Sleep Apnea and Heart Failure
Part II: Central Sleep Apnea

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In the first part of this 2-part review, we provided a synopsis of the cardiovascular effects of normal sleep and an overview of the diagnostic, pathophysiological, and therapeutic implications of obstructive sleep apnea (OSA) in the setting of heart failure (HF). In this second part, we turn our attention to central sleep apnea (CSA), commonly referred to as Cheyne-Stokes respiration. This breathing disorder has a strikingly higher prevalence in patients with HF as compared with the general population with normal left ventricular function, and when present appears to have adverse prognostic implications. Our objective in Part II of this review is to provide a broad perspective of the pathophysiological and clinical significance of CSA in HF.

Pathophysiology

CSA associated with Cheyne-Stokes respiration is a form of periodic breathing in which central apneas and hypopneas alternate with periods of hyperventilation that have a waxing-waning pattern of tidal volume. Figure 1 illustrates the proposed mechanisms that underlie periodic oscillations in ventilation in HF. Unlike OSA, CSA likely arises as a consequence of HF. Thus, the presence of CSA may alert the physician to the necessity of intensifying HF therapy. The current debate is whether CSA is simply a reflection of severely compromised cardiac function with elevated left ventricular filling pressures, or whether, for the same degree of cardiac dysfunction, CSA exerts unique and independent pathological effects on the failing myocardium. Although there are not yet sufficient data to resolve this controversy within the confines of this review, we will discuss evidence on both sides of this issue.

Most HF patients with CSA hyperventilate chronically because of stimulation of pulmonary vagal irritant receptors by pulmonary congestion[1–3] and enhanced central and peripheral chemosensitivity.[4,5] When patients lie flat, increased venous return from the extremities causes central fluid accumulation and pulmonary congestion that stimulates vagal irritant receptors in the lungs to elicit reflex hyperventilation. Central apnea is usually initiated during sleep by a further acute increase in ventilation and reduction in $PaCO_2$ that is triggered by a spontaneous arousal.[6] When $PaCO_2$ falls below the threshold level required to stimulate breathing, the central drive to respiratory muscles and airflow cease, and central apnea ensues.[7] Apnea persists until $PaCO_2$ rises above the threshold required to stimulate ventilation.[6,8]

In contrast to OSA, arousals are not required for the initiation of airflow at the termination of central apneas. Indeed, arousals frequently follow the resumption of breathing and thereby facilitate the development of oscillations in ventilation by recurrently stimulating hyperventilation and reducing $PaCO_2$ below the apneic threshold.[6] The length of the subsequent ventilatory phase is inversely proportional to cardiac output, reflecting delayed transmission of changes in arterial blood gas tensions from the lungs to the chemoreceptors. Accordingly, compared with subjects with CSA but without HF, those with HF have a longer ventilatory phase during which tidal volume rises and falls more gradually.[9] Thus, the prolonged circulation time in HF sculpts this Cheyne-Stokes respiratory pattern. However, among HF patients with and without CSA, no significant differences in lung to peripheral chemoreceptor circulation time or cardiac output have been observed.[2,9] Consequently, prolonged circulation time appears not to play a key role in initiating central apneas. Rather, its major influence is on the lengths of the hyperpneic phase and of the total periodic breathing cycle. Once triggered, the pattern of alternating hyperventilation and apnea is sustained by the combination of increased respiratory chemoreceptor drive, pulmonary congestion, arousals, and apnea-induced hypoxia, which cause oscillations in $PaCO_2$ above and below the apneic threshold.[4–6] Inhalation of a CO_2-enriched gas to raise $PaCO_2$ abolishes CSA.[8]

CSA elicits chemical, neural, and hemodynamic oscillations similar to those observed in OSA.[10–12] Apnea, hypoxia, CO_2 retention, and arousal provoke periodic elevations in sympathetic activity[13,14] (Figure 2). In patients with pulmonary congestion whose lung compliance is reduced, the increased inspiratory efforts between apneas will also lower intrathoracic pressure and increase left ventricular transmural pressure, and therefore afterload.[15] Potential relationships between CSA and markers of inflammation, oxidative stress, or vascular endothelial dysfunction have yet to be reported.

