Central Sleep Apnea in Kidney Disease

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Summary: Sleep is an essential function of life and serves a crucial role in the promotion of health and performance. Poor sleep quality and sleep disorders have been a recurrent finding in patients with chronic kidney disease (CKD). Sleep disorders such as obstructive sleep apnea (OSA) can contribute to hypertension, diabetes, cardiovascular disease, and worsen obesity, all of which are implicated in the etiology of CKD, but CKD itself may lead to OSA. Relationships between CKD/end-stage renal disease (ESRD) and OSA have been the subject of numerous investigations, but central sleep apnea (CSA) also is highly prevalent in CKD/ESRD but remains poorly understood, underdiagnosed, and undertreated in these patients. Emerging literature has implicated CSA as another contributor to morbidity and mortality in CKD/ESRD, and several studies have suggested that CSA treatment is beneficial in improving these outcomes. Patients with CKD/ESRD co-existing with congestive heart failure are particularly prone to CSA, and studies focused on managing CSA in congestive heart failure patients have provided important information concerning how best to manage CSA in kidney disease as well. Adaptive servo-ventilation ultimately may represent the treatment of choice in these patients, although a stepped approach using a variety of therapeutic modalities is recommended.

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Sleep, an essential function of life, serves a crucial role in the health and well-being of all individuals. Sleep-disordered breathing (SDB) is quite widespread among end-stage renal disease (ESRD) patients.[1,2] Seventy percent of ESRD patients are believed to have some form of SDB.[3,4] Severe sleep apnea is believed to be 4 times more prevalent in hemodialysis patients compared with the general population.[5] Central sleep apnea (CSA) is a subtype of SDB with a repetitive pattern of cessations (or reductions) and resumptions (or increases) of respiratory effort not accompanied by significant upper-airway obstruction. Although CSA and obstructive sleep apnea (OSA) may share some of the same attributes, including similar underlying mechanisms resulting in unstable control of breathing, the clinical manifestations, sequelae, and treatment can differ significantly. Not infrequently, the two forms of SDB may be manifest in the same individual, further complicating management.

Both central and obstructive events result in sleep disruption, hypoxemia, and increased overall sympathetic tone. Both OSA and CSA are associated with an increased prevalence of atrial fibrillation and ventricular arrhythmias. Congestive heart failure (CHF) complicated by CSA carries a greater risk of increased mortality[6] independent of other known risk factors such as impaired left ventricular ejection fraction (LVEF).[7] Augmented sympathetic stimulation in CSA has been implicated as the mechanism for worsening prognosis in CHF.[8] Although at this point in time OSA has been studied fairly extensively in kidney disease patients, there remains a scarcity of literature pertaining to CSA in renal disease, despite the fact that the approach to diagnosis and treatment of CSA often differs markedly from that of OSA.

We examine the role of CSA in kidney disease patients by summarizing the present knowledge on the significance, prevalence, pathogenesis, clinical features, and treatment options.

SLEEP APNEA DEFINITIONS

OSA is characterized by repetitive episodes of upper-airway obstruction or narrowing (usually in the oropharynx and/or retrolingual hypopharynx) that occur during sleep, whereas in CSA there is no significant upper-airway obstruction and inspiratory effort either decreases or is absent during each event (Fig. 1). Both usually are associated with a reduction in blood oxyhemoglobin saturation and both are identified by the absence of, or a decrease in, airflow. Apnea is defined as cessation of airflow (at least a 90% decrease from baseline) that lasts for more than 10 seconds and is classified as obstructive

