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Sleep apnea: epidemiology, pathophysiology, and relation to cardiovascular risk

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[1]*Department of Clinical Medicine and Prevention, University of Milano-Bicocca, and* [2]*Department of Cardiology, San Luca Hospital, Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Auxologico, Italiano, Milan, Italy;* [3]*Hypertension Unit; Department of Hypertension and Diabetology; Medical University of Gdansk, Gdansk, Poland*

Parati G, Lombardi C, Narkiewicz K. Sleep apnea: epidemiology, pathophysiology, and relation to cardiovascular risk. *Am J Physiol Regul Integr Comp Physiol* 293: R1671–R1683, 2007. First published July 25, 2007; doi:10.1152/ajpregu.00400.2007.— Several studies have shown the occurrence of an independent association between obstructive sleep apnea syndrome (OSAS) and cardiovascular disease, including arterial hypertension, ischemic heart disease, and stroke. The pathogenesis of the cardiovascular complications of OSAS is still poorly understood, however. Several mechanisms are likely to be involved, including sympathetic overactivity, selective activation of inflammatory molecular pathways, endothelial dysfunction, abnormality in the process of coagulation, and metabolic dysregulation. The latter may involve insulin resistance and disorders of lipid metabolism. The aim of this review, which reports the data presented at a workshop jointly endorsed by the European Society of Hypertension and by the European Union COST action on OSAS (COST B26), is to critically summarize the evidence available to support an independent association between OSAS and cardiovascular disease.

basic mechanisms; intermittent hypoxia; sleep-disordered breathing; autonomic cardiovascular regulation; obesity

IN NORMAL SUBJECTS, SLEEP is characterized by important physiological changes in respiratory and cardiovascular functions. With the exception of rapid eye movement (REM) sleep stage, these include an increase in parasympathetic cardiac modulation and a reduction in sympathetic drive to cardiac and vascular targets, leading to a pronounced reduction in blood pressure and heart rate mean levels and to changes in blood pressure and heart rate variability patterns, in association with an increase in arterial baroreflex sensitivity (105, 141). In parallel, sleep is also characterized by changes in breathing patterns, the control of respiration shifting from a combined behavioral and automatic regulation to a condition in which only automatic mechanisms are involved. As a result, respiration becomes slower and more regular than in the awake period, contributing itself to changes in the nocturnal modulation of blood pressure and heart rate (140).

An increasingly frequent problem affecting sleep is indeed the occurrence of sleep-related breathing disorders, leading to concomitant alterations in the neural and cardiovascular effects of sleep. Sleep-disordered breathing (SDB) syndromes include habitual snoring, sleep apnea, Cheyne-Stokes breathing syndrome, and sleep hypoventilation syndrome (2).

Sleep apnea syndromes are characterized by multiple cessations of respiration during sleep that induce partial arousals and interfere with the physiological cyclic shift between the various sleep stages, being responsible for a reduced depth of sleep and for daytime somnolence. Air-flow disturbance lasting >10 s is considered significant, apnea being defined as a complete breathing cessation and hypopnea as a 50% or more reduction in breathing amplitude. The occurrence of more or less frequent oxygen desaturations or of EEG arousals is taken as an additional diagnostic tool to identify these conditions (2). Sleep apnea episodes are typically classified as being central (CSA), obstructive (OSA), or mixed, the criterion differentiating between OSA and CSA being the concomitant presence or absence of efforts to breathe, respectively. Whereas OSA is due to upper airway obstruction, CSA is caused by a dysfunction of neural centers that regulate respiration. Mixed sleep apneas are events characterized by an initial CSA followed by an obstructive component. The most frequent clinical syndrome, defined as obstructive sleep apnea syndrome (OSAS), includes OSA and associated symptoms, often extending also to wakefulness, such as impaired cognitive function and daytime somnolence (144).

The present review will focus on the cardiovascular effects of such a widespread syndrome, being of particular relevance in obese subjects and characterized by an important impact on population health. This paper critically examines the available evidence linking sleep apnea with hypertension, coronary artery disease, stroke, congestive heart failure, and arrhythmias, focusing also on the potential mechanisms underlying this link.

