Cardiovascular afferent signals and drinking in response to hypotension in dogs

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Thrasier, Terry N., Craig R. Keenan, and David J. Ramsay. Cardiovascular afferent signals and drinking in response to hypotension in dogs. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R795–R801, 1999.—Arterial hypotension stimulates increases in plasma arginine vasopressin (AVP), plasma renin activity (PRA), and water intake in conscious dogs. We have previously reported that increasing left atrial but not right atrial pressure completely blocks the increase in plasma AVP and PRA induced by hypotension. The goal of the present study was to examine the effect of increasing right or left atrial pressure on water intake induced by arterial hypotension. Dogs were prepared with occluding cuffs on the thoracic inferior vena cava, the pulmonary artery, and the ascending aorta. We reduced mean arterial pressure (MAP) 25% below control by either inferior vena cava constriction (IVCC), pulmonary artery constriction (PAC), or ascending aorta constriction (AAC) and measured water intake over a 2-h period. Cumulative water intake during IVCC (n = 6) and PAC (n = 6) was 7.8 ± 2.0 and 6.7 ± 2.6 ml/kg, respectively. There was no difference between either the latency or the volume consumed between the two treatments. In contrast, none of the dogs drank during hypotension induced by AAC (n = 5). Because the degree of arterial baroreceptor unloading was the same in each treatment by design, we conclude that stimulation of left atrial receptors inhibits drinking in response to arterial hypotension but that stimulation of right atrial receptors has no effect on the response in dogs.

arterial baroreceptors; cardiac receptors; atrial receptors; blood volume; hypovolemia; renin-angiotensin system

HYPOVOLEMIA leads to activation of multiple mechanisms that are directed toward restoration of the lost vascular volume. These mechanisms include increases in plasma arginine vasopressin (AVP) (25), which maximizes renal water reabsorption, and activation of the renin-angiotensin system (5), which stimulates sodium reabsorption directly and via stimulation of aldosterone secretion (11). Equally important, hypovolemia stimulates water intake (6, 24) and, in some species, a salt appetite (6). The afferent receptors that control AVP and renin secretion during hypervolemia and hypovolemia have been investigated in numerous studies (25). The “volume receptor” hypothesis proposed by Gauer and Henry (9) postulates that atrial receptor activity is tonically inhibitory to secretion of AVP, presumably via inhibition of a pool of medullary neurons with connections to hypothalamic magnocellular neurons. Thus decreases in blood volume could stimulate AVP secretion via withdrawal of inhibition, whereas increases in blood volume would have the opposite effect. Although this hypothesis is broadly accepted, recent observations in conscious rabbits (4) and dogs (17, 22, 26) have found no evidence that atrial receptors tonically inhibit AVP secretion in the euvolemic condition. Arterial baroreceptor firing also tonically inhibits pools of medullary neurons, and thus AVP secretion could be stimulated by progressive unloading of these receptors during hypovolemia. Reflex control of renin secretion is thought to arise from similar mechanisms (25).

Fitzsimons (6) has proposed two mechanisms to account for the stimulation of thirst during hypovolemia. The first postulates that unloading cardiac and arterial baroreceptors during hypovolemia stimulates drinking reflexly; analogous to the volume receptor mechanism proposed to control AVP secretion. The second is a humoral mechanism based on circulating ANG II stimulating receptors in a forebrain circumventricular organ, e.g., the subfornical organ or the organum vasculosum laminae terminalis. ANG II is dipsonic in most species and is clearly elevated in all known models of hypovolemia (24). Thus thirst responses could be stimulated by unloading peripheral cardiovascular receptors, in response to increases in plasma ANG II, or both.

