Effect of Vasopressin on Cardiovascular and Renal Functions and ANP Release under Plasma Volume Expansion

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OHTA, M., KIMURA, T., OTA, K., SHOJI, M., INOUE, M., SATO, K., YAMAMOTO, T. and YOSHINAGA, K. *Effect of Vasopressin on Cardiovascular and Renal Functions and ANP Release under Plasma Volume Expansion.* Tohoku J. Exp. Med., 1991, 165 (2), 115-129 — To assess the mechanisms whereby arginine vasopressin (AVP) increases atrial natriuretic peptide (ANP) release and to examine whether AVP-mediated ANP release affects the effect of AVP on the cardiovascular and renal function, AVP was infused continuously at a rate of $20 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 75 min following 200 ng/kg bolus injection under stepwise increases in plasma volume in anesthetized dogs. Moreover, the effect of an AVP antagonist, a V_1 blocker, 1-(β -mercapto- β , β -cyclopentamethylenepropionic acid)-2-(α -methyl)tyrosine AVP (TMeAVP), on these parameters was also investigated. In the control study, saline alone was infused. AVP infusion increased total peripheral resistance (TPR), pulmonary capillary wedge pressure (PCWP), and plasma ANP, but decreased cardiac index (CI) and heart rate (HR) without increases in mean arterial blood pressure (MABP). Stepwise rises in plasma volume further increased plasma ANP, CVP, CI and PCWP, but gradually decreased TPR. TMeAVP curtailed AVP-induced increases in TPR and plasma ANP as well as decreases in CI and HR. The replacement of ANP to prevent a fall in plasma ANP following TMeAVP never affected cardiovascular function. AVP infusion increased plasma volume accompanied by a fall in urinary Na excretion (U_{NaV}) and urine flow (UF) under the stepwise plasma volume expansion compared to the control group, but did not affect mean circulatory filling pressure (MCFP). ANP

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Abbreviation: AVP, arginine vasopressin; ANP, atrial natriuretic peptide; TMeAVP, 1-(β -mercapto- β , β -cyclopentamethylenepropionic acid)-2-(α -methyl)tyrosine AVP; MABP, mean arterial blood pressure; CVP, central venous pressure; RAP, right atrial pressure; CO, cardiac output; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; TPR, total peripheral resistance; MCFP, mean circulatory filling pressure; VPR, venous plateau pressure; APP, arterial plateau pressure; RVR, resistance to venous return; VPG, venous pressure gradient; Uosm, urinary osmolality; UF, urine flow; U_{NaV} , urinary Na excretion; U_{KV} , urinary K excretion; CON, control group; AVPT, AVP + TMeAVP group; AVPTA, AVP + TMeAVP + ANP group.

administration enhanced $U_{Na}V$ and UF and decreased MCFP. These results indicate that AVP may preferentially increases ANP release via the increased cardiac afterload, not preload, but increased plasma ANP per se may not be involved directly in the AVP-induced cardiac suppression. ——— mean circulatory filling pressure, cardiac output, plasma volume, vasopressin blocker; natriuresis

It is well known that arginine vasopressin (AVP), besides antidiuretic effect via the V_2 -receptor, elicits vasopressor effect via the V_1 -receptor in relatively high circulating levels (Cowley and Liard 1982; Bennet and Gardiner 1985; Liard 1988). However, AVP-induced pressor response has been reported not to be remarkable compared to norepinephrine (Nor)-and angiotensin II (Ang II)-mediated responses, because, dissimilarly to the action of Nor and Ang II, AVP concomitantly decreases cardiac output and heart rate either via its direct cardiac suppression or the potentiation of baroreceptor reflex (Cowley et al. 1974; Osborn et al. 1987). Moreover, it has recently been reported that AVP enhances the release of atrial natriuretic peptide (ANP), which exerts vasorelaxation, a fall in cardiac output, and the natriuresis; this enhancement is due to increased atrial pressure in response to increases in blood pressure (afterload) and/or central venous pressure (preload) under hydrated states (Manning et al. 1985; Inoue et al. 1988).

