Systolic pressure predicts plasma vasopressin responses to hemorrhage and vena caval constriction in dogs

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Thresher, Terry N., and Lanny C. Keil. Systolic pressure predicts plasma vasopressin responses to hemorrhage and vena caval constriction in dogs. Am J Physiol Regulatory Integrative Comp Physiol 279: R1035–R1042, 2000.—We have proposed that the reflex increase in arginine vasopressin (AVP) secretion in response to hypovolemia is due to arterial baroreceptor unloading. If arterial pressure is the key to the mechanism, the slope relating plasma AVP to arterial pressure should be the same in response to hemorrhage, a model of true hypovolemia, and in response to thoracic inferior vena cava constriction (IVCC), a model of central hypovolemia. We tested this hypothesis in conscious, chronically instrumented dogs (n = 8). The mean coefficient of determination (r²) values obtained from the individual regressions of log AVP onto systolic pressure (SP) and mean arterial pressure (MAP) in response to hemorrhage were 0.953 ± 0.009 and 0.845 ± 0.047, respectively. Paired comparisons indicated a significant difference between the means (P < 0.05), hence, SP was used in subsequent analyses. The mean slopes relating the log of plasma AVP to SP in response to hemorrhage and IVCC were −0.034 ± 0.003 and −0.032 ± 0.002, respectively, and the means were not significantly different (P = 0.7). The slopes were not altered when the experiments were repeated during acute blockade of cardiac receptors by intrapericardial procaine. Finally, sinoaortic denervation (n = 4) markedly reduced the slope in both the hemorrhage and IVCC treatments. We conclude that baroreceptors monitoring arterial pressure provide the principal reflex control of AVP secretion in response to hypovolemia.

antidiuretic hormone; arterial baroreceptors; cardiac receptors; atrial receptors; ventricular receptors; blood volume; plasma AVP; blood pressure

INCREASED SECRETION of arginine vasopressin (AVP) is a homeostatic response to hypovolemia. Afferent signals from cardiac receptors and arterial baroreceptors both have been implicated in this response (16, 20). However, a number of recent studies have indicated the need to reevaluate the control of AVP secretion during hypovolemia. For example, we have observed that gradual constriction of the thoracic inferior vena cava (IVCC) sufficient to reduce left atrial pressure by up to 4 mmHg has no effect on either arterial pressure or plasma AVP (11). Greater constriction led to a fall in mean arterial pressure (MAP) and increases in both heart rate (HR) and plasma AVP. We have also reported that acute cardiac denervation (CD; by intrapericardial infusion of procaine) has no effect on basal plasma AVP or the increase in plasma AVP in response to either hemorrhage (10, 24) or hypotension caused by IVCC in conscious dogs (21). Shen et al. (17) also reported that cardiac denervation alone had no effect on the AVP response to hemorrhage in dogs. However, we (24) and Shen et al. (17) observed that sinoaortic denervation (SAD) significantly reduced the slope of the relationship between arterial pressure and plasma AVP during hemorrhage. These observations suggest that arterial baroreceptors and not cardiac receptors control the reflex increase in AVP secretion during hypovolemia in the dog.

Hemorrhage is a model of true extracellular hypovolemia. In contrast, IVCC is frequently referred to as a model of central hypovolemia because it unloads cardiac and arterial baroreceptors but does not result in a reduction in blood volume. Rather, blood is sequestered upstream from the constriction resulting in engorgement of the liver and splanchnic beds with underfilling of the heart and arterial tree. If the level of arterial baroreceptor firing is the critical factor controlling AVP secretion during hypovolemia, then the relationship between arterial pressure and plasma AVP should be the same in response to both maneuvers. It also follows that blocking signals from cardiac receptors should have no effect on these relationships. In contrast, if factors other than arterial baroreceptor firing affect AVP secretion differentially in response to hemorrhage and IVCC, one would predict differing relationships between arterial pressure and plasma AVP. Finally, if the hypothesis is correct, SAD should shift the arterial pressure-plasma AVP relationships similarly in both models of hypovolemia. The goal of this study was to test the hypothesis that the arterial pressure-plasma AVP relationship is correct, SAD should shift the arterial pressure-plasma AVP relationships similarly in both models of hypovolemia. The goal of this study was to test the hypothesis that the arterial pressure-plasma AVP relationship is correct, SAD should shift the arterial pressure-plasma AVP relationships similarly in both models of hypovolemia.
AVP relationships in response to hemorrhage and IVCC are similar within individual dogs.

