Mechanism of Impaired Water Excretion in Acute Right Ventricular Failure in Conscious Dogs

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SUMMARY Considerable controversy exists as to what extent left atrial receptors play a role in the physiological regulation of antidiuretic hormone (ADH) secretion. We studied conscious dogs during a stable water diuresis induced by continuous infusion of hypotonic saline, in whom acute inflation of a chronically implanted pulmonary artery balloon consistently produced antidiuresis. Following balloon inflation in nine dogs, glomerular filtration rate (GFR) (67 ± 8 to 70 ± 6 ml/min, P < 0.2) and osmolar clearance (C\textsubscript{osm}) (3.1 ± 0.2 to 3.3 ± 0.2 ml/min, P > 0.2) did not change. Despite a fall in plasma osmolality (287 ± 6 to 281 ± 5 mOsm/kg H\textsubscript{2}O, P < 0.025) and rise in mean systemic arterial pressure (100 ± 3.6 to 110 ± 3.8 mm Hg, P < 0.01), urine osmolality rose markedly (88 ± 8 to 234 ± 45 mOsm/kg H\textsubscript{2}O, P < 0.02), and urine flow (10.1 ± 0.8 to 6.3 ± 0.9 ml/min, P < 0.01) and renal free water clearance (C\textsubscript{free}) (7.1 ± 0.8 to 2.9 ± 0.7 ml/min, P < 0.01) both fell. This acute decrease in water excretion was shown to be the consequence of a rise in plasma levels of ADH (0.72 ± 0.07 to 2.06 ± 0.20 μU/ml) which returned toward control levels following balloon deflation (1.14 ± 0.18 μU/ml). The changes in ADH levels were shown to be associated with reciprocal changes in left atrial pressure (10.7 ± 1.7 to 6.1 ± 1.5 mm Hg after balloon inflation, returning to 12.2 ± 1.8 mm Hg after deflation). We conclude that in conscious dogs the effects of a small fall in left atrial pressure can predominate over the combined effects of a rise in systemic arterial pressure, continued infusion of hypertonic saline, and a fall in plasma osmolality, to produce a rise in plasma levels of ADH and antiadriuretic.

CHANGES in urine flow rate have been observed following experimental maneuvers in which left atrial pressure is altered. Henry and Gauer\textsuperscript{1} originally proposed 20 years ago that the increases in urine flow seen during left atrial distention were caused by decreased antiadriuretic hormone (ADH) secretion. Although in the ensuing years considerable evidence has accumulated which tends to support this hypothesis,\textsuperscript{3} there also is evidence suggesting that atrial receptors play little or no role in the physiological regulation of ADH secretion and that variations in urine flow rate associated with changes in left atrial pressure are the consequence of changes in solute excretion.\textsuperscript{4, 5, 9}

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Two recent reviews, in discussing this controversy, attempt to reconcile the discordant results.\textsuperscript{14, 15} It was concluded that, in the studies purporting to show an effect of left atrial pressure on vasopressin secretion, it was not possible to exclude concomitant alterations in right atrial pressure or in systemic arterial baroreceptor tone. Moreover, it is not known whether the receptors in the left atrium are more or less sensitive than receptors in the arterial circulation and which predominate when conflicting messages are sent to the hypothalamus.\textsuperscript{14} Recently, it has been shown that increased left atrial pressure induced by rapid atrial pacing\textsuperscript{16} or by balloon inflation of the mitral orifice\textsuperscript{17} was associated with a fall in urine osmolality and a rise in solute-free water clearance. Again the data were consistent with the view that a rise in left atrial pressure suppressed ADH release and resulted in an increase in water excretion. However, because the studies were performed on anesthetized dogs with markedly altered cardiovascular reflexes and high levels of ADH, possibly due to end-organ resistance to circulating vasopressin,\textsuperscript{17} the interpretation of these studies is open to question.

During the course of studies of renal sodium handling during the acute onset of right heart failure induced by inflation of a balloon in the main pulmonary artery of conscious dogs, we observed a highly consistent fall in urine flow rate and a rise in urine osmolality.\textsuperscript{18} The present series of experiments examined this phenomenon in greater detail and showed that this fall in the urine flow was a consequence of a rise in ADH secretion, triggered by a fall in left atrial pressure.