Therefore, it is likely that increased ANP release in response to AVP may participate in changes in cardiovascular function induced by AVP. However, it is unknown whether AVP-induced increases in ANP release decreases cardiac output and elicits the vasodilation, thereby attenuating the pressor response to AVP. Moreover, it remains to be clarified which one, cardiac preload or afterload, plays an essential role in ANP release exerted by AVP.

In the present study, in order to investigate the mechanisms whereby AVP stimulates the release of ANP and the role which the ANP response to AVP plays in AVP-induced cardiac depression, AVP was intravenously infused to pentobarbital anesthetized dogs under the stepwise extracellular fluid (ECF) volume expansion, and cardiovascular function, renal water and electrolytes handling and plasma concentrations of ANP and AVP were simultaneously determined. Additionally, the effect of a V_1 -receptor antagonist, 1- β -mercapto- β , β -cyclopentamethylenepropionic acid-2-(o-methyl)tyrosine AVP (TMeAVP), on ANP release and cardiovascular function was also investigated.

MATERIALS AND METHODS

Mongrel dogs of both sexes, weighing 7–12 kg, were anesthetized with pentobarbital sodium (30 mg/kg). Anesthesia was maintained by administering supplemental doses of pentobarbital sodium during the experiment. Femoral arteries and veins were cannulated with plastic catheter. Arterial catheters were placed in the abdominal aorta for mean arterial blood pressure (MABP) monitoring and blood sampling. A venous catheter was inserted to the height of the right atrium to monitor central venous pressure (CVP) and right

atrial pressures (RAP) and, in the present study, CVP was interchangeably used as RAP. Another venous catheter was inserted to the vena cava inferior for saline and drug infusions. A 5F Swan-Ganz catheter (TC504B, Nihon Kohden, Tokyo) was inserted via the right external jugular vein and advanced into the pulmonary artery to measure cardiac output (CO) and pulmonary capillary wedge pressure (PCWP). Arterial and Swan-Ganz catheters were connected to strain gauge transducers (Statham Instrument, Oxnard, CA, USA) and calibrated using a mercury manometer. The venous catheter was also connected to another strain gauge transducer (Statham Instrument, Oxnard, CA, USA) and calibrated using a water manometer. BP, CVP and PCWP were recorded with polygraph recorder (San-ei Sokki, Tokyo). Heart rate (HR) was calculated from the recording of pulsatile arterial blood pressure. The zero reference level for CVP, BP and PCWP was defined as approximately a half of the height between the sternum and back. CO was measured using a thermodilution method with a cardiac output computer (Nihon Kohden, Tokyo) and expressed as the cardiac index (CI) $\text{L}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$. Total peripheral resistance (TPR) was calculated as the MABP minus RAP (mmHg) divided by the CI ($\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$). Mean circulatory filling pressure (MCFP) was measured after a transient asystole (7–10 sec) produced by a bolus injection of acetylcholine (10 mg/3 ml saline; Sigma Chemical, St. Louis, MO, USA) (Lee et al. 1988). In addition, effects of reflexes are minimized because MCFP can be measured quickly after the circulatory arrest before the onset of secondary venous pressure changes due to reflexes (Samar and Coleman 1978; Yamamoto et al. 1980). This pressure was calculated as $\text{MCFP} = \text{VPP} + (\text{APP} - \text{VPP})$ times arterial compliance/venous compliance, where VPP is venous plateau pressure and APP is arterial plateau pressure measured at 7–10 s after the start of asystole. An arterial-to-venous compliance ratio of 1/30 was assumed (Shoukas and Brunner 1980). Resistance to venous return (RVR) was calculated as $\text{RVR} = (\text{MCFP} - \text{CVP})$ times 1,000/CI, and venous pressure gradient (VPG) as $(\text{MCFP} - \text{CVP})$. A Foley catheter was placed in the bladder to collect the urine sample. The experiments were started 120 min after the completion of surgery. The following experiments were undertaken in the 4 groups.

