Analysis of the Cardiovascular Effects of Arginine Vasopressin in Conscious Dogs

Udom Tipayamontri, David B. Young, Bahij S. Nuwayhid, and Robert E. Scott

SUMMARY  The effects of physiological elevations in arginine vasopressin on the cardiovascular system were studied in a group of nine conscious, chronically instrumented dogs. The animals were studied under normal conditions (plasma vasopressin, 4.1 ± 0.4 pg/ml), after 24 hours of dehydration (plasma vasopressin, 7.3 ± 1.5 pg/ml), after a 30-minute vasopressin infusion at 2.6 ng/kg/min (plasma vasopressin, 62.8 ± 10.3 pg/ml), and after a 4-day vasopressin infusion at 2.6 ng/kg/min (plasma vasopressin, 96.6 ± 8.1 pg/ml). These increases in vasopressin concentration resulted in no change in arterial pressure and significant changes in the following: a 13 and 29% decrease in resting cardiac output during dehydration and acute infusion, respectively; a 26% reduction in heart rate during acute infusion; a 12 and 54% increase in total peripheral resistance during dehydration and acute infusion; a 16 and 22% reduction in mean circulatory filling pressure during dehydration and chronic vasopressin infusion. In addition, maximum pumping ability of the heart was reduced 16 and 31% during dehydration and acute infusion, respectively. These data suggest that elevations of vasopressin such as those occurring during dehydration or volume depletion potentially may affect cardiovascular performance by three mechanisms: 1) greatly increasing resistance to flow, 2) reducing heart rate, 3) suppressing the pumping ability of the heart. (Hypertension 9: 371-378, 1987)

KEY WORDS  • arterial pressure • blood volume • cardiac output • dehydration • heart rate • mean circulatory filling pressure • right atrial pressure • total peripheral resistance

ALTHOUGH the pressor capabilities of arginine vasopressin (AVP) have been recognized since 1895, the physiological role of the hormone in cardiovascular regulation remains controversial (for reviews of this subject, see References 1 and 2). In normal, conscious animals or humans, elevations in AVP concentration into the high physiological range bring about small increases in arterial pressure, 3,4 small decreases in cardiac output (CO), 3,5 and some redistribution of blood flow. 6 Although these findings do not suggest that AVP has an important role in cardiovascular regulation, the results of other recent studies raise the possibility that AVP may be important in cardiovascular control, at least in some conditions. Some of the more provocative data have come from the studies of Cowley et al. 3 and Montani et al., 5 who showed that, although changes in plasma AVP concentration within the physiological range do not produce large cardiovascular alterations in intact animals, the same increases of AVP concentration in baroreceptor-denervated animals or patients with impaired cardiovascular reflexes 4 have prominent cardiovascular and hemodynamic effects. Therefore, these studies suggest that in the intact animals some aspect of baroreceptor function masks the cardiovascular effects of AVP. Additionally, administration of antagonists to the vascular receptor in several experimental models of hypertension 7-9 and during hemorrhage 10 results in transient decreases in peripheral resistance and arterial pressure. These findings suggest that AVP is an active element of cardiovascular regulation, at least in some pathological conditions.

Previous analyses of the effects of AVP on the cardiovascular system have dealt mainly with the effects of the hormone on CO and the arterial side of the circulation. The present study was designed to deter-
mine the importance of AVP in regulation of the venous side as well as the arterial side of the cardiovascular system. In addition, the effects of the hormone on the pumping ability of the heart were analyzed. The experiments were performed over a period of several weeks in chronically instrumented, conscious dogs whose AVP levels were manipulated by acute and chronic infusions of AVP or by dehydration.

Materials and Methods

Surgical Procedures

Nine large dogs of either sex (average body weight, 20 ± 3 kg), obtained from the research animal facilities of the University of Mississippi Medical Center, were used in this study. Techniques for surgery and for care of the dogs were in accordance with National Institutes of Health guidelines. The animals were surgically prepared at least 2 weeks before data collection in a sterile surgical procedure using pentobarbital anesthesia. The dogs were splenectomized, electromagnetic flow transducers were placed around the ascending aorta, and four different catheters were implanted in the femoral artery, right atrium (through the right femoral vein), left femoral vein, and jugular vein. The jugular catheter was large enough to permit rapid infusion (inside diameter, 2.5 mm; flow > 1500 ml/min at 300 mm Hg). The peripheral ends of all catheters and the electromagnetic flow probe cables were tunneled subcutaneously to the back between the shoulders and protected by a heavy canvas jacket. The animals were housed in metabolic cages and fed dry dog food containing approximately 60 mEq of sodium per day. Except for periods of dehydration (as described in Protocol), the dogs were allowed free access to water.

