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Sleep Disordered Breathing: Hypertension and Cardiac Structure and Function

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Abstract Obstructive sleep apnea (OSA) is a common form of sleep disordered breathing and has a relatively high prevalence in the general population. The frequency and severity of OSA is associated with age, male sex, and obesity, and OSA has been linked to cardiovascular complications and death. Importantly, OSA has a strong association with both prevalent and incidental hypertension and has a particularly high prevalence in patients with resistant hypertension. In these patients, CPAP and other OSA-directed treatments have been proposed as therapy to help control blood pressure (BP), especially in patients who have not attained optimal BP control despite maximum pharmacological therapy. OSA has also been associated with alterations in cardiac structure and function, although most studies are small and highly limited in study design. Existing data suggest an association between OSA greater left ventricle (LV) mass and hypertrophy that appears independent of confounders including hypertension and obesity. Although less clear and more controversial, OSA severity has been linked to LV systolic and diastolic function, pulmonary hypertension, and right ventricular hypertrophy. Further studies are needed to confirm the potential causal role of OSA in these observed associations with cardiac abnormalities.

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Introduction

Sleep-disordered breathing (SDB) refers to a broad range of syndromes of respiratory disturbance while sleeping, the most common of which are obstructive sleep apnea (OSA) and central sleep apnea (CSA). Although several questionnaires exist to screen for the presence of OSA, overnight polysomnography, either in-hospital or at home, is the gold standard for diagnosing SDB [1]. Polysomnography allows for the quantification of apneas (complete cessation of the airflow) and hypopneas (significant reduction in the airflow) lasting more than 10 s and accompanied by some degree of oxygen desaturation per hour of sleep. The number of apneas and hypopneas occurring per hour of sleep is used to generate the apnea-hypopnea index (AHI), which defines clinical categories of SDB as follows: none (AHI≤5), mild (AHI >5 to ≤15), moderate (AHI >15 to ≤30), and severe (AHI>30). Polysomnography can also determine whether the apneas-hypopneas are secondary to anatomical collapse and obstruction of the airway, as is the case in OSA, or by a reduction of central drive, as is the case in CSA.

Among middle-aged white cohorts, OSA is thought to have a prevalence of approximately 9 % in women and 17 % in men [2] but is likely underdiagnosed [3]. Although a similar prevalence of OSA has been described in white Europeans and Asians, there is little data regarding the prevalence among Hispanics and African-Americans. In addition to the well-recognized association with obesity, several additional patient characteristics influence the prevalence of OSA. The prevalence of OSA is higher with greater age. In addition, a higher

prevalence is observed among men compared to women in younger cohorts, although among women, the prevalence of OSA increases dramatically after menopause [4]. The high prevalence of obesity and the aging population are expected to contribute to a rising prevalence of OSA. Importantly, OSA is associated with cardiovascular morbidity and death [5, 6, 7•], which has led to significant interest in OSA diagnosis and treatment benefits.

OSA and Hypertension

The overlap between OSA and hypertension (HTN) is well-recognized, with up to 50 % of patients with OSA having concomitant HTN [8••] while an estimated 37 % [9] and 56 % [10] of patients with HTN have OSA. Although several animal studies support a causal role of OSA and hypoxemia in incident HTN [11, 12], it has been difficult to demonstrate a causal relationship in humans. This is largely due to the association of OSA with multiple other clinical characteristics and comorbidities which may confound the observed association between OSA and HTN, including age, sex, BMI, metabolic syndrome, and diabetes mellitus among others. Obesity is a particularly important potential confounder. The Wisconsin Sleep Cohort study demonstrated an association between OSA and prevalent HTN that was independent of other confounder factors, including BMI [2, 3]. Later, both the Wisconsin study [3, 13••] and the Sleep Heart Health Study (SHHS) confirmed a relationship between OSA and incident HTN that was independent of potential confounders. It has also been suggested that some potential confounders, such as age and sex, may also modify the association between OSA and HTN [4, 14••].

