Hypervolemia and Sleep Apnea in Kidney Disease

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Summary: In end-stage renal disease (ESRD) and heart failure, conditions characterized by fluid overload, both obstructive sleep apnea (OSA) and central sleep apnea (CSA) are highly prevalent. This observation suggests that fluid overload may be a unifying mechanism in the pathogenesis of both OSA and CSA in these conditions. An overnight rostral fluid shift from the legs to the neck and lungs has been shown to contribute to the pathogenesis of OSA and CSA, respectively, in various different patient populations. This article reviews the evidence that supports a role for fluid overload and overnight fluid shift in the pathogenesis of sleep apnea in ESRD. The diagnosis, epidemiology, and clinical features of sleep apnea in patients with ESRD also are considered.

Semin Nephrol 35:373-382

Keywords: End-stage renal disease, obstructive sleep apnea, central sleep apnea, fluid overload, fluid shift

Both types of sleep apnea, obstructive sleep apnea (OSA) and central sleep apnea (CSA), are far more common in patients with chronic renal failure than in the general population. OSA, which is characterized by repetitive collapse of the upper airway (UA) during sleep, triggers a cascade of noxious stimuli. During obstructive events, exaggerated negative inspiratory intrathoracic pressure is generated against the occluded UA, which increases left ventricular afterload and reduces cardiac output. Intermittent apnea-related hypoxia leads to repetitive arousals from sleep and surges of sympathetic nervous system activity, with consequent fragmentation of sleep as well as adverse cardiovascular, neurocognitive, and metabolic effects.[1–5] CSA, which is characterized by complete or partial cessation of airflow in the absence of UA obstruction caused by cessation of the central respiratory drive, has similar effects as OSA, but without the generation of exaggerated negative intrathoracic pressure. As a consequence of these pathophysiological mechanisms, sleep apnea can have adverse acute effects on cardiovascular function and, over time, can increase the risk of developing cardiovascular diseases.[1]

In patients with chronic renal disease, the presence of sleep apnea is associated with hypertension, left ventricular hypertrophy, cardiovascular complications, and increased mortality.[6–9] Furthermore, sleep apnea–associated arousals and sleep fragmentation may lead to unrefreshing sleep and excessive daytime sleepiness, which is associated with an increased risk of motor vehicle accidents.[10] Given that daytime fatigue and sleepiness are very common symptoms in patients with chronic renal failure and can arise from many causes,[11,12] sleep apnea is not always considered in the differential diagnosis of these complaints, which may explain, in part, why its presence is underrecognized.[13]

The high prevalence of sleep apnea in chronic renal disease is similar to that in heart failure.[14] These high prevalences are not fully explained by increased age or increased body mass index (BMI).[15] Because kidney and heart failure are characterized by fluid overload, these observations suggest that hypervolemia may contribute to the pathogenesis of sleep apnea in both of these conditions. There is also a substantial body of evidence from various different patient populations that supports the role of overnight fluid redistribution from the legs to the neck and lungs in the pathogenesis of OSA and CSA, respectively.[16–19] We summarize the current evidence on the role of hypervolemia and overnight rostral fluid shift in the pathogenesis of OSA and CSA in patients with end-stage renal disease (ESRD). The diagnosis, epidemiology, and clinical features of sleep apnea in patients with ESRD are also considered.

DEFINITIONS AND DIAGNOSIS

Obstructive apneas and hypopneas are caused by complete or partial UA collapse during sleep,

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Financial support: Supported by a joint Canadian Thoracic Society/European Respiratory Society Peter Macklem Research Fellowship and the Joseph M. West Family Memorial Fund Postgraduate Research Award (O.D.L.), by the R. Fraser Elliot Chair in Home Dialysis (C.T.C.), and by the Clifford Nordal Chair in Sleep Apnea and Rehabilitation Research (T.D.B.).

Conflict of interest statement: none.

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0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2015.06.008

respectively. The UA collapses when sleep-related loss in UA dilator muscle tone is superimposed on a narrow and/or collapsible UA. On the other hand, central sleep apneas and hypopneas arise from complete or partial reductions in central neural outflow to the respiratory muscles during sleep, which leads to complete or partial cessation of airflow, respectively.

The standard test to diagnose OSA or CSA is overnight polysomnography (PSG), during which sleep and respiration are monitored. Sleep stages are recorded by electroencephalography, electro-oculography, and submental electromyography. Respiratory movements of the rib cage and abdomen are recorded by respiratory inductance plethysmography (elasticized bands placed around the rib cage and abdomen). Airflow may be monitored by nasal pressure and/or thermistors, and arterial oxyhemoglobin saturation is measured by pulse oximetry. Heart rhythm is assessed by electrocardiography.

