PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **179**, 192–196 (1985)

# Systemic and Renal Hemodynamic Responses to Vascular Blockade of Vasopressin in Conscious Dogs with Ascites (42084)

RICHARD C. VARI, RONALD H. FREEMAN, JAMES O. DAVIS, AND WILLIAM D. SWEET

*Department of Physiology, University of Missouri, Columbia, Missouri 65212*

*Abstract.* A role for arginine vasopressin has been implicated in the compensatory control of arterial blood pressure in several animal models with reported increases in plasma levels of arginine vasopressin. A threefold elevation in plasma vasopressin has been reported in conscious dogs following constriction of the inferior vena cava. In the present study, infusion of the arginine vasopressin antagonist [1-(β-mercapto-β,β-cyclopentamethylenepropionic acid), 2-*O*-methyltyrosine] $Arg^8$-vasopressin into conscious dogs with chronic caval constriction did not decrease mean arterial blood pressure. However, the dose of infused antagonist completely blocked the pressor response to 2 μg of exogenous vasopressin. Also the antagonist produced no effect on heart rate, plasma renin activity, or urinary volume and electrolyte excretions. A slight, transient increase ($P \leq 0.05$) was observed in creatinine clearance and in PAH clearance following antagonist infusion, suggesting a possible decrease in renal vascular resistance. These data suggest that the direct vasoconstrictor actions of vasopressin contribute minimally, if at all, to blood pressure maintenance following chronic caval constriction. Alternatively, blockade of endogenous vasopressin receptors at the level of peripheral arterioles may have resulted in no depressor response due to a masking of this response by other compensatory hormonal and neural pressor systems. 

The participation of a direct pressor effect of endogenous vasopressin in the control of arterial blood pressure has been studied extensively (1, 2). Even though vasopressin is a very potent vasoconstrictor and hence possible effector of total peripheral resistance (3), there is very little evidence for a role of vasopressin in blood pressure regulation during basal, hydropenic states (1, 4–9). However, other studies suggest that vasopressin participates in compensatory blood pressure regulation in response to various physiological stimuli that increase plasma vasopressin levels (2, 10–15). Usually, however, the renin–angiotensin and sympathetic nervous systems are also activated by these stimuli and consequently an important role for vasopressin in compensatory blood pressure regulation has been questioned (2, 15). It has been reported that vasopressin partially maintains blood pressure following various degrees of hemorrhage in the conscious dog (16, 17) and the anesthetized rat (9, 18–20); however, this does not appear to be an important mechanism in response to hemorrhage in conscious rats (21). Also, Yamazaki and Sagawa could find no pressor contribution for vasopressin following a 10% blood volume hemorrhage in either the conscious or the anesthetized rabbit (22).

Constriction of the thoracic inferior vena cava to decrease venous return and atrial filling markedly elevates plasma renin activity and plasma aldosterone concentration and produces chronic salt and water retention and ascites in the dog (23). Threefold plasma levels of vasopressin have also been reported in this experimental model of low cardiac output (24, 25). To what extent this elevated level of plasma vasopressin contributes to the maintenance of a normal blood pressure in this experimental model is unknown. Therefore, the objectives of this study were to evaluate the changes in systemic and renal hemodynamics in the conscious dog with constriction of the thoracic inferior vena cava in response to blockade of the vascular vasopressin receptor with a specific competitive antagonist of arginine vasopressin.

**Methods.** Female mongrel dogs weighing between 21–30 kg were housed in metabolic cages and trained to lie quietly on a padded table. The dogs were fed a diet of 45 meq NaCl per day and daily electrolyte excretions



0037-9727/85 $1.50

were measured. The dogs were anesthetized with sodium pentobarbital and chronic femoral arterial and venous catheters were implanted, routed subcutaneously to the dorsal neck area, and exteriorized to the surface. One week later the dogs again were anesthetized with sodium pentobarbital and a constricting ligature was placed around the thoracic inferior vena cava to produce salt and water retention and ascites formation. Sodium and fluid retention were observed for at least 1 week postligation. The animals were placed on the padded table, and the mean arterial pressure and heart rate response to a 2 μg bolus injection of exogenous arginine vasopressin was obtained following control measurements. Several days later the acute experiment was performed in these conscious dogs according to the following protocol.

