Vasopressin and Arterial Pressure Regulation
Special Lecture

ALLEN W. COWLEY, JR. AND JEAN-FRANCOIS LIARD

SUMMARY Data from conscious rats, dogs, and humans show that plasma arginine vasopressin (AVP) begins to exert vasoconstrictor activity at concentrations in the same range as those associated with maximum antidiuretic activity. Minimum pressor responses are observed with elevated plasma AVP, due in part to decreases of cardiac output and in part to withdrawal of sympathetic neural tone to various regions of the systemic circulation. These responses appear to some extent to be species-dependent. In conscious dogs, but not in rats, the fall of cardiac output is mediated by AVP stimulation of baroreceptor reflex pathways. Studies in rats indicate that AVP inhibits the sympathetic nervous system by direct action on the central nervous system. No evidence was found for inhibition at peripheral sites such as autonomic ganglia or vascular smooth muscle receptors. Also, AVP plays an important role in the regulation of arterial pressure with blood loss by direct vasoconstriction and by AVP enhancement of the strength of the baroreceptor reflex responses. The role of AVP in the long-term control of arterial pressure in hypertension remains controversial, but plasma AVP is elevated in many experimental and human forms of hypertension. The link between plasma AVP and hypertension remains unclear because long-term elevation of AVP alone cannot sustain volume expansion or hypertension, and excess AVP does not enhance hypertension produced by sodium-retaining hormones or other vasoconstrictor agents. It appears that AVP plays mainly a permissive role by its fluid-retaining effects in most forms of hypertension. It is also possible that it acts as a central nervous system neural transmitter and modifies autonomic pathways in some forms of hypertension. (Hypertension 11 [Suppl I]: I-25–I-32, 1988)

KEY WORDS • vasopressin • arterial pressure • cardiac output • autonomic nervous system • hypertension • fluid volume

THE cardiovascular actions of arginine vasopressin (AVP) have been under intense investigation in recent years because of newly accumulated evidence that AVP acts as a vasoconstrictor in concentrations much lower than previously thought. Much of the data that revealed this were obtained in our own laboratories, and this article focuses primarily on these studies.

Hemodynamic Effects of Circulating AVP

The pressor activity associated with increasing plasma levels of AVP normally becomes apparent only at concentrations that exceed 30 pg/ml. These concentrations are in excess of those required for maximal antidiuretic activity, which occurs in the range of 10 to 20 pg/ml. This is true in normal human subjects, dogs, and rats, although the vasoconstrictor actions of AVP are buffered most potently in normal humans and least in rats. The changes of arterial pressure and plasma AVP resulting from 30- to 60-minute intravenous infusions are summarized in Figure 1.

Pressor responses to AVP have turned out to be an especially poor index of vasoconstrictor activity. The reason for this is clearly apparent in Figure 1. With increasing plasma levels of AVP in the three species that we have studied, there was a significant increase in total peripheral resistance of 10 to 20% between plasma levels of 5 and 20 pg/ml, indicating that small physiological increases of plasma AVP exert vasoconstrictor activity. This activity therefore begins to become apparent at plasma levels in the same range as those that are required to achieve maximum antidiuretic activity. Some of the expected rise of pressure is offset by a dose-dependent fall of cardiac output observed in all species studied so far (see Figure 1). These responses and its interactions with autonomic neural pathways make AVP a unique endogenous vasoconstrictor agent (i.e., one that only increases arterial pressure when infused at pharmacological levels into normal animals).

One important action of AVP has become apparent in recent years: That is, it is a potent modulator of the
autonomic nervous system and peripheral sympathetic nerve activity. Its neural interactions, however, are strongly species-dependent, as can be seen from data obtained in conscious rats and dogs (Figure 2). Dogs that have undergone denervation of the sinoaortic baroreceptors exhibit nearly a 10-fold reduction in AVP threshold sensitivity and an overall enhancement of pressor sensitivity of 60- to 100-fold above that observed in normal, conscious dogs. This is seen uniquely with AVP, since by comparison, only a five- to sixfold increase in pressor sensitivity was observed with infusions of angiotensin and norepinephrine in conscious, baroreceptor-denervated dogs. In contrast, sinoaortic baroreceptor-denervated (SAD) rats appeared to respond quite differently in that pressor sensitivity to AVP was not enhanced compared to other vasoconstrictor agents. Conscious, denervated rats compared to normal rats exhibited only a fivefold to sixfold enhancement of pressor sensitivity to AVP, similar to that observed with phenylephrine or angiotensin II.

