Volume overload as a mechanism for obstructive sleep apnea in CKD?

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Keywords: hemodialysis; sleep apnea fluid shifts

The prevalence rate of sleep apnea in the hemodialysis (HD) patient population is >50% [1, 2] as compared to only 2–4% in the general population [3]. Not only does sleep apnea contribute to hypertension (HTN) and increased cardiovascular morbidity and mortality in the end-stage renal disease (ESRD) population, but it also significantly impairs their quality of life. However, large gaps in knowledge exist in our understanding of the potential mechanisms for increased sleep apnea in this vulnerable population. Traditional risk factors such as age and body mass index (BMI) do not fully account for the significant increased risk of sleep apnea in these patients [4]. As HTN and fluid overload occur almost universally in HD patients, it is possible that fluid retention may increase the risk of developing obstructive sleep apnea (OSA). If, indeed, fluid overload contributes to sleep apnea and poor sleep efficiency in HD patients, then the treatment of sleep apnea among those with ESRD could be targeted to improving volume control rather than using continuous positive airway pressure (CPAP) or an oral device, which many patients are unable to tolerate or comply with.

In this issue of Nephrology Dialysis Transplantation, Elias et al. [5] addresses this important issue in their study evaluating the relationship of rostral fluid shift with OSA...
among ESRD patients. This is an observational cohort study of 26 patients with ESRD. Patients were on thrice-weekly HD, conducted at the dialysis unit of University Health Network's Toronto General Hospital. Patients who were treated for sleep apnea or who had left ventricular ejection fraction ≤45% were excluded from the study. All patients underwent in-center polysomnography on the day before their dialysis. The study used apnea–hypopnea index (AHI) and apnea–hypopnea time as a percentage of total sleep time (%AHT, defined as mean duration of apneas and hypopneas in seconds × total number of apneas and hypopneas/total sleep time × 100) as outcome measures. They also measured leg fluid volume (LFV) using bioelectrical impedance, neck circumference (NC) and calf circumference; these measurements were made before sleep and repeated on awakening the next morning. The overall AHI for the cohort was 22.8 ± 26.8 episodes/h of sleep and 46% of the patients had an AHI ≥ 15. The mean overnight change in LFV was −242.7 ± 278.2. There was a weak inverse relationship between change in LFV and NC (r = −0.587, P = 0.0016). There was no significant relationship between overnight change in LFV and total AHI (r = −0.356, P = 0.074). However, the study did find a significant relationship between overnight change in LFV and %AHT (r = −0.607, P = 0.001). This correlation remained statistically significant but greatly weakened after adjusting for age, gender and BMI (r = −0.356). In addition to the change in LFV, age (r = 0.403) and male gender (r = 0.322) remained independently associated with %AHT on multiple regression analysis. Thus, the study concluded that nocturnal rostral fluid shifts are associated with severity of OSA and may play a role in the pathogenesis of OSA in ESRD.

Although the study provides some interesting insights into the pathogenesis of OSA, it has several limitations. As the authors acknowledge, this being an observational study, it does not take into account other confounding variables that may be contributing to the development of OSA in ESRD. In addition, the study showed that change in LFV was associated with %AHT but not AHI. It is hard to interpret what this means since %AHT is not a standard index of OSA severity. As per the American Academy of Sleep Medicine guidelines, AHI is the most commonly used outcome variable for OSA [6]. Another commonly described parameter that correlates well with severity of OSA is the hypoxic index [7]. It may be interesting to see if there is any association between hypoxic index and LFV in this study cohort.

OSA causes gas exchange abnormalities, sleep fragmentation and autonomic activation which have all been implicated as causes of substantial adverse health effects. In addition to OSA as an independent risk factor for HTN [8], OSA has also been associated with cardiovascular disease including stroke, myocardial infarction and congestive heart failure after adjustment for obesity and other potential confounders [9, 10]. Additionally, OSA has been shown to be independently associated with resistant HTN [11]. In a study from a HTN clinic, moderate OSA was demonstrated in 83% of patients with resistant HTN [12]. These findings have led national committees to consider OSA as a cause of HTN and resistant HTN. However, despite strong observational data relating OSA to HTN and cardiovascular disease, treatment of OSA with CPAP has demonstrated only modest improvement in daytime blood pressure (BP) in randomized controlled trials [13, 14]. These somewhat disappointing observations highlight the importance of the work of Elias et al. since we could attenuate the harms of sleep apnea and HTN in ESRD patients by addressing volume overload.

In the ESRD population, fluid overload and HTN are closely linked and frequently coexist. One could posit that it is the high BP that causes OSA in these patients, and not the fluid overload. In fact, in a small study among healthy adults, a pharmacologically induced increase in systemic BP was associated with decreased genioglossus muscle activity and decreased upper airway tone, which may thus facilitate OSA [15]. Moreover, limited evidence suggests that intensive BP control may improve the severity of OSA. A small randomized double-blind trial of 54 hypertensive men showed that the AHI was significantly reduced during non-REM sleep with the use of cilazapril (−8.6 ± 3.2; P = 0.01) [16]. Although the findings from these studies are limited by the lack of an adequate control group, small sample size and selected patient population, the results support the need to examine the impact of intensive BP and volume control on sleep apnea in HD patients in a large randomized controlled trial. Could it be that volume overload exacerbates sleep apnea by worsening hypertension?

To this end, we are conducting a multicenter study to examine the impact of intensive BP control on sleep apnea and sleep efficiency among 80 patients on conventional HD. This study is ancillary to the NIH-sponsored Blood Pressure in Dialysis (BID) trial which is a multicenter randomized clinical pilot study to determine the feasibility and safety of treating HD patients to two pre-dialysis standardized systolic BP goals (110–140 versus 155–165 mmHg) and to evaluate the effect on cardiovascular function and health-related quality of life over a 12-month period. Achievement of the BP goal will be accomplished by a stepped care algorithm consisting of reduction in dry weight and up-titration of anti-hypertensive agents. The ancillary study (BID-SLEEP) will perform sleep assessments utilizing state-of-the-art home sleep apnea monitors, naturalistic measures of sleep–wake behavior and surveys of sleep quality at baseline and at 12 months. If intensive BP control improves sleep apnea and sleep efficiency in HD patients, then the treatment of sleep apnea among those with ESRD could be targeted to improving the treatment of BP. This may serve as a foundation for development of a clinical practice protocol for volume removal and intensive BP control to improve sleep quality in HD patients.

ESRD and chronic kidney disease (CKD) can provide excellent models for understanding the role of volume overload in exacerbating sleep apnea and HTN. In turn, work in this field addresses a main concern of patients with kidney failure. In a study of 100 patients undergoing thrice-weekly hemodialysis, fatigue and sleep were the biggest motivations to increase the frequency of dialysis, more so than a 3-year extension in life [17]. Future studies are needed to tease out the effect of volume overload versus blood pressure on sleep apnea in this population. Such understanding of the physiological mechanisms underlying OSA in ESRD and CKD patients could also be extended to other settings wherein patients suffer from extracellular volume overload, such as congestive heart failure and...
nephrotic syndrome. This will impact the care of patients with volume overload and future directions of research in sleep apnea and fatigue.

Acknowledgements. Dr. Jhamb is supported by grant funding from the American Heart Association (11FTF7520014). Dr. Unruh is supported by NIH NIDDK (R01DK77785).

Conflict of interest statement. None declared.


References


Received for publication: 12.12.11; Accepted in revised form: 16.1.12