

# Obesity, Sleep Apnea, and Hypertension

Robert Wolk, Abu S.M. Shamsuzzaman, Virend K. Somers

**Abstract**—Obesity has a high and rising prevalence and represents a major public health problem. Obstructive sleep apnea (OSA) is also common, affecting an estimated 15 million Americans, with a prevalence that is probably also rising as a consequence of increasing obesity. Epidemiologic data support a link between obesity and hypertension as well as between OSA and hypertension. For example, untreated OSA predisposes to an increased risk of new hypertension, and treatment of OSA lowers blood pressure, even during the daytime. Possible mechanisms whereby OSA may contribute to hypertension in obese individuals include sympathetic activation, hyperleptinemia, insulin resistance, elevated angiotensin II and aldosterone levels, oxidative and inflammatory stress, endothelial dysfunction, impaired baroreflex function, and perhaps by effects on renal function. The coexistence of OSA and obesity may have more widespread implications for cardiovascular control and dysfunction in obese individuals and may contribute to some of the clustering of abnormalities broadly defined as the metabolic syndrome. From the clinical and therapeutic perspectives, the presence of resistant hypertension and the absence of a nocturnal decrease in blood pressure in obese individuals should prompt the clinician to consider the diagnosis of OSA, especially if clinical symptoms suggestive of OSA (such as poor sleep quality, witnessed apnea, excessive daytime somnolence, and so forth) are also present. (*Hypertension*. 2003;42:●●●-●●●.)

**Key Words:** hypertension, obesity ■ sleep apnea syndromes ■ sympathetic nervous system ■ insulin resistance

## Obesity: Prevalence and Association With Hypertension

The National Institutes of Health (NIH) and World Health Organization (WHO) guidelines define individuals with body mass index (BMI)  $\geq 25$  as overweight and those with BMI  $\geq 30$  as obese. By these criteria, the prevalence of overweight and obesity are extremely high, approaching epidemic proportions. For example, it is estimated that  $\approx 60\%$  of men and 50% of women are currently overweight in the United States, which represents more than 97 million adults.<sup>1</sup> Trend analyses suggest that this epidemic continues to increase (Table).

The high prevalence of obesity represents a major public health problem, predisposing to cardiac and vascular morbidity and mortality. Most notably, epidemiologic data consistently support a link between obesity and hypertension.<sup>2</sup> The Framingham Heart Study suggests that 65% of the risk for hypertension in women and 78% in men can be related to obesity.<sup>3</sup> In some populations, an almost linear relation exists between BMI and systolic/diastolic blood pressure.<sup>4</sup> However, the relation between obesity and hypertension is complex and probably represents an interaction of racial, gender, demographic, genetic, neurohormonal, and other factors. In addition, upper body (android) obesity, especially in the presence of increased visceral fat, is more strongly associated with hypertension than lower body (gynoid) obesity.

Considering the significant impact of even modestly elevated blood pressure on cardiovascular morbidity and mor-

ality,<sup>5</sup> it is not surprising that hypertensive cardiac and vascular disease contributes very substantially to the high cardiovascular morbidity associated with obesity. Therefore, understanding the mechanisms of obesity-induced hypertension is important both for prevention and therapy. In this review, we present evidence that obstructive sleep apnea (OSA) might be an important mechanism underlying the association between obesity and hypertension.

## Sleep Apnea: Prevalence and Association With Hypertension

OSA is characterized by recurrent episodes of cessation of respiratory airflow caused by upper airway inspiratory collapse during sleep, with a consequent decrease in oxygen saturation. Although its prevalence may vary in different populations and age groups, it has been estimated that OSA affects  $\approx 24\%$  and 9% of middle-aged men and women, respectively.<sup>6</sup> Moreover, the 5-year incidence of sleep-disordered breathing in a community-based sample has recently been found to be  $\approx 16\%$  and 7.5% for mild-to-moderate and for severe sleep-disordered breathing, respectively.<sup>7</sup>

The evidence supporting the association between OSA and chronic, long-standing hypertension is compelling and is provided by several cross-sectional, longitudinal, and treatment studies. Several reports have shown that the prevalence of hypertension is greater in patients with OSA and vice

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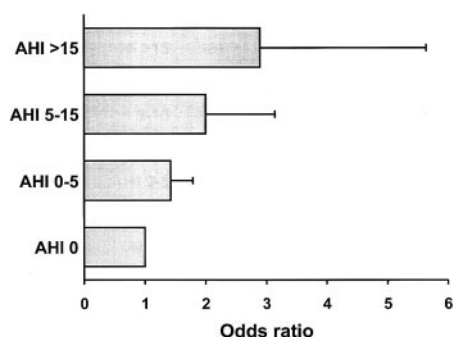
### Age-Adjusted Percentages of US Adults Aged 20–74 Years With BMI ≥ 25

Survey and Years	Men, %	Women, %	Total, %
NHES I (1960–1962)	48.2	38.7	43.3
NHANES I (1971–1974)	52.9	39.7	46.1
NHANES II (1976–1980)	51.4	40.8	46.0
NHANES III (1988–1994)	59.3	49.6	54.4

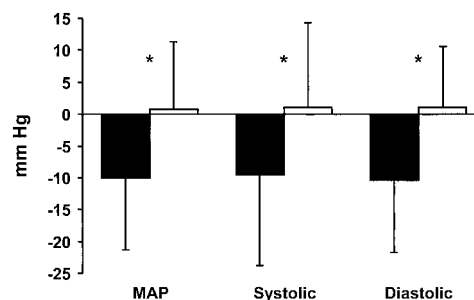
NHES indicates National Health Examination Survey; NHANES, National Health and Nutrition Examination Survey.

