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Sleep Disordered Breathing and Cardiovascular Disorders

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Introduction

Sleep disordered breathing (SDB), expressed most frequently as obstructive sleep apnea (OSA), is a common syndrome, and becomes progressively more prevalent with increasing age [1]. For the past several decades, a number of cross-sectional studies performed primarily in relatively small clinical cohorts or using surrogates such as snoring as markers of SDB have reported linkages between SDB and cardiovascular disease (CVD). For example, a high prevalence of OSA has been observed in patients with hypertension [2]. Conversely, hypertension is found in a large percentage of OSA patients. With respect to cardiac disease, early studies linked OSA to ischemic heart disease [3,4]. In addition, it has been shown that OSA is associated with deteriorations in left ventricular function [5] and that treatment of OSA with continuous positive airway pressure (CPAP) improves cardiac function. If SDB plays a causal role in the pathogenesis of CVD, increases in mortality would be expected among individuals with OSA. This hypothesis was supported in some [6,7], but not all [8] retrospective studies. Whether or not SDB is an independent risk factor for CVD is an important public health question. According to the 1999–2000 National Health and Nutrition Examination Survey (NHANES), the prevalence of hypertension in the United States in those over age 55 years is 48% [9]. According to the year 2000 census, there are ~59 million Americans age 55 or older. As previously noted, if 25–50% of these individuals also have OSA, then ~14.5–29 million people in the United States in this age category are at increased risk for CVD or excess mortality related to OSA.

In the past several years, a persuasive body of data now indicates a causal association, independent of obesity, between SDB and cardiovascular disorders such as hypertension, coronary artery disease (CAD), arrhythmias, congestive heart failure (CHF), and stroke. The association is strongest and most consistent between obstructive sleep apnea and hypertension. This review will summarize the most important studies demonstrating the linkages between SDB and cardiovascular disease, and outline potential responsible mechanisms.

Review of the Literature

OSA and Hypertension

Cogent data confirm the association between OSA and hypertension [10]. Several epidemiological and clinic-based studies conducted in cross-sectional as well as longitudinal

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designs have demonstrated a strong and consistent relationship between these disorders.. Peppard et al found a causal association between SDB at baseline and presence of hypertension four years later in 709 subjects in the Wisconsin Sleep Cohort, and the odds of hypertension increased with increasing baseline AHI [11]. The association was independent of age, sex, body mass index (BMI), waist and neck circumference, baseline hypertension, smoking and alcohol use. The odds ratios for hypertension continued to be significant when those hypertensive at baseline were excluded. Recent analyses of data from this cohort demonstrated dose-response increased odds of incident nocturnal nondipping of systolic blood pressure, a risk factor for hypertensive complications, in participants with SDB over an average of 7.2 years of follow-up [12].

A cross-sectional analysis of Sleep Heart Health Study arrived at similar conclusions [13]. Persons with an AHI $\geq$ 30 events/hr had 1.37-fold increased odds of hypertension in compared to those without OSA (AHI < 1.5 per hour) after adjusting for several confounders. However, recent prospective analyses of data from SHHS suggested that the relationship between the baseline AHI and the risk of developing hypertension approached but did not quite reach statistical significance after adjustment for BMI [14]. However, the odds ratio in the longitudinal analysis were quite similar to those observed in the cross-sectional analysis suggesting that a causal relationship is most likely present and obscured by residual confounding. The older age of participants in this study, exclusion of those with baseline hypertension and different methods of diagnostic testing are among various potential reasons why the results from these analyses differ from those of the Wisconsin Sleep Cohort [15–17].

Other epidemiological and clinic-based studies provide corroborating evidence for an association between SDB and hypertension. In the Nurses Health Study, snoring, a surrogate symptom of SDB, was associated with an increased risk of incident hypertension over an 8-year follow-up period [18]. The Outcomes of Sleep Disorders in Older Men Study (an ancillary study of the Osteoporotic Fractures in Men Study [MrOS]), revealed 1.6 fold higher odds of hypertension in elderly men with SDB [19]. Persons with OSA also have a significantly higher prevalence of non-dipping of blood pressure at night [20]. Conversely, drug-resistant or poorly controlled hypertension is associated with a high prevalence of concomitant undiagnosed SDB [21][22].

