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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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

mentioning that there is significant heterogeneity in the available studies in terms of patient baseline characteristics (age, criteria for the diagnosis of CSA by AHI, presence of arrhythmias) and the fact that CSA was sometimes treated in noncontrolled settings (**Table 1**).[23] Finally, further attesting to the link between CSA and the severity of HF, those with CSA-CSR during wakefulness or exercise have worse outcomes.

TREATMENT OF CSA

Treatment of CSA in patients with HF with sleep-related symptoms, such as daytime sleepiness or repetitive awakenings, seems warranted.[24] However, as noted earlier, such complaints are uncommon in HF populations, which raises the important question of whether or not otherwise asymptomatic patients with HF found to have CSA should be treated because of the potential for cardiovascular benefit. Similar questions have been asked about patients with OSA with comorbid cardiovascular disease where there is considerable observational and interventional published data but no clear answers. In the setting of CSA, there is even less guidance, though clinical opinion and sentiment are strong.

MEDICAL OPTIMIZATION: PHARMACOLOGIC INTERVENTION

The first intervention in patients with CSA and HF should be medical optimization.[25] In general, this involves pharmacologic therapy, which, among other mechanisms, improves hemodynamics and reduces cardiac filling pressures. Angiotensin-converting enzyme inhibitors[26] and β-blockers[27] attenuate CSA in HF. Acute diuretic therapy was found to improve sleep apnea in patients with volume overload and diastolic dysfunction.[28] Not all cases of medical optimization are effective; one study showed attenuation of breathing events in a minority of patients after 2 months of medical therapy following acute HF.[29]

MEDICAL OPTIMIZATION: SURGERY/ DEVICES/CARDIAC PACING

Beyond drug therapy, there is further evidence that invasive treatments for HF resulting in improvements in cardiac function will often have concordant improvements in CSA. Notably, such treatments are indicated as primary therapy for HF and are not recommended as first-line CSA treatment. Case reports of surgical correction of mitral valvular disease for HF management describe marked improvement in CSA-CSR.[30] Cardiac transplantation in severe HF resulted in eradication of CSA-CSR in 7 of 13 patients, although for reasons that are not clear, disordered breathing persisted in another 4 patients postoperatively.[31]

A high-profile publication suggesting an improvement in OSA by atrial overdrive pacing[32] was subsequently disproved by several larger, more rigorously conducted studies.[33] However, closer examination of the initial study results showed subtle reductions in recorded central apneas, suggesting that increases in cardiac output, with reduced circulation time, may enhance ventilatory stability in HF. Along the same lines, cardiac resynchronization therapy (CRT), also known as biventricular pacing, may hold promise in treating CSA in patients with HF with ventricular conduction delay. CRT has been shown to significantly decrease the number of apneas, increase oxygen saturation, and improve sleep quality in such patients.[34] Although seductive to consider, it is yet to be proven whether some of the survival benefit attributed to CRT in patients with HF in large-scale studies[35,36] may be related to the amelioration of central apnea in this population.

Finally, there are recent reports of the use of phrenic nerve stimulation (PNS) by an implanted transvenous device in patients with HF and CSA. One night of unilateral PNS improved some indices of CSA and was not associated with significant adverse events.[37] These patients had a high rate of HF related to rheumatic fever, and many were not on standard medical therapy. Much more research is needed to learn whether invasive treatments such as these are warranted in specific populations and whether any benefit is derived over and above that related to enhancing cardiac function.

POSITIVE AIRWAY PRESSURE

CPAP

Independent of its effects on the upper airway and ventilation, CPAP has salutary effects on cardiac function in HF on account of inspiratory muscle unloading and reduction of cardiac preload and afterload related to increasing intrathoracic pressure.[38] A small controlled trial of CPAP or usual care followed those with HF with and without CSA. CPAP was associated with an increase in ejection fraction and reduced risk of heart transplant only in those with CSA.[39] Another trial of CPAP in HF with CSA showed reductions in catecholamine levels.[40]

The multicenter CANPAP Trial randomized patients with systolic HF and CSA to CPAP or no CPAP.[14] Although the trial showed small improvements in CSA, ejection fraction, and sympathetic activity in the CPAP group, it failed to show

Table 1
Available observational studies describing outcomes in patients with HF with CSA

	Lanfranchi et al,[12] 1999	Sin et al,[39] 2000	Corra et al,[61] 2006	Javaheri et al,[21] 2007	Brack et al,[62] 2007	Roebuck et al,[22] 2004	Luo et al,[63] 2010
Patients (n)	62	66	133	88	60	78	128
Outcome	Death, Tx	Death, Tx	Death, Tx	Death	Death, Tx	Death	Death
Risk associated with CSR[a]	+	+ 2.53	+ 5.7	+ 2.1	(+) 3.8	–	–
AHI defining presence of CSR cycles per hour	≥30	≥15	>30	≥5	≥15	>5	≥5
LVEF (%)	23	22	23	24	26	20	36
Mean observation period (y)	2.3	2.2	3.2	4.3	2.3	4.3	2.9
Remarks	Patients, with AF excluded	CSR treated	CSR during exercise and sleep	CSR treated	CSR during daytime	CSR treated	—

Abbreviations: AF, atrial fibrillation; LVEF, left ventricular ejection fraction; Tx, survival without cardiac transplantation.