Several different mechanisms have been described as potential pathways to explain the association between OSA and HTN and other cardiovascular complications (Fig. 1). First, nocturnal cyclic hypoxemias and hypercapnias have been shown to trigger an increase in sympathetic activity as shown by an increase in noradrenaline plasma levels, elevated catecholamines in urine [5, 6, 7•, 15] and elevated muscle sympathetic activity [8••, 16]. Second, cyclic shifts in intrathoracic pressures due to respiratory effort against an occluded airway may produce significant changes in ventricular loading conditions [9, 17], increase intracardiac transmural pressures [10, 18], and associated secondary changes in autonomic activity [11, 12, 19]. Third, hypoxemia can lead to formation of free oxygen radicals [20], which in turn may lead to activation of inflammatory pathways, as reflected in circulating C-reactive protein levels [21], and to cytokine liberation—processes that have been implicated in the atherosclerosis [22].

OSA and Resistant Hypertension

Resistant hypertension is defined as a blood pressure (BP) above goal despite the appropriate use of three antihypertensive medications, including at least one diuretic, or controlled BP using more than three antihypertensive medications [23]. The prevalence of resistant hypertension is thought to be approximately 20–30 % of hypertensive patients [23] and has been associated with higher risks of cardiovascular complications and stroke [24]. OSA is the most prevalent comorbidity in patients with resistant hypertension [25]. In a cross-sectional study of 437 subjects, 82 % of patients with resistant hypertension also had some degree of OSA and 56 % of these patients had moderate or severe OSA [26]. Among the patients with OSA, those with resistant hypertension had more severe OSA than those without resistant hypertension [26]. Patients with resistant hypertension tended to be older, more frequently male, more obese, and had a higher prevalence of diabetes [26], features which have also been associated with OSA.

In addition to the previously discussed mechanisms that may mediate the relationship between OSA and hypertension, hyperactivation of the renin-angiotensin-aldosterone system has been proposed as an additional mechanism by which OSA may predispose to resistant hypertension. Several studies have found an association between OSA and hyperaldosteronism in patients with resistant hypertension [27, 28] although this finding has not been universal [29]. Whether resistant hypertension is directly related to OSA, as opposed to shared comorbidities, remains unclear.

Treatment with CPAP and Hypertension

Continuous positive airway pressure (CPAP) is the most effective and frequently prescribed treatment for OSA and is recommended for patients with severe OSA or with less severe OSA but associated diurnal hypersomnolence [30•]. CPAP is associated with reductions in BP, with the greatest reduction noted among patients with HTN on antihypertensive medications [31] or with uncontrolled HTN [32, 33]. However, the benefits of CPAP treatment are dependent on patient's OSA severity and, more importantly, on CPAP's adherence [34]. Adherence rates have been reported as low as 46 % [35], although strategies that enhance patient education have achieved adherence rates above 80 % [36]. Two mechanisms have been hypothesized to explain the BP reduction associated with CPAP. First, CPAP may stop the cyclic hypoxemias secondary to apneas. However, in a study of 381 patients with OSA, CPAP significantly reduced BP while the combination sham-CPAP with nocturnal oxygen was not associated with a reduction in BP, supporting the hypothesis that improvement in BP with CPAP is not only mediated through amelioration of intermittent hypoxemia [37••]. Second, CPAP may decrease BP by decreasing sympathetic tone [16]. However, here too, results have not been consistent [32, 38]. More generally, the magnitude of effect of CPAP on BP and the existence of patient subgroups particularly responsive to