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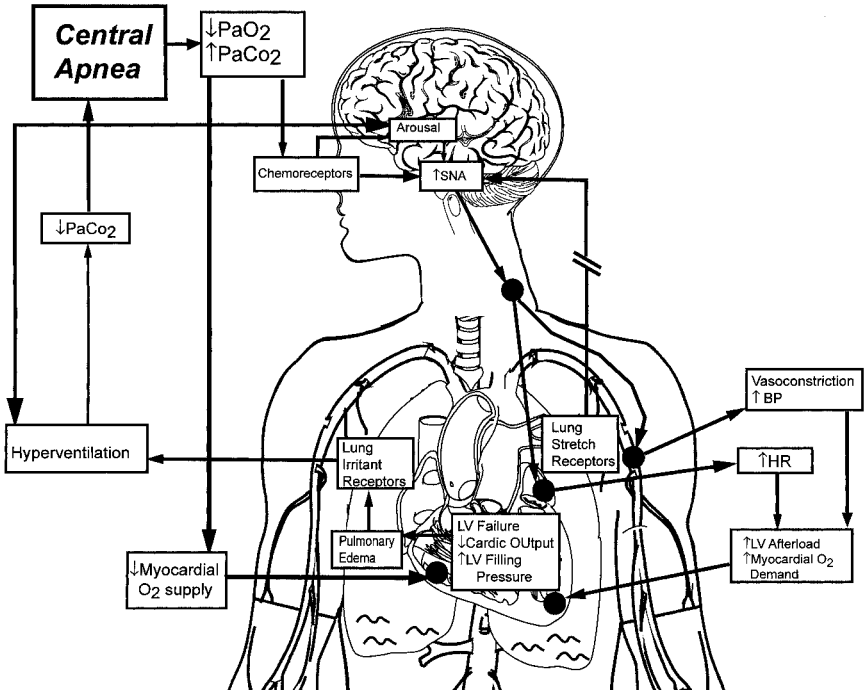

Figure 1. Pathophysiology of central sleep apnea in heart failure (HF). HF leads to increased left ventricular (LV) filling pressure. The resulting pulmonary congestion activates lung vagal irritant receptors, which stimulate hyperventilation and hypocapnia. Superimposed arousals cause further abrupt increases in ventilation and drive $PaCO_2$ below the threshold for ventilation, triggering a central apnea. Central sleep apneas are sustained by recurrent arousals resulting from apnea-induced hypoxia and the increased effort to breathe during the ventilatory phase because of pulmonary congestion and reduced lung compliance. Although central apneas have a different pathophysiology than obstructive apneas and are not associated with the generation of exaggerated negative intrathoracic pressure, they both increase sympathetic nervous system activity (SNA). The consequent increases in blood pressure (BP) and heart rate (HR) increase myocardial O_2 demand in the face of reduced supply. This chain of events contributes to a pathophysiological vicious cycle.

Central Sleep Apnea in Patients With Heart Failure

Epidemiology

There are few epidemiological studies in which the prevalence of CSA in patients with HF has been examined. The 2 largest studies involving 450 and 81 patients reported prevalences of 33% and 40%, respectively.[16,17] The principal risk factors for CSA are male sex, hypocapnia, atrial fibrillation, and increasing age, but not obesity (Table). For reasons that remain to be elucidated, CSA is rarely seen in women with HF.[16] This sex difference may be one explanation for the higher mortality rates suffered by men with HF.[18]