[a] Hazard ratio controlled for several confounders, with + and – denoting increased mortality and equal mortality of CSR versus no CSR, respectively.

Data from Brack T, Randerath W, Bloch KE. Cheyne-Stokes respiration in patients with heart failure: prevalence, causes, consequences and treatments. Respiration 2012;83(2):168.

a benefit in the primary outcome, transplant-free survival. In fact, an interim analysis after a mean follow-up of 24 months suggested a trend toward greater mortality in the CPAP group, a finding that eventually dissipated with further observation. As noted earlier, the investigators hypothesized that improvements in medical therapy over the course of the multi-year study (use of β-blockers in particular) reduced mortality in all patients to the point of irreversibly underpowering the study. In fact, death rates in both groups were considerably less than predicted in the power analysis. That said, it is noteworthy that the overall AHI was reduced by only about 50% in the CPAP group, and, as in many trials of CPAP, adherence to therapy was suboptimal. Yet, in a post hoc analysis of CANPAP, in those patients whom CPAP effectively suppressed CSA-CSR, LV ejection fraction (LVEF) and transplant-free survival were improved compared with controls, suggesting CPAP may be an effective therapy in selected individuals (**Fig. 1**).[41]

Adaptive Servo-Ventilation

Adaptive servo-ventilation (ASV) uses an algorithm to analyze a patient's ventilation and then adjusts pressure support to reach a calculated ventilation target. The algorithms by which the devices accomplish this are proprietary, and no comparative efficacy trials have been published to guide the selection of various machines that are available in the marketplace.

Although providing support during apneas and hypopneas, ASV is designed to avoid overventilation during the hyperpneic phase, promoting more uniform ventilation and reducing arousals from sleep. Available within the United States since 2006, ASV has been shown to effectively suppress CSA-CSR; improve LVEF, quality of life,[42] and exercise capacity[43]; and may be preferred over CPAP by patients.[11,44,45] A 1-month randomized trial comparing therapeutic ASV with subtherapeutic ASV showed significant improvements in daytime sleepiness and reductions in neurohormonal activity associated with active treatment in patients with stable HF and CSR-CSA.[46] A recent systematic review and meta-analysis identified 14 studies comparing ASV with control conditions, defined as other positive airway pressure (PAP) modes (including CPAP and bilevel PAP), oxygen therapy subtherapeutic ASV, or no treatment.[47] The investigators concluded that ASV was more effective than control conditions in reducing the AHI and improving cardiac function and exercise capacity. Based on these encouraging preliminary data, large multicenter trials are now underway to determine if ASV will impact important cardiovascular outcomes, such as mortality, on a larger scale.[48]

Nocturnal Gas (Oxygen and Carbon Dioxide) Supplementation

Supplemental oxygen as treatment of CSA is thought to suppress ventilatory drive,[49] thereby

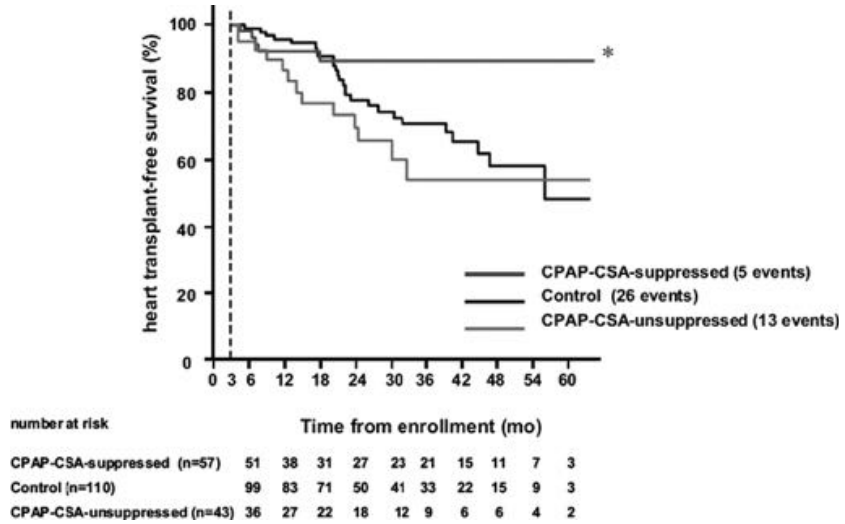

Fig. 1. Post hoc analysis of the CANPAP study suggests improved survival in a small number of patients in whom CPAP effectively suppressed CSA. * denotes *P*<.05. (*From* Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation 2007;115(25):3178; with permission.)