Fig. 1 Mechanisms triggered by nocturnal apneas through which OSA may cause cardiac remodeling
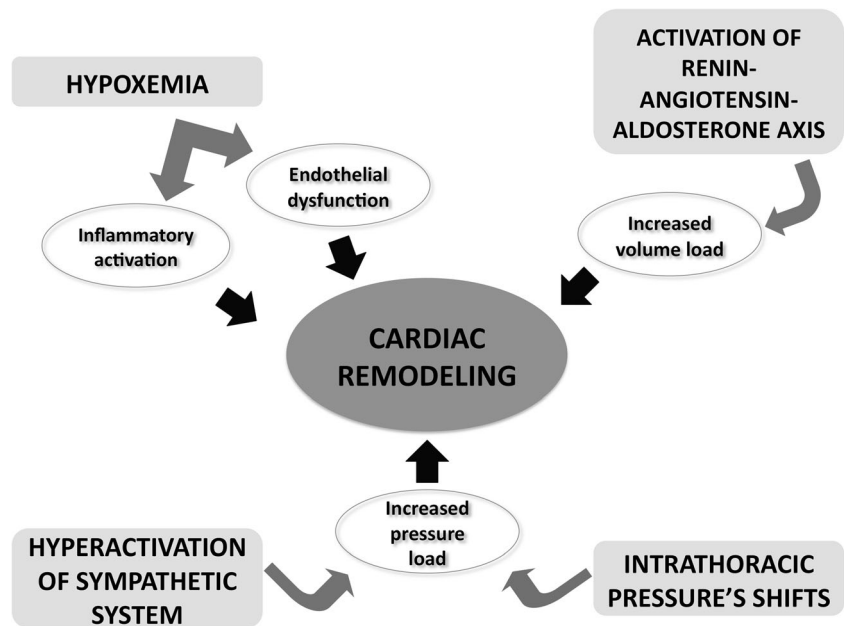
CPAP remain unclear. A recent meta-analysis evaluated 7 randomized clinical trials of patients with OSA diagnosed by PSG, and concomitant HTN included a total of 794 patients, the majority with moderate/severe OSA [31]. CPAP was associated with a significant reduction in 24-h ambulatory blood pressure, but not with a significant reduction in systolic blood pressure. The observed BP reduction was largely related to in a reduction of overnight BP [31]. Subjects with resistant hypertension showed the greatest benefit from CPAP treatment. However, as with a previous meta-analysis [34], this study was limited by the small sample sizes of included studies (only two of them surpassed 100 patients) and lack in uniformity when selecting the placebo group (sham-CPAP vs no treatment) and, in general, short follow-up [31]. It is suspected that greater reductions in ambulatory BP measures with CPAP are associated with higher initial AHI and with greater adherence to CPAP [34].

Although weight loss is difficult to achieve and to maintain, the combination of weight loss and CPAP may be the best strategy for BP reduction [39]. Weight loss is an important predictor of improvement in both OSA, with a reduction of 5 AHI for each decrease in 10 kg [40•], and HTN, with a reduction of 6 mmHg of SBP and 4.6 mmHg of DBP for each 10 kg weight loss [41]. Finally, recent attention has also focused on the potential use of renal denervation as a treatment for resistant hypertension in patients with OSA, although data are limited [42].

OSA and Cardiac Morphology and Function

OSA is associated with a higher risk of incident HF [43••]. Indeed, in the Sleep Heart Health Study, patients with

moderate to severe OSA had a 2.38-fold higher risk of having HF compared to those without OSA, independent of potential clinical confounders [44]. Much attention has focused on potential alterations in cardiac structure and function associated with OSA as in intermediate phenotype preceding overt HF. However, most existing studies are limited by relatively small sample size and variability in control groups making between study comparisons difficult.

Left Ventricle Hypertrophy

Left ventricular hypertrophy (LVH) is a common consequence of hypertension and a potent risk factor for HF. As discussed above, OSA is clearly associated with hypertension. Similarly, obesity is highly prevalent in OSA and is also associated with LVH [45]. Several studies have observed an association between OSA and LVH [46, 47••, 48], but it has been difficult to demonstrate an association between OSA and higher left ventricular mass index (LVMI) or LVH independent of obesity and hypertension (Table 1) [46]. However, in 2058 middle-age subjects (58 % women) from the SHHS who underwent echocardiography, severe OSA (AHI≥30) was associated with a higher odds of having concomitant LVH (OR of 1.78 [95 % CI 1.14–2.79]) independent of age, sex, BMI, hypertension, and prevalent cardiovascular disease [47••]. The association was stronger between LVH and nocturnal hypoxemia, especially among women, in whom the association between LVMI and AHI was not independent of potential confounders. Similarly, a recent study of 80 subjects free of HTN, diabetes, or known cardiovascular disease observed greater LVH among subjects with moderate or severe OSA compared to those with no or mild OSA [48]. These studies suggest that