Creatinine and paraaminohippurate (PAH) were infused into the venous catheter for estimations of glomerular filtration rate and effective renal plasma flow, respectively. Mean arterial pressure and heart rate were continuously monitored via the chronic femoral arterial catheter. A bladder catheter was inserted for timed-urine collections. Each control, experimental, and recovery urine collection period was 30 min in duration with an arterial blood sample taken at the 15-min midpoint for determinations of plasma creatinine, PAH, $Na^+$, and $K^+$ concentrations. Plasma samples were also collected in chilled tubes with disodium ethylenediaminetetraacetate (EDTA) for measurement of plasma renin activity. Following two control collection periods the arginine vasopressin antagonist specific for the vascular vasopressin receptor [1-(β-mercapto-β,β-cyclopentamethylenepropionic acid), 2-*O*-methyltyrosine] $Arg^8$-vasopressin (Peninsula Laboratories) was given as a 10 μg/kg body wt bolus injection. The antagonist, $d(CH_2)_5Tyr(Me)AVP$, was infused continuously at a rate of 10 μg/kg/hr for the following two experimental clearance periods. The infusion of $d(CH_2)_5Tyr(Me)AVP$ was then discontinued and a 2 μg bolus injection of exogenous vasopressin was given to confirm the blockade of the pressor response to vasopressin. A recovery clearance period was obtained after the bolus injection of exogenous vasopressin.

Urine and plasma electrolytes were measured by flame photometry and creatinine and PAH concentrations were measured by spectrophotometry. Plasma renin activity was measured by radioimmunoassay (26). All data are expressed as the means ± SEM. Statistical analysis was performed using a one-way analysis of variance for repeated measurements with the least significant difference test applied for statistical differences at the $P \leq 0.05$ level.

**Results.** Prior to constriction of the inferior thoracic vena cava, daily sodium excretion averaged 43 ± 5 meq in these dogs. Following constriction the daily sodium excretion averaged less than 4.0 ± 0.5 meq and ascites formation occurred in all dogs. The major cardiovascular and renal responses to infusion of the vasopressin antagonist in seven conscious chronic caval dogs are presented in Table I. Mean arterial pressure and heart rate, 118 ± 4 mm Hg and 132 ± 6 beats/min, respectively, are similar to previously reported values in conscious caval dogs (23) and were unaffected by $d(CH_2)_5Tyr(Me)AVP$ infusion. Plasma renin activity, while predictably elevated following caval constriction was also unaffected by $d(CH_2)_5Tyr(Me)AVP$. Plasma sodium concentration (135 ± 4 meq/liter), potassium concentration (4.7 ± 0.2 meq/liter), and hematocrit (38 ± 2%) remained unchanged during $d(CH_2)_5Tyr(Me)$-AVP infusion.

Creatinine clearance increased transiently, ($P \leq 0.05$), to 73 ± 8 ml/min and PAH clearance increased to 222 ± 37 ml/min during the first experimental period. Effective renal blood flow, calculated from the PAH clearance and the hematocrit, also transiently increased from 282 ± 32 to 366 ± 54 ml/min ($P \leq 0.05$) during the first experimental period. Basal urinary sodium excretion averaged 4.4 ± 0.9 μeq/min and was unaffected by $d(CH_2)_5Tyr(Me)AVP$ infusion. Urinary potassium excretion decreased significantly during the second experimental period and during the recovery clearance period. Urinary fluid excretion did not change during the two experimental periods, but it decreased from 1.5 ± 0.3 to 0.6 ± 0.1 ml/min ($P \leq 0.05$) during the recovery period in which adequate blockade of the vascular vasopressin receptor was checked by infusion of 2 μg of exogenous vasopressin; this observation is presumptive

TABLE I. EFFECTS OF BLOCKADE OF THE VASCULAR RECEPTOR OF VASOPRESSIN ON SYSTEMIC AND RENAL HEMODYNAMIC FUNCTION IN CONSCIOUS CAVAL DOGS

