Atrial distension, arterial pulsation, and vasopressin release during negative pressure breathing in humans

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During an antioorthostatic posture change, left atrial (LA) diameter and arterial pulse pressure (PP) increase, and plasma arginine vasopressin (AVP) is suppressed (20, 21, 24). The suppression of AVP release is absent when LA diameter and PP are prevented from increasing and is thus critically dependent on at least one of these stimuli (20, 21, 24). The suppression of AVP release during negative pressure breathing compared with similar increases in LA diameter, suppression of AVP release is dependent on the degree of increase in PP. LA diameter increased similarly during the posture change and negative pressure breathing (from 36 to 42 mmHg) from between 30 and 31 mmHg to 34 mmHg (P < 0.05). The increase in PP from 38 to 44 mmHg (P < 0.05) was sustained during the posture change but only increased during the initial 5 min of negative pressure breathing from 36 to 42 mmHg (P < 0.05). Aortic transmural pressure decreased during the posture change and increased during negative pressure breathing. Plasma AVP was suppressed to a lower value during the posture change (from 36 to 42 mmHg, P < 0.05) than during negative pressure breathing (from 1.5 to 1.4 pg/ml, P < 0.05). Plasma noradrenaline was decreased similarly during the posture change and negative pressure breathing compared with seated control. In conclusion, the results are in compliance with the hypothesis that during maneuvers with similar cardiac distension, suppression of AVP release is dependent on the increase in PP and, furthermore, probably unaffected by static aortic baroreceptor stimulation.

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H1584 VASOPRESSIN DURING POSTURE CHANGE AND NEGATIVE PRESSURE BREATHING

The experiment started at 9:00 AM and consisted of three interventions separated by 30 min of seated rest: 1) 45 min of a seated control, 2) 45 min in the seated position with NB from the 15th to the 30th minute, and 3) 15 min in the seated position, followed by a posture change to supine for 15 min and finally again 15 min of being seated. A stable level of NB over the 15-min period was achieved within 15 s, and the level was thereafter continuously adjusted (within 30 s after obtaining the LA diameter pictures) to obtain a LA diameter similar to that of the supine position. The mean value of NB over the 15-min period was $-15 \pm 1$ mmHg (range, $-9$ to $-24$ mmHg). The interferences were performed with the sequence in a balanced randomized order between the subjects.

NB was performed by having the subject breathe through a mouthpiece connected by inspiratory and expiratory valves and tubes to a ventilated hypobaric chamber [a lower body negative pressure (LBPN) box] in which the pressure could be manually adjusted. To obtain conditions as similar as possible during the three interventions, the subjects also breathed through the mouthpiece during supine and the middle 15 min of control (but with the tubes disconnected from the hypobaric chamber).

LA diameter was measured by echocardiography (Aloka SSD 500, Simonsen and Weel) according to the criteria of Feigenbaum (7) every fifth minute (and continuously during NB) during end expiration as an average of measurements from three M-mode pictures (printouts from a video recorder, Sony SVO 9500 MDP) obtained from the parasternal long axis view. All the measurements were performed in a blinded fashion (LA diameter was measured on the coded printouts after the experiments).

Systolic (SAP) and diastolic arterial pressures (DAP) were measured every fifth minute in the left brachial artery by conventional sphygmomanometry. PP was calculated as $PP = SAP - DAP$, and mean arterial pressure (MAP) was calculated as $MAP = DAP + 1/3\left(PP\right)$. The cuff for arterial pressure determination was kept horizontal and the trunk vertical with back and neck support while he was instrumented with chest electrodes and a cuff around the left upper arm for determination of heart rate (HR) and brachial arterial pressures, respectively. Furthermore, NB was tested to familiarize the subject with the procedure.

Room temperature was kept between 24.4 and 26.7°C, and humidity was kept between 35 and 48%.

A NOVA (Statgraphics plus for Windows, version 3.0) for repeated measures with the variables MAP, PP, LA diameter, AVP, etc. as the main variates and time and subject as factors was used to evaluate the effects of a variable over time within each series of experiments compared with the initial 15 min. Differences between mean values were evaluated by a post hoc multiple-range test (Newman-Keuls). Furthermore, an ANOVA with the variables MAP, PP, LA diameter, AVP, etc. as the main variates and intervention (control, supine, and NB, respectively) and subject as factors was used to detect differences between series at selected similar points in time. Differences between mean values were evaluated by post hoc multiple-range tests (Newman-Keuls). Furthermore, an ANOVA (GB Stat for Windows, version 5.3) was used to detect differences within and between the sessions, respectively. Logarithmic transformation of the AVP data was performed before analysis, because normal distribution cannot be expected for the low values. $P < 0.05$ was chosen as the level of significance.