Measurement Techniques

CO was measured using implanted electromagnetic flow probes (Micron Instruments, Los Angeles, CA, USA). Mean arterial pressure (MAP) and pulsatile arterial pressure were obtained from the femoral artery catheter using a P23ID pressure transducer (Statham, Hato Rey, Puerto Rico). Right atrial pressure (RAP) was measured from the catheter implanted in the right atrium using a Statham P23BC pressure transducer. Heart rate was obtained using a tachometer (Model 7P4F; Grass Instrument, Quincy, MA, USA) triggered by the arterial pressure pulse. Total peripheral resistance (TPR) was calculated from the MAP and CO. Mean circulatory filling pressure (MCFP) was measured using a modification of the technique originally described by Guyton et al. 11 MCFP is a measure of the degree of filling of the circulatory system. More specifically, it is the weighted average blood pressure throughout the circulatory system. Its importance is that it is the force that moves blood back to the heart; the difference between MCFP and RAP is the pressure gradient for venous return (PGVR). Therefore, because CO is determined to a great extent by the rate of venous return, changes in MCFP have profoundly important effects on CO regulation. MCFP is a function of three variables: blood volume, circulatory system compliance, and unstressed vascular volume, which is the blood volume in the system when MCFP is zero (approximately 85% of normal blood volume). Changes in any of these variables can affect MCFP.

Theoretically, MCFP could be measured by stopping the heart and allowing the pressures throughout the circulatory system to come to an equilibrium pressure. To decrease the time required to reach the equilibrium pressure, in their early experiments Guyton et al.11 pumped blood from the arterial to the venous side of the circulation through large catheters in anesthetized dogs. More recently, we12 developed a technique to permit serial measurements in lightly sedated dogs over a period of several weeks. The dogs were sedated with a combination of butorphanol tartrate (Stadol; Bristol Laboratories, Syracuse, NY, USA), 0.3 mg/kg, and diazepam (Valium), 0.5 mg/kg, both given intravenously. The heart was temporarily arrested by an i.v. bolus of 40 mg of acetylcholine. After approximately 4 to 5 seconds, the arterial (AP) and venous pressures (VP) reached stable values of approximately 20 to 25 and 8 to 10 mm Hg, respectively. Rather than pump blood from the arterial to the venous sides of the system to reach the equilibrium value, which is the MCFP, we calculated the equilibrium pressure as follows: MCFP = VP + (AP − VP)/(CV/CA), where CV and CA are the venous and arterial compliances, respectively. Based on other studies, a value of 30 was used for CV/CA. 13 14 Therefore, the MCFP is equal to the value of the venous pressure plateau plus the difference between the arterial and venous pressure plateaus divided by the venous to arterial compliance ratio; in practice the value added to the venous pressure was approximately 0.5 mm Hg or less.

The pressure gradient for venous return was calculated as the difference between MCFP and RAP, and resistance to venous return was determined from CO/PGVR.

While the dogs were sedated as already described, cardiac function curves were determined from changes in CO while RAP was rapidly increased by infusion of 3% of the body weight of Tyrode’s solution warmed to 38°C into the large jugular vein catheter. 15 16 The Tyrode’s solution was infused over a period of less than 30 seconds and resulted in an increase in RAP to at least 16 mm Hg. While the measurement was being made, the dog’s heart rate was stabilized by atropine, 800 µg i.v., injected 10 minutes before the procedure began.