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(OSA) in the presence of inspiratory effort, and as central (CSA) when inspiratory effort is absent. The definition of hypopnea has varied over the years and in the United States also is the subject of Centers for Medicare and Medicaid Services coverage determinations. Per the Centers for Medicare and Medicaid Services, there must be at least a 30% reduction in airflow or thoracoabdominal effort as compared with baseline, followed by at least a 4% oxyhemoglobin desaturation. The most recent American Academy of Sleep Medicine definition calls for at least a 30% decrease in airflow from baseline associated with at least a 3% oxyhemoglobin desaturation and/or polysomnographic evidence of arousal from sleep. A hypopnea is scored as central when there is no snoring during the event, no inspiratory air flow limitation, no thoracoabdominal paradox, and the esophageal pressure excursions (if available) are reduced.[9] If any of these characteristics are present, the hypopnea is scored as obstructive. Hunter-Cheyne-Stokes breathing (HCSB) is a form of CSA characterized by a regular, recurring pattern of gradually decreasing respiratory effort followed by an apnea or a period of hypopnea, followed by gradually increasing respiratory effort. The distinction between the HCSB pattern of CSA and CSA with abrupt onset and offset is often not clinically important, except that HCSB invariably is associated with hyperventilation at the peak of respiratory effort and therefore is associated most commonly with CHF and after stroke.[10,11] Finally, periodic breathing is defined as regular waxing and waning of respiration caused by fluctuations in respiratory drive, with events that are not isolated but rather recur over an extended period of time. According to the American Academy of Sleep Medicine criteria, periodic breathing is applied only to SDB in children; the pauses in respiration may be shorter than frank central apneas ($\geq$3 seconds), and there must be at least 3 pauses in a row.[9]

As previously mentioned, CSA and OSA also may co-exist because they both represent cyclic variations in outputs from the medullary respiratory center, which projects to both inspiratory muscles as well as upper-airway dilator muscles. The relative timing and magnitude of decreased drive to these separate groups of muscles determines whether obstructive or central events, or even mixed events (in adults a central apnea followed by one or more obstructive breaths), are manifest. Some patients with CSA also will have OSA, confirming that the underlying mechanisms responsible for these phenomena often overlap.[12–14]

Sleep apnea, as opposed to a sleep apnea syndrome, is a diagnosis made based on the frequency of apneas and hypopneas. An apnea-hypopnea index (AHI) is calculated as the number of apneas and hypopneas per hour of sleep (in the sleep laboratory) or per hour of recording time (for limited studies taking place in the home). An AHI of 5 or more per hour is diagnostic of sleep apnea. When both OSA and CSA are present, two different definitions have been proposed: CSA is diagnosed along with OSA when 50% or more of events are central,[15] or OSA and CSA are both diagnosed when the central AHI and obstructive AHI are both 5 or more per hour. Finally, a sleep apnea syndrome is present when an abnormal AHI is accompanied by symptoms or signs attributable to SDB.

Central sleep apnea can be associated with a wide variety of diseases and disorders. In most studies, 4% to 10% of sleep apnea (SA) patients predominantly have CSA.[16,17] Thus, published information on CSA is somewhat scant relative to the abundant availability of information published on OSA. Based on the range of $Paco_2$ levels during an event, CSA can be classified into two main categories: hypocapnic and hypercapnic. Underlying the former category is a reduction in $Paco_2$ to at or near the apneic threshold of the ventilatory response to CO_2, a phenomenon peculiar to nonrapid eye movement (NREM) sleep (described in more detail in the section Pathogenesis of Hyperventilatory CSA). This destabilizes the metabolic component of respiratory control leading to CSA as seen in patients with CHF, stroke, residence at high altitude, and in chronic kidney disease (CKD)/ESRD. Thus, the $Paco_2$ when asleep usually is found in a lower range in these patients (eg, $<$36 Torr). In general, patients with hypercapnic CSA suffer from neurologic or neuromuscular disorders affecting ventilation or respiratory drive, or chronically are exposed to drugs with respiratory depressant properties (most commonly, opioids).

CLINICAL FEATURES

Patients with hypocapnic CSA, including those with CKD/ESRD, present with a clinical picture that differs from that typical of OSA and of hypercapnic CSA. Table 1 contrasts these clinical features.

Patients with hypocapnic CSA most often will show a lesser degree of hypoxemia than other types of SDB, more often have normal body habitus, mild snoring, insomnia, restless sleep, frequent awakenings with shortness of breath, and a level of daytime sleepiness that is more variable and depends on the severity of the underlying sleep disruption, which usually is less profound.[18,19] Morning headaches are thought to be associated with hypercapnic vasodilation of the cerebral blood vessels, and therefore are most common in hypercapnic CSA and OSA. Hypocapnic CSA occurs more commonly in men, possibly owing to the higher prevalence of the comorbidities associated with this disorder (CHF, stroke) but also owing to the tendency of the ventilatory response to CO_2 to be more vigorous in males.

It is crucial to note that any given patient may show a mixture of SDB types. For instance, narcotic pain