The mechanism responsible for these species differences appears to be in large measure related to the neural pathways through which elevations of AVP reduce cardiac output. Baroreceptor reflex mechanisms appear to contribute to lowering the cardiac output in conscious dogs, since the fall is greatly blunted after sinoaortic denervation. The AVP-induced fall of cardiac output is nearly absent in baroreceptor-denervated dogs, except at high levels of AVP, despite substantial elevations of systemic vascular resistance. It is unlikely that negative inotropic actions of AVP contribute substantially to the fall of cardiac output at the lower concentrations of AVP, since baroreceptor-denervated dogs exhibit little drop in cardiac output.

For a given rise of arterial pressure, reflex bradycardia with AVP infusions is far greater than with other vasoconstrictor agents such as angiotensin or norepinephrine. An AVP-induced reflex bradycardia could account for some of the observed elevations of cardiac filling pressure and decreases of cardiac output with AVP infusions, since baroreceptor denervation abolishes both the bradycardia and the fall of cardiac output. Blockade of vagal activity with atropine reduced the drop in cardiac output associated with elevations of AVP. The mechanism for the fall of cardiac output is clearly different in conscious rats. Neither baroreceptor denervation nor total autonomic blockade attenuated the fall of cardiac output with graded infusions of AVP in rats, despite an absence of AVP-induced bradycardia. It should be recognized, however, that at higher concentrations of AVP, cardiac output decreased in dogs also in both the presence and absence of baroreceptor reflexes, probably indicating that a reduction of cardiac pumping ability, systemic vasoconstriction, and cardiac afterload participate in lowering cardiac output at these levels of AVP.

In addition to the species-dependent interaction of AVP and baroreceptor reflex control of cardiac output, there is evidence that circulating AVP influences other elements of the nervous system. Such interactions are demonstrated in Figure 3, which shows a 20- to 30-fold greater pressor responsiveness to AVP when compared to conscious, sinoaortic baroreceptor-denervated dogs to those in which the central nervous system has been totally eliminated. It is also shown that in conscious rats treated with hexamethonium and methscopolamine to produce total autonomic blockade, there is a 20-fold increase in AVP pressor sensitivity as compared to conscious, sinoaortic baroreceptor–denervated rats. These studies demonstrate that even in the absence of the baroreceptor reflexes, AVP can act somewhere in the nervous system to attenuate the rise of pressure expected from AVP vasoconstriction.

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**Figure 1.** Changes in mean arterial pressure (MAP), cardiac output (CO), and total peripheral resistance (TPR) with increasing levels of plasma AVP in normal conscious rats, dogs, and humans are summarized. All data represent steady state hemodynamic responses obtained during 30- to 60-minute intravenous infusions of AVP. (Reprinted from Cowley et al., with permission.)

![Figure 1](http://hyper.ahajournals.org/)

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<th>MAP</th>
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For a given rise of arterial pressure, reflex bradycardia with AVP infusions is far greater than with other vasoconstrictor agents such as angiotensin or norepinephrine. An AVP-induced reflex bradycardia could account for some of the observed elevations of cardiac filling pressure and decreases of cardiac output with AVP infusions, since baroreceptor denervation abolishes both the bradycardia and the fall of cardiac output. Blockade of vagal activity with atropine reduced the drop in cardiac output associated with elevations of AVP. The mechanism for the fall of cardiac output is clearly different in conscious rats. Neither baroreceptor denervation nor total autonomic blockade attenuated the fall of cardiac output with graded infusions of AVP in rats, despite an absence of AVP-induced bradycardia. It should be recognized, however, that at higher concentrations of AVP, cardiac output decreased in dogs also in both the presence and absence of baroreceptor reflexes, probably indicating that a reduction of cardiac pumping ability, systemic vasoconstriction, and cardiac afterload participate in lowering cardiac output at these levels of AVP.

In addition to the species-dependent interaction of AVP and baroreceptor reflex control of cardiac output, there is evidence that circulating AVP influences other elements of the nervous system. Such interactions are demonstrated in Figure 3, which shows a 20- to 30-fold greater pressor responsiveness to AVP when compared to conscious, sinoaortic baroreceptor-denervated dogs to those in which the central nervous system has been totally eliminated. It is also shown that in conscious rats treated with hexamethonium and methscopolamine to produce total autonomic blockade, there is a 20-fold increase in AVP pressor sensitivity as compared to conscious, sinoaortic baroreceptor–denervated rats. These studies demonstrate that even in the absence of the baroreceptor reflexes, AVP can act somewhere in the nervous system to attenuate the rise of pressure expected from AVP vasoconstriction.
These actions have not been observed with other vasoactive hormones such as angiotensin and norepinephrine.

