Effects of vasopressin on the circulation and its baroreflex control in healthy men

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ABSTRACT Information on the hemodynamic effects of vasopressin (AVP) in healthy humans is very limited despite its known importance in body fluid homeostasis and release in pathologic states such as hemorrhage and trauma. Although it is a potent vasoconstrictor in vitro, it does not cause the expected rise in arterial pressure when given systemically to animals with intact baroreflexes. It has been proposed that this is because AVP facilitates baroreflex control of the circulation. In this study, we assessed the effect of infusion of AVP on resting circulatory variables and on the baroreflex control of forearm vascular resistance and heart rate in healthy men. AVP in a dose of 0.4 ng/kg/min, which raised plasma level of AVP to 24 ± 4 pg/ml, a value known to have a significant antidiuretic effect, had little hemodynamic effect, producing only mild bradycardia and a slight increase in central venous pressure. Reflex changes in heart rate during neck suction (−15 and −30 mm Hg) and neck pressure (+15 and +30 mm Hg) were not altered. Reflex responses to lower body negative pressure and to its release were also unchanged by this dose of AVP. In contrast, a higher dose of AVP (4 ng/kg/min), which raised plasma levels to 290 ± 41 pg/ml, a concentration known to occur as a result of hemorrhagic hypotension and circulatory stresses, did cause hemodynamic changes. There was tachycardia (from 63 ± 2 to 68 ± 2 beats/min), a decrease in pulse pressure (from 62 ± 2 to 53 ± 2 mm Hg), an increase in central venous pressure (from 2.6 ± 0.5 to 4.1 ± 0.4 mm Hg), and surprisingly in view of the known vasoconstrictor effect of AVP, an increase in forearm flow (from 4.4 ± 0.7 to 5.9 ± 1.2 ml/min/100 ml tissue) and a decrease in forearm vascular resistance (from 24 ± 4 to 18 ± 3 U); there was no significant change in mean arterial pressure (from 83 ± 2 to 83 ± 3 mm Hg). Reflex changes in heart rate were unaltered. The maximal vasoconstrictor response in the forearm attained during lower body negative pressure was not influenced by AVP, but the reflex vasodilator response to the sudden release of lower body negative pressure was significantly augmented, vascular resistance falling to 23 ± 4 U before and 13 ± 2 U during AVP. The unanticipated findings in this study include the biphasic changes in heart rate with increasing doses of AVP, the absence of a pressor response, and the vasodilatation in forearm vessels. We speculate that the vasodilatation in the forearm is the result of an increase in central venous pressure and a facilitated baroreflex-mediated withdrawal of sympathetic tone.

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ARGININE VASOPRESSIN (AVP) is a potent vasoconstrictor of isolated arterial segments in vitro. However, when AVP is infused into intact animals it does not produce the expected rise in mean arterial pressure. It has been shown that this paradox occurs because the direct vasoconstrictor effects of AVP are buffered by baroreflex mechanisms, and that marked rises in mean arterial pressure do occur in animals with denervation of carotid and aortic baroreceptors. Because the magnitude of the depressor reflex effects of AVP is greater than that produced by other vasoconstrictor agents, it has been suggested that AVP has a specific facilitatory effect on the baroreflex control of the circulation.

Studies assessing the effect of AVP on baroreflexes directly have, however, yielded conflicting results. There appear to be species differences, as demonstrated by Sharabi et al., who showed that AVP augmented reflex-induced inhibition of lumbar sympathetic nerve activity in anesthetized rabbits but not in rats.
There are also differential effects on the efferent reflex pathways, as demonstrated by Cowley et al., who showed that in anesthetized dogs with isolated carotid sinuses, AVP increased the gain of the reflex control of vascular resistance but not that of heart rate.

There have been few studies on the effect of AVP on the circulation and no direct studies on its effect on baroreflex control in humans. Stead et al. demonstrated that intramuscular AVP had no effect on venous tone in normal humans after nitrites. Kitchen made the surprising and unexplained observation that the direct infusion of AVP into a brachial artery decreased forearm flow whereas intravenous infusion increased flow. Mohring et al. studied two patients with impaired cardiovascular reflexes and three normal subjects and reported that the pressor response to AVP was markedly enhanced in the patients, and that the enhancement was greater than with norepinephrine or angiotensin. Wagner and Braunwald reported that in four normal subjects, the pressor effect of a large intravenous dose of Pitressin (500 mU) became apparent only after ganglionic blockade. These investigators also indicated that the potency of the hormone was 500 to 1000 times greater in patients with orthostatic hypotension. These studies suggest that in man, as in animals, AVP may facilitate the inhibitory influence of baroreflexes on the circulation.

