Gravitational Influences and Shifting Propensity for Sleep Apnea
Another Source of Heterogeneity or a New Intervention Target?

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Sleep-disordered breathing occurs in as many as 17% of adults and is associated with increased mortality. Characterized by the occurrence of repetitive episodes of apneas and hypopneas resulting in intermittent oxyhemoglobin desaturation and sleep disruption, it is a common comorbid condition in patients with heart disease, who may have both obstructive and central variants. Apneas and hypopneas are classified as obstructive when reductions in ventilation result from episodic pharyngeal occlusion accompanied by concomitant respiratory effort. Obstructive sleep apnea (OSA) is diagnosed when an overnight sleep study shows that the total number of apneas plus hypopneas exceeds some threshold, with a predominance of events consisting of obstructive breathing events. Patients diagnosed with OSA are frequently overweight, tend to be male, and have a high prevalence of comorbidities, including hypertension and diabetes mellitus. The pathogenesis of OSA is complex and is likely influenced by both anatomic and physiological risk factors that reduce oropharyngeal area, including obesity with increased pharyngeal fat deposition, certain craniofacial morphologies, and ventilatory deficits that predispose to pharyngeal collapsibility during sleep, a time when neuromuscular output is reduced. In contrast, apneas that occur without evidence of increased upper-airway resistance and with absence of respiratory effort are considered to be central apneas. A predominance of this event subtype constitutes central sleep apnea (CSA), a disorder that may occur in individuals with a variety of genetic and neuromuscular disorders. However, central apneas also may manifest as components of Cheyne-Stokes respiration, a form of periodic breathing characterized by long cycles of alternating hyperventilation and hypoventilation associated with hypocapnia, prolonged circulation time, and/or reduction in ventilatory reserve. The combination of CSA and Cheyne-Stokes respiration occurs in as many as 40% of patients with heart failure, which reflects the predilection of this patient group to respiratory control system instability due to the effects of pulmonary congestion on stimulating pulmonary irritant receptors, increased chemoreceptor sensitivity, and reduced cardiac output and cerebrovascular blood flow, and possibly because of abnormalities in autonomic function. An increased risk of both Cheyne-Stokes respiration and CSA occurring in heart failure is associated with male gender, atrial fibrillation, older age, and hypocapnia (pCO₂ <38 mm Hg during wakefulness). Patients with heart failure and both Cheyne-Stokes respiration and CSA generally have poorer cardiac function than do other patients with heart failure, have augmented levels of sympathetic nervous system activity, and may be at risk for pulmonary hypertension and increased mortality. However, the specific role of treatment of this breathing disorder in attenuating risk is unclear.

Patients with heart failure also may have a high frequency of obstructive respiratory events. Although the causal association between CSA and heart failure is likely bidirectional, traditionally, OSA has been considered to be a risk factor for, rather than a consequence of, heart failure. A causal relationship between OSA and heart failure also is supported by the finding that treatment of OSA is associated with modest improvements in systolic function. Although controlled trials are lacking, observational data additionally suggest that treatment of OSA prolongs survival of patients with heart failure and OSA.

Observed differences in clinical presentation and responses to treatment have supported the consideration of OSA and CSA as representing distinct therapeutic targets in heart failure; however, given the multifactorial and complex pathophysiology of sleep-disordered breathing, it has been argued that OSA and CSA may be better conceptualized as representing relative extremes along a continuum of airway vulnerability that reflects the influences of both anatomic and physiological factors that shape the magnitude of ventilation and propensity for respiratory oscillations in sleep, including airway dimensions, chemical drive, load sensitivity, and arousal. OSA, CSA, or both may manifest, depending on the relative innervation of upper-airway dilator compared with diaphragmatic muscles. Even within 1 patient, the relative predominance of obstructive and central events may vary, both day to day and throughout the night. Further definition of the causes of sleep-disordered breathing and clarification of the underpinnings of obstructive and central events are needed to inform treatment decisions, design preventive interventions, and identify genetic variants.

In this issue of Circulation, Yumino and colleagues propose a unified concept for the pathogenesis of OSA and...
In the present study,9 those observations were extended to address the influence of overnight fluid shift in men with heart failure and OSA or CSA. Compared with the findings from their prior report on men with OSA without heart failure, almost identical observations were made for men with OSA and heart failure: Reciprocal associations between overnight changes in leg fluid and neck circumference with sleep apnea severity were observed. Furthermore, men with heart failure and CSA were observed to have greater leg edema and larger overnight shifts in leg fluid than men with heart failure and OSA. The overnight decrease in leg fluid in the CSA group also was correlated with the apnea-hypopnea index and with change in neck circumference; however, these associations were weaker than those observed in the OSA group. In the CSA but not the OSA group, overnight change in leg fluid also was inversely associated with overnight levels of CO2, which further suggests that leg fluid displacement in CSA may have redistributed not only to the neck but also to the lungs, where increased pulmonary congestion may have served as a ventilatory trigger.

