Hypertension and Obstructive Sleep Apnea

Bradley G. Phillips, PharmD, and Virend K. Somers, MD, DPhil

Address
College of Pharmacy, University of Iowa, Iowa City, IA 52242, USA.
E-mail: bradley-phillips@uiowa.edu

Current Hypertension Reports 2003, **5:**380–385
Current Science Inc. ISSN 1522-6417

Obstructive sleep apnea is a common disorder that is often unrecognized and underappreciated. Emerging evidence suggests that there is a causal link between obstructive sleep apnea and hypertension. This relationship appears to be independent of other comorbidities that have been previously linked to hypertension, such as obesity. The majority of studies support the contention that alleviation of sleep disordered breathing has a clinically significant beneficial impact on decreasing both nighttime and daytime blood pressure. A pathophysiologic basis for patients with sleep apnea having an increased risk for hypertension is not fully elucidated. However, there is consistent evidence that autonomic mechanisms are implicated. Sympathetic activation along with humoral responses to repetitive episodes of hypoxemia and apnea over the longer term may cause vasoconstriction, endothelial dysfunction, and possibly hypertension. Patients with sleep apnea are often obese and may be predisposed to weight gain. Hence, obesity may further contribute to hypertension in this patient population.

Introduction

Sleep apnea is common but often unrecognized and underappreciated, even in obese patients with hypertension. Several studies show that sleep disordered breathing is common in both men (25%) and women (10%) of varying ethnic groups [1,2]. In middle-aged Americans, the prevalence of symptomatic sleep apnea has been reported to be 4% for men and 2% for women [3,4]. The 5-year incidence of sleep disordered breathing in an American urban adult population may be up to 16% for mild to moderate sleep apnea and 7.5% for moderately severe sleep disordered breathing [5].

Obstructive sleep apnea (OSA) is characterized by repetitive pharyngeal collapse during sleep, which decreases or stops airflow, with subsequent arousal from sleep to resume breathing. The severity is evaluated by polysomnography, and severity is graded by the number of episodes of apnea and hypopnea the patient experiences during sleep (apnea and hypopnea index [AHI], events/hour). Obstructive apnea is defined as cessation of airflow for at least 10 seconds with respiratory effort: hypopnea is defined as greater than a 50% reduction in airflow or less than a 50% reduction in airflow with oxygen desaturation of at least 4% or with electroencephalographic evidence of arousal. One of the hallmarks of OSA is witnessed apneas, gasping, or both. Other recognized signs, symptoms, and considerations of sleep apnea include obesity, snoring, hypertension, daytime sleepiness, and family history. Resistant hypertension may also be common. In one study, 87% of hypertensive patients refractory to maximal medical therapy, had undiagnosed OSA [6].

Obstructive sleep apnea may exacerbate the cardiac and vascular risks of hypertension. Patients with sleep apnea, in the absence of hypertension, have elevated biomarkers of cardiovascular risk. C-reactive protein levels may be mildly elevated in men in proportion to the severity of their sleep apnea compared with similarly obese patients without sleep disordered breathing [7]. Emerging evidence suggests that obese and nonobese patients with sleep disordered breathing may have insulin resistance [8,9]. Currently, biomarkers are not used to screen for or evaluate severity of sleep apnea.

This review examines the evidence for an association between OSA and hypertension, the impact of treating sleep disordered breathing on blood pressure, and the pathophysiologic mechanisms of hypertension in patients with sleep apnea.