**METHODS**

**General procedures.** Experiments were performed on 12 mongrel dogs of both sexes (7 male and 5 female) weighing between 19 and 25 kg. The dogs were housed in a room maintained at 21 ± 2 °C and 70% humidity with a 12:12-h light-dark cycle. Each day between 1600 and 1800 the dogs were administered oral prophylactic antibiotic treatment with sulfamethoxazole (800 mg) and trimethoprim (160 mg) and fed a mixture of dry chow and canned food sufficient to maintain a constant body weight. The food was consumed within 10 min of presentation, and sodium intake on this diet averaged 2–3 meq kg⁻¹ day⁻¹. Water was available ad libitum.

**Surgical procedures.** In all surgical procedures, the dogs were sedated with acepromazine maleate (0.2 mg/kg iv; Tech America, Elwood, KS) and anesthetized with pentobarbital sodium (25 mg/kg iv; Fort Dodge Laboratories, Fort Dodge, IA). The first procedure was a right thoracotomy (fourth interspace) to implant catheters in the right atrium and pericardial space. In eight dogs a Silastic cuff (Hazan Everett, Teaneck, NJ) was placed on the inferior vena cava in the same procedure. After the chest was closed, negative intrapleural pressure was established to completely reinflate the lungs. Additional Tygon catheters were introduced into a femoral artery and vein and advanced to the abdominal aorta and inferior vena cava, respectively. All catheters were tunneled subcutaneously to exit between the shoulder blades and were protected by placement in a pouch sewn to the underside of a nylon jacket (Alice King Chatham Medical Arts, Los Angeles, CA). During the 7-day postoperative period following each surgical procedure, the dogs were treated with enrofloxacin (2.5 mg/kg, Baytril, Mobay, Shawnee, KS) twice daily to provide antibacterial coverage and with oxyphrine (Numorphan, DuPont Pharmaceuticals) as required to provide analgesia. At least 2 wk were allowed for recovery.

Patency and sterility of the vascular catheters was maintained by filling them with a mixture of heparin (1,000 U/ml, Elkins-Sinn, Cherry Hill, NJ) and penicillin G potassium (20,000 U/ml, Eli Lilly, Indianapolis, IN), which was replaced a minimum of every 72 h. To ensure that the dogs were free of infection throughout all aspects of the study, rectal temperatures were taken on a weekly basis and on the morning before experiments. Rectal temperatures were always below 39°C, indicating that the dogs were free of infection throughout the study.

In some dogs (n = 4), additional surgical procedures under pentobarbital anesthesia were performed to denervate the aortic arch and the carotid sinus region. Briefly, the carotid sinus region was exposed via a ventral midline neck incision. The internal carotid arteries were ligated and cut together with all other vessels originating from the external carotid proximal to the lingual artery. The adventitia between the cranial thyroid artery and the lingual artery was stripped and painted with 5% phenol in ethanol bilaterally. At least 2 wk were allowed for recovery from this procedure. Finally, the dogs were anesthetized, and the aortic arch was exposed via a left thoracotomy at the fourth intercostal space. All visible nerves in the region of the arch were cut, and the adventitia of the descending aorta to the level of the second thoracic artery was stripped. In addition, the adventitia of the brachiocephalic and subclavian trunks was stripped to the level of the second bifurcation of each vessel. Finally, the vessels were painted with 5% phenol solution. The chest was then closed and negative pressure reestablished to ensure complete expansion of the lungs. Posturgical antibiotic and analgesic treatment were as described above. At least 3 wk were allowed for recovery.