The control group (CON, $n=5$): An infusion of 0.9% saline was performed from –50 min to 75 min at a rate of $0.05 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ via the left femoral vein. Another infusion of 0.9% saline was initiated from 0 min to stepwise increase ECF volume at the increasing rates of 0.5 (0–25 min), 1.0 (25–50 min), and 2.0 (50–75 min) $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ using rotary pump via the left femoral vein.

The AVP group (AVP, $n=5$): A dose of 200 ng/kg AVP (Sigma Chemical) dissolved in saline was administrated at –50 min as a priming dose, and then a maintenance dose, dissolved in saline, was infused at a rate of $0.05 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ($20 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) throughout the experiment. The same saline infusion as the CON group was initiated from 0 min to increase ECF volume.

The AVP+TMeAVP group (AVPT, $n=5$): AVP administration and saline infusion were performed in the same way as in the AVP group. An antagonist of the pressor effect of AVP, TMeAVP ($10 \mu\text{g}/\text{kg}$, Bachem) dissolved in distilled water, was intravenously administrated as one bolus at 50 min. This dose of TMeAVP was confirmed to be enough to block the pressor effect of exogenously administered AVP (500 ng) by a preliminary study.

The AVP+TMeAVP+ANP group (AVPTA, $n=5$): Administration of AVP and TMeAVP and saline infusion were performed in the same way as in the AVPT group. ANP (Peptide Institute, Osaka) was dissolved into saline and an infusion of ANP at a rate of $2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ($0.02 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was initiated at 50 min in lieu of saline alone infusion to prevent a decrease in plasma ANP due to TMeAVP administration and to maintain. In all the groups, BP, HR, CVP, CO and PCWP were measured at the final minute of each 25 min periods. Blood samples were immediately obtained after recording of hemodynamics and replaced with an equal volume of 6% dextran saline. Arterial blood was collected in precooled tubes and kept on ice until it was centrifuged at 4°C . Plasma was separated and

stored at -20°C until the radioimmunoassay (RIA). Urine samples were consecutively collected at 25 min intervals. The completeness of urine collection was assured by flushing the bladder with air. In each experiment, 0.1% Evans-Blue (Sigma Chemical) dissolved in phosphate buffer (0.1 ml/kg) was administrated at -10 min and 65 min and plasma volume was measured using a dye dilution method at 0 and 75 min (Gregersen 1944). MCFP was measured at 75 min immediately after the urine collection.

Measurements: Plasma AVP and ANP were measured by the RIA after extraction using a C_{18} Sep Pak Cartridge (Waters Associates, Milford, MA, USA) as previously reported (Kimura et al. 1986). Evans-Blue was measured using spectrophotometry (Hitachi spectrophotometer, Model 100-60, Hitachi Ltd., Tokyo). Plasma and urinary osmolalities were measured by freezing-point depression (Advanced Instruments, Model 3D2, Needham Heights, MA, USA). Sodium and potassium concentrations in the plasma and urine were measured by flame photometry (model 205D; Hitachi Flame Photometer, Hitachi Ltd., Tokyo).

Statistical analysis. The evaluation of the data was performed by one-way and two-way analyses of variance (ANOVA) for repeated measurements. The significant differences between the groups and within the group were isolated by paired *t*-test and Dunnett's test, respectively. Changes were considered significant for $p < 0.05$. Square root transformation on hormonal data was performed before ANOVA. All reported values are means $\pm$ s.e. The values at 0 min or during the period of -25 to 0 min were considered as the base-line value in each study.

RESULTS

Plasma AVP concentrations at 0 min were significantly greater in AVP, AVPT and AVPTA groups than in the CON group (Table 1). In the CON group, plasma AVP started to decrease significantly at 50 min and reached 29 ± 7 pg/ml at 75 min ($p < 0.05$). In the other groups, plasma AVP did not change significantly throughout the studies. There were significant differences between CON and the other 3 groups ($p < 0.01$), but not among the AVP, AVPT and AVPTA groups (Fig. 1, A). The basal levels of plasma AVP (-50 min) before AVP infusion in AVP, AVPT and AVPTA groups were 45 ± 7 , 50 ± 9 and 48 ± 9 pg/ml, respectively. There were no significant differences among them. Since TMeAVP has a cross-reactivity for the antiserum used in the present study, plasma AVP was not measured at 75 min in the AVPT and AVPTA groups.