The purpose of the present study, therefore, was to assess the influence of AVP on the circulation and on the baroreflex control of vascular resistance and heart rate in healthy men. We first used a small dose of AVP (0.4 ng/kg/min) that was sufficient to cause increases in plasma AVP known to produce a maximal antidiuretic response. When this dose was found to have negligible or no hemodynamic effects, a higher dose, sufficient to cause increases in blood levels in the range reported with severe hemorrhagic hypotension, was given in an attempt to assess the potential contribution of AVP to circulatory adjustments under severe stresses.

Methods

Subjects. Eighteen healthy male volunteers from 18 to 35 years old were studied. Each subject gave written informed consent. The study protocols were approved by the Human Use Committee of the University of Iowa.

Measurements. Vascular pressures were measured with a Statham P231D pressure transducer and a Gould transducer amplifier calibrated with a mercury manometer using a horizontal plane 10 cm above the back of the supine subject as the zero reference point. Phasic and mean arterial pressures were measured directly with a radial arterial cannula placed in the nondominant arm. Central venous pressure was measured via a catheter passed into an intrathoracic vein from the antecubital fossa of the nondominant arm. Heart rate was measured with a cardiotachometer (Gould Instruments, Inc., Cleveland, OH) triggered by the electrocardiogram. RR intervals (in msec) were measured from the electrocardiogram by counting the time elapsed between successive beats recorded at fast paper speed of 50 mm/sec. All measurements were recorded on a Gould 2800S direct-writing physiologic recorder (Gould Instruments, Inc.).

Forearm blood flow was measured by venous occlusion plethysmography with a mercury-in-silicone rubber Whitney strain-gauge apparatus, as previously described. The strain gauge was placed approximately 5 cm below the antecubital crease of the dominant arm. The arm was elevated and supported so that the proximal forearm was approximately 10 cm above the anterior chest wall. The pressure in the venous occlusion cuff was 40 mm Hg. Circulation to the hand was arrested by inflation of the wrist cuff to 180 mm Hg during measurement of blood flow. Forearm flow (in ml/min/100 ml tissue) was calculated for each intervention from the mean of four to eight measurements made at 15 sec intervals over 2 min. Forearm vascular resistance (in U) was calculated by dividing the mean arterial pressure by the forearm flow.

Reflex stimulation. Two groups of studies were done. In the first, reflex responses to lower body negative pressure (LBNP) were assessed. In the second, reflex changes in heart rate in response to neck suction and neck pressure were measured. The first group included 11 subjects and the second included seven other subjects.

Group 1: responses to LBNP

Vasoconstriction. Reflex vasoconstriction was produced by LBNP of −10, −20, and −40 mm Hg. The lower half of the body was enclosed up to the iliac crest in a sealed chamber and LBNP was applied for 2 min at each level by variable suction. LBNP of −10 and −20 mm Hg lowers central venous pressure without changing arterial pressure significantly and the reflex changes are produced by unloading cardiopulmonary receptors and decreasing activity of sensory afferents. This intervention predominantly triggers vasoconstriction in the forearm. LBNP of −40 mm Hg, however, lowers both central venous and mean arterial pressure. As a result of the unloading of both arterial and cardiopulmonary receptors, the reflex response includes more pronounced forearm vasoconstriction and tachycardia.

Vasodilation. Reflex vasodilation was produced by the sudden cessation of LBNP of −40 mm Hg with a consequent immediate increase in venous return and elevation of central venous and arterial pressures. The reflex responses reported are the average hemodynamic variables over a 1 min period after cessation of LBNP. Because of the steepness and variability of the first flow curve immediately after release of LBNP and the potential for an inaccurate calculation, we excluded the first curve and averaged the flow curves during the following minute.