**Experimental protocols.** Experiments were conducted between 0800 and 1300 in a quiet room with the dog in a sling (Alice King Chatham Medical Arts), which provided support but minimal restraint. The hemorrhage protocol required a total of 90 min. The first 20 min constituted a control period. Pericardial (PC) infusion of either saline or 2% procaine (Abbott Laboratories, North Chicago, IL) began at minute 21 at a rate of 1 ml/min for 10 min and was then reduced to 0.2 ml/min during the experiment. The hemorrhage was begun at 40 min, and blood was removed at a rate of 1 ml·kg⁻¹·min⁻¹. Blood samples (10 ml each) were collected at 10, 20, and 40 min and at 5 ml/kg intervals of hemorrhage. The control blood samples were replaced with equal volumes of saline, but blood collected during the hemorrhage was considered part of the hemorrhage volume. The blood samples were immediately aliquoted into chilled tubes containing heparin for measurement of plasma osmolality and AVP. The control and PC infusion intervals were identical in the IVCC experiments. The degree of vena caval cuff inflation was adjusted to reduce MAP below control in four or five steps of ~10 mmHg each. The steps lasted 10 min and a blood sample was collected at the end of each reduction in MAP. The experiments were conducted in a randomized order, and at least 4 days were allowed between experiments.

**Verification of cardiac nerve blockade and effectiveness of SAD.** Tests to determine the effectiveness of cardiac nerve blockade and completeness of SAD were performed at least 2 wk after surgical preparation and separated from the experimental protocols described above. Blockade of cardiac efferent nerves during PC infusion of procaine was tested by measuring HR responses to bolus administration of nitroglycerine (NG, 15 μg/kg, American Critical Care, McGaw Park, IL) and phenylephrine (PE, 5 μg/kg, Winthrop-Breon Laboratories, New York, NY) before and during acute CD. Cardiac afferent nerve blockade was tested by a bolus injection of veratridine (50 μg) into the right atrium before and during acute CD. Effectiveness of SAD was determined by measuring the HR responses to bolus injections of NG and PE. HR responses reported below are based on a 10-s sample corresponding to the peak of the change in MAP. In the intact condition, PE increased MAP 34 ± 3 mmHg and HR decreased 27 ± 2 beats/min, whereas NG decreased MAP 29 ± 3 mmHg and HR increased 56 ± 9 beats/min. During acute CD, PE increased MAP 50 ± 4 mmHg with no change in HR (−0.1 ± 0.1 beats/min) and NG decreased MAP 56 ± 7, again with no change in HR (−0.1 ± 0.1 beats/min). After SAD, PE increased MAP 49 ± 5 mmHg with no change in HR (0.4 ± 3.7 beats/min), and NG decreased MAP 50 ± 5 mmHg with no change in HR (1.2 ± 1.1 beats/min). HR fell 44 ± 5 beats/min in response to veratridine in the intact condition, did not change during CD (−0.2 ± 0.1), and fell 77 ± 15 beats/min after SAD.

**Methods of measurement.** Arterial and right atrial pressures (RAP) were measured using Cobe transducers and recorded on a Grass model 7d polygraph. The pressure transducers were adjusted to heart level for each dog. Each analog signal from the polygraph was sampled at 100 Hz and digitized using a Biopac Systems data-acquisition system (Biopac Systems, Santa Barbara, CA). The data were saved to disk for subsequent analysis. Note that the MAP referred to in RESULTS is equivalent to the average or electronically damped pressure signal and not to calculated MAP. Plasma
osmolality was determined by freezing-point depression (Advanced model 3W). Plasma AVP was determined by radioimmunoassay following extraction with bentonite (8, 18). Recovery of AVP averaged 70 ± 2%, and the values reported are not corrected for recovery. Synthetic AVP (357 U/mg) was used to prepare standards, and the minimum level of detectability was 0.3 pg AVP/ml. The intra- and interassay coefficients of variability were 9 and 12%, respectively.

