Difference in upper airway collapsibility during wakefulness between men and women in response to lower-body positive pressure


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ABSTRACT

Fluid shift from the legs to the neck induced by LBPP (lower-body positive pressure) increases UA (upper airway) collapsibility in healthy men. Rostral fluid displacement during recumbency may therefore contribute to the pathogenesis of OSA (obstructive sleep apnoea). There is a higher prevalence of OSA in men than in women. We therefore hypothesized that UA collapsibility increases more in men in response to rostral fluid displacement than in women. UA collapsibility was assessed in healthy, non-obese men and women while awake by determining UA $P_{\text{crit}}$ (critical closing pressure) during application of different suction pressures to the UA. Subjects were randomized to 5 min control or LBPP arms after which they crossed-over into the other arm following a 30 min washout. LBPP was applied by inflating anti-shock trousers wrapped around both legs to 40 mmHg. $P_{\text{crit}}$, leg fluid volume and neck circumference were measured at baseline and after 5 min of both control and LBPP periods. LBPP caused a decrease in leg fluid volume and an increase in neck circumference that did not differ between men and women. However, compared with the control period, LBPP induced a much greater increase in $P_{\text{crit}}$ in men than in women ($7.2 \pm 1.8$ compared with $2.0 \pm 1.5$ cmH$_2$O, $P = 0.035$). We conclude that rostral fluid displacement by LBPP increases UA collapsibility more in healthy, non-obese men than in women. This may be one mechanism contributing to the higher prevalence of OSA in men than in women.

INTRODUCTION

OSA (obstructive sleep apnoea) is more common in men than in women [1–3], but the reasons why have not yet been fully elucidated. Factors that influence UA (upper airway) collapsibility, and therefore susceptibility to OSA, may differ between men and women. For example, the longer collapsible pharyngeal segment [4] and greater increase in UA resistance after sleep onset in men than in women [5] may contribute to a greater UA collapsibility in men. However, Rowley et al. [6] reported that UA $P_{\text{crit}}$ (critical closing pressure), an index of increased UA collapsibility, did not differ between normal men and women. $P_{\text{crit}}$ can be influenced by some physiological changes such as changes in lung volume [7] and posture [8], and in particular, by fluid displacement from the legs to the neck [9].

Shepard et al. [10] first attempted to test the effects of rostral fluid shift from the legs on UA size by leg raising; however, since they did not measure the fluid volume of

**Key words:** fluid displacement, lower-body positive pressure, obstructive sleep apnoea, gender difference, upper airway critical closing pressure.

**Abbreviations:** BP, blood pressure; DBP, diastolic BP; EELV, end-expiratory lung volume; LBPP, lower-body positive pressure; OSA, obstructive sleep apnoea; $P_{\text{crit}}$, critical closing pressure; SBP, systolic BP; UA, upper airway.

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the legs, they were not able to quantify how much fluid, if any, they displaced from the legs. Although they found a tendency for the UA to narrow, this was not significant. This might have been because they did not discharge enough fluid from the legs to affect UA properties. In contrast, using a more potent means of displacing fluid from the legs, application of LBPP (lower-body positive pressure), we demonstrated that fluid displacement from the legs to the neck narrowed the UA and increased its resistance to airflow in healthy non-obese subjects [11,12]. We also demonstrated that such fluid displacement increased $P_{\text{crit}}$ in healthy men while awake [9]. These findings suggest that rostral fluid displacement from the legs when moving from the upright to the recumbent position at bedtime may play a role in the pathogenesis of OSA in susceptible individuals. They may also help to explain the higher prevalence of OSA in patients with fluid overload states, such as heart failure and renal failure, than in the general population [13–15]. However, UA responsiveness to rostral fluid displacement has not been compared between men and women. Since men have a higher prevalence of OSA than women, we hypothesized that rostral fluid shift will increase UA collapsibility more in men than in women. To test this hypothesis, in the present study we compared the effect of rostral fluid shift in men than in women. To explain the higher prevalence of OSA in patients with fluid overload states, such as heart failure and renal failure, than in the general population [13–15]. However, UA responsiveness to rostral fluid displacement has not been compared between men and women. Since men have a higher prevalence of OSA than women, we hypothesized that rostral fluid shift will increase UA collapsibility more in men than in women. To test this hypothesis, in the present study we compared the effect of rostral fluid shift induced by LBPP on UA collapsibility, determined by $P_{\text{crit}}$, between men and women. Results from some of the male subjects have been reported previously [9].