Group 2: responses to neck suction and pressure. Reflex changes in heart rate (RR interval) were produced with a variable-pressure neck chamber. Neck pressure of +15 and +30 mm Hg and neck suction of −15 and −30 mm Hg were applied 800 msec before the P wave of the electrocardiogram for 10 sec. The resting RR interval was contrasted to the longest RR interval occurring during the application of neck suction and to the shortest RR interval during neck pressure. The measurements were made during held expiration both before and during the interventions. Each intervention (pressure or suction) was repeated five times and the results in each subject represent the average of five such measurements.

AVP. AVP (Pitressin, Parke-Davis, Inc.) diluted with 5% dextrose to a concentration of 150 ng/ml was infused constantly via the central venous catheter to a total of 18 subjects. AVP was...
infused at a rate of 0.4 ng/kg/min (low dose) to elevate plasma levels into the range where they have their maximal antidiuretic action (10 to 30 pg/ml)\(^2\) and at a rate of 4 ng/kg/min (high dose) to elevate plasma levels to the range seen in severe hemorrhagic hypotension and circulatory stresses (50 to 500 pg/ml).\(^2, 11, 12, 13\) Plasma AVP levels were measured by the radioimmunoassay technique.\(^20\) Resting AVP levels were calculated as the mean of levels in three samples, one taken immediately after obtaining informed consent but before placement of any instrumentation, one taken after the insertion of arterial and venous lines and placement of the electrocardiogram equipment, strain gauge, LBNP chamber, and neck chamber as appropriate but before any interventions, and a third taken after the completion of the reflex stimulation protocol. AVP values at each dose level represent the mean of those in two samples, one taken 10 min after commencement of the infusion just before the reflex intervention and the other one on completion of the reflex stimulation protocol after approximately 30 min of infusion. The recovery levels of AVP were taken 30 min after cessation of the infusion.

**Experimental protocols**

*Responses to LBNP — group 1.* Resting circulatory variables and the effect of the application and release of LBNP were assessed in four sequential periods, each lasting approximately 30 min. Period 1 was a control period during which the subject received a vehicle (saline), period 2 was a period of infusion of AVP at 0.4 ng/kg/min, period 3 was a period of infusion of AVP at 4 ng/kg/min, and period 4 was another control/recovery period beginning 30 min after cessation of the higher dose of AVP. During period 4 the subjects received the vehicle.

Four of the 11 subjects received only one dose of AVP (4 ng/kg/min) because of technical difficulties that prolonged the experimental period, and two did not undergo recovery period assessments because of discomfort.

*Responses to neck suction and pressure — group 2.* Resting circulatory variables and the effects of reflex stimulation with neck pressure or suction were assessed in each of seven subjects during three sequential periods lasting approximately 30 to 40 min each. Period 1 was a control period during which vehicle (saline) was infused, period 2 was a period of infusion of AVP at 0.4 ng/kg/min, and period 3 was a period of infusion of AVP at 4 ng/kg/min. We did not carry out any studies during a recovery period after AVP in this group because of the discomfort caused by the neck collar over a period of 2 to 3 hr. Furthermore, the responses were unchanged by AVP.

**Statistical analysis.** Results were expressed as a mean ± SEM. Statistical analysis was done by paired t test. Because multiple comparisons were made, the Bonferroni correction was used.\(^21\)

**Results**

**Blood levels of AVP during infusions.** Plasma AVP was 5.5 ± 0.4 pg/ml (\(n = 18\)) during the control period before the AVP infusion. After the infusion of 0.4 ng/kg/min, AVP plasma levels rose to 24 ± 4 pg/ml (\(n = 14\)) and after 4 ng/kg/min AVP they rose to 290 ± 41 pg/ml (\(n = 18\)). Thirty minutes after the AVP infusion plasma levels had fallen to 20 ± 4 pg/ml (\(n = 9\)).

**Influence of AVP on resting hemodynamics**

*AVP, 0.4 ng/kg/min.* In 14 subjects this low dose of AVP decreased resting heart rate from 64 ± 2 to 61 ± 2 beats/min and increased central venous pressure from 2.8 ± 0.6 to 3.5 ± 0.6 mm Hg (\(p < .05\)). Systolic, diastolic, and mean arterial pressures as well as pulse pressure, forearm flow, and forearm vascular resistance were unchanged (tables 1 and 2).

*AVP, 4 ng/kg/min.* AVP, 4 ng/kg/min, caused a significant increase in heart rate and central venous pressure, a fall in systolic and pulse pressures without a change in diastolic or mean arterial pressure, and a rise in forearm flow with a fall in forearm vascular resistance (\(p < .05\); tables 1 and 2; figure 1).

