Influence of Lower Body Positive Pressure on Upper Airway Cross-Sectional Area in Drug-Resistant Hypertension

Oded Friedman, T. Douglas Bradley, Alexander G. Logan

Abstract—We previously showed that in hypertensive patients the amount of fluid displaced from the legs overnight is directly related to the severity of obstructive sleep apnea (OSA) and that the rostral fluid shift was greater in drug-resistant hypertensive patients. The findings suggested that this fluid redistribution increases upper airway collapsibility, yet more direct evidence is lacking. The present study examines the effects of graded lower body positive pressure on leg fluid volume, upper airway cross-sectional area, and neck circumference in patients with drug-resistant hypertension (n=25) and controlled hypertension (n=15). In both groups, the reduction in mean upper airway cross-sectional area and oropharyngeal junction area, assessed by acoustic pharyngometry, and the increase in neck circumference, determined by mercury strain gauge plethysmography, were related to the amount of fluid displaced from the legs (R²=0.41, P<0.0001; R²=0.42, P<0.0001; and R²=0.47, P<0.0001, respectively). Displacement of leg fluid volume was significantly greater in patients with drug-resistant hypertension than in controlled hypertension (P<0.0001), and as a consequence, the former experienced greater reductions in mean upper airway cross-sectional area and oropharyngeal junction area (P=0.001 and P<0.0001, respectively). The findings support the concept that in hypertensive subjects, rostral fluid displacement may participate in the pathogenesis of obstructive sleep apnea by narrowing the upper airway and making it more susceptible to collapse during sleep. The exaggerated fluid volume displacement from the legs and upper airway response to lower body positive pressure in patients with drug-resistant hypertension provide additional evidence of an important link between drug-resistant hypertension and obstructive sleep apnea.

Key Words: hypertension ■ drug-resistant hypertension ■ obstructive sleep apnea ■ volume overload ■ fluid redistribution ■ lower body positive pressure

Drug-resistant hypertension (DRH) is a major risk factor for cardiovascular disease, and a growing health problem as ≤15% of treated hypertensive patients are drug resistant. Although the cause of treatment resistance is often unknown, the frequent occurrence of obstructive sleep apnea (OSA) in DRH raises the possibility of a common abnormality linking these 2 conditions. One factor to be considered is hypervolemia, a defining feature of DRH and an important contributor to OSA in edematous states such as heart and kidney failure.

Over the past several years, we have been studying the relationship between overnight fluid redistribution from the legs to the neck and OSA. In studies of hypertensive patients, we showed that the apnea-hypopnea index (AHI), a measure of OSA severity, was strongly related to the amount of leg fluid volume displaced overnight during sleep and that the volume displaced was greater in DRH patients than in controlled hypertensive subjects, potentially accounting for their higher prevalence of OSA. Other studies from our group demonstrated that the amount of fluid displaced spontaneously from the legs during sleep relates to the amount of time spent sitting during the day and strongly correlates with the severity of sleep apnea in healthy subjects and patients with heart failure. However, these associations do not imply causality. A recent study suggested that a significant fluid shift rostrally to the neck overnight was not related to worsening of OSA. In that study, determination of fluid shift was based only on tape-measured changes in leg and neck circumferences without taking into account actual changes in leg fluid volume or the impact of the changes in leg circumference on the cross-sectional area of the upper airway.

The present physiological study was undertaken to provide more direct evidence that fluid redistribution in DRH may be causally related to OSA. We previously showed that fluid displacement from the legs by the application of lower body positive pressure (LBPP) narrows the upper airway and...
increases pharyngeal resistance and upper airway collapsibility in healthy subjects. In this study, we examined the effects of LBPP on the upper airway cross-sectional area of patients with DRH and controlled hypertension (CH). We hypothesized that the degree of upper airway narrowing would be related to the amount of fluid shifted from the legs and the extent of narrowing would be greater in patients with DRH than those with CH.

