Renal and neurohormonal responses to increasing levels of lower body negative pressure in men

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Background. The stimulation of efferent renal sympathetic nerve activity induces sequential changes in renin secretion, sodium excretion, and renal hemodynamics that are proportional to the magnitude of the stimulation of sympathetic nerves. This study in men investigated the sequence of the changes in proximal and distal renal sodium handling, renal and systemic hemodynamics, as well as the hormonal profile occurring during a sustained activation of the sympathetic nervous system induced by various levels of lower body negative pressure (LBNP).

Methods. Ten healthy subjects were submitted to three levels of LBNP ranging between 0 and −22.5 mm Hg for one hour according to a triple crossover design, with a minimum of five days between each level of LBNP. Systemic and renal hemodynamics, renal water and sodium handling (using the endogenous lithium clearance technique), and the neurohormonal profile were measured before, during, and after LBNP.

Results. LBNP (0 to −22.5 mm Hg) induced an important hormonal response characterized by a significant stimulation of the sympathetic nervous system and gradual activations of the vasopressin and the renin-angiotensin systems. LBNP also gradually reduced water excretion and increased urinary osmolality. A significant decrease in sodium excretion was apparent only at −22.5 mm Hg. It was independent of any change in the glomerular filtration rate and was mediated essentially by an increased sodium reabsorption in the proximal tubule (a significant decrease in lithium clearance, \( P < 0.05 \)). No significant change in renal hemodynamics was found at the tested levels of LBNP. As observed experimentally, there appeared to be a clear sequence of responses to LBNP, the neurohormonal response occurring before the changes in water and sodium excretion, these latter preceding any change in renal hemodynamics.

Conclusions. These data show that the renal sodium retention developing during LBNP, and thus sympathetic nervous stimulation, is due mainly to an increase in sodium reabsorption by the proximal segments of the nephron. Our results in humans also confirm that, depending on its magnitude, LBNP leads to a step-by-step activation of neurohormonal, renal tubular, and renal hemodynamic responses.

The kidneys play a critical role in the maintenance of water and sodium homeostasis and hence contribute to the regulation of blood pressure [1]. Among the various hormonal factors affecting renal function, the renin-angiotensin-aldosterone and the sympathetic nervous systems exert a strong influence on the kidney through their direct and indirect effects on the renal circulation, the secretion of vasoactive substances, and the renal handling of sodium and water. These two systems not only have independent properties, but they also interact both centrally and peripherally [2, 3].

Several experimental studies have shown that under normal physiological conditions, the basal efferent renal sympathetic nerve activity is low (below 2.0 Hz) and does not influence renal hemodynamics, although it may be sufficient to affect renin secretion and renal tubular sodium handling [3–5]. In various animal species, a stimulation of efferent renal sympathetic nerve activity by either direct or reflex stimulations has been reported to induce changes in renal hemodynamics, renin secretion, and sodium excretion that are in proportion to the magnitude of the stimulation of sympathetic nerve activity [3]. In this respect, DiBona and Kopp have demonstrated that changes in renin secretion, renal sodium excretion, and renal hemodynamics occur at different threshold frequencies [3]. Thus, upon sympathetic nerve stimulation, renin appears to be released at thresholds that are below those needed to affect sodium excretion, and changes in renal hemodynamics occur only at high frequencies.

These graded renal and hormonal responses to increasing levels of renal sympathetic nerve stimulation have been described essentially in animals, but whether the same pattern occurs in humans has not been demonstrated definitively. Several studies in normal subjects have reported that activation of renal sympathetic nerve activity using high levels of lower body negative pressure (LBNP)
increases renal vascular resistance and in parallel stimulates the activity of the renin-angiotensin system [6–8]. Unfortunately, few studies have measured renal water and sodium excretion, renin secretion, and renal hemodynamics simultaneously in subjects exposed to a sustained period of LBNP. Moreover, investigations of the effects of renal sympathetic nerve stimulation on sodium excretion generally have been limited to the determination of the overall sodium excretion. Thus, little is known about the changes in renal proximal and distal tubular sodium handling that develop during a prolonged stepwise activation of efferent renal sympathetic nerve activity. Therefore, the aims of the present study were to (1) investigate the changes in proximal and distal tubular sodium handling in humans occurring during a sustained, one-hour activation of the sympathetic nervous system induced by stepwise increases in LBNP; and (2) characterize the sequential changes in neurohormonal, renal tubular, and renal hemodynamic responses to LBNP.

