

Sleep Disordered Breathing in Patients with Heart Failure: An Update

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Introduction

Sleep disordered breathing, including Cheyne Stokes Breathing-Central Sleep Apnea (CSB-CSA) and Obstructive sleep apnea hypopnea syndrome (OSAHS), is common among patients with heart failure (HF) and may occur in as many as 82% of patients.¹ These conditions may occur individually or in combination and may result in exacerbation of cardiovascular disease, increased mortality, and consequences for daytime functioning, and quality of life. The purposes of this article are to discuss the epidemiology, pathophysiology, and consequences of sleep disordered breathing as relevant to HF and to review the clinical management of heart failure patients who have sleep disordered breathing.

Cheyne-Stokes Breathing/Central Sleep Apnea

Cheyne-Stokes breathing/Central Sleep Apnea (CSB-CSA) is a condition associated with waxing and waning respiration during sleep, with periods of central apnea, or cessation of breathing. Periodic breathing is a term that denotes waxing and waning patterns of tidal volume with hypopneas, rather than apneas. Estimates of the prevalence of CSB-CSA among patients with systolic HF have generally ranged from 27 to 63%.¹⁻⁵ However, more recently, Ferrier and colleagues⁶ reported a rate of 15% in stable systolic HF patients managed in a HF disease-management program, and Redeker and colleagues⁷ found a rate of 9% in mixed systolic and diastolic patients. Similarly, Rao et al.⁸ found a rate of sleep disordered breathing of 27% in stable HF patients, but

did not differentiate between Cheyne-Stokes breathing and obstructive apnea. Variability in rates may be due to differences in demographic characteristics (e.g., gender, age), the clinical characteristics of the patients studied (e.g., ejection fraction and medications), estimation of rates in patients referred to sleep clinics vs. the general population of HF patients (referral bias) and sensors and criteria used to evaluate sleep disordered breathing. Given the fact that the studies showing reduced prevalence of CSB-CSA are more recent, these differences may reflect changes in treatment patterns favoring improvement.

Risk factors for CSB-CSA appear to be male gender, hypocapnea, and atrial fibrillation,² but low ejection fraction has also been implicated.⁹ Differences in prevalence may also reflect changes in treatment, as Cheyne Stokes Breathing is associated with changes in fluid congestion, and recent evidence suggest that use of beta blockers may decrease it.¹⁰ These findings suggest that current evidence-based approaches to managing HF may decrease rates of CSB-CSA, although further research is needed to support this inference.

CSB-CSA may confer higher risk for ventricular tachycardia,¹ and some research findings have found that it contributed to mortality, especially in men.¹¹⁻¹³ Others found no difference in one or 2 year survival¹⁴ or at 52-month follow-up.¹⁵ It is possible that the higher levels of mortality associated with CSA-CSB found in some studies may reflect the greater association of poorer cardiac status with CSB-CSA.¹²

CSB-CSA is a respiratory abnormality that results from increased ventricular filling pressure, pulmonary congestion, and hyperventilation due to vagal stimulation of pulmonary irritant receptors, factors in HF pathophysiology. Hyperventilation secondary

to these abnormalities leads to reductions in PaCO₂, which, in turn contribute to central apneas due to the loss of the respiratory stimulus of CO₂. Low cardiac output and prolonged circulation time contribute to the waxing-waning pattern of CSB-CSA. CSB-CSA results in intermittent hypoxia, frequent arousals, sympathetic nervous system activation, and surges in blood pressure and heart rate. These cardiovascular alterations may, in turn, exacerbate the pathophysiologic processes associated with HF.^{16, 17} The cardiorespiratory changes result in frequent brief arousals during lighter states of sleep that prevent its progression into deeper stages.