Most of the evidence suggesting a reflex mechanism in the stimulation of thirst during hypovolemia is based on the observation that drinking is frequently maintained in the presence of drugs that block various components of the renin-angiotensin system. For example, we have shown that blocking ANG II receptors with saralasin has no effect on water intake in response to hypotension caused by thoracic inferior vena cava constriction (IVCC) in dogs, suggesting complete dependence on reflex signals (27). In contrast, Fitzsimons and Moore-Gillon (7) reported that saralasin reduced water intake by ~50% in a similar experiment in dogs, suggesting that both reflex signals and ANG II participated in the response. Many studies have reported that blocking various aspects of the renin-angiotensin system in hypovolemic rats reduces the drinking response, but some have produced negative results (6, 24). There appears to be only two studies that directly tested the effects of removing reflex influences on hypovolemic-induced water intake. Quillen et al. (18) reported that surgical removal of both cardiac and arterial baroreceptors eliminated the drinking response to arterial hypotension in dogs. Because plasma ANG II levels were increased to the same level in intact and total baroreceptor-denervated animals, these results suggest that reflex signals are essential to stimulate drinking in...
response to hypovolemia in the dog. In contrast, Schreinofer et al. (21) reported that drinking in response to subcutaneous polyethylene glycol in rats was unaffected by destruction of the nucleus of the solitary tract (the termination of cardiac and arterial baroreceptor afferents). Thus the rat would appear to differ markedly from the dog with respect to reflex stimulation of drinking.

Previous studies from this laboratory have focused on interactions between cardiac and arterial baroreceptor influences on the stimulation of renin and vasopressin secretion. We have observed that stimulating left atrial receptors suppresses increased secretion of renin and AVP in response to arterial hypotension (1), but we have observed no effect of stimulating right atrial receptors (2). The goal of the present study was to determine the effect of stimulating left or right atrial receptors on drinking induced by arterial hypotension in dogs. Dogs were prepared with constricting cuffs on the thoracic inferior vena cava, the pulmonary artery, and the ascending aorta. We measured water intake over a 2-h period in response to a 25% reduction in mean arterial pressure (MAP) induced by IVCC, which unloads receptors on both sides of the heart; pulmonary artery constriction (PAC), which loads right atrial and ventricular receptors and simultaneously unloads left atrial and ventricular receptors; and ascending aortic constriction (AAC), which loads left heart receptors. Because the signal to the arterial baroreceptors was the same in each case (i.e., a 25% reduction in MAP), alterations in the drinking responses could be evaluated with respect to the changes in load on atrial and/or ventricular receptors. We also measured plasma renin activity (PRA) to assess the activity of the renin angiotensin system and plasma atrial natriuretic factor, because this hormone is released in response to increases in left or right atrial pressure (1, 2) and has been reported to inhibit water intake (19).

METHODS

General. The experiments were performed on six mongrel dogs (3 females and 3 males) with weights ranging from 26 to 37 kg. The dogs were housed in a room maintained at 22 ± 2°C and 70% humidity and set to a 12:12-h light-dark cycle. Each day at ~1530 the dogs were administered prophylactic oral antibiotic treatment (sulfamethoxazole, 800 mg, and trimethaprim, 160 mg) and fed a mixture of dry chow (Purina) and canned dog food sufficient to maintain a constant body weight. The sodium intake on this diet averaged 2–3 1 · day⁻¹. Water was available to the dogs ad libitum. In addition, the dogs were provided an opportunity to socialize and exercise for a minimum of 60 min each day in an outside run.

To ensure that the dogs were free of infection, complete blood counts were performed weekly, and rectal temperatures were taken immediately before all experiments to document that the dogs were not febrile (i.e., <39°C). Within these parameters, all of the dogs were free of infection for the duration of the study.