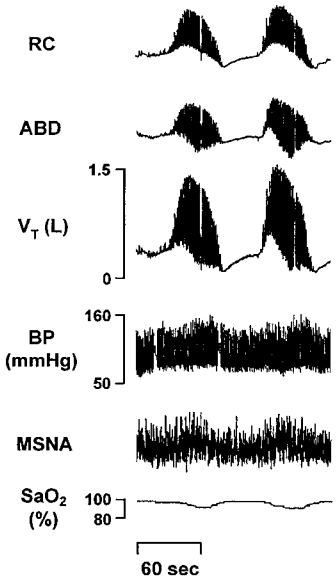

Figure 2. Recording of CSA with Cheyne-Stokes respiration in a patient with advanced heart failure and atrial fibrillation. Note typical waxing-waning pattern of tidal volume (V_T) during hyperpnea and dips in oxyhemoglobin saturation (SaO_2) associated with apneas. The central nature of apnea is indicated by the absence of rib cage (RC) and abdominal (ABD) motion. Normally, muscle sympathetic nervous activity (MSNA) is quiescent during sleep. However, in this patient, each cardiac cycle is accompanied by a burst of MSNA, indicating marked sympathetic activation. In addition, note the waxing and waning of MSNA burst amplitude in synchrony with the oscillation of V_T and blood pressure (BP).

Clinical Features

It is unclear whether there are symptoms specific to CSA. Patients who awake during the peak of ventilation after apnea may report paroxysmal nocturnal dyspnea.[19] Although sleep is fragmented by frequent arousals, only a minority of patients report habitual snoring and excessive daytime sleepiness.[17]

In some HF patients, OSA and CSA coexist. In such cases, there is a gradual shift from predominantly obstructive apneas at the beginning of the night to predominantly central apneas toward its end.[20] This change occurs in association with a prolongation in circulation time and a downward drift in PCO_2 toward the threshold for apnea. These observations

Independent Odds Ratios for Central Sleep Apnea in Patients With Heart Failure

	Adjusted Odds Ratio (95% Confidence Interval)
Male	4.33 (2.50 to 7.52)
Awake $PCO_2 \leq 38$ mm Hg	4.33 (2.50 to 7.52)
Atrial fibrillation	4.08 (1.74 to 9.57)
Age ≥ 60 years	2.37 (1.35 to 4.15)

Odds ratios are in comparison to patients without sleep-related breathing disorders. PCO_2 indicates partial pressure of CO_2.

Data are modified from Sin D, Fitzgerald F, Parker JD, et al. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med.* 1999;160:1101–1106.[16]

suggest that the repetitive surges in afterload induced by OSA, combined with increased venous return in the recumbent position, cause an overnight deterioration in left ventricular systolic function and an increase in left ventricular filling pressure that lead to hyperventilation and hypocapnia.[3,21–23] These unique observations raise the possibility of a spectrum of periodic breathing in patients with systolic HF that can manifest as predominantly OSA at one point in the time course of the disease and predominantly CSA at another, according to the underlying degree of cardiac dysfunction. They also raise the possibility that over months or years, the presence of OSA could predispose HF patients to CSA, which has more ominous implications for prognosis.

Implications for Progression of Heart Failure

The main clinical significance of CSA in HF is its association with increased mortality. Whether this is simply because Cheyne-Stokes respiration with CSA is a reflection of very poor cardiac function or whether its presence constitutes a separate and additive adverse influence on outcomes remains uncertain. However, where multivariate analyses have been performed to control for potentially confounding risk factors, CSA remained an independent risk factor for death or cardiac transplantation.[24,25] This pathological relationship may be attributed to marked neurohumoral activation, surges in blood pressure and heart rate, and a greater propensity to lethal arrhythmia induced by CSA.[10–12,26,27]

Unlike OSA, no negative intrathoracic pressure is generated during central apneas.[6,28] Therefore, its impact on afterload should be less than in OSA. Consequently, attention has focused primarily on the adrenergic effects of CSA as the mechanism for disease progression. Compared with HF patients matched for ejection fraction and other clinical characteristics but without sleep-related breathing disorders, those with CSA have higher urinary and circulating norepinephrine concentrations during both sleep and wakefulness.[26] The magnitude of these increases is proportional to the frequency of arousals from sleep and the degree of apnea-related hypoxia.