Sleep deprivation resulting from CSB-CSA may have functional and quality of life consequences, such as excessive daytime sleepiness (EDS), poor cognitive function, disturbed mood, poor functional performance, and self-care deficits, although research findings are somewhat conflicting.¹⁸ Forty-four percent of systolic HF patients had EDS, compared with 18% of a comparison group who did not have HF.¹⁹ In contrast, groups of HF patients were no sleepier, as evaluated by self-report than community residing adults, but were sleepier when evaluated with objective tests.²⁰ Recent evidence suggests that SDB did not confer additional risk of EDS in HF patients.^{21, 22} HF patients are at-risk for poor cognitive function,²³ and sleep deprivation may worsen it, yet cognitive function was not associated with CSB-CSA.²⁴ Some researchers have found that CSB-CSA was associated with poorer New York Heart functional classification, decreased six minute walk test performance, and other functional consequences,^{5, 20, 25, 26} while others found no associations of SDB with self-reported physical function,^{21, 22} fatigue,²¹ or six minute walk.²⁷ Although the relationships between SDB and symptom and functional consequences are not clear-cut, there is sufficient evidence suggesting that the potential

functional and quality of life consequences should be considered in clinical evaluation of HF patients. Riegel and colleagues^{28,29} found that excessive sleepiness in people with HF contributed to decrements in self-care. Therefore, HF may have an impact on the self-care/self-management of people with HF. These issues are discussed in detail in a forthcoming paper.¹⁸

Obstructive Apnea –Hypopnea Syndrome

OSAHS is a respiratory disturbance that results from repetitive intermittent partial or complete obstruction of the upper airway during sleep. It is defined as upper airway instability that is associated with snoring, reduction in airflow (hypopnea) or complete cessation of airflow (apnea).³⁰ Like CSB-CSA, it is associated with excessive daytime somnolence because of the frequent brief arousals from sleep. These respiratory events vary in frequency and may include snoring, hypopnea, and complete cessation of breathing (apnea), or a combination of events. Nocturnal oxygen desaturation accompanies the respiratory events. It is usually, but not always, associated with loud snoring. Persons with OSAHS may report gasping or snorting during sleep and dry mouth and/or headache upon awakening. Bed partners may observe apneic events.

Epidemiological data suggest that OSAHS occurs in 4% of American middle-aged adults population.³¹ However, it is believed that OSAHS is under-diagnosed, and estimates of prevalence vary based on measurement and cut-off scores on diagnostic criteria. Studies of HF patients suggest that OSAHS occurs in as 11-53% of systolic and mixed groups of people with class II-IV HF.^{1, 6, 32} OSAHS appears to be the most prevalent form of sleep disordered breathing among diastolic HF patients, occurring in 55%,³³ although data are sparse. Chan and colleagues³³ found that more severe sleep

disordered breathing was associated with poorer diastolic function. Unlike CSB-CSA which is thought to be a consequence of HF, OSAHS may be one of the pathways to HF through its contributions to hypertension.

There is a growing body of epidemiological and clinical research evidence for a link between OSAHS and hypertension and cardiovascular morbidity and mortality. However, a causal relationship has not yet been identified. Two large-scale studies provide the most powerful epidemiological evidence to date for the linkage between OSAHS and cardiovascular morbidity and mortality. Researchers for the Wisconsin Sleep Cohort Study³⁴ found that there was a linear increase in blood pressure as the apnea-hypopnea index (AHI) (total number of apneas and hypopneas/hour) increased in a sample of 1,060 employed men and women between the ages of 30 and 60 years. Longitudinal follow-up of 760 of these participants demonstrated that there was a dose-response relationship between sleep disordered breathing at baseline and the development of hypertension four years later.³⁵

The Sleep Heart Health Study (SHHS) is a large multi-center community based, prospective study designed to evaluate the linkages between OSAHS and cardiovascular morbidity and mortality. Data obtained from 6,132 middle-aged men and women revealed that mean systolic and diastolic blood pressure and prevalence of hypertension increased significantly at higher levels of the apnea-hypopnea index. The odds ratio for hypertension, comparing the highest AHI level (>30/hour), compared with the lowest (<1.5/hour) was 1.37 (confidence interval = 1.03 – 1.83, $p < .005$). There was also a statistically significant relationship between oxygen saturation of less than 90% and hypertension.³⁶ SHHS participants with higher levels of the AHI were 2.38 times more

likely to have HF than those with the lowest AHI levels. Although AHI was also associated with coronary disease, the likelihood of having HF was higher at the highest levels of AHI.³⁷ Although these data are not causal, they strongly implicate sleep disordered breathing as a pathway to HF.

