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PREVENTION OF HEART FAILURE (M ST. JOHN SUTTON, SECTION EDITOR)

Sleep Apnea, Heart Failure, and Pulmonary Hypertension

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Abstract Despite the emergence of sleep apnea (SA) as a significant risk factor for heart failure (HF) mortality, data indicate that SA remains under-diagnosed and under-treated. Less well established, though perhaps more emphasized, is the role of sleep apnea in pulmonary hypertension (PH). SA occurs in approximately 50 % of HF patients, and its consequences include intermittent hypoxemia, arousal, and intrathoracic pressure swings leading to neurohormonal stimulation, oxidative stress and inflammation. While SA is also considered a cause of PH, severe PH due solely to SA is rare. Combining the results of several studies using Swan-Ganz catheters for diagnosis of PH, approximately 10 % of patients with OSA have PH. Effective treatment of SA in HF is associated with improved survival, while treatment of SA in PH is typically associated with modest hemodynamic improvement.

Keywords Sleep · Sleep apnea · Heart failure · Pulmonary hypertension

Introduction

Chronic congestive heart failure (CHF) is a highly prevalent disease with excess morbidity, mortality, and healthcare expenditures. Because CHF carries a high, 50 % 5-year mortality [1] in addition to high costs due to the nearly one million annual hospital days and 30 % rate of re-hospitalization, treatment of co-morbid conditions is critically important [2••]. Sleep apnea (SA) is an important risk factor for both heart failure with reduced ejection fraction (HFREF) and heart failure with preserved ejection fraction (HFPEF) [3••, 4].

SA is characterized by repetitive apneas and hypopneas resulting in adverse cardiovascular consequences. The two main phenotypes of SA, obstructive (OSA) and central sleep apnea (CSA), have qualitatively similar pathophysiologic consequences in heart failure (HF) and increase both morbidity and mortality [5, 6]. Several studies indicate that effective treatment of SA improves survival in patients with HF [7, 8••]. Despite this, SA remains under-diagnosed and under-treated in these individuals [9••].

Diagnosis of Sleep Apnea

Prior to understanding the complex interactions between sleep disordered breathing (SDB), HF, and pulmonary hypertension (PH), we will define how SA is diagnosed. The montage for recording sleep is called polysomnography (PSG). PSG includes the continuous recording of brain waves, nasal and oral airflow, thoracoabdominal excursions, pulse oximetry, electrocardiogram and anterior tibialis muscle electromyogram. With these tracings, detailed information regarding total sleep time, sleep onset, rapid-eye-movement (REM) sleep, non-REM and sleep-related breathing is obtained. Anterior tibialis muscle electromyogram provides information on leg movements.

One apnea is defined as a cessation of breathing for 10 sec or more. Assuming a respiratory rate of 12 breaths per minute during sleep, one apnea corresponds to an average of 2 missed breaths. A hypopnea is a reduction in breathing for 10 seconds

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or more. The number of apneas and hypopneas is counted and divided by the total sleep hours based on electroencephalography, yielding an apnea hypopnea index (AHI). This quantitative metric has been a valuable tool in diagnosing SA and defining severity. An AHI of 5 to <15 is considered mild, ≥15 to <30 moderate and ≥30 severe sleep apnea.

The minimum oxygen saturation, the total time spent below 90 % saturation, and the number of times oxygen saturation drops by 4 % (ODI, oxygen desaturation index) are recorded by pulse oximetry.

Normal Sleep Physiology and Cardiovascular System

In order to understand how the negative pathophysiological consequences of SA may influence HF and PH, the effects of normal sleep architecture on nervous system activity should be understood. Sleep consists of two neurophysiologically distinct states: non-REM sleep occupies 80 % of total sleep time, and REM sleep accounts for the remaing 20 %. Non-REM sleep is divided into stages N1, N2, and N3. As sleep deepens from the lightest stage of sleep (N1) to the deepest stage (N3), there is an orchestrated decrease in sympathetic activity and increase in parasympathetic activity. These autonomic changes have been demonstrated in several ways. Sympathetic outflow from the vascular bed, monitored by continuous peroneal nerve recordings, demonstrates progressive decrease from wakefulness through deep sleep. This is concomitant with decreased cerebrospinal fluid norepinephrine levels and a fall in plasma norepinephrine and epinephrine concentrations, indicating reduced sympatho-adrenal activity. As a result, arterial blood pressure progressively decreases as sleep deepens by approximately 10–20 % relative to the mean daytime arterial blood pressure. This phenomenon is known as "dipping" [10]. Interestingly, normal dipping does not occur in SA (termed non-dipping), a phenomenon associated with increased mortality.