**MATERIALS AND METHODS**

**Subjects**

We enrolled healthy non-obese (body weight < 120% of ideal body weight [16]) men and women (≥ 18 years of age) without any history of cardiovascular, renal, respiratory or neurological disorders, nor any history of habitual snoring, excessive daytime sleepiness or UA surgery. We also excluded women who were pregnant. The body weight of the subjects is expressed as a percentage of the ideal weight (% of IBW) based on gender, age and height [16,17]. This measure was used because it is a better way of comparing body habitus between the genders than is BMI (body mass index), since it normalizes to lean body weight adjusted for age and height, and takes into account differences in body composition between the genders. The protocol was approved by the local research ethics board and written informed consent was obtained from subjects prior to participation.

**LBPP, leg fluid volume and neck circumference**

With subjects supine, a pair of deflated medical anti-shock trousers (MAST III-AT; David Clark, Inc.) was wrapped around both legs from the ankles to the upper thighs. LBPP was applied by inflating the trousers to 40 mmHg for 5 min after which the trousers were deflated. Total fluid volume of one leg was measured using a bio-impedance spectrum analyser (model 4200; Xitron Technologies) with electrodes attached to the ankle and upper thigh of one leg. A mercury strain-gauge plethysmograph (EC4; D.E. Hokanson) was wrapped around the neck above the thyroid cartilage and secured in place with tape to measure the percentage changes in neck circumference as previously described [11,12].

**EELV (end-expiratory lung volume) and BP (blood pressure)**

Changes in EELV were monitored by respiratory inductance plethysmography (Respirtrace; Ambulatory Monitoring) calibrated against a spirometer in the DC-coupled mode [18]. SBP (systolic BP), DBP (diastolic BP) and heart rate were measured by an automated sphygmomanometer (Dinamap 1846SX NIBP; Critikon).

$P_{\text{crit}}$

Experiments were conducted with subjects awake and lying supine with the head and neck fixed in the neutral position supported by a small pillow. Subjects were instructed to breathe normally and exclusively through the nose. $P_{\text{crit}}$ was measured as described previously [9,19,20]. Airflow was measured using a pneumotachograph (Hans Rudolph Model 4700; Hans Rudolph) connected to a tightly fitting facemask (model 9000; Vital Signs). Nasal pressure was measured through a sealed opening in the mask [8] with a differential pressure transducer (Validyne MP45; Validyne Engineering) referenced to atmospheric pressure. A vacuum source with a regulator was attached to the inspiratory circuit to apply various negative pressures to the mask [20]. Two series of four different pressures (−2, −6, −10 and −14 cmH2O) were applied consecutively to obtain $P_{\text{crit}}$. Each pressure was applied abruptly at end-expiration and was held for five breaths, between which the resistance was removed for 60 s. The third and following breaths at a given pressure were used to calculate $P_{\text{crit}}$ if flow limitation was apparent on the inspiratory flow tracing [8,9]. For all flow-limited breaths, nasal pressure was plotted against maximal inspiratory flow and linear regression was used to extrapolate the nasal pressure at zero flow as a measure of $P_{\text{crit}}$ [19].