Figure 4 summarizes the mechanisms whereby AVP influences hemodynamic and autonomic function in conscious rats. In normal rats, 60-minute intravenous infusions produced dose-related increases of arterial pressure and total peripheral resistance, with marked decreases of both heart rate and cardiac output. Conscious, unrestrained, SAD rats in which baseline levels of mean arterial pressure, cardiac output, and total peripheral resistance were not different prior to infusion exhibited a fourfold to fivefold increase in pressor sensitivity to AVP and significantly greater elevations of total peripheral resistance. Cardiac output responses to AVP were not significantly different between control and SAD rats, but the bradycardia response was greatly attenuated. Rats treated with hexamethonium and methscopolamine to produce total autonomic blockade exhibited nearly a 100-fold increase in AVP sensitivity as compared to normal conscious rats. Cardiac output, however, fell by as much or more, as was observed in either normal or SAD rats. Thus, the large increase in pressor sensitivity to AVP during gangli-
Figure 4. Changes in mean arterial pressure (MAP), cardiac output (CO), total peripheral resistance (TPR), and heart rate (HR) determined during 60-minute intravenous infusion of AVP in conscious, normal rats (CON, solid line), sinoaortic denervated rats (SAD, dashed line), and total autonomic blockade (TAB, dotted line).

Somnic blockade resulted from a greater increase in total peripheral resistance compared to normal or SAD rats. Although it is not surprising that an increase of total peripheral resistance with administration of vasoconstrictor agents is greatest in animals lacking autonomic reflexes, the magnitude of the shift in the dose-response curves is far greater than can be explained by normal baroreceptor reflex inhibition of sympathetic tone. Pharmacological blockade or surgical removal of sympathetic efferent pathways removes a non-baroreceptor reflex buffering mechanism and results in further potentiation of the pressor activity of AVP. This demonstrates that AVP acts somewhere in the nervous system, independent of baroreceptor reflex neural pathways, to reduce vascular sympathetic tone.

The specific site(s) of AVP interaction with non-baroreceptor reflex neural pathways remains to be determined precisely. Several sites have been considered, including direct actions within the central nervous system, synapses of the autonomic ganglia, and postganglionic sympathetic terminals. Others have shown that elevations of plasma AVP result in decreases of renal and lumbar sympathetic nerve activity. Some of these effects appear to be mediated by AVP actions on baroreceptor reflex pathways, since Undesser et al. reported that intravenous AVP augmented baroreceptor reflex inhibition of renal nerve traffic in conscious rabbits, which was markedly attenuated by sinoaortic denervation and lesions of the area postrema. Imaizumi and Thames reported that intravenously administered AVP continued to inhibit renal nerve traffic in sinoaortic denervation in anesthetized rats. Furthermore, renal nerve traffic continued to be decreased with AVP administration in high concentrations after transection of the spinal cord.

It was also recently reported that AVP decreases ganglionic postsynaptic sympathetic activity. These studies implied that AVP inhibits sympathetic ganglionic transmission. The importance of such changes to the overall level of sympathetic activity and vascular tone, however, could not be assessed from these neurophysiological studies. In addition, the importance of AVP-induced decreases of sympathetic tone in offsetting the direct vasoconstrictor activity remains unclear, since other studies have suggested that AVP potentiates the response of vascular smooth muscle to norepinephrine, which would counteract the sympathetic inhibitory responses.

Recent studies in our laboratory determined the importance of these potential neural interactions on arterial pressure by evaluating the effects of intravenously infused AVP on pressor responses elicited by electrical stimulation of the spinal cord and by intravenous injections of norepinephrine in areflexic rats. A stainless steel electrode was inserted into the spinal canal, with the electrode insulated so that the area of stimulation was restricted primarily to the thoracolumbar region of the spinal cord. The central nervous system was surgically removed after compression of the cervical region with a blunt clamp. Arterial pressure was stabilized by continuous infusion of norepinephrine, and respiration was maintained by positive pressure ventilation. The arterial pressure responses to increasing frequency of electrical stimulation of the spinal cord during and
after 30-minute graded infusions of three doses of AVP, 0.02, 0.2, and 2.0 ng/kg/min, were then obtained. Results of these studies (Figure 5) showed that AVP had no measurable influence on the arterial pressure responses. This can be seen by the nearly identical stimulus-response curves. Similar responses were seen to increasing voltage.