DIAGNOSIS

The occurrence of symptoms such as habitual and intermittent snoring, abrupt awakening during sleep, and witnessed apneas may suggest the occurrence of OSA. However, OSA diagnosis is most commonly based on polysomnographic examinations, i.e., an overnight monitoring of a number of parameters (nasal air flow, snoring sounds, thoracic move-

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ments, blood oxygen saturation, intra-esophageal pressure, ECG, and others), usually in a controlled hospital setting. An extensive monitoring including at least 12 channels is termed polysomnography and constitutes the gold standard for the diagnosis and classification of sleep apneas (2). The evaluation of OSA severity is obtained through the assessment of the apnea-hypopnea index (AHI), defined as the average number of apneas and hypopneas per sleep hour. The American Academy of Sleep Medicine Task Force recommends an AHI ≥ 5 associated with the presence of symptoms such as excessive daytime sleepiness (2) as a criterion for OSAS diagnosis. Subjects who have an AHI < 5 but who snore most of the night on most nights are classified as habitual snorers (2).

Other indices of OSAS severity include Respiratory Disturbance Index [RDI, i.e., average number per sleep hour of apneas, hypopneas, and respiratory effort-related arousals (RERAs)], oxygen desaturation index (ODI, i.e., the average number of significant oxygen desaturations per hour of sleep), and the arousal index (number of EEG arousals per hour of sleep). More recently proposed methods for quantification of OSAS are the cross-power index (CPI, the integral of the cross-spectrum modulus between concomitant fluctuations in systolic blood pressure and blood oxygen saturation), aimed at assessing the cardiovascular impact of OSAS, and the peripheral arterial tonometry index (PAT), an indicator of acute arousal responses to OSA.

CPIs provide a quantitative assessment of the beat-by-beat changes in systolic blood pressure [measured noninvasively with a finger-pressure device (Portapres; Finapres Medical Systems, Arnheim, The Netherlands)] (53) that follow changes in blood oxygen saturation continuously assessed by pulse oxymetry. The relation between these changes is quantified as the modulus of the transfer function between fluctuations in blood oxygen saturation and the corresponding fluctuations in systolic blood pressure (19).

The PAT signal measures the pulsatile finger arterial volume changes that are regulated by the α-adrenergic innervation of the smooth muscles of the finger vasculature and thus reflects sympathetic nervous system activity. PAT may indirectly detect apnea/hypopnea events by identifying surges of sympathetic activation associated with the termination of these events. This information is further combined with heart rate and pulse oxymetry data that are considered by the automatic algorithm of the analysis system. This detects respiratory events and calculates the PAT RDI (120).

Given the cost and limited availability of full polysomnography in a sleep lab, in practice the screening for OSAS is mostly based on portable polysomnographic devices, often supported by use of questionnaires (e.g., Berlin questionnaire) (98).

EPIDEMIOLOGY OF OSAS

The prevalence of SDB may vary in different settings, being influenced by criteria used for the definition of apnea and hypopneas as well as by the characteristics of the population under study. SDB can be affected by age, gender, and body mass index (BMI). It is estimated that $\sim 20\%$ of a general population displays obstructive apneas (AHI ≥ 5), whereas a full clinical picture of OSAS is seen in 1–5% of men and in 0.5–2% of women of premenopausal age (77). The prevalence of habitual snoring is even higher, reaching 25–35%. SDB,
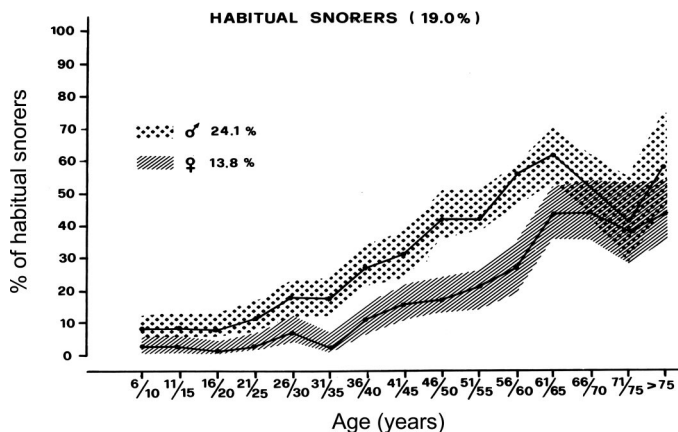