Table 1   Summary of studies looking for the association between OSA and LVMI

Study	Population	Statistical approach	Main finding
Niroumand et al. AJRCCM 2008 [46]	422 subjects free of CVD, HTN of DM	Compared: Non OSA (AHI<5) vs OSA (AHI≥5)	In men, AHI was associated with LVMI, but was not significant after adjusting by age, sex, and BMI
Chami et al. Circulation 2008 [47••]	2058 community-dwelling subjects	Linear association between AHI and echocardiographic variables	Higher AHI is independently associated with LVMI
Aslan et al. Cardiol. J 2013 [48]	80 subjects free of CVD, HTN, or DM	Compared subjects with AHI<15 vs subjects with AHI≥15	The interventricular septum was thicker in subjects with OSA in unadjusted analysis. No adjustment for potential confounders performed
Dobrowolski Hypert Res 2015 [49]	155 patients with RH	Predictors of LV concentric hypertrophy were determined	OSA severity, measured by AHI, is independently associated with having LV concentric hypertrophy
Prejbisz Hypert Res 2014 [50]	121 untreated hypertensive patients	Multivariable linear regression	LVMI is positively associated with AHI independent of blood pressure or other confounders
Otto et al. Am J Cardiol 2007 [81]	41 obese middle-aged otherwise healthy subjects	Mod/severe OSA (AHI≥15) vs none OSA (AHI<5)	No significant unadjusted difference in LVMI by OSA severity. Analyses of differences were not studied adjusting by potential confounders
Drager et al. Chest 2007 [82]	60 subjects	4 groups: healthy controls, OSA, HTN w/o OSA, and OSA and HTN	The prevalence of LVH was similar between patients with either OSA or HTN but greater than healthy controls. Patients with both OSA and HTN had a higher prevalence than those with either alone or healthy controls
Usui et al. Sleep 2011 [56]	74 healthy non-obese men	Mild/moderate OSA (AHI >5 and <30) vs severe OSA (AHI≥30)	No significant differences in LVMI by OSA severity

OSA obstructive sleep apnea, *AHI* apnea-hypopnea index, *LVMI* left ventricular mass index, *BMI* body mass index, *LV* left ventricle, *LVH* left ventricular hypertrophy

OSA is associated with LVH even in the absence of concomitant HTN.

Both concentric and eccentric LV remodeling are common in OSA, although significant variability in prevalence estimates exists between studies [47••, 49, 50]. In a recent study of 121 patients (mean age 35.9±10.1, 80 % men) with newly diagnosed essential HTN, moderate to severe OSA was associated with greater concentric remodeling (based on the relative wall thickness) compared to those with no or mild OSA [50]. Similarly, in Resist-POL, which included 155 patients with resistant hypertension, concentric hypertrophy was independently associated with both OSA severity and night-time SBP [49]. However, the SHHS observed a higher prevalence of both concentric and eccentric hypertrophy in subjects with OSA compared to those without OSA, although only eccentric hypertrophy was independently associated with OSA severity (OR for eccentric hypertrophy of 1.84 [95 % CI 1.12–3.03] for severe OSA compared to no OSA) [47••].

As BP lowering in hypertensive persons is associated with reduction in LV mass [51] and CPAP is associated with BP reduction in OSA, it has been hypothesized that CPAP treatment may reduce LV mass. Indeed Cloward et al. described that CPAP treatment was able to reverse LVH in 25 patients

newly diagnosed of severe OSA with very significant nocturnal hypoxemia after 6 months of treatment with CPAP [52]. However, this finding of an association between CPAP treatment and reduction in LV mass has not being confirmed in bigger trials.