Methods

Study Design

The study was carried in a human physiology laboratory during the daytime. The human subjects review committee of Mount Sinai Hospital, University Health Network, and Toronto Rehabilitation Institute, all in Toronto, approved the study. All subjects provided written informed consent before participation.

Study Subjects

Patients with CH and DRH were recruited from the Hypertension Clinic at the Mount Sinai Hospital in Toronto. DRH was defined as uncontrolled hypertension on optimal doses of a diuretic and 2 additional antihypertensive medications or normal blood pressure (BP) on ≥4 drugs and CH as normal BP on ≤3 agents. In determining the number of antihypertensive medications, dihydropyridine and nondihydropyridine calcium channel blockers were considered as 2 separate drugs as were diuretics with actions on different nephron sites. Patients were excluded if they indicated poor medication adherence (self-report), had a correctable form of hypertension, ingested exogenous substances (including alcohol) that can raise BP (currently or before 2 weeks), had systolic heart failure (left ventricular ejection fraction <50%), were morbidly obese (body mass index [BMI] ≥40 kg/m²), or required nitrates for symptomatic coronary artery disease. Sociodemographic, anthropometric, and medical variables were collected on each patient. Laboratory testing included ambulatory BP monitoring (SpaceLabs 90207 recorders; SpaceLabs Healthcare Inc, Issaquah, WA), 2-dimensional echocardiography, and 24-hour urine collection to measure creatinine clearance and urinary excretion of sodium, potassium, microalbumin, and, if appropriate, protein.

Table. Lower Body Positive Pressure Study Measurements of Cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CH Cohort*</th>
<th>DRH Cohort*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in leg fluid volume, mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBPP=10 mm Hg</td>
<td>-16.7±2.5</td>
<td>-42.0±4.6</td>
<td>&lt;0.0001</td>
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<tr>
<td>LBPP=20 mm Hg</td>
<td>-31.3±4.1</td>
<td>-71.6±6.8</td>
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<td>LBPP=30 mm Hg</td>
<td>-42.7±5.0</td>
<td>-94.8±8.5</td>
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<tr>
<td>LBPP=40 mm Hg</td>
<td>-52.9±5.4</td>
<td>-114.7±9.2</td>
<td></td>
</tr>
<tr>
<td>Change in mean upper airway cross-sectional area, cm²</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LBPP=10 mm Hg</td>
<td>-0.06±0.01</td>
<td>-0.19±0.03</td>
<td>0.001</td>
</tr>
<tr>
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<td>-0.35±0.07</td>
<td></td>
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<tr>
<td>LBPP=30 mm Hg</td>
<td>-0.18±0.03</td>
<td>-0.39±0.06</td>
<td></td>
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<tr>
<td>LBPP=40 mm Hg</td>
<td>-0.21±0.03</td>
<td>-0.49±0.09</td>
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<tr>
<td>Change in oropharyngeal junction area, cm²</td>
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<td></td>
<td></td>
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<tr>
<td>LBPP=10 mm Hg</td>
<td>-0.04±0.01</td>
<td>-0.13±0.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
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<td>-0.08±0.01</td>
<td>-0.22±0.04</td>
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<tr>
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<td>-0.13±0.01</td>
<td>-0.31±0.04</td>
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<tr>
<td>LBPP=40 mm Hg</td>
<td>-0.19±0.02</td>
<td>-0.45±0.06</td>
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<tr>
<td>Change in neck circumference, cm</td>
<td></td>
<td></td>
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<tr>
<td>LBPP=10 mm Hg</td>
<td>+0.02±0.004</td>
<td>+0.06±0.008</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LBPP=20 mm Hg</td>
<td>+0.04±0.006</td>
<td>+0.10±0.010</td>
<td></td>
</tr>
<tr>
<td>LBPP=30 mm Hg</td>
<td>+0.05±0.007</td>
<td>+0.14±0.014</td>
<td></td>
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<tr>
<td>LBPP=40 mm Hg</td>
<td>+0.07±0.011</td>
<td>+0.20±0.019</td>
<td></td>
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</tbody>
</table>

CH indicates controlled hypertension; DRH, drug-resistant hypertension; LBPP, lower body positive pressure.