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versa. In the largest of those cross-sectional studies, with a total of 6132 participants, an elevated odds ratio for hypertension was found in subjects with sleep-disordered breathing after adjusting for demographics, anthropometric measurements (including BMI, neck circumference, and waist-to-hip ratio), alcohol consumption, and smoking.<sup>8</sup> In stratified analyses, the association between sleep-disordered breathing and hypertension was seen in men and women, older and younger ages, all ethnic groups, and among normal-weight and overweight individuals.<sup>8</sup> Similarly, in a retrospective analysis of 182 men without any cardiovascular disease at baseline and with follow-up information obtained 7 years after the baseline measures, incompletely treated OSA was found to be an independent predictor of cardiovascular disease, including hypertension.<sup>9</sup> Perhaps the most convincing prospective data in support of a causal relation between OSA and hypertension have been provided by the Wisconsin Sleep Cohort Study.<sup>10</sup> This study demonstrated an independent dose-response relation between sleep-disordered breathing at baseline and the development of new hypertension 4 years later. The odds ratios for the presence of incident hypertension at follow-up were 1.42, 2.03, and 2.89 with an apnea-hypopnea index of <5, 5 to 15, and >15 events per hour at baseline, respectively (Figure 1). Effective treatment of OSA with continuous positive airway pressure (CPAP) leads to a decrease in both daytime and nighttime blood pressure<sup>11–13</sup> (Figure 2), further



**Figure 1.** Adjusted odds ratios for the presence of incident hypertension at 4-year follow-up according to the apnea-hypopnea index (AHI) at baseline. Data are shown as odds ratio (line bars indicate lower and upper 95% confidence intervals). *P* for trend=0.002. Based on data from Peppard et al.<sup>10</sup> (Copyright © 2000. *New England Journal of Medicine*. All rights reserved. Reproduced with permission.)



**Figure 2.** Changes in mean (MAP), systolic, and diastolic blood pressure with effective (closed bars) and subtherapeutic (open bars) CPAP. \*Significant difference. (From Becker et al.<sup>13</sup> Copyright © 2003. Lippincott, Williams & Wilkins. All rights reserved. Reproduced with permission.)

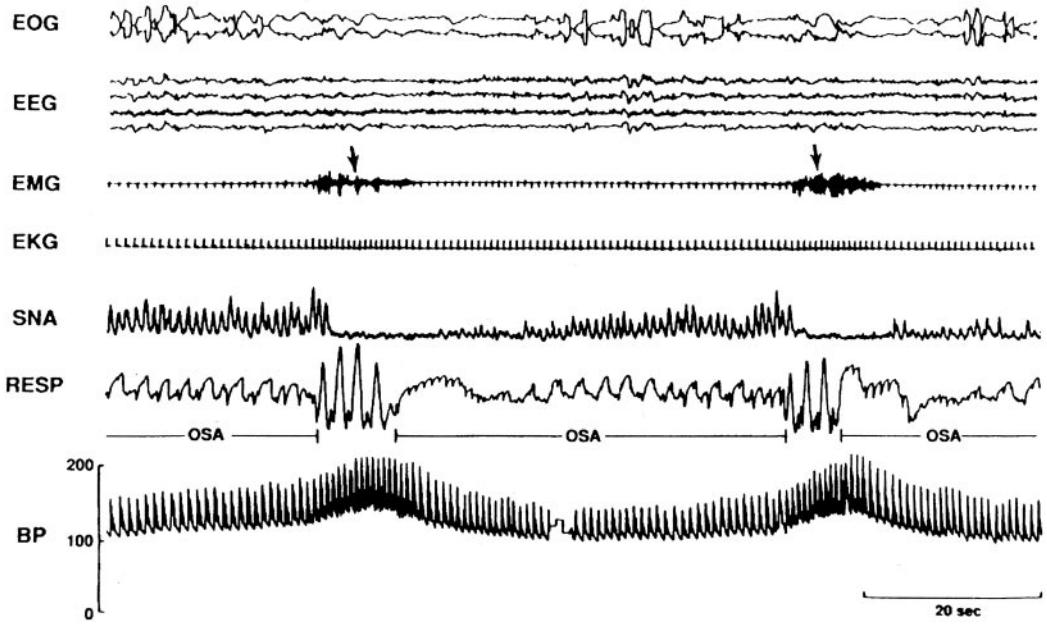
supporting the concept of a causal association between OSA and chronic hypertension.

In addition to established daytime hypertension, OSA also causes acute nocturnal surges in blood pressure in response to chemoreflex-mediated hypoxic stimulation of sympathetic activity, with a resultant increase in peripheral vascular resistance.<sup>14</sup> These nocturnal increases in blood pressure may reach levels as high as 240/120 mm Hg and are readily reversed by CPAP (Figure 3).<sup>14</sup> It is possible that OSA, at least in part, contributes to the nocturnal “nondipping” pattern of hypertension, which may be associated with an adverse cardiovascular prognosis.<sup>15</sup>

### Interactions Between Obesity and Sleep Apnea

Among the risk factors for OSA, obesity is probably the most important. Several cross-sectional studies have consistently found an association between increased body weight and the risk of OSA.<sup>16</sup> Significant sleep apnea is present in ≈40% of obese individuals,<sup>17</sup> and ≈70% of OSA patients are obese. Furthermore, in a population-based prospective study of 690 randomly selected Wisconsin residents, a 10% weight gain was associated with a 6-fold increase in the odds of development of sleep apnea (Figure 4).<sup>18</sup> In the same study, a 10% weight loss predicted a 26% decrease in the apnea-hypopnea index (Figure 4). Similarly, in several other case-control studies, weight loss in OSA patients led to a significant decrease in apnea frequency.<sup>19,20</sup> The exact mechanisms underlying the effects of obesity on the risk of OSA are still unclear. It may be related to effects of fat deposition on airway anatomy or changes in upper airway function. Weight loss has been shown to be associated with a decrease in upper airway collapsibility in OSA.<sup>20</sup> Obesity-induced changes in central mechanisms regulating airway tone or ventilatory control stability may also be implicated. Leptin, for example, which is increased significantly in obesity, has important effects on regulation of chemoreflex function and hence breathing control.<sup>21</sup>

