Atriopeptin Alters the Vasopressin and Renin Responses Elicited by Hemorrhage

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Abstract. **This study was designed to investigate whether an infusion of atrial peptide is capable of modulating the hormonal and hemodynamic responses elicited by acute hemorrhage. Conscious dogs were bled at a rate of 0.8 ml·kg^{-1}·min^{-1} until 20 ml of blood/kg body wt had been removed. Two experiments were performed on each dog; in one experiment the animal was given α-human atrial natriuretic peptide (α-hANP) (50 ng·kg^{-1}·min^{-1}) dissolved in saline; in the other only the saline vehicle was given. Right and left atrial pressures decreased during hemorrhage in all experiments; the absolute decreases were greater when the animals received atriopeptin, but the differences between treatments were statistically significant only for right atrial pressure. Cardiac output decreased ($P < 0.05$) and total peripheral resistance increased ($P < 0.05$) during hemorrhage when atriopeptin was infused; although these variables showed similar trends when vehicle alone was infused during hemorrhage, no significant changes occurred. Infusion of atrial peptide did not affect the decrease in arterial blood pressure that occurred during hemorrhage. The increase in plasma vasopressin induced by hemorrhage was potentiated, but the increase in plasma renin activity was attenuated when α-hANP was infused. Hemorrhage increased circulating aldosterone levels in each experiment, but the response was less pronounced when α-hANP was given during the experiment. Intravenous administration of α-hANP modulates the hemodynamic responses elicited by hemorrhage, potentiates the rise in plasma vasopressin, and attenuates the rise in plasma renin activity induced by acute blood loss in conscious dogs.**
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The ability of atriopeptin to modulate plasma concentrations of vasopressin, angiotensin II, and catecholamines has attracted considerable attention. There is, however, no consensus concerning the effects of atriopeptin on the secretion of these hormones (1). For example, atriopeptin has been reported either to increase (2) or to decrease (3) vasopressin secretion from the isolated pituitary gland. Two reports indicate that atriopeptin decreases vasopressin secretion from hypothalamo-hypophyseal explants (4, 5). However, intravenous infusions of atriopeptin do not significantly alter the basal level of circulating vasopressin in anesthetized dogs (6), conscious humans (7–10), or conscious sheep (11). Furthermore, intravenous infusion of a large dose of atriopeptin has been shown to increase plasma vasopressin in conscious dogs (12). On the other hand, when the plasma concentration of vasopressin had been increased by either dehydration or hemorrhage, injection of a large dose of atriopeptin reduced plasma vasopressin in conscious rats (13). However, the administration of atriopeptin does not appear to alter the increase in plasma vasopressin that occurs in response to hemorrhage in conscious sheep (11).

Atriopeptin administration has been shown to produce either a decrease (8, 14–16) or no change (6, 7, 9, 17–19) in plasma renin activity and plasma aldosterone in experimental animals and humans. Unchanged concentrations of plasma renin and aldosterone often have been noted when the basal values of these substances are normal or low (1). The effect of atriopeptin on plasma catecholamine concentrations appears to vary; infusion of atriopeptin has been shown to elicit a decrease (19) in circulating epinephrine and no change (19) or an increase in circulating norepinephrine (8, 11, 20).

Because the possible inhibitory actions of atriopeptin on the secretion of vasopressin, renin, aldosterone, and catecholamines may be difficult to detect when

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these hormones are circulating at relatively low basal levels, we used the model of acute hemorrhage, a well-known stimulus for the release of these substances, to examine the effect of plasma atriopeptin on the secretion of these hormones. Experiments were performed on conscious dogs to avoid the confounding effects of anesthesia and acute surgery (21).

Materials and Methods

Surgical Preparations. Eight female mongrel dogs weighing 18.9 ± 0.6 kg were anesthetized with pentobarbital sodium (25–30 mg/kg iv) and given supplements as needed. The chest was entered through the fourth intercostal space on the left side. Catheters were placed in the descending aorta, right and left atria, and pulmonary artery; an electromagnetic flow probe was placed around the ascending aorta. The chest was closed in layers, and all catheters and the flow cable were tunneled subcutaneously to the back and passed through the skin. A vinyl catheter was inserted into the pleural cavity and connected to a vacuum pump for 1 to 2 hr to remove residual air and fluid from the chest.The catheter was sealed and left in place for 3 to 4 days to allow daily removal of any accumulated fluid. Penicillin (500,000 units im daily) was given for 3 days after surgery. Catheters were flushed three times per week with saline and filled with a solution of sodium heparin (1000 units/ml) to prevent clotting. The dogs were allowed at least 2 weeks to recover before experiments were performed; they were fed a diet that provided 45 mEq of sodium/day.