These intriguing findings suggest that in addition to peripheral fat, cervical fluid, displaced from the legs during the overnight sleep period, may be an anatomic risk factor for sleep apnea that changes dynamically over the night, and that in those with more severe heart disease, fluid shifts also may contribute to pulmonary congestion and ventilatory instability. As a unifying concept, rostral fluid shifts might influence the precipitation of both obstructive and central apneas. This concept is consistent with the importance of airway collapsibility as a common distal mechanism for sleep-disordered breathing. The stronger association between change in leg edema and change in frequency of apnea and hypopnea in OSA than in CSA is consistent with the relatively greater vulnerability of the airway to collapse in the former condition. The association between shift in leg fluid and hypocapnia in CSA also is congruent with the important role of chemosensitivity in this condition.

Although the sample reported in the present study9 is small and highly selected, and the evidence for some of the proposed effects is somewhat circumstantial, the findings raise several important questions and opportunities that may influence screening, treatment, and approaches for prevention. A key initial question is how generalizable the findings are, especially to obese patients (who constitute a growing majority of patients with these conditions) and to women.

Given the complexity of risk factors that likely interact to precipitate airway collapsibility, including hormonal influences, fixed anatomy, and obesity, it is possible that the impact of fluid shifts may be substantially lower in more heterogeneous patient groups not assessed in the present study. It also is possible that the findings were influenced disproportionately by data from a small proportion of patients with fluid overload and elevated filling pressures. Degree of leg edema (0 to 3+) was reported to correlate with the apnea-hypopnea index and overnight change in leg fluid edema, but fluid status at the time of onset of sleep was not measured. Although patients with acute decompensated heart failure were excluded from this study, it is common for patients to have unrecognized elevated filling pressures. Given the heterogeneity of patients with OSA/CSA, identification of reproducible markers of edema or fluid balance might improve the recognition of patient subsets who might be most sensitive to the effects of rostral fluid shifts. Aging and diabetes mellitus both are associated with lower-leg edema and sleep-disordered breathing; thus, it also would be important for future studies to explicitly address these potential confounding influences. Given the dynamic nature of fluid shifts and sleep, a further understanding of how the time course of fluid shifts interacts with circadian changes in bronchomotor tone and blood pressure, dynamic changes in sleep-stage distributions, and body position to influence ventilation across the sleep period would be of interest.

Noting that patient reports of “sitting time” were correlated with overnight changes in leg fluid, the authors speculated that increased walking may prevent the accumulation of lower-extremity fluid and reduce sleep apnea. In more than 4000 relatively healthy Sleep Heart Health Study participants, regular vigorous physical activity was associated with a reduced prevalence of OSA, an effect that was not well understood.14 Future evaluation of interventions aimed at promoting physical activity in heart failure may address whether any improvement in OSA/CSA is mediated by reducing leg fluid or rather through general effects on cardiovascular status, as well as whether such interventions vary in effectiveness in the presence of venous stasis disease, which is common with obesity and in women. Finally, the findings suggest the opportunity to identify whether simple changes in sleeping position, the daytime use of compression stockings, or timing of diuretic administration might influence the redistribution of leg fluid and improve sleep apnea.

It is clear that the pulmonary system, the cardiovascular system, and sleep-wake systems interact to influence a wide variety of clinical phenotypes. The article by Yumino et al9 provides yet another example of the interface among these
systems. It also identifies the potential opportunities to develop creative approaches for improving health by addressing interactions across physiological systems. It has long been recognized that improving cardiac output in patients with heart failure improves sleep apnea. Conversely, improving sleep apnea in heart failure may also improve cardiac function and reduce mortality. The present report additionally provides evidence that volume status and fluid redistribution over the night may be important determinants of both OSA and CSA. Potential effects were observed in a group of subjects that included individuals without visible peripheral edema and in those whose cardiac function was considered stable, and in prior work, effects were reported even in subjects without heart disease. Future research is needed to address the role of volume status and fluid distribution as a direct contributor to sleep-disordered breathing and to consider that the clinical assessment of fluid status may need to extend beyond the office visit to an assessment of how these change with sleep. Implantable hemodynamic monitoring may provide an opportunity to explore this interaction further.

Several years ago, a family practitioner published several case series describing a high prevalence of peripheral edema in his patients who were later identified to have sleep apnea, and he reported that in many patients, edema resolved with OSA treatment. He speculated that unrecognized sleep apnea may have led to volume overload and/or cardiac dysfunction. The findings from Yumino et al suggest that perhaps the edema observed in these case series was both a cause and a consequence of sleep-disordered breathing. It is likely that there are many other bidirectional interactions between sleep-disordered breathing and the cardiovascular system that await discovery, which provides opportunities for novel interventions in high-risk patients.

Disclosures

None.

References


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