Methods

In nine male mongrel dogs weighing 15–22 kg, surgical procedures and insertion of catheters were as described previously in detail.\textsuperscript{19, 20} Under pentobarbital anesthesia (27 mg/kg, iv), a small right cervical incision was made above the great vessels. A 3 luminal balloon catheter (Laks catheter, Edward Lab) was guided under fluoroscopy via the jugular vein and right heart until the catheter tip was lodged in the periphery of the lung. The deflated balloon was then in the main pulmonary artery, the proximal catheter opening in the right ventricle, and the distal opening in the pulmonary artery beyond the balloon. Through the carotid artery a single lumen catheter was passed into the descending aorta. In six dogs, a third catheter was passed via the jugular vein through the right atrium, transeptally into the left atrium. All catheters were exteriorized through a midscapular incision and their ends were maintained in a close-fitting jacket (Alice Cathom Medical Arts). The experiment was performed 4–10 days after surgery, during which time the dog was trained to stand comfortably restrained in a Pavlov sling. After priming with p-aminohippuric acid (PAH) and inulin, a maintenance infusion of PAH and inulin was administered at 1 ml/min to ensure constant plasma levels. Right ventricular, pulmonary arterial, left atrial, and systemic arterial pressures were monitored by means of Statham transducers and an Electronic for Medicine DR-8 recorder (Physiotronics Inc.). A lubricated Swan-Ganz no. 7 French catheter was passed via the urethra into the bladder without anesthesia and the balloon was inflated with 1 ml of saline.\textsuperscript{21}

Initially, 600 ml of isotonic Ringer’s lactate solution was infused intravenously over a period of 30 minutes, following which half-isotonic Ringer’s lactate was administered at a rate approximately 5 ml above the urine flow rate. Control measurements of cardiac and renal function were performed after a stable hypotonic saline diuresis was achieved, usually after 2–3 hours of continuous infusion. Three urine collections, each 10 minutes in duration, were made, with mid-point blood sampling (period 1). Intracardiac and vascular pressures were measured and cardiac output was determined in triplicate, using the indocyanine green dye dilution technique and a Gilson DTL dye tracer (Gilson Medical Electronics). A sample was taken to measure plasma renin activity and arginine vasopressin level.

At the conclusion of the final control urine collection, the intrapulmonary artery balloon was gradually inflated with saline to the point at which systemic arterial pressure dropped slightly. The balloon was immediately deflated in order to just abolish this drop in systemic arterial pressure. One-half hour was allowed for re-equilibration, during which time the infusion rate was usually adjusted downward in order not to exceed urine flow by more than 5 ml/min. Three 10-minute urine collections, measurements of intracardiac and vascular pressures, determination of cardiac output, and a collection of plasma for renin activity and arginine vasopressin levels were repeated (period 2). Finally, intracardiac pressures, plasma renin activity, and arginine vasopressin were measured one-half hour after deflating the balloon (period 3). In three dogs, left atrial pressure and plasma arginine vasopressin were measured prior to the initial infusion of Ringer’s lactate.

Inulin was measured in plasma and urine by a colorimetric method using anthrone in H\textsubscript{2}SO\textsubscript{4}.\textsuperscript{22} PAH was measured by the method of Smith et al.\textsuperscript{23} Sodium and potassium were measured on a model 143 Instrumentation Laboratory flame photometer and osmolality on an Advanced Instruments osmometer. Cardiac output was calculated from the dye curve tracings by the cosine method.\textsuperscript{24} Plasma renin activity was measured by a modification of the radioimmunoassay of Haber et al.\textsuperscript{25} Plasma arginine vasopressin was measured by the radioimmunoassay method of Skowsky et al.\textsuperscript{26} with an intra-assay variation of 7% and an inter-assay variation of 15%. The limit of detection was 0.3–0.5 μU/ml.