**Recovery.** Central venous pressure, pulse pressure, forearm flow, and forearm vascular resistance all returned to control levels in the recovery period. Heart rate fell slightly below the control value (table 1).

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### TABLE 1

**Effect of two doses of AVP on resting hemodynamic measurements**

<table>
<thead>
<tr>
<th></th>
<th>Period 1 (control)</th>
<th>Period 2 (0.4 ng/kg/min AVP)</th>
<th>Period 3 (4 ng/kg/min AVP)</th>
<th>Period 4 (recovery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>63 ± 2</td>
<td>61 ± 2(^a)</td>
<td>68 ± 2(^a)</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>128 ± 3</td>
<td>128 ± 4</td>
<td>120 ± 4(^a)</td>
<td>122 ± 4</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>66 ± 2</td>
<td>67 ± 3</td>
<td>66 ± 2</td>
<td>68 ± 2</td>
</tr>
<tr>
<td>PP (mm Hg)</td>
<td>62 ± 2</td>
<td>59 ± 3</td>
<td>53 ± 2(^a)</td>
<td>55 ± 2</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>83 ± 2</td>
<td>85 ± 3</td>
<td>83 ± 3</td>
<td>83 ± 6</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>2.6 ± 0.5</td>
<td>3.5 ± 0.6(^a)</td>
<td>4.1 ± 0.4(^a)</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>Forearm flow (ml/min/100 ml)</td>
<td>4.4 ± 0.7</td>
<td>5.4 ± 1.3</td>
<td>5.9 ± 1.2(^a)</td>
<td>4.8 ± 0.9</td>
</tr>
<tr>
<td>Forearm vascular resistance (U)</td>
<td>24 ± 4</td>
<td>18 ± 3</td>
<td>18 ± 3(^a)</td>
<td>23 ± 5</td>
</tr>
</tbody>
</table>

The data are mean ± SE and include values from two groups of 18 subjects (group 1, 11 subjects and group 2, seven subjects). Measurements of forearm blood flow were carried out in group 1. Four subjects in group 1 did not receive the low dose of AVP. The recovery period (4) was limited to group 1 and in two subjects the study was ended before the recovery period (see text for explanation).

SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; MAP = mean arterial pressure; CVP = central venous pressure.

\(^a\)\(^p < .05\) compared with control.
TABLE 2

Effect of two doses of AVP on hemodynamic measurements before and during the application and release of LBNP (-40 mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>0.4 ng/kg/min AVP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resting -40 mm Hg Release of LBNP</td>
<td>Resting -40 mm Hg Release of LBNP</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>2.1 ± 0.7 -2.8 ± 0.6 3.3 ± 0.4</td>
<td>2.6 ± 1.0 -2.3 ± 0.7 2.5 ± 0.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>63 ± 3 81 ± 5 64 ± 3</td>
<td>60 ± 3 86 ± 7 66 ± 3</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>125 ± 5 121 ± 5 124 ± 5</td>
<td>122 ± 5 113 ± 5 120 ± 6</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>65 ± 3 69 ± 4 67 ± 3</td>
<td>64 ± 4 64 ± 6 63 ± 5</td>
</tr>
<tr>
<td>PP (mm Hg)</td>
<td>60 ± 2 53 ± 3 58 ± 3</td>
<td>56 ± 2 51 ± 3 56 ± 3</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>82 ± 3 81 ± 4 83 ± 3</td>
<td>81 ± 4 78 ± 5 80 ± 5</td>
</tr>
<tr>
<td>Forearm flow (ml/min/100 ml)</td>
<td>4.4 ± 0.7 2.7 ± 0.6 4.7 ± 0.8</td>
<td>5.4 ± 1.3 3.6 ± 1.0 7.1 ± 1.4</td>
</tr>
<tr>
<td>Forearm vascular resistance (U)</td>
<td>24 ± 4 40 ± 6 23 ± 4</td>
<td>18 ± 3 29 ± 5 14 ± 2</td>
</tr>
</tbody>
</table>

Data are mean ± SE. Eleven subjects were in this group. Four did not receive the low dose of AVP and in two the study was ended before the recovery period (see text for explanation).

SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; MAP = mean arterial pressure; CVP = central venous pressure.