METHODS

Ten healthy normotensive male subjects without any clinical history of vaso-vagal syncope, orthostatic hypotension, clinical or laboratory evidence of heart, liver, kidney, and endocrine diseases were included in this study. Their mean age was 26.6 (range 24 to 33 years). Their mean weight and height were 73 kg (range 63 to 86 kg) and 178 cm (range 163 to 188), respectively. All subjects were well-trained athletes. A full medical history and a complete physical examination, including an orthostatic test, were performed before inclusion. Women were not included because of the effects of the menstrual cycle on renal hemodynamics described in an earlier study [9]. The protocol was approved by the local hospital ethical committee, and written informed consent was obtained from each subject.

Study design

Each subject was submitted to three levels of LBNP ranging between 0 and −22.5 mm Hg for one hour according to a triple crossover design, with a minimum of five days between each level. Three combinations were used: 0, −7.5, −15 mm Hg or 0, −7.5, −22.5 mm Hg or 0, −15, −22.5 mm Hg. These levels of LBNP corresponded to 0, −10, −20, and −30 mBar. Consequently, exposure to 0, −7.5, −15, and −22.5 mm Hg was studied with an N of 10, 5, 8, and 7. The control phase (0 mm Hg) was randomized within each sequence, and the lower level of LBNP was always tested before the higher level. All subjects received a fixed sodium diet (130 mmol Na/day) provided by the hospital for four days before each study day. Fluid intake was allowed ad libitum. Two 24-hour urine collections were performed to monitor the compliance to the diet and to evaluate the baseline sodium, potassium, and creatinine excretions. Subjects were asked to refrain from smoking and drinking caffeine-containing and alcoholic beverages for 24 hours before each study day.

After an overnight fast, the volunteers were installed in a supine position and an infusion of inulin and para-aminohippurate (PAH) was started to measure the glomerular filtration rate (GFR) and renal plasma flow (RPF). A light breakfast and an oral water load of 5 mL/kg were ingested before 8 a.m. Subsequently, subjects received a fixed amount of water (150 mL/hour p.o.) to maintain a stable urine output. They remained in supine position during the entire study day except for voiding. After a 2-hour equilibrium period, the study days were divided in three periods: one hour of baseline (T−60 to T0), one hour of LBNP (T0 to T60), and one hour of recovery (T60 to T120). LBNP was applied with subjects in the supine position in a solid plexiglass box sealed tightly just below the iliac crests, that is, below the level of the kidneys. A footplate was inserted in the box to prevent inward movement of the subject. LBNP was obtained within a couple of minutes. Subjects were not voiding during the LBNP period.

Vital signs (blood pressure and heart rate) were recorded automatically using a noninvasive oscillometric monitor placed on the arm (ASM 2000; Elmed, Augsburg, Germany). Measurements were done every five minutes from time T−30 to T60 and every 15 minutes thereafter. Forearm blood flow and vascular resistance were determined by venous occlusion plethysmography (Hokanson TL400; Totalab System, Belleville, WA, USA) on the other arm twice during the baseline period, at the beginning and the end of the period of LBNP, and once (T120) during the recovery period. At each time, four measurements were performed. Urine was collected hourly throughout the study to measure urine output and urinary electrolyte excretion (Na, K, endogenous trace lithium) and to evaluate the changes in GFR and RPF. The same parameters were measured hourly in the plasma. Blood was collected on times T−60, T0, T60 and T120 for the measurements of plasma norepinephrine, epinephrine, vasopressin, atrial natriuretic peptide, aldosterone, and plasma renin activity.