**Experimental protocol**

Subjects underwent a double-crossover protocol as described previously [9]. After lying supine for 5–10 min, they were initially randomized into the control or LBPP arm and then crossed over to the other arm, between which there was a 30-min washout period. During the control period, $P_{\text{crit}}$ was determined at baseline and 5 min later, with the anti-shock trousers deflated. In the LBPP arm, $P_{\text{crit}}$ was determined at baseline and after 5 min of LBPP. Leg fluid volume, neck circumference, EELV, BP
and heart rate were measured just before each \( P_{\text{crit}} \) determination. All experiments began between 13.00 hours and 14.00 hours and were carried out in a climate-control room with the temperature between 21 and 23°C.

**Data analysis**

Values are expressed as means ± S.E.M. unless otherwise stated. Linear regression analysis was used to determine \( P_{\text{crit}} \). Two-way repeated-measures ANOVA was used to compare values obtained during the control and LBPP periods, and those obtained from men and women, followed by a post hoc Tukey’s test as appropriate. If the variables were non-normally distributed, the Wilcoxon rank-sum test and Mann–Whitney \( U \) test were used for comparisons between the control and LBPP arms, and between men and women respectively. The relationships between the change in \( P_{\text{crit}} \) and that of both leg fluid volume and neck circumference were assessed by Pearson’s correlation analysis. Statistical analyses were performed by a commercial statistical analysis package (SPSS version 13.0; SPSS Inc). A two-sided \( P \) value < 0.05 was considered significant.

**RESULTS**

**Characteristics of the subjects**

The characteristics of the 14 men and 13 women who participated in the study are shown in Table 1. There was no significant difference in age between men and women (33.2 ± 3.7 compared with 33.8 ± 2.7 years old respectively, \( P = 0.906 \)). Compared with men, women had a smaller neck circumference, height and weight (\( P < 0.001 \)); however, weight expressed as a percentage of ideal body weight \( P = 0.956 \). As demonstrated in Table 2, there were significant reductions in leg fluid volume in both women and men in response to LBPP (both \( P < 0.001 \) when compared with the control). There was a trend for a greater leg fluid volume reduction in men than in women, but this difference was not significant \( P = 0.091 \). The difference between men and women in the change in leg fluid volume in response to LBPP was also not significant when we normalized for height \( (-110 ± 13\text{ ml/m}) \) in men and \(-92 ± 13\text{ ml/m}) \) in women, \( P = 0.315 \), or for total leg fluid volume at baseline \( (-37 ± 4\text{ ml/l}) \) in men and \(-38 ± 4\text{ ml/l}) \) in women, \( P = 0.825 \). LBPP also induced a significant increase in neck circumference in both genders \( P = 0.007 \) in women, \( P = 0.001 \) in men, but the difference between the genders was not significant \( P = 0.394 \). There was no significant change in EELV during either control or LBPP periods in women \( P = 0.646 \) or men \( P = 0.260 \), and no significant difference between the genders \( P = 0.785 \).

**BP and heart rate**

No significant difference in SBP, DBP and heart rate during either control or LBPP periods was observed in women or in men (Table 3).

**DISCUSSION**

The present study has given rise to two novel and important observations. First, fluid displacement from the
legs to nuchal structures induced by application of LBPP caused an increase in $P_{\text{crit}}$ in healthy non-obese men, but not in healthy non-obese women. The increase in $P_{\text{crit}}$ in men was significantly greater than in women. This difference was present even though LBPP caused similar amounts of fluid displacement and similar increases in neck circumference in both genders. Secondly, the increase in $P_{\text{crit}}$ correlated significantly with the amount of fluid displaced from the legs in men, but not in women. Taken together, these findings indicate that LBPP-induced fluid displacement from the legs increases UA collapsibility to a greater extent in men than in women of comparable age and body habitus. Accordingly, the UA of men may become more vulnerable to collapse than that of women in response to rostral fluid shift when moving from the upright to the recumbent position at bedtime, and contribute to the higher prevalence of OSA in men than in women [1–3].

