Central Sleep Apnea and Cardiovascular Disease

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KEYWORDS

• Central sleep apnea • Heart failure • Cheyne-Stokes respiration • Cardiovascular disease

KEY POINTS

- Central sleep apnea (CSA) is thought to occur as a consequence of heart failure (HF), with a prevalence estimated at 1 in 3.
- Some evidence suggests that the presence of CSA worsens the prognosis and outcomes in HF.
- The optimization of medical management should be the first step in the management of CSA in HF.
- Positive airway pressure devices, such as adaptive servo-ventilation, are effective at controlling CSA, but the results of large clinical trials are awaited to determine whether the targeted treatment of CSA improves important outcomes in HF.
- Atrial fibrillation (AF) seems to be a risk factor for CSA in HF populations, but CSA is also commonly encountered in AF without left ventricular dysfunction.

EPIDEMIOLOGY: HEART FAILURE

Because of the varied definitions and tools to define and measure heart failure (HF), precise estimates of its epidemiology are lacking. In general, HF may be subclassified into left ventricular (LV) systolic dysfunction, whereby there are measurable reductions in contractility, and LV diastolic dysfunction, also known as HF with preserved ejection fraction. The proportion of HF attributed to diastolic dysfunction may be as high as 50%.[1,2] Furthermore, it is estimated that as many as half of the people in the community with measurable LV dysfunction are asymptomatic.

HF is a public health problem, with most recent estimates of more than 5 million individuals in the United States afflicted.[3] With an aging population, the incidence of HF continues to increase, with now greater than 500,000 new cases per year. Over the course of a lifetime, one's risk for HF approaches 20%.[4] Despite the development of increasingly sophisticated drug and device therapies, mortality rates related to HF remain high. It is among these reasons that there is an intense interest in the interplay between HF and central sleep apnea (CSA) in the hopes of better understanding pathophysiologic mechanisms and building a greater armamentarium of treatments to combat HF.

EPIDEMIOLOGY: CSA IN HF

There are similar imprecisions in determining the epidemiology of CSA in HF. For the most part, existing literature is composed of small case series, which generally originate from sleep laboratory referral populations. The range of CSA in HF reported in these studies range from 15% to 30%.[5–8] Such studies, also influenced by participatory bias, may overestimate the true occurrence of CSA in those with HF. On the other hand, accounting for the substantial proportion of those in the community with asymptomatic LV dysfunction, it is just as possible that the true prevalence of CSA is underestimated.

Because efforts to establish a causal relationship between CSA and important outcomes in HF rely in part on an accurate accounting of the burden of CSA in the HF population, other limitations to the existing epidemiologic literature are

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Sleep Med Clin 9 (2014) 27–35
http://dx.doi.org/10.1016/j.jsmc.2013.10.007

worth mentioning. First, it is important to recognize that patients with HF also have a high rate of obstructive sleep apnea (OSA), often in combination with CSA.[8] This coupling likely represents an overlap of the pathophysiologic and neuromuscular mechanisms that govern aspects of both ventilatory control and upper airway patency. Traditionally, prevalence studies in HF, rather than focusing purely on CSA, have reported rates of *sleep-disordered breathing* (SDB), encompassing both OSA and CSA. Rates of SDB in these series have been reported as high as 50% to 60%. In such instances, it is difficult to disentangle the effects of CSA in patients with HF from those caused by OSA. In speaking to the differential effects of OSA and CSA in HF, there is an overnight shift in predominance of obstructive apneas early in the sleep period to central apneas later on, an effect that may be mediated by deteriorating cardiac function attributable to obstructive breathing events.[9]

Second, there are shortcomings to the use of the apnea-hypopnea index (AHI) in quantifying the severity of CSA and, therefore, in determining a dose-response effect of CSA on cardiovascular outcomes. By convention and ease of application, but without sound evidence for validation, clinicians and researchers traditionally apply the AHI to CSA as they would to OSA. Although the AHI has been well established to correlate with outcomes in OSA, similar validation data do not exist in the setting of CSA, as outlined in the American Academy of Sleep Medicine's scoring manual.[10] Various metrics are scattered in the literature, including the central apnea index[11]; the central AHI; sleep time spent with an oxyhemoglobin saturation of less than 90%; and the Cheyne-Stokes respiration (CSR) time, which measures the proportion of sleep time with periodic breathing.[7,12] One study found prognostic significance in the central AHI but not in the percentage of sleep time spent with periodic breathing.[12] Future standardization will be needed to help better delineate the relationship between CSA and cardiovascular outcomes.

Finally, important temporal trends in the management of HF may confound the relationship between CSA and HF. Because CSA is generally thought to occur as a consequence of HF, the first approach to treatment is medical optimization of HF, which, as discussed later, attenuates CSA. The paradigm shift to include β-blockers as the standard therapy for HF gained traction in the late 1990s,[13] a period *after* most of the existing epidemiologic literature on CSA and HF was established. A suggestion was made by the investigators of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP), a large randomized controlled trial of continuous positive airway pressure (CPAP) therapy in CSA and HF, that such medical treatments of HF substantially reduced the rates of CSA in HF, to the point that recruitment to the trial was fatally wounded,[14] and that more contemporary analyses would prove that CSA has become less common over time. However, a more recent ascertainment of sleep apnea in consecutive patients with HF, all of whom were treated with β-blockers, showed a historically similar prevalence of CSA (31%).[7]

CLINICAL IMPLICATIONS OF CSA IN HF

There are important signs and symptoms seen in patients with HF that may directly link to CSA. The cycles of apnea and hyperpnea characteristic of CSA-CSR can result in the paroxysmal nocturnal dyspnea classically associated with HF. CSA-CSR tends to be augmented by the supine position,[15] which may contribute to the classic HF symptom of orthopnea. Finally, in CSA-CSR, sleep is studded with arousals that tend to occur at the height of the hyperpneic phase.[16] By virtue of the typical CSA-CSR cycle length, these arousals often number in excess of 40 per hour. With few exceptions,[17] studies specifically measuring sleep-related complaints in patients with pure CSA are lacking; but there is a notable lack of such symptoms in community-based HF samples with a high rate of severe OSA.[18]

Rather than these uncommonly reported symptoms, sleep and nonsleep clinicians remain focused on whether or not the presence of CSA is detrimental to important cardiovascular outcomes in patients with HF, such as mortality and HF exacerbations. Proof of the concept comes from observations of repeated hypoxemia, evidence for sympatho-excitation, and sleep fragmentation in fragile patients with compromised cardiac function. The finding of CSA in patients with asymptomatic LV dysfunction, independent of hemodynamic measures, suggests that CSA may precede the development of and, therefore, pose a risk factor for overt HF.[19]

Despite what may seem like an intuitive relationship, available small studies have been conflicting in their conclusions. CSA-CSR in HF has been associated with increased mortality in some studies,[12,20] with multivariate analysis suggesting that CSA-CSR may be an independent risk factor for mortality.[12,21] However, one of the largest studies to date, of patients with HF referred for cardiac transplantation, did not find an effect of CSA on long-term outcomes.[22] It is worth