Role of Cardiopulmonary Mechanoreceptors in ADH Release in Normal Humans

BRENT EGAN, ROGER GREKIN, HANS IBSEN, KARL OSTERZIEL, AND STEVO JULIUS

SUMMARY Although animal studies have shown that cardiopulmonary receptors regulate the release of antidiuretic hormone (ADH), human studies have produced conflicting results. Consequently, we studied 17 normal healthy men to determine the ADH response to selective unloading (decreased stretch) of cardiopulmonary low-pressure receptors by thigh cuff inflation in the supine position. Thigh cuff inflation of 30 to 40 mm Hg decreased the central blood volume and right atrial pressure (cardiopulmonary receptor load), while mean arterial pressure and pulse pressure were unchanged (arterial baroreceptor load). Thigh cuff inflation to this level did not alter plasma osmolality or cardiac output. Plasma ADH increased an average of 67% (p < 0.01) following thigh cuff inflation compared to the preceding supine baseline. After thigh cuff deflation (n = 6), the ADH decreased toward preinflation values. We conclude that selective unloading of the cardiopulmonary receptors in humans increases plasma ADH levels. (Hypertension 6: 832-836, 1984)

KEY WORDS • vasopressin • cardiopulmonary receptors • hemodynamics

ABNORMALITIES in antidiuretic hormone (ADH) levels and in blood volume distribution have been described in some hypertensive patients. It is conceivable that differences in blood-volume distribution, through an effect on cardiopulmonary low-pressure receptors, influence the plasma ADH level. This hypothesis can be seriously entertained only if it were shown that low-pressure (volume) receptors play a role in regulating ADH release in humans. The literature on volume control of ADH release is filled with controversies.

Although decreases in blood volume, carotid sinus pressure, and cardiopulmonary low-pressure receptor restraint all increase ADH release in dogs, the results of human studies are less clear. For example, standing and tilting, which decrease central blood volume, right atrial pressure, and pulse pressure, unload both arterial high-pressure and cardiopulmonary low-pressure receptors simultaneously. These orthostatic stresses have reportedly caused either no change or increases in plasma ADH. Others have noted that upright posture increases plasma ADH after but not before the induction of mild volume depletion. Increasing the effective blood volume with water immersion has more uniformly suppressed urinary and plasma ADH in upright subjects. Although this suppression has been attributed primarily to the increased load on low-pressure receptors, high-pressure receptor load may have been altered since cardiac output (CO) increased and total peripheral resistance (TPR) decreased. Furthermore, the state of osmotic balance during water immersion is controversial and may account for the ADH suppression during this maneuver.

The results of studies attempting to unload only low-pressure receptors in humans by either nonhypotensive hemorrhage or lower body negative pressure (LBNP) have also yielded conflicting results. Both Goetz et al. and Goldsmith et al. reported no change in plasma ADH with unloading of low-pressure receptors alone. Rogge and Moore reported significant increases in plasma ADH after 30 minutes of LBNP at 30 mm Hg. Since mean blood pressure (MAP) and pulse pressure did not change, they concluded that the ADH increase resulted from selective unloading of low-pressure receptors. However, invasive hemody-
namic data were not obtained. Therefore, the intensity and selectivity of this stimulus are questionable.

In summary, the literature on the volume control of ADH release in humans abounds with controversies. Factors that regulate the relationship between intravascular volume and ADH release need to be better understood before the pathophysiology of some disease states can be elucidated, including hypertension. Therefore, we studied the ADH response to selective unloading of low-pressure receptors induced by thigh cuff inflation in normal human volunteers.

Methods

Subjects

Seventeen healthy paid male volunteers, aged 18 to 34 years, participated in one of two invasive hemodynamic studies, after they had understood and signed an informed consent form approved by the University’s Human Use Committee. All had normal results from physical and laboratory examinations. They were put on a standardized sodium diet (150 mEq/day) for 4 days and were given instruction sheets that included sample menus for the 20 mEq/day Na+ diet that was to be used in the study. The diet was to be supplemented to 150 mEq NaVday by the addition of salt tablets. The sodium content of 24-hour urine samples was determined before the study began and was 142.0 ± 7.9 (SEM) mEq.

