Respir Care. Author manuscript; available in PMC 2010 Nov 3.
Published in final edited form as:
Respir Care. 2010 Oct; 55(10): 1322–1332.

PMCID: PMC2972194
NIHMSID: NIHMS244911

Sleep Disordered Breathing and Cardiovascular Disorders

Rohit Budhiraja, M.D.,[1,2,3] Pooja Budhiraja, M.D.,[1,2] and Stuart F Quan, M.D.[4,3]

[1] Department of Medicine, Southern Arizona Veterans Affairs Health Care System (SAVAHCS)
[2] Department of Medicine, University of Arizona College of Medicine Tucson, AZ
[3] Arizona Respiratory Center, University of Arizona College of Medicine, Tucson, AZ
[4] Division of Sleep Medicine, Harvard Medical School and Brigham and Womens Hospital, Boston, MA
Address correspondence to: Stuart F. Quan, M.D., Division of Sleep Medicine, Harvard Medical School and Brigham and Womens Hospital, 401 Park Dr., 2nd Floor East Boston, MA 02215, squan@arc.arizona.edu, Phone: 617-998-8842, Fax: 617-998-8823

Introduction

Go to:

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.

Go to:

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 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).

Figure 1

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

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

Go to:

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.

Acknowledgments

Go to:

Research support provided by HL53938.

References

Go to:

1. Tishler PV, Larkin EK, Schluchter MD, Redline S. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. Jama. 2003;289(17):2230–7. [PubMed]

2. Fletcher EC. The relationship between systemic hypertension and obstructive sleep apnea: facts and theory. Am J Med. 1995;98(2):118–28. [PubMed]

3. Franklin KA, Nilsson JB, Sahlin C, Naslund U. Sleep apnoea and nocturnal angina. Lancet. 1995;345(8957):1085–7. [PubMed]

4. Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. Lancet. 1990;336(8710):261–4. [PubMed]

5. Malone S, Liu PP, Holloway R, Rutherford R, Xie A, Bradley TD. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet. 1991;338 (8781):1480–4. [PubMed]

6. He J, Kryger MH, Zorick FJ, Conway W, Roth T. Mortality and apnea index in obstructive sleep apnea. Experience in 385 male patients. Chest. 1988;94(1):9–14. [PubMed]

7. Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients. Mortality Chest. 1988;94(6):1200–4. [PubMed]

8. Gonzalez-Rothi RJ, Foresman GE, Block AJ. Do patients with sleep apnea die in their sleep? Chest. 1988;94(3):531–8. [PubMed]

9. Fields LE, Burt VL, Cutler JA, Hughes J, Roccella EJ, Sorlie P. The burden of adult hypertension in the United States 1999 to 2000: a rising tide. Hypertension. 2004;44(4):398–404. [PubMed]

10. Budhiraja R, Sharief I, Quan SF. Sleep disordered breathing and hypertension. J Clin Sleep Med. 2005;1(4):401–4. [PubMed]

11. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342(19):1378–84. [PubMed]

12. Hla KM, Young T, Finn L, Peppard PE, Szklo-Coxe M, Stubbs M. Longitudinal association of sleep-disordered breathing and nondipping of nocturnal blood pressure in the Wisconsin Sleep Cohort Study. Sleep. 2008;31(6):795–800. [PMC free article] [PubMed]

13. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. 2000;283(14):1829 –36. [PubMed]

14. O'Connor GT, Caffo B, Newman AB, et al. Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. Am J Respir Crit Care Med. 2009;179(12):1159–64. [PMC free article] [PubMed]

15. Logan A. Sleep-disordered breathing and hypertension. Am J Respir Crit Care Med. 2009;179 (12):1082–3. [PubMed]

16. Peppard PE. Is obstructive sleep apnea a risk factor for hypertension? --differences between the Wisconsin Sleep Cohort and the Sleep Heart Health Study. J Clin Sleep Med. 2009;5(5):404–5. [PMC free article] [PubMed]

17. Redline S. Does sleep disordered breathing increase hypertension risk? A practical perspective on interpreting the evidence. J Clin Sleep Med. 2009;5(5):406–8. [PMC free article] [PubMed]

18. Hu FB, Willett WC, Colditz GA, et al. Prospective study of snoring and risk of hypertension in women. Am J Epidemiol. 1999;150(8):806–16. [PubMed]