The primary pathophysiological explanations for the linkages between OSAHS and hypertension include hypoxemia, increased respiratory effort, and cortical arousal associated with respiratory events. Patients with OHS have higher levels sympathetic nervous system activation, as measured by elevated circulating catecholamines and skeletal muscle sympathetic nerve activity that may result from obstructive respiratory events and cortical arousals. These changes may lead to higher peripheral vascular tone and subsequent hypertension.

There is evidence that CSB-CSA and OSAHS co-exist among HF patients and the predominance of either conditions may change over the course of a night. Tkacova and colleagues³⁸ found that obstructive apneic events decreased and central apneic events increased among HF patients with both forms of sleep disordered breathing over the course of a night. These changes appeared to correspond to cardiovascular deterioration over the course of the night associated with increased circulation time and decreasing PCO₂. The nature of may also change between nights, alternating between primarily obstructive and central apnea.³⁹ Co-occurrence of OSAHS and CSB-CSA is referred to as complex sleep disordered breathing and is associated with highly unstable sleep and unmasking of CSA-CSB with CPAP treatment.⁴⁰

Clinical Evaluation of Sleep Disordered Breathing

Given the high prevalence of sleep disordered breathing among patients with HF, assessment of sleep and sleep disorders and their consequences should be an important component of routine clinical care. Non-specific signs and symptoms associated with both CSB and OSAHS include excessive daytime sleepiness, cognitive dysfunction, fatigue, and disturbed mood. Since fatigue and activity intolerance are almost universal experiences for patients with HF, it is important to consider the potential contributions of sleep disordered breathing to these problems. Excessive daytime sleepiness presents safety concerns, as it may have a negative impact on reaction time, decision making, and safe operation of machinery and motor vehicles. Therefore, patients who are suspected of being excessively sleepy should be cautioned about behaviors that may be a safety hazard. Daytime performance usually improves with effective treatment of sleep disordered breathing.

Seventy percent of systolic and diastolic HF patients report disturbed sleep.^{19, 41} It is likely that a significant proportion of this group may have sleep disordered breathing, given that it is associated with frequent brief nocturnal arousals. However, disturbed sleep is also characteristics of insomnia, another common sleep disorder. HF patients also report prolonged sleep latency (difficult with falling asleep) and early morning awakenings that may be more characteristics of insomnia. Therefore, factors other than sleep disordered breathing that may contribute to these problems should be addressed. Some of these may include medications (e.g., diuretics), nocturnal pain or dyspnea, poor sleep habits that result in sleep deprivation, and environmental factors. Depression and/or anxiety may also contribute to insomnia.⁴² Periodic limb movement disorder (PLMD) has also been found to be more common in a small group of male HF patients compared to a

healthy comparison group, and may contribute to sleep fragmentation,⁴³ and restless leg syndrome (RLS) is associated with cardiovascular disease.⁴⁴ Therefore, the presence of RLS periodic limb movements should also be considered.

Both CSB and OSAHS result in apneas during sleep that may be observed by the bed partner. However, unlike CSB, OSAHS is usually associated with loud snoring and may be associated with choking or gagging, or snorting. In the absence of a bed partner, however, the HF patient may not be aware of these events.