Fig. 1. Prevalence of habitual snorers by age and gender. Increasing age is reported on horizontal axis, and differently shaded areas refer to males and females. Reprinted from Ref. 79, with permission.

including snoring (Fig. 1), and OSAS display a peak of prevalence in middle-aged subjects, with a decline after the age of 65 (79, 157). Indeed, the increase in the overall prevalence of sleep apneas with age seems to depend mainly on an increased prevalence of CSA. In postmenopausal women, the OSAS prevalence tends to increase, particularly in women without hormone replacement therapy, but it remains lower than in men in the same age stratum (11, 60, 71, 155).

The main epidemiological factor associated with the presence of OSAS is an increased body mass. The increasing prevalence of OSAS in Western countries parallels the progressive increase in frequency of overweight and obesity, OSAS being seen in as much as 40% of obese men and 70% of OSAS patients being obese (151, 157). Although OSAS mainly affects adult subjects, its presence in children should not be neglected. This not only because of its relatively high prevalence (2% in children aged 2–8 years, apparently related to adenotonsillar hypertrophy) but also because of its clinical consequences, including hypertension, nocturnal enuresis, growth retardation, cognitive impairment, and hyperactivity (40).

MECHANISMS

Mechanisms linking sleep apnea to cardiovascular disease. The mechanisms underlying the development of cardiovascular disease in patients with OSAS are still poorly understood. The most likely hypothesis is that of a multifactorial process involving a diverse range of mechanisms, including sympathetic overactivity, selective activation of inflammatory pathways, endothelial dysfunction, and metabolic dysregulation, the latter particularly involving insulin resistance and disorders in lipid metabolism. Each of these issues will now be addressed.

Increased sympathetic nerve activity. OSA is responsible for repeated blood oxygen desaturations and for concomitant increases in arterial carbon dioxide levels. Apnea-dependent hypoxia and hypercapnia increase sympathetic neural tone, which in turn causes vasoconstriction (159). Sympathetic nerve activity rises progressively during the time of apnea and eventually is enhanced further by the arousal. On resumption of breathing, cardiac output increases on the background of constricted peripheral vasculature. This concurrence may provoke abrupt and sometimes marked increases in arterial pres-

sure (systolic blood pressure up to 250 mmHg), which induce a reflex and transient reduction in sympathetic efferent traffic. Remarkably, in chronic OSA an elevated sympathetic drive is present even during daytime wakefulness when subjects are breathing normally and both arterial oxygen saturation and carbon dioxide levels are also normal (18, 96). Even in normal-weight OSA patients, an increase in sympathetic activity as measured by microneurography can be observed. Urinary catecholamine levels have been reported as increased in patients with OSAS, and these levels fell after treatment by tracheostomy (35). A direct link between hypoxemia and elevated sympathetic activity has also been proposed (75, 139), and elevated muscle sympathetic nerve activity (MSNA) has been reported to be attenuated during apnea where hyperoxic conditions were maintained (75). Other reports have indicated a significant fall in both plasma and urinary catecholamines and in MSNA following OSA treatment by nasal continuous positive airway pressure (nasal CPAP) (48, 49, 93, 158). A support to the role of sympathetic overactivity in the pathogenesis of hypertension in OSAS also comes from animal models. An increase in blood pressure was found in both dog and rat models of OSAS, and this declined once the airway occlusion or intermittent hypoxia was abolished (16, 33). These blood pressure changes were not observed with induced recurrent arousals without airway occlusion, indicating that it was the obstructive events rather than the associated arousals that were responsible for the observed effects (16). These changes in blood pressure were prevented by pharmacological and surgical blockade of the sympathetic nerve system in a rat model of chronic intermittent hypoxia (6, 34).