Results

The dogs were outwardly unperturbed by inflation of the balloon in the pulmonary artery. The cardiovascular effects of balloon inflation are shown in Table 1. There was an increase in peripheral vascular resistance and a small but significant increase in systemic arterial pressure. Heart rate rose markedly (108 ± 6 to 145 ± 11, \(P < 0.005\)), whereas cardiac output fell in only five of nine dogs, the decrease in all dogs averaging 15%. Right ventricular systolic pressure doubled and end-diastolic pressure rose into the range commonly associated with incomplete ventricular emptying and acute congestive
heart failure. In Table 2 it can be seen that the clearance of PAH fell whereas GFR remained relatively constant after balloon inflation. There was an immediate fall in urine flow and free water clearance, and a rise in urine osmolality. There was a slight but not significant rise in osmolar clearance (Table 2) and sodium excretion (238 ± 33 to 305 ± 48 μEq/min). During the period 1 urine collections, several hours after the initial Ringer’s infusion and induction of a stable diuresis, PRA was low (0.54 ± 0.01) from period 1 to period 2. Associated with the continued hypotonic infusion, there was a small decrease in plasma osmolality (287.4 ± 6.2 to 280.8 ± 5.4 mOsm/kg H2O, P < 0.025) and sodium concentration (149.1 ± 1.0 to 144.5 ± 1.7 mEq/liter, P < 0.01) from period 1 to period 2.

### Table 1

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Cardiac output (liters/min)</th>
<th>Right ventricular systolic pressure (mm Hg)</th>
<th>Right ventricular end-diastolic pressure (mm Hg)</th>
<th>Mean systemic arterial pressure (mm Hg)</th>
<th>Peripheral vascular resistance (mm Hg/liter per min)</th>
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<td>4.6</td>
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</table>

Mean ± SE

- Mean ± SE: 5.1 ± 4.2, 4.6
- Mean ± SE: 33 ± 66, 34.5
- Mean ± SE: 1.5 ± 7.1
- Mean ± SE: 3.4 ± 100
- Mean ± SE: 104
- Mean ± SE: 104
- Mean ± SE: 104
- P < 0.005

### Table 2

<table>
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<tr>
<th>Dog no.</th>
<th>Urine volume (ml/min)</th>
<th>GFR (ml/min)</th>
<th>C_ex (ml/min)</th>
<th>C_mm (ml/min)</th>
<th>C_no (ml/min)</th>
<th>Plasma renin activity (ng/ml per hr)</th>
<th>Urine sodium excretion (μEq/min)</th>
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<td>56.0</td>
<td>305</td>
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<td>56.0</td>
<td>305</td>
<td>182</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Mean ± SE

- Mean ± SE: 10.1 ± 0.3, 7.0, 6.0, 7.5, 6.6, 262, 219, 3.07, 3.3, 3.7, 7.1, 2.9
- Mean ± SE: 0.54 ± 0.48, 238 ± 305
- Mean ± SE: 0.8 ± 0.9, 8 ± 6, 27 ± 28, 0.2 ± 0.2, 0.81 ± 0.7, 0.21 ± 0.2, ± 33.2 ± 48.4
- P < 0.01

After consistently noting a fall in urine flow rate with no change in osmolar clearance or GFR in our previous studies, we suspected that ADH, whose secretion would be suppressed by hypotonic infusions before and during period 1, was being acutely secreted in response to the balloon inflation. As seen in Table 3, this was the case. Noting that ADH secretion was enhanced in dogs 1–3 despite continued hypotonic infusion and despite elevation of arterial blood pressure, we suspected that left atrial pressure must be falling after inflation of the balloon. The results in dogs 4–9 confirmed that this was correct (Table 3). The relationship between left atrial pressure, plasma ADH, and urine osmolality are depicted graphically in Figure 1. Dog no. 5 reacted differently from the others in that, despite a fall in left atrial pressure, plasma ADH, and thus urine osmolality failed to rise (Table 3),

* Numbers in parentheses = period 1 or 2.
† For technical reasons, no urinary data are available for dog no. 8.
and solute-free water clearance did not fall (Table 2). However, this dog did not differ from the other animals with respect to other renal and cardiovascular parameters.

Following balloon deflation (period 3) cardiovascular parameters tended to return towards control values (Table 1). Left atrial pressure rose to or above control values and plasma ADH fell (Table 3). Plasma renin activity (0.25 ± 0.07 ng/ml per hr) fell slightly, but not significantly. In three dogs, left atrial pressure was lower and plasma ADH levels higher before, rather than after, hypotonic Ringer's lactate infusion was begun.

