

Contemporary Insights and Novel Treatment Approaches to Central Sleep Apnea Syndrome in Heart Failure

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Opinion statement

Central sleep apnea (CSA) is a common and under-diagnosed condition commonly associated with Cheyne-Stokes respiration. It is particularly prevalent in the heart failure population affecting up to 40 % of all patients with heart failure. The pathophysiology associated with CSA is based on the underlying effects of hypoventilation and hyperventilation, with neurologic dysregulation of respiratory control as the primary defect. However, therapeutic options are limited because of the prevailing perception that CSA is a consequence, rather than cause of morbidity and mortality. At present, the main focus remains treating the underlying problem (ie, intensifying heart failure therapeutics, decongestion), whereas additional suggestions of using acetazolamide, progesterone, nocturnal oxygen, and theophylline have not been validated with contemporary clinical trials. Positive pressure ventilation is currently the primary recommendation for all patients with sleep-disordered breathing (CSA included), and in some patients may effectively reduce the apnea-hypopnea index. However, significant research is ongoing to determine how to treat this complex patient population.

Introduction

Central sleep apnea (CSA, or “central sleep apnea syndrome”) is a form of sleep-disordered breathing whereby the respiratory effort is diminished or absent, either intermittently or in cycles (so-called “periodic

breathing"). This syndrome usually includes exaggerated daytime fatigue, nightly awakenings, or both [1•]. It was first described as a distinct entity by a French neurologist Dr. Henri Gastaut and his colleagues in 1965, who distinguished different types of sleep apnea based on measurements of mouth and nostril airflow in addition to chest movements by their strain-gauge and thermistor recording techniques

[2, 3]. They recognized that individuals who lacked both airflow and respiratory efforts for at least 10 seconds were distinctively different from those with upper airway obstruction despite continuous respiratory efforts. This observation led to the discovery of an alternative, neurologic etiology in the pathogenesis of one form of sleep disordered breathing.

Epidemiology and clinical manifestations of central sleep apnea

Definition of central sleep apnea

In contemporary perspectives, CSA is a heterogeneous syndrome with a phenotypically descriptive definition. The complexity of CSA is highlighted by the latest International Classification of Sleep Disorders (ICSD-2), which described five distinctive types of CSA in adults that are largely attributed to its clinical phenotypes (Table 1) [4]. In cardiac patients, the most common form is related to CSA with and without Cheyne-Stokes respiration (CSR). There is a sixth category, an evolving concept of a "Complex Sleep Apnea Syndrome" [5], which is still highly debated and is not firmly established (and therefore, not incorporated into ICSD-2 definition). In fact, complex sleep apnea often appears following treatment of concomitant obstructive sleep apnea syndromes [6] and may even be explained by the development of airway obstruction as a consequence of underlying CSA progression.

Patients with CSA may complain of nonspecific and largely subjective symptoms. Common complaints include chronic fatigue, excessive daytime drowsiness, impaired cognitive function, and reduced exercise capacity—commonly attributed to aging or unhealthy lifestyles. However, the typical signs and symptoms of sleep disordered breathing often cannot distinguish between CSA and other forms of sleep disordered breathing [7•]. Because this is seldom recognized by patients and their relatives, CSA is largely overlooked. In some cases, the manifestations of CSA may even be accompanied by neurologic symptoms like difficulty swallowing, subtle voice changes, weakness, and even numbness.

Table 1. Classification of central sleep apnea

Subtype	Description
Primary central sleep apnea (idiopathic)	Has no known related diseases
Central sleep apnea due to Cheyne-Stokes breathing pattern	May be a consequence of heart failure or stroke
Central sleep apnea due to medical condition not Cheyne-Stokes	May be associated medical conditions such as heart and kidney disorders.
Central sleep apnea due to high-altitude periodic breathing	Often appears during sleep at altitudes above 15,000 feet, and induces a form of Cheyne-Stokes breathing with relatively shorter cycles.
Central sleep apnea due to drug or substance	Includes the use of centrally-active medications such as opiates
Primary sleep apnea of infancy	Congenital in nature