*Reported as mean±SE.
†P values for comparisons of subjects with CH vs DRH (ie, BP status×LBPP interaction term).

LBPP Studies

LBPP was applied by wrapping the deflated medical antishock trousers (David Clark Inc, Worcester, MA) around both legs from the ankles to upper thighs with subjects lying supine. Leg fluid volume of the right leg was measured using a bioelectrical impedance spectrum analyzer (model 4200; Xitron Technologies Inc, San Diego, CA) with impedance to electrical current being inversely proportional to fluid content. Electrodes, imbedded in an adhesive-containing pad, were placed on the right upper thigh and ankle and fixed to the skin. A mercury strain gauge plethysmograph (EC6; D.E. Hokanson Inc, Bellevue, WA) was wrapped around the neck above the thyroid cartilage and the percentage changes in neck circumference were monitored continuously. The gauge, of which the resistance to electrical flow is altered in proportion to the change in its length, is sensitive, accurate, and reproducible. Upper airway cross-sectional area was determined at end expiration using acoustic pharyngometry (Eccovision Acoustic pharyngometry; Sleep Group Solutions, Miami, FL), a valid, reproducible measurement technique. Given that lung volume is a determinant of upper airway cross-sectional area, changes in end-expiratory lung volume (ie, functional residual capacity) were assessed by respiratory inductance plethysmography calibrated against a spirometer in the direct current coupled mode.

BP and heart rate were monitored during LBPP experiments by an automated sphygmomanometer (Dinamap 1846SX NIBP; Critikon, Tampa, FL).

After a 30-minute stabilization period, baseline measurements of all variables were made. Subjects were then exposed to increasing LBPP beginning at 10 mm Hg and ending at 40 mm Hg, at 10-mm Hg increments. Each of the 4 applied pressures was maintained for 5 minutes and measurements of all variables were made at the end of the 5-minute period.

Statistical Analysis

Continuous variables were expressed as means±SE, whereas categorical variables were expressed as proportions. The unpaired t test, Wilcoxon rank sum test, and Fisher exact test were used, as appropriate, to compare baseline differences between the CH and DRH groups. For LBPP-related changes, between-group comparisons were evaluated using 2-way repeated-measures ANOVA. The impact of several covariates (age, sex, race, BMI, diabetic status, body surface area-adjusted creatinine clearance, and left ventricular ejection fraction) were examined to ascertain whether they were associated with the LBPP-related changes in leg fluid volume as well as whether they confounded the observed differences between the CH and DRH groups. Missing data values for continuous variables were handled using multiple imputation. Logistic regression was also used to assign each subject a predicted probability of DRH (ie, a propensity score) based on age, sex, race, BMI, and diabetic status that was then entered as a single covariate in the between-group comparisons of the LBPP-related leg fluid volume shifts. Tests for interactions between BP status and antihypertensive drug class were also performed. Scatter plots were constructed to determine the curve of best fit for the univariable relationship between the change in upper airway cross-sectional area or neck circumference at all LBPP levels and the LBPP-induced reduction in leg fluid volume using data from the entire cohort of hypertensive subjects. Residual plots were then constructed to determine the appropriateness of the fit. Given the repeated nature of the LBPP-related measurements, mixed-effects regression was
used to model the relationship between the change in upper airway cross-sectional area or neck circumference and the LBPP-induced leg fluid volume shift. Regression coefficients were calculated for the subjects with CH or DRH and tests for interactions were performed to ascertain whether the coefficients differed according to BP status. A 2-tailed P value of <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

Characteristics of the Subjects

Forty hypertensive subjects were studied, of whom 25 had DRH and the remaining 15, CH. The demographic and clinical characteristics of study participants are listed in Tables S1 and S2 in the online-only Data Supplement. Compared with the CH group, the DRH group had a significantly higher mean 24-hour systolic BP (142±3.3 versus 125±2.1 mm Hg; P<0.0002), proportion of nondippers, (85% versus 47%; P=0.01), and AHI (43±5.4 versus 18±4.2 events per hour; P=0.001). The prevalence of OSA was high in both groups (DRH, 85%; CH, 60%).

