hemorrhage were not determined in the present study. A number of investigators have reported that low rates of infused vasopressin constrict both veins and arterioles (Altura and Altura, 1977), especially in the splanchnic and skeletal muscle circulation (Heyndrick et al., 1976).

In summary, the present study confirms the idea that vasopressin release can function in the dog as a rapid and potent arterial pressure control system. The fractional compensation of 71% is in fact even greater than that found individually for the renin-angiotensin system or for the arterial baroreceptor reflex system. The removal of both of these systems, however, was required to unmask the effects of vasopressin. The mechanism of release and the associated hemodynamic changes remain to be determined as to the dynamic interactions with the other pressure control systems.

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