Surgical procedures. The surgical procedures were performed with sterile technique after the National Institutes of Health guidelines. After pretreatment with acepromazine maleate (0.2 mg/kg sc; TechAmerica, Elwood, KS), the dogs were anesthetized with pentobarbital sodium (25 mg/kg iv; Fort Dodge Laboratories, Fort Dodge, IA) and intubated. A left thoracotomy at the fourth costal interspace was used to expose the heart. After the pericardial sac was opened and the roots of the aorta and pulmonary artery were exposed, occluding cuffs made of Silastic (Hazen Everett, Teaneck, NJ) were secured around the base of these vessels. In addition, catheters made of Tygon tubing (1.3 mm ID, 2.3 mm OD) were inserted into the right and left atrial appendages. The pericardial sac and chest wall were then closed. Fluid that had accumulated in the thoracic cavity was removed, and negative intrapleural pressure was restored by applying a vacuum to a chest tube. Oxymorphone (Numorphan, 0.2 mg/kg im, DuPont Pharmaceuticals) was given to provide analgesia as required after surgical procedures, and enrofloxacin (Baytril, 2.5 mg/kg orally; Mowlay, Shawnee, KS) was given twice a day for 7 days after surgery. A second thoracotomy in the right sixth costal interspace was performed 2–3 wk later with the same anesthesia and dosing technique as in the first. At this time, a third Silastic occluding cuff was implanted around the inferior vena cava just below its junction with the right atrium. In addition, Tygon catheters were introduced into the femoral artery and vein and advanced to the abdominal aorta and inferior vena cava, respectively, at a level below the kidneys. Oxymorphone and enrofloxacin treatment was provided postsurgically as above. At least 2 wk of recovery time was allowed before the dogs were used in experiments.

The vascular catheters and cuff lines were routed subcutaneously and passed through the skin between the shoulder blades. These lines were wrapped in gauze and stored in a pocket sewn to the underside of a nylon jacket worn by the dogs (Alice King Chatham Medical Arts, Los Angeles, CA). The vascular catheters were maintained by filling them with a mixture of heparin (1,000 U/ml; Elkins-Sinn, Cherry Hill, NJ) and penicillin G potassium (20,000 U/ml; Eli Lilly, Indianapolis, IN) to maintain patency and prevent infection. Every 2–3 days, the dead space of the catheters was removed, and the lines were flushed with 0.9% NaCl and then refilled with the heparin-penicillin mixture.

Experimental protocol. The experiments were conducted between 0900 and 1400 in a quiet room with the dog in a sling (Alice King Chatham Medical Arts) that provided support but minimal restraint. After being placed in the sling, the dogs were provided access to a water bowl within easy reach. If presentation of the water induced drinking in excess of 100 ml, it was presumed that the dog was in negative fluid balance and the experiment was postponed to another day. Otherwise, the dogs were allowed 30 min to become accustomed to their surroundings before data collection. The dogs had unlimited access to the water throughout the remainder of the experimental period. All of the dogs used had previously undergone at least one drinking experiment involving hypertonic saline infusion, and thus were accustomed to drinking while in the sling.

After a 30-min control period, during which atrial and systemic arterial pressures were monitored, the IVCC, PAC, or AAC was begun to reduce MAP distal to the cuff by 25% of the average MAP during the control period. This reduction was achieved within 2–4 min and maintained constant for 120 min by making continuous adjustments to the volume in the cuff. At the end of the constriction period, the cuff was deflated, and a 15-min recovery period was monitored. The order of vessel constriction was randomized, and the same experimental protocol without vessel constriction served as the control time. Venous blood samples (12 ml each and replaced with 12 ml of 0.9% NaCl) were taken at the
beginning and end of the control period and after 30, 60, 90, and 120 min of cuff inflation. In addition, a threshold blood sample was taken immediately after the dog's first drink of three laps or more of water after IVCC, PAC, or AAC. The blood samples were immediately aliquoted into chilled tubes containing either 0.3 M EDTA (pH 7.4) for subsequent measurement of PRA and atrial natriuretic peptide (ANP) or heparin for measurement of plasma osmolality and AVP. All blood samples were stored on ice until centrifuged and subsequently frozen at −20°C until assayed. The water intake of the dogs was measured during the control and recovery periods and at 30-min intervals during the cuff inflation. At least 3 days were allowed between experiments. A total of six dogs completed the IVCC, PAC, and time control protocols. In one of these six dogs, the cuff on the ascending aorta failed, and thus n = 5 for the AAC treatment.