Therefore, the formal diagnosis of CSA requires a full polysomnography evaluation. The hallmark feature of CSA is the repetitive cessation or decrease of both airflow and ventilatory effort during sleep. This produces the same abnormal respiratory patterns of apneas, hypopneas, or respiratory effort-related arousals, as well as alterations in the quantity of ventilation during sleep. In terms of determining disease severity of CSA, the same measurement of the number of apneas and hypopneas per hour (apnea-hypopnea index or "AHI") during polysomnography evaluation can be used, although more descriptions on "central events" can be described. There is still some debate regarding the measure of severity. Nevertheless, it is generally agreed that an AHI <5 is not significant while an AHI \geq 30 is considered severe.

Central sleep apnea is not confined to the sleeping state. Occasionally, CSA is noticeable in the awake state, but not very prominent because of the presence of the "wakefulness drive to breathe." However, when an individual transitions into the sleep state, the physiological controls are reduced or withdrawn, therefore, making it critical that a proper balance is maintained by the ventilatory feedback loop.

Prevalence of central sleep apnea

Given the requirements of formal polysomnography study to define CSA, a large ascertainment bias in determining its true epidemiology exists. Based

Table 2. Prevalence of central sleep apnea in contemporary population studies

Study population	Sample size	SDB definition	CSA definition	CSA prevalence	Reference
All newly implanted CRT	700	AHI >5/h	\geq 50 % of all events	40 %	[60]
LVEF <40 % NYHA II-III	203	AHI >10/h		28 %	[61]
LVEF <40 % NYHA II-IV	108	AHI \geq 15/h	\geq 33 % of all events	31 % (44 % NYHA II; 56 % NYHA III-IV)	[62]
LVEF \leq 45 %	316	AHI \geq 10/h	\geq 50 % of all events	30 %	[63]
LVEF \leq 35 % NYHA II-III	50	AHI >10/h		30 %	[64]
AF and normal LVEF (>55 %) NYHA II-IV	150	AHI \geq 5/h		31 %	[9]
Acute decompensated systolic HF admission (LVEF <45 %)	784	AHI \geq 15/h	\geq 50 % of all events	21 %	[65]
HF pts NYHA I-III	88	AHI >5/h		64 % (91 % NYHA II or greater)	[66]

AF atrial fibrillation, AHI apnea-hypopnea index, CRT cardiac resynchronization therapy, CSA central sleep apnea, HF heart failure, LVEF left ventricular ejection fraction, NYHA New York Heart Association Functional Class, SDB sleep-disordered breathing

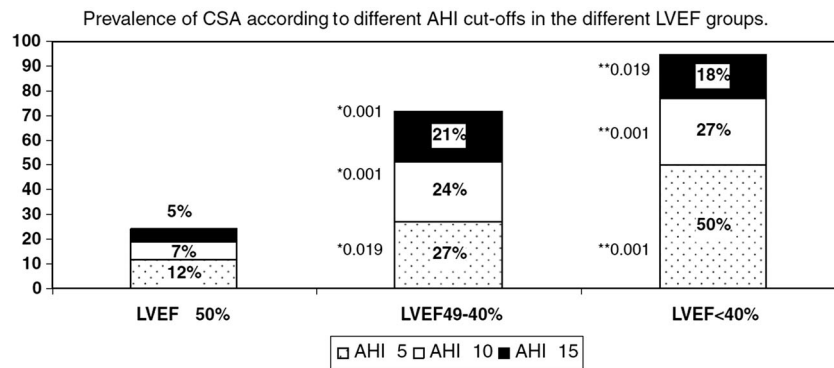


Fig. 1. Prevalence of CSA According to different apnea-hypopnea index cut-offs in different left ventricular ejection fraction subgroups in community-dwelling elderly patients (adapted from Reference [7•]). The bars represent normal (LVEF $\geq 50\%$), mild impaired (LVEF 49 %–40 %) and moderate impaired systolic function (LVEF $< 40\%$). The different values within the bars describe the percentages of CSA according to AHI cut-offs ≥ 5 , 10, 15. The numbers outside the bars represent the *P* values for the differences of CSA at AHI ≥ 5 , 10, 15 between the different LVEF groups. Key: AHI/h – apnea–hypopnea index; LVEF – left ventricular ejection fraction. *LVEF 49 %–40 % compared with LVEF $\geq 50\%$ at same AHI level. **LVEF $< 40\%$ compared with LVEF $\geq 50\%$ at same AHI level.