| | MAP (mm Hg) | HR (beats/min) | $C_{cr}$ (ml/min) | $C_{PAH}$ (ml/min) | PRA (ng A1/ml/hr) | $\dot{V}$ (ml/min) | $\dot{V}_{NA}$ (μeq/min) | $\dot{V}_K$ (μeq/min) |
|---|---|---|---|---|---|---|---|---|
| $C_1$ | 117 ± 4 | 132 ± 4 | 58 ± 6 | 156 ± 17 | 19.3 ± 5.5 | 1.4 ± 0.3 | 5.2 ± 1.1 | 49.9 ± 10.8 |
| $C_2$ | 118 ± 4 | 133 ± 7 | 66 ± 7 | 192 ± 28 | 23.7 ± 6.8 | 1.5 ± 0.4 | 3.6 ± 0.7 | 66.1 ± 12.4 |
| $E_1$ | 121 ± 3 | 135 ± 7 | 73 ± 8* | 222 ± 37* | 25.1 ± 6.8 | 1.4 ± 0.4 | 3.2 ± 0.7 | 46.5 ± 10.5 |
| $E_2$ | 120 ± 3 | 130 ± 7 | 63 ± 9 | 170 ± 29 | 22.3 ± 5.6 | 1.2 ± 0.4 | 4.9 ± 1.2 | 35.5 ± 9.1* |
| Recovery | 120 ± 4 | 132 ± 6 | 62 ± 7 | 179 ± 24 | 20.4 ± 5.2 | 0.6 ± 0.1* | 3.4 ± 0.8 | 31.7 ± 9.1* |
| | ($n$ = 7) | ($n$ = 7) | ($n$ = 6) | ($n$ = 5) | ($n$ = 6) | ($n$ = 6) | ($n$ = 6) | ($n$ = 6) |

*Note.* MAP, mean arterial pressure; HR, heart rate; $C_{cr}$, creatinine clearance; $C_{PAH}$, PAH clearance; PRA, plasma renin activity; $\dot{V}$, urinary volume; $\dot{V}_{Na}$ and $\dot{V}_K$, urinary excretions of sodium and potassium. Data are expressed as means ± SEM. Animal numbers are given in parentheses.

* $P \leq 0.05$ from $C_1 + C_2$.

evidence that the tubular vasopressin receptor was not blocked by this antagonist.

The blood pressure and heart rate responses to 2 μg vasopressin before and after blockade with $d(CH_2)_5Tyr(Me)AVP$ are shown in Fig. 1. During the pretest, 2 μg of exogenous vasopressin produced a pressor response of 44 ± 4 mm Hg and decreased heart rate by 37 ± 10 beats/min. These responses were completely abolished and were not observed with infusion of the 2 μg of exogenous vasopressin following blockade with $d(CH_2)_5$-Tyr(Me)AVP.

**Discussion.** Current evidence suggests that arginine vasopressin may play a role in the compensatory support of arterial blood pressure in response to hemorrhage and water deprivation (5, 13, 16, 18). Plasma vasopressin levels have recently been shown to be elevated following chronic constriction of the inferior vena cava in conscious dogs (25). In the present study, infusion of a vasopressin antagonist $d(CH_2)_5Tyr(Me)AVP$, to block the vascular receptor for vasopressin, failed to produce a decrease in arterial blood pressure in this experimental animal model. Creatinine and PAH clearances, as well as effective renal blood flow, showed a transient but significant increase after infusion of $d(CH_2)_5Tyr$-(Me)AVP. These results might suggest that endogenous vasopressin possibly produces renal vasoconstriction and, thereby, decreases both glomerular filtration rate and effective renal blood flow in this experimental model. The direct contribution of endogenous vasopressin to blood pressure maintenance via its vasoconstrictor actions appears to be minimal in the caval dog, however, at least as judged by the failure of blood pressure to fall in response to vasopressin blockade. An indirect effect of vasopressin on blood volume and pressure in this experimental model through its actions on renal water excretion cannot be excluded from the present data.

From previous reports vasopressin has been shown to be a potent inhibitor of renin release (27). Both plasma vasopressin and renin levels have been reported to be elevated in conscious dogs following caval constriction (23, 25). Plasma renin activity was elevated 20-fold in the caval dogs in this study and was unaffected by infusion of $d(CH_2)_5Tyr$-(Me)AVP. Since there was no further increase

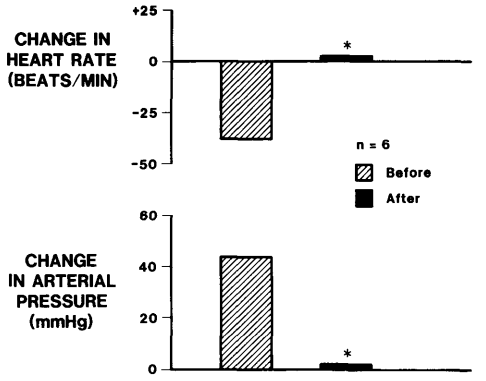


FIG. 1. Changes in heart rate and mean arterial pressure to vasopressin (2 μg, iv) before and after vascular vasopressin receptor blockade with $d(CH_2)_5Tyr(Me)AVP$ in conscious caval dogs. $*P \leq 0.05$ compared to response before $d(CH_2)_5Tyr(Me)AVP$ infusion.