Apneas are defined as the absence of tidal volume for at least 10 seconds and hypopnea is defined as a decrease in the tidal volume of more than 30% or more for at least 10 seconds that is accompanied by at least a 3% decrease in oxygen saturation or terminated by an arousal from sleep.[20] Apneas are classified as obstructive if they are accompanied by inspiratory effort against the occluded pharynx and are classified as central if they are not accompanied by inspiratory efforts. Determining if hypopneas are obstructive or central can be more challenging: hypopneas are classified as obstructive if there are signs of UA flow limitation such as out-of-phase thoracoabdominal movements or inspiratory flattening of the nasal pressure signal, or are classified as central in the presence of in-phase thoracoabdominal motion and without airflow limitation on nasal pressure.[20] The apnea–hypopnea index (AHI) is calculated as the number of apneas and hypopneas per hour of sleep. Sleep apnea severity can be classified according to the AHI; no sleep apnea is defined as an AHI of less than 5, mild sleep apnea is defined as an AHI of 5 to 15, moderate sleep apnea is defined as an AHI of 15 to 30, and severe sleep apnea is defined as an AHI greater than 30.[21] However, these cut-off values are arbitrary. A sleep apnea disorder or syndrome is defined as an AHI of at least 5 accompanied by either hypersomnolence or at least two of the following: choking or gasping during sleep, recurrent awakenings, unrefreshing sleep, daytime fatigue, or impaired concentration or memory.

EPIDEMIOLOGY AND CLINICAL FEATURES

Prevalence of Sleep Apnea in ESRD

In the general population, the prevalence of OSA is estimated at 3% to 14% in men and 4% to 9% in women, whereas the prevalence of CSA is less than 1%.[22–25] The prevalence of sleep apnea in ESRD is much higher: from 50% to 60%,[15,26–28] and is similar to that described in heart failure.[14] Unruh et al[15] compared 46 patients on conventional hemodialysis with 137 controls from the Sleep Heart Health Study who were matched for age, sex, BMI, and race. They found that patients with ESRD had significantly higher odds of severe sleep apnea than controls (crude odds ratio, 4.07; 95% confidence interval, 1.83-9.07), and that the association of hemodialysis with sleep apnea was independent of age, sex, BMI, and the presence of cardiovascular diseases. In an observational study of 30 ESRD patients, sleep apnea was found in 9 of the 15 peritoneal dialysis patients and in 8 of the 15 hemodialysis patients.[28] These findings suggest that it is the underlying renal disease itself that predisposes to sleep apnea rather than the particular type of dialysis they are receiving. Similar to the general population, sleep apnea is more common in male than in female ESRD patients.[29,30] In patients with nephrotic syndrome and lower-limb edema, Tang et al[31] reported that the prevalence rate of sleep apnea (AHI >5) was 48%.

Clinical Features of Sleep Apnea in ESRD

Risk factors for OSA in the general population include increased BMI, increased neck circumference, tonsillar hypertrophy, macroglossia, orofacial skeletal abnormalities, and family history.[4,5] Although an increased BMI remains a risk factor for OSA in patients with ESRD, OSA patients with ESRD tend to have a lower mean BMI than OSA patients with normal renal function.[9,32,33] In the general population, patients with OSA typically present with a history of several of the following symptoms: poor sleep quality, witnessed snoring and apneas by the bed partner, waking unrefreshed, morning headaches, fatigue, and excessive daytime sleepiness.[34,35] In ESRD patients with OSA, bed partners report apneas and snoring during sleep less frequently than among OSA patients with normal renal function.[33] Because tiredness and fatigue are common in patients with ESRD and can result from the renal disease itself or from co-existing diseases or poor sleep quality as a result of other causes,[11,36,37] they are not reliable predictors of sleep apnea. Furthermore, among patients with ESRD, the prevalence of typical symptoms of OSA and poor sleep quality do not differ between those with and without OSA, which makes it difficult to predict which patients may have OSA from the clinical presentation alone.[38]

Risk factors for CSA have not been addressed specifically in patients with ESRD, however, in patients with heart failure, they include male sex, hypocapnia, atrial fibrillation, and increasing age.[39] Unlike OSA, symptoms specific to CSA have not been