TABLE 1. Control values at 0 min of plasma AVP and ANP and plasma volume in control, AVP (AVP), AVP + TMeAVP (AVPT), and AVP + TMeAVP + ANP (AVPTA) groups

	Plasma AVP	Plasma ANP	Plasma volume
	(pg/ml)	(pg/ml)	(ml/kg body weight)
Control	90 ± 23	91 ± 20	44 ± 3
AVP	$860 \pm 166^*$	$441 \pm 160^*$	62 ± 9
AVPT	$800 \pm 26^*$	$540 \pm 144^*$	50 ± 3
AVPTA	$780 \pm 40^*$	$243 \pm 34^*$	48 ± 5

* $p < 0.01$ compared to the Control group.

Fig. 1. Changes in plasma vasopressin (P_{AVP}) (A) and plasma atrial natriuretic peptide (P_{ANP}) (B) in the control (CON; open circle), vasopressin (AVP, closed circle), AVP+TMeAVP (AVPT, open triangle) and AVP+TMeAVP+ANP (AVPTA, closed triangle) groups under the stepwise plasma volume expansion.

* $p < 0.05$ and ** $p < 0.01$, compared to CON level at 0 min. †† $p < 0.01$, compared to CON group. ○○ $p < 0.01$, compared to the value at 50 min.

Plasma ANP concentrations at 0 min were significantly greater in AVP, AVPT and AVPTA groups than in the CON group (Table 1). Plasma ANP at 0 min in the AVP, AVPT, and AVPTA groups were significantly greater than that in the CON group ($p < 0.01$), but no differences were noticed among the former 3 groups. In the CON group, plasma ANP significantly increased to 182 ± 20 pg/ml at 75 min compared to the value at 0 min ($p < 0.01$). In the AVP group, plasma ANP started to significantly increase at 50 min and reached $1,181 \pm 338$ pg/ml at 75 min ($p < 0.01$). In the AVPT group, plasma ANP significantly increased to 754 ± 178 pg/ml at 50 min and decreased to 485 ± 79 pg/ml at 75 min after TMeAVP compared to the value at 50 min ($p < 0.01$). In the AVPTA group, plasma ANP significantly increased to 548 ± 68 pg/ml at 50 min ($p < 0.01$) and ANP infusion further increased plasma ANP to 996 ± 112 pg/ml ($p < 0.01$).

significant differences between the CON and AVPTA groups at 25 and 50 min as well as between the CON and AVPTA at 50 min ($p < 0.05$, Fig. 2, A).

HR did not change significantly in the CON group during the study, but decreased at 75 min in the AVP group compared to the values at 0 or 50 min ($p < 0.05$ – 0.01). In the AVPT and AVPTA groups, HR did not change at 25 and 50 min, but significantly increased at 75 min after TMeAVP ($p < 0.01$). There were differences at 75 min between the CON and AVPT or AVPTA groups as well as between the AVP and AVPT or AVPTA groups ($p < 0.01$, Fig. 2, B).

TPR significantly decreased at 25 min and thereafter in the CON group and at 75 min in the AVP group. However, TPR in the latter was significantly greater than that in the former throughout the study ($p < 0.01$). TPR did not change at 25 and 50 min in the AVPT group, but significantly decreased in the AVPTA ($p < 0.01$). TPR in the AVPT and AVPTA groups were significantly greater than that in the CON group at 0 through 50 min, but sharply decreased at 75 min after TMeAVP compared to the values at 0 and 50 min ($p < 0.01$). There were significant differences at 75 min between the CON and AVPT or AVPTA groups as well as between the AVP and AVPT or AVPTA groups ($p < 0.05$ – 0.01 , Fig. 2, C).

