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Recognition and Management of Sleep-Disordered Breathing in Chronic Heart Failure

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Abstract

It is increasingly recognized that sleep-disordered breathing (SDB) is a common modifiable risk factor for cardiovascular disease with significant impact on morbidity and potentially mortality. SDB is highly prevalent in patients with systolic or diastolic heart failure. A high index of suspicion is necessary to diagnose SDB in patients with heart failure because the vast majority of affected patients do not report daytime symptoms. Recent clinical trials have demonstrated improvement in heart function, exercise tolerance, and quality of life after treatment of SDB in patients with heart failure. Accumulating evidence suggests that treatment of SDB should complement the established pharmacologic therapy for chronic heart failure. However, mortality benefit has yet to be demonstrated.

Keywords

Obstructive sleep apnea; Central sleep apnea; Chronic systolic heart failure; Respiration; Positive airway pressure

Introduction

Sleep-disordered breathing (SDB), commonly referred to as sleep apnea, denotes an abnormal respiratory pattern or reduction in gas exchange during sleep. The most common types of respiratory events are apneas and hypopneas. Apnea refers to a cessation of upper airway flow, whereas hypopnea is a reduction in airflow. Apneas and hypopneas are further classified into obstructive and central. The hallmark of obstructive events is upper airway obstruction with continued thoracoabdominal respiratory effort against the narrowed or closed airway. Central events result from periodic loss of central respiratory drive with cessation or decrease in both airflow and effort. Patients with SDB may experience both

obstructive and central events and therefore, their disorder is classified according to the predominant pattern. SDB is diagnosed when a patient has more than five apneas or hypopneas per hour, or an apnea hypopnea index (AHI) more than five events per hour. Obstructive sleep apnea (OSA) is diagnosed when more than half of the events are obstructive in etiology. Central sleep apnea (CSA) is diagnosed when more than half of the events are central. The nocturnal polysomnography (PSG) is the reference standard test for the diagnosis and characterization of SDB. Sleep and arousal are monitored by electroencephalography, electrooculography, and electromyography. Concomitant monitoring of airflow, oxygen saturation, and chest wall movements are used to quantify and characterize the respiratory events (Fig. 1).

A periodic pattern of breathing with crescendo-decrescendo change in effort followed by subsequent CSA is described as Cheyne–Stokes respiration (CSR). This morphological pattern of ventilation can occur during restful wakefulness and exercise in patients with heart failure as well as during sleep. CSR is the most common morphology of CSA seen on PSG in patients with heart failure.

SDB is highly prevalent in patients with systolic and diastolic heart failure. However, it remains largely unrecognized and untreated because the vast majority of affected patients do not report daytime symptoms such as excessive sleepiness. SDB alters the cardiovascular structure and function through acute hemodynamic perturbations, neurohormonal activation, oxidative stress, and inflammation. OSA likely contributes to the progression of heart failure, whereas CSA often results from advanced heart failure. Recent studies have demonstrated improvement in exercise tolerance, cardiac function, and quality of life after treatment of OSA in patients with heart failure [1]. Accumulating data suggest that OSA treatment should complement the well-established evidence-based pharmacologic therapy for patients with chronic heart failure [1, 2•]. CSA is a negative prognostic indicator in heart failure. Small trials have demonstrated that treatment of CSA with novel pressure devices may improve left ventricular ejection fraction (LVEF) [3].

This review will discuss the epidemiology and impact of OSA and CSA on the heart failure syndrome. We will review recent advancements in SDB surveillance strategies and current recommendations in OSA and CSA management for patients with heart failure.

Epidemiology and Risk Factors for Sleep-Disordered Breathing in Heart Failure

The prevalence of OSA among middle-aged adults in the general population is estimated at 9% to 24% [4]. Obesity, male sex, African-American ethnicity, and age greater than 60 years are strong risk factors for OSA. Other risk factors for OSA in the general population include craniofacial and upper airway soft tissue abnormalities, cigarette smoking, nasal congestion, and heredity. These risk factors remain relevant and applicable in patients with heart failure. CSA has been estimated to occur in less than 4% of the general population, but is most commonly encountered in patients with heart failure.

