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Central Sleep Apnea:

Implications for Congestive Heart Failure

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Abstract

Congestive heart failure (HF), an exceedingly common and costly disease, is frequently seen in association with central sleep apnea (CSA), which often manifests as a periodic breathing rhythm referred to as Cheyne-Stokes respiration. CSA has historically been considered to be a marker of heart disease, since improvement in cardiac status is often associated with the attenuation of CSA. However, this mirroring of HF and CSA may suggest bidirectional importance to their relationship. In fact, observational data suggest that CSA, associated with repetitive oxyhemoglobin desaturations and surges in sympathetic neural activity, may be of pathophysiologic significance in HF outcomes. In light of the disappointing results from the first large trial assessing therapy with continuous positive airway pressure in patients with CSA and HF, further large-scale interventional trials will be needed to assess the role, if any, of CSA treatment on the outcomes of patients with HF. This review will discuss epidemiologic, pathophysiologic, diagnostic, and therapeutic considerations of CSA in the setting of HF.

Keywords

central sleep apnea; congestive heart failure; continuous positive airway pressure; control of breathing; sleep-disordered breathing

There is mounting evidence that sleep-related breathing disorders play an important pathophysiologic role in cardiovascular (CV) disease, a finding that may afford therapeutic opportunities. This is most notable in the setting of obstructive sleep apnea (OSA), due in large part to its high prevalence not only in the general population but also in the setting of comorbid CV diseases such as hypertension and stroke. On the other hand, central sleep apnea (CSA) is intimately and more specifically linked to heart failure (HF). This association is not exclusive, and, in fact, CSA and OSA may coexist within the same patient.¹

HF afflicts > 5 million individuals in the United States, with an incidence of > 500,000 cases per year and, despite advances in drug and device therapy, unacceptably high morbidity and mortality; the lifetime risk for HF approaches 20%.² Innovative management strategies will be necessary to further reduce morbidity and mortality in affected patients.

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Although CSA is generally thought to occur as a consequence of HF, there is some evidence to suggest that its presence may promote disease progression and confer an increased risk of mortality independent of underlying cardiac dysfunction. What remains unresolved is whether targeted therapy of CSA is warranted and if such treatment affords improvement in outcomes in HF populations.

Classification and Characteristics of CSA

As opposed to patients with OSA, in whom breathing is interrupted primarily by upper airway narrowing or collapse in the face of continued respiratory effort, disordered breathing in patients with CSA results from a reduction in or lack of output from the central respiratory generator in the brainstem, manifesting as apneas and hypopneas without discernible breathing efforts. Nevertheless, despite this fundamental distinction, OSA and CSA do share some commonalities, since both often coexist in the same individual,^{1,3} and there is evidence for upper airway narrowing in patients with CSA.⁴ Perhaps on the basis of an overnight deterioration in cardiac function, some individuals may transition from predominantly obstructive apnea to central apnea over the course of 1 night of sleep.⁵

The reader is referred to a recent comprehensive review by Eckert et al⁶ of the various forms and manifestations of CSA, as well as the physiologic underpinnings related to the ventilatory control system. We will refer to components of that system that may relate more intimately, either directly or indirectly, to HF. The form of CSA most commonly observed in the setting of HF is Cheyne-Stokes respiration, which was first recognized 2 centuries ago.^{7,8} (For the purpose of this review, the term CSA will be inclusive of the Cheyne-Stokes respiratory pattern.) Cheyne-Stokes respiration, also referred to by some as *periodic breathing*, is characterized by oscillatory ventilation, with periods of central apneas or hypopneas alternating with intervals of hyperpnea. As in patients with OSA, disordered breathing events result in polysomnographic evidence of CNS arousals and sleep disruption. In patients with CSA, arousals are more likely to occur at the height of hyperpnea and may contribute to complaints of paroxysmal nocturnal dyspnea in patients with HF. Based on a 1999 consensus statement,⁹ the severity of CSA, like OSA, has been quantified by the hourly frequency of disordered breathing events (known as the apnea-hypopnea index [AHI]). While an obstructive AHI of at least five events per hour has traditionally been considered the minimum for the development of daytime symptoms that may respond to treatment, evidence to support any equivalent threshold for the treatment of CSA is absent.⁹ In fact, in a recently published revision of the sleep scoring manual,¹⁰ an American Academy of Sleep Medicine task force found insufficient evidence linking the extent of Cheyne-Stokes breathing with morbidity and mortality to provide a recommendation on the severity rating.