Obstructive Sleep Apnea and Hypertension

There is compelling evidence for an association between sleep apnea and hypertension. Up to 60% of patients with sleep apnea may have hypertension [10]. Hypertension in patients with sleep apnea is often resistant to antihypertensive therapy [6]. Simulated sleep apnea in an animal model results in sustained increases in blood pressure [11]. The most convincing data to support an association between OSA and hypertension come from two large epidemiologic studies that suggest sleep disordered breathing is a likely risk factor for new onset hypertension, and perhaps consequent morbidity and mortality. The Wisconsin Sleep Cohort Study showed a linear relationship between severity of sleep apnea and incidence of new hypertension that was not explained by other factors, such

as baseline blood pressure, body habitus, age, gender, and cigarette and alcohol consumption [12••]. A similar relationship between sleep apnea and hypertension was observed in the Sleep Heart Health Study [13••]. In this study, the odds ratio (OR) in the group with the most severe sleep apnea (AHI ≥ 30) was 1.37 (95% confidence interval [CI], 1.03–1.83; *P* for trend = 0.005) compared with those with lowest AHI (< 1.5) after adjusting for confounding factors, including obesity. These data add to the mounting evidence for a causal relationship between hypertension and sleep disordered breathing. Further, the recent seventh report of the Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure now recognizes sleep apnea as an identifiable cause of secondary hypertension [14].

Effects of Treatment of Sleep Disordered Breathing on Blood Pressure

Therapies to alleviate sleep disordered breathing include nasal continuous positive airway pressure (CPAP), dental devices, weight loss in obese individuals, surgery, and positional therapy for those individuals that have sleep apnea mainly when sleeping on their backs. Of these, CPAP therapy has become the standard treatment for OSA [15]. Treatment of sleep disordered breathing often confers improvements in subjective symptoms, especially daytime somnolence. Most studies, but not all, show that CPAP therapy modestly improves nocturnal and diurnal blood pressure in patients with sleep apnea. The discordance between studies, in part, may reflect one or more of the following: small sample size, lack of a control arm, compliance with CPAP therapy, varying lengths of therapy, methods used to evaluate blood pressure, and inclusion of hypertensive and normotensive patients.

In a recent study, effective longer-term CPAP therapy (approximately 9 weeks) in 32 normotensive and hypertensive OSA patients substantially decreased daytime and nighttime mean systolic and diastolic blood pressures by approximately 10 mm Hg compared with subtherapeutic CPAP therapy (Fig. 1) [16••]. Although subtherapeutic CPAP decreased AHI by 50%, blood pressure did not significantly change. Interestingly, with the exception of AHI and Epworth sleepiness scale scores, only mean oxygen saturation was significantly higher ($P = 0.04$) at the end of the study in those randomized to therapeutic CPAP. This study demonstrates that effective CPAP in moderate to severe OSA improves blood pressure, and highlights the importance of administration of and adhering to optimal CPAP therapy, particularly to eliminate hypoxemia. In a similarly designed study, 4 weeks of therapeutic CPAP modestly reduced mean arterial ambulatory blood pressure by 2.5 mm Hg compared with subtherapeutic CPAP, which increased blood pressure by 0.8 mm Hg ($P = 0.0013$) [17]. These studies are in agreement with earlier trials that show a reduction in blood pressure with 1 week to 6 months of CPAP therapy [18–21]. In patients with resistant hypertension, CPAP therapy has been shown to significantly reduce systolic blood pressure on the first night of treatment and reduce both daytime and nighttime blood pressure after 2 months of chronic therapy [22]. Conversely, in two randomized controlled trials, 1 week of CPAP in OSA patients only lowered nighttime blood pressure [23]; in the other, CPAP decreased blood pressure only in those study patients who were nondippers [24].