Studies in patients with chronic systolic heart failure confirm a far higher prevalence of SDB than that in the general population, approaching 60% of patients [4, 5, 6•]. Both OSA and CSA are more common in patients with heart failure. It is sometimes noted that heart failure is the most important risk factor for both types of SDB.

OSA causes hypertension [7, 8], accelerates coronary artery disease [9], and worsens other cardiovascular diseases [10], all of which lead to heart failure. Therefore, it is not surprising that OSA is an independent risk factor for heart failure in middle-aged men [11•]. The

increasing incidence of obesity, a known risk factor for both OSA and heart failure, lends further explanation to the high prevalence of OSA in patients with heart failure. The prevalence of OSA in diastolic heart failure is less known, but recent reports suggest a comparable prevalence to that seen in systolic heart failure. Chan et al. [12] reported OSA in 50% of patients with isolated diastolic heart failure.

CSA is common in older males with advanced systolic heart failure [2•] and is a poor prognostic indicator in these patients [13]. Earlier studies estimated the prevalence of CSA in patients with heart failure at nearly 40% [5, 14]. This estimate recently has been called into question by multiple studies demonstrating higher prevalence of OSA than CSA in patients with chronic [15] and decompensated [6•] heart failure. Earlier studies evaluated only [5] or predominantly [14] elderly males with severe systolic heart failure. However, women and patients with diastolic or mild systolic dysfunction represent a large portion of the heart failure population [16]. More recent trials have included a higher percentage of women (a more representative population) and demonstrated a lower prevalence of CSA [15]. Along with the increasing incidence of obesity in the general adult population, changes in pharmacologic management of chronic heart failure may explain the increasing prevalence of OSA compared to CSA in recent studies [17].

Mechanism of Sleep-Disordered Breathing in Heart Failure

The mechanism of OSA is similar in patients with heart failure compared to the general population. However, heart failure may contribute further to upper airway instability and, subsequently, OSA via its effect on cervical venous congestion. The increased filling pressure, especially when patients assume the supine position during sleep, appears to contribute to increased airway collapsibility [18]. The contribution of this mechanism to the high prevalence of OSA in patients with heart failure is not well established. Likely, it represents one factor among many that contribute to the pathogenesis of OSA in heart failure, including obesity and aging. The increased cardiac filling pressure associated with positional shift also may contribute to the occurrence of CSA as discussed below. It is likely that this fluid shift is responsible for the significant overlap between obstructive and central events in a patient with heart failure and the shift between OSA and CSA on repeated testing [19•].

CSA is rarely seen in the general population and is encountered mainly in patients with heart failure. CSA appears to participate in a vicious cycle in which heart failure leads to CSA, while CSA exerts further negative effects on disease progression, resulting in worsening CSA (Fig. 2). The mechanism by which CSA exacerbates heart failure could in part be related to increased cardiac filling pressures, as previously discussed. The conditions by which heart failure leads to CSA are even less known.

During sleep, the metabolic rate is stable and CO₂ production is at a steady state. Behavioral control of breathing is abolished by the sleep state, and the arterial carbon dioxide level (PaCO₂) becomes the main stimulus for ventilation. The central and peripheral chemoreceptors maintain a tight balance of respiratory effort and the PaCO₂ via a negative feedback system. As such, respiration ceases if PaCO₂ falls below a tightly regulated level called the apnea threshold. Patients with heart failure have a pattern of chronic hyperventilation, characterized by close proximity between their baseline sleep (eupneic) level of PaCO₂ (steady-state level of ventilation) and their apnea threshold [20]. The mechanism of this chronic hyperventilation in patients with heart failure is thought to be related to pulmonary interstitial congestion. In animal models, respiratory control instability and CSA were induced in response to increased left atrial pressure [21], a typical situation in patients with systolic dysfunction. Any slight increase in ventilation during sleep, as occurs

with arousal or changes in sleep stages, will result in a drop in PaCO_2 below the apnea threshold precipitating apneic events [22]. Given the inertia in the respiratory control system, breathing does not resume until an excessive chemical stimulus (hypercapnia) has accumulated, producing an “overshoot” of ventilation that is likely to drop PaCO_2 again below the apnea threshold and create periodic breathing and CSR. This chemoreceptor response to hypercapnia is increased in patients with heart failure and CSA [23].