Blood volume was determined using a 20-minute dilution of 51Cr-labeled red blood cells, 17 and sodium and potassium concentrations of plasma were measured by flame photometry. Plasma AVP was determined by Dr. Allen W. Cowley, Jr. 10 using a specific and highly sensitive radioimmunoassay. The assay standard was obtained from the United States Pharmacopeia and had an activity of 0.385 µU/pg. During the period the samples for this study were run, the recovery was 77%, the interassay variation was 8%, and the intraassay variation was 4 to 6%.
Protocol

During the 2 weeks following operation the animals were brought to the laboratory and trained to lie quietly while unrestrained. On Day 1 of the protocol, the animals were moved to cages in a room near the laboratory, where they were housed for the duration of the experiment. On Day 3, the animals were brought to the laboratory, where they rested comfortably, and an infusion of normal saline was begun at a rate of 0.2 ml/min. After 30 minutes of the infusion, CO, heart rate, MAP, and RAP data were collected as already described. A 10-ml arterial blood sample was drawn for analysis of AVP and measurement of electrolyte concentrations; the blood volume measurement was also made at this time. Finally, the MCFP measurement was made, and the dogs were returned to their cages. On the following day, the dogs were brought to the laboratory and the saline infusion was begun again at the same rate. After 30 minutes of infusion, the cardiac function curve was recorded by rapidly raising RAP with a Tyrode’s solution infusion while measuring CO.

Following the first set of measurements, the animals returned to their cages for 2 days, Days 5 and 6. On Days 7 and 8 the same set of measurements were made as already described, the only difference being that the animals received an AVP infusion of 2.6 ng/kg/min (V-0377, synthetic grade VI); Sigma Chemical, St. Louis, MO, USA) in saline starting 30 minutes before data collection.

After the second 2-day set of measurements, the animals were again returned to their cages for 2 days of rest, Days 9 and 10. On Days 11, 12, and 13, the animals remained in their cages with food, but without water. On Days 12 and 13, the same 2-day set of measurements already described was repeated, this time with only saline infusion during the measurement. Therefore, the first day’s measurements on Day 12 were made after the animals had been without water for 24 hours, while the second day’s measurements were made after 48 hours of dehydration.

Following the third set of measurements, the animals were returned to their cages, where they were again allowed access to water. An aluminum harness was attached to their jackets and fixed to a flexible metal reinforced plastic tube through which passed a cannula connected to the implanted venous catheter. This arrangement permitted continuous infusion from a pump mounted outside the cage. Infusion of AVP was begun at a rate of 2.6 ng/kg/min in 50 ml of saline per day and continued for 4 days. AVP infused in this manner has a strong natriuretic effect. To prevent a negative sodium balance, sodium chloride was added to the 50 ml infused each day. The amount of sodium needed to replace that lost in the AVP natriuresis on the first day was determined to be approximately 7.5% of the product of the normal plasma sodium concentration and the sodium space (determined in pilot studies). On the second and third day of the infusion, the amounts of sodium replaced were 50 and 40%, respectively, of the amount replaced on the first day. To keep the animals in water balance during the infusion of AVP, the dogs were not given any drinking water during the infusion period. On the final 2 days of the study, the animals were brought to the laboratory, where the same cardiovascular measurements were repeated while the AVP infusion was maintained.

Data Analysis

Group means and standard errors are presented throughout the study. Statistical evaluation of the data was performed using a paired t test as modified by Dunnett for two-sided comparison of three treatments with one control. A p value of less than 0.05 was considered significant.

Results

The effects of the butorphanol-diazepam sedation on the cardiovascular system are presented in Table 1. The only significant change produced by the combination was a 14% reduction in arterial pressure, which may have resulted from the cerebral effects of the sedatives. AVP concentration was measured in two dogs before and after sedation. In one, the concentration changed from 4.7 to 5.6 pg/ml; in the other, there was no change from the initial level of 4.2 pg/ml.

During the control period the mean AVP concentration for the group was 4.1 ± 0.4 pg/ml. A 24-hour dehydration resulted in an increase in the concentration to 7.5 ± 1.5 pg/ml. Short-term infusion of AVP at a rate of 2.6 ng/kg/min raised the mean concentration to 62.8 ± 10.3 pg/ml, while chronic infusion at the same rate further increased the level to 96.6 ± 8.1 pg/ml. Data from Dogs 7 and 8 (262.1 and 240 pg/ml) were 17 to 18 standard errors beyond the group mean and were therefore considered to be invalid and probably due to experimental error. No other measured variables from these two dogs were unusual.