*p < .05 compared with corresponding values before AVP (control).

Influence of AVP on reflex responses to LBNP — group 1

Reflex vasoconstriction in response to LBNP. With the application of LBNP of -10, -20, and -40 mm Hg there were graded increases in forearm vascular resistance (figure 2). During the infusion of 0.4 ng/kg/min AVP there was no change in the response to LBNP (table 2 and figure 3).

After the high dose of AVP (4 ng/kg/min), resting forearm vascular resistance fell, but the maximal vasoconstrictor level attained with the application of -40 mm Hg LBNP was similar to that seen in the control state (table 2; figures 2 and 3). The stimulus for reflex vasoconstriction is the fall in central venous and arterial pressure. The absolute levels of central venous and mean arterial pressures during LBNP were comparable before (-2.8 ± 0.6 and 81 ± 4 mm Hg, respectively) and during 4.0 ng/kg/min AVP (-2.8 ± 0.6 mm Hg; 78 ± 5 mm Hg, respectively). The fall in central venous pressure with LBNP was greater during infusion of 4.0 ng/kg/min AVP because of the higher resting levels of central venous pressure (table 2 and figure 3).

During the recovery period, resting values and responses to LBNP were not statistically different from control (table 2 and figure 3).

Reflex vasodilatation in response to sudden cessation of LBNP. With the sudden cessation of -40 mm Hg LBNP there was a rise in central venous and arterial pressure and a reflex fall in forearm vascular resistance (table 2). There were no differences between the rise in central venous pressure, the rise in arterial pressure, and the maximum pulse pressure with the release of LBNP during the control period, low- and high-dose AVP, and recovery (table 2). Thus, the stimulus for reflex dilatation was similar during each period. There was no difference in the degree of reflex dilatation obtained with the stimulus during the control period, during low-dose AVP, and after the recovery from the high dose of AVP (table 2). During the high dose of AVP, however, vasodilatation was significantly enhanced (figure 3). Forearm vascular resistance fell from 39 ± 9 to 13 ± 2 U during infusion of AVP compared with a fall from 40 ± 6 to 23 ± 4 U dur-

FIGURE 1. Typical tracing from one subject showing the effect of 4 ng/kg/min AVP. Forearm flow was measured by venous plethysmography, an increased slope indicating an increase in flow. AVP caused a fall in pulse pressure and an increase in central venous pressure (CVP), heart rate, and forearm flow.
ing the control period (p < .05; table 2 and figure 3).

Reflex changes in heart rate in response to LBNP. During the application of LBNP, increases in heart rate were similar during the control period, the infusions of AVP at both levels, and recovery (table 2).

The reflex bradycardia seen with sudden cessation of LBNP was similar during the control period, the period of infusion of AVP at both levels, and the recovery period (table 2).

Effect of AVP on reflex heart rate responses to carotid suction and pressure — group 2. Application of -15 and -30 mm Hg neck suction caused reflex bradycardia, with increases in RR interval of +105 ± 23 and +154 ± 34 msec, respectively, over that at control. This increase was not influenced significantly by 0.4 or 4 ng/kg/min AVP (table 3).

Neck pressure of 15 and 30 mm Hg caused an increase in heart rate with a fall in RR interval of -49 ± 12 and -101 ± 15 msec from the control state and similar changes were obtained during infusion of AVP at 0.4 and 4 ng/kg/min (table 3).

AVP thus did not alter the reflex changes in heart rate during the application of neck pressure or neck suction.

Discussion

We have measured circulatory responses to low and high doses of AVP in healthy men. These responses represent the net result of the direct and indirect (reflex) effects of AVP. The major findings are as follows:

1. The low dose of AVP, which increased blood
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levels from 5 to 24 pg/ml, levels at which AVP has a potent antidiuretic effect (a) had essentially a minor circulatory response, producing a mild bradycardia and a small increase in central venous pressure, and (b) did not alter reflex circulatory responses to LBNP, nor the heart rate responses to neck pressure or suction. Thus, it appears that at this blood level the hormone does not play an important role in circulatory adjustments but is predominantly an antidiuretic hormone regulating blood volume.