Normal vascular responses at the level of cerebral perfusion (cerebrovascular reactivity), are essential for the function of the central chemoreceptors. During sleep, cerebral perfusion is tightly coupled to cerebral metabolism. Similarly, ventilation also is coupled to the reduced metabolism during sleep and to the stable level of CO_2 production. Patients with heart failure have reduced cerebral blood flow response to changes in PaCO_2 , which reduces the ability of the respiratory control center to dampen the overshoot and undershoot in the ventilatory response to CO_2 [22].

The Cardiovascular Consequences of Sleep-Disordered Breathing in Heart Failure

SDB alters the cardiovascular structure and function via multiple pathways, including sympathetic activation, neurohormonal perturbations, oxidative stress, and inflammation (Fig. 2). These pathways occur in both CSA and OSA and result in strikingly similar cardiovascular consequences.

The recurrence of apneas and hypopneas in patients with SDB results in a pattern of nocturnal intermittent hypoxia that is unique to OSA. Nocturnal intermittent hypoxia is a unique physiological state with a profile of biological consequences that is distinct from other types of hypoxia [24]. Each episode of hypoxia produces sympathetic nerve activation and a subsequent surge in blood pressure [25]. Therefore, patients with SDB spend their sleep period in this state of intermittent hypoxia with increased sympathetic activity and hypertension. The sympathetic activation in intermittent hypoxia is associated with plasticity in the response. Subsequently, sympathetic activation and the resulting increase in blood pressure persist during the daytime in patients with SDB. These hemodynamic changes result in renovascular constriction and activation of the renin-angiotensin-aldosterone axis, which may provide another explanation to the relationship between OSA and hypertension. Furthermore, these neurohormonal abnormalities are particularly relevant to patients with heart failure. These negative effects of intermittent hypoxia resolve with treatment of OSA.

Intermittent hypoxia also is associated with oxidative stress. Patients with OSA, as well as animal models of intermittent hypoxia, have increased circulating oxidative stress markers. Oxidative stress appears to mediate endothelial dysfunction in SDB and subsequently contribute to the pathogenesis of atherosclerosis in these patients. The increase in oxidative stress also results in lipid peroxidation and subsequent acceleration of atherosclerosis. C-reactive protein, an important marker of inflammation, is increased in patients with OSA and decreases with treatment (Fig. 2) [26].

In addition to the critical effects of intermittent hypoxia, OSA is associated with a distinct mechanical abnormality. That is, in OSA, the loss of pharyngeal dilator tone during sleep results in extrathoracic airflow obstruction despite the continued respiratory effort of the thoracoabdominal muscles. The continued respiratory effort against an occluded pharynx increases the negative intrathoracic pressure. The resultant increase in the left ventricular transmural gradient causes increased cardiac afterload and decreased cardiac output [27]. Augmentation of this negative intrathoracic pressure enhances right ventricular venous return. These deleterious hemodynamics effects of OSA are accentuated in the setting of

heart failure. Overfilling of the right ventricle can push the intraventricular septum toward the left ventricular cavity, compromising left-sided filling mechanics and, thus, decreasing preload [28]. However, it remains that the sympathetic and neurohormonal abnormalities induced by intermittent hypoxia are the most important contributors to morbidity in heart failure. OSA has been shown to be associated with increased mortality in patients with heart failure [29].