The likelihood of CSB-CSA is thought to be increased in the presence of low ejection fraction, inadequate HF medication management, and atrial fibrillation. Obesity, a large neck, smoking, consumption of alcohol before bedtime, and use of sedatives that reduce upper airway dilator muscle function contribute to risk of snoring, apneas and hypopneas. Among HF patients, obesity was associated with OSAHS in men, while more advanced age was associated with OSAHS in women.²

Indications for referral of HF patients for specialized sleep evaluations are the subject of ongoing discussion. However, patients who snore and demonstrate excessive daytime sleepiness, or those who have witnessed apneas should be referred for polysomnographic evaluations. Those who complain of frequent nocturnal arousals that are unexplained by environmental factors, disturbed mood, or nocturnal discomfort (e.g., pain or nocturia) are also candidates for evaluation in a sleep laboratory setting. Those HF patients who have received optimal medical management and are symptomatic and/or continue to remodel should also be referred for sleep evaluation.

The gold standard for evaluation of sleep disordered breathing is nocturnal polysomnography (NPSG) conducted in a sleep laboratory. Polysomnography consists of

electro-encephalography, chin electromyography, and electro-oculography to evaluate sleep duration, sleep latency, and sleep stages. Central or obstructive apneas and hypopneas are diagnosed by through measurement of effort (chest and abdominal expansion), air flow or pressure (thermistor or nasal cannula), and oxygen saturation (pulse oximetry). Continuous ECG is also obtained, thereby allowing evaluation of the association of dysrhythmias with respiratory events. Other physiological parameters can be measured, such as periodic limb movements, depending on the purposes of the sleep study. Excessive daytime sleepiness can be evaluated by self-report, using such instruments as the Epworth Sleepiness Scale or a Multiple Sleep Latency Test, an objective measure of EDS.

A clinical PSG report includes information on the duration of sleep, sleep stages, sleep latency (time from lights out until sleep onset), and sometimes, an evaluation of the frequency of brief nocturnal arousals. Essential to the diagnosis of sleep disordered breathing is the Apnea Hypopnea Index (AHI) or Respiratory Index (RDI) (sum of the apneas and hypopneas/hour of sleep) and oxygen saturation. Apneas and hypopneas will also be described as central or obstructive depending on their association with respiratory effort (Central apneas and hypopneas are not associated with effort; obstructive apneas are associated with effort).

There has been great interest in the application of home sleep studies for the assessment of sleep disordered breathing, particularly in settings where PSG is not readily available. Such monitors fall into the following classifications: 1) devices that are capable of full portable PSG; 2) devices that permit modified portable sleep apnea testing (at least 2 channels of respiratory movement or respiratory movement and airflow, heart

rate or ECG, and oxygen saturation; and 3) devices that obtain continuous recordings of oxygen saturation or airflow. These devices may be used in an attended (laboratory) or unattended (home) setting. An evidence-based review concluded that their use is not recommended for patients with HF at this time, as the validation studies have been conducted primarily on patients without comorbid illness, and these studies have focused primarily on screening for OSAHS and not CSB-CSA.⁴⁵ A more recent study found poor correlations between polysomnographic measures of sleep and sleep disordered breathing and a commercially available portable device designed to measure respiratory variables associated with SDB.⁴⁶ Therefore, use of these devices is not indicated for HF patients at this time.

Treatment of sleep disordered breathing

There is no clear-cut indication for treatment of CSB-CSA, but treatment should be considered when sleep is fragmented and non-restorative, there are frequent nocturnal desaturations, or the patient suffers from excessive daytime sleepiness. Improvement of cardiac output through optimal medical management appears to improve CSB. Although there have been no longterm clinical trials, the application of nocturnal oxygen has been shown in small studies to reduce nocturnal periodic breathing. Nocturnal oxygen reduced apneas, periodic breathing,⁴⁷ and frequency of oxygen desaturations during sleep,⁴⁸ but did not improve ventricular function or sleep architecture.⁴⁷ Beta blocker drugs also reduce central apneas,^{10,49} but there is also some evidence that their use may contribute to nightmares.⁵⁰ Therefore, there may be some negative effects on sleep.