19. Mehra R, Stone KL, Blackwell T, et al. Prevalence and correlates of sleep-disordered breathing in older men: osteoporotic fractures in men sleep study. J Am Geriatr Soc. 2007;55(9):1356–64. [PMC free article] [PubMed]

20. Kario K, Shimada K, Pickering TG. Abnormal nocturnal blood pressure falls in elderly hypertension: clinical significance and determinants. J Cardiovasc Pharmacol. 2003;41 (Suppl 1):S61 –6. [PubMed]

21. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens. 2001;19(12):2271–7. [PubMed]

22. Lavie P, Hoffstein V. Sleep apnea syndrome: a possible contributing factor to resistant. Sleep. 2001;24(6):721–5. [PubMed]

23. Duran-Cantolla J, Aizpuru F, Martinez-Null C, Barbe-Illa F. Obstructive sleep apnea/hypopnea and systemic hypertension. Sleep Med Rev. 2009;13(5):323–31. [PubMed]

24. Giles TL, Lasserson TJ, Smith BJ, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. Cochrane Database Syst Rev. 2006;(1):CD001106. [PubMed]

25. Robinson GV, Smith DM, Langford BA, Davies RJ, Stradling JR. Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. Eur Respir J. 2006;27(6):1229–35. [PubMed]

26. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med. 2001;163(2):344–8. [PubMed]

27. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet. 2002;359(9302):204–10. [PubMed]

28. Shibata N, Nishimura T, Hasegawa K, Hattori C, Suzuki K. Influence of sleep respiratory disturbance on nocturnal blood pressure. Acta Otolaryngol Suppl. 2003;(550):32–5. [PubMed]

29. Budhiraja R, Quan SF. When Is CPAP an Antihypertensive in Sleep Apnea Patients? J Clin Sleep Med. 2009;5:108–109. [PMC free article] [PubMed]

30. Sorajja D, Gami AS, Somers VK, Behrenbeck TR, Garcia-Touchard A, Lopez-Jimenez F. Independent association between obstructive sleep apnea and subclinical coronary artery disease. Chest. 2008;133(4):927–33. [PMC free article] [PubMed]

31. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001;163(1):19–25. [PubMed]

32. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010;122(4):352–60. Epub 2010 Jul 12. [PMC free article] [PubMed]

33. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med. 2002;166(2):159–65. [PubMed]

34. Mooe T, Franklin KA, Holmstrom K, Rabben T, Wiklund U. Sleep-disordered breathing and coronary artery disease: long-term prognosis. Am J Respir Crit Care Med. 2001;164(10 Pt 1):1910–3. [PubMed]

35. Peker Y, Hedner J, Kraiczi H, Loth S. Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. Am J Respir Crit Care Med. 2000;162(1):81–6. [PubMed]

36. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365(9464):1046–53. [PubMed]

37. Steiner S, Schueller PO, Hennersdorf MG, Behrendt D, Strauer BE. Impact of obstructive sleep apnea on the occurrence of restenosis after elective percutaneous coronary intervention in ischemic heart disease. Respir Res. 2008;9:50. [PMC free article] [PubMed]

38. Yumino D, Tsurumi Y, Takagi A, Suzuki K, Kasanuki H. Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome. Am J Cardiol. 2007;99(1):26–30. [PubMed]

39. Nakashima H, Katayama T, Takagi C, et al. Obstructive sleep apnoea inhibits the recovery of left ventricular function in patients with acute myocardial infarction. Eur Heart J. 2006;27(19):2317–22. [PubMed]

40. Cassar A, Morgenthaler TI, Lennon RJ, Rihal CS, Lerman A. Treatment of obstructive sleep apnea is associated with decreased cardiac death after percutaneous coronary intervention. J Am Coll Cardiol. 2007;50(14):1310–4. [PubMed]

41. Milleron O, Pilliere R, Foucher A, et al. Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study. Eur Heart J. 2004;25(9):728–34. [PubMed]

42. Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi GF. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med. 2007;176(7):706–12. [PubMed]

43. Steiropoulos P, Tsara V, Nena E, et al. Effect of continuous positive airway pressure treatment on serum cardiovascular risk factors in patients with obstructive sleep apnea-hypopnea syndrome. Chest. 2007;132(3):843–51. [PubMed]