Analytical methods

Urinary and plasma sodium and potassium were measured by flame photometry (IL-943; Instrumentation Laboratory, Milan, Italy) and creatinine by the picric acid method (Cobas-Mira; Roche AG, Basel, Switzerland). Hematocrit was determined using microhematocrit tubes. Urine osmolality was measured using the freezing point technique as described previously [10]. Plasma and urinary inulin and PAH were determined by photometry (Autoanalyzer II-Technicon; Bran & Luebbe, Norderstedt, Germany). Endogenous trace lithium was measured by atomic absorption spectrophotometry [11]. This
method, which does not need the administration of lithium, has been validated in several previous clinical studies [12–14]. Plasma renin activity [15], plasma aldosterone [16], arginine vasopressin [10], atrial natriuretic factor [17], and plasma catecholamines [18] were determined as described previously.

Urinary electrolyte excretion rate was calculated as $U_x \cdot V (\mu mol/min)$ and clearances (mL/min) using the standard formula $C_x = U_x \cdot V/P_x$, where $U_x$ and $P_x$ are the urine and plasma concentrations of $x$ and $V$ is the urine flow rate in mL/min. The fractional excretions were calculated as the clearance of $x$ divided by the GFR. Fractional distal reabsorption of sodium ($FDR_{Na}$) was calculated as $FDR_{Na} = (1 - FE_{Na}/FE_{Li})$, where $FE_{Na}$ and $FE_{Li}$ indicate fractional excretion of sodium and lithium, respectively. Filtration fraction was calculated by dividing the GFR by the RPF. Forearm vascular resistance (FVR) was calculated as the mean blood pressure/forearm blood flow.

Statistics

All results are expressed as means ± SEM. Within-group analyses were performed using the Student paired t test. Intergroup comparisons were analyzed using one-way analysis of variance followed by the Student unpaired t test. To assess the LBNP level/effect relationship, linear regressions across LBNP levels were calculated on the values measured after one hour of LBNP to evaluate whether the relationship was significantly different from zero. Values with a $P < 0.05$ were considered as statistically significant.

RESULTS

The three steps of LBNP were well tolerated, and none of the subjects fainted during the study. One subject had to stop the experiment on the third study day due to a skin rash one hour after starting the infusion of PAH and inulin.

Neurohormonal response to LBNP

The neurohormonal responses to LBNP are presented in Figure 1. After one hour of LBNP, significant increases in plasma norepinephrine levels were observed at all levels of LBNP. The increase in plasma epinephrine was LBNP-level dependent (Table 2). Plasma renin activity and plasma aldosterone levels rose significantly only at −15 and −25 mm Hg. Similarly, plasma vasopressin levels increased with the highest levels of LBNP. Plasma ANP levels did not vary significantly. All neurohormonal parameters returned back to baseline at the end of the one-hour recovery period, except for norepinephrine, which remained higher than baseline values after the recovery period of the −15 and −22.5 mm Hg LBNP.

Systemic and renal hemodynamic response to LBNP

The changes in systemic and renal hemodynamics obtained during the three steps of LBNP are presented in Table 1. A significant increase in FVR reflecting the peripheral vasoconstriction induced by the neurohormonal activation was found at −15 and −22.5 mm Hg ($P < 0.05$). No significant change in heart rate occurred at either level, although it tended to increase with a stronger suction. Interruption of the LBNP (T60) was always followed by the occurrence of a significant bradycardia, which was most important at −15 and −22.5 mm Hg. Blood pressure increased at all levels of LBNP, but the changes were not consistent. In the kidney, no significant change in GFR and RPF was found during the LBNP period. At −22.5 mm Hg, a slight but nonsignificant decrease in GFR and RPF was observed that was followed by renal vasodilation during the recovery period.