Laboratory Preparation

All studies began at 8:00 a.m. and ended by 1:00 p.m. Upon arrival at the laboratory, subjects assumed the supine position and had electrocardiographic (ECG) leads attached for heart rate (HR) monitoring. Then, an 18-gauge, 2-inch Teflon catheter (Angiocath, Deseret Company, Sandy, Utah) was introduced percutaneously into the left brachial artery. A No. 4 French Swan-Ganz catheter in Study 1 (Edwards Laboratories, Inc., Santa Ana, California) or a polyethylene catheter with an internal diameter of 0.58 mm in Study 2 (Clay Adams, Division of Becton, Dickinson and Company, Parsippany, New Jersey) was introduced percutaneously into the left basilic vein, advanced to the right atrium, and withdrawn to the right atrium. Statham strain gauges (Statham Instruments, Inc., Oxnard, California) were placed at midaxillary level in the fourth intercostal space for recording brachial artery (P23Db) and right atrial (P23BB) pressures.

Hemodynamic Measurements

Details of the measurements in our laboratory have been explained previously. In brief, the HR was determined from the ECG recording. Brachial artery and right atrial pressures were obtained from the Statham transducers connected to a Hewlett-Packard 4578 polygraph (Hewlett-Packard Company, Palo Alto, California). The CO was measured by dye dilution (Cardiogreen, Hynson, Westcott and Dunning, Inc., Baltimore, Maryland) with an Electronics for Medicine densitometer (Honeywell Corporation, Van Nuys, California). Central blood volume was estimated by multiplying the CO by the mean transit time from the right atrial to the brachial artery catheter. In addition to cardiopulmonary blood volume, the method measures an arterial volume temporarily equidistant to the brachial arterial sampling site.

Humoral Measurements

Plasma renin activity (PRA) was measured by radioimmunoassay of generated angiotensin I after a 60-minute incubation period at a pH of 6.0. All samples for each subject were determined in a single assay run.

Plasma ADH was measured by a radioimmunoassay technique developed by Pierce et al. The ADH was extracted from plasma samples with octadecylsiline cartridges (Sep-pack C-18; Waters Associated, Milford, Massachusetts) by a modified method of LaRochelle et al. Dried extracts were then reconstituted in 1 ml of buffer for assay. Buffer was the same as described by Skowksi et al., and antiserum was graciously supplied by Dr. Gary Robertson. I-arginine vasopressin (New England Nuclear, Boston, Massachusetts) was used as tracer, and synthetic arginine vasopressin (Sigma Chemical Company, St. Louis, Missouri) was used for the standard curve. Standard curves based on USP and WHO arginine vasopressin standards in the range of from 0.63 to 80 pg/ml (0.25 to 32 uU) were linear and parallel to curves obtained with the synthetic standard. After 7 days of incubation at 4°C, with tracer added after 2 days, bound ADH was separated by rabbit gamma globulin and PEG 6000 (J.T. Baker Chemical Company, Philipsburg, New Jersey). Bound and free fractions were counted with a Searle 1197 gamma counter. The lower limit of sensitivity in this assay was 0.63 pg/ml. The intraassay and interassay coefficients of variation were 6.8% and 10.4%, respectively.

Plasma osmolality was measured by freezing point depression with a Microosmette osmometer (Precision Systems Inc., Sudbury, Massachusetts).

Study 1

Eleven subjects participated in Study 1. After 30 minutes supine, baseline measurements were obtained of HR, arterial and right atrial pressures, CO, central blood volume, PRA, and ADH. Thigh cuffs were then inflated to 30 mm Hg for 30 minutes, and the variables were remeasured.

Study 2

Six subjects participated in Study 2. The measurements were taken 30 minutes after insertion of the catheters with the subjects in the supine position. The variables were the same as in Study 1, with the addition of plasma osmolality. After baseline measurements were obtained, thigh cuffs were inflated to 40 mm Hg for 30 minutes, and the variables were remeasured. At 45 minutes after thigh cuff deflation, a second set of supine baseline measurements was obtained.
TABLE 1. Hemodynamic Measurements After Thigh-Cuff Inflation of 30 and 40 mm Hg Compared to the Preceding Supine Baseline in 17 Men