In addition to blood pressure dipping, heart rate, cardiac output, metabolic rate and ventilation also decrease. Therefore, non-REM sleep is associated with cardiovascular quiescence as cardiac workload decreases. Although the body is paralyzed during REM sleep, the brain is actively engaged in dreaming. Like emotions, dreams are associated with increased sympathetic activity, increased heart rate, and increased blood pressure, which may result in arrhythmias or increased myocardial oxygen demand and myocardial ischemia. In contrast to CSA, which occurs primarily in non-REM sleep, OSA can become prolonged or exclusively occur in REM sleep. One potential mechanism is that during REM-induced paralysis, there is atonia of the genioglossus muscle, causing the tongue to fall backwards and close the upper airway. There is also intercostal muscle atonia though the diaphragm is spared. Overall, therefore, in contrast to non-REM, REM sleep could have potential adverse cardiovascular consequences.

Pathophysiologic Consequences of SA

The mechanism by which sleep disordered breathing leads to adverse consequences is threefold: first, large negative intrathoracic pressure swings lead to increased transmural left and right ventricular pressures. This increase in afterload can cause atrial distension, arrhythmias, and pulmonary congestion. Larger negative intrathoracic pressure swings occur during obstructive apneas, but smaller swings occur during the hyperventilation that follows central apneas. Second, the apneas and hypopneas cause recurrent arousals [10, 11] which disrupt and fragment sleep leading to increased sympathetic activity, withdrawal of parasympathetic activity, and increased blood pressure and heart rate. Finally, the apneas and hypopneas result in oxygen desaturations and hypercapnia followed by a recovery period where reoxygenation and hypocapnia occur as ventilation increases. These fluctuations in arterial oxygen and carbon dioxide levels also contribute to sympathetic activation. Both alveolar hypoxia and hypercapnia may cause pulmonary arteriolar vasoconstriction, increased pulmonary artery pressures, increased right ventricular afterload, and eventually *cor pulmonale*. Recurrent cycles of hypoxia and re-oxygenation, via reactive oxygen species, result in redox gene activation and up-regulation of inflammatory cytokines culminating in endothelial cell dysfunction.

Prevalence of Sleep Apnea in Heart Failure

Prevalence varies according to the AHI applied in each study, but an AHI≥5 is the minimum threshold to diagnose SA. Even when using an AHI threshold of 15; however, many studies demonstrate a high prevalence of SA in both HFREF and HFPEF, though there is more data on SA and HFREF.

Heart Failure with Reduced Ejection Fraction

Many recent studies demonstrate a high prevalence of SDB in patients with HFREF. Our group performed a detailed systematic prospective study [12] involving 100 ambulatory male veterans with stable, treated HF. One hundred and fourteen consecutive eligible patients were asked to take part in the study and 100 accepted. All had HFREF (mean left ventricular ejection fraction of 25 %), and at the time of recruitment no questions were asked regarding symptoms or risk factors for SA. Further, each patient spent two nights in the sleep laboratory, the first night for habituation. Attended polysomonography was performed during the second night.

Forty-nine percent of the subjects had SA as defined by a minimum AHI of 15, and 68 % had SA using a threshold AHI of 5. Patients with OSA were obese and had habitual snoring and high blood pressure when compared to CSA patients who were thin and snored less. These findings have been substantiated by subsequent studies [12].

The largest prospective study screened 700 European patients with NYHA classes II-IV HF using cardiorespiratory polygraphy (brain waves were not recorded; therefore, the number of apneas and hypopneas was divided by the recording time, not the sleep time). Seventy-six percent had some form of SDB of which 40 % had CSA and 36 % had OSA. CSA appeared to be a marker of more severe HF as these patients suffered from lower EF and higher NYHA class [13]. A study of 126 consecutive symptomatic HF patients in China demonstrated similar findings. All patients underwent screening with polysomnogram (PSG) and 71 % had SA of which 65 % had CSA and 35 % had OSA. New York Heart Association (NYHA) class III and IV were independent risk factors for CSA, and higher body mass index (BMI), snoring, nocturia, and metabolic syndrome were independent risk factors for OSA [14]. Another prospective study screening 103 stable HF patients found approximately 73 % to have SDB. Unlike previous reports, however, OSA predominated: 60 % of individuals with SA had OSA. Furthermore, this study demonstrated that left atrial diameter was an independent predictor of SA [15].

Prevalence of SA in Heart Failure with Preserved Ejection Fraction

There is minimal data on SA in HFPEF patients. In a prospective study evaluating a general HF population selected from a Norwegian HF clinic, SDB was present in 80 % of those with HFPEF and 82 % of those with HFREF [4]. Unlike the patients with HFREF, the predominant type of SDB in HFPEF patients was OSA (62 %). The largest prospective study to date evaluated 244 consecutive patients with HFPEF and found the overall prevalance of SA was 70 % with approximately 40 % OSA and 30 % CSA. Similar to HFREF, CSA was associated with more severe HF [16••].