(2) After high doses of AVP that induced blood levels of more than 200 pg/ml, which are similar to those seen with significant circulatory stresses and hemorrhagic shock, the hormone had an influence on the cardiovascular system. (a) It caused an increase in resting heart rate and central venous pressure, and a fall in pulse pressure that may reflect a fall in stroke volume. Despite its known vasoconstrictor effect, AVP did not increase arterial pressure and caused vasodilation in the forearm rather than the expected vasoconstriction. (b) AVP did not facilitate the baroreflex control of heart rate nor the vasoconstrictor response to LBNP in humans. It did, however, augment reflex vasodilation observed after the sudden cessation of LBNP.

There were thus several unanticipated results that had not been heretofore described in healthy humans. The discussion will cover the following points: (1) the selection of the dose levels used in these studies, (2) heart rate responses to the low dose of AVP, (3) interpretation of the cardiovascular response to high-dose infusions of AVP, and (4) speculation on the mechanisms involved in the reflex responses to LBNP and carotid suction and pressure.

Selection of the dose levels. AVP will exert potent antidiuretic effects with small changes in plasma levels. Our low dose of AVP produced blood levels similar to those found with water deprivation. We had anticipated that there might be significant effects on resting hemodynamics and reflex responses to LBNP and to changes in carotid sinus pressure. Because this dose did not produce major hemodynamic changes and because it was important to determine whether the hormone had any significant cardiovascular effects in healthy humans, we gave a higher dose to produce the blood levels seen under severe circulatory stresses.

### TABLE 3

Effect of two doses of AVP on carotid reflex control of HP in seven subjects

<table>
<thead>
<tr>
<th></th>
<th>HP (msec) before and during neck suction</th>
<th>HP (msec) before and during neck pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>0.4 ng/kg/min</td>
</tr>
<tr>
<td></td>
<td>AVP</td>
<td>AVP</td>
</tr>
<tr>
<td>Before</td>
<td>1018 ± 44</td>
<td>1034 ± 66</td>
</tr>
<tr>
<td>During</td>
<td>1125 ± 26</td>
<td>1124 ± 55</td>
</tr>
<tr>
<td>Δ HP</td>
<td>+ 105 ± 23</td>
<td>+ 89 ± 20</td>
</tr>
<tr>
<td></td>
<td>1026 ± 48</td>
<td>1031 ± 55</td>
</tr>
<tr>
<td>Before</td>
<td>1179 ± 49</td>
<td>1177 ± 57</td>
</tr>
<tr>
<td>Δ HP</td>
<td>+ 154 ± 34</td>
<td>+ 146 ± 27</td>
</tr>
</tbody>
</table>

Data are mean ± SE. Seven subjects were in this group (group 2).

HP = heart period.

<sup>^</sup>p < .05 compared with control.

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Heart rate responses to low-dose AVP. The low dose of AVP caused a small fall in resting heart rate. This occurred at a time when there was no change in mean arterial or pulse pressure and there was no vasoconstriction that might trigger reflex bradycardia through activation of the baroreceptors; it cannot therefore be ascribed to a reflex change in autonomic tone. Furthermore, there was no indication from the reflex responses to neck suction and pressure or to LBNP that there were alterations in the reflex autonomic control of heart rate. We speculate, therefore, that there may have been a central effect of AVP with activation of vagal efferents as has been reported in animals. Many workers have shown that infusion of AVP in animals produces bradycardia, and this may occur even if there is no rise in arterial pressure. It has been proposed by most investigators that this is due to enhanced vagal tone. Others, however, have postulated an effect of AVP on heart rate independent of the efferent vagus since they observed bradycardia in rabbits after administration of atropine. The mechanism of this effect, however, remains unclear since it has not been possible to demonstrate a direct negative chronotropic effect of AVP in vitro. It has also been proposed that the negative chronotropic effect may be indirectly mediated by a significant reduction in coronary flow.

Interpretation of cardiovascular effects of infusions of the high dose of AVP

Increase in heart rate. The high dose of AVP produced a significant increase in heart rate (table 1).

The mechanism of this tachycardia could well be related to the decrease in systolic and pulse pressure with an increase in sympathetic drive to the heart. Tachycardia with AVP has not been previously reported in animals, but Morhing et al. noticed an increase in heart rate in two of three normal subjects with the infusion of high-dose AVP (2.4 pmol/kg/min). The increase in heart rate obtained with this higher dose of AVP may thus represent the net response to a slowing effect of vagal efferents and an increase in sympathetic drive secondary to a fall in pulse pressure. Tachycardia became manifest in these normal men possibly because of their high resting vagal and low sympathetic tones.