OSA is characterized by repetitive partial or complete collapse of the UA during sleep. UA properties are related to the presence and severity of OSA. For example, patients with OSA have a narrower, more compliant and more collapsible UA than subjects without OSA during both wakefulness and sleep [22–25]. UA collapsibility has also been shown to correlate with the severity of OSA [22,23]. Obesity is a major risk factor for OSA and one way by which it predisposes to OSA is through pharyngeal fat deposition that increases peripharyngeal soft tissue pressure, resulting in a narrower and more collapsible UA [26]. In addition, obesity is often accompanied by corticosteroid and aldosterone excess, both of which enhance sodium and water retention [27]. We have previously demonstrated that rostral fluid displacement induced by a physiological manipulation, LBPP, decreases UA cross-sectional area and increases UA resistance [11,12]. The amount of rostral fluid displacement induced by LBPP is similar to that occurring spontaneously during the night in non-obese patients with OSA [28]. It therefore seems possible that spontaneous UA fluid accumulation in the recumbent position while sleeping might predispose subjects, especially oedematous ones, to OSA.

Mechanisms responsible for the higher prevalence of OSA in men than in women are not well understood, but neuromuscular and anatomical–mechanical factors that influence UA patency appear to be involved. With respect
There was no significant change in $P_{crit}$ during the control periods in either gender (female: $\Delta = 0.0 \pm 0.6 \text{cmH}_2\text{O}, P = 0.600$; male: $\Delta = -1.3 \pm 1.1 \text{cmH}_2\text{O}, P = 0.249$). After 5 min of LBPP, the $P_{crit}$ did not change significantly from baseline in the females ($\Delta = 2.0 \pm 1.3 \text{cmH}_2\text{O}, P = 0.133$), but increased significantly from baseline in the males ($\Delta = 5.9 \pm 1.2 \text{cmH}_2\text{O}, P < 0.001$).

Compared with the change in $P_{crit}$ during the control period, the change in $P_{crit}$ during the LBPP period was greater in males than in females (by 5.2 cmH$_2$O, $P = 0.035$).

Trinder et al. [5] demonstrated that, after sleep onset, there is a greater decrease in genioglossus muscle activity and a greater increase in UA resistance in men than in women, that would increase susceptibility to UA occlusion. Popovic and White [29] also showed that awake genioglossal activity is significantly higher in healthy women than in men. However, several studies demonstrated no difference in genioglossus muscle activity in healthy men and women during either wakefulness or sleep [4,30,31], nor in UA muscle activation in response to inspiratory resistive loading [31]. This leaves uncertain the contribution of differences in neural control of pharyngeal dilator muscle to the differences in susceptibility to OSA between men and women.

Regarding UA collapsibility, $P_{crit}$ determined either by acute intermittent lowering of continuous positive airway pressure during sleep in patients with OSA, or by acute intermittent application of negative airway pressure either during wakefulness or sleep, minimizes the neuromuscular (i.e. active) component of $P_{crit}$ [9,32] and thus provides an estimate of the passive component of $P_{crit}$.

Rowley et al. [6] studied healthy subjects from the general population and demonstrated no significant difference in the UA collapsibility assessed by passive $P_{crit}$ between men and women. The finding in the present study of no difference in $P_{crit}$ between men and women during waking control conditions is consistent with that finding.

Regarding anatomical–mechanical factors, anatomical narrowing of the pharynx plays an important role in predisposing to OSA [33–35]. However, since women have smaller UA luminal dimensions than men [36], this cannot explain the lower prevalence of OSA in women.