44. Peker Y, Glantz H, Thunstrom E, Kallryd A, Herlitz J, Ejdeback J. Rationale and design of the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea--RICCADSA trial. Scand Cardiovasc J. 2009;43(1):24–31. [PubMed]

45. Khayat RN, Jarjoura D, Patt B, Yamokoski T, Abraham WT. In-hospital testing for sleep-disordered breathing in hospitalized patients with decompensated heart failure: report of prevalence and patient characteristics. J Card Fail. 2009;15(9):739–46. [PMC free article] [PubMed]

46. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail. 2007;9(3):251–7. [PubMed]

47. Paulino A, Damy T, Margarit L, et al. Prevalence of sleep-disordered breathing in a 316-patient French cohort of stable congestive heart failure. Arch Cardiovasc Dis. 2009;102(3):169–75. [PubMed]

48. Schulz R, Blau A, Borgel J, et al. Sleep apnoea in heart failure. Eur Respir J. 2007;29(6):1201–5. [PubMed]

49. Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation. 1998;97 (21):2154–9. [PubMed]

50. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol. 2007;49(20):2028–34. [PubMed]

51. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med. 1999;160(4):1101–6. [PubMed]

52. Hanly PJ, Zuberi-Khokhar NS. Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure. Am J Respir Crit Care Med. 1996;153(1):272–6. [PubMed]

53. Lanfranchi PA, Somers VK, Braghiroli A, Corra U, Eleuteri E, Giannuzzi P. Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. Circulation. 2003;107 (5):727–32. [PubMed]

54. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med. 2003;348(13):1233–41. [PubMed]

55. Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. Am J Respir Crit Care Med. 2004;169(3):361–6. [PubMed]

56. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation. 2000;101(4):392–7. [PubMed]

57. Bitter T, Faber L, Hering D, Langer C, Horstkotte D, Oldenburg O. Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. Eur J Heart Fail. 2009;11(6):602–8. [PubMed]

58. Cloward TV, Walker JM, Farney RJ, Anderson JL. Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with nasal continuous positive airway pressure. Chest. 2003;124(2):594–601. [PubMed]

59. Laaban JP, Pascal-Sebaoun S, Bloch E, Orvoen-Frija E, Oppert JM, Huchon G. Left ventricular systolic dysfunction in patients with obstructive sleep apnea syndrome. Chest. 2002;122(4):1133–8. [PubMed]

60. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med. 2005;353(19):2025–33. [PubMed]

61. Naughton MT, Lorenzi-Filho G. Sleep in heart failure. Prog Cardiovasc Dis. 2009;51(4):339–49. [PubMed]

62. Garrigue S, Bordier P, Jais P, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med. 2002;346(6):404–12. [PubMed]

63. Simantirakis EN, Schiza SE, Chrysostomakis SI, Chlouverakis GI, Klapsinos NC, Siafakas NM, Vardas PE. Atrial overdrive pacing for the obstructive sleep apnea-hypopnea syndrome. N Engl J Med. 2005;353(24):2568–77. [PubMed]

64. Krahn AD, Yee R, Erickson MK, et al. Physiologic pacing in patients with obstructive sleep apnea: a prospective, randomized crossover trial. J Am Coll Cardiol. 2006 Jan 17;47(2):379–83. Epub 2005 Dec 20. [PubMed]

65. Melzer C, Fietze I, Duru F, et al. Nocturnal overdrive pacing for the treatment of sleep apnea syndrome. Sleep. 2006 Sep 1;29(9):1197–202. [PubMed]

66. Gabor JY, Newman DA, Barnard-Roberts V, et al. Improvement in Cheyne-Stokes respiration following cardiac resynchronisation therapy. Eur Respir J. 2005 Jul;26(1):95–100. [PubMed]

67. Lüthje L, Renner B, Kessels R, et al. Cardiac resynchronization therapy and atrial overdrive pacing for the treatment of central sleep apnoea. Eur J Heart Fail. 2009 Mar;11(3):273–80. [PMC free article] [PubMed]

68. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med. 2006;173(8):910–6. [PMC free article] [PubMed]

69. Mehra R, Stone KL, Varosy PD, et al. Nocturnal Arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study. Arch Intern Med. 2009;169(12):1147–55. [PMC free article] [PubMed]

70. Garrigue S, Pepin JL, Defaye P, et al. High prevalence of sleep apnea syndrome in patients with long-term pacing: the European Multicenter Polysomnographic Study. Circulation. 2007;115(13):1703–9. [PubMed]