Presented in Table 2 are the means and standard errors for all data collected under normal conditions, after dehydration, during acute infusion of AVP (2.6 ng/kg/min), and during chronic AVP infusion (2.6 ng/kg/min). The MAP did not change from the normal

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Table 1. Cardiovascular Changes Produced by Butorphanol (0.3 mg/kg) and Diazepam (0.5 mg/kg) Sedation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Presedation</th>
<th>15 min postsedation</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>94 ± 4</td>
<td>81 ± 4</td>
<td>-14*</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>2028 ± 193</td>
<td>1958 ± 197</td>
<td>-3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>84 ± 5</td>
<td>88 ± 7</td>
<td>+5</td>
</tr>
<tr>
<td>TPR (mm Hg/L/min)</td>
<td>49 ± 5</td>
<td>44 ± 4</td>
<td>-10</td>
</tr>
</tbody>
</table>

Agents were introduced by slow i.v. injection before mean circulatory filling pressure and cardiac function curves were determined. Values are group means ± SEM. Statistical analysis was performed using two-sided paired t test as modified by Dunnett for comparison of one treatment with one control.

MAP = mean arterial pressure; CO = cardiac output; HR = heart rate; TPR = total peripheral resistance.

*p < 0.01, compared with presedation value.
level of 101 ± 3 mm Hg as a result of any of the manipulations. Dehydration and acute AVP infusion resulted in 13 (p<0.01) and 29% (p<0.01) decreases, respectively, from the control CO of 125 ± 6 ml/min/kg, although chronic infusion of AVP did not reduce CO. Only the acute AVP infusion altered heart rate; heart rate was 67 ± 6 beats/min during the acute AVP infusion, 26% less than the control heart rate (p<0.01). TPR was elevated 12% by dehydration (p<0.01) and 54% by acute AVP infusion (p<0.01) and was not significantly affected by chronic AVP infusion. Dehydration produced a slight but consistent decrease in stroke volume, although neither acute nor chronic AVP infusion altered this variable.

MCFP averaged 8.2 ± 0.5 mm Hg in the normal condition. Dehydration and chronic AVP infusion produced decreases in MCFP to 7.1 ± 0.5 (p<0.01) and 6.5 ± 0.6 mm Hg (p<0.05), respectively, although acute AVP infusion did not produce a significant change in this variable. RAP decreased in dehydration and chronic AVP infusion from a control level of 6.5 ± 0.6 mm Hg (p<0.05) and 29% by acute AVP infusion (p<0.01) and 54% by chronic AVP infusion, 26% less than the control heart rate (p<0.01) and 54% by acute AVP infusion (p<0.01) and was not significantly affected by chronic AVP infusion. Dehydration produced a slight but consistent decrease in stroke volume, although neither acute nor chronic AVP infusion altered this variable.

Values are means ± SEM. Values in parentheses indicate percentage change from normal values. Dehydration data collected after 24 to 48 hours of dehydration. Acute AVP data collected after a 30-minute infusion of AVP, 2.6 ng/kg/min. Chronic AVP data collected after a 4-day infusion of AVP, 2.6 ng/kg/min.

AVP = arginine vasopressin; SV = stroke volume; MCFP = mean circulatory filling pressure; RAP = right atrial pressure; PGVR = pressure gradient for venous return; RVR = renal vascular resistance; BV = blood volume; PNa = plasma Na concentration; PK = plasma K concentration. See Table 1 for other abbreviations.

*p < 0.01, †p < 0.05, compared with normal values.
Effects of AVP Increases Resulting from Dehydration

The cardiovascular alterations that resulted from the smaller increases in plasma AVP concentration elicited by 24 to 48 hours of dehydration differed both quantitatively and qualitatively from the changes resulting from acute AVP infusion. There was no change in arterial pressure, a 13% fall in CO, a slight increase in arterial pressure, a 13% fall in CO, a slight increase in resistance to blood flow, and a decrease in cardiac function. However, during acute AVP infusion arterial pressure increased by approximately 15 mm Hg during determination of the cardiac function curve. However, during acute AVP infusion arterial pressure increased by approximately 40 to 50 mm Hg during analysis of the curve. To determine if the afterload effect during the acute AVP infusion contributed to the suppression of cardiac function, cardiac function curves were measured in two dogs, first under normal conditions, then during infusion of phenylephrine, 5 ng/kg/min, which raised MAP to 160 to 170 mm Hg. With increased afterload resulting from phenylephrine infusion, maximum CO was 98% of that measured during normal conditions. This finding is in agreement with those of Herndon and Sagawa, who found little effect of an increase in afterload below 180 mm Hg on ventricular function in anesthetized dogs.