on epidemiologic studies, the prevalence of CSA is considered rare in the general population, yet CSA is far more prevalent in patients with heart failure (Table 2). Several estimates from single-center series have suggested CSA to be present in up to 50 % of stable patients with heart failure and reduced ejection fraction [7•, 8] and 30 % in patients with heart failure and preserved ejection fraction [7•, 9]. Meanwhile the severity of CSA (estimated by AHI) also increases with impairment of left ventricular ejection fraction (LVEF) especially in elderly patients (Fig. 1) [7•]. More contemporary heart failure cohorts revealed lower rates (25 %–40 %), although still quite prevalent [10–12]. A single center cohort study observed that 35 % of patients with severe heart failure had CSA, and of the patients who had sleep-disordered breathing, 69 % of them had CSA [13]. Meanwhile, CSA occurs in up to 30 % of patients with atrial fibrillation in the setting of preserved LVEF [9].

Risk factors of central sleep apnea

The risk factors for developing CSA have been studied primarily in the setting of heart failure, and include male sex, older age, sedentary lifestyle, diagnosis of atrial fibrillation, increased ventricular filling pressure, and more advanced cardiac remodeling as manifested by increased end diastolic volume. By far, the most striking risk factors are age and sex, whereby the prevalence of CSA is higher in men with heart failure even with mild symptoms [14], and it occurs in up to 15 % of patients over the age of 70 [7•]. Patients with CSA also have higher circulating natriuretic peptide levels and lower oxygen saturations as compared with those without sleep disordered breathing, and definitely higher natriuretic peptide levels in CSA when compared with obstructive sleep apnea [13]. In addition, CSA appeared to be more prevalent in patients with renal failure [15].

Since CSA has a primary neurologic origin, the presence of a stroke has been associated with the development of CSA in $\sim 40\%$ of patients, with 26 % exhibiting

Cheyne Stokes breathing pattern. However, the symptoms of CSA resolved in ~50 % of patients within 12 months of their neurological event [16, 17]. Opioid users (perhaps a form of alteration in neurologic state) have higher likelihood of developing CSA as well, but true prevalence studies are lacking.

Central sleep apnea has also been associated with hormonal imbalance. Premenopausal women are less likely to get CSA as opposed to postmenopausal women due to the lack of testosterone and the presence of estrogen [18]. Testosterone was shown to increase the apneic threshold when it was administered to premenopausal women [19]. The increase in apneic threshold was associated with the instability in breathing and the presence of CSA. Other studies have shown that suppressing testosterone in men results in a decreased apneic threshold and decrease in CSA [20]. CSA was also found to be present in patients with conditions such as hypothyroidism [21] and acromegaly [22].

Specific breathing patterns of central sleep apnea

The unique breathing patterns of CSA deserve some discussion. Some patients with CSA may display periodic shallow breathing or under-breathing that alternates with deep over-breathing, a condition known as Cheyne-Stokes respiration (CSR, sometimes known as “Cheyne-Stokes breathing pattern”) [23]. However, one should be careful not to confuse CSR with signs and symptoms of dyspnea with minimal exertion or even at rest (NYHA class III-IV), even though they can both be clinical manifestations of advanced congestive heart failure. The key is to assess at the most optimal volume status and to observe the cyclic nature of CSA at the bedside.