**Discussion**

Inflation of a balloon in the main pulmonary artery of conscious, trained dogs was consistently associated with an immediate fall in urine flow rate and an interruption of a stable water diuresis. This occurred in the face of a small rise in systemic arterial pressure and despite continued rapid infusion of half-isotonic Ringer's lactate solution at a rate at all times in excess of urine flow. The rise in systemic arterial pressure also seen by others is mediated by the sympathetic nervous system since it can be blocked by phentolamine. GFR did not change and there was not a concomitant reduction in solute excretion; indeed, mean osmolar clearance and sodium excretion actually rose slightly. Upon deflation of the balloon, urine flow rate returned toward control values. These results strongly suggested that ADH secretion had been stimulated during the inflation of the balloon. To examine this possibility, a sensitive radioimmunoassay for plasma arginine vasopressin was employed. The rise in plasma ADH during period 2 and the return to control levels after balloon deflation confirmed this hypothesis (Table 3).

The plasma levels of ADH measured during period 1 are similar to values reported by Weitzman et al. and Boykin et al. in water-loaded conscious dogs. The rise in ADH induced by balloon inflation, although modest, is within the physiological range and is sufficient to explain the marked rise in urine osmolality and fall in free water clearance observed. The correlation between rises in ADH and urine osmolality was good ($r = 0.84$). Dog no. 5, which did not show a rise in ADH, likewise did not show either a rise in urine osmolality or a fall in free water clearance, further confirming the cause and effect relationship of the changes in ADH, urine osmolality, and urine flow in the other dogs.

Serum sodium concentration and osmolality fell slightly, and the continued hypotonic infusion ruled out an osmolar stimulus for ADH release during period 2. Since systemic arterial pressure rose, it also seemed unlikely that the arterial baroreceptors in the aortic arch or carotid body had been stimulated; therefore, our attention was directed to the possible role of changes in left atrial pressure in this

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**Table 3** Left Atrial Pressure, ADH Plasma Level, and Urine Osmolality before, during, and after Balloon Inflation in the Main Pulmonary Artery

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Left atrial pressure (mm Hg)</th>
<th>ADH* (μU/ml)</th>
<th>Urine osmolality (mOsm/kg H2O)</th>
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</tr>
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</table>

Mean ± se 10.7 ± 1.7 6.1 ± 1.5 12.2 ± 1.8 0.72 ± .07 2.06 ± .2 1.14 ± .18 87.7 ± 8.2 234 ± 45

| P       | <0.05                      | <0.005       | <0.001                       | <0.025                       | <0.0125                     |

* ADH = immunoreactive arginine vasopressin.
† Numbers in parentheses = period 1, 2, or 3.
response. It was shown that balloon inflation regularly resulted in a significant fall in left atrial pressure. In all dogs save one (dog no. 5), this fall in left atrial pressure and the subsequent rise following balloon deflation were associated with oppositely directed or reciprocal changes in plasma ADH. These findings strongly suggest that the changes in left atrial pressure caused the changes in plasma ADH. They also demonstrate that, under some conditions, a fall in left atrial pressure can predominate over opposing stimuli at the osmoreceptors and arterial baroreceptors and result in ADH release. In most other studies, both left atrial and arterial baroreceptors were stimulated concomitantly, such that their effects on ADH and renal water excretion probably were additive. It is likely but not proven that changes in systemic circulating renin and angiotensin have no effect upon neurohypophyseal release of ADH. However, it should be noted that, in the present studies, PRA remained low and unchanged in periods 1 and 2 and could not have played a role in the changes in ADH secretion. The low PRA is expected in volume-expanded dogs experiencing a rise in right atrial pressure.

Two recent studies showed that a marked rise in left atrial pressure was associated with a fall in urine osmolality and rise in free water clearance, despite a small fall in systemic arterial blood pressure. In only one of these studies was plasma ADH actually measured. However, in this study at all times the urine remained hypertonic to plasma and the levels of ADH found were so high (10 times higher than in the present study), even after the rise in left atrial pressure, that the study is difficult to interpret.

In summary, we have shown that relatively modest changes in left atrial pressure resulted in reciprocal small changes in plasma levels of immunoreactive arginine vasopressin, which in turn had the expected marked effects upon urine osmolality, urine flow, and free water clearance. Avoided were the problems associated with anesthe-sia and positive pressure ventilation, extensive abdominal and thoracic surgery, possibly incomplete hypophysectomy, uncertainty about appropriate doses of exogenous vasopressin and steroids, and the bioassay of arginine vasopressin, all encountered and discussed previously. These dogs showed many of the cardiovascular changes frequently associated with acute right-sided heart failure (Table 1). It is suggested that one possible factor in the hyponatremia and impaired water excretion of acute cor pulmonale in patients is stimulation of ADH secretion associated with a reduction in left atrial pressures.

Acknowledgments

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