Evidence in favor of a significant contribution to the pathogenesis of OSA-related cardiovascular complications by alterations in autonomic cardiovascular control has been obtained also through the use of techniques exploring spontaneous sensitivity of baroreflex control of the heart (10, 105). OSAS patients are characterized by a reduced baroreflex sensitivity during both wakefulness and sleep (106), and such an impairment can be reversed by CPAP. This improvement is particularly evident with chronic treatment (12), although a small but significant improvement can also be detected even after short-term CPAP application (13).

The high levels of sympathetic activity in OSA patients, due to baroreflex (95, 106) and chemoreflex (25, 97) dysfunction, are associated with profound abnormalities in cardiovascular variability during both wakefulness and sleep. This alteration occurs even in the absence of hypertension or heart failure. In OSA patients, blood pressure variability is markedly increased, heart rate is faster, and the R-R variability is decreased during daytime (94), whereas it is increased at night due to the effects of changes in intrathoracic pressure and in the patterns of ventilation due to OSA (13, 106). The degree of derangement in cardiovascular variability is closely linked to the severity of OSA.

Both sympathetic overactivation and abnormal cardiovascular variability in sleep apnea patients may contribute to their increased risk of future hypertension and hypertensive end-organ damage (107). The dependency of the increased cardiovascular variability on the occurrence of OSA episodes is clearly demonstrated by its reduction when OSA patients are successfully treated with CPAP ventilation, both acutely (13) and chronically (14).

Endothelial dysfunction. Endothelial dysfunction has been shown to occur in OSAS patients with little evidence of cardiovascular disease. The Sleep Heart Health Study has reported evidence of vascular dysfunction among older participants (99) and has identified OSAS as an independent risk factor for impaired flow-mediated vasodilation, in agreement with other studies. A role for endothelial dysfunction in the pathogenesis of cardiovascular complications in OSAS has been supported by various studies demonstrating impairment in the endothelium-dependent vasodilatation (57, 64, 66). Furthermore, treatment with nasal CPAP has been reported to reverse endothelial dysfunction (103). An important vasodilator substance released by the endothelium is nitric oxide (NO), decreased production or activity of NO being an early sign of atherosclerosis. NO levels were found to be decreased in OSAS patients and to increase following CPAP therapy (54, 134). Among postulated theories of decreased release of NO, elevated levels of endothelial NO synthase (eNOS) antagonists might play an important role. Patients with SDB present higher levels of plasma asymmetric dimethylarginine (ADMA), an endogenous eNOS antagonist (103). CPAP treatment has been shown to decrease ADMA plasma levels, which was paralleled by improvement of NO-dependent vessel relaxation (103).

The endothelium also produces vasoconstrictor substances, such as endothelin and angiotensin II, and their levels have been reported to increase in OSAS, although not invariably (41), and to fall with effective CPAP therapy (119).

Both the reduced NO release and the increased endothelin-1 levels could contribute to OSA-related hypertension. However, such a conclusion needs to be made with caution, because of the confounding effects of comorbidities. Indeed, endothelial dysfunction is often seen in patients with hypertension, hyperlipidemia, diabetes, or smoking, and these associations may limit the importance of OSAS as an independent risk factor for endothelial dysfunction, an issue that thus deserves further investigation by studies able to account for these confounders.

Inflammation and oxidative stress. Inflammation is one of the postulated links between OSA and increased cardiovascular morbidity. Several studies indicate elevated levels of inflammatory markers in OSA patients compared with matched healthy subjects. Either elevated C-reactive protein (CRP) (65, 136), IL-6, TNF-α (88, 129), or adhesion molecules (102) in OSA syndrome may contribute to acceleration of atherosclerosis. Furthermore, a gene polymorphism associated with increased TNF-α production has recently been reported to be more common in OSAS (127) than in controls. Treatment with nasal CPAP has been reported to be associated with decreased levels of these markers (154). However, recent studies have failed to find an association between CRP and OSAS, and such a relationship has thus been challenged (43, 61). Studies including larger numbers of patients, and adequately controlled for potential confounding factors, will thus be required to clarify the occurrence of an independent association between OSA and inflammation.