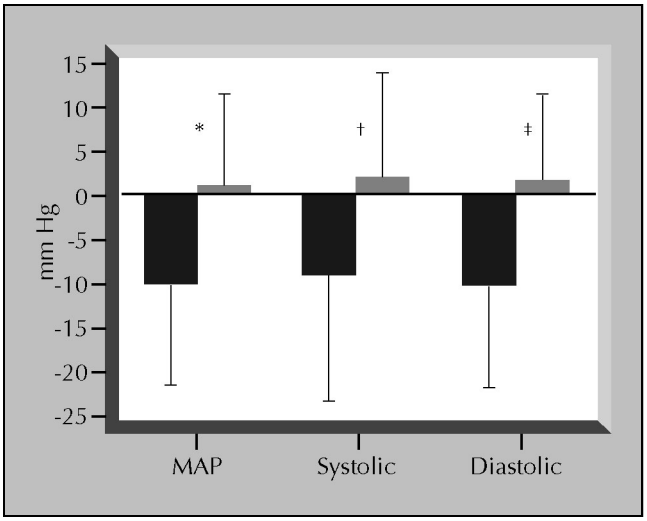

Figure 1. Changes in blood pressure with effective (*darkly shaded bars*) and subtherapeutic (*lightly shaded bars*) continuous positive airway pressure. $^{*}P = 0.01$; $^{\dagger}P = 0.04$; $^{\ddagger}P < 0.005$. Diastolic—diastolic blood pressure; MAP—mean arterial blood pressure; Systolic—systolic blood pressure. (*Adapted from* Becker *et al*. [16••].)

It is not known if treating sleep apnea negates the potential risk of developing hypertension or completely normalizes blood pressure in hypertensive OSA patients. This may depend, in part, on the duration that sleep apnea remains untreated and the efficacy of treatments to alleviate sleep disordered breathing. As cardiovascular morbidity and mortality associated with hypertension take years to manifest, the impact of treating OSA may not be fully apparent until longer-term trials are completed. Regardless, patients with undiagnosed sleep apnea and those patients who fail treatment strategies, are noncompliant, or cannot tolerate therapy to alleviate sleep disordered breathing, may remain at risk for hypertension, which is often refractory to conventional antihypertensive therapy.

Mechanisms of Hypertension in Sleep Apnea

While the mechanisms underlying the link between obstructive sleep apnea and hypertension are not completely established, there is evidence to support several possibilities. First, increased sympathetic activity in response to hypoxemia and hypercapnia with consequent chemoreflex activation may increase peripheral vascular tone. The sympathetic activation persists even into daytime normoxia. Second, hypoxemia may elicit

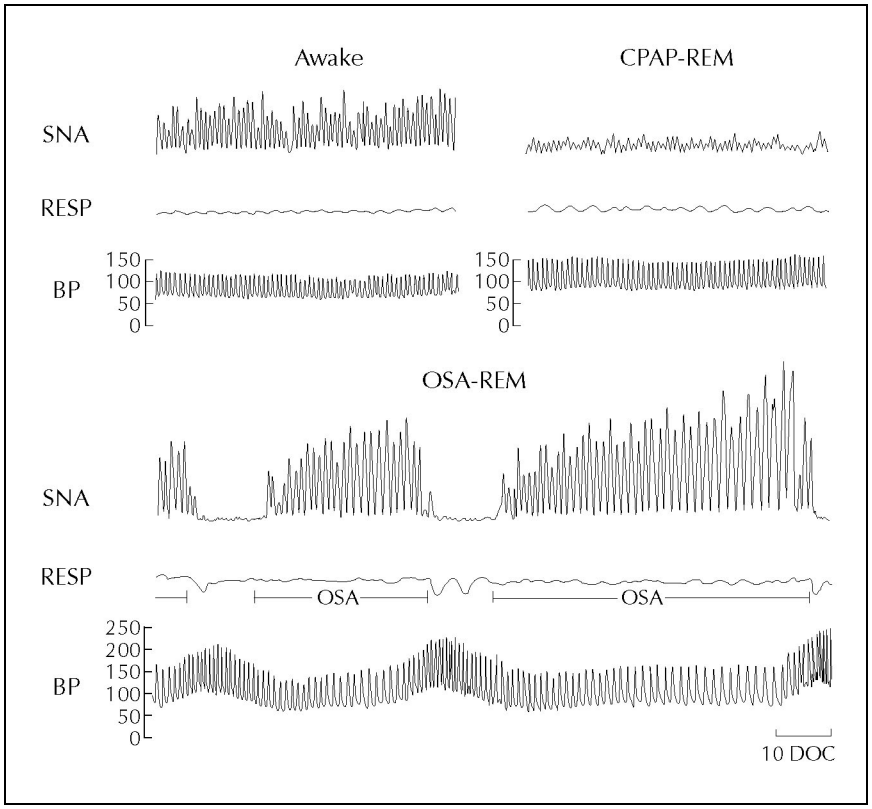

Figure 2. Recordings of sympathetic nerve activity (SNA), respiration (RESP), and intra-arterial blood pressure (BP) in the same subject when awake (*top left*), with obstructive sleep apnea (OSA) during rapid eye movement (REM) sleep (*bottom*), and with elimination of OSA by continuous positive airways pressure (CPAP) therapy during REM sleep (*top right*). (*Adapted from* Somers *et al*. [25].)