Table 2 Changes in leg fluid volume, neck circumference and EELV
Values are means ± S.E.M. NC, neck circumference; $\Delta$, change.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Women</th>
<th>Men</th>
<th>$P$ value</th>
<th>$P$ value between genders</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$ Leg fluid volume (ml)</td>
<td>11 ± 5</td>
<td>25 ± 10</td>
<td>$&lt; 0.001$</td>
<td>0.091</td>
</tr>
<tr>
<td>$\Delta$ % of baseline NC (%)</td>
<td>0.03 ± 0.02</td>
<td>−0.02 ± 0.05</td>
<td>0.11 ± 0.04</td>
<td>0.001</td>
</tr>
<tr>
<td>$\Delta$ EELV change (litres)</td>
<td>0.06 ± 0.06</td>
<td>0.00 ± 0.07</td>
<td>0.08 ± 0.06</td>
<td>0.260</td>
</tr>
</tbody>
</table>

Table 3 Changes in BP and heart rate
Values are means ± S.E.M.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control</th>
<th>S min</th>
<th>LBPP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>102.7 ± 2.0</td>
<td>102.6 ± 2.1</td>
<td>105.5 ± 2.2</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>62.7 ± 1.5</td>
<td>64.2 ± 1.5</td>
<td>65.5 ± 2.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64.9 ± 2.7</td>
<td>64.5 ± 2.3</td>
<td>64.4 ± 2.8</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120.0 ± 3.8</td>
<td>117.4 ± 4.2</td>
<td>117.4 ± 4.0</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>68.0 ± 2.3</td>
<td>66.7 ± 2.3</td>
<td>65.5 ± 2.8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64.0 ± 1.8</td>
<td>63.3 ± 1.6</td>
<td>64.5 ± 3.2</td>
</tr>
</tbody>
</table>
than in men. There is also no difference in UA resistance during wakefulness and sleep between healthy men and women [6,29]. UA resistance is related to UA cross-sectional area and UA length. Although women have a narrower UA [36], the UA resistance is similar in both genders [6,29], it appears that the collapsible segment of the UA is longer in men than in women [4]. This difference in UA length, which develops after puberty, [37] is not a function of men being taller than women, since the male pharyngeal collapsible segment is still longer when normalized to height. A greater length of the collapsible UA segment would increase the propensity for collapse, all other factors being equal. Therefore, based on these anatomical factors, pharyngeal collapsibility would be greater in men than in women for a given negative pressure during inspiration. However, Rowley et al. [6] found no difference in $P_{crit}$ between healthy men and women during sleep and, in the present study, we found no difference in $P_{crit}$ at baseline between men and women during wakefulness. Thus it is unclear the extent to which differences in pharyngeal length between men and women might influence their susceptibility to UA collapse. Nevertheless, men have been shown to be more vulnerable to resistive loading- and position-induced UA collapse than women [31,38]. The studies above did not assess the potential role of fluid shift on the collapsibility of the UA.

Using the well-validated method of Schwartz et al. [20] to assess $P_{crit}$, we have demonstrated that, at least during wakefulness, men and women have similar UA collapsibility under baseline conditions [6], but that UA collapsibility increases more in men than in women when fluid is displaced from the legs into the neck. This phenomenon may contribute to the higher prevalence of OSA in men than in women, both in the general population and in those with congestive heart failure [39,40]. It is also possible that, owing to the longer collapsible segment of the pharynx in men than in women [4], accumulation of a similar amount of nuchal fluid secondary to LBPP could increase collapsibility (i.e. higher $P_{crit}$) more in men. Further work will be required to examine the potential interaction of UA length and collapsibility in response to alterations in nuchal fluid content.

As in our previous studies [11,12], we demonstrated no significant decrease in EELV in response to LBPP, in either men or women. Accordingly, differences in the $P_{crit}$ response to LBPP between men and women cannot be attributed to any lung-volume-related differences in UA calibre [7]. Similarly, the difference in the change in $P_{crit}$ in response to LBPP between the genders cannot be attributed to differing BP and heart rate response to LBPP. We did not document the phase of the menstrual cycle in our female subjects, so cannot comment on any possible effect it might have had on $P_{crit}$.