CI significantly increased at 25 min and thereafter in the CON group and at 75 min in the AVP group. CI in the latter was smaller than that in the former throughout the study ($p < 0.05$ – 0.01). In AVPT and AVPTA groups, CI did not change at 25 and 50 min but was significantly smaller than that in the CON group ($p < 0.05$). In both groups, CI markedly increased at 75 min after TMeAVP compared to the values at 0 and 50 min ($p < 0.05$ – 0.01). Significant differences were noticed between the AVP and AVPT or AVPTA groups at 75 min ($p < 0.01$), but there were no differences between the CON and AVPT or AVPTA group (Fig. 3, A).

PCWP in the AVP and CON groups significantly increased at 25 min and thereafter compared to the values at 0 min and at 75 min compared to the values at 50 min, and PCWP in the former was significantly greater than that in the latter throughout the study ($p < 0.05$). In the AVPT and AVPTA groups, PCWP significantly increased in the similar manner to the AVP group, but did not change significantly at 75 min compared to the value at 50 min. Differences were noticed between the CON and the AVPT or AVPTA group throughout the studies ($p < 0.05$, Fig. 3, B).

In the AVP and AVPT groups, CVP significantly increased at 25 min and thereafter compared to the values at 0 min and at 75 min compared to the values at 50 min. In the CON group, CVP increased significantly at 50 and 75 min compared to the value at 0 min ($p < 0.05$ – 0.01). In AVPTA group, CVP significantly increased at 50 and 75 min compared to the value at 0 min ($p < 0.05$), but ANP administration prevented the further increase in CVP. There were differences between the AVP and AVPT groups at 0 and 75 min as well as between

Fig. 3. Changes in cardiac index (CI) (A), pulmonary capillary wedge pressure (PCWP) (B) and central venous pressure (CVP) (C) in CON, AVP, AVPT, and AVPTA groups under the stepwise plasma volume expansion. All abbreviations and symbols are the same as those in Fig. 1.

* $p < 0.05$ and ** $p < 0.01$, compared to the baseline level. † $p < 0.05$ and †† $p < 0.01$, compared to the CON group. ○ $p < 0.01$, compared to the value at 50 min. Δ $p < 0.05$ and ΔΔ $p < 0.01$, compared to the value at 75 min in the AVP group.

the AVP and AVPTA groups at 75 min ($p < 0.05-0.01$, Fig. 3, C).

Urinary osmolality (Uosm) decreased significantly at the 2nd period and thereafter in all the groups except for AVPTA (the 3rd period and thereafter) compared to respective values at the initial period ($p < 0.05-0.01$). There were significant differences between the CON and AVPT groups ($p < 0.05-0.01$), but not among the CON, AVP, and AVPTA groups (Fig. 4, A) Urine flow (UF) and urinary sodium excretion ($U_{Na}V$) significantly increased during the 2nd period and thereafter in all the groups ($p < 0.05-0.01$, Fig. 4, B and C). There were

Fig. 4. Changes in urinary osmolality (Uosm) (A), urine flow rate (UF) (B), urinary Na excretion (U_{NaV}) (C), and, urinary K excretion (U_{KV}) (D) in CON (open circle and open column), AVP (closed circle and hatched column), AVPTA (open triangle and cross hatched column) and AVPTA (closed triangle and dotted column). All abbreviations are the same as those in Fig. 1. * $p < 0.05$ and ** $p < 0.01$, compared to the baseline value. † $p < 0.05$ and †† $p < 0.01$, compared to CON group.

significant differences in UF between the CON and AVPT during the 1st and 2nd periods as well as between the CON and AVPTA groups during the 3rd and 4th periods. In U_{NaV} , significant differences were noticed between the CON and AVPTA groups during the 3rd and 4th periods ($p < 0.05$). Urinary potassium excretion (U_{KV}) did not change throughout the studies in all the groups and no differences were noticed among the groups (Fig. 4, D). Plasma osmolality and plasma Na did not change throughout the studies, but plasma K significantly decreased at 25 min and thereafter in all the groups ($p < 0.05-0.01$). No significant differences were noticed among the groups (Table 2).