The cardiovascular consequences of CSA are similar to OSA in that they are mainly induced by the intermittent hypoxia. Patients with heart failure and CSA have higher baseline sympathetic tone than those with heart failure alone. Subsequently, patients with heart failure who have CSA are more predisposed to arrhythmia and have worse prognosis than those without CSA. CSA has a pronounced component of periodic arousals after the hypoxic episodes. These arousals are associated with further increases in heart rate and blood pressure [30]; increased sympathetic tone was demonstrated in patients with CSA, which improves with treatment. Concurrent CSA is a predictor of mortality in patients with heart failure [13].

Diagnosis of Sleep-Disordered Breathing in Patients with Heart Failure

SDB remains largely unrecognized and, subsequently untreated in patients with heart failure despite a high prevalence and known detrimental effects on the cardiovascular disease [2•]. A high index of suspicion is necessary to diagnose SDB in patients with chronic heart failure. Excessive daytime sleepiness, fatigue, lethargy, and paroxysmal nocturnal dyspnea are common symptoms of both SDB and heart failure. This clinical syndrome additionally overlaps with common side effects from frequently used cardiovascular medications such as β -adrenergic antagonists. The most common method in diagnosing SDB involves an overnight in-laboratory sleep study. It is likely that lack of systematic surveillance programs for SDB in patients with heart failure is responsible for inadequate identification of SDB. Delays in obtaining a sleep laboratory appointment and patient reluctance to a mandatory overnight stay are further barriers to diagnosis.

Several ambulatory modalities have been introduced in recent years to enable sleep testing at home. The most accepted modalities are the ambulatory cardiorespiratory testing devices [31]. These are a wide variety of systems that monitor airflow, respiratory effort, and oximetry in addition to heart rate and body positioning. These devices recently have been accepted by Medicare for the diagnosis of OSA and for the justification of continuous positive airway pressure (CPAP) device prescription. Ambulatory and abbreviated sleep testing is increasingly gaining acceptance and should become widely used to survey patients with high pretest probability for SDB, such as patients with heart failure [6•, 32]. In addition to the convenience of these modalities, their relatively low costs and adequate sensitivity make them perfectly suited for a surveillance program in high-risk populations in general.

Treatment of Sleep-Disordered Breathing in Patients with Heart Failure

The mainstays of OSA treatment in the general population are CPAP devices. These devices are highly effective and function as a pneumatic splint eliminating the upper airway collapse or closure pathognomonic to OSA. CPAP eliminates sleepiness and improves the cognitive and functional status in patients with OSA. Furthermore, in the general population, CPAP treatment improves daytime blood pressure [33] and decreases fatal and nonfatal cardiovascular events [10]. In patients with chronic heart failure, nocturnal CPAP increases the LVEF and improves the quality of life. Few small randomized controlled trials have evaluated nocturnal CPAP therapy in patients with chronic systolic heart failure with OSA. In one trial, the treatment group experienced a 9% improvement in LVEF as well as

improvement in left ventricular dilatation, heart rate, and systolic blood pressure after 1 month of CPAP treatment [34]. Another small randomized controlled trial in patients with chronic systolic heart failure with OSA demonstrated a significant improvement in LVEF, sympathetic activity, and quality of life with CPAP treatment [35]. These two studies provided evidence for the safety and efficacy of CPAP in patients with chronic heart failure. Improvement in LVEF after nocturnal CPAP therapy was demonstrated further in a recent study of hospitalized patients with decompensated systolic heart failure and newly diagnosed OSA [6•]. These effects of CPAP are mediated by elimination of OSA and should not be confused by the ventilatory effects of CPAP in patients with pulmonary edema. In the latter case, patients would benefit regardless of the presence of underlying OSA.

Other therapeutic modalities for OSA, such as positional therapy, upper airway surgery, and dental appliances, continue to have a limited role in patients with heart failure. This is particularly due to their limited role in the general population. Additionally, the cardiovascular benefits of CPAP treatment have not been sufficiently demonstrated with these other modalities. Therefore, the current standard of care includes treatment with CPAP for patients with heart failure and OSA.