Another breathing pattern commonly associated with CSA is exercise oscillatory ventilation (EOV), which is a breathing disorder seen during exercise that is characterized by prominent, slow and steady fluctuations in breathing. The presence of EOV has been observed in patients with systolic heart failure, even though it may not be directly linked to clinically defined CSA [24]. Early work suggested that a large majority of patients with advanced heart failure may demonstrate some kind of oscillatory breathing pattern during graded exercise [25] and that the frequency and severity of the breathing pattern may be related to the severity of heart failure, including exercise intolerance, low O₂ consumption, and a steep ventilation/CO₂ production slope [26–28]. The presence of the oscillatory pattern of breathing was attributed to the cyclic changes in arterial PO₂, which diminished oxygen delivery to peripheral tissue by a failing heart. No changes in alveolar hypoventilation or arterial PaCO₂ were noted [25]. Some have even demonstrated that the presence of EOV was associated with an AHI ≥30 in 98 % of patients with heart failure, and the combined presence of EOV and CSA was associated with a significantly increased mortality [24, 29]. A more recent study even showed that EOV was a strong predictor for diastolic HF [30]. Therefore, screening for sleep disordered breathing in patients with heart failure who demonstrated EOV during cardiopulmonary exercise testing is warranted.

Cardiovascular consequences and prognosis of central sleep apnea

The hypoxia that follows CSA increases the oxidative stress and leads to inflammation, which leads to over-activation of the sympathetic nervous system

and further increases myocardial workload. Other adverse consequences of hypoxia include plaque rupture, vasoconstriction, and dementia. Development of hypercapnia in CSA patients also contributes to additional deleterious effects, such as sleep arousals and increased breathing work associated with apneic events. In addition, hypercapnic events are linked to the increased risk of atrial fibrillation in patients with CSA [4, 31–33].

The presence of CSA may have important prognostic implications. In fluid-retaining states such as heart failure, CSA may indicate increasing fluid retention (such as worsening heart failure), poor cardiopulmonary function, and adverse long-term outcomes [34, 35]. Recent studies have further identified the presence of CSA as a strong independent predictor of cardiac death and hospital readmission rates in patients with established heart failure. Khayat et al showed that not only do patients hospitalized with CSA have a 50 % readmission rate at 6 months, but 25 % have more than one repeat hospitalization within that time frame. The presence of CSA may also be associated with increased arrhythmic risk and disease progression in patients with asymptomatic left ventricular dysfunction [36].

Pathophysiology and clinical insights of central sleep apnea

The pathophysiology associated with CSA is based on the underlying effects of hypoventilation and hyperventilation, with neurologic dysregulation of respiratory control as the primary defect. Regardless of whether a hypoventilation or hyperventilation event starts the CSA cycle, the result is the same—a waxing-and-waning breathing pattern resulting in increased CO₂ levels and decreased O₂ levels. The resulting hypoxia causes additional sympathetic nervous system activation, which may lead to worsening of heart failure.

Hyperventilation-induced central sleep apnea

Post-hypocapnia hyperventilation is the primary underlying pathophysiological mechanism for CSA associated with high-altitude sickness, and primary CSA. Changes in respiratory patterns may affect arterial blood gas values and trigger activation of the sympathetic nervous system and a subsequent increase in peripheral vascular resistance. Central and peripheral chemoreceptors use oxygen and carbon dioxide levels in the blood to regulate ventilation and are sensitive to autonomic balance. Increased sensitivity of these receptors further leads to CSR, which can lead to intermittent arousals from sleep and a fragmented and disordered sleep state.

In fluid-retaining states, the excess fluid leads to an increase in venous pressure, which in turn causes more filtration into the interstitial space [31–33]. Upon lying down, the fluid filtered into the interstitial space gets redistributed and moves rostrally accumulating in the lungs and increasing the pulmonary capillary wedge pressure (PCWP), therefore, leading to pulmonary congestion [32, 33]. The congestion causes pulmonary vagal irritant receptors in the lungs to respond by a reflexive hyperventilation. The hyperventilation causes hypocapnia and the slight change in PaCO₂ causes spontaneous arousals. The spontaneous arousal further the ventilation instability and further decrease the PaCO₂ (because of an increase in

chemosensitivity) causing it to fall below apneic threshold once the person goes back to sleep. The decrease in PaCO₂ below apneic threshold stops the central ventilatory drive to breathe until the PaCO₂ rises. The hyperventilation-apnea cycle is sustained because of the pulmonary congestion, increased PCWP, increased chemoreception, and the apneic threshold [32, 33].