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Cuff 30-40 mm Hg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>55.1 ±2.4</td>
<td>58.8 ±2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>MAP</td>
<td>81.2 ±3.1</td>
<td>82.6 ±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>PP</td>
<td>60.2 ±2.4</td>
<td>62.4 ±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>CO</td>
<td>5.9 ±0.5</td>
<td>5.7 ±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>CBV</td>
<td>1824 ±109</td>
<td>1666 ±70</td>
<td>0.01</td>
</tr>
<tr>
<td>RAP</td>
<td>3.9 ±0.7</td>
<td>2.8 ±0.5</td>
<td>0.03</td>
</tr>
<tr>
<td>ADH (a)</td>
<td>1.7 ±0.4</td>
<td>7.5 ±5.1</td>
<td>0.01</td>
</tr>
<tr>
<td>ADH (b)</td>
<td>1.5 ±0.3</td>
<td>2.5 ±0.6</td>
<td>0.01</td>
</tr>
<tr>
<td>PRA</td>
<td>0.95 ±0.17</td>
<td>1.47 ±0.26</td>
<td>0.03</td>
</tr>
<tr>
<td>OSM (n = 6)</td>
<td>284.7 ±1.6</td>
<td>285.7 ±1.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

HR = heart rate, bpm; MAP = mean arterial pressure, mm Hg; PP = pulse pressure, mm Hg; CO = cardiac output, liter/min; CBV = central blood volume, ml; RAP = right atrial pressure, mm Hg; ADH = antidiuretic hormone, pg/ml; PRA = plasma renin activity, ng/ml/hour; OSM = plasma osmolality, milliosmoles/liter. (a) includes and (b) excludes the subject whose ADH increased to 87.5 pg/ml.

Statistical Analysis

Data are presented as means ± SEM. The p values were obtained from Wilcoxon’s rank-sum test of paired differences from the supine baseline. Baseline values of Group 1 (30 mm Hg inflation of the thigh cuff) and of Group 2 (40 mm Hg inflation) were similar, and both levels of inflation induced similar changes. Consequently, the data of these groups were pooled to obtain hemodynamic and hormonal profiles of a larger sample.

Results

Inflation of thigh cuffs to 30 to 40 mm Hg caused an increase of ADH, PRA, and HR compared to the supine baseline. Central blood volume and right atrial pressure decreased. The MAP, pulse pressure, CO, and plasma osmolality did not change (Table 1).

Following the 40 mm Hg thigh cuff inflation period, deflation of thigh cuffs was associated with a decrease in ADH (Figure 1), although the level remained significantly (p = 0.05) higher than at the initial baseline.

Discussion

In this study, unloading cardiopulmonary low-pressure receptors was associated with increases in plasma ADH levels. The ability of thigh cuff inflation to unload low-pressure receptors was confirmed by decreases in central blood volume and right atrial pressure. The selective nature of this stimulus was confirmed by an absence of changes in MAP and pulse pressure. Therefore, it is unlikely that the high-pressure receptor load was significantly altered.

The increases in plasma renin and HR in response to selective unloading of low-pressure receptors confirm our previous findings.

Our current results show that selective unloading of low-pressure receptors increases ADH release in humans and are in agreement with results in animals. Claybaugh and Share found that removal of as little as 2.6% of total blood volume in dogs increased plasma vasopressin.

Thames and Schmid reported that vagotomy (low-pressure receptor afferents) increased plasma vasopressin before and after carotid sinus denervation. These findings indicated that cardiopulmonary receptors with vagal afferents tonically inhibit vasopressin release in dogs.

However, the results in humans are less uniform. Human studies have focused on ADH responses to relatively selective increases and decreases in cardiopulmonary low-pressure receptor load. Water immersion in upright subjects, which consistently suppresses urinary and plasma ADH, is associated with significant increases in right atrial pressure and central blood volume.

Thus, low-pressure receptor load is increased and likely contributes to the suppression of ADH. Although arterial pressures are not substantially altered, interpretation is complicated by major acute changes in arterial hemodynamics, which are sustained, and possible hypoosmotemia, which could also contribute to ADH suppression.
Nonhypotensive hemorrhage, lower body negative pressure, and thigh-cuff inflation have been utilized by various investigators to induce selective unloading of cardiopulmonary low-pressure receptors. Rogge and Moore observed an increase in plasma ADH after 30 minutes of LBNP at 30 mm Hg in humans. They assumed that LBNP elicited a selective unloading of low-pressure receptors, but they had no hemodynamic data obtained invasively to support the assumption. Our study uses another method to unload the low-pressure receptors, namely, thigh-cuff inflation, and provides information that confirms the stimulus selectivity. Only those hemodynamic determinants that affect the low-pressure receptor function were altered by thigh-cuff inflation.