Experimental Protocols. Experiments were carried out on conscious dogs as they stood quietly in a Pavlov-type sling. Pressures in the aorta and left and right atria were monitored with Statham P23Db pressure transducers. Cardiac output was measured with an electromagnetic flowmeter (Biotronex Laboratory, Silver Spring, MD) coupled to an auto-zeroing circuit (22) to minimize baseline shifts in the aortic flow tracing. Blood pressures and aortic flow were monitored continuously throughout the experiment by an oscillographic recorder. Hemodynamic variables were sampled 100 times/sec and averaged each minute by a computer (PDP-11/34; Digital Equipment, Corp., Maynard, MA). Minute averages of each hemodynamic variable were displayed on a video screen during the experiment and stored for later analysis.

Two experimental hemorrhages were performed on each animal. On one day, the dog was bled while it received an infusion of α-human atrial natriuretic peptide (α-hANP) in isotonic saline; on another day it received an infusion of isotonic saline only (vehicle control) during hemorrhage. An interval of at least 4 days separated the two hemorrhages. After the hemodynamic variables had been stable for 30 min, a control blood sample (32 ml) was withdrawn from the pulmonary arterial catheter. Part of the sample was placed in a chilled tube containing EDTA (0.3% w/v) for subsequent measurement of plasma atriopeptin concentration and plasma renin activity. Another part of the sample was placed in a chilled tube containing EGTA for measurement of epinephrine and norepinephrine. The remainder of the blood sample was placed in a chilled tube containing lithium heparin for determination of vasopressin, aldosterone, osmolality, electrolytes, and hematocrit. The blood sample was replaced with an equal volume of iso-oncotic dextran in isotonic saline. Immediately after the control blood sample was taken, either α-hANP (50 $ng \cdot kg^{-1} \cdot min^{-1}$ dissolved in isotonic saline) or isotonic saline alone was infused intravenously (0.388 ml/min) for the remainder of the experiment (48 min). Twelve minutes after the α-hANP or saline infusion began, a second blood sample (32 ml) was taken from the catheter in the pulmonary artery. The dog then was given 3000 units of sodium heparin intravenously to prevent clotting, and hemorrhage was begun. A pump (model 375A; Sage Instruments, Orion Research Inc., Cambridge, MA) was used to withdraw blood continuously from the pulmonary arterial catheter at a rate of approximately 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$. A total of 20 ml of blood/kg body wt was removed. Additional blood samples were taken after 10 and 20 ml/kg of blood had been removed and 12 min after the end of hemorrhage. The samples taken at the 10 and 20 ml/kg hemorrhage levels were considered to be a part of the hemorrhage and were not replaced. The last blood sample was taken at the end of the experiment so it also was not replaced. Plasma was separated by centrifugation at 4°C for 20 min and stored at −20°C for subsequent analysis of vasopressin, renin activity, aldosterone, epinephrine, norepinephrine, and atriopeptin. After the experiment had ended, the shed blood was filtered and reinfused into the animal. In addition, the packed cells from the blood samples were suspended in isotonic saline and returned to the dog.

Chemical Analysis. Plasma concentrations of immunoreactive atriopeptin were determined by radioimmunoassay (23). Plasma was extracted with Sep-Pak C18 cartridges (Waters Associates, Milford, MA). The plasma extract was analyzed by radioimmunoassay using α-hANP from Peninsula Laboratories (Belmont, CA) and ^{125}I-α-hANP from Amersham Corp. (Arlington Heights, IL). Arginine vasopressin also was extracted from plasma with Sep-Pak C18 cartridges and measured according to radioimmunoassay methods described by Goetz *et al.* (24) and modified by Wang *et al.* (25). Plasma renin activity was determined according to the method of Haber *et al.* (26) using antiserum and standards purchased from Clinical Assays (Cambridge, MA). Plasma aldosterone was measured with a solid-phase radioimmunoassay kit (Diagnostic Products, Los Angeles, CA). Plasma epinephrine and norepinephrine concentrations were measured by the single radioenzymatic method (Cat-A-Kit; Amersham Corp., Arlington Heights, IL). Plasma sodium and potassium concentrations were measured by flame photometry

(model 943; Instrumentation Laboratory, Lexington, MA) and plasma osmolality by freezing point depression (model 3M0; Advanced Micro-Osmometer, Needham Heights, MA). Hematocrit was measured in triplicate with microcapillary tubes.