Plasma volume at 0 min was not different among AVP, AVPT and AVPTA groups (Table 1). Plasma volume in each group significantly increased at 75 min

TABLE 2. *Changes in plasma osmolality (Posm) and Na (P_{Na}) and K (P_K) concentrations in the control (CON), vasopressin (AVP), AVP + TMeAVP (AVPT) and AVP + TMeAVP + atrial natriuretic peptide (ANP, AVPTA) groups*

	Time (min)			
	0	25	50	75
Posm (mOsm/kg)				
CON	299.4 $\pm$ 3.6	229.4 $\pm$ 3.2	300.2 $\pm$ 3.2	301.4 $\pm$ 3.1
AVP	295.4 $\pm$ 1.9	294.8 $\pm$ 2.5	295.6 $\pm$ 2.9	297.6 $\pm$ 2.8
AVPT	297.4 $\pm$ 3.1	296.0 $\pm$ 1.3	296.8 $\pm$ 0.6	298.4 $\pm$ 1.4
AVPTA	296.0 $\pm$ 1.8	298.8 $\pm$ 1.9	301.8 $\pm$ 1.5	301.8 $\pm$ 1.8
P_{Na} (mEq/liter)				
CON	150.6 $\pm$ 1.3	150.9 $\pm$ 2.1	150.9 $\pm$ 2.3	153.8 $\pm$ 2.2
AVP	150.7 $\pm$ 1.3	150.4 $\pm$ 2.4	151.2 $\pm$ 3.5	151.7 $\pm$ 2.3
AVPT	152.9 $\pm$ 0.9	153.4 $\pm$ 1.9	153.5 $\pm$ 1.3	154.9 $\pm$ 1.4
AVPTA	151.8 $\pm$ 2.7	150.9 $\pm$ 1.9	151.9 $\pm$ 2.8	154.2 $\pm$ 4.2
P_K (mEq/liter)				
CON	3.57 $\pm$ 0.14	3.36 $\pm$ 0.13*	3.13 $\pm$ 0.13**	3.10 $\pm$ 0.12**
AVP	4.26 $\pm$ 0.10	3.74 $\pm$ 0.09*	3.57 $\pm$ 0.13**	3.31 $\pm$ 0.15**
AVPT	3.78 $\pm$ 0.17	3.26 $\pm$ 0.10*	2.98 $\pm$ 0.19**	2.82 $\pm$ 0.19**
AVPTA	3.83 $\pm$ 0.17	3.41 $\pm$ 0.11*	3.06 $\pm$ 0.09**	2.98 $\pm$ 0.11**

* $p < 0.05$, ** $p < 0.01$ compared to the baseline value at 0 min.

to 73.5 $\pm$ 8.9, 128.3 $\pm$ 9.2, 126.1 $\pm$ 12.8 and 106.3 $\pm$ 6.0 ml/kg, respectively ($p < 0.05$ –0.01). There were significant differences between the CON and other groups ($p < 0.05$ –0.01). As shown in Table 3, there were significant differences in MCFP between the CON and AVPTA groups as well as between AVP and AVPTA groups ($p < 0.05$ –0.01), but not among the CON, AVP and AVPT groups. VPG

TABLE 3. *Changes in mean circulatory filling pressure (MCFP), venous pressure gradient (VPG) and resistance to venous return (RVR) in the control (CON), vasopressin (AVP), AVP + TMeAVP (AVPT) and AVP + TMeAVP + atrial natriuretic peptide (ANP, AVPTA) groups*

	MCFP	VPG	RVR
	(mmHg)	(mmHg)	(mmHg $\cdot$ ml $^{-1}\cdot$ min $^{-1}\cdot$ kg $^{-1}$)
CON	18.8 $\pm$ 2.1	11.3 $\pm$ 1.7	48.8 $\pm$ 3.7
AVP	16.5 $\pm$ 0.9	5.7 $\pm$ 1.5*	63.9 $\pm$ 7.3
AVPT	15.8 $\pm$ 2.2	8.8 $\pm$ 1.4	26.5 $\pm$ 3.2**‡
AVPTA	11.9 $\pm$ 1.0*‡	7.9 $\pm$ 0.5	25.4 $\pm$ 2.7**‡

* $p < 0.05$, ** $p < 0.01$ compared to CON group.