Changes in central venous pressure and pulse pressure. Central venous pressure increases during the infusion of AVP. Elevation of cardiac filling pressures has been described previously in animals. This rise in central venous pressure may reflect impairment of left ventricular function or vasoconstriction with decreased compliance of capacitance vessels and shift of blood volume centrally. There is little evidence that AVP has a direct effect on veins in animals, and indeed Stead et al. found no effect of intramuscular AVP on venous tone in humans. However, it is possible that in humans AVP has a specific effect on the splanchnic bed and constriction of this bed may be the mechanism of elevation of venous pressure.

The reduction in pulse pressure may reflect reduced stroke volume also as a result of impaired left ventricular function. If the decrease in stroke volume were sufficient to cause a fall in cardiac output, then one would have to postulate that there was an overall increase in total systemic resistance to maintain arterial pressure at control levels. This is the situation reported in animals. Such an increase in total systemic resistance in the face of vasodilatation in the forearm may indicate significant constriction in other vascular beds. Indeed, Bosch et al. reported that AVP caused significant splanchnic vasoconstriction in man.

Forearm vasodilatation. AVP caused forearm vasodilatation, which, in view of its known vasoconstrictor effect, was an unexpected result. Kitchen, also showed that prolonged intravenous infusions of AVP caused an increase rather than a decrease in forearm flow in contrast to direct intra-arterial infusions, which caused a transient fall in forearm flow. They were unable to explain these observations. We postulate that the direct vasoconstrictor effect of AVP seen with intra-arterial infusions is counterbalanced by an indirect effect, that of withdrawal of sympathetic tone from forearm vessels. This withdrawal may be the result of central inhibition of sympathetic outflow or of reflex withdrawal due to elevation of central venous pressure, which stimulates cardiac sensory afferents and has inhibitory influences on the sympathetic nervous system. This vasodilatation may be specific to forearm vessels, which appear to be preferentially controlled by cardiopulmonary afferents. Although there is vasodilatation in this bed, there may be vasoconstriction in others where the indirect or reflex effects are not so great as to counterbalance stronger direct vasoconstrictor effects of the hormone. Our interpretation that the vasodilatation caused by AVP is the net effect of a direct vasoconstrictor action and a reflex sympathetic withdrawal is speculative and cannot be definitely confirmed without selective blockade of the V, receptors and of the sympathetic nervous system.

Speculation on mechanisms involved in reflex responses to LBNP and carotid suction and pressure

Baroreflex control of heart rate. In animal experiments, the pressor effect of AVP is counterbalanced by reflex effects and the bradycardia observed after AVP is
greater in magnitude than that seen with equipressor doses of phenylephrine.26 For these reasons, it has been suggested that the hormone specifically facilitates the baroreflex control of heart rate. This hypothesis was supported by Imai et al.,36 who demonstrated impairment of the gain of baroreflex control of heart rate that could be restored to normal by the addition of AVP in Brattleboro rats. AVP has been shown to augment the arterial baroreflex inhibition of heart rate in anesthetized6 and conscious rabbits.37 However, recent studies by Elliott et al.28 in conscious rabbits and Cowley et al.7 in anesthetized hypophysectomized dogs with isolated carotid sinuses have not confirmed this observation. Both groups of workers showed that AVP caused resting bradycardia, but the gain of the baroreflex as assessed by the slope of the line relating heart rate to the change in arterial or carotid sinus pressure was not influenced by the hormone. In our experiments in healthy men we were unable to demonstrate an influence of AVP on the reflex changes in heart rate produced by neck suction or pressure and stimulation of the carotid baroreflex. Furthermore, we were unable to demonstrate any influence of AVP on the increase in heart rate that occurred with the application of LBNP or on the bradycardia that followed the sudden release of LBNP when cardiopulmonary, aortic, and carotid afferents were stimulated. It appears, therefore, that AVP influences the resting heart rate but does not alter the changes in rate in response to arterial or cardiopulmonary reflexes in humans. These findings are similar to some of the experimental results in animals.7,28

Modification of baroreflex control of forearm resistance. The maximal constrictor response obtained during LBNP was the same before and during the infusion of AVP. The resting forearm vascular resistance, however, was lower during AVP and one therefore might have expected the increase in resistance during LBNP to be less.28 An important question is whether the stimulus for the increase in resistance was the same. The values for central venous and arterial pressure during LBNP were similar before and during the infusion of AVP. However, the fall in central venous pressure with LBNP during AVP was greater because the baseline central venous pressure was higher. Thus, although one might speculate that the vasoconstrictor response was greater because of lower baseline resistance, the stimulus (i.e., the fall in central venous pressure) was also greater, and a definitive conclusion about facilitation of reflex vasoconstriction during LBNP cannot be reached.