Methods of measurement. The arterial and atrial pressures were measured with Cobe CDX III transducers (COBE Laboratories, Lakewood, CO) and recorded on a Grass model 7d polygraph. The pressure transducers were attached to the dogs' jackets at approximately heart level. The output from the polygraph was fed into a Buxco cardiovascular analyzer (model CVA-1, Buxco Electronics) connected to an online data acquisition system, and the digitized data were stored magnetically. Plasma osmolality was determined by freezing point depression (Advanced model 3W). Plasma AVP was determined by RIA after extraction with bentonite (14, 23). Recovery of AVP averaged 70 ± 2%, and the values reported are not corrected for recovery. Synthetic AVP (357 U/mg) was used to prepare standards, and the minimum level of detectability was 0.3 pg AVP/ml. The intra- and interassay coefficients of variability were 9 and 12%, respectively. PRA was measured with an RIA for ANG I and expressed as nanograms of ANG I generated per milliliter of plasma during a 3-h incubation at pH 6.0 (RIANEN RIA Kit; DuPont, Wilmington, DE). Plasma ANP was extracted by means of Sep-Pac columns according to a method described by Hartter et al. (12), and was measured with a kit obtained from Peninsula Laboratories (Belmont, CA). Recovery of cold ANP added to plasma was 88 ± 4%, and the values have not been corrected for recovery. The intra- and interassay coefficients of variability were 7 and 17%, respectively. Water intake was measured by reading the height of a column of water in a tube attached to the water container.

Data analysis. A two-way repeated-measures ANOVA was used to compare responses to IVCC and PAC (28). Because only five dogs were tested using the AAC treatment, the results were reanalyzed based on the five dogs common to all four treatments. Newman-Keuls procedure was used to make multiple comparisons among the means (29). Comparison of selected variables at the threshold of drinking in response to the IVCC and PAC treatments was performed with a paired t-test. In all cases, differences were considered significant if P < 0.05. The values for plasma AVP during hemorrhage displayed excessive heterogeneity (Bartlett's test; Ref. 29) and were transformed logarithmically before analysis.

RESULTS

Control values for MAP were similar in all four treatments. Consequently, reducing MAP by 25% in the IVCC, PAC, and AAC protocols resulted in absolute reductions in MAP that were nearly identical (Fig. 1A). There were no changes in MAP in the time control experiment. Each of the experimental treatments resulted in dramatic differences in atrial pressures (Fig. 1B). During IVCC, both right atrial pressure (RAP) and left atrial pressure (LAP) were reduced significantly below control (P < 0.01). During PAC, the decrease in LAP was similar to the change recorded during IVCC, but RAP increased significantly above the control level. During AAC, LAP increased significantly, but RAP declined to a level similar to that observed during IVCC. There were no changes in either LAP or RAP during the time control experiment.

Cumulative water intake in response to each treatment is shown in Fig. 2A. Both IVCC and PAC stimulated significant water intake, and the volumes consumed were not significantly different. In contrast, none of the dogs drank during AAC. During the time control experiment, two of six dogs took an occasional lap during the 2-h experiment, but overall the response did not differ from zero.

The changes in plasma AVP mirrored the effect of the treatments on water intake (Fig. 2B). Thus there were

![Fig. 1. A: initial values for mean arterial pressure (MAP) in 4 treatments and reductions in MAP during inferior vena cava constriction (IVCC; n = 6), pulmonary artery constriction (PAC; n = 6), and ascending aorta constriction (AAC; n = 5) are shown. Reductions in MAP in each experimental treatment were not significantly different, and there were no changes in MAP during time control. B: average changes in right atrial pressure (ΔRAP) and left atrial pressure (ΔLAP) from means during control period in each of 4 treatments. *Significant changes (P < 0.05 or greater) from both withintreatment control mean and mean during time control experiment.](image-url)
significant increases in plasma AVP in response to both PAC and IVCC, and the increases were not different between these two treatments. However, plasma AVP did not change from control levels during 2 h of hypotension induced by AAC or during the time control experiment (Fig. 2B).

The changes in plasma ANP and PRA in response to each of the treatments are shown in Fig. 3. PRA increased significantly in response to IVCC and PAC but did not change during AAC, even though MAP, and hence renal perfusion pressure, was reduced to \(65\) mmHg. Plasma ANP increased in response to both AAC and PAC. During the first 60 min the increase in plasma ANP in response to AAC tended to be larger compared with PAC, but the difference did not reach statistical significance. Also, plasma ANP tended to decline during IVCC, but the change did not reach statistical significance.