RESULTS

LA diameter increased similarly during the posture change from seated to supine and during NB from between $30 \pm 1$ and $31 \pm 1$ mmHg to between $33 \pm 1$ and $35 \pm 1$ mmHg ($P < 0.05$; Fig. 1). No significant changes occurred during control. During the posture change to supine, PP increased from a mean value of 38 $\pm 2$ mmHg to a maximum of 45 $\pm 3$ mmHg ($P < 0.05$; Fig. 1). PP increased only at the beginning of NB from a mean value of $36 \pm 3$ to $44 \pm 3$ mmHg ($P < 0.05$; Fig. 1) and was thereafter indistinguishable from that of control. MAP decreased during the posture change to supine from a mean value of $92 \pm 2$ to $85 \pm 1$ mmHg ($P < 0.05$; Fig. 2). During NB, the decrease in MAP was attenuated (from $94 \pm 2$ to $90 \pm 2$ mmHg) and did not significantly decrease throughout the 15 min of intervention (Fig. 2). SAP varied insignificantly during all of the three interventions between 115 $\pm 3$ and $122 \pm 4$ mmHg. The values of DAP exhibited a pattern very similar to that of MAP, with a decrease during the posture change to supine and an attenuated decrease during NB ($P < 0.05$; Table 1). The estimated aortic transmural pressure decreased during the posture change from seated to supine (identically with MAP) and increased during NB by $11 \pm 1$ to $14 \pm 2$ mmHg compared with the mean of preintervention values (Fig. 2). HR decreased during the posture change from seated to supine ($P < 0.05$), whereas no changes occurred during NB or control (Table 1).
Plasma AVP decreased during the posture change from seated to supine from 1.5 $\pm$ 0.3 to 1.2 $\pm$ 0.2 pg/ml ($P < 0.05$; Fig. 1). During NB, the decrease in AVP did not reach a significant level ($P = 0.07$), but the values were decreased compared with those of control ($P < 0.05$) and were above the values of the supine position ($P < 0.05$; Fig. 1). Plasma AVP increased again when going from the supine to the seated position, whereas this was not the case after the termination of NB (Fig. 1). The slightly higher level of plasma AVP at the end of control compared with during the other interventions was caused by an increase from 1.2 to 2.5 pg/ml in one subject only.

The values of plasma NE during control were above those of the posture change to supine and NB ($P < 0.05$; Table 1). This was due to a numeric but nonsignificant decrease in the plasma concentration of NE of 15 $\pm$ 6 and 16 $\pm$ 12 pg/ml during the posture change to supine and during NB, respectively (Table 1), whereas plasma concentration of NE tended to increase during control ($P = 0.05$). Values of supine and NB did not differ significantly. The plasma concentration of epinephrine tended to decrease during the posture change from seated to supine ($P = 0.05$) so that values of supine were below those of control ($P < 0.05$; Table 1).

![Fig. 1. Plasma concentration of arginine vasopressin (AVP), left atrial (LA) diameter, and arterial pulse pressure (PP) during seated control, a posture change to the supine position (supine), and seated continuous negative pressure breathing (NB). Each intervention is preceded and followed by 15 min of being seated. Values are means $\pm$ SE; $n = 8$ subjects. #Significant difference compared with mean values in the initial 15 min in the seated position ($P < 0.05$). *Significant difference between two interventions at similar points of time ($P < 0.05$).](image1)

![Fig. 2. Mean arterial pressure (MAP) and estimated aortic transmural pressure (AORTA TP) calculated from (MAP minus the level of NB) during control, a posture change to the supine position, and seated continuous NB. Values are means $\pm$ SE; $n = 8$ subjects. #Significant difference compared with values of the initial 15 min in the seated position ($P < 0.05$). *Significant difference between two interventions at similar points of time ($P < 0.05$).](image2)
baroreceptor activity. In humans, plasma AVP decreases during water immersion (5, 6, 11, 14, 17). Because PP is increased during water immersion simultaneously with an increase in LA diameter and central venous pressure (11, 14, 17), these observations suggest that AVP release in humans is suppressed by an interaction of low-pressure and arterial baroreflexes through changes in arterial pulsation.