Left Ventricular Diastolic Function

OSA has also commonly been associated with diastolic dysfunction. Using three-dimensional echocardiography, Oliveira et al. found that, compared to controls without OSA, patient with OSA had larger left atrial (LA) size and worse LA function and that LA size was proportional to the severity of OSA [53]. In addition, subjects with OSA had mild diastolic dysfunction compared to controls, based on transmitral inflow velocities and mitral tissue Doppler velocities. However, multivariable adjustment for relevant potential confounders—including BMI and SBP—was not performed [53]. In a subsequent analysis of 30 patients with moderate or severe OSA (AHI ≥20), the same group found that treatment with CPAP was associated with improvement in diastolic function and in measures of LA function compared to a control sham CPAP group. The treatment effect on BP was not reported but could

have informed whether changes in BP explained the observed changes in diastolic function [54]. Additional studies have demonstrated abnormalities of diastolic function, based on transmitral flow patterns and LA enlargement, in OSA [55, 56], although this finding has not been universal (Table 2). Indeed, some have argued that observed association of OSA with diastolic measures is primarily due to OSA-associated comorbidities and as opposed to OSA itself [46]. In addition, while improvement in diastolic measurements has been observed with OSA treatment, it is unclear if this is primarily related to improvement in OSA itself, or to concomitant improvement in hypertension [54].

Of note, the association of OSA with LA enlargement and LA functional impairment [57] is concordant with the observed association of OSA with a higher risk of incident atrial fibrillation (AF) [58], in addition to recurrent atrial fibrillation after electrical ablation [59]. Indeed patients with OSA who were CPAP users demonstrate lower rates of recurrence than CPAP nonusers following electrical ablation for AF [60].

Left Ventricular Systolic Function

Despite the association of OSA with incident HF, studies have failed to show any association between OSA severity and LVEF [47••, 61]. More recently, global longitudinal strain (GLS) has been proposed as a more sensitive measurement of LV systolic function [62]. OSA does appear to be associated with impaired GLS despite preserved LVEF [63]. In a study of 60 patients, comparing patients with OSA to obese controls, GLS was impaired in OSA. Intriguingly, improvement in GLS following surgical correction of OSA was highly correlated with the reduction in AHI [64].

Although OSA has not been associated with LVEF, among HFrEF patients in particular, CPAP has been proposed as an intervention to improve LVEF [65•]. In a recent meta-analysis including a total of 259 patients from 10 studies, CPAP was associated with a significant improvement in LVEF, an effect that was most prominent among patients with concomitant OSA and HF [66]. Notably, this study was limited by the inclusion of very small studies (none included more than 50 patients) and significant heterogeneity in definition of both OSA cases and controls [66].

Pulmonary Hypertension and Right Ventricular Hypertrophy

OSA has been listed as a cause of pulmonary hypertension secondary to hypoxemia [67]. However, the evidence that links OSA and pulmonary hypertension is not strong and published studies are in general small. In a study of 27 subjects with OSA free of coexistent cardiac or pulmonary disease, one third had mild pulmonary hypertension [68]. Comparing those with versus without pulmonary hypertension, no differences in pulmonary function or BMI were noted that could explain the differences in pulmonary pressures, although no

Table 2 Summary of studies regarding the association between diastolic function and OSA

Study	Population	Statistical approach	Main finding
Oliveira et al. JASE 2008 [53]	105 subjects free of CVD	56 OSA patients (AHI≥5) vs 50 controls (AHI<5)	OSA patients had larger LA volumes and higher LA active ejection fraction compared with age-matched controls. Differences were independent of night-time BP. OSA patients presented lower E' and higher A' than controls
Niroumand et al. AJRCCM 2008 [46]	356 subjects free of CVD, HTN of DM	Compared: non OSA (AHI<5) vs OSA (AHI≥5)	Unadjusted difference in E/A was noted that was no longer significant after adjusting for confounders
Aslan et al. Cardiol. J 2013 [48]	80 subjects free of CVD, HTN, or DM	Compared subjects with AHI<15 vs subjects with AHI≥15	In moderate/severe OSA, E/A is lower, LA diameter is bigger and E' is lower than those in none/mild OSA. Differences were not adjusted for potential confounders
Prejbisz Hypert Res 2014 [50]	121 untreated hypertensive patients	Multivariable linear regression	E wave is negatively associated with AHI independent of blood pressure or other confounders
Otto et al. Am J Cardiol 2007 [81]	41 obese middle-aged otherwise healthy subjects	Mod/severe OSA (AHI≥15) vs none OSA (AHI<5)	Subjects with OSA had higher LA volumes, A', and E'/A'. However, no differences were found in E wave, A wave, or E'. Differences were not adjusted for potential confounders
Usui et al. Sleep 2011 [56]	74 healthy non-obese men	Mild/moderate OSA (AHI >5 and <30) vs severe OSA (AHI≥30)	Patient with severe OSA had lower E wave, E/A ratio and E' independent of potential confounders