Very low-frequency oscillations in ventilation during periodic breathing disorders, such as CSA, cause heart rate to oscillate at the same frequency, such that heart rate falls during apnea and rises during hyperpnea.[10] This entrainment of heart rate by periodic breathing causes a shift in power spectral density of heart rate from predominantly high frequency during regular breathing (ie, respiratory sinus arrhythmia) to predominantly very low frequency ($<$0.5 Hz).[12,29–31] CSA entrains cyclical oscillations in heart rate and blood pressure through mechanisms similar to those described for OSA: hypoxia, arousals from sleep, and adrenergic activation.[10] Another likely mechanism is direct cyclic activation of cardiovascular sympathetic neurons by respiratory neurons in the brain stem.[12,32] Although such synchronized oscillations of heart rate with ventilation may optimize ventilation/perfusion matching and thereby maintain efficient gas exchange,[33] they are also associated with detrimental effects. The presence of periodic breathing, very low-frequency oscillations in heart rate, and enhanced peripheral chemoreceptor sensitivity in patients with HF are together associated with a higher mortality rate.[31,34]

Treatment of Central Sleep Apnea in Heart Failure

The principal reason for treating CSA is the potential to improve cardiovascular function, quality of life, and longevity.[25,35] At present, there is no consensus as to whether CSA should be treated, and if so, what optimum therapy of CSA in HF might be. Because CSA is to some extent a manifestation of advanced HF, the first consideration is to optimize drug therapy. Aggressive diuresis to lower cardiac filling pressure along with angiotensin-converting enzyme inhibitors and β-blockers may reduce the severity of CSA.[2] In some cases, however, metabolic alkalosis arising from diuretic use may predispose to CSA by narrowing the difference between ambient $PaCO_2$ and the $PaCO_2$ threshold for apnea.[36–38] β-adrenergic blockade may also reduce the adverse effects of excessive sympathetic activation that is associated with CSA. Should CSA persist despite aggressive medical therapy for HF, other interventions may be considered.

Nocturnal supplemental O_2 has been shown to abolish apnea-related hypoxia, alleviate CSA, and decrease nocturnal norepinephrine levels over periods of 1 night to 1 month.[39–41] Its administration has also been associated with improvements in maximum oxygen uptake during a graded exercise test.[42] The effects of supplemental oxygen on cardiovascular endpoints over more prolonged periods have not been assessed. However, O_2 has been reported not to cause improvements in cardiac function or quality of life over 1 month.[41] In a 5 day trial, theophylline reduced the severity of CSA but did not cause any improvements in right or left ventricular ejection fraction, quality of life, or clinical outcomes.[43] The potential adverse consequences of theophylline's inotropic and arrhythmogenic effects in patients with advanced HF preclude its long-term use at the present time.

Various forms of noninvasive positive airway pressure, including continuous positive airway pressure (CPAP), bilevel and adaptive pressure support servo-ventilation have been shown in randomized trials to alleviate CSA in HF patients over periods of 1 day to 3 months.[35,44] However, thus far, the only intervention whose effects on cardiovascular outcomes have been evaluated is CPAP. In patients with HF and elevated left ventricular end-diastolic pressure who were studied while awake, CPAP decreases left ventricular afterload by increasing intrathoracic pressure,[15] augments stroke volume,[45] and reduces cardiac sympathetic activity.[46] It also decreases preload by impeding venous return and reducing right and left ventricular end-diastolic volume.[47] In patients with CSA, short-term application of CPAP also reduces the frequency of ventricular ectopic beats.[48] Randomized trials of 3-months' duration have demonstrated that nightly application of CPAP increases left ventricular ejection fraction, reduces mitral regurgitation and nocturnal and daytime sympathetic nervous system activity, and improves quality of life.[26,35,49] Of 29 patients with HF and CSA who participated in a randomized trial of CPAP, those who complied with this intervention experienced a significant reduction in the combined rate of mortality and cardiac transplantation over a