Renal tubular response

The LBNP-induced variations in renal tubular sodium and water handling are presented in Figures 2 and 3. While urine output decreased progressively with higher negative pressures, urine osmolality increased at each step (absolute change from baseline, −23 ± 80 mOsm/L at 0 mm Hg, +36 ± 86 mOsm/L at −7.5 mm Hg, +107 ± 83 mOsm/L at −15 mm Hg, and +146 ± 82 mOsm/L at −22.5 mm Hg; Fig. 2). As shown in Table 1, plasma osmolality increased slightly but not significantly at −15 and −22.5 mm Hg ($P = 0.08$). Free water clearance increased from 0.13 to 0.43 mL/min in the control group and decreased only in the −22.5 mm Hg from −0.03 to −0.45 mL/min ($P = NS$). Urinary sodium excretion was not decreased until the −22.5 mm Hg level of LBNP was reached (Fig. 3). The changes in renal sodium handling occurred mainly in the proximal segments of the nephron as illustrated by the changes in endogenous lithium clearances. The fractional excretion of lithium also was reduced significantly after one hour of LBNP at −22.5 mm Hg (decrease in $FE_{Li}$ from 22 ±1.6% to 19 ± 2.1, $P = 0.004$). There was no change in the fractional distal reabsorption of sodium ($FDR_{Na}$) during LBNP, but a slight decrease was found at −22.5 mm Hg during the recovery period.

Table 2 shows the analysis of the relationships found between the levels of LBNP and the parameters measured at the end of the one-hour LBNP. These relationships allowed us to determine in which respect the variations of any parameter were truly linked to the changes in LBNP. As can be seen, a clear relationship between the level of LBNP and the response was found after one hour of LBNP with some parameters such as epinephrine, PRA, aldosterone, urinary volume, urine osmolality, and urinary sodium excretion. Other parameters such as lithium clearance or norepinephrine levels, showed
Fig. 1. Effect of one hour of lower body negative pressure (LBNP) on plasma norepinephrine (NE), epinephrine (E), plasma renin activity (PRA), aldosterone, arginine vasopressin (AVP), and atrial natriuretic peptide (ANP). Values are means ± SE and are expressed as the changes in hormonal values observed at one hour (60 min – baseline value). *P < 0.05; **P < 0.01 vs. level 0 in the analysis of variance.

Table 1. Systemic and renal hemodynamic response to lower body negative pressure (LBNP) in normal subjects

<table>
<thead>
<tr>
<th>Level of LBNP, mm Hg</th>
<th>0 mm Hg</th>
<th>−7.5 mm Hg</th>
<th>−15 mm Hg</th>
<th>−22.5 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Recovery</td>
<td>Baseline</td>
<td>Recovery</td>
</tr>
<tr>
<td>FVR units</td>
<td>22.8±3.1</td>
<td>25.1±3.1</td>
<td>26±5</td>
<td>NA</td>
</tr>
<tr>
<td>HR bpm</td>
<td>60±2.2</td>
<td>59±1.8</td>
<td>58±1</td>
<td>NA</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>107±3</td>
<td>110±4</td>
<td>114±3</td>
<td>111±3</td>
</tr>
<tr>
<td>DBP mm Hg</td>
<td>62±2</td>
<td>68±2</td>
<td>66±2</td>
<td>65±1</td>
</tr>
<tr>
<td>PP mm Hg</td>
<td>45±3</td>
<td>44±2</td>
<td>48±2</td>
<td>47±3</td>
</tr>
<tr>
<td>GFR mL/min</td>
<td>103±6</td>
<td>94±8</td>
<td>91±8</td>
<td>106±7</td>
</tr>
<tr>
<td>RPF mL/min</td>
<td>543±51</td>
<td>463±38</td>
<td>459±50</td>
<td>574±64</td>
</tr>
<tr>
<td>FF %</td>
<td>19.7±1.1</td>
<td>20.4±0.8</td>
<td>20±1</td>
<td>19.4±2.5</td>
</tr>
<tr>
<td>P(osmol) mOsm/kg</td>
<td>293±2</td>
<td>294±2</td>
<td>NA</td>
<td>299±5</td>
</tr>
</tbody>
</table>

Abbreviations are: FVR, forearm vascular resistance(unit = mm Hg/mL/100 mL tissue/min); HR, heart rate expressed as beats per minute (bpm); SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction; P(osmol) plasma osmolality. Values are means ± SE; NA is not available.