Recent evidence from a cell-culture model of intermittent hypoxia supports a selective activation of inflammatory over adaptive pathways in response to intermittent hypoxia, which contrasts with sustained hypoxia, where activation of adaptive and protective pathways predominate (129). This preferential activation of inflammatory pathways may be a consequence of the intermittent reoxygenation that is characteristic of intermit-

tent hypoxia and thus represents a variant of reperfusion injury (72). Levels of circulating soluble adhesion molecules, which mediate adhesion of leucocytes to the vascular endothelium, such as intracellular adhesion molecule-1 (ICAM-1), are elevated in patients with OSAS and improve with CPAP therapy (102). Furthermore, increased adhesion of lymphocytes to vascular endothelial cells has been demonstrated in OSA patients compared with controls (30). Inflammatory cytokines, such as TNF-α and interleukin-8 (IL-8) induce the expression of cellular adhesion molecules known to be involved in atherosclerotic processes (69, 121), thus providing further evidence of an important role for inflammation in the cardiovascular morbidity of OSAS. Studies based on animal models have recently shown that intermittent hypoxia increases susceptibility of the heart to oxidative stress (108, 109). Evidence of increased release of reactive oxygen species has been provided in patients with OSAS (29, 133), likely as a consequence of intermittent reoxygenation associated with recurring apnea. However, their interaction with other molecular mechanisms such as inflammatory pathways has not been fully evaluated and requires further investigation.

Alterations in platelet function and blood coagulation. Impaired platelet function, which may play an important role in the incidence of cardiovascular events, has also been reported in OSA patients. In vitro studies by Sanner et al. (131) have implicated OSA as a cause of increased platelet aggregability. Experiments in vivo have revealed a higher degree of platelet activation in OSA patients compared with the control subjects, whereas treatment with CPAP may decrease platelet activity (51). However, no evidence has been provided that decrease in platelet activity and aggregability by CPAP treatment leads to better cardiovascular prognosis for OSA patients.

Although there have been several studies suggesting hypercoagulability in patients with OSAS (148), in several instances the value of these observations has been limited by small numbers and/or by inadequate control for potential confounding factors such as BMI and smoking. Blood viscosity has been reported to be elevated in OSAS in addition to fibrinogen levels, several coagulation factors, and plasminogen activator inhibitor type-1 (20, 128, 142). Fibrinolytic activity has been reported to be reduced in OSAS in addition to abnormal platelet function (125). These changes in coagulation may contribute to endothelial dysfunction, although preexisting hypertension appears to be an important potential confounding factor in a number of papers.

Metabolic dysregulation. A number of studies have reported an independent association of OSAS with several components of the metabolic syndrome, particularly insulin resistance and abnormal lipid metabolism (23). This association may further increase cardiovascular risk, because the metabolic syndrome is, in itself, recognized to be a risk factor for cardiovascular disease, particularly hypertension (70). OSAS-related factors that may contribute to metabolic dysregulation include increased sympathetic activity, sleep fragmentation, and intermittent hypoxia.(118).

A number of studies carried out both in animals (52) and in humans found increased insulin resistance and impaired glucose tolerance in OSA. In OSAS patients, this association was independent from body weight (55, 143), whereas worsening of insulin resistance was paralleled by increasing AHI (124). In particular, both the Sleep Heart Health Study and the Wiscon-

sin Cohort Study have recently identified OSAS as an independent risk factor for insulin resistance, after adjustment for potential confounding variables such as age, sex, and BMI (123, 126).

There is evidence of an independent association between OSAS and abnormalities in lipid metabolism. Several studies have reported that OSAS is associated with hyperleptinemia, although some were not adjusted for obesity and visceral fat distribution. One study reported that elevated leptin levels in OSAS were only found in obese subjects (7), whereas other reports found that sleep hypoxemia was the principal determinant (145). Effective treatment with CPAP has been reported to be associated with a decrease in leptin levels, although in one report the fall in leptin levels was only observed in nonobese patients (44). Shimizu and co-workers (137) related changes in plasma leptin levels to cardiac sympathetic function. Although the results were not conclusive, the findings indicated a significant fall in leptin levels with CPAP therapy. However, another report found that leptin levels, when adjusted for body-fat distribution, were not related to indices of OSA, and a further study indicated that leptin levels were more closely associated with indices of obesity and lipid dysfunction than with indices of OSA (56). Thus, the possibility of an independent relationship between lipid metabolism dysfunction and OSA should still be considered as a research issue.

