Sleep Apnea with Intermittent Hemodialysis: Time for a Wake-Up Call!

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In an attempt to explain the elevated cardiovascular mortality of ESRD patients, novel prognosticators of adverse events such as sleep apnea and nocturnal hypoxemia have emerged as important, modifiable, cardiovascular risk factors in our patient population (1).

The sleep apnea syndrome (SAS) is characterized by repetitive cessation of respiration during sleep resulting in oxygen desaturation and arousal. In addition to hypoxemia and hypercapnia, subjects with sleep apnea endure sudden and profound changes in cardiac loading conditions, secondary to the abrupt generation of negative intrathoracic pressure. Acutely, each of these stimuli acts independently to trigger central sympathetic outflow to the heart and periphery. The gas exchange abnormalities, sleep fragmentation, and autonomic activation have all been implicated as causes of the substantial adverse health effects attributed to SAS (2).

The prevalence of SAS in the middle-aged general population has been reported to be 2 to 4% (3). In contrast, studies in the dialysis population have demonstrated a prevalence rate of >50% (4). Multiple authors have attributed this increase in the prevalence of SAS in ESRD to potential patient selection bias and comorbid conditions such as cardiovascular disease, diabetes mellitus, and obesity. In this issue of JASN, Unruh et al. (5) have demonstrated that ESRD patients undergoing thrice-weekly hemodialysis were associated with a four-fold increase in developing sleep apnea and severe nocturnal hypoxemia after adjusting for the presence of cardiovascular disease and diabetes when compared with participants from the Sleep Heart Health Study matched for age, sex, race, and body mass index. In addition, the ESRD cohort was associated with shorter sleep time, greater sleep fragmentation, and higher systolic blood pressure (BP). Taken together, this data adds to the growing body of evidence implicating the direct association between kidney failure and its conventional treatment with SAS.

Why would ESRD patients be at such high risk in developing SAS? From a simplistic viewpoint, kidney failure may exacerbate sleep apnea in ESRD by accumulation of uremic toxins, by volume overload, or by both. The basis of uremia-induced SAS is best exemplified by the corrective potential of nocturnal hemodialysis (NHD) [5 to 6 times per week, 8 h per treatment]. Hanly et al. studied 14 conventional hemodialysis patients before and after conversion to NHD with overnight polysomnography and found a significant reduction in the severity of sleep apnea in all patients (apnea-hypopneas index fell from 25 ± 25 to 8 ± 8 per hour, P < 0.05) (6). Subsequent research has reported restoration of autonomic modulation of heart rate related to the correction of SAS in ESRD with the use of NHD (7). Similar findings have also been reported in case reports with the use of renal transplantation (8). The results from these studies affirm the importance of uremic clearance in the development of sleep apnea in ESRD. However, the exact mechanisms remain elusive.

Although uremia may lead to the development of SAS, the role of volume overload in the contribution of upper airway obstruction should not be minimized. In a recent report, Tang et al. used a cross-over study design to demonstrate that nocturnal cyclic peritoneal dialysis (NPD) to alleviate sleep apnea in a cohort of ESRD patients when compared with continuous ambulatory peritoneal dialysis (9). The investigators found no demonstrable differences in respiratory mechanics or dialysis adequacy between the two modes of peritoneal dialysis. The documented improvement in sleep apnea by NPD was therefore best accounted for through improved extracellular fluid control (as demonstrated by bioelectrical impedance analysis). This observation is further supported by elegant human experiments implying that edema in the neck and pharyngeal mucosa will contribute to increased upper airway collapsibility, therefore predisposing to obstructive sleep apnea. To this aim, Chiu et al. (10) studied 11 normal subjects while supine and used a 5-min application of 40 mmHg of lower body positive pressure by antishock trousers to simulate volume overload. Of note, these investigators demonstrated significant increases in neck circumference and pharyngeal resistance with only 0.5 L of fluid displacement. At this time, most North American ESRD patients undergoing thrice-weekly hemodialysis require, on average, 2 to 3 L of ultrafiltration per session. Based on the emerging importance of fluid overload in the pathogenesis of upper airway obstruction, it is tempting to speculate that intermittent hemodialysis does not have the capacity to reduce upper airway edema (especially during sleep while supine), therefore contributing to the elevated prevalence of sleep apnea in ESRD.
The exaggerated presence of sleep apnea in ESRD offers a new avenue of therapeutic intervention for our patient population. In hemodialysis patients, sleep apnea and nocturnal hypoxemia have been linked to the development of sympathetic hyperactivity and left ventricular hypertrophy (11,12). Additionally, SAS has been associated with daytime sleepiness, impaired cognitive function, and poor vocational abilities. Thus, correction of SAS may have the potential to improve the quality of life and clinical outcomes of ESRD patients. In the general population, the treatment of sleep apnea with continuous positive airway pressure (CPAP) improves quality of life (13) and cognition, and normalizes nocturnal BP profile (14). In the ESRD population, CPAP was only used in a small study of 8 patients with some improvement in nocturnal oxygenation and 5 of 6 patients reporting improved daytime alertness (15). Finally, given the proposed pathophysiology of SAS in kidney failure, the roles of intensification of dialysis and aggressive control of extracellular fluid volume deserve urgent attention and further research (16).

The awareness of SAS as a potent cardiovascular risk factor in ESRD has generated new enthusiasm in examining novel therapeutic strategies to modify sleep apnea in our patient population. The identification of etiologic mechanisms underlying uremia-associated sleep apnea will not only enhance our understanding of its pathophysiology but will likely realign the goal and objectives of renal replacement therapy for the ESRD population.

**References**


See the article, “Sleep Apnea in Patients on Conventional Thrice-Weekly Hemodialysis: Comparison with Matched Controls from the Sleep Heart Health Study,” on pages 3503–3509.