Whereas obesity increases the risk for OSA, sleep apnea may predispose to weight gain and obesity. Indeed, patients with newly diagnosed OSA have a history of excessive recent weight gain in the period preceding the diagnosis.<sup>22,23</sup> In addition, chronic CPAP therapy has been shown to decrease



**Figure 3.** Superimposed recordings of the electrooculogram (EOG), electroencephalogram (EEG), electromyogram (EMG), ECG (EKG), sympathetic nerve activity (SNA), respiration (RESP), and blood pressure (BP) during REM sleep in a patient with OSA. (From Somers et al.<sup>14</sup> Copyright © 1995. *Journal of Clinical Investigation*. All rights reserved. Reproduced with permission.)

body fat and visceral fat accumulation in patients with OSA,<sup>24</sup> further strengthening the evidence for an etiologic link between OSA and body mass. The mechanisms of this association are probably multifactorial. It may be related to changes in patients' lifestyle, so that subjects with OSA may be predisposed to weight gain because of daytime somnolence and a decrease in physical activity. Weight gain in OSA may also be related to endocrine dysregulation. Leptin, the protein product of the *ob* gene, is produced by adipocytes.<sup>25</sup> Leptin suppresses appetite and increases energy expenditure, hence inducing weight loss. Obese individuals have high leptin levels,<sup>26</sup> and their obesity persists because of a presumed resistance to the appetite suppressant and metabolic effects of leptin ("leptin resistance"). Male patients with OSA have ≈50% higher plasma leptin levels compared with similarly obese control subjects free of sleep disordered

breathing.<sup>23</sup> Therefore, it is likely that sleep apnea is accompanied by potentiated leptin resistance (which already exists in obesity alone), so that the weight-reducing effects of leptin are especially blunted in OSA, hence predisposing to a cycle of weight gain and worsening OSA. Potential effects of leptin on respiratory control<sup>21</sup> may also contribute to disorders of breathing in the obese, hyperleptinemic patients with OSA.

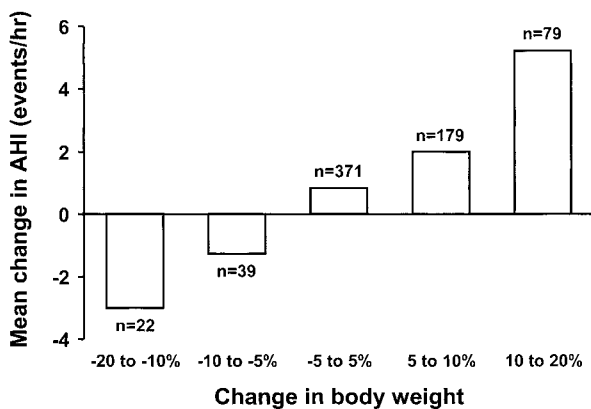
It appears then that there may be a reciprocal relation between obesity and OSA that triggers a feed-forward mechanism, whereby obesity and OSA mutually enhance their progression and severity.

### Potential Contribution of OSA to Obesity-Related Hypertension

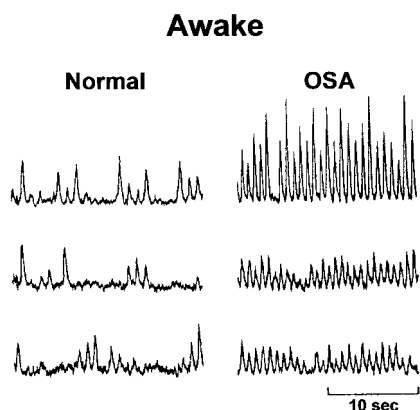
As discussed above, obesity and OSA are each very strongly associated with hypertension. Furthermore, obesity and OSA often coexist and, in fact, one may be conducive to the other. It is therefore plausible that at least part of the association between obesity and hypertension is related to the presence of OSA (and perhaps vice versa). Below we will discuss some pathophysiological mechanisms whereby OSA may contribute to obesity-related hypertension.

### Obesity and Sympathetic Activation

The role of the sympathetic nervous system in the pathogenesis of obesity-related hypertension has attracted much interest. It has been proposed that human obesity is associated with increased sympathetic activity. The techniques used in those studies include microneurography, with direct recordings of muscle sympathetic nerve activity,<sup>27-29</sup> or measurements of catecholamine levels.<sup>30,31</sup> Such a mechanism of obesity-induced hypertension is attractive, with higher levels of sympathetic drive leading to increased heart rate and cardiac output, increased peripheral vascular resistance, in-



**Figure 4.** Mean change in the apnea-hypopnea index (AHI) by weight change category. (From Peppard et al.<sup>18</sup> Copyright © 2000. American Medical Association. All rights reserved. Reproduced with permission.)