‡ $p < 0.01$ compared to the AVP group.

in the AVP group was significantly smaller than that in the CON group ($p < 0.05$), but no significant differences were noticed between the CON and the AVPT or AVPTA groups. RVR in the CON group was significantly greater than those in the AVPT and AVPTA groups ($p < 0.01$), but no difference was noticed between the CON and AVP group. The value in the AVP group was significantly greater than those in the AVPT and AVPTA groups ($p < 0.05$).

DISCUSSION

The present study clearly showed that the supraphysiological dose of AVP administered intravenously increased TPR, PCWP and plasma ANP with no apparent rise in MABP and CVP, and markedly suppressed CI. A stepwise increase in plasma volume in the presence of AVP tended to increase blood pressure, but further increases in plasma volume gave rise to a fall in blood pressure associated with a reduction in TPR. PCWP and CVP continuously increased in response to the plasma volume expansion, and the addition of AVP potentiated the former, but not the latter.

The addition of a V_1 -blocker apparently decreased MABP with increases in HR and CI as well as with decreases in TPR and plasma ANP, and attenuated a further elevation in PCWP and CVP. Moreover, the supplementation of ANP to restore the initial level of plasma ANP after a V_1 -blocker had no effect on MABP, HR, TPR and CI, but increments in CVP observed after a V_1 -blocker were obviously abolished by the addition of ANP.

Plasma volume increased about 1.7-fold under AVP infusion compared to saline alone, but MCFP was almost the same in the two groups. A V_1 -blocker per se never affected AVP-induced changes in MCFP, but the supplementation of ANP decreased MCFP. AVP infusion tended to increase RVR, but a V_1 -blocker markedly decreased it. However, the addition of ANP did not affect RVR after a V_1 -blocker. The supraphysiological dose of AVP tended to decrease U_{osm} and the plasma volume expansion further decreased U_{osm} accompanied by increased $U_{Na}V$ and UF. The addition of a V_1 -blocker per se had no effect on these parameters despite decreased plasma ANP. However, the supplementation of ANP further enhanced $U_{Na}V$ and UF compared with the AVP-infused groups.

These results may indicate that AVP suppresses cardiac output by the mechanisms which make the heart hypoeffective, attenuating the pressor responses to AVP. In order to decipher the mechanisms of the hypoeffective heart elicited by AVP, the following several explanations have so far been documented. Firstly, AVP may suppress the sympathetic nervous activity and enhance the parasympathetic nervous system via the potentiation of sino-atrial reflexes, thereby resulting in cardiac hypofunction. Montani et al. (1980) reported that the removal of the sino-aortic reflex attenuated a fall in cardiac output in response to AVP. Secondly, it is possible that AVP directly affects the heart with subsequent negative chronotropic and inotropic function. Cowley et al. (1985) showed

Fig. 5. Schema of effects of AVP on cardiovascular function and ANP release. ANP, atrial natriuretic peptide; AVP, arginine vasopressin; V₁-R, V₁ receptor; COP, cardiac output; LAP, left atrial pressure; RAP, right atrial pressure; SAR, sinoatrial reflex; TPR, total peripheral resistance; VR, venous return. ↑, increase; ↓, decrease; +, enhance; −, suppress.

that AVP at supraphysiological levels could decrease cardiac pumping ability due to its negative inotropic effect secondary to decreased coronary blood flow. Thirdly, it is likely that either increased TPR may rise cardiac afterload leading to a fall in cardiac output and/or increased RVR may decrease venous return with ensuring the reduction in cardiac output. Indeed, Tipayamontri et al. (1987) reported that AVP increased both RVR and TPR, leading to a fall in cardiac output in dogs. Therefore, taken together, it appears likely that all the mechanisms above-mentioned may be possible explanations for the hypoeffective heart observed in the present study as shown in Fig. 5. However, a rise in plasma ANP in response to AVP per se may not be the reason for the fall in cardiac output and the attenuation of pressor response produced by AVP, because the addition of ANP never affected cardiac output and MABP. On the other hand, ANP has been found to decrease cardiac output via the reduction in venous return induced by an increase in venous capacitance and/or intravascular volume contraction (Atlas and Laragh 1987). In the present study, however, it is likely that the acute plasma volume expansion may prevent the ANP-induced intravascular volume contraction enough to decrease cardiac output.