OSA obstructive sleep apnea, *CVD* cardiovascular disease, *HTN* hypertension, *DM* diabetes mellitus, *AHI* apnea-hypopnea index, *LA* left atrium, *BP* blood pressure, *E wave* early transmitral flow velocity, *A wave* late transmitral flow velocity, *E/A* ratio between early and late transmitral velocities, *E'* mitral annular early diastolic velocity, *A'* mitral annular late diastolic velocity, *E'/A'* ratio between early and late mitral annular diastolic velocities

significant difference in OSA severity (assessed by the AHI) was noted either. The authors suggested that individual susceptibility to nocturnal hypoxemia secondary to OSA could be the cause for observed pulmonary hypertension [68]. Indeed, most studies have shown that pulmonary hypertension is less linked to AHI and more to daytime hypoxemia [69], obstructive ventilatory pattern [70], obesity and secondary hypoventilation syndrome [71]. Therefore, given our current knowledge, it is hard to determine whether OSA is a cause of pulmonary hypertension or if it is only a contributory factor in patients with hypoxemia due to other conditions [72]. Despite this controversy, in at least one study of 20 subjects with pulmonary hypertension and OSA, pulmonary pressures and pulmonary vascular resistance were significantly reduced after 4 months of treatment with CPAP [73].

Limited data exists regarding the relationship between OSA and right ventricular structure and function. From individuals participating in both the Framingham Heart Study and SHHS, a case-control analysis of 90 subjects with severe OSA and controls with low AHI matched for age, sex, and BMI demonstrated thicker right ventricular free walls—consistent with right ventricular hypertrophy—among the severe OSA cases [74•]. This finding is potentially consistent with higher pulmonary pressure and right ventricular afterload in severe OSA. No other abnormalities in structure or function were noted [74•] and similar findings have not been described in other studies, possibly due to the infrequency with which RV wall thickness is assessed.

Patent Foramen Ovale

The prevalence of a permanent foramen ovale (PFO) in the general population is approximately 25 % [75]. However, the prevalence in series of OSA patients has been significantly higher, between 47 % [76] and 69 % [77]. Additionally, a high prevalence of right-to-left shunt has been observed in OSA [78]. Both findings may help explain the association between OSA and stroke [79], supporting the hypothesis of potential paradoxical embolization. However, these studies were small and subject of significant limitations. Further studies are needed to confirm these observations and inform the potential of benefit with PFO closure in this population [80].

Conclusions

OSA is a cause of HTN and can contribute to the development of uncontrollable HTN. Treatment of OSA with CPAP appears to improve BP in subjects with OSA, although further study is required to define the magnitude of treatment benefit. OSA is associated with left ventricular hypertrophy, diastolic dysfunction, and subtle impairments of systolic function. OSA has also been associated with pulmonary hypertension and right

ventricular hypertrophy. Importantly, however, our current understanding of the impact of OSA on cardiac structure and function is limited due to the small size of most studies, inter-study variability in selecting OSA cases and defining controls, and inadequate adjustment for potential confounders. Disentangling the cardiovascular effects of OSA from the confounding effects of shared risk factors is a major challenge. Further prospective studies in large, diverse populations are necessary to clarify the impact of OSA on cardiac structure and function independent of common comorbidities.

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