increased production of various circulating vasoconstrictors that increase blood pressure. Third, patients with sleep apnea may be predisposed to vasculopathy, which may be due to long-term sympathetic activation, humoral factors such as endothelin-1 (ET-1), and endothelial dysfunction. Fourth, patients with sleep apnea may be predisposed to weight gain. The presence of obesity and sleep apnea likely indicates an increased risk for hypertension.

Sympathetic activation

Sympathetic activity is increased during sleep and during the day when sleep apneic patients are awake and breathing normally with normal oxygen saturation and carbon dioxide levels. Marked increases in sympathetic drive during sleep apnea are explained by repetitive episodes of apnea and hypoxia (Fig. 2) [25]. Surges in blood pressure as high as 250/110 mm Hg may be observed as resumption of breathing increases cardiac output to a severely constricted peripheral vasculature. Baroreflex and chemoreflex dysfunction in patients with sleep apnea may, in part, contribute to sustained sympathetic activation and increased blood pressure during the daytime [26–29]. Plasma and urine catecholamines are elevated during the night and day in patients with OSA. Other humoral factors such as leptin may also be implicated in sympathetic activation.

Obesity does not appear to explain increased sympathetic activity in patients with sleep apnea. Muscle sympathetic nerve activity recordings in 24 healthy normal weight subjects and 30 healthy obese subjects, nine of whom had unrecognized OSA, showed that muscle sympathetic nerve activity was significantly elevated in patients with untreated OSA (61 ± 8 bursts per 100 heartbeats) compared with similarly obese subjects (42 ± 3 bursts per 100 heartbeats) and lean subjects (41 ± 3 bursts per 100 heartbeats), all of whom were free of sleep disordered breathing ($P = 0.02$) [30]. Alleviation of sleep disordered breathing decreases muscle sympathetic activity at 6 months, and remains lower for at least up to a year with CPAP therapy [31]. Taken together, these results indicate that high sympathetic drive may contribute to increases in blood pressure during the night and day; long-term CPAP therapy attenuates the sympathetic activation observed in patients with sleep apnea.

Endothelin-1

The endothelin system has been implicated in the chronic pressor effects of sleep apnea [32]. Endothelin-1 (ET-1) is a potent and long-acting vasoconstrictor with mitogenic properties. Hypoxia is a powerful stimulus for ET-1 production. In animal models, intermittent hypoxia increased ET-1 and blood pressure [33]. Treatment with an ET-1 blocker in this study decreased blood pressure in a dose-dependent manner. In untreated sleep apneics, 4 to 5 hours of untreated sleep apnea with a mean oxygen saturation low of 73% ± 9% was accompanied by a significant increase in both blood pressure and ET-1 (Fig. 3) [34]. Treatment with CPAP to alleviate sleep disordered breathing over the subsequent 4 hours normalized oxygen saturation (91% ± 3%) and was accompanied by a reduction in both blood pressure and ET-1. In control subjects without