LBPP Study Measurements

Leg fluid volume and neck circumference before LBPP application were significantly greater in the DRH group (4025±161 mL and 42±0.8 cm, respectively) than in the CH group (3225±245 mL and 39±1.3 cm, respectively; P=0.01 and 0.04, respectively); however, the baseline oropharyngeal junction area and mean upper airway cross-sectional area were comparable in the DRH (1.40±0.1 and 1.79±0.1 cm², respectively) and CH (1.34±0.1 and 1.62±0.2 cm², respectively) groups (P=0.70 and 0.46, respectively). The LBPP measurements of the cohort stratified by BP status, are summarized in the Table. Compared with the CH group, the LBPP-induced reductions in oropharyngeal junction area and mean upper airway cross-sectional area were significantly greater in the DRH group (P<0.0001 and 0.001, respectively) and the increase in neck circumference was greater (P<0.0001). However, there were no differences in end-expiratory lung volume and BP between groups during LBPP (Table S3). Figure 1 displays the grouped data for the changes in mean upper airway cross-sectional area, oropharyngeal junction area, and neck circumference in response to LBPP in the CH and DRH groups. Importantly, the LBPP-induced reduction in leg fluid volume was significantly greater in the DRH group compared with the CH group (P<0.0001, Table). There was no significant modification of the foregoing association between BP status and the LBPP-induced leg fluid volume reduction according to use of any of the antihypertensive drug classes (P=0.14 [BP status×antihypertensive drug class interaction term]). Of the covariates, only a greater BMI was associated with increased LBPP-induced leg fluid volume reduction (P<0.0001). Furthermore, the LBPP-induced leg fluid volume reduction remained significantly greater in the DRH group despite adjustment for age, sex, race, BMI, diabetic status, body surface area-adjusted creatinine clearance, and left ventricular ejection fraction (P=0.004) or the propensity score (P=0.001).

The relationship between the reduction in mean upper airway cross-sectional area and the LBPP-induced reduction in leg fluid volume was fit best using log-transformed values of the reduction in mean upper airway cross-sectional area as depicted in Figure 2A (R²=0.41; P<0.0001). There was no difference between the regression coefficients in the DRH group and the CH group (P=0.31 [BP status×LBPP-induced leg fluid volume reduction interaction term]). Similarly, the relationship between the reduction in oropharyngeal junction area and the LBPP-induced reduction in leg fluid volume was fit best using log-transformed values of the reduction in oropharyngeal junction area and is depicted in Figure 2B (R²=0.42; P<0.0001). Once again, there was no difference between the regression coefficients in the DRH group and the CH group (P=0.20 [BP status×LBPP-induced leg fluid volume reduction interaction term]). There was also a significant correlation between the increase in neck circumference (using log-transformed values) and the LBPP-induced reduction in leg fluid volume as depicted in Figure 2C (R²=0.47; P<0.0001).
cross-sectional area was strongly related to the amount of
found that the LBPP-induced reduction in upper airway
tial underlying basis of OSA in a hypertensive cohort.
This study extends our previous work by addressing a poten
induced leg fluid volume reduction interaction term\]).
DRH group and the CH group (with no difference between the regression coefficients in the
fluid volume (LFV, mL). BP indicates blood pressure.
pressure (LBPP) levels and the LBPP-induced reduction in leg
area (UAXSA, cm²; Figure 2). Data from drug-resistant hypertensive (DRH) and
and neck circumference (NC, cm; A) at all lower body positive
Because the fluid volume in the pelvic and abdominal
the legs but also on the pelvis and the lower abdomen.
The most likely explanation for the difference is the body
previously reported, which was not related to the volume of
fluid displaced from the legs after LBPP application. In fact,
the LBPP-induced change in leg fluid volume accounted for
two fifths of its variability and applied similarly in subjects with either CH or DRH. In addition, the LBPP-induced dis
placement of leg fluid volume was significantly greater in the
DRH group than in the CH group and as a consequence DRH
patients experienced greater reductions in oropharyngeal junction area and mean upper airway cross-sectional area.
These data suggest that in hypertensive subjects, rostral fluid
displacement may participate in the pathogenesis of OSA by narrowing the upper airway and making it more susceptible to
collapse during sleep.