*P < 0.05; **P < 0.01 LBNP vs baseline
no clear correlation because the changes occurred either very late (only at -22.5 mm Hg for lithium clearance) or very early (as in the case of norepinephrine). Other factors such as renal hemodynamics showed no significant change at all.

**DISCUSSION**

Lower body negative pressure has been used extensively to investigate the function of cardiopulmonary reflexes and the neurocirculatory responses to decreases in venous return to the heart [19–25]. Our study shows that a one-hour exposure to LBNP (0 to -22.5 mm Hg) induces a marked neurohormonal response, a significant decrease in sodium excretion that is apparent only at the level of -22.5 mm Hg, and no major change in renal hemodynamics. The sodium retention is independent of the changes in GFR and is mediated by an increase in sodium reabsorption in the proximal tubule. Although renal sympathetic nerve activity was not measured directly, our data in humans confirm previous experimental observations suggesting that stimulation of efferent renal sympathetic nerve activity induces changes in renin secretion, renal sodium handling, and renal hemodynamics at different thresholds. Indeed, upon the application of stepwise increases in LBNP, first renin release appears to be affected, followed by sodium excretion, the latter decreasing before there is any change in renal hemodynamics, as one would expect if a greater unloading of cardiopulmonary and arterial baroreceptors is achieved.

**Neurohormonal response to LBNP**

Lower body negative pressure has been shown to activate both the sympathetic nervous system and the renin-
Table 2. Relationships between the levels of lower body negative pressure (LBNP) and renal and neurohormonal parameters measured after one hour of LBNP in normotensive subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>slope</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular filtration rate</td>
<td>0.006</td>
<td>-0.0116</td>
<td>0.87</td>
</tr>
<tr>
<td>Effective renal plasma flow</td>
<td>0.02</td>
<td>0.268</td>
<td>0.99</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.52</td>
<td>-0.098</td>
<td>0.003</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.25</td>
<td>-1.63</td>
<td>0.793</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>0.43</td>
<td>-0.056</td>
<td>0.018</td>
</tr>
<tr>
<td>Plasma aldosterone</td>
<td>0.37</td>
<td>-1.213</td>
<td>0.044</td>
</tr>
<tr>
<td>Plasma vasopressin</td>
<td>0.40</td>
<td>-0.011</td>
<td>0.028</td>
</tr>
<tr>
<td>Urinary volume</td>
<td>0.50</td>
<td>0.044</td>
<td>0.006</td>
</tr>
<tr>
<td>Urinary osmolality</td>
<td>0.45</td>
<td>-6.676</td>
<td>0.018</td>
</tr>
<tr>
<td>Urinary sodium excretion</td>
<td>0.46</td>
<td>1.548</td>
<td>0.013</td>
</tr>
<tr>
<td>Lithium clearance</td>
<td>0.17</td>
<td>0.093</td>
<td>0.38</td>
</tr>
</tbody>
</table>

A P value <0.05 indicates when the slope is significantly different from 0.