Another line of evidence supporting SDB as a causal factor in hypertension is provided by trials demonstrating amelioration, albeit modest, of hypertension with therapy of sleep apnea [23]. The changes in mean blood pressure after CPAP have been suggested to be of the order of 2–5mm Hg [24]. Studies cumulatively suggest better antihypertensive response with CPAP in patients with daytime sleepiness than those without excessive sleepiness [25-27]. Refractory hypertension may also improve with CPAP therapy in persons with comorbid OSA [21]. Mandibular advancement devices and otolaryngological surgery are also associated with improvement in blood pressure in patients with OSA [28].

However, there has been a lack of consistent demonstration of antihypertensive effects of OSA therapy [29]. This discrepancy may emanate from diverse populations and sample sizes, varying diagnostic techniques and different definitions for apneas and hypopneas, as well as dissimilar follow up periods in different studies.

In conclusion, consistent data suggest a strong association between OSA and hypertension. Preliminary trials evaluating therapy of OSA suggest amelioration of hypertension in some subgroups with sleep apnea. However larger prospective trials are clearly needed to unambiguously elucidate the effects of OSA therapy on blood pressure and related outcomes.

OSA and Coronary Artery Disease

The evidence suggesting an association between OSA and coronary artery disease (CAD) continues to accrue. One study showed increased prevalence and extent of coronary artery calcium, a marker of subclinical CAD, in patients with OSA [30]. Presence of sleep apnea in the MrOS cohort was associated with 1.2 fold increased odds of presence of cardiovascular disease [19]. Cross-sectional analyses of data from the Sleep Heart Health Study revealed higher odds of self-reported CAD, heart failure and stroke in persons with a high AHI [31]. Preliminary longitudinal analyses of SHHS data indicate that the risk of incident CAD is primarily in men less than age 70 years[32].

Other prospective observational studies in clinical populations have demonstrated a higher incidence of cardiovascular disorders in persons with OSA [33,34]. Cardiovascular mortality is also increased in OSA [35]. One study with a mean of 10.1 years of follow-up found that participants with untreated severe OSA had a higher incidence of fatal cardiovascular and non-fatal cardiovascular events compared to healthy participants [35]. However, this latter study was recruited from a clinical population and was comprised of only men.

In persons with CAD undergoing elective percutaneous intervention [PCI], OSA is associated with restenosis and vessel remodeling [37]. There is also an increase in the incidence of major adverse cardiac events such as revascularizations and cardiac mortality after percutaneous intervention in patients with OSA [38]. Furthermore, the OSA patients demonstrate smaller increases in left ventricular ejection fraction and regional wall motion within the infarct area days after PCI [39]. Finally, treatment of OSA after percutaneous intervention is associated with a reduction in the number of cardiac deaths [40].

Treatment of OSA may alleviate cardiovascular risk. One study revealed significantly lower combined endpoints of cardiovascular death, acute coronary syndrome, hospitalization for heart failure, or need for coronary revascularization in persons treated for OSA compared to those with OSA who declined therapy (hazard ratio 0.24) [41]. In the study by Marin et al [36], CVD risk in those with severe OSA treated with CPAP was the same as non OSA patients.

As outlined in the foregoing discussing, accumulating data in cross-sectional and longitudinal observational studies implicate SDB as an independent risk factor for CVD. In addition, evidence suggests that CPAP therapy improves early signs of atherosclerosis and may impede progression to clinically significant cardiovascular disease [42]. Cardiac biomarkers such as CRP may decline with CPAP treatment as well [43]. Nevertheless, there have been no large-scale randomized studies demonstrating that treatment of SDB reduces CVD risk. Recently, however, 2 large randomized clinical trials have been started to determine whether OSA treatment has an impact on CVD risk. In Europe, a large prospective randomized intervention of 400 patients with CPAP in CAD and OSA (RICCADSA) trial is aimed at assessing the impact of CPAP treatment on a composite endpoint of new revascularization, myocardial infarction, stroke and cardiovascular mortality over a 3-year period in persons with CAD and OSA [44]. In the United States, the multi-center HeartBEAT study will randomize 352 subjects with OSA and CAD or CAD risk factors to CPAP, low flow nocturnal oxygen and health lifestyle instruction to determine whether CPAP or oxygen will change cardiac biomarkers. Another clinical trial, Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea to Prevent Cardiovascular Disease (SAVE) is being conducted in several international sites to determine whether CPAP will reduce incident CVD. Enrollment of 5000 subjects is planned with study sites in Australia, China, India and New Zealand.