In contrast to OSA, CSA treatment in patients with heart failure is not well defined. The Canadian Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure (CANPAP) [36] trial is the largest prospective randomized controlled trial to date testing the efficacy of nocturnal CPAP in reducing mortality and transplant-free survival in patients with advanced heart failure. In CANPAP, 258 patients with severe chronic systolic heart failure and CSA were randomized to nocturnal CPAP versus standard medical therapy. There was no difference in mortality, number of hospitalizations, quality of life, or B-type natriuretic peptide levels at mean 2-year follow-up. Therefore, routine use of CPAP in patients with heart failure with CSA is not recommended at present.

Cardiac resynchronization therapy (CRT), nocturnal oxygen supplementation, and respiratory stimulants are additional modalities studied for the treatment of CSA in patients with heart failure. A small study evaluating the effect of CRT on CSA in patients with advanced heart failure [37] demonstrated an improvement in AHI, sleep quality, and oxygen saturation in the treatment group at mean 17 ± 7 weeks follow-up. Patients displayed an increased LVEF and exercise capacity, with New York Heart Association functional class improving from class II to III after CRT. The benefits of CRT were attributed to overall improvement in cardiac function. Continuous nocturnal oxygen supplementation has been shown to improve AHI, cognitive function, quality of sleep, and functional capacity in patients with CSA [38], but has not yet been studied in an adequately powered randomized controlled trial. A novel method of treating CSA by increasing the respiratory drive with CO₂ rebreathing was evaluated in patients with heart failure [39]. The respiratory stimulant acetazolamide also was found to have positive impact on CSA in this population [40]. Additional safety and feasibility data are required for both of these modalities before consideration in patients with heart failure and CSA.

The recent introduction of positive pressure devices with advanced ventilator capacity is promising for the treatment of CSA. Teschler and colleagues [3] evaluated adaptive pressure support servoventilation (AVS) versus nasal oxygen, nasal CPAP, and bilevel ventilation in patients in the general population with CSA. They confirmed prior evidence that nasal oxygen, nasal CPAP, and bilevel ventilation improve the AHI and quality of sleep in patients with CSA. However, AVS was shown to be superior to each modality. The central apnea index decreased an additional 83% versus nasal CPAP at similar pressure. AVS-

treated patients felt subjectively better, had significant improvement in CSA and respiratory arousal indices, and displayed a 50% reduction in AHI compared to bilevel ventilation.

Given the reciprocal relation between CSA and heart failure, treatments that improve the cardiac function also may improve CSA. The effect of ventricular assist device (VAD) implantation or cardiac transplantation on SDB in patients with advanced heart failure is unclear because data are limited to small case series that reported improvement in CSA after VAD implantation. This was attributed to overall improvement in cardiopulmonary hemodynamics with full circulatory support [41]. Early reports indicate a tendency to change the pattern of SDB from CSA to OSA after cardiac transplantation [42]. The improvement in cardiac function after transplant may improve CSA but often predisposes patients to weight gain and, therefore, OSA. A study of 13 patients who received cardiac transplantation demonstrated resolution of SDB in 6 patients, improved but persistent CSA in 3 patients, and new-onset OSA in 4 patients [35]. A similar study noted resolution of CSA in 23 out of 29 patients after cardiac transplantation [43].

Suggested Clinical Approach to Sleep-Disordered Breathing in Patients with Chronic Heart Failure

The high prevalence of SDB in patients with heart failure and its established negative consequences on cardiovascular disease justify some level of case finding. Furthermore, presence of sensitive diagnostic tools and effective treatment lend further support for case finding in patients with heart failure. The emergence of accurate and inexpensive diagnostic modalities, such as home sleep testing, and the improvement in pressure device technology in the past several years have contributed further to the management of SDB in heart failure.