Data analysis. Because of the exponential increase in plasma AVP during progressive hemorrhage, all analyses were performed on the logarithm of the plasma AVP values. The initial goal was to determine whether systolic pressure (SP), MAP, RAP, or a combination of these variables provided the best prediction of plasma AVP in responses to hypovolemia. We tried two approaches to answer this problem. First, we used multiple linear regression analysis (Sigma Stat 2.0, Jandel Scientific) to determine the significance of SP, MAP, and RAP as predictors of plasma AVP in the hemorrhage and IVCC protocols for each dog. Nonsignificant variables were eliminated from the equation in a stepwise manner according to the rules described by Zar (28). That is, variables were removed in the order of smallest absolute $t$ value first, and the analysis was repeated with two predictor variables, etc. The second approach was to perform simple linear regressions of plasma AVP onto each variable for each dog and compare the resultant coefficient of determination ($r^2$) using the Wilcoxon signed-rank test (28). The rational for this approach is that $r^2$ provides a quantitative estimate of the variability in plasma AVP that is accounted for by regression onto SP, MAP, and RAP. If the $r^2$ within each dog is consistently greater when AVP is regressed onto systolic SP compared with MAP or RAP, then it is logical that this signal is more closely linked to the mechanism stimulating AVP secretion. The results of both approaches indicated that SP was the best predictor of plasma AVP (see RESULTS). We then performed simple linear regressions of plasma AVP onto SP for the remaining treatment conditions (i.e., during acute CD and after SAD). Comparison of slopes between the hemorrhage and IVCC protocols utilized a two-way repeated measures analysis of variance (27). Differences were considered significant if $P < 0.05$.

RESULTS

The changes in SP, MAP, RAP, HR, and plasma AVP during a 30 ml/kg hemorrhage in a representative dog are shown in Fig. 1, left. Each cardiovascular data point represents a 60-s mean for the indicated variable. Hemorrhage of 15 ml/kg resulted in a fall in SP of 7 mmHg and RAP of 3.6 mmHg but no change in MAP. HR at this level of hemorrhage was clearly increasing, but plasma AVP was within 1 pg/ml of control. At 20 ml/kg of hemorrhage, MAP was still at control levels but SP had declined by 40 mmHg, RAP was 4.8 mmHg below control, and both HR and plasma AVP were increasing. At 23 ml/kg, SP, MAP, and HR all began a precipitous decline with little further change in RAP, and plasma AVP rose exponentially. Of the 12 dogs studied with both arterial and cardiac receptors functioning normally, one maintained MAP at control levels throughout the 30 ml/kg hemorrhage. However, SP fell by 16 mmHg during the hemorrhage while HR and plasma AVP increased by 55 beats/min and 7.5 pg/ml, respectively. The other 10 dogs followed the pattern shown in Fig. 1 except that the volume of blood loss required to trigger the sharp decline in MAP varied from 13 to 24 ml/kg.

The changes in cardiovascular variables and plasma AVP in response to IVCC in the same representative dog are shown in Fig. 1, right. Inspection of the two panels in Fig. 1 shows that the sequence of events differ markedly in the two protocols. That is, the initial period of IVCC forced a reduction in both SP and MAP by design, accompanied by a 3-mmHg fall in RAP and increases in both HR and plasma AVP. Subsequent periods of IVCC had little further effect on RAP, but graded decreases in SP and MAP were associated with graded increases in plasma AVP. The pattern of responses in the other dogs undergoing graded IVCC was similar.

