The article by Friedman et al1 in the present issue of Hypertension represents a thoughtfully designed study. Their report connects previously established but loosely connected lines of research into a coherent and credible theme with important therapeutic and research implications.

First, treatment-resistant hypertension is associated with obstructive sleep apnea. Many patients with treatment-resistant hypertension are abdominally obese and insulin resistant, which is also characteristic of most patients with clinically significant obstructive sleep apnea (OSA). However, body weight and neck girth do not appear to explain the strength of the association between treatment-resistant hypertension and OSA. Of note, the roles of increased abdominal girth and increased aldosterone and incident sleep apnea,2,3 as insulin resistance (hyperinsulinemia), which are associated with increased aldosterone and incident sleep apnea,2,3 as potential mediators of the treatment-resistant hypertension-OSA relationship, are not addressed.4,5 Nevertheless, the importance of the observation of greater overnight rostral fluid shift and severity of OSA in patients with treatment-resistant hypertension is not diminished.

Second, treatment-resistant hypertension and OSA are associated with extracellular fluid volume expansion.1

Third, factors that increase central and/or total fluid volumes worsen OSA or its surrogate markers, whereas interventions that decrease fluid volumes improve OSA and treatment-resistant hypertension. As the authors note, lower-body positive pressure and ineffective dialysis exacerbate surrogate markers for or actual OSA, whereas effective dialysis and diuretic therapy in patients with OSA reduce the apnea-hypopnea index. Moreover, diuretic therapy, especially with spironolactone, improves blood pressure control and reduces the severity of OSA.1,6

Based on these observations, the investigative team designed the current study to test a 2-part hypothesis, that the rostral fluid shift is greater in patients with treatment-resistant rather than controlled hypertension.

The authors, in fact, document that the measured changes in overnight (recumbent) fluid displacement from the legs account for approximately twice as large in patients with treatment-resistant hypertension as in patients with controlled hypertension (346.7 versus 175.8 mL; P<0.01).

Collectively, the observations support a more unified and coherent picture in which fluid volume expansion contributes to both treatment-resistant hypertension and OSA. When a patient with treatment-resistant hypertension assumes the recumbent position, which is typical for sleep, there is a large shift in gravitational forces, which reduces capillary and venous pressures in the lower extremities and increases them in the neck and pharyngeal areas. The changes in Starling forces lead to net loss of fluid volume from the lower extremities and a net gain of fluid volume in the neck and upper airways. Based on the authors’ report and the studies they cite, the fluid volume translocated rostrally overnight is a key factor determining the severity of OSA.1

The authors cite studies indicating that plasma renin activity and responses to spironolactone are surrogate markers for plasma volume expansion. Although the authors did not provide details of diuretic dose and subclass or report plasma renin activity, these variables would be of interest in future studies of fluid volume expansion and rostral fluid shifts in patients with treatment-resistant hypertension and OSA.

Separate reports indicate that patients with OSA and high aldosterone/renin ratios (suppressed plasma renin) are characterized by blood pressures that fail to show the expected nocturnal decline, that is, nondippers.7,8 Thus, it would be of interest to determine the contribution of volume expansion and rostral fluid shifts in nondipper or reverse-dipper status, the relationship to plasma renin activity and OSA, and the potential return to a more normal dipping status with reduction in fluid volume and rostral fluid shifts. Evidence suggests that both OSA and nondipper status increase cardiovascular risk. Thus, the findings raise the possibility that, in addition to diuretic and dietary interventions to reduce fluid volumes, other measures to limit overnight rostral fluid translocation, for example, reverse Trendelenburg position or modest levels of lower body negative pressure or thigh cuff inflation, could serve as alternative or adjunctive therapies for OSA (and possibly nondipper status).

In summary, the present study by Friedman et al1 connects the volume expansion in treatment-resistant hypertension to OSA via a greater overnight rostral fluid shift. The clearer
pathophysiological portrait that they have generated has important therapeutic and research implications.

**Disclosures**

None.

**References**

Overnight Rostral Fluid Shift and Obstructive Sleep Apnea in Treatment Resistant Hypertension: Connecting the Dots Clarifies the Picture
Brent M. Egan