Statistical Analysis. Hemodynamic variables from each dog were averaged for consecutive 4-min periods. Data are expressed as the mean ± SE. All data within each experiment were analyzed by a one-way analysis of variance for repeated measurements of the same variable. Dunnett's test was used to determine which means differed statistically from control means. A two-way analysis of variance was used to detect differences between the saline control and ANP infusion experiments, and a series of completely randomized F tests was used to determine which periods of these experiments differed significantly from each other (27). The concentrations of vasopressin in plasma demonstrated a nonhomogenous variance and therefore were transformed logarithmically prior to statistical analysis (28). A value of $P < 0.05$ was considered to be statistically significant.

Results

Infusion of α-hANP during the 12-min control period increased plasma levels of atriopeptin from a control level of 121 ± 6 to 1080 ± 93 pg/ml; further increases occurred during hemorrhage (Fig. 1). When only vehicle was infused, hemorrhage caused a slight but significant decrease in the plasma concentration of atriopeptin from 95.3 ± 10.0 to 82.8 ± 9.1 pg/ml (Fig. 1).

The hemodynamic data recorded during infusion of α-hANP and during the control experiments with vehicle alone are shown in Figure 2. Control hemodynamic variables did not differ statistically between experiments although minor variations were apparent.

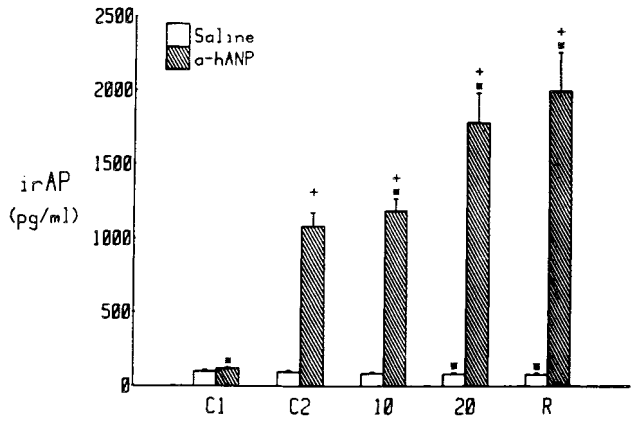

Figure 1. Effect of hemorrhage on plasma atriopeptin concentration in dogs infused with either vehicle (saline) or atriopeptin (α-hANP). C1, control period prior to infusion of either vehicle or atriopeptin; C2, control period after infusion of either vehicle or atriopeptin for 12 min; 10, after removal of 10 ml/kg of blood; 20, after removal of 20 ml/kg of blood; and R, 12 min after the termination of hemorrhage. * Significantly different from C2 of the respective experiment. + Significantly different from the vehicle experiment.

Hemodynamic variables were not affected by infusion of either α-hANP or vehicle in the period before hemorrhage started. Although arterial blood pressure did not change significantly during the first 10 ml/kg of hemorrhage in either experiment, arterial pressure had decreased by 12.6 and 14.0 mm Hg when 20 ml/kg of blood had been removed during vehicle and α-hANP infusion, respectively. There were no statistical differences in arterial pressure changes during the hemorrhage in the two treatment groups. Left and right atrial pressures decreased significantly during each hemorrhage. The decrease in right atrial pressure was significantly greater when α-hANP was infused during hemorrhage. Left atrial pressure also tended to decline more when α-hANP was infused, but the difference between treatment groups was not significant.

Cardiac output decreased and total peripheral resistance increased during hemorrhage when α-hANP was infused. In contrast, cardiac output was maintained quite well during hemorrhage when vehicle only was infused. Although there was a tendency for total peripheral resistance to increase during the latter part of hemorrhage during vehicle infusion, the only significant change occurred after the hemorrhage had ended. A significant difference in total peripheral resistance was evident between treatment groups during the last period of the experiment. Although minor fluctuations occurred, heart rate did not change significantly during hemorrhage in either experiment.