Chronic hypoventilation-associated central sleep apnea

In patients with CSR, hypoventilation is observed first as a total cessation of respiratory drive followed by hyperventilation as a result of delayed responses to hypercapnia and hypoxemia. CSR is usually present in patients with heart failure, who are chronically hyperventilating because of the heart's inability to pump blood efficiently and, therefore, the CSA pattern of breathing is started with hyperventilation. However, the instability in ventilation observed in this form of CSA usually occurs because of three reasons: (1) decrease cardiac index leading to a lengthened circulatory time (delay in data transfer to chemoreceptors); (2) increased chemosensitivity (increased controller gain); and (3) deterioration of the baroreflex mechanism (reduced damping effect). It is known that during sleep, ventilation is primarily driven by metabolic factors especially PaCO₂ as opposed to awake ventilation, which is mainly governed by the wakefulness drive to breath. During non-REM sleep, the apneic threshold is usually reset to a higher value and the PaCO₂ levels are relatively elevated. However, in patients with HF and CSR-CSA, the PaCO₂ levels do not increase upon sleep, thereby falling below apneic threshold and leading to a lack of ventilatory drive. The spontaneous arousals that were coupled with the lack of ventilatory drive cause the PaCO₂ to fall back to the lower apneic threshold while also re-instating the "wakefulness drive to breath." Ventilation is triggered to decrease the PaCO₂ to wakefulness threshold, and a ventilatory overshoot is observed due to increased chemosensitivity. When the person goes back to sleep, the sudden change in state causes the apneic threshold to rise, again without an increase in the PaCO₂. Therefore, the likelihood of CSA is dependent on two aspects of this cycle: arousal (apneic) threshold and ventilatory response (which is in turn dependent on the sensitivity of the chemoreceptors).

Treatment option for patients with central sleep apnea

The lack of uniform agreement in the definition of CSA, coupled with the complex and ill-defined pathophysiology, the perceived lack of specific therapeutic options, as well as the transient nature of the presentation (especially in the setting of acute hypervolemic or neurologic states) all contribute to the under-diagnosis (and perhaps under-treatment) of CSA. The central doctrine of managing CSA is to target the underlying conditions that trigger the development of CSA—namely conditions such as heart failure, atrial fibrillation, and stroke. Nevertheless, there are several therapeutic options targeting the sleep apnea itself, including lifestyle modifications, medications, and therapeutic devices (Table 3). Simple lifestyle changes such as raising the head of the bed, wearing compression stockings, or elevating the legs while asleep are considered low risk and potentially helpful in preventing lower extremity edema while reducing pulmonary congestion that contributes to CSA [37].

Table 3. Specific treatment options for central sleep apnea

Study intervention	Duration	N	Outcome	Reference
Acetazolamide 250 mg (low dose) vs placebo	1 mo	14	Decreased central apnea index and reduced number of night-time arousals	[39]
Acetazolamide vs placebo	1 wk	6	Decreased apnea frequency and improved sleep quality	[40]
Acetazolamide (250 mg BID) vs placebo	4 d	12	Decreased AHI and duration of hypoxemia	[41]
Theophylline vs placebo	5 d	15	Decreased apnea, hypopnea, and duration of hypoxemia	[45]
CPAP vs No CPAP (CANPAP study)	2 y	258	Decreased apnea. Improved nocturnal oxygenation, LVEF, and 6 minute walk distance. No proven survival benefit.	[47•]
CANPAP post hoc analysis				
CPAP: on treatment AHI <15 vs AHI >15	3 mo	100	Improved transplant-free survival and greater LVEF improvement with adequate AHI suppression (AHI<15)	[48•]
ASV vs no ASV	6 mo	19	Improved AHI, LVEF, and QOL scores	[50]
Nocturnal oxygen + CO ₂ vs air	1 night	9	Reduced CSR and increased arterial oxygenation, but increased sympathetic activation.	[53]
Dynamic CO ₂ administration during periodic breathing	1 night	7	Significant reduction in periodic breathing, especially if administered during hyperventilation	[54•]
Effect of 3 % CO ₂ on CSR	3 nights	6	Near abolition of CSR	[56]
Phrenic nerve stimulation	2 nights	16	Significant reduction in CSA indices	[57•]