The clinician must always maintain a high index of suspicion to identify patients at risk for SDB. With a prevalence of over 60% for SDB in patients with heart failure, the pretest probability is staggering. The absence of highly sensitive and specific signs and/or symptoms adds to the challenge in managing SDB. Currently, governing bodies and insurers do not endorse universal sleep testing for patients with heart failure. This is probably due to the perceived cost more than due to lack of evidence. Therefore, some degree of risk stratification is required in determining which patients should undergo in-laboratory sleep study. We propose an algorithm for stable patients with heart failure that we utilize in our institution. This algorithm has not been validated in a randomized controlled trial but is based on current evidence and findings (Fig. 3).

All patients with chronic heart failure in our institution are considered at moderate pretest probability for concomitant SDB. Patients with heart failure with known risk factors or symptoms of SDB similar to those in the general population are considered at high pretest probability. Identification of common risk factors in the heart failure clinic patients requires close collaboration between the heart failure team and the sleep medicine team. Demographic factors and questionnaires that are validated in the general population can be used to determine these risk factors. For example, a patient with heart failure with body mass index of 32 kg/cm² self-reported snoring and sleepiness is at extremely high pretest probability. A patient with heart failure who does not report sleepiness and has normal weight still is considered at moderate risk, given the pretest probability exceeding 50%. High-risk patients are referred for in-lab sleep studies. Patients with moderate risk undergo further interview or ambulatory home sleep testing (Fig. 3).

Conclusions

SDB is a common modifiable risk factor for cardiovascular disease with significant impact on morbidity and potentially mortality. Despite a high prevalence and demonstrated negative consequences toward cardiovascular disease in patients with heart failure, this disorder often goes unrecognized and untreated. Diagnosis may be improved in chronic heart failure populations with appropriate surveillance strategies. Recent heart failure clinical trials have demonstrated improvement in LVEF, exercise tolerance, and quality of life after treatment of SDB. Treatment of SDB should complement the well-established pharmacologic therapies for chronic heart failure. There is significant overlap between OSA and CSA in mechanism, presentation, and treatment in patients with heart failure. Active involvement of the sleep specialist is necessary to establish an appropriate surveillance and treatment program in partnership with the heart failure team. There now are several promising devices that address both CSA and OSA, and patient acceptance and adherence are enhanced with new technology, but mostly with close follow-up and team approach.

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Fig. 1.

Obstructive sleep apnea as seen on nocturnal polysomnography. Note the cessation of nasal air flow, continued chest and abdominal muscle movement, and pattern of intermittent hypoxemia. *C3-A2* electroencephalogram of the left central brain region; *chest, abdomen* movement measured by inductive plethysmography; *chin EMG* electromyography of the chin; *EKG* electrocardiogram; *LOC* left eye oculogram; nasal flow—pressure changes at the nose measured by modified pneumotachography; *O2-A1* electroencephalogram of the right occipital region; *ROC* right eye oculogram; *SaO₂* oxygen saturation measured by oximetry

Fig. 2. Chronic cardiovascular consequences of sleep apnea. *HTN*hypertension; *LV*left ventricle; *RV*right ventricle; *SDB* sleep-disordered breathing; *SVR* systemic vascular resistance; ↑—increased; ↓—decreased

Fig. 3.

Suggested algorithm for the management of SDB in an advanced heart failure practice.

*Several questionnaires, including the Berlin questionnaire, are used in clinical practice.

Sleep centers may use individualized questionnaires. A common feature in these questionnaires is the inclusion of questions about snoring, sleepiness, and sleep disruption. High-risk patients are those who have the typical symptoms of SDB who can undergo polysomnography immediately. Moderate-risk patients are those patients with heart failure who do not have typical symptoms that are captured on the questionnaire. In some practices, these patients are further evaluated by interview. In our practice, we use home sleep testing to rule in or rule out significant disease. *ASV* adaptive servoventilation; *CPAP* continuous positive airway pressure; *PAP* positive airway pressure; *SDB* sleep-disordered breathing