in plasma renin activity following blockade of the vascular vasopressin receptor, the data suggest that endogenous levels of vasopressin are not sufficiently elevated to tonically suppress renin release in this animal model. Alternatively, vasopressin may suppress renin release by a mechanism not blocked by the antagonist used in this study. Relevant to this issue are the observations that exogenously infused arginine vasopressin inhibits renin secretion in dogs with either filtering or nonfiltering kidneys, suggesting that vasopressin's inhibition of renin secretion occurs by a nontubular action of the peptide. Further, since neither renal blood flow nor blood pressure changed during vasopressin infusion in the experiments of Shade *et al.* (28), these investigators suggested a direct inhibitory action of vasopressin on the juxtaglomerular cell membrane.

Urinary volume and electrolyte excretions also were unaffected by infusion of $d(CH_2)_5Tyr(Me)AVP$. Infusion of 2 μg of exogenous vasopressin for the purpose of checking the completeness of pressor blockade, however, produced a marked reduction in urinary volume. This observation coupled with no change in blood pressure following vasopressin infusion (Fig. 1) confirms adequate and specific blockade of the pressor response to exogenous vasopressin by the antagonist.

Several possible explanations may account for the apparent lack of a role of vasopressin in blood pressure regulation following chronic caval constriction. Although plasma vasopressin levels were not measured in this study, they have been reported elevated from a control level of 1.3 to 3.4 pg/ml in similar conscious caval dogs (25). While this indeed was a threefold elevation in plasma vasopressin concentration, these values are still well within normal physiological limits ranging from 0.3 to 30 pg/ml which has been reported in a variety of species (3). Therefore, the lack of a pressure fall during vasopressin blockade could have been due to an insufficient elevation of plasma vasopressin levels. Second, the high levels of plasma renin activity measured in these dogs and a possible increase of sympathetic nervous system activity (29) may have masked any effect of vasopressin's contribution to blood pressure maintenance.

Based on the observation that infusion of $d(CH_2)_5Tyr(Me)AVP$ failed to produce a decrease in arterial blood pressure, we therefore suggest that endogenous vasopressin contributes minimally to the maintenance of arterial blood pressure via its direct vasoconstrictor actions in conscious dogs following chronic constriction of the thoracic inferior vena cava.

However, since a transient increase in both glomerular filtration rate and effective renal blood flow was observed following infusion of $d(CH_2)_5Tyr(Me)AVP$, endogenous vasopressin might contribute to increased renal arteriolar tone in this experimental model.

We thank Mr. C. Gay, Ms. M. Flood, and Ms. G. Mortensen for their expert technical assistance and Ms. A. Nelson and Mr. S. Ozark for their secretarial assistance in the completion of this manuscript.

1. Reid IA, Schwartz J. Role of vasopressin in the control of blood pressure. In: Frontiers in Neuroendocrinology. New York, Raven Press, Vol 8:pp177–197, 1984.
2. McNeill JR. Role of vasopressin in the control of arterial blood pressure. Canad J Physiol Pharmacol **61**:1226–1235, 1983.
3. Cowley AW, Quillen EW, Skelton MM. Role of vasopressin in cardiovascular regulation. Fed Proc **42**:3170–3176, 1983.
4. Lohmeier TE, Smith MJ, Cowley AW, Manning RD, Guyton AC. Is vasopressin an important hypertensive hormone? Hypertension **3**:416–425, 1981.