Control values of plasma osmolality, plasma sodium and potassium concentrations, and hematocrit did not differ between experimental groups (Table I). Hematocrit increased significantly following removal of 20 ml/kg of blood in the experiments in which α-hANP was infused but not in the experiments in which vehicle was infused (Table I). Plasma potassium decreased significantly during the last period of the experiment in the group of dogs receiving α-hANP.

Plasma vasopressin (Fig. 3) increased from a control value of 3.2 ± 0.7 pg/ml before hemorrhage to 8.6 ± 3.2 and 126.3 ± 37.1 pg/ml after removal of 10 and 20 ml/kg of blood, respectively, when vehicle was infused and remained essentially constant at 125.1 ± 23.9 pg/ml 12 min after the hemorrhage had ended. In the experiment in which α-hANP was infused, plasma vasopressin increased from a control value of 2.8 ± 0.4 pg/ml to 26.7 ± 8.7 and 627.1 ± 140.3 pg/ml after removal of 10 and 20 ml/kg of blood, respectively; vasopressin remained elevated at 496.5 ± 135.3 pg/ml 12 min after hemorrhage had ended. These increases were significantly greater than those that occurred when vehicle was infused during hemorrhage in these same animals.

Plasma renin activity prior to hemorrhage was comparable in the two treatment groups. In the experiments in which vehicle was infused, plasma renin activity (Fig. 4A) increased from a control value of 1.7 ± 0.3 ng angiotensin I (AI)·ml^{-1}·hr^{-1} to 3.5 ± 0.3 ng

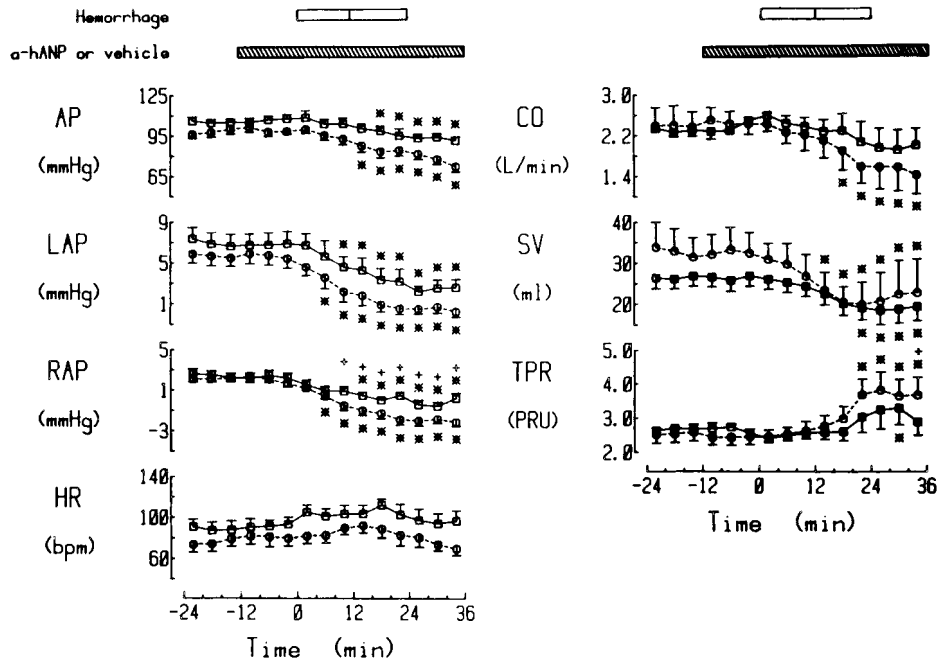

Figure 2. Effect of hemorrhage on mean aortic pressure (AP), left atrial pressure (LAP), right atrial pressure (RAP), heart rate (HR), cardiac output (CO), stroke volume (SV), and total peripheral resistance (TPR) in dogs infused with vehicle (solid lines) or atriopeptin (dashed lines). * Significantly different from the averages obtained during the period immediately preceding hemorrhage. + Significantly different from the vehicle experiment.