An angiotensin system, as assessed by the changes in circulating catecholamines levels and changes in plasma renin activity, plasma angiotensin II, and aldosterone levels [6, 24–28]. In accordance with those studies, we found a significant increase in plasma norepinephrine concentrations at all levels of LBNP, confirming that activation of the sympathetic nervous system occurs as soon as the low pressure baroreceptors are unloaded, whereas the rise in plasma epinephrine was more gradual depending on the level of stimulation. As expected, this activation of the sympathetic nervous system resulted in a peripheral vasoconstriction, as measured by the increases in FVR (Table 1). However, no direct relationship between the level of LBNP and plasma norepinephrine was found. This may be explained by the small number of subjects included in the study and also by the fact that the stimulation was already present at low levels of LBNP. In addition, an increase in forearm norepinephrine extraction could have accounted for the lack of “dose”-response relationship [29]. In contrast to the norepinephrine response, an increase in plasma renin activity and plasma vasopressin and aldosterone levels occurred only at higher levels of LBNP, that is, at −15 and −22.5 mm Hg. These observations are thus in agreement with those published previously by Tidgren et al [6] and Leimbach, Schmid, and Mark [30]. High levels of LBNP also have been shown to induce a threefold increase in plasma vasopressin levels [24].

Systemic and renal hemodynamic responses to LBNP

The sympathetic nervous system and the renin-angiotensin system play an important role in the control of systemic and renal hemodynamics. As reported previously, minor or no changes in systolic and diastolic blood pressure were observed within the range of tested LBNP levels, which may be attributed to the neurohormonal stimulation [7, 23, 25]. Interestingly, heart rate did not increase during LBNP. However, the abrupt release of suction was associated with a level-dependent slowing of the heart rate during the recovery period. This phenomenon has been described in very early studies when the LBNP technique was established [19, 20]. It appears to be associated with the rapid retransfusion of blood pooled in the lower extremities into the central circulation [19]. More recent data have suggested that thoracic fluid content remains reduced during recovery after orthostatic loading [22]. This latter observation does not exclude, however, that the shift of volume from the extremities to the central circulation plays a major role in reducing the heart rate. Of note, all subjects reported the feeling of a wave coming from their legs as LBNP was interrupted and their heart rate was decreasing.

In the 1960s, Gilbert et al demonstrated that the application of 60 mm Hg LBNP for one hour produces a moderate decline in GFR and RPF [8]. More recently, two studies conducted in normal subjects have also reported that low levels of LBNP (below −20 mm Hg) unloading cardiopulmonary—but not arterial baroreceptors—do not affect renal vascular resistance, whereas renal blood flow in normal subjects decreases with the application of prolonged and more intense LBNP sufficient to unload both arterial and cardiopulmonary baroreceptors [6, 7]. In accordance with these observations, no changes in renal hemodynamics were found in our subjects up to −22.5 mm Hg. At −22.5 mm Hg, a trend toward a decrease in GFR and RPF was seen. Thus, it cannot be excluded that with a greater number of subjects, the slight changes in renal hemodynamics measured at −22.5 mm Hg may have become statistically significant, suggesting that at this level of LBNP the threshold for changes in renal hemodynamics might be reached. Our results therefore suggest that arterial baroreceptors were not unloaded at −22.5 mm Hg. However, it is difficult to form a conclusion on the mechanism, since the relative contribution of arterial and cardiopulmonary baroreceptors at low levels of LBNP is not as clearly defined [23, 31, 32].

Renal tubular response to LBNP

Experimentally, an abundant literature studying various animal species has demonstrated that reflex maneuvers that increase efferent renal sympathetic nerve activity produce antidiuresis and antinatriuresis without any change in GFR or renal blood flow [3]. On the contrary, maneuvers that decrease efferent renal sympathetic activity increase urinary water and sodium excretion even in the absence of changes in renal hemodynamics [3]. In humans, very few studies have examined the effect of LBNP on renal sodium and water handling. In Gilbert et al’s study, the decrease in urinary sodium excretion observed at −60 mm Hg was attributed primarily to the diminished GFR [8]. In the studies published by Hirsch et al [7] and Tidgren et al [6], renal sodium and water excretion were not evaluated. Therefore, the assessment
of the renal tubular response to LBNP was the primary objective of the present study.