Discussion

Although the dogs were only lightly sedated with butorphanol and diazepam, and the sedation caused only minor changes in the measured cardiovascular variables, these studies should be repeated in fully conscious animals before our conclusions can be applied to cardiovascular physiology in general.

Effects of Acute AVP Infusion

The 15-fold increase in plasma AVP concentration resulting from the acute infusion of AVP at 2.6 ng/kg/min did not produce a consistent increase in MAP. However, it did result in a striking decrease in CO and a 54% increase in TPR. The 29% decrease in CO, 26% decrease in heart rate, and 54% increase in TPR that we found in this study are similar to the findings of others in similar experimental situations. The decrease in CO observed during the acute AVP infusion probably was due to several factors, including the reduction in heart rate and the suppressive effects of AVP on the pumping ability of the heart independent of changes in heart rate. Even when heart rate was stabilized with atropine, AVP infusion had a very strong negative effect on the pumping ability of the heart, as assessed by the cardiac function curve (see Figures 1 and 2). During the acute infusion the effects of AVP on the peripheral circulation were not the cause of the reduction in CO. Although resistance to venous return increased 59% during acute AVP infusion, the RAP was not changed; therefore, changes in the peripheral circulation that may have affected the dynamics of return of blood to the heart and, consequently, RAP did not contribute to the reduction in CO that occurred during acute AVP infusion.

Effects of AVP Increases Resulting from Dehydration

The cardiovascular alterations that resulted from the smaller increases in plasma AVP concentration elicited by 24 to 48 hours of dehydration differed both quantitatively and qualitatively from the changes resulting from acute AVP infusion. There was no change in arterial pressure, a 13% fall in CO, a slight increase
in peripheral resistance, but no change in heart rate following the period of dehydration (see Table 2). In addition, there was a 1.1 mm Hg reduction in MCFP with no change in blood volume and a slight but significant decrease in PGVR. These two factors contributed to the 0.9 mm Hg fall in RAP observed after dehydration. Because of the steep slope of the cardiac function curve in this range of RAP, this 0.9 mm Hg decrease in preload could account for as much as a 25 ml/min/kg decrease in CO (Figure 1). In addition to the effects of AVP on the peripheral circulation, which resulted in a decrease in preload to the heart, the dehydration-induced increases in AVP also had a suppressive effect on the pumping ability of the heart, as indicated by the downward shift in the cardiac function curve (see Figures 1 and 2). Therefore, the reduction in CO observed after 48 hours of dehydration was due to a combination of both the decrease in preload and a decrease in contractility of the heart.

Effects of Prolonged AVP Infusion

After 4 days of AVP infusion at a rate of 2.6 ng/kg/min the cardiovascular system had returned to the control state with the exception of MCFP and RAP, both of which remained significantly below the control level. The escape of the pumping ability of the heart from the suppressive effects of AVP and the escape of the resistance vessels from the constrictive effects of the hormone are interesting phenomena: they suggest that either tachyphylaxis to AVP develops or that compensatory mechanisms overcome the effects of AVP. In most cases in which competitive antagonists to AVP have been injected into hypertensive rats with longstanding high endogenous AVP levels, arterial pressure or TPR (or both) has fallen and CO has increased. These findings suggest that AVP is capable of having a prolonged cardiovascular effect. In the present experiment AVP infusion may have suppressed renin levels, in which case the resulting withdrawal of angiotensin II could have compensated in part for the effects of the elevation in AVP concentration. The quantitative importance of this type of compensation would be limited by the low initial renin levels; in this laboratory animals in similar conditions have plasma renin activity measurements of 0.5 ng angiotensin I/ml/hr or less. A second possible compensatory mechanism may have been withdrawal of sympathetic nervous system activity, which also could have offset the effects of the increase in AVP concentration. Here again, the potential importance of such an effect would be limited by the low level of sympathetic nervous system activity in the unstressed conscious dog before AVP infusion. In this laboratory total ganglionic blockade with hexamethonium in conscious normal dogs results in no more than a 10 mm Hg fall in arterial pressure. Furthermore, the fact that heart rate was the same before and after the 4-day AVP infusion is evidence against any major change in activity of the sympathetic system.