ASV adaptive servo-ventilation, CO₂ carbon dioxide, CPAP continuous positive airway pressure, CSA central sleep apnea, CSR Cheyne-Stokes Respiration, LVEF left ventricular ejection fraction

Medical therapies currently used for the treatment of CSA include diuretics such as acetazolamide and mineralocorticoid receptor antagonists, hypnotics and sedatives, progesterone agonists, and theophylline [1•, 38]. Acetazolamide works by blunting the peripheral chemosensitivity to hypoxia and increasing the central chemosensitivity to hypercapnia [5]. These changes can clinically be seen via reductions in the AHI. Two prior studies showed a significant improvement in the AHI in patients with primary CSA at both low dose (250 mg/day) and high dose (1000 mg/day) acetazolamide [39, 40]. In addition, Fontana et al observed similar results in heart failure patients with CSA when they evaluated the effect of acetazolamide 250 mg twice daily on AHI suppression [41].

Hypnotics and sedatives treat CSA by limiting the number of spontaneous arousals during sleep. This helps decrease the frequency of low CO₂ reserve and the apneic cycle that would otherwise follow [23, 42]. However, at the same time, opioids increase the prevalence of ataxic breathing, and can, therefore, exacerbate central apnea. As a result, practitioners should minimize opioid use whenever possible.

Progesterone agonists have been shown to facilitate proper gas exchange resulting in fewer fluctuations in blood gas values [43], however, its effect on the AHI, and thus its clinical efficacy is unknown at this time [44]. On the other hand, theophylline has received mixed reviews regarding its use in CSA patients [1•]. As a phosphodiesterase inhibitor, this drug competes with adenosine, a respiratory depressant, resulting in a significant reduction in the AHI in a small cross-over study [45]. However, this beneficial effect must be weighed against the potential increase in cardiac events. Some studies have shown that long-term usage of theophylline leads to increased sympathetic activity; a detrimental outcome for patients with heart failure. Meanwhile, other studies have shown that

low doses of theophylline did not increase sympathetic activity in such patients and would otherwise be well tolerated. As a result, the routine use of theophylline in these patients remains controversial [46].

The recently published Practice Parameters Statement from American Academy of Sleep Medicine recommends that positive airway pressure therapy be considered for all patients with primary CSA [1•]. More specifically, they recommend continuous positive airway pressure (CPAP) therapy targeted to normalize the apnea hypopnea index (AHI) of <15 for the initial treatment of CSA related to heart failure [1•]. These recommendations are largely based on the CANPAP study [47•], which showed a dramatic decrease in the AHI and improvement in left ventricular ejection fraction with CPAP therapy [47•, 48•]. Interestingly, they did not find a significant difference in their primary outcome, transplant-free survival, during their initial analysis. However, when patients were divided into optimally treated (AHI <15) vs those treated without adequate suppression (AHI >15), the transplant-free survival became significantly higher in the optimally treated group [48•]. Therefore, a trial of CPAP to reduce AHI remains a logical, first-line therapeutic approach. In addition, nocturnal supplemental oxygen therapy is also recommended leading to improved AHI suppression and LVEF comparable to positive airway pressure (PAP) treatment. In addition to its ease of use and availability, supplemental oxygen therapy is relatively inexpensive compared with PAP.