There have been several recent reports of the promising effects of cardiac resynchronization therapy (CRT) on ejection fraction, apnea hypopnea index, oxygen

saturation and sleep quality.⁵¹⁻⁵³ These effects are thought to be due to the effects of CRT on circulation time. Therefore CRT may be beneficial in some patients.

CPAP is thought to be particularly beneficial for HF patients because of the effect of increasing intrathoracic pressure, reduction of cardiac afterload and preload and reducing venous return to the right atrium. CPAP reduces apneas and hypopneas and improves left ventricular function, norepinephrine levels, nocturnal oxygen saturation and functional performance in people with CSB-CSA.^{54, 55} Its beneficial effects appear to occur primarily through the improvement of periodic breathing. In a randomized study of HF patients with and without periodic breathing there were improvements in ejection fraction and mortality only in those patients who had periodic breathing.⁵⁵ However, evidence obtained from the Canadian Positive Airway Pressure (CANPAP study,⁵⁶ a randomized clinical trial of the effects of CPAP only on CSB-CSA, demonstrated that there was no improvement in the treatment group at 18-month follow-up, despite early trends toward improvement in the treatment group. Therefore, use of CPAP is not currently recommended for HF patients who have only CSB-CSA, although these findings have generated a great deal of controversy.^{49, 57} One interesting outcome of the CANPAP trial was the low accrual of patients, a factor that may be associated with reduce levels of CSB-CSA with the advent of beta blocker therapy. It is also important to note that the CANPAP findings do not apply to HF patients who have OSAHS or complex sleep disordered breathing, as these patients were not included in the study.

Treatment of OSAHS is directed at reducing obesity, a primary risk factor, and maintaining a patent airway during sleep. Nasal continuous positive airway pressure (NCPAP) serves as a splint that prevents the collapse and narrowing of the airway the

airway throughout the night. CPAP improves apneas and hypopneas in HF patients with OSAHS, but data on cardiovascular outcomes are conflicting.⁵⁸ CPAP improved left ventricular function in two studies that were not placebo-controlled.^{59, 60} However, only one study found improvements in blood pressure.⁵⁹ Reducing the use of alcohol and sedating medications that reduce the function of the upper airway dilator muscles is beneficial in improving OSAHS, but little is known about the impact of these strategies in HF patients. Patients whose OSAHS is more severe in the supine position may benefit from sleeping in a lateral position. Dental appliances that cause mandibular advancement and tongue protrusion are successful about 50% of the time. Surgical treatments such as laser-assisted uvulopalatoplasty and reduction of the tongue volume are generally effective in reducing snoring, but are not as effective as NCPAP or weight loss in reducing obstructive events. For a detailed, but concise description of evaluation and management of the patient with OSAHS refer to the article by Sanders and Redline.⁶¹

Adherence to NCPAP is a significant concern, particularly since nightly use for the duration of the sleep period is necessary for a positive outcome. Patients may experience discomfort due to the mask and have difficulty tolerating the nightly treatment. Some patient education is usually provided in the sleep laboratory at the time of the mask fitting and CPAP titration. However, patient education and coaching should be continued in the heart failure clinic. Ongoing evaluation of any problems, misperceptions, and response to CPAP treatment is critical to assuring a positive outcome. This may be especially relevant to HF patients and their caregivers, who must incorporate the OSAHS treatment into an already complex self-management regimen. Outcomes assessment should include improvements in daytime functioning, including

mood, cognition, and sleepiness, as well as self-reports of improved sleep. Despite growth in knowledge about CPAP adherence over the past several years, little is known about levels of adherence in these patients are strategies to enhance it.

There has been exponential growth in the science and the awareness of heart failure clinicians about the importance of sleep and sleep disordered breathing over the past several years. Clearly evaluation and management of these conditions needs to be a component of ongoing disease management for heart failure patients.

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