It was also shown that AVP had no significant effect on the pressor responses to exogenous norepinephrine administration carried out in a similar manner while determining arterial pressure responses to intravenous bolus injections of norepinephrine. The results of these studies indicate that inhibitory effects of AVP on the peripheral sympathetic nervous system are not of measurable importance to the systemic circulation. It is also unlikely that the failure to observe effects of AVP on arterial pressure responses to spinal stimulation was due to opposing effects on ganglionic transmission (inhibition) and vascular smooth muscle (potentiation of catecholamine vasoconstrictor activity), since AVP did not potentiate pressor responses to exogenous norepinephrine.

In summary, the overall effect of circulating AVP on the nervous system appears to be one of lowering sympathetic nerve activity, and this response appears to be mediated through central neural pathways. The buffering of AVP pressor responses can be attributed in part to decreases of cardiac output, which may or may not be neurally mediated depending on the species studied, and withdrawal of sympathetic tone to various regions of the systemic circulation by way of neural pathways.

Other studies that we have reviewed in detail elsewhere indicate that AVP plays an important role in the immediate defense of blood pressure in situations of hypotensive blood loss through direct vasoconstrictor actions and enhancement of baroreceptor reflex gain.1, 15

**AVP in Hypertension**

**Human Essential Hypertension**

The role of AVP in the long-term regulation of arterial pressure and in hypertension remains controversial, contrary to its involvement in short-term blood pressure control, which is now firmly established. Clear interest in this subject evolved from observations that plasma AVP was elevated in many models of experimental hypertension and in human essential hypertension. We reported in two separate studies16, 17 that plasma AVP levels were elevated in 25 to 30% of hypertensive subjects. Moreover, it was found that high AVP essential hypertension was confined almost exclusively to male hypertensive subjects, as fewer than 7% of females exhibited elevated plasma AVP. A highly significant correlation was found between plasma AVP levels and systolic and diastolic blood pressures in the male population. Os et al.18 recently observed plasma AVP to be two times higher in 48 males with low renin hypertension than in 29 normotensive subjects. Preibusz et al.,19 with a smaller number of patients, found that plasma AVP levels were significantly elevated in male compared to female subjects with established hypertension. Earlier studies had indicated that antidiuretic activity in the urine of hypertensive patients was elevated. 20, 21

We sought to determine whether the changes in AVP concentrations in essential hypertension were primary or secondary, and whether they contributed to the elevation of blood pressure. Recent studies from our laboratory showed that subjects with moderate hypertension were as capable as normal subjects of suppressing plasma AVP in response to water load. Both the fall of plasma osmolality and the magnitude of AVP suppression were similar in normal and hypertensive subjects. The latter were also able to increase their plasma AVP and to concentrate their urine to a level as high as that in normotensive subjects in response to 24-hour water restriction and stimulation by l-deamino-8-D-AVP. 22 In other recent studies we demonstrated that AVP secretion in response to removal of 480 ml of whole blood over an 8- to 15-minute period did not differ in normal and hypertensive subjects. 23 These data indicate that the elevations of AVP in essential hypertension are probably a result of the primary overactivity of the AVP system.

**Long-term AVP Administration**

It has been shown that long-term administration of AVP resulting in plasma levels similar to those seen in hypertension does not sustain elevated arterial pressure. As shown in Figure 6, we continuously infused AVP for 2 to 4 weeks in normal dogs in amounts that increased plasma AVP levels to nearly 15 pg/ml. 24 When water intake was maintained at a fixed and constant level, a progressive increase in mean arterial pressure of nearly 40 mm Hg, together with an increase of total body weight of 1000 g, was observed by the ninth day of AVP infusion. Thereafter, arterial pressure and body weight decreased toward control values. The level of arterial pressure appeared to correlate best with plasma volume changes.

Infusion of the same amount of AVP for 2 weeks in dogs in which the total body fluid volume was servo-controlled to remain constant within ± 100 g through-

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**Figure 5. Changes in mean arterial pressure (MAP) response to increasing frequency of spinal cord stimulation.** Shown are five stimulus-response relationships determined during control (solid line), three doses of vasopressin, 0.02, 0.2, and 2.0 ng/kg/min, (dashed line), and recovery (solid line). Vasopressin had no measurable influence on MAP responses. (Modified from Osborn et al. 14 with permission.)
out the infusion demonstrated the role of fluid retention in high AVP states (see Figure 6). Specifically, in the absence of fluid retention, arterial pressure remained normal throughout the entire 2-week infusion period, indicating that AVP in these amounts produced hypertension solely by fluid retention. It is our present belief that if circulating AVP does contribute to hypertensive states, it does so primarily in a permissive manner through its water-retaining actions on the kidney. When renal mass is severely compromised, continuous infusion of AVP does appear to be capable of sustaining an elevated state of arterial pressure.