Epidemiology of CSA

In case series,^{1,3,11–15} the frequency of CSA in HF patients secondary to left ventricular (LV) systolic dysfunction is reportedly high (range, 45 to 82%). This wide range may depend on a number of variables such as HF etiology and severity, as well as gender and age biases. Many prevalence studies are composed of highly selected populations, based on a suspicion of apnea or on referrals to a sleep laboratory. Therefore, caution is warranted in applying these limited observations to the HF population at large. Finally, and perhaps most temporally important, much of the data was obtained prior to the widespread treatment of HF with β -blockers and aldosterone antagonists, the effects of which, by improving cardiac function, may be expected to attenuate CSA.

The literature strongly indicates that men have a higher prevalence than women^{3,16}; men comprised 95% of the randomized subjects in the Canadian Trial of Continuous Positive

Airway Pressure for Heart Failure Patients with Central Sleep Apnea (CANPAP) trial,¹⁷ a large interventional treatment trial of CSA with HF.

Diastolic dysfunction, often asymptomatic,¹⁸ has been increasingly recognized as a cause of HF. While isolated diastolic dysfunction may account for up to a third of all cases of HF,¹⁹ the prevalence and implications of CSA in patients with diastolic HF are relatively unknown. In a small study²⁰ (20 patients), there was a 20% prevalence of CSA in those patients with diastolic HF and New York Heart Association (NYHA) class II or III symptoms. The reportedly high prevalence of CSA in patients with asymptomatic LV dysfunction, independent of hemodynamic measures, suggests that CSA may contribute to the development of more symptomatically overt HF.^{16,21}

Mechanisms in the Genesis of CSA

As has been noted elsewhere,⁶ respiration during sleep is regulated by a feedback control system²² that is governed primarily by blood tensions of CO₂ and, to a lesser extent, O₂ content. The following three factors are known to regulate ventilation: (1) the efficiency by which CO₂ is removed from the lungs, by way of the parenchyma and respiratory muscles, which is referred to as *plant gain*; (2) the ventilatory control system response to changes in PaCO₂ (and to a lesser extent to PaO₂), which is known as *controller gain*; and (3) circulation time, which refers to the interval between CO₂ originating in the periphery and arriving at the central chemoreceptors.

CSA is most prominent during non-rapid eye movement sleep,⁶ and is characterized by a prolonged ventilatory cycle length (*ie*, the duration of a single apnea plus a single ventilation period) and a delay in the measured nadir of arterial oxygen saturation. There is a very high correlation among ventilatory cycle length, prolonged circulation time,²³ and LV ejection fraction (LVEF),²⁴ suggesting that the characteristic long cycle length seen in CSA patients may be related to low cardiac output and the delayed transport of chemical signals from the lungs and peripheral tissues to central chemoreceptors.

A prevailing pathophysiologic paradigm holds that the predisposition to CSA in HF patients derives from a tendency to hyperventilate.^{25–27} The stimulation of pulmonary vagal and irritant afferents by pulmonary congestion, increased adrenergic stimulation, or an exaggerated ventilatory response to CO₂ may each contribute to hyperventilation.^{28–30} The resolution of CSA after the correction of mitral regurgitation^{31,32} is evidence of the potential importance of mechanical factors including atrial stretch and/or pulmonary congestion in the development of CSA.