In conclusion, data suggesting an association between OSA and clinical and subclinical coronary artery disease continue to accrue. Large prospective trials will help better elucidate the impact of OSA therapy on improvement of cardiovascular morbidity.

SDB and Congestive Heart Failure

SDB is present in approximately three-fourths of patients with symptomatic or decompensated systolic heart failure [45,46]. The prevalence is very high even in those with stable chronic heart failure [47–49]. Cross-sectional analyses from Sleep Heart Health Study data revealed an adjusted odds ratio of 2.2 for self-reported heart failure amongst subjects with OSA [31]. Of all heart failure patients with sleep apnea in one study, 40% had AHI>30 [47]. Patients with SDB were older, and had higher BMI and brain-natriuretic peptide (BNP) levels despite similar left ventricular ejection fraction and functional class of heart failure. There is little longitudinal data, but preliminary longitudinal analyses of data from SHHS indicate that men, but not women have an increased risk of incident congestive heart failure as a consequence of SDB even after exclusion of subjects with CSA [32].

Both OSA and central sleep apnea (CSA) are encountered in heart failure patients, and the proportion of these events has varied in different studies. It has been suggested that the reduction in arterial partial pressure of CO_2 ($PaCO_2$) and increase in lung-chemoreceptor circulation time in such patients can result in overnight shift in the predominant apnea type from obstructive to central. CSA is frequently accompanied by Cheyne-Stokes respiration (CSA-CSR), a breathing pattern characterized by repetitive sinusoidal waxing and waning of tidal volume amplitude.

CSA is an independent predictor of mortality in patients with heart failure or cardiac transplantation [50,51]. The hazard ratio for early mortality in heart failure patients with CSA in one study was 2.1 relative to those without CSA [50]. Cheyne-Stokes respiration is also associated with higher mortality [52]. Furthermore, CSA-CSR may also promote cardiac electrical instability, with impaired heart rate variability and enhanced occurrence of cardiac arrhythmias [53].

Obstructive events are associated with a marked, negative swing in intrathoracic pressure, which can lead to increased preload and afterload. Furthermore, sympathetic activation resulting from SDB and arousals can deteriorate cardiac function. CPAP therapy improves left ventricular ejection fraction and quality of life in heart failure patients with OSA [54,55]. CPAP use also decreases myocardial irritability and risk of arrhythmias [56].

The prevalence of SDB is high not only in systolic heart failure, but also heart failure with normal ejection fraction (HFNEF). One study of 247 patients with HFNEF revealed presence of SDB in 69%, 40% with OSA and 29% with CSA [57]. CSA was associated with higher pulmonary artery wedge pressures and BNP and lower $PaCO_2$. Persons with CSA had a larger left atrial diameter compared those with OSA, who in turn had more pronounced atrial enlargement than those with no SDB. However, whether diastolic dysfunction leads to SDB or vice versa is yet to be clearly elucidated. Presence of left ventricular hypertrophy in OSA and regression of hypertrophy with CPAP use has been documented in smaller studies [58, 59].

The effect of PAP therapy on CSA in patients with heart failure is not clearly understood. The Canadian Continuous Airway Pressure for Patients With Central Sleep Apnea and Heart Failure (CANPAP) Trial was designed to answer this question [60]. The use of CPAP therapy in this trial improved nocturnal oxygenation, cardiac ejection fraction, six minute walk distance and lowered norepinephrine levels, but did not improve heart transplant-free survival. However, CPAP was unable to significantly alleviate CSA in many of the trial participants. Post-hoc analyses from this study revealed significantly better transplant-free survival (hazard ratio 0.371, P=0.043) in subjects whose AHI had been reduced to less than 15 compared to control subjects. Whether advanced methods of applying PAP in heart failure patients will be more efficacious is unknown. Small clinical studies suggest that both bilevel positive airway pressure

and adaptive servo ventilation may benefit some patients with CSA and heart failure [61]. Larger trials are currently underway.

Some studies have evaluated the effect of cardiac pacing on SDB. While one study suggested that atrial overdrive pacing can improve sleep disordered breathing [62], other studies have failed to consistently confirm this effect [63,64]. It appears that pacing may have some benefits in alleviating SDB in patients with heart failure with predominantly central sleep apnea [65]. However, larger trials are required to clearly understand the magnitude and physiologic basis of this effect. The effect of cardiac resynchronization therapy on CSA/CSR in patients with chronic heart failure has been more consistently demonstrated [66,67]. An improvement in cardiac output and decreased pulmonary vascular congestion may be responsible for improvement of central events in heart failure.