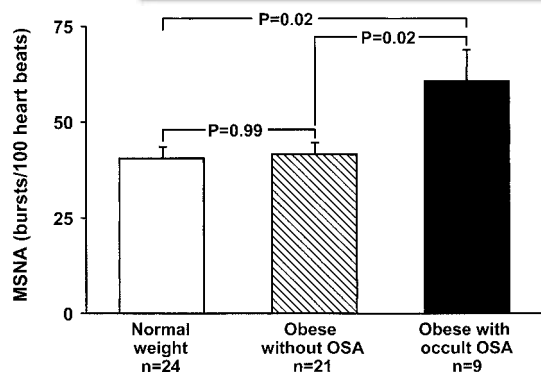


**Figure 5.** Recordings of sympathetic nerve activity (SNA) during wakefulness in patients with OSA and matched control subjects showing high levels of SNA in patients with OSA. (From Somers et al.<sup>14</sup> Copyright © 1995. *Journal of Clinical Investigation*. All rights reserved. Reproduced with permission.)

creased tubular sodium reabsorption in the kidney, and consequent elevation of systemic blood pressure. However, several experimental<sup>32,33</sup> and human<sup>28,34,35</sup> studies suggest that global indices of sympathetic activity may be unaffected by obesity.

Three possible explanations may help to reconcile these apparently discrepant findings. First, there is a possibility of the confounding influence of OSA in studies of obesity in humans. OSA results in persistently increased sympathetic activity even during daytime normoxia and in the absence of any comorbidities (Figure 5).<sup>14</sup> Sleep apnea was not accounted for in most previous human studies of sympathetic activation and obesity. Occult OSA in some obese patients might therefore explain the inconsistent findings on the role of sympathetic activation in obesity, and elevated muscle sympathetic activity associated with obesity may to some extent reflect merely the presence of OSA (Figure 6).<sup>36</sup>

Second, recent studies suggest that an important adipose tissue depot linking obesity with sympathetic neural activation in humans is abdominal visceral fat.<sup>29</sup> Because there may be differences in visceral fat between various study cohorts



**Figure 6.** Muscle sympathetic nerve activity (MSNA) in normal-weight subjects without OSA, obese subjects without OSA, and apparently normal obese subjects found on overnight polysomnography to have occult OSA. (From Narkiewicz et al.<sup>36</sup> Copyright © 1998. Lippincott, Williams & Wilkins. All rights reserved. Reproduced with permission.)

(despite the similar body mass index), it is possible that these differences in visceral fat may explain some of the observed differences between studies investigating the effects of obesity on sympathetic activation.

Finally, global indices of sympathetic activity may be inadequate to assess the influence of obesity on regional neural efferent activity. Although whole-body plasma catecholamine spillover may not be related to body mass, obesity is associated with a reduction in sympathetic activity in the heart but an increase in sympathetic activity in the kidney.<sup>34,35</sup> Thus, human obesity may be associated with a selective renal sympathetic activation.<sup>37</sup> Indeed, experimental evidence suggests that the renal sympathetic nerves mediate sodium retention and hypertension associated with obesity.<sup>38</sup> Further studies are needed to clarify the issue of global and regional sympathetic activation in various types of human obesity, in the absence of other comorbidities.

### Renal Function

Alterations in renal hemodynamics and function play an important role in obesity-induced hypertension, especially in central obesity. Specifically, obesity is associated with sodium retention and volume expansion, as a result of impaired pressure natriuresis and increased tubular reabsorption.<sup>39,40</sup> The precise mechanisms of these abnormalities are unclear but may be related to the activation of the sympathetic nervous system and the renin-angiotensin system. Although as yet unproven, it cannot be excluded that coexisting OSA also contributes to this process through increased sympathetic activity (as discussed above) or an increase in insulin resistance.<sup>41,42</sup>

An interesting and intriguing aspect of renal function in obesity-induced hypertension is mechanical compression of the kidney.<sup>43</sup> The latter is related to the presence of a capsule of extrarenal fat, which may penetrate into the renal hilum and further into the sinuses surrounding the renal medulla. The renal medulla can also be compressed by accumulation of extracellular matrix between the tubules.<sup>40</sup> It has been proposed that these changes may lead to a large increase in interstitial fluid pressure, with a reduction in renal medullary blood flow and increased sodium reabsorption as well as activation of the renin-angiotensin system.<sup>40</sup> Whether OSA also plays a role in this process by means of visceral fat accumulation<sup>24</sup> remains to be established.

### Hyperleptinemia and Leptin Resistance

In addition to effects on the regulation of body fat mass, leptin also exerts important effects on the cardiovascular system. The predominant cardiovascular response to chronic hyperleptinemia is a pressor effect.<sup>44–46</sup> Therefore, elevated leptin levels in obesity may provide yet another link between obesity and hypertension.

Leptin (through its effects on appetite and energy expenditure) is expected to decrease body weight. The observation that circulating leptin rises in proportion to obesity<sup>26</sup> suggests the presence of leptin resistance in obese subjects. Recent findings that plasma leptin levels are elevated in patients with OSA beyond the levels seen in similarly obese healthy control subjects suggest that leptin resistance may be further

increased in OSA.<sup>23</sup> Leptin resistance in obese subjects could be selective, with the loss of metabolic effects and the preservation of pressor effects of leptin.<sup>45,47,48</sup> Selective preservation of cardiovascular and hence pressor effects of leptin may contribute to the hypertension associated with coexisting OSA and obesity.

### Insulin Resistance

Obesity is associated with insulin resistance, which denotes decreased sensitivity of the peripheral tissues to the metabolic effects of insulin with compensatory hyperinsulinemia. A hallmark of the insulin-resistant state in obesity is enhanced sympathetic adrenergic activity, endothelial dysfunction, and impairment of peripheral vasodilation.<sup>49</sup> Thus, insulin resistance may contribute to obesity-induced hypertension through these mechanisms.