### Table 1. Means for selected variables at threshold of drinking

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Latency, min</th>
<th>AVP, pg/ml</th>
<th>PRA, ng ALA/3 h</th>
<th>ANP, pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVCC</td>
<td>34 ± 9</td>
<td>16.4 ± 4.0</td>
<td>3.0 ± 0.4</td>
<td>18.6 ± 5.5</td>
</tr>
<tr>
<td>PAC</td>
<td>31 ± 13</td>
<td>15.6 ± 3.0</td>
<td>2.3 ± 0.4</td>
<td>104 ± 44*</td>
</tr>
</tbody>
</table>

Values are means ± 1 SE. IVCC, inferior vena caval constriction \((n = 6)\); PAC, pulmonary artery constriction \((n = 6)\); AVP, arginine vasopressin; PRA, plasma renin activity; ANP, atrial natriuretic peptide. *P < 0.05 compared with IVCC treatment.
(Table 1). In contrast, plasma ANP was fivefold higher at the threshold of drinking in the PAC treatment compared with the IVCC condition.

Measurements of plasma osmolality were performed to verify that drinking responses and changes in plasma AVP were independent of osmoregulatory mechanisms. There were no differences in the control values for plasma osmolality among the four treatments and no significant changes in plasma osmolality during each of the 120-min protocols (data not shown).

**DISCUSSION**

The induction of thirst in response to hypotension could result from unloading low-pressure atrial receptors, high-pressure arterial baroreceptors, increases in plasma ANG II, or any combination of these factors (6, 24). Because a previous study demonstrated that baroreceptor mechanisms are essential for drinking in response to hypotension in the dog (18), we will consider reflex factors in the response first and hormonal inputs thereafter. The volume receptor hypothesis assumes that atrial receptors are tonically active at rest, and their firing is inhibitory to mechanisms controlling both AVP secretion (9) and drinking (6). However, recent studies from this and other laboratories have reported that acutely blocking the cardiac nerves by intrapericardial procaine (or lidocaine) has no effect on plasma AVP in either conscious dogs (17, 22, 26) or rabbits (4). Based on these observations, we have concluded that atrial receptor activity in the euolemic condition is so low as to have no inhibitory effect on AVP secretion (26). By analogy, it is very unlikely that atrial receptor firing in animals with normal blood volumes is sufficient to tonically inhibit thirst mechanisms. In contrast, we have demonstrated that increasing the load on left but not right atrial receptors completely inhibits hypotension-induced secretion of AVP in dogs (1, 2). Thus the goal of the present study was to determine if stimulation of left atrial receptors inhibited drinking in response to hypotension. We used IVCC to unload receptors on both the right and left sides of the heart and maintain a constant degree of arterial baroreceptor unloading by reducing MAP 25% below control. Because all inhibitory inputs from cardiac and arterial baroreceptors are reduced during IVCC, we assumed that the drinking response obtained would be maximal for these conditions. During PAC the unloading of the arterial baroreceptors was the same by design; the fall in LAP was similar, but right atrial receptors were clearly stimulated by the increase in RAP (Fig. 1). If receptors in the right atrium contribute an important inhibitory signal to mechanisms controlling drinking, then a decrease in water intake should occur. Similarly, if stimulating left atrial receptors contributes an important inhibitory signal, then hypotension caused by AAC should reduce the volume of water consumed.

The results indicate that water consumed during 2 h of PAC was not different from the volumes consumed in response to IVCC (Fig. 2A). In contrast, there was no drinking during AAC. Previous studies from this laboratory have shown that graded hypotension induced by either IVCC or PAC cause similar increases in plasma AVP, but hypotension caused by ACC has no effect on plasma AVP (3). Thus it would appear reasonable to conclude that stimulating right atrial receptors has little or no inhibitory influence on mechanisms controlling thirst as well as AVP secretion in dogs. The results also indicate that stimulation of left atrial receptors can completely suppress the stimulation of both thirst and AVP secretion arising from arterial hypotension (Fig. 2).