Both Goetz et al. and Goldsmith et al., who studied the response of normal humans to nonhypotensive decreases in effective blood volume, found the plasma ADH unchanged. However, in both studies, plasma for assay of ADH was obtained only 5 to 10 minutes after unloading low-pressure receptors, which may have been an inadequate time in which to detect ADH changes. It is also possible that the stimulus in these two studies was insufficient to induce increases in plasma ADH, since Rogge and Moore, who found increased plasma ADH after 30 minutes of LBNP at 30 mm Hg, did not find increased ADH after 30 minutes of LBNP at 20 mm Hg. In addition, Rogge and Moore and Goetz et al. used an ADH bioassay that may have been insensitive to small changes in plasma ADH. Nevertheless, Goldsmith et al. obtained similarly negative results with the more sensitive radioimmunoassay.

An alternative explanation for the absence of an ADH increase with 20 mm Hg LBNP may be inherent to the method itself. Lower body negative pressure, even when applied to the level of the iliac crests and distally, causes decreases in gastric relaxation pressures and lowering of the diaphragm. Therefore, negative pressure is applied to the abdominal cavity. This negative intraabdominal pressure may elicit mesenteric reflexes that could oppose those induced by unloading cardiopulmonary low-pressure receptors. This may account for the controversy surrounding ADH, PRA, and HR responses to unloading of low-pressure receptors in humans. Dietary salt intake may be another confounding variable, since most human studies that have investigated baroreceptor control of ADH release have not standardized dietary sodium intake. The baseline volume status may well influence the responsiveness of this hormone to alterations in baroreceptor load.

For this reason, sodium intake in our study was standardized at 150 mEq/day. Thigh-cuff inflation to 30 to 40 mm Hg caused the elevation in plasma ADH, since the levels of this hormone decreased following cuff deflation. Our laboratory demonstrated previously that thigh-cuff inflation causes a reflex release of renin. We believe that the increase of ADH with thigh-cuff inflation in the present study also represents a reflex response to selective unloading of low-pressure receptors. Because systemic hemodynamics were unchanged, the increase in ADH more likely reflects enhanced secretion rather than diminished clearance. However, unloading low-pressure receptors may have decreased ADH clearance by reflexly reducing hepatic blood flow and by increasing renal sympathetic nerve activity. In either case, the plasma ADH increased as the result of a reflex response with the afferent limb in the low-pressure receptors.

While the preceding discussion encompasses the most credible reasons for the increase of ADH following thigh-cuff inflation, other explanations require consideration. First, although two important determinants of arterial baroreceptor load were unchanged, namely, MAP and pulse pressures, the rate of arterial pressure changes (dp/dt) is also important. It was not measured in this study, arterial dp/dt, which was not measured in this study, may have changed and contributed to ADH release. In another study that elicited even larger decreases in right atrial pressure than those recorded in this study, arterial dp/dt was unchanged. Therefore, it is unlikely that changes in high-pressure receptor load during thigh-cuff inflation contributed significantly to the increase in ADH.

Second, since thigh-cuff inflation increased PRA, elevation of angiotensin levels may have augmented ADH release. In humans, angiotensin infusion significantly increases plasma ADH only at supraphysiologic concentrations. Furthermore, we found no correlation between the magnitude of renin and ADH responses to thigh-cuff inflation (r = 0.02). Consequently, it is improbable that increases in angiotensin caused the increase in plasma ADH.

Finally, an acute increase in the capillary-filtration pressure of the lower extremity following thigh-cuff inflation may have caused a temporary increase in plasma osmolality, because of the different reflection coefficients of the capillary membrane for water and solutes. In our study, however, the plasma osmolality was unchanged after 30 minutes of thigh-cuff inflation to 40 mm Hg.

In summary, inflation of thigh cuffs in supine healthy volunteers increased plasma ADH levels. Thigh-cuff inflation decreased right atrial pressure and central blood volume (cardiopulmonary low-pressure receptor load), but this maneuver did not change the MAP and pulse pressure (arterial high-pressure receptor load). The CO and plasma osmolality were also unchanged. Our data indicate that selective unloading of low-pressure receptors reflexly increases plasma ADH in normal men.

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