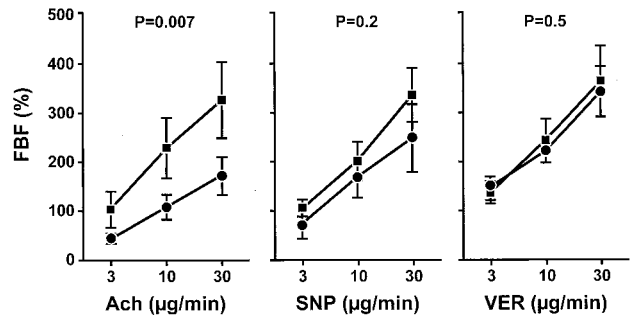
It is likely that OSA can cause metabolic changes independent of obesity. The association between sleep-disordered breathing and abnormal glucose metabolism (insulin resistance) has been investigated in a number of small studies, many of which provided conflicting results. However, recent studies, on much larger patient samples, have provided convincing evidence in favor of an independent association between OSA and insulin resistance. Although increased insulin resistance was also related to obesity, in multiple regression the association between OSA and insulin resistance was independent of obesity (including central obesity, assessed as waist/hip ratio) and was seen in both obese and nonobese subjects.<sup>41,42</sup>

### Renin-Angiotensin System

Several reports suggest that the renin-angiotensin system is activated in obesity (both systemically and locally), and there is a positive correlation between BMI and plasma aldosterone levels, angiotensinogen levels, plasma renin activity, and plasma angiotensin-converting enzyme activity.<sup>50</sup> There are several possible mechanisms whereby the renin-angiotensin system may be activated in obesity, including activation of the sympathetic nervous system, release of adipocyte-derived mediators, increased sodium reabsorption in the kidney, hyperinsulinemia, or even hyperleptinemia. Intriguingly, it has been reported that OSA may be associated with significantly higher levels of angiotensin II and aldosterone compared with healthy control subjects matched by body mass.<sup>51</sup> Furthermore, in that study, there was a significant positive correlation between angiotensin II and daytime blood pressure. Thus, the activation of the renin-angiotensin-aldosterone system in obesity may be augmented by the presence of OSA and may contribute to obesity/OSA-related hypertension. Nevertheless, further clinical and experimental studies are needed to confirm this supposition.

### Oxidative Stress

Recent studies have implicated oxidative stress in blood vessels and the kidney in the pathophysiology of hypertension.<sup>52,53</sup> The mechanisms whereby oxidative stress can cause vasoconstriction include blockade of nitric oxide synthase or inactivation of nitric oxide, activation of angiotensin II and thromboxane receptors, increased generation of endothelin-1,



**Figure 7.** Percent change in forearm blood flow (FBF) during infusion of acetylcholine (ACh; left), sodium nitroprusside (SNP; middle), and verapamil (VER; right) in patients with OSA (●) and matched normal control subjects (■). (From Kato et al.<sup>69</sup> Copyright © 2000. Lippincott, Williams & Wilkins. All rights reserved. Reproduced with permission.)

and the effects of superoxide anion and hydrogen peroxide on vascular smooth muscle cells.<sup>54,55</sup> There is experimental evidence that endothelial dysfunction and hypertension may be related to chronic oxidative stress induced by obesity.<sup>56,57</sup> At the same time, there are data to suggest that oxidative stress is also characteristic of OSA.<sup>58,59</sup> Whether OSA exerts a synergistic, additive, or redundant effect on the magnitude of oxidative stress and consequent hypertension in obesity remains to be established.

### Inflammation

Obesity is associated with the presence of systemic inflammation, including elevated C-reactive protein (CRP) levels.<sup>60</sup> OSA has also been linked to activation of systemic inflammation, as evidenced by increased levels of CRP in healthy subjects with OSA compared with matched control subjects.<sup>61</sup> CRP may contribute to atherosclerotic risk and endothelial dysfunction through several mechanisms. In addition, there are preliminary data suggesting that increased CRP levels may also be associated with a heightened risk for hypertension,<sup>62,63</sup> perhaps by induction of endothelial damage.

### Endothelial Dysfunction

Abnormalities of endothelial function are characterized by decreased vasodilation and potentiated vasoconstriction and have been linked to the pathophysiology of hypertension. Obesity is associated with endothelial dysfunction.<sup>64–68</sup> Several potential mechanisms of endothelial dysfunction in obesity are discussed above. Endothelial dysfunction is also a characteristic of OSA per se, that is, independent of obesity<sup>69</sup> (Figure 7). It is likely, therefore, that OSA may contribute to and/or exacerbate the endothelial dysfunction related to obesity.

Consequences of endothelial dysfunction in OSA may include attenuated nitric oxide production. Lower levels of nitric oxide levels are found in patients with OSA, with increases in nitric oxide after sustained CPAP treatment.<sup>70</sup> Endothelial dysfunction and inhibition of nitric oxide production in OSA may be implicated in the OSA-related hypertension, and the lowering of blood pressure induced by CPAP therapy may conceivably be related to improved endothelial function.