Table I. Effect of Hemorrhage on Plasma Osmolality, Plasma Sodium and Potassium Concentrations, and Hematocrit in conscious dogs infused with vehicle (Veh) or with α-hANP (ANP)

		Control		Hemorrhage		Recovery
		C1[a]	C2[a]	10 ml/kg	20 ml/kg	R[b]
Plasma osmolality (mOsmol/kg H_2O)	Veh	301.2 ± 2.9	301.0 ± 0.7	300.4 ± 2.5	299.6 ± 2.1	301.6 ± 2.1
	ANP	304.4 ± 0.9	304.4 ± 0.5	305.2 ± 0.9	305.0 ± 0.9	305.8 ± 1.4
Plasma sodium (μEq/ml)	Veh	147.1 ± 1.1	146.9 ± 1.1	147.1 ± 0.9	147.1 ± 0.9	147.4 ± 1.2
	ANP	145.5 ± 0.7	145.8 ± 0.7	145.6 ± 0.7	145.5 ± 0.4	146.3 ± 0.5
Plasma potassium (μEq/ml)	Veh	4.3 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	4.1 ± 0.1	4.1 ± 0.1
	ANP	4.2 ± 0.1	4.0 ± 0.1	4.2 ± 0.1	4.0 ± 0.1	3.8 ± 0.1[c]
Hematocrit (%)	Veh	39.4 ± 1.3[c]	37.4 ± 1.2	36.8 ± 1.3	38.1 ± 1.4	38.0 ± 1.4
	ANP	36.5 ± 1.1	35.9 ± 0.8	36.8 ± 1.6	39.3 ± 1.4[c]	39.6 ± 1.5[c]

[a] C1, Control values obtained before infusion of either vehicle or α-hANP; C2, Control values obtained after infusion of either vehicle or α-hANP (50 ng·kg^{-1}·min^{-1}) for 12 min.
[b] R, Recovery value obtained 12 min after hemorrhage ended.
[c] $P < 0.05$ compared with C2.

AI·ml^{-1}·hr^{-1} (NS) after removal of 10 ml/kg of blood and to 6.8 ± 1.2 ng AI·ml^{-1}·hr^{-1} ($P < 0.05$) after removal of 20 ml/kg of blood; plasma renin activity declined slightly to 4.8 ± 0.9 ng AI·ml^{-1}·hr^{-1} 12 min after hemorrhage had ended. When α-hANP was infused, plasma renin activity did not change after removal of 10 ml/kg of blood, but it increased significantly from the control level of 1.3 ± 0.2 to 3.8 ± 1.2 ng AI·ml^{-1}·hr^{-1} after removal of 20 ml/kg of blood. Twelve minutes after hemorrhage had ended, plasma renin activity, although still somewhat elevated, was not significantly different from the control value. The increase in plasma renin activity that occurred during hemorrhage when α-hANP was infused was significantly less than the increase that occurred when vehicle alone was infused.

Hemorrhage increased circulating aldosterone levels in each protocol (Fig. 4B). Although the increase was less pronounced where α-hANP was infused during hemorrhage, this difference was not statistically significant.

Hemorrhage caused significant and comparable increases in plasma epinephrine in each treatment group (from 138 ± 40 to 720 ± 300 pg/ml in the group receiving vehicle and from 80 ± 20 to 1100 ± 165 pg/ml in the group receiving α-hANP), but plasma norepinephrine did not change significantly during the hemorrhage in either treatment group.

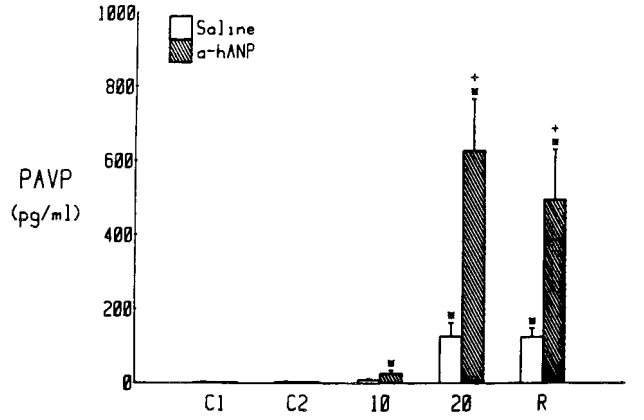

Figure 3. Effect of hemorrhage on plasma vasopressin concentration in dogs infused with either vehicle or atriopeptin. The abbreviations and symbols are identical to those shown in Figure 1.