MAP in the brachial artery was more decreased during the posture change from seated to supine than during NB. Thus, in the supine position, aortic baroreceptors were statically inhibited not only by the decrease in MAP induced by carotid baroreceptor stimulation, but actually further so by the decrease in aortic transmural pressure due to an intrathoracic pressure increase (16). In contrast with this, intrathoracic pressure must have decreased during NB, caused by NB per se with a subsequent mechanically induced decrease in MAP. The aortic transmural pressure during NB, however, was increased due to the intrathoracic pressure decrease with a subsequent static stimulation of aortic baroreceptors (Fig. 2). Thus the aortic baroreceptors were inhibited during the posture change from seated to supine and stimulated during NB, as depicted in Fig. 2. The fact that plasma AVP was lower during the posture change than during NB therefore strongly suggests that static aortic baroreceptor stimulation is of little or no importance for regulation of AVP release during central blood volume expansion in humans.

Several studies have focused on changes in MAP as the stimulus for regulation of AVP release (26). Our present results that MAP per se does not affect plasma AVP are, however, supported by those of Goldsmith (10), who observed no changes in the plasma concentration of AVP during a decrease in MAP induced by

Table 1. Cardiovascular and neuroendocrine variables during control, during Supine and during NB, with each intervention preceded and followed by 15 min of being seated.

<table>
<thead>
<tr>
<th>DAP, mmHg</th>
<th>Seated 5 Min</th>
<th>Seated 10 Min</th>
<th>Seated 15 Min</th>
<th>Intervention 20 Min</th>
<th>Intervention 25 Min</th>
<th>Intervention 30 Min</th>
<th>Seated 35 Min</th>
<th>Seated 40 Min</th>
<th>Seated 45 Min</th>
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<td>78 ± 2</td>
<td>80 ± 2</td>
<td>79 ± 2</td>
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<td>81 ± 2</td>
<td>81 ± 2</td>
<td>81 ± 1</td>
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<tr>
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<td>79 ± 2</td>
<td>81 ± 1</td>
<td>70 ± 1‡</td>
<td>72 ± 2‡</td>
<td>71 ± 2‡</td>
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<td>78 ± 2</td>
<td>83 ± 2</td>
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<td>81 ± 3</td>
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<td>62 ± 2</td>
<td>57 ± 2‡</td>
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<td>NE, pg/ml</td>
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<tr>
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Values are means ± SE; n = 8 subjects. DAP, diastolic arterial pressure; HR, heart rate; NE, norepinephrine; Supine, posture change from seated to supine; NB, negative pressure breathing. *Significantly different from control at a similar time point (P < 0.05); †significantly different from mean value of the initial 15 min (P < 0.05); ‡significantly different from the other two interventions at similar time point (P < 0.05).

DISCUSSION

The results show that suppression of AVP release is more pronounced during an antioorthostatic posture change from seated to supine than during continuous NB with a similar increase in LA diameter but an attenuated increase in PP. Therefore, the results are in compliance with the hypothesis that during maneuvers with similar cardiac distension, suppression of AVP release is dependent on the increase in PP. Furthermore, static aortic baroreceptor stimulation seems to be of little or no importance for regulation of AVP release during antioorthostatic maneuvers in humans.

We (20) previously observed that the suppression of AVP release during a posture change from seated to supine is dependent on an increase in LA diameter, PP, or both. Gabrielsen et al. (9) demonstrated graded AVP suppression by water immersion to the Xiphoid process and to the neck, respectively, where PP increased to a similar degree but with gradually increased LA diameter. On the basis of these findings, it was suggested that cardiopulmonary receptors modulate AVP release when PP is increased (9). In the present study, however, we compared two interventions with similar increases in LA diameter but with different degrees of increase in PP. Like Gabrielsen et al. (9), we observed a graded suppression of AVP release. Therefore, it is conceivable that cardiopulmonary low-pressure receptors as well as arterial baroreflexes modulate AVP release but that they augment the effects of each other and that both sets of receptors must be stimulated to obtain a maximal effect.

Experiments in dogs support the notion that loading of LA receptors inhibits AVP secretion (29). Furthermore, Share and Levy (27) have shown that huge changes in PP can modulate plasma antidiuretic hormone (bioassay) through changes in pulsatile carotid
pression of sodium nitroprusside. Furthermore, Andersen et al. (1) concluded that increasing the load on LA baroreceptors completely suppresses any stimulatory effect on AVP release of static unloading of the arterial baroreceptors. They did, however, not observe any suppression in plasma AVP and did not report the effects on PP. Thus findings from human as well as animal studies are consistent with our present finding that aortic baroreceptors are unimportant for the regulation of plasma AVP during simultaneous central blood volume expansion (with a following increased low-pressure baroreceptor stimulation and pulsatile arterial baroreceptor stimulation by increased PP).