In summary, SDB in the form of both OSA and CSA are frequently observed in patients with heart failure. Improvement in cardiac function with cardiac resynchronization therapy may improve CSA. OSA may be a risk factor for incident heart failure, but it is currently unclear whether treatment of either OSA or CSA, or both forms of SDB will reduce the incidence of heart failure or improve survival in patients with heart failure.

SDB and arrhythmias

Diverse cardiac arrhythmias such as atrial fibrillation, nonsustained ventricular tachycardia, and complex ventricular ectopy have been described in persons with SDB [68]. It has been suggested that atrial fibrillation has a strong association with central sleep apnea, whereas complex ventricular ectopy is more closely associated with OSA [69]. Conversely, the prevalence of undiagnosed OSA in patients with cardiac pacemaker implantation for diverse reasons is extremely high [70]. Several mechanisms such as hypoxia, sympathetic activation and swings in intrathoracic pressure may explain this association. Recent analyses from the Sleep Heart Health Study demonstrated a 17-fold increased odds of an arrhythmia (atrial fibrillation and nonsustained ventricular tachycardia) occurring after a respiratory disturbance than an arrhythmia occurring after normal breathing during sleep [71], providing corroborating evidence for the link between SDB events and arrhythmias. Arrhythmias can be severe, and potentially life threatening. One study of 112 persons who had undergone polysomnography and had died suddenly from cardiac cause suggested that the peak in sudden cardiac death in those with OSA occurs primarily from midnight to 6 am, i.e., during the sleeping hours (relative risk 2.6) [72].

The risk of arrhythmias in OSA significantly decreases with CPAP therapy. In an elegant study, arrhythmias were evaluated in 23 patients with moderate to severe OSA over a 14 month period using a subcutaneously implanted loop recorder. The follow-up duration included 2 months with no OSA therapy, and 12 months thereafter on CPAP. The occurrence of severe arrhythmias was common prior to CPAP therapy, but decreased rapidly after initiation of CPAP therapy, with no ectopy recorded during the last 6-months of follow-up [73]. Another study demonstrated lower recurrence of atrial fibrillation after elective cardioversion in OSA patients who were treated with CPAP therapy [74].

In summary, substantial evidence links SDB as an etiologic factor in the pathogenesis of various arrhythmias, particularly atrial fibrillation. Treatment of SDB with CPAP appears to reduce this risk.

SDB and Stroke

Several studies suggest that SDB is a risk factor for stroke [75]. However, these studies have been primarily case series, case control studies or have used snoring as a surrogate for objective

documentation of SDB. More recently, an observational cohort study in a clinical population found an increased rate of the composite outcome of stroke or death in patients with OSA over a 4 year interval in comparison to those without OSA with an adjusted hazard ratio of 1.97 [76]. Similar findings have been observed in the Wisconsin Cohort Study over a 4 year interval although the fully adjusted odds ratio failed to reach statistical significance in part because of inadequate study power [77]. More recently, analysis of prospective data from SHHS suggests that severe SDB is an independent risk factor for stroke only in men [78]. Whether treatment of SDB reduces stroke risk remains to be determined.

Although there is now substantial data indicating that SDB is a risk factor for stroke, the converse also is true in that stroke appears to be a risk factor for the development of SDB [75]. Unfortunately, CPAP is not well tolerated in post-stroke patients and long-term compliance is low. Nevertheless, it appears that long-term survival post stroke is improved among those patients who are compliant with CPAP therapy [79].

To summarize, SDB appears to be a risk factor for stroke, and conversely stroke is a risk factor for SDB. However, it is unclear whether treatment of SDB reduces long-term stroke risk. SDB also is a risk factor for subsequent CVD events post stroke. Treatment of SDB post stroke with CPAP may reduce this risk, but long-term adherence is difficult to achieve.