Genetic factors. Although the genetic contribution to essential hypertension is widely recognized, there is surprisingly little information on the role of genetic factors in pathogenesis of OSA (122). Hypertensive subjects with a positive family history of hypertension are characterized by a greater oxygen desaturation and higher AHI than those with a negative family history (58). Lin et al. (76) have recently assessed the association of the insertion/deletion polymorphism of the angiotensin converting enzyme gene with SDB and hypertension in 1,100 subjects of the Wisconsin Sleep Cohort. SDB and the insertion/deletion polymorphism had an interactive effect on blood pressure independently of age, sex, ethnicity, and BMI. An association of the deletion allele with hypertension was found in patients with mild-to-moderate OSA but not in subjects without SDB (76).

It has been suggested that approximately half of the genetic variance in the AHI is shared with obesity phenotypes and that genetic polymorphisms that increase weight are also risk factors for apnea (112).

CLINICAL RELEVANCE OF SLEEP APNEA: ASSOCIATION WITH CARDIOVASCULAR DISEASE, HYPERTENSION, AND HYPERTENSION-RELATED ORGAN DAMAGE

Evidence linking OSA to arterial hypertension. Early concerns about possible consequences of SDB in patients with severe OSAS focused on the possibility that nocturnal hypoxemia might cause pulmonary hypertension and cor pulmonale, but it has become progressively clear that the systemic circulation is the most important target of OSAS. As far back as in 1980, the San Marino epidemiological study by Lugaresi and co-workers (79) highlighted the association of systemic hypertension and snoring in the general population. Ten years later, a high prevalence of cardiovascular disease (systemic hypertension, coronary artery disease, and cerebrovascular disease) in OSAS patients at diagnosis, and a dose-response effect
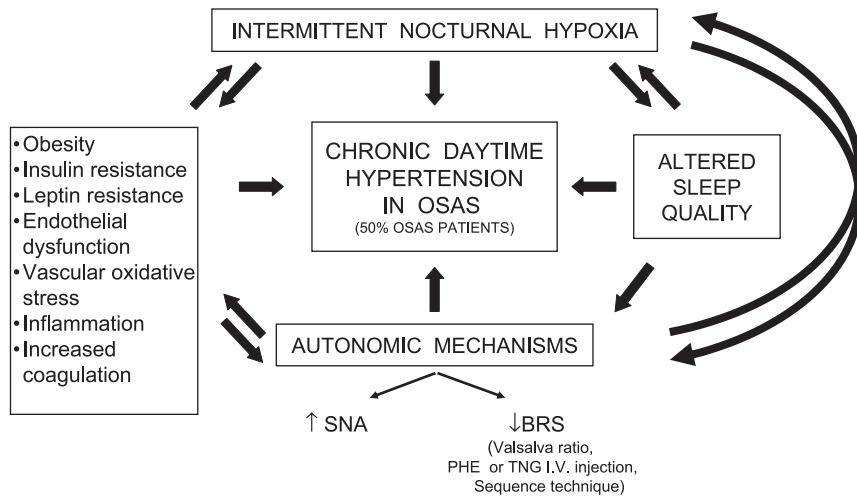
Fig. 2. Mechanisms suggested to be involved in appearance of chronic daytime hypertension in obstructive sleep apnea syndrome (OSAS) patients, and their possible interactions. SNA, sympathetic nerve activity; BRS, baroreflex sensitivity; PHE, phenylephrine intravenous injection method; TNG, trinitroglycerine intravenous injection method.