A posture change from seated to supine does not only stimulate cardiopulmonary low-pressure receptors but also baroreceptors at the carotid sinus due to abolition of the hydrostatic pressure gradient between the heart and neck. One could argue that this static stimulation of carotid baroreceptors modulates AVP release. We (20) have, however, previously compared the effects of a posture change from seated to supine with and without simultaneous LBNP to keep LA diameter and PP unchanged. AVP release was suppressed during the posture change from seated to supine, but the suppression was abolished when LBNP was applied (20). Thus the hydrostatically posture-induced carotid baroreceptor stimulation was not sufficient to reduce AVP secretion.

As previously observed (20, 21, 24), plasma AVP increased when going from supine to seated. After NB was terminated, however, no increase in plasma AVP was detected. This is in compliance with results of water immersion studies (5, 24), where no increases in plasma AVP after cessation were observed. These data therefore suggest that a decrease of a certain magnitude in arterial high-pressure receptor stimulation (decreased PP or hydrostatic carotid pressure) is a necessity for AVP release to increase during orthostasis.

Even though the changes in plasma AVP in this study were small, it is very likely that these changes have significant effects on renal water excretion. We (11) previously observed that during water immersion in hydrated humans, plasma AVP is suppressed by ~0.4 pg/ml with a concomitant marked increase in renal water output. Furthermore, Andersen et al. (2) found increased urine osmolalities of 58% in subjects undergoing water diuresis after AVP infusion with an amount of 1 pg·min⁻¹·kg⁻¹ AVP, which was too small to alter plasma AVP concentrations. Thus the changes in plasma AVP observed in this study are probably enough to alter renal water excretion.

As expected from previous investigations (19–24), HR decreased during the posture change from seated to supine, whereas it was, in compliance with results of Norsk et al. (18) and Tanaka et al. (28), unchanged during NB. When HR during NB are compared with those of water immersion to the Xiphoid process in earlier studies (8, 14, 17, 25), where similar increases in LA diameter as in the present study were observed (22, 25), one would expect some decrease in HR during NB. This discrepancy in the HR response to water immersion and NB is probably caused by the opposite direction of changes in intrathoracic pressure. NB induces a decrease in intrathoracic pressure, which leads to some decrease in carotid sinus pressure and to an increase in static aortic baroreceptor stimulation, whereas water immersion increases intrathoracic pressure (8) with opposite effects. Furthermore, different degrees of increase in PP during NB and water immersion could explain the different HR responses (24). Thus the combined effect of the two opposing stimuli (carotid vs. aortic) during NB could have counteracted the bradycardic effects of central blood volume expansion.

The plasma concentration of NE decreased during the posture change from seated to supine compared with that during the seated control, which confirms our previous findings (20, 21, 24). In accordance with the concept that forearm sympathetic nervous activity is primarily governed by low-pressure reflexes (15, 20, 21, 24), the NE values during the posture change were statistically indistinguishable from those of NB. The numeric decreases during the two interventions did not differ significantly from values of the initial 15 min, but they were clearly lower than that during control.

In conclusion, suppression of AVP release is more pronounced during a posture change from seated to supine than during continuous NB, with a similar increase in LA diameter but with an attenuated increase in PP. Therefore, the results are in compliance with the hypothesis that during maneuvers with similar cardiac distension, suppression of AVP release is dependent on the increase in PP. Furthermore, static aortic baroreceptor stimulation seems to be of little or no importance for regulation of AVP release during antithorostatic maneuvers in humans.

**Perspectives.** The relative importance of arterial high and cardiopulmonary low-pressure baroreceptors, respectively, on the regulation of AVP release has long been debated. Especially in humans, it is difficult to stimulate each type of receptor selectively and thereby determine the relative contribution. In this study, we compared the effects of two experimental models with similar atrial distension (LA diameter) but with graded increases in PP. Our results support the notion that AVP release is modulated through an interaction between high- and low-pressure receptors in such a way that the pulsatile high-pressure baroreceptor component modulates AVP release during simultaneous static low-pressure receptor stimulation.

Several investigations have focused on changes in MAP as the stimulus for changes in plasma AVP. Thus it is noteworthy that the estimated increase in aortic transmural pressure of ~20 mmHg during NB compared with that during supine in the present study did apparently not affect AVP release. Therefore, future studies should focus on the pulsatile component of the arterial baroreceptor stimulation. A further understanding of the interaction of arterial high- and cardiopulmonary low-pressure receptors and their relative contribution to the regulation of plasma AVP may elucidate the pathophysiological mechanisms of dis-
eases with, e.g., disturbances in autonomic regulation of the cardiovascular system.

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