buffering the apneic threshold; but it is also possible that oxygen improves cardiac function, thereby indirectly reducing CSA. A small, 2-night, randomized controlled trial yielded a reduced AHI in men with severe HF and nocturnal hypoxemia[50]; there is evidence for improved quality of life and exercise capacity associated with oxygen therapy in HF. As in device therapy discussed earlier, whether such improvements are directly attributable to attenuation of CSA remains speculative.

Because hypocapnia seems to be intimately related to the pathogenesis of CSA-CSR, it would follow that increasing $Paco_2$ by the inhalation of carbon dioxide (CO_2) or by increasing dead space may ameliorate ventilatory instability characteristic of the breathing disorder. One night of inhaled CO_2 administered to 6 patients with severe stable HF resulted in virtual eradication of CSA-CSR.[51] However, longer-term studies are lacking; there is evidence for worsened sleep quality and fragmented sleep architecture associated with CO_2 treatment. Moreover, the finding of an increase in sympathetic activity after a single night of CO_2 treatment may be harmful in those with HF.[52]

NOVEL DRUG THERAPY

Theophylline

Theophylline, a phosphodiesterase inhibitor with bronchodilatory properties, has been shown to be a central respiratory stimulant,[53] possibly by antagonizing adenosine in the brainstem. Historically, use of theophylline has fallen out of favor because of the risk of neuro-excitatory effects, such as tachycardia, which are typically coupled to serum concentrations more than the therapeutic range of 10 to 20 μg/mL. In a controlled trial of 15 men with stable congestive heart failure (LVEF <45%), 5 days of oral theophylline, resulting in modest serum concentrations (11 μg/mL), reduced the frequency of central apneas and hypopneas as well as the duration of arterial oxyhemoglobin desaturation.[54] Safety concerns related to the risk of arrhythmogenesis in patients with HF, a population with sympathetic overactivity, may be tempered by a subsequent study that showed similarly modest serum theophylline levels do not increase sympathetic activity or heart rate in patients with HF as they do in healthy individuals.[55] Nevertheless, caution is warranted because the long-term use of another oral phosphodiesterase inhibitor, milrinone, was shown to actually increase mortality in patients with HF.[56]

Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor, has 2 effects that may be beneficial in the setting of CSA and HF. First, diuretic effects reduce pulmonary congestion. Second, it induces a metabolic acidosis to stimulate respiration. In a randomized placebo controlled trial of 6 nights of single-dose acetazolamide in a small group of men with stable HF and CSA, acetazolamide significantly improved the central apnea index (mean 44 to 23 per hour) as well as the nadir oxygen saturation value compared with placebo.[57] That the $Paco_2$ was found to be lower in the treatment group confirms the importance of the *difference* between the prevailing $Paco_2$ and the $Paco_2$ associated with the apneic threshold, rather than the absolute values, in triggering ventilatory instability.

CSA and Atrial Fibrillation

Because it is the most common arrhythmia encountered in clinical practice and is associated with serious conditions, such as stroke, HF, and mortality,[58] there is increasing interest in the relationship between atrial fibrillation (AF) and sleep apnea syndromes. Most of the focus has been on AF and OSA because the sequelae of obstructive apneas, particularly sympathetic surges and swings in intrathoracic pressure, are a neat pathophysiologic fit to explain the alterations in the electrical properties of the thin-walled atria there is ongoing interest in whether PAP therapy for OSA may alter important outcomes.

However, there is also evidence for a link between AF and CSA. On the one hand, the presence of LV dysfunction or overt HF may mediate (if not confound) the relationship because AF and HF frequently coexist. Sin and colleagues,[8] in their polysomnographic assessment of 450 men and women with HF, found AF to be more tightly associated with CSA than OSA. A recent case report provides evidence for a bidirectional relationship between CSA and AF, with the onset of CSA following a paroxysm of AF, presumably because of acute deterioration in cardiac function associated with arrhythmia onset.[59]

On the other hand, evidence arguing against the prerequisite of LV dysfunction in the interaction between AF and CSA comes from Leung and colleagues,[60] who showed a high prevalence of AF in those with idiopathic CSA and free of overt HF. Further research is needed to better explain this relationship and, in the absence of any interventional trials, whether the treatment of CSA impacts measurable outcomes in AF.

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