Adaptive servo-ventilation (ASV), with optimal AHI suppression, is also recommended for the treatment of CSA in patients with heart failure. ASV is a ventilator-based therapy that is capable of counterbalancing periods of hyperpnoea and hypoventilation by applying variable degrees of pressure support. The device uses these pressure-supported breaths to maintain a prespecified minute ventilation target [49]. Several small studies have shown similar effects on AHI and left ventricular ejection fraction as with CPAP therapy [50, 51], however, ASV lacks evidence of a long-term morbidity and mortality benefit. A large randomized control trial with 1200 patients is currently underway to definitively evaluate the long-term outcomes associated with ASV therapy [52]. In addition, another large trial is currently enrolling to look at ASV in heart failure patients with both obstructive and central patients (ADVENT-HF). A third large trial is enrolling patients with acute heart failure decompensation with ASV to prevent recurrent hospitalizations (CAT-HF). In contrast, bilevel positive airway pressure (BiPAP) in spontaneous mode has not been recommended as this can aggravate CSA associated with hyperventilation [1•]. However, BiPAP in the spontaneous-timed mode titrated to an AHI <15 is an acceptable alternative if adequate trials of CPAP, ASV, and supplemental oxygen fail [1•].

Other treatment options for CSA patients include gas exchange therapy and implantable electrical devices. Patients with heart failure who develop CSA tend to be hypocapnic and, thus, thought to respond to CO₂ administration. Several small studies have shown an improved AHI and reduction in Cheyne-Stokes breathing with supplemental CO₂ administered in both continuous and dynamic forms [53, 54•, 55, 56]. However, the data were not robust and the treatment effect was evaluated based on one night of sleep. In addition, CO₂ is not easily available in most centers thereby limiting its routine use. Meanwhile, cardiac resynchronization therapy (CRT), involves implanting one pacemaker lead in the right ventricle and one in a vein overlying the left ventricle such that the synchronized contraction of both ventricles can be restored. In the setting of heart

failure with concomitant CSA, CRT is associated with improved O₂ saturation, reduced apneas, and improved sleep, although it is likely that such improvements are largely attributed to improvement in heart failure rather than CSA.

The newest device in development for the treatment of CSA is an implantable device, which stimulates the phrenic nerve to prevent periods of apnea. The pilot study of this device included approximately 40 patients with CSA and an AHI \geq 20. The average left ventricular ejection fraction was 30 % and most patients were NYHA functional class II-III. The primary endpoints included AHI, oxygen desaturation index, sleep quality, and quality of life scales at 3 and 6 months following device implant. The device therapy was well tolerated, and all major endpoints were significantly improved with stimulation of the phrenic nerve by 3 months [57•]. A larger scale trial with long-term outcomes still needs to be completed, however, stimulation of the phrenic nerve seems to be a promising new therapy for CSA.

Conclusion

Central sleep apnea is a common and often overlooked condition that is particularly prevalent in the setting of heart failure and in the elderly. Our understanding of the pathophysiology and clinical manifestations of CSA has largely been hampered by the perceived lack of therapeutic options and the conceptual approach that CSA is a consequence rather than cause of morbidity and mortality. None of the current treatment options specific for CSA have been supported by robust data. At present, the main focus remains therapies to stabilize underlying medical conditions, but there are many other complementary treatment modalities available for CSA. Upcoming results from clinical trials will hopefully better define the role for ASV as well as phrenic nerve stimulation in CSA. In the meantime, positive pressure ventilation by way of CPAP should still be considered for all patients with sleep disordered breathing as supported by the latest heart failure guideline recommendations [58, 59].

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Compliance with Ethics Guidelines

Conflict of Interest

Dr. Ryan L. Grayburn and Ms. Yaquta Kaka have no relationships to disclose. Dr. Wilson Tang is a site investigator for the Respicardia clinical study, but does not receive any personal honorarium or support. Dr. Tang is a section editor for *Current Treatment Options in Cardiovascular Medicine*.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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