![Fig. 1. Left: systolic pressure (SP, ●), mean arterial pressure (MAP, ○), heart rate (HR, ▲), right atrial pressure (RAP, ◆), and arginine vasopressin (AVP, △) responses to a progressive hemorrhage in a representative dog. The hemodynamic data points represent 1-min averages. Right: hemodynamic and AVP responses in the same dog in response to five-step increases in vena caval constriction (IVCC) experiment.](http://api.regu.physiology.org/)
Five-minute averages of SP, MAP, and RAP were selected as independent determinants of plasma AVP and subjected to stepwise multiple regression analysis. The choice to average over 5-min periods was largely arbitrary, because surprisingly, there was very little difference between the 5-min average and averaging over lesser periods of time. For example, simple regression of AVP onto the 5-min average of SP produced the highest mean $r^2$ for the group ($0.953 \pm 0.009, n = 12$). However, regression of AVP onto a 1-min average of SP at the time of the blood sample resulted in an $r^2 = 0.935 \pm 0.019$, or nearly the same mean obtained using the 5-min averages. Furthermore, averaging over intermediate time periods produced similar $r^2$ values. Because none of the averages between 1 and 5 min offered any clear advantage, we chose the 5-min average for two reasons: 1) it appeared to be the most conservative choice and 2) the rate of hemorrhage was 1 ml·kg$^{-1}$·min$^{-1}$; therefore, the 5-min averages represented the sum of all events preceding each blood sample.

Hemorrhage responses in nine dogs with functional atrial catheters (catheters failed in 3 dogs) were analyzed by stepwise regression analysis, and SP was a significant predictor of AVP in all nine dogs (i.e., MAP and RAP were removed from the regression one at a time because the contribution of these variables did not significantly improve the prediction). In one of nine dogs, both MAP and RAP also reached statistical significance and thus were not removed from the regression equation. The analysis was repeated using all 12 dogs based on SP and MAP as predictors, and SP was significant in the 12 dogs, and MAP was significant in 2 of 12 dogs. Thus this analysis indicates that including MAP as a variable improves the prediction in 2 of 12 dogs and RAP in only 1 of 9 dogs.

Applying the same stepwise approach to the AVP responses in the IVCC protocol in dogs with functional atrial catheters indicated that SP was significant in 5 of 5 dogs, RAP was significant in 1 of 5, and MAP was significant in none. In the total group of 8 dogs subjected to IVCC, SP was significant in those 8 dogs and MAP was significant in none. Thus, as was the case with hemorrhage, only SP consistently predicts the AVP response to graded IVCC.

The principal reason that MAP fails to improve the prediction for plasma AVP in the above analyses is most likely due to the fact that SP and MAP display a high degree of collinearity during either hemorrhage or IVCC. To get around this issue, we reanalyzed the data using simple linear regression to determine the relationships between plasma AVP and each of the predictor variables in both the hemorrhage and IVCC protocols. The individual $r^2$ values derived from each regression were averaged and are graphed in Fig. 2. The ratio below each column indicates the number of dogs in which the slope relating the predictor to plasma AVP reached statistical significance over the total number in the group. This approach indicates that in both the hemorrhage and IVCC protocols, the slope relating SP to plasma AVP was significant in all dogs examined. MAP used alone to predict AVP was significant in 11 of 12 dogs in the hemorrhage protocol and significant in 7 of 8 dogs in the IVCC protocol. The dog in which MAP did not reach statistical significance is the dog that maintained MAP at control levels throughout the hemorrhage. Finally, RAP used alone to predict AVP was significant in 7 of 9 dogs in the hemorrhage protocol and 3 of 5 dogs in the IVCC protocol. To determine whether SP and MAP are equal predictors of plasma AVP, we compared the individual $r^2$ values using the Wilcoxon signed rank test (28, to avoid any assumptions concerning normality of the data). The $r^2$ values obtained from the regression on SP was significantly different from the $r^2$ obtained with MAP in the hemorrhage protocol ($P < 0.01$) but not in the IVCC protocol ($P = 0.11$). The $r^2$ obtained in the regressions based on SP and RAP were different in both the hemorrhage and IVCC protocols ($P < 0.05$). On the basis of the results of these two different analyses of the data, we conclude that SP is superior to either MAP or RAP as a predictor of plasma AVP in response to hypovolemia. Consequently, we used the relationship between SP and plasma AVP in subsequent analyses of the data.