Also important to understanding the genesis of CSA is the concept of the difference between the prevailing PaCO₂ and the apneic threshold (*ie*, the PaCO₂ below which rhythmic breathing ceases). The normal response to sleep onset is a modest (3 to 8 mm Hg) increase in PaCO₂ compared with wakefulness.³³ In a study³⁴ of stable HF subjects, those subjects without CSA showed similarly expected increases in end-tidal CO₂ with sleep onset, while levels in those with CSA were little changed, demonstrating a greater than expected response to carbon dioxide during the transition from wakefulness to sleep. The importance of CO₂ is further confirmed by the finding that inhaled CO₂ can reverse CSA.³⁵ Low prevailing PaCO₂ during wakefulness, which likely translates into relative hypocapnia during sleep, is also predictive of CSA.^{36,37}

PaCO₂ alone, however, does not fully explain periodic breathing in HF patients, since the frequency of central events, as quantified by AHI, has been shown to be independent of prevailing PaCO₂ levels during wakefulness.¹⁵ Furthermore, hypocapnia is absent in as many as 20% of HF patients with CSA.²⁵ Accordingly, other alterations of the ventilatory control

system may promote CSA. Reduced plant gain due to decreased functional residual capacity, small lung volumes (associated with cardiomegaly or pleural effusions), and high alveolar-atmospheric CO₂ differences appear to be important.³⁸

The concept of prolonged circulation time and its contribution to ventilatory instability is controversial. Data from physiologic studies³⁹ have suggested that an isolated prolongation of circulatory time is unlikely to produce periodic breathing. On the other hand, human experiments²⁴ have suggested that the prolongation of circulation time, in concert with other physiologic perturbations ascribed to HF, as will be discussed subsequently, appears to modulate the ventilatory period.

An exaggerated ventilatory response to CO₂ (*ie*, increased controller gain) may be key to the development of CSA³⁸ and may explain why only a subset of HF patients is affected.⁴⁰ There is a significant positive correlation between the sensitivity to PaCO₂ and the AHI.⁴⁰ In the presence of this increased chemosensitivity, even small increments of circulatory time further contribute to ventilatory control instability.³⁸ Data from the last few years^{41,42} have suggested that impaired cerebrovascular reactivity to CO₂ may contribute to ventilatory overshoot in HF patients.

Implications of CSA in the HF Patient

Putative Mechanisms

CSA results in repetitive arterial oxyhemoglobin desaturations, such that a considerable portion of the night may be spent with an oxyhemoglobin saturation of < 90%.⁴³ Hypoxia and apnea may induce an increase in sympathetic neural drive due to the activation of sympathetic-excitatory chemoreceptors and the inactivation of sympathetic-inhibitory thoracic mechanoreceptors.⁴⁴ It is plausible that further increases in sympathetic neural activity in patients with HF, who are already in a state of adrenergic overactivity, are clinically important. Throughout central apnea, sympathetic nerve traffic increases progressively, causing modest but significant increases in BP.⁴⁵ Arousals from sleep are an additional stimulant for sympathetic activation and increased BP.⁴⁶ Some studies^{47,48} have shown that overnight urinary norepinephrine and daytime plasma norepinephrine concentrations are higher in HF-CSA patients compared to HF patients without CSA. Patients with HF-CSA have impaired autonomic CV homeostasis as manifested by depressed heart rate variability⁴⁷ and arterial baroreflex gain.⁴⁸

Hypoxia may induce pulmonary vasoconstriction⁴⁹ resulting in acute elevations in pulmonary arterial pressure.^{50,51} Whether repetitive episodes of hypoxemia secondary to CSA may be relevant in initiating or perpetuating pulmonary hypertension in patients with HF is not known.

Arrhythmias are a leading cause of death in HF patients. The higher mortality rate reported in CSA patients compared to HF patients without CSA may be plausibly attributed to arrhythmogenesis mediated by sympathetic activation and hypoxemia.⁵² A higher incidence of atrial fibrillation, ventricular ectopy, and nonsustained ventricular tachycardia has been demonstrated in patients with CSA and ischemic or idiopathic LV dysfunction.^{1,21,25}