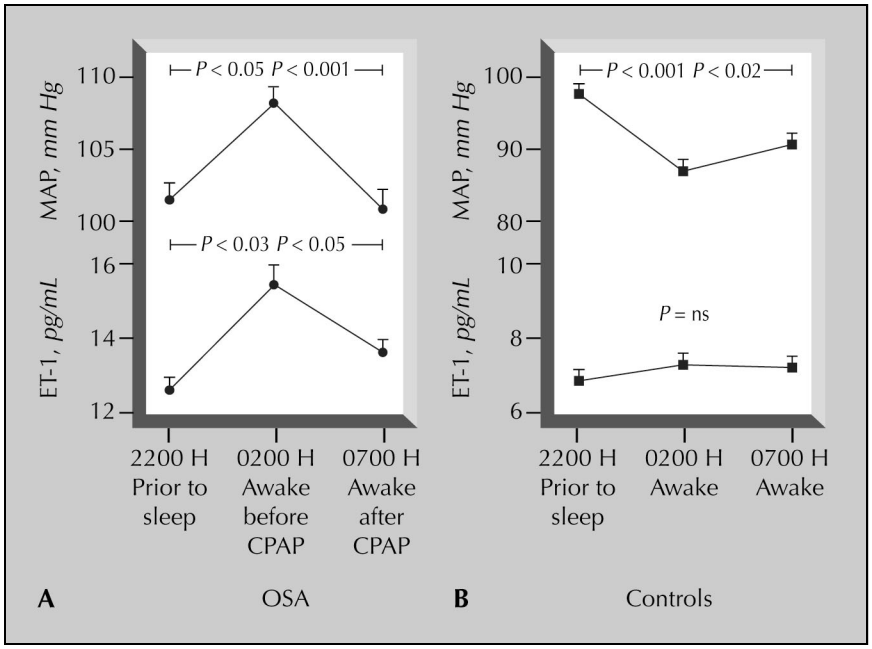

Figure 3. **A**, Comparison of mean arterial pressure (MAP) and endothelin-1 (ET-1) in 22 patients with severe obstructive sleep apnea (OSA) before sleep at approximately 22:00 hours, before nasal continuous positive airways pressure (CPAP) therapy at approximately 02:00 hours, and on waking at approximately 07:00 hours after 5 hours of CPAP therapy. **B**, Measurements in control subjects without sleep apnea. Data are means ± SEM. (*Adapted from* Phillips *et al*. [34].)

sleep apnea, ET-1 levels did not change during sleep. While these data do not prove any causal association, they suggest that the potent long-lasting pressor effects of endothelin may be implicated in the increased blood pressure in patients with sleep apnea.

Vascular mechanisms

Impaired endothelium-dependent vasodilation is an established early accompaniment of hypertension [35]. Reduced nitric oxide production, sympathetic activation, and endothelin may elicit an imbalance in the regulation of vascular tone and function in patients with sleep apnea. Repetitive nocturnal episodes of hypoxemia may suppress endothelial nitric oxide synthase. Circulating nitric oxide has been shown to be significantly decreased and to correlate inversely with severity of sleep apnea and oxygen desaturation time in patients with sleep apnea [36,37]. In otherwise healthy male patients with moderate to severe OSA (AHI 52 ± 22 events/h), endothelium-dependent vasodilation in response to intra-arterial acetylcholine was markedly impaired compared with closely matched control subjects without sleep disordered breathing [38]. Moderate vasculopathy in seemingly healthy patients with OSA may thus be involved in the pathogenesis of hypertension in patients with OSA.

Obesity and leptin

Obesity is a well established and major risk factor for hypertension. Up to 30% of obese individuals may have unrecognized and undiagnosed OSA. Male and female patients with OSA are predisposed to weight gain in the year prior to the diagnosis being made [39]. In obese male OSA patients, recent weight gain (approximately 5 kg) and plasma leptin levels are significantly more (approximately 50%) compared with similarly obese controls who were free of sleep disordered breathing (Fig. 4) [40•]. Leptin correlates with measures of