In contrast to the vasoconstrictor response to LBNP, the reflex vasodilatation seen after the release of LBNP was markedly enhanced during the infusion of high-dose of AVP. This finding is compatible with previous results that demonstrate enhanced withdrawal of sympathetic nerve activity, both lumbar6,39 and renal.37,40 These studies showed that AVP produced a greater fall in sympathetic nerve activity than equipressor doses of other agents. Cowley et al.7 showed in anesthetized hypophysectomized dogs with isolated carotid sinuses that, despite the lack of effect of AVP on the reflex control of heart rate, there was an alteration in the gain of the reflex control of total peripheral resistance. The gain was increased when carotid sinus pressure was lowered, suggesting enhanced vasoconstriction, but there was no change with increases in carotid sinus pressure (i.e., no enhancement of vasodilatation). These results are not necessarily in conflict with ours because they reflect changes in total peripheral resistance whereas we examined only one vascular bed.

It appears that the resting vasodilatation and the enhancement of reflex vasodilatation in our study could be related to activation of cardiopulmonary receptors. At rest, there was an elevation in central venous pressure that stimulated cardiopulmonary afferents and caused reflex vasodilatation. At the same time, mean arterial pressure was unchanged and pulse pressure was decreased, which would be expected to cause forearm vasoconstriction. Zoller, Johnson, and Abboud and their colleagues16-18 have shown that the reflex control of forearm resistance is principally via the “low pressure” rather than “high pressure” receptors. Other authors have also shown activation of cardiopulmonary afferents in the presence of AVP.40,41 Central venous pressure is increased by AVP23,32 and Hasser et al.40 have shown that AVP interacts with cardiopulmonary afferents to inhibit sympathetic outflow. Indeed, in recent experiments by Undesser et al.37 it was shown that in the presence of sinoaortic denervation, there was still a significant inhibition of lumbar sympathetic nerve activity by AVP that was not seen with phenylephrine and appeared to be due to stimulation of cardiopulmonary afferents. Recent animal work in our laboratory has demonstrated that AVP sensitizes left ventricular receptors to changes in cardiac filling pressures.41 Thus, the vasodilatation at rest and the enhanced reflex vasodilatation may be due to the mechanical stimulation of the cardiopulmonary afferents by the increase in central venous pressure and to sensitization of the receptors. In addition, a central facilitation of the baroreflex may also contribute to the augmented reflex vasodilatation.37

Several important conclusions are arrived at in these studies. First, AVP does not produce in humans the
circulatory responses, and in particular the pressure responses, that one would have anticipated from a review of the animal work. At low doses of AVP that cause significant antidiuretic activity, the hormone has negligible cardiovascular effects. At high doses that cause blood levels comparable to those observed during severe hemorrhagic hypotension, the circulatory responses do not seem to be optimal for the maintenance of cardiovascular homeostasis. Specifically, the vasodilatation in forearm vessels along with a high central venous pressure and a fall in pulse pressure suggest some myocardial depression and maldistribution of blood flow. We speculate that these hemodynamic responses represent the balance of direct effects and indirect or reflex effects induced by AVP.

There was no alteration of reflex responses to activation of arterial baroreflexes or cardiopulmonary reflexes induced by a small dose of AVP in humans. Facilitation of reflex changes in heart rate and reflex vasoconstriction was not seen in humans even after the high dose of AVP. Conversely, facilitation of reflex vasodilatation was apparent. This finding explains the unusually pronounced enhancement of pressor sensitivity to AVP in humans with impaired cardiovascular reflexes. 10, 11

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References
AYLWARD et al.


Effects of vasopressin on the circulation and its baroreflex control in healthy men.
P E Aylward, J S Floras, W N Leimbach, Jr and F M Abboud

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