### Arterial Baroreflex

The baroreflex plays a key role in the beat-to-beat regulation of arterial blood pressure. Impaired baroreflex function may therefore play an important role in the pathophysiology of cardiovascular disease, including hypertension. Several studies have found that baroreflex gain may be reduced in obese humans.<sup>28,71</sup> Interestingly, the reduced baroreflex gain appears to be related to a higher level of abdominal visceral fat.<sup>72</sup>

Patients with OSA have blunted heart rate variability and increased blood pressure variability,<sup>73</sup> both of which are associated with baroreflex dysfunction. Baroreflex impairment has indeed been demonstrated in OSA.<sup>74–76</sup> Hence, impairment of baroreflex function may be a potential mechanism linking OSA to an increased risk of hypertension in obesity. Furthermore, decreased heart rate variability and increased blood pressure variability<sup>73</sup> might increase the risk of future hypertension<sup>77</sup> and hypertensive end organ damage.<sup>78</sup>

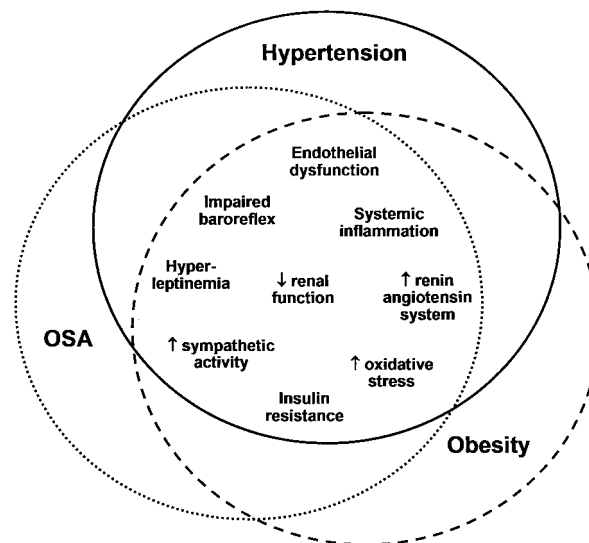
### OSA and Menopause

Understanding the interactions between obesity, OSA, and hypertension may have implications for menopause-associated cardiovascular morbidities. The incidence of cardiovascular disease, including hypertension, increases dramatically in women after the onset of menopause.<sup>79</sup> The exact mechanisms of this transition are not well understood, especially since it is not readily reversed by estrogen therapy. Menopause is also associated with an increase in central obesity and the metabolic syndrome<sup>80</sup> and may also be a risk factor for sleep-disordered breathing, independent of body habitus.<sup>81,82</sup> The potential interaction of OSA with the development of central obesity in postmenopausal women might contribute to the postmenopausal increase in hypertension and cardiovascular disease.

### Conclusions

OSA and obesity often coexist and interact, sharing multiple pathophysiological mechanisms and consequences (Figure 8). OSA may contribute, at least in part, to some of the pathological processes traditionally ascribed to obesity alone, most notably sympathetic overactivity and humoral, metabolic, and neuroendocrine abnormalities. Compelling data support the association of OSA with hypertension, including in obese individuals. OSA probably contributes to or exacerbates the obesity-related hypertension. The diagnosis of OSA in this context is therefore of considerable clinical importance. Indeed, the most recent JNC guidelines place sleep apnea at the top of the list of causes of secondary hypertension.<sup>83</sup> OSA should be strongly suspected in obese individuals with resistant hypertension, those with the absence of a nocturnal decrease in blood pressure (nondippers), those with unexplained weight gain or difficulty losing weight, and in those with symptoms suggestive of OSA (such as witnessed apneas, poor sleep quality, snoring, and excessive daytime somnolence).

OSA in obese individuals may also have implications beyond the pathogenesis of hypertension. It is important to understand better the role of visceral (as opposed to global)



**Figure 8.** Putative pathophysiological mechanisms involved in the interactions between obesity, OSA, and hypertension.

obesity in the pathophysiological interactions between OSA, obesity, and cardiovascular and metabolic abnormalities. Excess visceral fat is a characteristic feature of the metabolic syndrome—a constellation of abnormalities including insulin resistance, dyslipidemia, inflammation, hypertension, and so forth (Syndrome X). Clustering of these metabolic factors increases the risk of many cardiovascular diseases, especially atherosclerosis. Central adiposity and visceral fat deposition appear to be also the hallmark of increased risk for OSA. The stigmata of Syndrome X should therefore be broadened to incorporate OSA, perhaps a “Syndrome Z.”<sup>84</sup> By contributing to and/or inducing some of the above abnormalities, coexisting OSA may have implications for understanding first, cardiovascular and metabolic control in obesity; second, the risk of hypertension in obese individuals; and third, the potentiating effects of OSA in eliciting cardiovascular consequences in the obese patients with hypertension.

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### References

1. Kuczmarski RJ, Flegal KM. Criteria for definition of overweight in transition: background and recommendations for the United States. *Am J Clin Nutr.* 2000;72:1074–1081.
2. Kannel WB, Brand N, Skinner JJ Jr, Dawber TR, McNamara PM. The relation of adiposity to blood pressure and development of hypertension: the Framingham study. *Ann Intern Med.* 1967;67:48–59.
3. Garrison RJ, Kannel WB, Stokes J III, Castelli WP. Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. *Prev Med.* 1987;16:235–251.
4. Jones DW, Kim JS, Andrew ME, Kim SJ, Hong YP. Body mass index and blood pressure in Korean men and women: the Korean National Blood Pressure Survey. *J Hypertens.* 1994;12:1433–1437.
5. Kannel WB. Historic perspectives on the relative contributions of diastolic and systolic blood pressure elevation to cardiovascular risk profile. *Am Heart J.* 1999;138:205–210.
6. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328:1230–1235.