Increased plasma ANP in response to AVP may be brought about by increased PCWP, which stretches the left atrium, secondary to increased TPR rather than by increased CVP. Manning et al. (1985) and Inoue et al. (1988) reported that increased ANP release occurred in accordance with the pressor response, which might increase left atrial pressure. Metzler et al. (1986) reported that the constriction of the ascending aorta increased ANP release with a rise in left atrial pressure, accompanied by a fall in right atrial pressure. However, it is well known that the plasma volume expansion increases left as well as right atrial

pressure, but preferentially the latter, thereby resulting in increased ANP release (Diets 1984; Lang et al. 1987). Therefore, taken together, it is feasible that increased left atrial pressure, but not right, may mainly be responsible for increased ANP release in response to AVP-induced increases in TPR (Fig. 5). Indeed, Lachance et al. (1988) suggested that the right atrium responded to the low pressure system and the left atrium to the high pressure system, thereby resulting in ANP release.

In the present study, it is likely that AVP may increase the compliance of the capacitance vessel, because MCFP did not increase despite the presence of increased plasma volume exerted by AVP. This result suggests that sympathetic nervous activity in the capacitance vessel also may be attenuated by the potentiation of sino-aortic reflex exerted by AVP, thereby resulting in the venous pooling. Indeed, Cowley et al. (1983) predicted that AVP might produce the relaxation of the large vein via the potentiation of baroreflex buffering from the theoretical analysis. Moreover, it is also possible that the V_2 -receptor, eliciting antidiuresis and vasodilation, may exist in the venous vessel and dilate the veins in response to AVP. Indeed, the V_2 -receptors have been reported to exist in the cardiovascular system and to produce vasodilation (Liard 1986; 1988). To our knowledge, however, whether or not V_2 -receptors exist in the venous system has not been worked out.

Increased plasma volume observed during AVP infusion may be due to the reduction in urine flow, since a rise in urine flow in the saline alone group at the final period compared to the initial period (12-fold) was greater than its rise in AVP group (3-fold). Indeed, Tipayamontori et al. (1987) also found that acute administration of AVP increased blood volume without any changes in MCFP in conscious dogs. On the other hand, increased plasma ANP in response to AVP may counteract the increase in plasma volume produced by AVP, thereby resulting in a fall in MCFP. Trippodo et al. (1986) reported that ANP increased urine volume and capillary permeability due to changes in the ratio of precapillary-to-postcapillary resistance with a consequent fall in MCFP in rats, and also potentiated the venoconstriction. In the present study, however, the venoconstrictive response to ANP was not fully studied.

AVP infusion gradually attenuated increases in TPR with a parallel rise in plasma ANP, but the similar response also occurred in the saline group without a marked rise in plasma ANP. Therefore, ANP may not participate directly in the fall in TPR in the present study. On the other hand, it is possible that the blood volume expansion might reduce the sympathetic outflow via the potentiation of cardio-pulmonary reflexes and suppress the renin-angiotensin system, thereby resulting in the attenuation of TPR. Moreover, a possibility is not ruled out that AVP may stimulate vascular V_2 -receptors (Schwartz et al. 1985) as well as the release of vasodilator substances such as prostaglandins and endothelium-derived relaxing factor (Katusic et al. 1984; Seino et al. 1985), which in turn reduce TPR.

In conclusion, the supraphysiological dose of AVP suppressed increases in cardiac output in response to ECF volume expansion with a rise in TPR and increased the venous capacitance and plasma volume without any increases in MCFP.

Plasma ANP increased in response to V_1 -receptor-mediated increases in PCWP, but did not affect directly the AVP-mediated reduction in cardiac output.

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