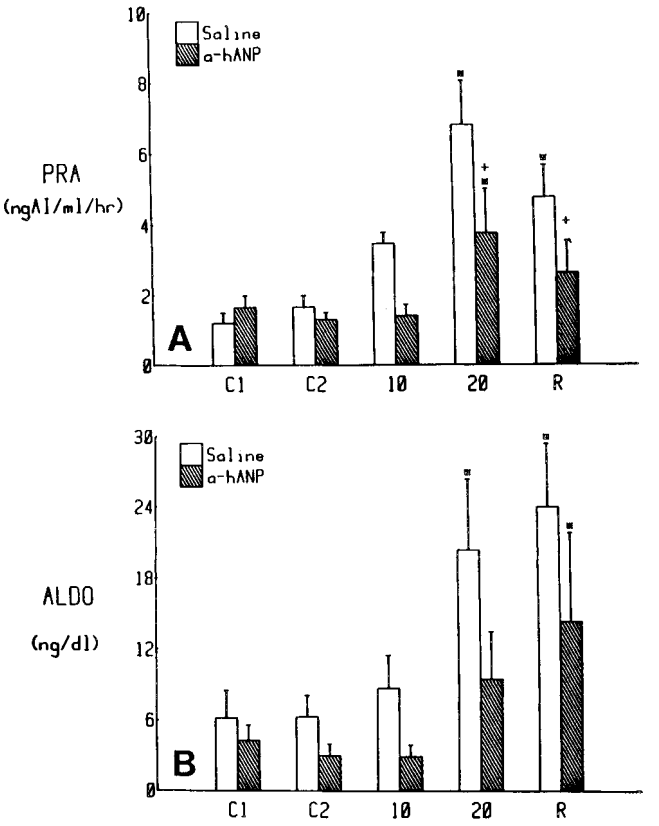

Figure 4. Effect of hemorrhage on plasma renin activity (A) and plasma aldosterone concentration (B) in dogs infused with either vehicle or atriopeptin. The abbreviations and symbols are identical to those shown in Figure 1.

Discussion

Intravenously administered atriopeptin potentiated the increase in circulating vasopressin that occurred during hemorrhage in these experiments on conscious dogs. Several mechanisms may have contributed to the augmented release of vasopressin that occurred when atriopeptin was given. Cardiovascular reflexes almost certainly played a role. Significantly greater decreases in right atrial pressure were recorded when atriopeptin was given during the hemorrhage, and cardiac output declined in this experiment, but not during the control hemorrhage. These changes were accompanied by a greater increase in total peripheral resistance when compared with results obtained when only vehicle was infused during hemorrhage. It seems reasonable to conclude that the augmented increase in total peripheral resistance was caused by greater reflex effects elicited by cardiac and arterial baroreceptors when atriopeptin was given. Reflexes from these receptor areas during hemorrhage also elevate plasma vasopressin (12, 25) and the greater reflex response, evident in total peripheral resistance, presumably was responsible for at least part of the elevation in plasma vasopressin when atriopeptin was given.

The greater decline in atrial pressure that occurred during hemorrhage when atriopeptin was given was not unexpected; atriopeptin causes a decrease in cardiac filling pressures in the absence of hemorrhage (e.g., 1, 12, 29), and the modest increase in plasma vasopressin observed previously when atriopeptin was given to conscious dogs was attributed to a reflex stimulation by cardiac receptors as cardiac filling pressures declined (12). In contrast, the decline in arterial blood pressure induced by hemorrhage in our experiments was unaffected by the concomitant infusion of α-hANP, an observation consistent with the data obtained from conscious sheep by Cameron *et al.* (11).