between cardiovascular involvement and OSAS severity, was reported by the Stanford group (111). Nowadays, additional evidence is available that OSAS may represent an important independent risk factor for systemic hypertension. Multivariate analysis and careful case-control studies have confirmed that the association of sleep apnea and increased blood pressure is independent of confounders such as obesity (24, 116, 152). A strikingly high prevalence of OSAS was in particular seen in patients with drug-resistant hypertension (96% in men and 65% in women), which suggests that OSAS might be one of the most important causes of refractory hypertension (78) (Fig. 2). Thus OSA should also be considered in those hypertensive patients who respond poorly to combination therapy with antihypertensive medications. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure had recommended that OSA be considered in patients with resistant hypertension (59). The more recent Seventh Report from this committee cites OSA as first on the list of identifiable causes of hypertension (21). The very recent European Hypertension Guidelines further emphasize the important role of OSA as a determinant of high blood pressure levels (31).

Animal models of OSA have provided strong evidence for its causal relationship with hypertension (16). A causal relationship between intermittent hypoxia during sleep, systemic hypertension, and cardiac hypertrophy has been shown in a chronic dog model of OSAS (16, 110) and in rats exposed to intermittent hypoxia (33). Conversely, sleep disruption did not increase daytime blood pressure (16). The importance of the link between OSAS and hypertension is also supported by the reports on the improvement in hypertension management after correction of OSA. The best available evidence for a causal role of OSA in the pathogenesis of systemic hypertension has been obtained in humans by prospective randomized trials on the short-term effects of therapeutic vs. sham CPAP therapy of OSA. In these studies systemic blood pressure was found to decrease only after therapeutic CPAP (32, 117) (Fig. 3). Blood pressure after CPAP therapy decreased only slightly in normotensive OSA patients and to a greater degree in OSA hypertensive subjects (9, 26).

When the risk of having hypertension is expressed as an odds ratio, after adjusting for confounders, the figures seen in different studies range from 1.3 to as high as 9.7, depending on the population under study and on the method used to define OSAS (28, 100, 101). There are some discrepancies between studies as to whether blood pressure levels correlate with the severity of OSAS (28), but in at least two large studies a clear-cut dose-effect relationship was seen (73, 100) (Fig. 4).

The prevalence of hypertension may be underdiagnosed in OSA patients if blood pressure is assessed by office readings only. Baguet et al. (5) have shown that ambulatory blood pressure monitoring might be of particular significance in the diagnosis of hypertension in OSA patients. Whereas 42% of OSA patients had high blood pressure in the office, 58% had elevated ambulatory daytime blood pressure and 76% had nighttime hypertension. Indeed, OSA subjects have a significantly elevated blood pressure during the night even more
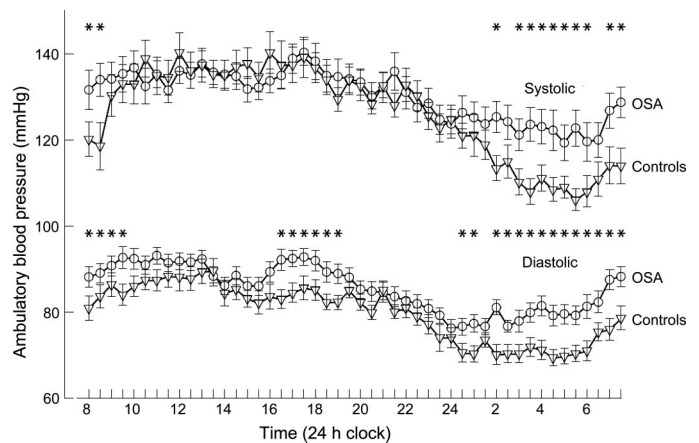