Outcomes

Irrespective of these mechanisms, controversy remains as to whether CSA contributes to morbidity and mortality in HF patients or whether it is an epiphenomenon. Discrepant views are fueled in part by conflicting literature. Two articles^{15,53} from the late 1990s were among the first to identify an increased mortality risk associated with CSA in HF patients, particularly in those patients with more frequent disordered breathing events; those findings have been

bolstered by more recent observations.⁵⁴ Regression modeling suggests that CSA portends a poor prognosis independent of other known risk factors, including LVEF, peak exercise oxygen consumption, and indexes of elevated filling pressure. The risk of cardiac death also progressively rises as left atrial dimension increases (Fig 1), suggesting a potentiating interaction between CSA severity and structural heart disease.^{15,53} In addition, Cheyne-Stokes respiration identified during the daytime is recognized as a sign of poor short-term prognosis.^{55,56} The observation of periodic breathing during exercise also independently predicts cardiac mortality in HF patients who have been referred for cardiopulmonary exercise testing.⁵⁷ How the presence of periodic breathing during wakefulness and exercise relates to CSA has not been established, although some data⁵⁸ have suggested that the combined presence of daytime and sleep-related CSA may have additive effects on mortality.

On the other hand, some studies^{59,60} have shown no impact of CSA on mortality or other important outcomes, such as heart transplantation. In the largest study with the longest follow-up, Roebuck and colleagues⁵⁹ found that mortality after a median duration of 52 months of follow-up was unrelated to the presence of CSA. Mechanistically, the same group showed catecholamine levels to be unrelated to CSA in a group of subjects with HF.⁶¹

Why the results from studies describing similar populations and study methods are disparate is not entirely clear. One explanation is that the observational nature of the available (and relatively small) studies has inherent and often hidden biases, for which the best statistical regression methods are unable to fully control. In a disease as complex as HF, it may be too simplistic to assume that covariates such as age, gender, ejection fraction, and central AHI can fully account for outcomes. Furthermore, the varied measures used to grade the severity of CSA, such as central AHI, while readily obtained in a sleep laboratory, are not validated against important outcomes, as previously noted.¹⁰

Clinical Presentation and Diagnosis of CSA in HF

Whereas patients with OSA are often readily identifiable by excessive sleepiness, snoring, and obesity, there are no specific symptoms related to CSA, particularly in the context of coexisting HF. CSA has not yet been shown to contribute to the impaired vigilance measured in HF patients.⁶² Frequent polysomnographic arousals from sleep in patients with CSA may be expected to result in complaints of insomnia or poor sleep quality, and the hyperpneic phase of ventilatory oscillation may prompt paroxysmal nocturnal dyspnea. However, sleep-specific complaints are conspicuously infrequent in HF patients with CSA¹ as well as OSA.⁶³

A definitive diagnosis of CSA is made by polysomnography, although when and in whom this should be performed has not been established. The strongest indication for polysomnography in the setting of HF is to evaluate sleepiness and suspicion for OSA, which often coexists with CSA, and is more readily apparent on clinical grounds. Some short-term treatment trials of OSA have suggested beneficial effects on LV systolic function in patients with HF,^{63,64} while others have not.⁶⁵

There are no proven screening tools for the detection of CSA. While the systematic use of overnight oximetry in the diagnosis of OSA is controversial, and the evidence for its use in CSA patients is limited, oximetry has been shown to be a sensitive indicator of sleep-disordered breathing in the setting of a non-referral-based HF population,⁶⁶ though it does not discriminate well between central and obstructive apnea. Since the purpose of a screening tool is to identify at-risk patients who may benefit from an intervention, the role of the systematic use of oximetry in HF populations remains in question.⁶⁷

Treatment of CSA

Given the paucity of controlled clinical trials, it remains unclear as to whether the targeted treatment of CSA in the setting of HF is warranted for improvement in outcomes related to sleep quality, daytime function, or CV indexes. As such, there is currently no standardized approach to the management of CSA. This may relate to the fact that, until the recent introduction of specialized positive airway pressure devices, specific treatments for CSA were lacking. We outline herein the limited evidence for or against various treatment options.