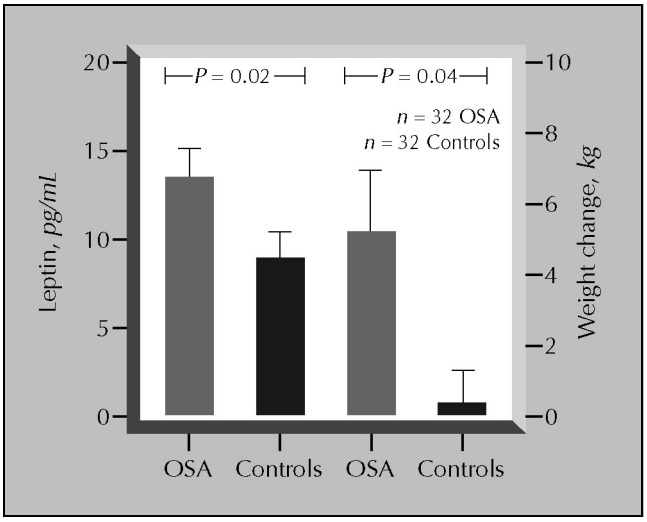

Figure 4. Difference in plasma leptin levels (*lightly shaded bars*) and change in body weight (*darkly shaded bars*) over the year before the study in 32 male patients with sleep apnea and 32 matched controls who were without sleep disordered breathing. Data are mean ± SEM. OSA—obstructive sleep apnea. (*Adapted from* Phillips *et al*. [40•].)

adiposity, low-density lipoprotein cholesterol, and blood pressure in OSA, and is decreased after 6 months of CPAP therapy [41]. Thus, OSA may be accompanied by resistance to the metabolic effects of leptin, greater than the resistance evident in obesity alone. Leptin may also play a role in the pathogenesis of obesity-related hypertension. Administration of leptin to animals results in increases in blood pressure [42] and in renal sympathetic nerve traffic [43]. Leptin has been implicated in the development of sustained hypertension and may be a risk factor for cardiovascular disease [44,45]. Thus, there appears to be an important interaction between sleep disordered breathing and both the metabolic and cardiovascular effects of heightened leptin levels.

Conclusions

Recent epidemiologic data suggest that sleep apnea is an independent risk factor for hypertension. Alleviation of sleep disordered breathing improves symptoms of sleep apnea. The majority of studies support the concept that effective CPAP therapy can also have an early and sustained beneficial effect on daytime and nighttime blood pressure. Sympathetic, humoral, and vascular responses to sleep apnea may increase blood pressure, and over the longer term may cause functional and structural cardiovascular changes predisposing to hypertension. Treatment of sleep disordered breathing has been shown to attenuate many of these potential pressor mechanisms. Obesity likely contributes to cardiovascular risk associated with sleep apnea and to hypertension in particular. Efforts to carefully screen for and treat patients with sleep apnea would likely impact on the risk of and treatment for hypertension, and on consequent cardiovascular morbidity and mortality.

Acknowledgments

This work was supported by HL-14388 (BGP), and by HL-61560 (VKS and BGP). VKS is also supported by HL-65176, HL-70602, and RR 00585. BGP and VKS were past recipients of a Sleep Academic Award from the National Institutes of Health.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Bixler EO, Vgontzas AN, Lin HM, *et al.*: **Association of hypertension and sleep-disordered breathing.** *Arch Intern Med* 2000, **60:**2289–2295.
2. Ohayon MM, Guilleminault C, Priest RG, *et al.*: **Is sleep-disordered breathing an independent risk factor for hypertension in the general population (13,057 subjects)?** *J Psychosom Res* 2000, **48:**593–601.
3. Young T, Palta M, Dempsey J, *et al.*: **The occurrence of sleep-disordered breathing among middle-aged adults.** *N Engl J Med* 1993, **328:**1230–1235.
4. Young T, Peppard PE, Gottlieb DJ: **Epidemiology of obstructive sleep apnea: a population health perspective.** *Am J Respir Crit Care Med* 2002, **165:**1217–1239.
5. Tishler PV, Larkin EK, Schluchter MD, *et al.*: **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:**2230–2237.
6. Logan AG, Perlikowski SM, Mente A, *et al.*: **High prevalence of unrecognized sleep apnoea in drug-resistant hypertension.** *J Hypertens* 2001, **19:**2271–2277.
7. Shamsuzzaman AS, Winnicki M, Lanfranchi P, *et al.*: **Elevated C-reactive protein in patients with obstructive sleep apnea.** *Circulation* 2002, **105:**2462–2464.
8. Punjabi NM, Sorkin JD, Katzel LI, *et al.*: **Sleep-disordered breathing and insulin resistance in middle-aged and overweight men.** *Am J Respir Crit Care Med* 2002, **165:**677–682.
9. Ip MS, Lam B, Ng MM, *et al.*: **Obstructive sleep apnea is independently associated with insulin resistance.** *Am J Respir Crit Care Med* 2002, **165:**670–676.
10. Silverberg DS, Oksenberg A, Iaina A: **Sleep-related breathing disorders as a major cause of essential hypertension: fact or fiction?** *Curr Opin Nephrol Hypertens* 1998, **7:**353–357.
11. Brooks D, Horner RL, Kozar LF, *et al.*: **Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model.** *J Clin Invest* 1997, **99:**106–109.
12. •• Peppard P, Young T, Palta M, *et al.*: **Prospective study of the association between sleep-disordered breathing and hypertension.** *N Engl J Med* 2000, **342:**1378–1384.