Increased Morbidity and Mortality in Patients with SA and HF: Impact of Treatment

OSA and CSA both increase mortality in patients with HF [17, 18]. Furthermore, treatment of both CSA and OSA decreases hospitalizations and improves survival in HF patients [8••, 9••, 19]. A prospective observational cohort study of 784 hospitalized patients with HFREF demonstrated a significantly increased rate of cardiac readmissions for those with CSA compared to those without after adjusting for systolic function, comorbidities, length of stay, medications, and renal function [20]. There is evidence that severe SA is also associated with increased risk of heart transplant and implantation of a left ventricular assist device. In a recent study of 384 patients with LVEF≤45 %, those with any form of SDB had significantly poorer prognosis and risk of death compared to those without. Furthermore, treatment of SA improved outcomes compared to untreated severe SA (AHI≥20) [21••].

Kasai et al. also showed a significantly increased risk of both death and hospitalization in patients with moderate to severe OSA and HF with untreated OSA (HR 2.03, 95 % CI 1.07 to 3.68, $P=0.030$) and those with OSA who were non-adherent with their CPAP therapy (HR, 4.02; 95 % CI, 1.33 to 12.2; $p=0.014$) [22]. Another study prospectively following 88 patients with left ventricular ejection fraction ≤45 % found that median survival of patients with CSA was 45 months compared to 90 months in those without CSA (HR 2.14, $P=0.02$) [17]. One of the largest studies to date prospectively analyzed a cohort of 30,719 Medicare beneficiaries with newly diagnosed HF. Only 2 % (553) of patients received SA testing, of which 545 were treated. After adjustment for age and comorbidties, those who were treated had a significantly better 2-year survival rate than those who were never tested for SA (HR 0.33, 95 % CI 0.21–0.51, $P<0.0001$). Those who were treated also had a better 2-year survival rate than those who were diagnosed with SA but untreated (HR 0.49, 95 % CI 0.29–0.84, $P=0.009$). This study demonstrates the importance of screening and treating for SA as the Medicare beneficiaries were under-diagnosed and subsequently undertreated despite evidence that appropriately treated SDB confers significant improvement in outcomes in HF patients [23••].

Pulmonary Hypertension and Sleep Apnea

Pulmonary hypertension (PH), historically categorized as either primary or secondary, is simply defined as a mean pulmonary artery pressure greater than 25 mmHg. Pressure estimates from echocardiography suggest that up to 20 % of the population may have PH, but most of this PH encompasses mild elevation in pulmonary artery pressures due to left ventricular disease [24]. Because the historical classification of PH has proven insufficient to describe its broad range of etiologies, the World Health Organization proposed a reclassification of five broad categories and recognized SA as a cause of PH. In brief, the first category is PH that was classically known as pulmonary arterial hypertension (PAH), the second category is PH due to left heart disease, the third includes pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and SA, the fourth

is chronic thromboembolic pulmonary hypertension, and the fifth a miscellaneous category which includes PH due to various disorders such as sarcoidosis. Discussion of these categories is beyond the scope of the present work; here we focus on a discussion of the contribution of SA to PH.

Though SA is categorized along with COPD as a pulmonary cause of PH, this categorization fails to underscore the diverse mechanisms by which SA may contribute to PH. SA contributes to systemic hypertension and may cause left sided HF, either HFREF or HFPEF, and in this setting may contribute to further worsening of pulmonary pressures. Additionally, SA may contribute to PH via nocturnal desaturation and hypercapnia which are known reversible (in the short term) constrictors of pulmonary arterioles. The pathophysiological consequences of SA, the negative effects of intermittent hypoxia, sleep fragmentation, and (in its common obstructive form) wild swings in intrathoracic pressure could, in theory, result in diurnal PH via direct remodeling of pulmonary arteries or the myocardium, or via indirect consequences such as systemic hypertension [25].

The effects of chronic hypoxia on remodeling may have untoward effects on pulmonary arteries. Canine models of pulmonary hypertension have established that hypoxia can increase pulmonary pressures, albeit to a lesser degree than that achieved by micro-bead injection directly into the pulmonary circulation [26]. Data from OSA patients with Swan-Ganz catheters in place has shown that the mean PA pressure increases during sleep with large oscillations during intrathoracic pressure swings associated with obstructive apnea [27, 28]. Additionally, a small study showed decreases in right ventricular stroke volume at the end of the apneic phase [29] suggesting an increase in right ventricular afterload. However, in order to accurately assess the precise increase in PA pressure during obstructive apneas, it is necessary to simultaneously measure intrathoracic pressure. Studies that have measured the transmural PA pressure (intravascular minus intrathoracic measured with esophageal balloon as a surrogate of the perivascular pressure) show small PA pressure elevations during apnea [30, 31]. However, the question is whether this process translates into diurnal PH as defined by recent WHO criteria.