Observations drawn from other patient populations also
suggest that covert fluid accumulation in the extracellular fluid
compartment may be causing or aggravating OSA. Patients
with chronic renal failure who were converted from daytime
to nocturnal forms of dialysis showed amelioration of sleep
apnea.\(^4\)\(^5\) Additional studies in dialysis-dependent patients showed that a significant relationship between overnight
mean change in leg fluid volume and severity of OSA\(^2\)\(^3\) and that more intense fluid removal during sleep using noctur
nal cycler-assisted peritoneal dialysis significantly increased
upper airway caliber and reduced tongue volume, as assessed
by volumetric magnetic resonance imaging, and AH\(I\)\(^2\)\(^4\) A study in nondialysis obese subjects with OSA and diastolic
heart failure demonstrated a reduction in AH\(I\) with an increase
in upper airway cross-sectional area after a 3-day course of
furosemide and spironolactone.\(^2\)\(^5\) Our group demonstrated
in systolic heart failure with coexisting OSA that overnight
reduction in leg fluid volume was significantly correlated with
an increase in AH\(I\) and neck circumference.\(^1\)\(^2\) Finally, in a
study of DRH patients, spironolactone significantly reduced
the AH\(I\) and BF, likely secondary to the volume-depleting
action of the drug.\(^2\)\(^6\)

A previous study using acoustic pharyngometry to assess
upper airway cross-sectional area in healthy, nonobese adult
found that within 1 minute of LBPP there was a significant
narrowing of the upper airway lumen.\(^1\)\(^5\) In our study, we observed a greater mean reduction in upper airway cross-
sectional area of 0.38 cm² overall than the value of 0.28 cm²
previously reported, which was not related to the volume of
fluid displaced from the legs with LBPP at equivalent pres-
ures (40 mm Hg). The reason for this is not clear, but it does
suggest that hypertensive patients are more susceptible to
the upper airway narrowing effects of LBPP than otherwise
healthy subjects and may account for their higher prevalence
of OSA.\(^4\)

In our study, we observed no change in BP during the
application of positive pressure to the legs, in keeping with
previous results from our group.\(^1\)\(^4\)\(^1\)\(^6\) However, other studies
of LBPP in humans have observed a rise in arterial pressure.
The most likely explanation for the difference is the body
area compressed. In our study, positive pressure was applied
only from the ankles to the upper thighs, whereas the trousers
used in other studies exerted a positive pressure not only on
the legs but also on the pelvis and the lower abdomen.\(^2\)\(^7\)\(^2\)\(^8\) Because the fluid volume in the pelvic and abdominal
compartments is substantially greater than that in the legs,
the volume displaced during inflation likely was much larger.

**Discussion**

This study extends our previous work by addressing a poten
tial underlying basis of OSA in a hypertensive cohort.\(^1\)\(^0\) We
found that the LBPP-induced reduction in upper airway
cross-sectional area was strongly related to the amount of

**Figure 2.** Data from drug-resistant hypertensive (DRH) and
controlled hypertensive (CH) cohorts showing relationships between
the reduction in mean upper airway cross-sectional area (UAXSA, cm²; A) oropharyngeal junction area (OPJ, cm²; B)
and neck circumference (NC, cm; C) at all lower body positive pressure (LBPP) levels and the LBPP-induced reduction in leg fluid volume (LFV, mL). BP indicates blood pressure.

with no difference between the regression coefficients in the
DRH group and the CH group (\(P=0.12\) [BP statusxLBPP-
induced leg fluid volume reduction interaction term]).
than in our study (unfortunately not measured) and, therefore, more likely to have hemodynamic consequences including an increase in BP.