The individual lines relating log plasma AVP to SP in the hemorrhage and IVCC protocols are shown for two dogs in Fig. 3. The lines on the top panel were calculated from the data shown in Fig. 1. The slopes relating log AVP to SP in this dog deviated the most of the all the dogs studied. The lines in the bottom panel of Fig. 3 were obtained in a different dog and the slopes are identical. The slopes in the other six dogs with paired hemorrhage and IVCC experiments fell within these limits.

The means of the individual slopes and intercepts were used to construct lines relating the change in log
plasma AVP to the change in SP in response to hemorrhage and IVCC for the eight dogs with paired experiments (Fig. 4, note that the symbols limiting each line indicate the mean control and final SP in each protocol). The mean (± SE) slopes in the hemorrhage and IVCC protocols were $-0.034 ± 0.003$ and $-0.032 ± 0.002$, respectively. During acute CD, the slopes in the hemorrhage and IVCC protocols were $-0.033 ± 0.003$ and $-0.036 ± 0.003$, respectively. There were no significant differences among the slopes relating log plasma AVP to SP in the intact and CD conditions in response to either model of hypovolemia. However, after SAD ($n = 4$), the slopes relating plasma AVP to SP in the hemorrhage ($-0.017 ± 0.002$) and IVCC ($-0.019 ± 0.002$) protocols were reduced compared with control ($P < 0.05$).

**DISCUSSION**

The novel finding of this study is the remarkable similarity of the slopes relating log plasma AVP to SP in individual dogs obtained during two very different models of hypovolemia. Previous studies that examined responses to hemorrhage in the dog have suggested that reflex increases in plasma AVP can be explained by unloading atrial receptors (4), unloading arterial baroreceptors (15), or by loading ventricular mechanoreceptors (26). A mechanism based on atrial or arterial baroreceptor firing assumes that the afferent activity tonically inhibits a pool of neurons, presumably located in the medulla, and which are stimulatory to hypothalamic vasopressinergic neurons. Ventricular mechanoreceptors, on the other hand, are typically silent under control conditions (7) and thus when activated these mechanoreceptors must be directly stimulatory to mechanisms controlling AVP secretion.

There is considerable evidence that stimulating left atrial receptors in a euvolemic dog can reduce plasma AVP (3, 6). Furthermore, it has been shown that inflating a balloon in the left atrium prevents the increase in plasma AVP in response to carotid occlusion in anesthetized dogs (15). Similarly, Anerson et al. (1) have shown that loading receptors in the left atrium can inhibit hypotension-induced AVP secretion. However, there is little evidence that firing of left atrial receptors in the normally hydrated conscious dog is sufficient to inhibit AVP secretion. For example, we have observed large reductions in left and right atrial pressures in response to either hemorrhage (10, 24 and Fig. 1) or IVCC (11) with no increase in plasma AVP unless or until there is a clear fall in SP. Furthermore, if atrial receptor firing is sufficient to inhibit AVP secretion at rest, acutely blocking cardiac nerve impulses should lead to a rise in plasma AVP. However, we (10, 24) and others (17) reported that blocking cardiac nerve transmission has no effect on basal plasma AVP levels in either intact or SAD dogs. Finally, acute CD has no effect on the AVP response to either hemorrhage or hypotension induced by IVCC in the dog (10, 17, 21, 24). Thus we conclude that the rise in plasma AVP in response to hypovolemia in conscious dogs is not due to unloading atrial receptors.

Arterial baroreceptors are active in the euvolemic state, and unloading these receptors by carotid occlusion leads to an increase in plasma AVP (15). The current results provide additional evidence that arte-

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**Fig. 3.** Regressions of log AVP onto SP in two dogs in response to hemorrhage (HEM) and IVCC. Top: slopes of the lines illustrate the largest divergence of the eight dogs studied. Bottom: identical slopes in one of the dogs.