A caveat is necessary because the techniques used cannot distinguish between stimulation of atrial and ventricular receptors with certainty. This would not seem important for the right side of the heart, because the responses obtained during PAC and IVCC were similar. In contrast, many studies have shown that stimulation of left ventricular receptors alone results in powerful reflex responses, including inhibition of sympathetic outflow (see Ref. 10 for review) and renin secretion (8). We are unaware of any previous studies that examined the effect of stimulating left ventricular receptors on drinking, but Zucker et al. (30) examined the effects of intracoronary infusion of veratridine on hypotension-induced AVP secretion in conscious dogs. They reported that intracoronary veratridine did not reduce plasma AVP below control levels and had no effect on stimulated increases in plasma AVP in response to hypotension caused by intravenous infusion of nitroprusside. Thus Zucker et al. (30) concluded that stimulation of left ventricular receptors has no effect on either basal or hypotension-induced stimulation of AVP secretion. Because mechanisms that stimulate AVP secretion and water intake appear similar, one could argue by analogy that ventricular receptors are unlikely to be important in the control of thirst.

The hypothesis that stimulation of left atrial receptors can inhibit thirst mechanisms is not new. An earlier study by Moore-Gillon and Fitzsimons (16) reported that inflating a balloon in the junctional region where one pulmonary vein joins the left atrium attenuated drinking induced by isoproterenol or intravenous hypertonic saline. Although inflating a balloon at the junction of a pulmonary vein with the left atrial junction cannot replicate physiological stimulation of these receptors, it certainly localizes the afferent receptors to the left atrium. Furthermore, it indicates that the effect is inhibitory, which is compatible with known effects of stimulating left atrial receptors on AVP secretion (10).

What is surprising is that hypotension-induced stimulation of both AVP secretion and water intake is completely suppressed if the hypotension is caused by AAC (Fig. 2). Because drinking is a behavioral activity, it is possible that it was inhibited by severe stress associated with increased left heart pressure. However, there were no obvious signs that the dogs were agitated or debilitated and thus unable to drink. We have also observed that AAC does not prevent hypertonic saline-induced drinking, although the response is reduced compared with hypertonic saline alone (unpublished
observations). Thus the lack of drinking in response to arterial hypotension during AAC does not appear to be the result of behavioral incompetence. Furthermore, we have shown that normalizing the pressure in the left atrium during AAC leads to an immediate increase in AVP secretion (1), suggesting that an inhibitory neural signal was blocking the response to hypotension. Thus we conclude that when left atrial receptors are stimulated, the effect is a dominant inhibitory signal that overrides responses caused by reducing inhibitory input from arterial baroreceptors.

The cumulative intakes of water and the increases in plasma AVP in response to IVCC are smaller (8 ± 2 ml/kg) compared with our previous study (2 h intake of 13 ± 2 ml/kg) (27) and other studies in the literature (2 h intake of 19 ± 2 ml/kg) (e.g., Ref. 16). We have no explanation for the reduced intake other than to ascribe it to between-dog variability. However, responses in individual dogs appeared consistent. For example, the smallest intake in response to IVCC was 1 ml/kg, and this animal drank 2.5 ml/kg during PAC. In contrast, the largest intake during IVCC was 18 ml/kg, and this dog consumed 19 ml/kg during PAC. It is worth noting that the animal that drank the least also had a very small increase in plasma AVP, whereas the dog that drank the most had a large increase in plasma AVP. Regardless of the highly variable between-dog differences in response to IVCC, the within-subject design of the experiment allows unambiguous comparisons of responses to different treatments.

Our conclusion that right atrial receptors are unimportant in hypovolemic thirst in dogs is at odds with previous observations in rats. Kaufman (13) reported that infating a balloon in the region where the superior vena cava joins the right atrium abolished water intake in response to subcutaneous hyperoncotic colloid administration and attenuated drinking induced by isoproterenol administration or 24 h of water deprivation. The results reported by Kaufman (13) indicate that stimulation of right atrial receptors is inhibitory to thirst induced by various models of hypovolemia in rats. The divergent results obtained by Kaufman (13) in rats and the current study in dogs are most likely a result of species differences.