7. 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;289:2230–2237.
8. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study: Sleep Heart Health Study. *JAMA*. 2000;283:1829–1836.
9. 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;166:159–165.
10. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378–1384.
11. 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;163:344–348.
12. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. 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.
13. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation*. 2003;107:68–73.
14. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96:1897–1904.
15. Pickering TG, Kario K. Nocturnal non-dipping: what does it augur? *Curr Opin Nephrol Hypertens*. 2001;10:611–616.
16. 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.
17. Vgontzas AN, Tan TL, Bixler EO, Martin LF, Shubert D, Kales A. Sleep apnea and sleep disruption in obese patients. *Arch Intern Med*. 1994;154:1705–1711.
18. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000;284:3015–3021.
19. Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. *Ann Intern Med*. 1985;103:850–855.
20. Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S, Smith PL. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis*. 1991;144:494–498.
21. O'Donnell CP, Tankersley CG, Polotsky VP, Schwartz AR, Smith PL. Leptin, obesity, and respiratory function. *Respir Physiol*. 2000;119:163–170.
22. Phillips BG, Hisel TM, Kato M, Pesek CA, Dyken ME, Narkiewicz K, Somers VK. Recent weight gain in patients with newly diagnosed obstructive sleep apnea. *J Hypertens*. 1999;17:1297–1300.
23. Phillips BG, Kato M, Narkiewicz K, Choe I, Somers VK. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol*. 2000;279:H234–H237.
24. Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakao K, Ohi M. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation*. 1999;100:706–712.
25. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature*. 1994;372:425–432.
26. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med*. 1996;334:292–295.
27. Scherrer U, Randin D, Tappy L, Vollenweider P, Jequier E, Nicod P. Body fat and sympathetic nerve activity in healthy subjects. *Circulation*. 1994;89:2634–2640.
28. Grassi G, Seravalle G, Cattaneo BM, Bolla GB, Lanfranchi A, Colombo M, Giannattasio C, Brunani A, Cavagnini F, Mancia G. Sympathetic activation in obese normotensive subjects. *Hypertension*. 1995;25:560–563.
29. Alvarez GE, Beske SD, Ballard TP, Davy KP. Sympathetic neural activation in visceral obesity. *Circulation*. 2002;106:2533–2536.
30. Troisi RJ, Weiss ST, Parker DR, Sparrow D, Young JB, Landsberg L. Relation of obesity and diet to sympathetic nervous system activity. *Hypertension*. 1991;17:669–677.
31. Tuck ML. Obesity, the sympathetic nervous system, and essential hypertension. *Hypertension*. 1992;19:167–177.
32. Bray GA, York DA, Fislis JS. Experimental obesity: a homeostatic failure due to defective nutrient stimulation of the sympathetic nervous system. *Vitam Horm*. 1989;45:1–125.
33. Bray GA. MONA LISA hypothesis: most obesities known are low in sympathetic activity. In: *Progress in Obesity Research*. London, UK: John Libbey & Co; 1990:61–66.
34. Vaz M, Jennings G, Turner A, Cox H, Lambert G, Esler M. Regional sympathetic nervous activity and oxygen consumption in obese normotensive human subjects. *Circulation*. 1997;96:3423–3429.
35. Rumantir MS, Vaz M, Jennings GL, Collier G, Kaye DM, Seals DR, Wiesner GH, Brunner-La Rocca HP, Esler MD. Neural mechanisms in human obesity-related hypertension. *J Hypertens*. 1999;17:1125–1133.
36. Narkiewicz K, van de Borne PJ, Cooley RL, Dyken ME, Somers VK. Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation*. 1998;98:772–776.
37. Somers VK. Debating sympathetic overactivity as a hallmark of human obesity: an opposing position. *J Hypertens*. 1999;17:1061–1064.
38. Kassab S, Kato T, Wilkins FC, Chen R, Hall JE, Granger JP. Renal denervation attenuates the sodium retention and hypertension associated with obesity. *Hypertension*. 1995;25:893–897.
39. Hall JE. Mechanisms of abnormal renal sodium handling in obesity hypertension. *Am J Hypertens*. 1997;10:49S–55S.
40. Hall JE, Brands MW, Henegar JR. Mechanisms of hypertension and kidney disease in obesity. *Ann NY Acad Sci*. 1999;892:91–107.
41. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med*. 2002;165:670–676.
42. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med*. 2002;165:677–682.
43. Hall JE. Pathophysiology of obesity hypertension. *Curr Hypertens Rep*. 2000;2:139–147. Heart Disease and Stroke
44. Shek EW, Brands MW, Hall JE. Chronic leptin infusion increases arterial pressure. *Hypertension*. 1998;31:409–414.
45. Aizawa-Abe M, Ogawa Y, Masuzaki H, Ebihara K, Satoh N, Iwai H, Matsuoka N, Hayashi T, Hosoda K, Inoue G, Yoshimasa Y, Nakao K. Pathophysiological role of leptin in obesity-related hypertension. *J Clin Invest*. 2000;105:1243–1252.
46. Carlyle M, Jones OB, Kuo JJ, Hall JE. Chronic cardiovascular and renal actions of leptin: role of adrenergic activity. *Hypertension*. 2002;39:496–501.
47. Rahmouni K, Haynes WG, Morgan DA, Mark AL. Selective resistance to central neural administration of leptin in agouti obese mice. *Hypertension*. 2002;39:486–490.
48. Mark AL, Correia ML, Rahmouni K, Haynes WG. Selective leptin resistance: a new concept in leptin physiology with cardiovascular implications. *J Hypertens*. 2002;20:1245–1250.
49. Abate N. Obesity and cardiovascular disease. Pathogenetic role of the metabolic syndrome and therapeutic implications. *J Diabetes Complications*. 2000;14:154–174.
50. Engeli S, Sharma AM. The renin-angiotensin system and natriuretic peptides in obesity-associated hypertension. *J Mol Med*. 2001;79:21–29.
51. Moller DS, Lind P, Strunge B, Pedersen EB. Abnormal vasoactive hormones and 24-hour blood pressure in obstructive sleep apnea. *Am J Hypertens*. 2003;16:274–280.
52. Lerman LO, Nath KA, Rodriguez-Porcel M, Krier JD, Schwartz RS, Napoli C, Romero JC. Increased oxidative stress in experimental renovascular hypertension. *Hypertension*. 2001;37:541–546.
53. Reckelhoff JF, Romero JC. Role of oxidative stress in angiotensin-induced hypertension. *Am J Physiol*. 2003;284:R893–R912.
54. Somers MJ, Harrison DG. Reactive oxygen species and the control of vasomotor tone. *Curr Hypertens Rep*. 1999;1:102–108.
55. Wilcox CS. Reactive oxygen species: roles in blood pressure and kidney function. *Curr Hypertens Rep*. 2002;4:160–166.
56. Poirier B, Lannaud-Bournoville M, Conti M, Bazin R, Michel O, Bariety J, Chevalier J, Myara I. Oxidative stress occurs in absence of hypergly-