Two original observations were made in our experiments. The first is that LBNP induces sodium retention at −22.5 mm Hg, which is mediated by an increased sodium reabsorption in the proximal segments of the nephron and is not mediated by a fall in GFR. To demonstrate this effect, endogenous lithium clearance was used. We and others have demonstrated previously in several experimental situations that endogenous lithium clearance is a reliable marker of sodium handling by the renal proximal tubule in humans [11–14]. There is no evidence in humans that lithium is reabsorbed in the distal nephron, particularly when subjects are on a regular or high-sodium diet [33, 34]. Even in salt-depleted subjects, amiloride has no effect on the fractional excretion of lithium, although a natriuretic response is present [34]. In conditions of high vasopressin activity, a disproportionately large decrease in lithium excretion could have been observed if lithium was reabsorbed in the late distal and collecting tubules, but this was obviously not the case in our experimental conditions. In the present study, the −22.5 mm Hg level of LBNP induced a significant decrease in endogenous lithium clearance. The fractional excretion of lithium was also reduced, indicating that the change in proximal reabsorption is independent of the variations in GFR. In this respect, our data differ from those of Hansen et al, who reported an LBNP-induced decrease in lithium clearance mediated by the fall in GFR in normal subjects [35]. In this latter study, only one level of LBNP (−27.5 mm Hg) was evaluated, and LBNP was applied above the kidneys, that is, just below the chest. This may have influenced their results as the negative pressure could have been transmitted to the kidneys, resulting in modifications of renal hemodynamics. Since both angiotensin II and the activity of the sympathetic nervous system have been shown to modulate sodium reabsorption in the proximal nephron [3, 13, 36], the increase in proximal reabsorption of sodium obtained in our study most likely can be attributed to the rise in plasma renin activity and circulating catecholamine levels. Of note, plasma aldosterone levels were also markedly increased during LBNP, particularly at −22.5 mm Hg. However, we did not find any significant change in fractional distal reabsorption of sodium during the 60 minutes of LBNP. This apparent discrepancy can be explained by the time needed for aldosterone to exert a tubular response, which exceeds one hour [37].

The second observation is that each step of LBNP was associated with a further decrease in urine output and a dose-dependent increase in urine osmolality. As shown in Table 2, there was a clear relationship between the level of LBNP and urine output and urinary osmolality. These changes in renal water handling are most readily attributed to the measurable rise in plasma vasopressin observed from −15 to −22.5 mm Hg, which also were related to the level of LBNP. The increase in plasma vasopressin levels can be attributed to osmotic and non-osmotic stimuli. Indeed, plasma osmolality increased slightly at the higher levels of LBNP. In addition, prolonged unloading of cardiopulmonary receptors through an orthostatic stress could act as a nonosmotic stimulus for vasopressin release in healthy subjects. Whether unloading of cardiopulmonary baroreceptors by low levels of LBNP is a nonosmotic stimulus for vasopressin release is still under discussion [30, 38]. Norsk et al have reported that high but not low levels of LBNP can stimulate vasopressin release [24, 39]. However, in contrast to our study, their LBNP protocols were of a shorter duration. Thus, the length of the stimulus (one hour) might have contributed to the stimulation of vasopressin release in our experimental conditions.

Finally, the results of the present study tend to confirm that the stimulation of efferent renal sympathetic nerve activity in man induces changes in renal hemodynamics, renin secretion and sodium handling that are proportional to the degree of activation of the renal sympathetic nerve activity. In accordance with DiBona and Kopp’s observation in experimental animals [3], our data demonstrate that the renin response to LBNP precedes the tubular response, which leads to sodium retention, and this latter also precedes the renal hemodynamic response. Thus, depending on its magnitude, LBNP leads to a step-by-step activation of neurohormonal, renal tubular, and renal hemodynamic responses.

Taken together, these results provide new insights into the renal physiological responses to orthostatic stress, which may result in a reduction of the cardiac preload. They may improve our understanding of the renal response to orthostasis and of the contribution of the kidney to the pathophysiology of diseases such as congestive heart failure, which are characterized by an activation of the systemic and renal sympathetic nervous systems.

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