Our observation that intravenously infused α-hANP potentiated the secretion of vasopressin during hemorrhage differs from that of Samson (13) and Cameron *et al.* (11). Samson (13) reported that atriopeptin suppressed plasma vasopressin levels that had been increased by hemorrhage in conscious rats. Cameron *et al.* (11) reported that atriopeptin administration did not alter the magnitude of the rise in vasopressin elicited by hemorrhage in sheep. These apparent discrepancies may be attributable to differences in experimental design or differences in the species studied. For example, in Samson's study, conscious rats received a large dose of atriopeptin III (~5 μg) as a bolus 10 min after the end of the hemorrhage. In Cameron's study, a large dose of a 26-amino acid rat ANP (3 μg/kg) was given as a bolus, immediately followed by a constant infusion of 50 $ng \cdot kg^{-1} \cdot min^{-1}$ before a hemorrhage in conscious sheep. In our study, α-hANP, the circulating form of atriopeptin in dogs, was infused at a rate of 50 $ng \cdot kg^{-1} \cdot min^{-1}$ starting 12 min before the beginning of the hemorrhage in conscious dogs. Any or all of these differences may account for the apparent differences between the previous studies (11, 13) and the present data.

Although infusion of α-hANP failed to affect basal levels of plasma renin activity in our experiments, the rise in plasma renin activity induced by hemorrhage was attenuated. Similarly, Scheuer *et al.* (30) reported that small amounts of atriopeptin do not affect basal levels of plasma renin activity, but they do markedly attenuate the rise in plasma renin activity caused by

constriction of the renal artery. It would appear, therefore, that infusion of atriopeptin decreases plasma renin activity only when the basal level of this hormone is elevated. This attenuated release in renin probably is not caused by hemodynamic changes because the decreases in cardiac filling pressure in our experiments presumably would have potentiated, not attenuated, the rise in plasma renin activity. It is unlikely that atriopeptin acts on the juxtaglomerular cells to inhibit renin release (31–33). The data of Opgenorth *et al.* (34) and Villarreal *et al.* (35) suggest that the inhibition of renin release by atriopeptin is due to an effect at the macula densa and perhaps a vascular effect. Alternately, the greater increase in plasma vasopressin that occurred when atriopeptin was infused during hemorrhage may have contributed to the renin response; an increase in plasma vasopressin has been shown to inhibit renin secretion (36).

Although our data suggest that the rise in plasma aldosterone during hemorrhage is suppressed by the infusion of atriopeptin in the conscious dog, it is difficult to draw firm conclusions concerning the effects of atriopeptin on aldosterone secretion in animals and men. Several studies have shown that the administration of atriopeptin decreases plasma aldosterone in intact animals and humans (8, 14–16). On the other hand, the acute administration of atriopeptin may cause no decrease in aldosterone, especially if the basal levels of this hormone are normal or low (6, 7, 9, 17, 18).

The effect of atriopeptin on plasma catecholamines during hemorrhage also appears to be variable and probably depends upon the amount of peptide given, the rate of hemorrhage, and the species studied. We found that atriopeptin did not affect the rise in plasma catecholamines elicited by blood loss. These factors may explain why the experiments of Holtz *et al.* (19) indicated that infusion of atriopeptin at a rate of 100 $ng \cdot kg^{-1} \cdot min^{-1}$ decreases the release of epinephrine but not norepinephrine in conscious dogs and that the data of Cameron *et al.* (11) indicated that atriopeptin augments the increase in plasma norepineprhine elicited by hemorrhage in conscious sheep.

Our finding that plasma atriopeptin concentrations decreased significantly during hemorrhage in the vehicle-treated group is consistent with that of Geer *et al.* (23) who found that plasma atriopeptin concentrations tended to decrease during hemorrhage in both intact and cardiac-denervated dogs, but the decrease became significant only in cardiac-denervated dogs. The decrease in atriopeptin concentration is probably caused by a decreased secretion of the peptide resulting from a decrease in cardiac filling pressure. It has been demonstrated that plasma concentrations of α-hANP achieve essentially steady-state elevations within the first 20-min period when α-hANP is infused at 50 $ng \cdot kg^{-1} \cdot min^{-1}$ for 60 min into conscious dogs (29). In the present experiment, however, plasma concentrations of α-hANP continued to increase during hemorrhage when the same rate of α-hANP was infused. We suspect that the reduction of cardiac output that occurred when atriopeptin was infused during hemorrhage reduced the metabolic clearance rate and thereby accounted for the progressive rise in plasma atriopeptin in this experiment.

Intravenous infusion of α-hANP potentiates the rise in plasma vasopressin and attenuates the rise in plasma renin activity elicited during acute blood loss in conscious dogs. The potentiation of the vasopressin response is probably attributable to reflexes originating from cardiac receptors.

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