5. Schwartz J, Reid IA. Role of vasopressin in blood pressure regulation in conscious water-deprived dogs. Amer J Physiol **244**:R74–R77, 1983.
6. Bussien JP, Waeber B, Nussberger J, Schaller MD, Gavras H, Hofbauer K, Brunner HR. Does vasopressin sustain blood pressure on normally hydrated healthy volunteers? Amer J Physiol **246**:H143–H147, 1984.
7. Paller MS, Linas SL. Role of vasopressin in support of blood pressure in potassium deficient rats. Kidney Int **24**:342–347, 1983.
8. Liard JF, Spadone JC. Hemodynamic effects of antagonists of the vasoconstrictor action of vasopressin in conscious dogs. J Cardiovasc Pharmacol **6**:713–719, 1984.
9. Laycock JF, Penn W, Shirely DG, Walter SJ. The role of vasopressin in blood pressure regulation immediately following acute hemorrhage in the rat. J Physiol **296**:267–275, 1979.
10. Gellai M, Silverstein JH, Hwang J, LaRochelle FT, Valtin H. Influence of vasopressin on renal hemodynamics in conscious Brattleboro rats. Amer J Physiol **246**:F819–F827, 1984.
11. Gavras H, Hutzinikolaou P, North WG, Bresnahan M, Gavras I. Interaction of the sympathetic nervous system with vasopressin and renin in the maintenance of blood pressure. Hypertension **4**:400–405, 1982.
12. Houck PC, Fisken-Olsen JJ, Britton SL, Romero JC. Role of Angiotensin and vasopressin on blood pressure of ganglionic blocked dogs. Amer J Physiol **244**:H115–H120, 1983.
13. Aisenbrey GA, Handelman WA, Arnold P, Manning M, Schrier RW. Vascular effects of arginine vasopressin during fluid deprivation in the rat. J Clin Invest **67**:961–968, 1981.
14. Mikami H, Kosoglov AT, Ferrario CM. Blood pressure regulation in chronic spinal dogs. Physiologist **25**:329, 1982.
15. Ryan KL, Thornton RM, Proppe DW. Effect of vasopressin blockade on blood pressure in euhydrated and dehydrated baboons. Physiologist **27**(4):215, 1984.
16. Cowley AW, Switzer SJ, Guinn MM. Evidence and quantification of the vasopressin arterial pressure control system in the dog. Circ Res **46**:58–67, 1980.
17. Schwartz J, Reid IA. Effect of vasopressin blockade on blood pressure regulation during hemorrhage in conscious dogs. Endocrinology **109**:1778–1780, 1981.
18. Azzawi SA, Shirley DG. Renal blood flow and its distribution following hemorrhage in the rat. The role of vasopressin. J Physiol **346**:171–179, 1984.
19. Pang CCY. Effect of vasopressin antagonist and saralasin on regional blood flow following hemorrhage. Amer J Physiol **245**:H749–H755, 1983.
20. Pang CCY. Vasopressin and angiotensin in the control of arterial blood pressure and regional blood flow in anesthetized, surgically stressed rats. Canad J Physiol Pharmacol **61**(2):1494–1500, 1983.
21. Allen DE, Edwards BR. Influence of vasopressin (VP) on cardiac output (CO) and blood pressure (BP) during hemorrhage in conscious rats. Physiologist **27**(4):215, 1984.
22. Yamaski T, Sagawa K. Vasopressin is unimportant for acute arterial pressure compensation after quick 10% hemorrhage in the rabbit. Fed Proc **43**(4):1067, 1984.
23. Freeman RH, Davis JO, Williams GM, DeForrest JM, Seymour AA, Rowe BP. Effects of the oral converting enzyme inhibitor, SQ 14225, in a model of low cardiac output in dogs. Circ Res **45**:540–545, 1979.
24. Thrasher TN, Keil LC, Ramsay DJ. Hemodynamic, hormonal and drinking responses to reduced venous return in the dog. Amer J Physiol **243**:R354–R362, 1982.
25. Thrasher TN, Moore-Gillon M, Wade CE, Keil LC, Ramsay DJ. Inappropriate drinking and secretion of vasopressin after caval constriction in dogs. Amer J Physiol **244**:R850–R856, 1983.
26. Sealey JE, Laragh JH, Gerten-Barnes J, Accto RM. Hypertension Manuel. New York, Dun Donnelly, pp621–640, 1974.
27. Keeton TK, Campbell WB. The pharmacological alteration of renin release. Pharmacol Rev **32**(2):81–227, 1980.
28. Shade RE, Davis JO, Johnson JA, Gotshall RW, Spielman WS. Mechanisms of action of angiotensin II and antiduretic hormone on renin secretion. Amer J Physiol **224**:926–929, 1973.
29. Sweet WD, Freeman RH, Davis JO, Vari RC. Effects of ganglionic blockade in conscious dogs with thoracic caval constriction and ascites. Fed Proc **43**: 994, 1984.

---

Received October 23, 1984. P.S.E.B.M. 1985, Vol. 179.
Accepted February 7, 1985.