Optimization of Medical Pharmacotherapy for Underlying HF—While systematic evidence is scant, the optimal treatment of HF may improve or even abolish CSA, probably because of improved hemodynamics. Complete resolution or attenuation of CSA has been described^{31,32} after the successful surgical treatment of severe mitral regurgitation in patients with CSA-HF. Hemodynamic improvement following medical treatment is often also associated with significant improvement of CSA (Fig 2, right, B).^{13,68,69} Hence, the optimization of medical therapy with a reduction of cardiac filling pressures should be the initial step in CSA treatment.

In patients with persistent CSA, despite receiving optimized medical therapy, alternative treatment of the breathing disorder may be considered, especially in those patients who have subjective or objective evidence of sleep fragmentation or poor sleep quality. Several therapeutic approaches have been shown to be potentially effective in attenuating CSA.

Nocturnal O₂ Supplementation—Oxygen supplementation during sleep has been utilized in CSA patients and theoretically may act by reducing ventilatory drive. Short-term studies^{70–73} (with follow-up ranging from 1 day to 4 weeks) have shown reductions in the number of central respiratory events and improvements in O₂ saturation. O₂ administered by a nasal cannula may reduce arousals from sleep^{70–73} and enhance exercise capacity,⁷¹ though not consistently.⁷⁴ In HF-CSA patients, nocturnal O₂ supplementation may also decrease daytime and overnight sympathetic activity, as measured by urinary catecholamine excretion.^{73,75} Unfortunately, improvement in the measurement of daytime symptoms and cognitive function in HF and CSA patients have not been found with O₂ therapy.^{69,71,76}

In HF patients who are in NYHA functional class III and IV,⁷⁷ crossover studies⁷² have demonstrated that single-night treatments with O₂ supplementation and nasal continuous positive airway pressure (CPAP) were equally effective in decreasing AHI, arousal index, and degree of desaturation. However, less than half of patients manifest a reduction of the AHI to < 15 events per hour. The data regarding the effects of nocturnal O₂ supplementation on long-term clinical and functional end points have yet to be seen.

It should be noted that, in short-term experiments,^{78,79} high concentrations of oxygen (100%) have been associated with adverse hemodynamic consequences in the setting of HF. The understanding of how a more conventional administration of supplemental oxygen in the outpatient setting, such as 1 or 2 L/min, impacts on these outcomes awaits long-term clinical trials.

Inhaled CO₂—Given the likely role of hypocapnia in the genesis of CSA in HF patients, as previously discussed, it follows that increasing CO₂ blood tensions by inhalation or by increasing ventilatory dead space may ameliorate ventilatory instability. In fact, small case series in patients with idiopathic CSA⁸⁰ as well as in those with CSA-HF⁸¹ have occasionally shown marked improvement in sleep-disordered breathing.^{34,35} However, the effects on AHI are not consistent between studies, and the treatment may actually prolong sleep-onset latency. Furthermore, there is evidence that this treatment could be deleterious due to the activation of the sympathetic nervous system.⁸² Experiments^{83,84} inducing hypercapnia in healthy

volunteers have resulted in increased pulmonary artery pressure and prolongation of the QT interval.

Theophylline—The administration of theophylline, a phosphodiesterase inhibitor, stimulates breathing by competing with adenosine (a known respiratory depressant).⁸⁵ Short-term oral administration of theophylline has improved sleep-disordered breathing and reduced associated arterial blood oxyhemoglobin desaturation in stable patients with HF.⁸⁶ The mechanisms remain unclear, since only subtherapeutic levels were reached and there was no evident improvement in ventricular function. Theophylline therapy has also been shown to improve CSA in the setting of normal LV function.⁸⁷ Safety concerns exist due to potential arrhythmogenesis with long-term theophylline treatment, due to an increase in sympathetic activity. However, a 2004 study⁸⁸ showed that, in contrast to healthy subjects, theophylline administered in the low therapeutic range does not increase sympathetic activity or heart rate in HF patients.