A limitation of the present study was that experiments were conducted during wakefulness rather than sleep. This was unavoidable since it would not have been feasible for subjects to sleep uninterrupted with anti-shock trousers in the deflated, then inflated state while wearing the tightly fitting facemask during application of intermittent negative airway pressure. It is therefore possible that the present findings may not be exactly reproducible during sleep. However, pharyngeal dilator muscle activity along with the active component of $P_{crit}$, diminishes [32], UA luminal size decreases, and pharyngeal resistance increases at the transition from wakefulness to sleep. Rostral fluid displacement might therefore have a greater effect on $P_{crit}$ during sleep than wakefulness, and the difference in $P_{crit}$ in response to rostral fluid displacement during sleep between the genders might become greater as well. In addition, the present results during wakefulness are probably relevant to sleep because UA collapsibility during wakefulness has been shown to correlate significantly with UA collapsibility during sleep [41].

Another possible limitation of the present study is that we did not determine what phase of the menstrual cycle our female subjects were in, or whether they were using oral contraceptive pills; however, there is no clear evidence that fluid volume alters in response to the menstrual cycle or oral contraceptives. Although, theoretically, oestrogen should favour fluid retention by activating the renin–angiotensin–aldosterone system and progesterone should antagonize this [42], it has been shown that there is no difference in body weight or total plasma volume during the follicular or luteal phases of the menstrual cycle, or during oral contraception administration either during rest, exercise or during post-exercise rehydration [43]. In addition, oral contraceptives usually contain both ethinyloestradiol and gestodene (or drospirenone) and have been shown not to influence total body water or fat mass during the menstrual cycle [44]. Nevertheless, further studies will be required to determine whether the menstrual cycle or oral contraceptives influence $P_{crit}$ in response to LBPP. Although pregnancy may be associated with fluid retention [45], we excluded pregnant women from the present study.

Sleep studies were not performed to rule out sleep-disordered breathing in our subjects. However, since we studied young non-obese adults with no history of snoring or symptom of sleep-disordered breathing, it is likely that very few or no-one had sleep apnoea. We matched men and women for weight by the percentage of ideal body weight and studied only non-obese subjects (all within $\pm 15\%$ ideal body weight) to minimize any potential confounding influence of obesity on LBPP-induced fluid shift and $P_{crit}$. Thus differences in the $P_{crit}$ response to LBPP between men and women cannot be attributed to differences in body habitus. Further work will be required to determine whether the collapsing effects of LBPP on the UA of obese subjects differ from non-obese subjects.
In conclusion, rostral fluid displacement induced by LBPP increases UA collapsibility during wakefulness in healthy, non-obese men, but not in women. This suggests that nuchal fluid accumulation has a greater effect on UA collapsibility in men than in women that may predispose them to OSA. Women may possess some protective mechanisms, such as a shorter collapsible pharyngeal segment than men [4], that prevents nuchal fluid accumulation from increasing UA collapsibility. Further studies will be required to determine whether fluid displacement out of the neck reduces UA collapsibility, and if such effects differ between men and women.

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**REFERENCES**


SUPPLEMENTARY ONLINE DATA

Difference in upper airway collapsibility during wakefulness between men and women in response to lower-body positive pressure


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Figure S1  Representative tracings of airflow and nasal pressure from the same subjects as shown in Figure 1 of the main text (i.e. a 37-year-old man 104% of ideal body weight) and a 36-year-old woman 106% of IBW) during application of negative airway pressures

In the man, the maximal inspiratory flow during negative pressure application was markedly lower after 5 min of LBPP than during the comparable control period. This was most pronounced during application of −14 cmH2O (indicated with arrows). In contrast, there was no discernible effect of LBPP on the maximal inspiratory flow during negative airway pressure application in the woman, particularly at −14 cmH2O (arrows). These findings indicate that LBPP increased UA collapsibility more in the man than the woman. PN = nasal pressure.

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