The increase in plasma sodium concentration observed during the chronic AVP infusion protocol resulted from an overcompensation for the AVP-induced natriuresis. What effect the 5% increase had on the measured variables is not clear. In short-term and in vitro studies hypernatremia causes a relaxation of vascular smooth muscle that persists for several minutes. The cardiovascular effects of hypernatremia of longer duration in the whole animal have not been adequately studied. In a study similar to the present study, the same increase in sodium concentration for 6 days had no effect on arterial pressure or plasma renin activity. In an acute study, Cowley and Lohmeier demonstrated that a similar degree of hypernatremia did not affect the pressor response to angiotensin II in the intact dog. Furthermore, three intensively studied experimental models that typically have elevated plasma sodium concentrations (the Brattleboro rat; the lateral, ventral, third ventricle-lesioned rat; and the deoxycorticosterone-salt hypertensive rat) do not have any cardiovascular abnormalities attributed to their hypernatremia. Therefore, at present we have no evidence that the hypernatremia associated with the AVP infusion protocol had any effect on the measured cardiovascular responses.

Suppression of Cardiac Function by AVP

Infusion of AVP into intact animals has been reported to reduce CO to a degree similar to that which we observed. The mechanism of the reduction could have been due to a direct effect on the myocardium or an indirect effect acting through the autonomic innervation of the heart or on the regulation of venous return to the heart. In pharmacological amounts AVP has a positive chronotropic and negative inotrophic effect on the isolated atrium; however, neither effect has been observed at physiological concentration in the in vitro atrium preparation. The autonomic effects of AVP result in large reductions in heart rate during acute infusions (26% in the present study), large enough to reduce significantly the pumping ability of the heart and suppress the cardiac function curve. It has also been reported that a reduction in coronary flow accompanies AVP infusion, although in the intact animal this effect appears to be secondary to the decrease in work associated with the reductions in heart rate and CO. In the present study we recorded cardiac function curves to determine the effects of AVP on the pumping ability of the heart independent of changes in venous return, which were controlled, and heart rate, which was held at a high rate during the measurement procedure by previously administered atropine. Through its effect on heart rate atropine augments the pumping ability of the heart and moves the cardiac function curve upward and to the left; this effect of atropine was constant during the analysis of the effect of AVP, both during the measurement of the control curves and the AVP curves. Therefore, with heart rate held constant and vagal input blocked by atropine, the suppression of the cardiac function curve produced by the acute AVP infusion could have resulted from a direct effect on the myocardium or possibly from a withdrawal of sympathetic input to the heart.
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Stone and Bishop found that total adrenergic blockade by propranolol could reduce the plateau of the cardiac function curve by a maximum of 25%, enough to account for the suppression seen in the present study. Therefore, the possibilities that AVP influences the sympathetically innervated heart and that it exerts a direct effect on the myocardium deserve continued study.

The effects of increases in AVP concentration on the cardiovascular system of the unstressed conscious dog revealed in the present study include the following: 1) suppression of the pumping ability of the heart independent of changes in heart rate; 2) a reduction in heart rate; 3) an increase in resistance to flow, both TPR and resistance to venous return. All of the effects were relatively short-lived; none persisted as long as 4 days. The functional benefits of these mechanisms in short-term cardiovascular regulation are difficult to determine; however, these effects would appear to be operative during periods of severe cardiovascular stress resulting from hypovolemia when AVP levels would be elevated into the range studied in these experiments. Under such conditions other regulatory factors besides AVP would affect cardiovascular function; especially prominent would be the effects of the sympathetic nervous system, which would strongly stimulate the strength of cardiac contraction and elevate heart rate. It is probable that the well-known inotropic effects of the catecholamine are several-fold more powerful than the negative effect of AVP. Since AVP concentrations do not rise to levels that we found produce important cardiac suppression, except in conditions of severe hypovolemia and circulatory stress when the activity of the sympathetic nervous system would be greatly elevated, the negative effects of AVP are likely outweighed by the concomitant positive effects of catecholamines under most such pathophysiological conditions. This situation may also be the case for the heart rate effect of AVP, which would leave only the peptide's vasoconstrictive effect with functional importance. To answer the questions raised by this speculation will require additional analysis of the effects of AVP during cardiovascular stress.

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