Potential pathogenetic mechanisms for CVD in SDB—Several SDB-related mechanisms including endothelial dysfunction, hypoxia, inflammation, obesity, metabolic dysregulation and sympathetic activation may potentially influence the pathogenesis of CVD in persons with SDB. Obstructive sleep apnea is associated with intermittent hypoxemia consequent to intermittent upper airway occlusion. Hypoxia, as well as attendant hypercapnia, augment sympathetic nervous system activity. Recurrent hypoxemia-reoxygenation has been demonstrated to produce sustained hypertension in rodents by sympathetic activation [80]. The intrathoracic pressure swings and arousals associated with hypopneic and apneic events also boost sympathetic activity

Intermittent hypoxemia may also be pivotal in the genesis of systemic inflammation in OSA. Intermittent hypoxemia increases expression of transcription factors such as activator protein (AP)-1 and nuclear factor kappa B (NF-kB), which then up-regulate expression of inflammatory cytokines and adhesion molecules [81]. Indeed, the circulating levels of C-reactive protein (CRP) [82,83], soluble IL-6 receptors [84], intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are elevated in persons with OSA [85,86]. Furthermore, the propensity of monocytes to adhere to vascular endothelium is increased [87]. Increased levels and adherence of inflammatory mediators contribute to atherosclerosis [88]. Production, migration and adherence of these mediators is favorably modified with OSA treatment [87,89].

Additionally, hypoxia-reoxygenation, sympathetic activation and increased lipid peroxidation amplify free radical production [90]. There is enhanced free radical production from neutrophils and monocytes in OSA, with amelioration with therapy [87,92]. Oxidant stress contributes to endothelial injury, increased production of adhesion molecules in the endothelium, diminish vasodilator production and atherosclerosis [93].

The hypoxia-regeneration, inflammation and oxidative stress contribute to endothelial injury and thence, vasoconstriction, hypercoagulability and atherosclerosis [87]. These pathways may constitute the mechanistic paradigm whereby OSA mediates the genesis or worsening of hypertension and other cardiovascular disorders (Figure 1).

SDB and Excess Mortality

As previously discussed, most retrospective studies indicate that OSA is a risk factor for decreased long-term survival. More recently, 3 observational cohort studies have confirmed that SDB appears to increase mortality rates. In an 18 year follow-up of the Wisconsin Sleep Cohort, the adjusted hazard ratio for all-cause mortality with severe versus no SDB was 3.0 and the CVD specific hazard ratio was 5.2 [94]. Similarly, a 14 year follow-up of the Busselton Health Study found the fully adjusted hazard ratio for all-cause mortality associated with moderate to severe OSA was 6.24 [95]. However, in both studies, confidence intervals were wide, and the precision of the estimate is uncertain. More recently, with an average follow-up duration of 8.2 years, SHHS found a fully adjusted hazard ratio for all-cause mortality of 1.46 with much narrower confidence intervals. In addition, death in men accounted for most of this effect. Coronary heart disease specific mortality showed the same pattern, and it appeared that nocturnal hypoxemia was an important mediating factor [96]. Although treatment of OSA with CPAP has been shown to reduce the risk of fatal and non-fatal cardiovascular events in a clinically derived observational cohort comprised of only men [36], a randomized controlled trial has not been performed. Thus, it remains to be definitively determined whether treatment of SDB reduces all-cause mortality.

Summary

There is compelling evidence suggesting an association, probably causal, between sleep disordered breathing, especially, obstructive sleep apnea, and diverse cardiovascular disorders as well as increased mortality. Large, prospective, long-term studies will help further confirm this relationship. The current data also suggest a beneficial role of CPAP therapy in attenuating the risk of adverse cardiovascular sequelae. However, conclusive evidence of the salutary role of SDB therapy will require large randomized controlled studies designed with careful attention to the potential confounders, as well as aimed at elucidating the mechanistic pathways whereby SDB therapy provides cardiovascular benefits.

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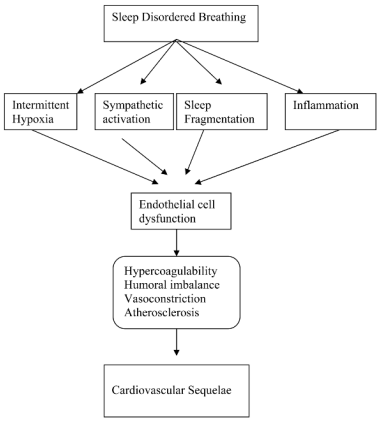

Figure 1.
Pathogenetic mechanisms whereby sleep disordered breathing leads to cardiovascular sequelae (Modified from Reference [85], Budhiraja et al).