**Fig. 4.** The slopes of the lines represent the average of the individual slopes relating plasma AVP to the change in SP in each experimental condition. The top and bottom limits of each line indicate the mean control values of SP and the final SP at the end of the indicated protocol. There were no significant differences among the slopes obtained in the intact (I) and cardiac-denervated (CD) conditions during either HEM or IVCC. However, the slopes were significantly reduced following sinoaortic denervation (SAD).
The arterial baroreceptor signals are key to the stimulation of AVP secretion in response to hypovolemia. The pattern of change in the representative dog (Fig. 1) shows that as blood loss progresses, small decreases in SP are accompanied by small increments in plasma AVP. At the critical point when both SP and MAP plummet, indicating rapid unloading of the arterial baroreceptors, plasma AVP increases exponentially. Similarly, step reductions in arterial pressure during IVCC initially cause a small increase in plasma AVP, but each additional reduction in blood pressure is associated with a greater increase in plasma AVP. The fact that the slopes relating plasma AVP to SP are virtually identical in these two models strongly suggests that the baroreceptors are the link between pressure and rate of AVP secretion.

If the arterial baroreceptors are controlling AVP release during hypovolemia, the hypothesis predicts that acutely blocking signals from cardiac receptors should have no effect on the slopes relating SP to plasma AVP. As shown in Fig. 4, the slopes relating plasma AVP to SP during either hemorrhage or IVCC are not affected by acute CD. Thus there is no need to hypothesize an essential role for ventricular receptors in the stimulation of AVP secretion. Finally, if arterial baroreceptor firing is the primary signal controlling AVP secretion during hypovolemia, SAD should cause a dramatic reduction in the magnitude of the AVP response to hypovolemia and this was observed (Fig. 4). The mean decrease in SP at the end of the 30 ml/kg hemorrhage was 71 mmHg in the intact condition and was associated with a mean rise in plasma AVP of 247 pg/ml. In the SAD condition, the mean increase in plasma AVP accompanying a similar drop in SP was 16 pg/ml. Thus the arterial baroreceptors accounted for 94% of the increase in plasma AVP in response to a 71 mmHg fall in SP.

Observations in other species have also noted a strong association between arterial pressure and plasma AVP during hypovolemia. For example, Arnauld et al. (2) reported no increase in plasma AVP in response to hemorrhage in conscious monkeys until the animals became hypotensive. Numerous studies in human subjects using various models to simulate hypovolemia report no increase in plasma AVP unless arterial pressure declines (see Ref 20 for review).

In the intact rabbit, there is no change in plasma AVP as long as arterial pressure is maintained (12). However, there is a significant effect of CD on the AVP response to hemorrhage in this species, suggesting that additional reflex mechanisms (presumably stimulation of ventricular receptors) may also participate (5).

It has been argued that arterial baroreceptors cannot account for the initial increases in plasma AVP during the "nonhypotensive" phase of progressive hypovolemia, and thus some other mechanism must mediate the response. However, a recent study by Taylor et al. (19) tested this hypothesis in human subjects undergoing mild levels of lower body suction together with measurements of the cross-sectional area of the ascending aorta by nuclear magnetic resonance imaging. They observed that aortic pulse area decreased progressively and significantly during lower body suction. They concluded that even small reductions in central blood volume reduce aortic baroreceptive areas and activate reflex adjustments that are so efficient that alterations in arterial pressure are undetectable by conventional means. Functional evidence supporting the extreme sensitivity of baroreceptors to small decreases in blood volume is also available. Hemorrhage leads to significant declines in MAP in SAD dogs at levels of blood loss that had no effect on either MAP or SP with baroreceptors intact (24). Thus it is reasonable to argue that arterial baroreceptors are sufficiently sensitive to account for the stimulation of AVP secretion in response to reductions in blood volume that have no effect on MAP.