5-year period.[25] A larger, long-term, multicenter trial to test the effects of CPAP on the combined rate of mortality and cardiac transplantation in HF patients with CSA (the CANadian Positive Airway Pressure trial for patients with congestive heart failure and central sleep apnea [CANPAP]) is presently underway.[50]

In a recent randomized trial, the effect of atrial overdrive pacing on sleep apnea was tested.[51] This study involved a group of patients with no history of HF who had cardiac pacemakers implanted because of symptomatic bradyarrhythmias. Sleep studies were performed, and among those found to have sleep apnea, the pacing rate was increased to 15 bpm above the intrinsic heart rate. This overdrive pacing led to a reduction in the frequency of both central and obstructive apneas by approximately 50%. Because these effects were studied only over a single night, clinical outcomes were not assessed and the mechanism responsible for this effect was not determined. One possibility is that some of these patients may have had pulmonary congestion while in the recumbent position owing to their bradyarrhythmias, or possibly diastolic dysfunction. This may have stimulated hyperventilation and predisposed to CSA.[2,3] Overdrive pacing could have augmented cardiac output and relieved pulmonary congestion, thereby dampening respiratory controller gain, reducing ventilation, increasing $PaCO_2$, and reducing central apneas and hypopneas. This mechanism would explain a reduction in central but not obstructive events. If upper airway edema accumulated while the patient was in the recumbent position,[52,53] augmentation of cardiac output by overdrive pacing could have alleviated this edema and increased pharyngeal lumenal dimensions. Although the observations of Garrigue et al[51] have generated considerable interest, their implications for the treatment of sleep apnea in general and for sleep apnea in patients with HF in particular are not clear. Further studies will be required to determine the mechanism(s) by which pacing achieves those effects, and to determine whether this approach exerts sustained benefits in selected patients with HF and bradyarrhythmias.

Indications for Sleep Studies in Heart Failure

Indications for sleep studies in patients with HF have not been definitively established. Because the pretest probability of sleep apnea in such patients is approximately 50%[16,17] and treatment may provide at least short-term improvements in cardiovascular function and relief of some of the symptoms of HF,[24,25,35,41,42,54,55] an argument could be made for the liberal application of this test in the HF population. However, until a clearer picture emerges of how treatment of sleep apnea influences cardiovascular outcomes, polysomnography should be reserved for those patients with the highest likelihood of sleep-related breathing disorders. In addition to risk factors listed in Table 2 of Part I and the Table in Part II, other factors that should raise suspicion of sleep apnea and prompt consideration of polysomnography include a history of loud snoring, witnessed apneas during wakefulness or sleep, paroxysmal nocturnal dyspnea, restless sleep, morning headaches, excessive daytime sleepiness, and insomnia. Until other methods, such as home ambulatory monitoring, are validated for this purpose, in-laboratory polysomnography remains the diagnostic tool of choice.

Conclusions

Sleep-related breathing disorders are common in HF, and the pathophysiologies of these 2 conditions are intimately linked. Nevertheless, the clinical implications of these breathing disorders are not widely recognized and are seldom taken into account in the evaluation and management of HF. The conventional approach to the evaluation and management of HF may therefore need to be modified in view of the growing body of evidence that the acute and chronic mechanical, hemodynamic, autonomic, and chemical effects of OSA and CSA place patients with HF at increased risk of accelerated disease progression. Indeed, CSA is now known to be an independent risk factor for diminished life expectancy in HF. Standard pharmacological approaches to HF may have little or no impact on these breathing disturbances and their consequences. However, promising results of small scale randomized trials of therapy aimed at relieving these sleep-related breathing disorders suggest that this strategy has the potential to improve cardiovascular outcomes in patients with HF.[24,25,35,41,42,54,55] More intensive investigation of potential diagnostic algorithms and therapies, including large scale randomized controlled clinical trials, will be required to test these hypotheses and determine the optimal approach to such patients.

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