In 709 participants followed over a 4-year period, the presence of sleep apnea was associated with an increased risk of hypertension, adjusted for other factors known to increase blood pressure, such as weight and cigarettes. The association between sleep apnea and hypertension was dose dependent.

13. •• Nieto FJ, Young T, Lind B, *et al.*: **Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study.** *JAMA* 2000, **283:**1829–1836.

Sleep apnea has been associated with the development of hypertension. Using a cross-sectional analysis of 6132 participants of different gender and ethnic backgrounds, sleep apnea was associated with hypertension after adjusting for demographic and anthropometric variables. Data from this trial indicate that sleep apnea is associated with hypertension.

14. Chobanian AV, Bakris GL, Black HR, *et al.*: **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report.** *JAMA* 2003, **289:**2560–2572.
15. Sullivan CE, Issa FG, Berthon-Jones M, *et al.*: **Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares.** *Lancet* 1981, **1:**862–865.
16. •• Becker HF, Jerrentrup A, Ploch T, *et al.*: **Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea.** *Circulation* 2003, **107:**68–73.

Continuous positive airway pressure has become the primary therapy for OSA. Blood pressure in 16 moderate to severe OSA patients decreased dramatically by 10 mm Hg following 9 weeks of therapeutic CPAP compared with no change in blood pressure in those patients ($n = 16$) randomized to subtherapeutic CPAP. This study demonstrates that effective CPAP has substantial effects on reducing daytime and nighttime blood pressure.

17. 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:**204–210.
18. Wilcox I, Grunstein RR, Hedner JA, *et al.*: **Effect of nasal continuous positive airway pressure during sleep on 24-hour blood pressure in obstructive sleep apnea.** *Sleep* 1993, **16:**539–544.
19. Voogel AJ, van Steenwijk RP, Karemaker JM, *et al.*: **Effects of treatment of obstructive sleep apnea on circadian hemodynamics.** *J Auton Nerv Syst* 1999, **77:**177–183.
20. Jennum P, Wildschiodtz G, Christensen NJ, *et al.*: **Blood pressure, catecholamines, and pancreatic polypeptide in obstructive sleep apnea with and without nasal continuous positive airway pressure (nCPAP) treatment.** *Am J Hypertens* 1989, **2:**847–852.
21. Faccenda JF, Mackay TW, Boon NA, *et al.*: **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:**344–348.
22. Logan AG, Tkacova R, Perlikowski SM, *et al.*: **Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex.** *Eur Respir J* 2003, **21:**241–247.
23. Dimsdale JE, Loredo JS, Profant J: **Effect of continuous positive airway pressure on blood pressure: a placebo trial.** *Hypertension* 2000, **35:**144–147.
24. Engleman HM, Gough K, Martin SE, *et al.*: **Ambulatory blood pressure on and off continuous positive airway pressure therapy for the sleep apnea/hypopnea syndrome: effects in "non-dippers".** *Sleep* 1996, **19:**378–381.