Positive Airway Pressure—In addition to the expected improvement in sleep quality from the treatment of possible coexisting OSA, short-term studies^{89,90} of CPAP treatment in CSA patients have demonstrated reductions in central respiratory events, O₂ desaturation, and the frequency of arousals. The mechanisms by which CPAP may improve CSA are unclear and may relate to the optimization of intrathoracic hemodynamics. CPAP decreases preload⁹¹ and afterload⁹² (probably by increasing intrathoracic pressure), and reduces right ventricular and LV end volumes. CPAP treatment of HF-CSA patients has also been associated with an improvement of LVEF,⁹⁰ reduced mitral regurgitation,⁹³ and lower plasma and urinary levels of norepinephrine.⁸⁹ CPAP therapy may also reduce the number of ventricular arrhythmias, paralleling the reduction in respiratory events.⁴³ A small, randomized, controlled trial⁹⁴ of 66 HF patients (with CSA, 29 patients; without CSA, 37 patients) seemed to provide further strong evidence for the efficacy of CPAP (Fig 3). Compared with no treatment, CPAP reduced the combined mortality-cardiac transplantation rate in HF patients with CSA, but not in HF patients without CSA, over a median follow-up period of 2.2 years.⁹⁴

The CANPAP,¹⁷ which is the largest randomized, controlled trial published to date evaluating the efficacy of CPAP treatment for patients with CSA, was terminated early when an interim analysis suggested that a difference in transplant-free survival time between groups was unlikely to be detected. At that point, in fact, there was a trend toward greater mortality in the CPAP-treated group. As suggested by the CANPAP¹⁷ investigators, it is possible that improvements in survival conferred by the increased use of β -blockers and spironolactone over the past several years may have rendered the trial underpowered. Importantly, CPAP treatment reduced the central AHI by only about 50% (from about 40 to 20 events per hour) and, while only 15% of subjects dropped out of the study, the mean duration of the nightly use of CPAP was about 4 h. The significance of modest improvements in secondary outcomes such as LVEF and exercise capacity in the CPAP-treated group, within the context of the primary findings, is unclear.

Adaptive servoventilation (ASV) has become available in the United States after an initial experience in Europe. In a small, crossover trial⁹⁵ conducted in 14 patients who were in NYHA class II–III, the use of ASV for 1 night provided an additional 83% reduction in central apneas when compared with treatment using nasal CPAP, and appeared to be better tolerated. Pepperell et al⁹⁶ demonstrated reductions in sleepiness and neurohormonal activation with a month of ASV use in HF-CSA patients. Based on a mean pretreatment LVEF of 37%, which did not appreciably change with therapy, this study may have represented a population with milder HF than those studied in previous interventional trials. While there is evidence for the sustained efficacy of and adherence to ASV out to 6 months,⁹⁷ more comprehensive, long-term studies will be needed to determine whether ASV yields benefits for CV outcomes or mortality.

Cardiac Pacing—An often-cited article⁹⁹ suggesting that there was a reduction of the AHI in patients with OSA achieved by atrial overdrive pacing was subsequently not confirmed by a number of larger, more rigorously conducted studies.^{98,99} However, a closer examination of the initial study results showed subtle reductions in recorded central apneas associated with pacing. It was subsequently suggested that increases in cardiac output, with reduced circulation time, may have enhanced ventilatory stability.

In contrast to atrial pacing, cardiac resynchronization therapy (CRT) [with the placement of an additional pacemaker to improve the mechanical sequence of left and right ventricular activation and contraction] may hold promise in treating CSA in selected HF patients with ventricular conduction delay. CRT has been shown to significantly decrease the number of apneas, to increase O₂ saturation, and to improve sleep quality (Fig 4).^{100,101} These beneficial effects are likely explained by the improvement of cardiac function associated with CRT. Larger-scale longitudinal studies designed to prove the long-term efficacy of atrial overdrive pacing or CRT, and consequent improvement in CV outcomes, are needed before such invasive and expensive tools are accepted as therapeutic options in HF patients with CSA.

Cardiac Transplantation—The normalization of heart function after cardiac transplantation may not always immediately abolish CSA, which, in one series,^{102,103} persisted for at least 6 months in 23% of patients after successful transplantation with normalized LV function. Though transplantation may lead to the abolition of CSA,¹⁰⁴ OSA develops in many cardiac transplant recipients,^{105,106} probably due to the weight gain associated with immunosuppression.