71. Monahan K, Storfer-Isser A, Mehra R, et al. Triggering of nocturnal arrhythmias by sleep-disordered breathing events. J Am Coll Cardiol. 2009;54(19):1797–804. [PMC free article] [PubMed]

72. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med. 2005;352(12):1206–14. [PubMed]

73. Simantirakis EN, Schiza SI, Marketou ME, et al. Eur Heart J. 2004;25(12):1070–6. Severe bradyarrhythmias in patients with sleep apnoea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder. [PubMed]

74. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation. 2003;107(20):2589–94. [PubMed]

75. Dyken ME, Im KB. Obstructive sleep apnea and stroke. Chest. 2009;136(6):1668–77. [PubMed]

76. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. 2005;353(19):2034–41. [PubMed]

77. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med. 2005;172(11):1447–51. [PMC free article] [PubMed]

78. Redline S, Diener-West M, Geraghty E, et al. Obstructive Sleep Apnea Hypopnea and Incident Stroke: The Sleep Heart Health Study. Am J Respir Crit Care Med. 2010;182(2):269–77. Epub 2010 Mar 25. [PMC free article] [PubMed]

79. Martinez-Garcia MA, Soler-Cataluna JJ, Ejarque-Martinez L, et al. Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5-year follow-up study. Am J Respir Crit Care Med. 2009;180(1):36–41. [PubMed]

80. Fletcher EC. Invited review: Physiological consequences of intermittent hypoxia: systemic blood pressure. J Appl Physiol. 2001;90(4):1600–5. [PubMed]

81. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? Thorax. 2009;64(7):631–6. [PubMed]

82. Shamsuzzaman AS, Winnicki M, Lanfranchi P, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation. 2002;105(21):2462–4. [PubMed]

83. Larkin EK, Rosen CL, Kirchner HL, et al. Variation of C-reactive protein levels in adolescents: association with sleep-disordered breathing and sleep duration. Circulation. 2005;111(15):1978–84. [PubMed]

84. Mehra R, Storfer-Isser A, Kirchner HL, et al. Soluble interleukin 6 receptor: A novel marker of moderate to severe sleep-related breathing disorder. Arch Intern Med. 2006;166(16):1725–31. [PubMed]

85. Ohga E, Nagase T, Tomita T, et al. Increased levels of circulating ICAM-1, VCAM-1, and L-selectin in obstructive sleep apnea syndrome. J Appl Physiol. 1999;87(1):10–4. [PubMed]

86. El-Solh AA, Mador MJ, Sikka P, Dhillon RS, Amsterdam D, Grant BJ. Adhesion molecules in patients with coronary artery disease and moderate-to-severe obstructive sleep apnea. Chest. 2002;121 (5):1541–7. [PubMed]

87. Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. Am J Respir Crit Care Med. 2002;165 (7):934–9. [PubMed]

88. Price DT, Loscalzo J. Cellular adhesion molecules and atherogenesis. Am J Med. 1999;107(1):85 –97. [PubMed]

89. Yokoe T, Minoguchi K, Matsuo H, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation. 2003;107(8):1129–34. [PubMed]

90. Zhang GX, Kimura S, Nishiyama A, et al. Cardiac oxidative stress in acute and chronic isoproterenol-infused rats. Cardiovasc Res. 2005;65(1):230–8. [PubMed]

91. Schulz R, Mahmoudi S, Hattar K, et al. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. Am J Respir Crit Care Med. 2000;162(2 Pt 1):566–70. [PubMed]

92. Deanfield J, Donald A, Ferri C, et al. Endothelial function and dysfunction. Part I. Methodological issues for assessment in the different vascular beds: a statement by the Working Group on Endothelin and Endothelial Factors of the European Society of Hypertension. J Hypertens. 2005;23(1):7–17. [PubMed]

93. Budhiraja R, Parthasarathy S, Quan SF. Endothelial dysfunction in obstructive sleep apnea. J Clin Sleep Med. 2007;3(4):409–15. [PMC free article] [PubMed]

94. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep. 2008;31(8):1071–8. [PMC free article] [PubMed]

95. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. Sleep. 2008;31(8):1079 –85. [PMC free article] [PubMed]

96. Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med. 2009;6(8):e1000132. [PMC free article] [PubMed]