We recently reported a series of studies carried out in normal, conscious dogs to determine the ability of AVP to enhance the hypertensive action of sodium-retaining hormones or other vasoconstrictor agents. The combined and singular effects of long-term administration of angiotensin II, norepinephrine, aldosterone, and AVP were determined. Doses were chosen that resulted in only a small chronic rise of arterial pressure when each agent was administered alone. The results of these studies indicate that excess AVP, even in the presence of elevations of sodium-retaining hormones and other vasoconstrictor agents, does little to raise arterial pressure chronically.

Experimental Hypertension

AVP has been implicated in the pathogenesis of various types of experimental hypertension, especially in the sodium-dependent forms with mineralocorticoid excess. Its participation has been demonstrated in a number of ways. For example, deoxycorticosterone-salt hypertension does not develop in an AVP-deficient Brattleboro rat. Hofbauer et al. provided evidence that AVP contributes to the development of deoxycorticosterone-salt hypertension through both vascular and renal tubular effects, and showed attenuation of the hypertensive state with blockade. Long-term administration (6 weeks) of a vascular (V1) antagonist lowered blood pressure 15 mm Hg, while rats receiving a vascular and renal tubular (V1, V2) antagonist showed a 38 mm Hg reduction of pressure. Short-term AVP blockade by injections of either specific antiseraum or competitive antagonists of AVP have not provided a clear-cut answer to the question of the involvement of AVP as a vasoconstrictor agent. Some laboratories have reported a substantial fall of pressure, while others found no such decrease using various antagonists.

The effects of AVP vascular antagonists were recently studied in greater depth, and results in our laboratory indicate that in addition to the classic V1 receptors that mediate vasoconstriction, blood vessels may also contain V2-like receptors that result in vasodilatation. These effects can be seen when AVP is infused in the presence of a vascular (V1) antagonist in conscious dogs. With V1 receptors blocked, intravenously infused AVP results in a decrease of total peripheral resistance and an elevation of cardiac output (i.e., opposite to the hemodynamic responses normally seen with AVP infusion). Still to be determined is the extent to which reductions of vascular resistance in hypertensive states observed with AVP vascular antagonists are a result of AVP stimulation of unblocked vascular V2 vasodilator responses.

Other models of hypertension with increased salt intake have been examined for AVP dependency. These include renal clip hypertension, rats with reduced renal mass, Dahl salt-sensitive rats, and spontaneously hypertensive rats. In the early phase of renal hypertension, rats fed a high sodium diet show a significant fall in blood pressure in response to an AVP antagonist. DiPette et al. found that AVP played an important role in hypertension obtained in rats with...
85% of their renal mass removed while they were receiving 24-hour intravenous infusion of isotonic saline. AVP may play a role, particularly in the very early stages of saline hypertension, as seen by the significant lowering of arterial pressure with an AVP vascular antagonist in acute hypertension induced in anephric rats by infusion of hypertonic saline.\textsuperscript{37, 38} Plasma AVP does not appear to play an important role in the maintenance of hypertension in Dahl salt-sensitive rats\textsuperscript{39} or spontaneously hypertensive rats even though plasma AVP levels are slightly increased.\textsuperscript{39, 40} We reviewed the evidence for this recently.\textsuperscript{15}

In summary, plasma AVP is believed to participate in hypertension because of its potent vasconstrictor actions, potent interactions with the autonomic nervous system, and effects of fluid and electrolyte homeostasis, and because it has been found to be inappropriately elevated in many forms of hypertension. The link between plasma AVP and hypertension remains unclear, however, because long-term elevations of AVP alone cannot sustain volume expansion or hypertension, elevated AVP does not increase the hypertension produced by chronic elevations of other vasoconstrictors and sodium-retaining hormones, and the hypertensive effects of AVP vascular antagonists are difficult to interpret due to the recent discovery of vascular vasodilatorlike receptors.

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### VASOPRESSIN AND ARTERIAL PRESSURE REGULATION/Cowley and Liard

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