However, it is also evident that mechanisms other than arterial baroreceptors can influence AVP secretion during hypovolemia. Schreihofer et al. (14) reported that lesions of the nucleus of the solitary tract (NTS) combined with cervical vagotomy had no effect on the AVP response to serial hemorrhage in rats. A subsequent study by the same group (13) observed that renal denervation attenuated but did not eliminate the hemorrhage-induced increase in plasma AVP in the NTS-lesioned rats. However, renal denervation had no effect on the AVP response in neurologically intact rats. These results suggest that a renal sensor with afferents in the renal nerve can stimulate AVP secretion in the absence of functional baroreceptor input. Whether a similar mechanism can explain the residual AVP response to hemorrhage (17, 24) and IVCC (21) in the SAD dog is unknown but appears an interesting possibility.

Potential limitations of the slope analysis. Progressive hemorrhage is a dynamic event compared with IVCC, which represents a series of quasi steady-state steps as performed in the present study. For the slope analysis to be valid, the relationship between SP and plasma AVP should be virtually instantaneous, whereas in fact there must be some lag between secretion of the hormone and equilibration throughout the vascular compartment. However, a time lag is not a serious problem if the half-time of the hormone response is relatively short relative to the change causing the increase in secretion. For example, if the hemorrhage had stopped at 20 ml/kg, but plasma AVP continued to increase significantly, the predictive value of SP is lost. Similarly, a step decrease in MAP by IVCC should produce stable increases in plasma AVP over time for the slope analysis to be valid. We did not directly address the time dependency issue in the present study, but two previous studies conducted in the laboratory bear on this question. In one study (23), AVP was measured at the conclusion of a 20 ml/kg hemorrhage (1.5 ml kg^-1 min^-1) and at 15-min intervals for 60 min. Plasma AVP was elevated at the end of hemorrhage and remained at the same level over the next hour. In the other study, Thrasher and colleagues (9) used IVCC to reduce MAP by 25% over 10 min and then hold that reduction for 40 min. The increase in...
plasma AVP in response to the 25% fall in MAP was stable in measurements made 5, 10, 25, and 40 min later. These studies suggest that there is very little time delay between the stimulus to AVP secretion and the attainment of a steady-state concentration of the hormone in blood. Thus it is unlikely that a delay between the stimulus and subsequent plasma AVP level invalidates the use of slope analysis to compare AVP responses to hemorrhage and IVCC under the conditions used in this study.

In summary, the results of the present study indicate that SP is a better predictor of AVP responses to hemorrhage compared with either MAP or RAP. Furthermore, the results show that the slopes relating the log plasma AVP to SP are remarkably similar during either progressive hemorrhage or graded IVCC in individual dogs. This finding strongly supports the hypothesis that arterial baroreceptors are the primary signaling mechanism in the reflex stimulation of AVP secretion in response to hypovolemia in the dog.

Perspectives. The results of the present study were narrowly focussed on identifying the cardiovascular receptors that control release of AVP in response to hypovolemia. This is the fifth study from this laboratory that has concluded that atrial receptors play no role in the response, at least in the conscious dog. However, other studies in the same laboratory (e.g., Ref. 1) indicate that cardiac, presumably atrial, receptors can have a dominant influence on secretion of AVP. For example, constriction of the ascending aorta can be used reduce arterial pressure as effectively as constriction of the vena cava, yet the former maneuver has no effect on plasma AVP (1), whereas the latter causes large increases in plasma AVP. Similarly, hypotension caused by constriction of the ascending aorta has no effect on plasma cortisol or renin activity and does not stimulate thirst, whereas hypotension caused by IVCC stimulates all three responses (1, 22). Taken together, these observations suggest a general hypothesis that reflex stimulation of mechanisms, which act to restore extracellular fluid volume in response to hypovolemia, are dependent on decreased arterial baroreceptor firing. In contrast, stimulation of atrial receptors appears to be the dominant afferent signal leading to inhibition of these same responses and thus promotes decreases in extracellular fluid volume.

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