Because of the study’s physiologic interventional study design, the potential remains for residual confounding to have accounted for the study findings. Furthermore, despite all subjects receiving instructions to reduce dietary sodium intake, there was a greater dietary sodium intake in the DRH group (Table S1, available in the online-only Data Supplement); parenthetically, however, the LBPP-induced leg fluid volume reduction remained significantly greater in the DRH group despite adjustment for the sodium excretion rate \( (P<0.0001) \). Moreover, although the literature on the effect of specific non-diuretic antihypertensive medications on OSA severity is limited,\(^9\) it remains possible that certain antihypertensive drug classes may be potential confounders (eg, calcium channel blockers, especially dihydropyridines that can cause peripheral edema), despite there being no significant interactions between BP status and antihypertensive drug class.

Given that the effects of LBPP application on neck circumference and upper airway cross-sectional area were assessed during the wake period, the findings may not be wholly applicable to those occurring during the sleep period. However, it would have been impractical for subjects to sleep uninterrupted while undergoing simultaneous LBPP application and acoustic pharyngometry, because they would be unable to sleep or would move if they did fall asleep causing artifactual changes in the acoustic pharyngometry signal. Additionally, the literature would suggest that rostral fluid shift may have an even more pronounced effect on upper airway cross-sectional area during the sleep than the wake cycle because of a withdrawal of neural input to the pharyngeal dilator muscles at sleep onset resulting in pharyngeal luminal narrowing with a corresponding increase in pharyngeal resistance and collapsibility.\(^9\) A limitation of acoustic pharyngometry, given that transmitted sound waves travel below the soft palate, is its inability to evaluate the lumen size at the level of the retropalatal pharynx, the site at which the pharynx collapses in most patients with OSA.\(^3\) Nonetheless, significant changes in the mean upper airway cross-sectional area and oropharyngeal junction area have already been documented after LBPP application and diuretic therapy.\(^15,15\) Furthermore, several studies have shown consistently that the upper airway cross-sectional area from the velum to the glottis in the awake state is narrowed in patients with OSA, both while upright and supine.\(^32\) Change in leg fluid volume was measured and presented using only the right leg; this, of course, assumes that the corresponding total leg fluid shift was twice that of the one leg. Finally, there was no control period during which LBPP was not applied in the present study; however, a number of studies have already convincingly demonstrated that leg fluid volume, neck circumference, upper airway cross-sectional area, upper airway resistance, and upper airway collapsibility remain unchanged during a control period of similar duration.\(^14,15\)

**Perspectives**

The present study suggests that the greater degree of upper airway narrowing induced by LBPP in patients with DRH than in those with CH may be one factor that contributes to the higher prevalence and severity of OSA in the former group. In view of the existing literature, such data strongly support the hypothesis that volume overload may be pathogenically related to the DRH state and, further, may contribute to the development of OSA. Given this possibility, it might be anticipated that intensifying diuretic therapy or markedly restricting dietary salt intake would not only lower BP but also decrease OSA severity by reducing the amount of leg fluid accumulation during the daytime and its overnight fluid shift from the legs into the neck during sleep. This remains to be tested.

**Sources of Funding**

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**Disclosures**

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**References**


**Novelty and Significance**

**What Is New?**

- The greater degree of upper airway narrowing induced by lower body positive pressure in patients with drug-resistant hypertension than in those with controlled hypertension may be one factor that contributes to the higher prevalence and severity of obstructive sleep apnea in the former group.

**What Is Relevant?**

- The findings strongly support the hypothesis that volume overload may be pathogenically related to the drug-resistant hypertension state and, further, may contribute to the development of obstructive sleep apnea.

**Summary**

By reducing overnight fluid displacement, it might be possible to attenuate obstructive sleep apnea, and in turn the severity of hypertension.