25. Somers VK, Dyken ME, Clary MP, *et al.*: **Sympathetic neural mechanisms in obstructive sleep apnea.** *J Clin Invest* 1995, **96:**1897–1904.
26. Hedner JA, Wilcox I, Laks L, *et al.*: **A specific and potent pressor effect of hypoxia in patients with sleep apnea.** *Am Rev Respir Dis* 1992, **146:**1240–1245.
27. Narkiewicz K, Pesek CA, Kato M, *et al.*: **Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea.** *Hypertension* 1998, **32:**1039–1043.
28. Narkiewicz K, van de Borne PJ, Pesek CA, *et al.*: **Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea.** *Circulation* 1999, **99:**1183–1189.
29. Carlson JT, Hedner J, Elam M, *et al.*: **Augmented resting sympathetic activity in awake patients with obstructive sleep apnea.** *Chest* 1993, **103:**1763–1768.
30. Narkiewicz K, van de Borne PJ, Cooley RL, *et al.*: **Sympathetic activity in obese subjects with and without obstructive sleep apnea.** *Circulation* 1998, **98:**772–776.
31. Narkiewicz K, Kato M, Phillips BG, *et al.*: **Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea.** *Circulation* 1999, **100:**2332–2335.
32. Saarelainen S, Seppala E, Laasonen K, *et al.*: **Circulating endothelin-1 in obstructive sleep apnea.** *Endothelium* 1997, **5:**115–118.
33. Kanagy NL, Walker BR, Nelin LD: **Role of endothelin in intermittent hypoxia-induced hypertension.** *Hypertension* 2001, **37:**511–515.
34. Phillips BG, Narkiewicz K, Pesek CA, *et al.*: **Effects of obstructive sleep apnea on endothelin-1 and blood pressure.** *J Hypertens* 1999, **17:**61–66.
35. Panza JA, Quyyumi AA, Brush JE Jr, *et al.*: **Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension.** *N Engl J Med* 1990, **323:**22–27.
36. Schulz R, Schmidt D, Blum A, *et al.*: **Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnoea: response to CPAP therapy.** *Thorax* 2000, **55:**1046–1051.
37. Ip MS, Lam B, Chan LY, *et al.*: **Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure.** *Am J Respir Crit Care Med* 2000, **162:**2166–2171.
38. Kato M, Roberts-Thomson P, Phillips BG, *et al.*: **Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea.** *Circulation* 2000, **102:**2607–2610.
39. Phillips BG, Hisel TM, Kato M, *et al.*: **Recent weight gain in patients with newly diagnosed obstructive sleep apnea.** *J Hypertens* 1999, **17:**1297–1300.
40.• Phillips BG, Kato M, Narkiewicz K, *et al.*: **Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea.** *Am J Physiol Heart Circ Physiol* 2000, **279:**H234–H237.

Despite the weight reducing effects of leptin, obese subjects have marked increases in leptin levels (*ie*, leptin resistance). Male patients with sleep apnea ($n = 32$) had a significant history of weight gain and increased circulating leptin levels compared with matched controls ($n = 32$). These findings suggest that sleep apnea may be accompanied by further resistance to the metabolic effects of leptin, greater than the resistance evident in obesity alone.

41. Ip MS, Lam KS, Ho C, *et al.*: **Serum leptin and vascular risk factors in obstructive sleep apnea.** *Chest* 2000, **118:**580–586.
42. Shek EW, Brands MW, Hall JE: **Chronic leptin infusion increases arterial pressure.** *Hypertension* 1998, **31:**409–414.
43. Haynes WG, Morgan DA, Walsh SA, *et al.*: **Receptor-mediated regional sympathetic nerve activation by leptin.** *J Clin Invest* 1997, **100:**270–278.
44. Sheu WH, Lee WJ, Chen YT: **High plasma leptin concentrations in hypertensive men but not in hypertensive women.** *J Hypertens* 1999, **17:**1289–1295.
45. Wallace AM, McMahon AD, Packard CJ, *et al.*: **Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS).** *Circulation* 2001, **104:**3052–3056.