- caemia and inflammation in the onset of kidney lesions in normotensive obese rats. *Nephrol Dial Transplant*. 2000;15:467–476.
57. Dobrian AD, Davies MJ, Schriver SD, Lauterio TJ, Prewitt RL. Oxidative stress in a rat model of obesity-induced hypertension. *Hypertension*. 2001;37:554–560.
  58. Schulz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, Seeger W, Grimminger F. 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;162:566–570.
  59. 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;165:934–939.
  60. Das UN. Is obesity an inflammatory condition? *Nutrition*. 2001;17:953–966.
  61. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, Somers VK. Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation*. 2002;105:2462–2464.
  62. Bautista LE, Lopez-Jaramillo P, Vera LM, Casas JP, Otero AP, Guaracao AI. Is C-reactive protein an independent risk factor for essential hypertension? *J Hypertens*. 2001;19:857–861.
  63. Chul Sung K, Suh JY, Kim BS, Kang JH, Kim H, Lee MH, Park JR, Kim SW. High sensitivity c-reactive protein as an independent risk factor for essential hypertension. *Am J Hypertens*. 2003;16:429–433.
  64. Parrinello G, Scaglione R, Pinto A, Corrao S, Cecala M, Di Silvestre G, Amato P, Licata A, Licata G. Central obesity and hypertension: the role of plasma endothelin. *Am J Hypertens*. 1996;9:1186–1191.
  65. Al Suwaidi J, Higano ST, Holmes DR Jr, Lennon R, Lerman A. Obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries. *J Am Coll Cardiol*. 2001;37:1523–1528.
  66. Higashi Y, Sasaki S, Nakagawa K, Matsuura H, Chayama K, Oshima T. Effect of obesity on endothelium-dependent, nitric oxide-mediated vasodilation in normotensive individuals and patients with essential hypertension. *Am J Hypertens*. 2001;14:1038–1045.
  67. Peticone F, Ceravolo R, Candigliota M, Ventura G, Iacopino S, Sinopoli F, Mattioli PL. Obesity and body fat distribution induce endothelial dysfunction by oxidative stress: protective effect of vitamin C. *Diabetes*. 2001;50:159–165.
  68. Sasaki S, Higashi Y, Nakagawa K, Kimura M, Noma K, Hara K, Matsuura H, Goto C, Oshima T, Chayama K. A low-calorie diet improves endothelium-dependent vasodilation in obese patients with essential hypertension. *Am J Hypertens*. 2002;15:302–309.
  69. Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, Somers VK. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation*. 2000;102:2607–2610.
  70. Ip MS, Lam B, Chan LY, Zheng L, Tsang KW, Fung PC, Lam WK. 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.
  71. Grassi G, Seravalle G, Dell’Oro R, Turri C, Bolla GB, Mancia G. Adrenergic and reflex abnormalities in obesity-related hypertension. *Hypertension*. 2000;36:538–542.
  72. Beske SD, Alvarez GE, Ballard TP, Davy KP. Reduced cardiovagal baroreflex gain in visceral obesity: implications for the metabolic syndrome. *Am J Physiol Heart Circ Physiol*. 2002;282:H630–H635.
  73. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation*. 1998;98:1071–1077.
  74. Carlson JT, Hedner JA, Sellgren J, Elam M, Wallin BG. Depressed baroreflex sensitivity in patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 1996;154:1490–1496.
  75. Parati G, Di Rienzo M, Bonsignore MR, Insalaco G, Marrone O, Castiglioni P, Bonsignore G, Mancia G. Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analysis during sleep. *J Hypertens*. 1997;15:1621–1626.
  76. Narkiewicz K, Pesek CA, Kato M, Phillips BG, Davison DE, Somers VK. Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea. *Hypertension*. 1998;32:1039–1043.
  77. Singh JP, Larson MG, Tsuji H, Evans JC, O’Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. *Hypertension*. 1998;32:293–297.
  78. Parati G, Di Rienzo M, Ulian L, Santucci C, Girard A, Elghozi JL, Mancia G. Clinical relevance blood pressure variability. *J Hypertens*. 1998;16:S25–S33.
  79. Wyss JM, Carlson SH. Effects of hormone replacement therapy on the sympathetic nervous system and blood pressure. *Curr Hypertens Rep*. 2003;5:241–246.
  80. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab*. 2003;88:2404–2411.
  81. Dancey DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea. *Chest*. 2001;120:151–155.
  82. Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med*. 2003;167:1181–1185.
  83. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *JAMA*. 2003;289:2560–2571.
  84. Wilcox I, McNamara SG, Collins FL, Grunstein RR, Sullivan CE. “Syndrome Z”: the interaction of sleep apnoea, vascular risk factors and heart disease. *Thorax*. 1998;53:S25–S28.



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