Though there are several postulated mechanisms from the basic literature, the prevalence and clinical severity of PH related to SA remains uncertain. Severe PH is not commonly seen in sleep apnea patients in the absence of other comorbidites, such as obesity and COPD. Several small to medium sized studies have aimed to determine the prevalence of PH in SA patients. In the largest study, Chaouat et al. performed right ventricular catheterization in 220 unselected patients with OSA. This study defined PH as a mean pulmonary artery pressure of greater than 20 mmHg, and 17 % of unselected OSA patients exhibited PH by this definition [32]. However, using higher than 25 mm Hg as the threshold, only 16 patients (7 %) met the current criterion of PH. Combining the data from the aforementioned study and five other studies [33–37] using cardiac catheterization, the prevalence of PH (mean PAP>25 mm Hg) is 10 % in 519 patients. In most of these patients PH is mild with mean PAP of less than 40 mmHg; however, mean PAP could exceed this value in the so-called overlap syndrome, a combination of OSA and COPD.

Not surprisingly, the prevalence and severity of PH is quite high among patients who are referred for cardiac catheterization. In a retrospective study of 83 such patients who happened to have PSG with 6 months of cardiac catheterization, Minai et al. found that 70 % of patients with OSA had PH, and 10 % of these patients had severe PH and higher mortality. As noted, this was a retrospective study of patients who underwent right ventricular catheterization, for unknown reasons noted by the authors, within 6 months of PSG. Thus, it does not reflect the true prevalence of PH in patients with sleep apnea, but does show that in a select subpopulation, severe PH can occur in the setting of OSA and is associated with increased mortality [38].

The prevalence of sleep disordered breathing in PH patients appears to be much higher than that in the general population. In a recent study, Dumitrascu and colleagues found that over 25 % of patients referred from PH clinic who were NYHA Class II or III had an apnea-hyponea index >10. Of these, approximately 60 % had OSA while 40 % had CSA [39••]. Other small studies have reported a higher than expected prevalence of CSA in patients with idiopathic PH as well as nocturnal desaturations unrelated to apneic events [40–42].

To legitimize a link between OSA and PH, evidence is needed from randomized controlled trials showing that pulmonary hemodynamics improve after CPAP treatment. Sajkov and colleagues showed that PVR decreases with CPAP therapy in a small study of 22 patients, but this study had no control group [43]. Another small, randomized, cross-over study showed a small decrease in pulmonary artery systolic pressure from 28.9 to 24.0 by echocardiography. However, these effects may have been due to changes in LV diastolic function rather than intrinsic effects on pulmonary vasculature, and pulmonary vascular resistance was not measured [44]. Many of these studies are hindered by the fact that they lack invasive hemodynamic assessment and that the patients did not necessarily have significant PH at study entry.

Taken together, the aforementioned studies are consistent with the notion that most patients with SA and no other major comorbidities have normal PA pressures, and a minority, perhaps 10 %, exhibit mild diurnal elevation of PA pressures. Treatment with CPAP likely attenuates this small increase in PA pressure by multiple mechanisms,

including elimination of altered blood gases and via effects on left-sided filling pressures and left ventricular diastolic function. Severe elevation of PA pressure can occur in the setting of sleep apnea, comorbid with COPD and morbid obesity.

Conclusions

Sleep apnea is highly prevalent in both HFREF and HFPEF. Studies of consecutive patients with stable HF on maximal therapy show that about 50 % have either obstructive or central SA. The polysomnographic phenotype of the disordered breathing, either central or obstructive, varies considerably among different studies, though pathophysiological consequences are qualitatively similar. Overnight acute pathobiogical consequences of apneas and hypopneas include altered blood gases, sleep fragmentation, and negative swings in intrathoracic pressure, which are most pronounced in OSA, though also occur in CSA. Chronic exposure to sleep apnea and hypopnea ultimately results in oxidative stress, inflammation, increased sympathetic activity and endothelial dysfunction. Multiple studies show that co-morbid SA, both obstructive and central, is associated with excess mortality in HF patients. Also, two studies have suggested that SA is associated with excess readmission, and one study of Medicare beneficiaries indicates that treatment of SA reduces rehospitalizations. In addition, several observational studies show that effective treatment of both CSA and OSA improves survival of HF patients.

PH has an estimated prevalence of 10 % in patients with SA, and though SA is classified as a cause of PH it is more likely an exacerbating factor in patients with multifactorial PH. Treatment of SA in patients with PH results in modest hemodynamic improvement likely via improvement in altered blood gases and reduction in left-sided filling pressures and subsequent improvement in left ventricular diastolic function. Randomized control trials are still needed to establish hemodynamic effects of PAP therapy in patients with SA and PH.

Compliance with Ethics Guidelines

Conflict of Interest Sogol Javaheri declares that he has no conflict of interest.

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