A recent study by Schreihofer et al. (21) underscores the differences between dogs and rats in terms of mechanisms controlling thirst in response to hypovolemia. They reported that lesions of the nucleus of the solitary tract, which is the termination of both cardiac and arterial baroreceptors afferents, had no effect on water intake induced by subcutaneous injection of polyethylene glycol. Schreihofer et al. (21) proposed a dual mechanism with baroreceptor afferents and plasma ANG II providing redundant signals. In contrast, Quillen et al. (18) reported that combined cardiac and arterial baroreceptor denervation eliminated drinking in response to hypovolemia in dogs. Few studies have examined drinking responses to hypovolemia in species other than rats and dogs, thus it is difficult to determine which species may be more representative.

Previous studies have reported that administration of atrial natriuretic peptide can inhibit drinking and the increase in plasma AVP in response to various stimuli (19). In the present study we observed large increases in plasma ANP in response to both PAC and AAC but no change during IVCC as reported earlier (3). Because water intake and the increases in plasma AVP were similar during 2 h of either IVCC or PAC, the results offer no evidence that increased plasma ANP alone can inhibit either response in dogs. However, it is possible that the rise in plasma ANP during AAC contributed to the suppression of water intake.

In a previous study (3) we observed that graded reductions in MAP caused by IVCC resulted in significantly greater increases in PRA compared with identical reductions in MAP during PAC. Because a number of studies have reported that ANP can inhibit renin secretion, we suggested that the increases in plasma ANP during PAC could account for the reduction in PRA. In the present study, there was no difference in the PRA response to IVCC compared with PAC (Fig. 3A). Because both studies used within-subject designs, variability is not a likely explanation for the discrepancy. Rather, the most likely explanation is differences in other aspects of the experimental design. For example, in the previous study (3) it was noted that the inhibition of renin secretion was greater during 5%, 10%, and 20% reductions in MAP compared with a 30% reduction in MAP, presumably reflecting an interaction between a gradually increasing stimulus to renin secretion (i.e., increased renal perfusion pressure plus engagement of reflex mechanisms) and the inhibitory effect of increasing plasma ANP. In the present study, the stimulus to intrarenal mechanisms was large (25% reduction in renal perfusion pressure) and constant. Thus the inhibitory effect of elevated plasma ANP may have been overwhelmed by the stimulatory signals arising from decreases in renal perfusion pressure and reflex stimulation arising from unloading arterial baroreceptors. It should be noted that we found no increase in PRA during AAC even though renal perfusion pressure was reduced by 25% in the present study, consistent with earlier studies from this laboratory (1, 3, 15, 20). Thus the inhibitory effect of loading left atrial receptors on renin secretion during AAC was clearly present in this population of dogs.

Perspectives

The current results, together with previous studies from this laboratory, illustrate an important interaction between receptors in the left heart, presumably in the left atrium, and arterial baroreceptors. Normally, hypovolemia results in unloading of both cardiac and arterial baroreceptors and the activation of reflex responses to defend blood pressure and restore blood volume, for example, increased secretion of renin and AVP and activation of thirst mechanisms. It is clear that all of these responses can be activated by arterial hypotension. However, when the brain receives an inappropriate combination of signals, as results from acute constriction of the ascending aorta, the inte-
grated response is clearly in favor of inhibiting the normal responses to arterial hypotension. In contrast, chronic conditions of elevated atrial pressure, such as in congestive cardiac failure, do not lead to suppression of renin and AVP secretion or water intake; in fact, the opposite is often the case. Thus a fundamental change must have taken place in the central integration of responses to elevated left heart pressure and reduced arterial pressure in chronic disease states compared with the responses described here. The underlying cause of the change in reflex responses elicited by loading left heart receptors in diseased hearts is unknown at present and clearly represents an important gap in our understanding of mechanisms regulating blood volume and pressure.

The authors gratefully acknowledge the technical assistance of Eva Kojak, Toni Meld, and Shirleko Dai in the course of these studies. The authors are also indebted to Lanny Keil for performing the AVP assays.

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Received 23 November 1998; accepted in final form 21 May 1999.

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