Conclusions

Despite advances in treatment, HF continues to be associated with excess morbidity and mortality. Although CSA is probably a consequence of LV dysfunction and HF, once established it may play an important role in HF progression, morbidity, and mortality. As yet, however, causality has not been proven.

Whether routine polysomnography is indicated in HF patients has been extensively debated.^{62,99} Given the epidemic of HF, the high cost of polysomnography, and the very limited data regarding options, indications, and benefits of CSA treatment, in the absence of significant sleep-related symptomatology, there does not appear to be a compelling argument for performing routine polysomnography in patients with HF.

The management of CSA should be tailored to individual patients, depending on symptoms referable to poor sleep quality and the possibility of coexisting OSA. Initial efforts should be directed at the optimization of medical therapy, with further treatment directed at symptomatic improvement in sleep quality and associated daytime symptoms.

The high prevalence of severe HF, evidence linking CSA to the activation of CV disease mechanisms, and increased mortality in HF patients with CSA all speak to the importance of CSA as a potential diagnostic and therapeutic priority. However, at virtually every level, the available data are circumstantial and observational. Before a targeted approach to CSA can be considered as part of routine evaluation and treatment, more robust studies of contemporary prevalence, prognostic implications and randomized interventional studies of therapeutic safety and outcomes are needed.

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Abbreviations

AHI	apnea-hypopnea index
ASV	adaptive servoventilation
CANPAP	Canadian Trial of Continuous Positive Airway Pressure for Heart Failure Patients with Central Sleep Apnea
CPAP	continuous positive airway pressure
CRT	cardiac resynchronization therapy
CSA	central sleep apnea
CV	cardiovascular
HF	heart failure
LV	left ventricular
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
OSA	obstructive sleep apnea

Figure 1.

Prognostic value of CSA in patients with HF. The risk of cardiac death (vertical axis) progressively increases with an increase in the AHI and in left atrial (LA) dimensions; patients who are at very high risk for fatal outcome can be identified by an AHI of > 30 events per hour and LA enlargement of > 25 cm². Reprinted from the study by Lanfranchi et al¹⁵ with permission.

Figure 2.

Influence of pulmonary capillary wedge pressure (PCWP) on central apnea in patients with HF. PCWP is elevated in HF patients with CSA compared with those with OSA or without apnea. *Left, A:* in patients with CSA, PCWP correlated with the frequency and severity of CSA. *Right, B:* in patients with CSA and high PCWP, intensive medical therapy for 1 to 6 months reduced both mean ($\pm$ SD) PCWP (from 29 ± 3 mm Hg [range, 20 to 38 mm Hg] to 22 ± 2 mm Hg [range, 17 to 27 mm Hg]; $p < 0.001$) and mean AHI (from 39 ± 8 events per hour [range, 7 to 62 events per hour] to 19 ± 5 events per hour [range, 1 to 31 events per hour]; $p = 0.005$). Arrows indicate the direction of change with time and therapy. Reprinted from the study by Solin et al¹³ with permission.

Figure 3.

Long-term effects of CPAP therapy in HF patients. Sin et al⁹⁴ reported a significant reduction of the combined mortality-cardiac transplantation rate (and therefore improved transplant-free survival time) in HF patients who were randomized to receive treatment with CPAP who complied with therapy compared to control subjects (relative risk reduction, 60%; 95% confidence interval, 2 to 84%; $p = 0.047$). From Sin et al⁹⁴ with permission. These findings are not supported by those of the larger CANPAP study.¹⁷

Figure 4. Effects of CRT on AHI in patients with and without CSA. Area under the dotted line = normal AHI (less than five events per hour); square = mean $\pm$ SD of all patients; triangle = mean $\pm$ SD of patients with CSA; octagon = mean $\pm$ SD of patients without CSA; star = $p < 0.005$ vs baseline. Reprinted from the study by Sinha et al¹⁰⁰ with permission.