Fig. 3. 24-h Ambulatory blood pressure profiles in a group of patients with OSA ($n = 45$) and in a group of controls ($n = 45$) matched for age ($\pm10\%$), body mass index (BMI; $\pm5\%$), alcohol intake (>10 or <10 units/wk), smoking (never vs. ex/current), treated hypertension, ischemic heart disease (documented history of angina and/or previous myocardial infarction), and diabetes. Data are separately shown for systolic and diastolic blood pressure profiles. Note clear differences at night with reduced nocturnal fall in systolic and diastolic blood pressure in patients with OSA, accompanied by increased diastolic blood pressure during morning and afternoon. Asterisks indicate times at which differences in hourly blood pressure reached a statistically significant level of $P < 0.05$ (Student's t-test). Reprinted from Ref. 24, with permission.
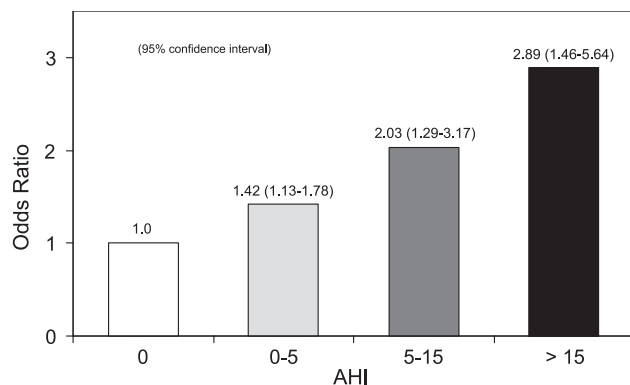
Fig. 4. Odds ratios for presence of incident hypertension at 4-yr follow-up according to apnea-hypopnea index (AHI) at baseline. Data are derived from Wisconsin Sleep Cohort Study. Even mild forms of OSA were associated with increased probability of developing arterial hypertension. Reprinted from Ref. 116, with permission.

frequently than during daytime. This is reflected by a reduced nocturnal blood pressure fall or a "nondipping" profile (24), which appears to characterize OSA patients and might further contribute to the adverse cardiovascular prognosis of this condition (Fig. 3).

The risk of developing hypertension is particularly high in young and nonobese subjects with severe OSAS, in contrast with the tendency of increased hypertension prevalence with advancing age observed in the general population. The reasons for this phenomenon are unclear, but it could be hypothesized that a lower cardiovascular reactivity and the impairment in cardiovascular control mechanism that characterize elderly subjects might render them partly immune from the effects of repeated nocturnal airway obstruction and hypoxia, which increase blood pressure through a hypoxia-related impairment of the same mechanisms (see above).

Although OSAS is certainly the most important type of SDB in terms of hypertension development, it should be emphasized that habitual snoring without association with a clinically relevant number of apneas also seems to play an independent role in determining an increased blood pressure level (156). Habitual snoring is frequently observed in pregnant women, in whom it is an independent predictor of maternal hypertension and fetal growth retardation (36).

OSA increases the prevalence of hypertension target organ damage, such as left-ventricular hypertrophy (68). Furthermore, OSA affects functional and structural properties of large arteries, contributing to hypertension and atherosclerosis progression. Increased pulse-wave velocity and increased intima-media thickness have been frequently reported in middle-aged OSA patients free of overt cardiovascular disease (89, 92). The acceleration of the atherosclerosis by OSA may also deteriorate aorta elastic properties, whereas OSA-related repetitive systemic blood pressure surges and intrathoracic negative pressure swings may contribute to aortic wall dissection in predisposed subjects. In fact, Sampol et al. (130) have documented a high prevalence of previously undiagnosed and frequently severe OSA in patients with thoracic aorta dissection.

Evidence linking OSA to other cardiovascular diseases. As for the role played by OSA in the pathogenesis of other cardiovascular diseases, clinical evidence is much more limited than for hypertension, although the amount of information on

this issue is growing (27, 82, 114). In the relatively elderly Sleep Heart Health Study cohort, OSA emerged as an independent risk factor for congestive heart failure [odds ratio, 2.2 (1.11–4.37)], cerebrovascular disease [odds ratio, 1.58 (1.02–2.46)], and coronary artery disease (CAD) [odds ratio, 1.27 (0.99–1.62), confidence interval 95%] (135). According to retrospective uncontrolled studies, untreated moderate-to-severe OSA was associated with increased rates of nonfatal cardiovascular events in a relatively short follow-up (115). At least four longitudinal studies have subsequently found increased cardiovascular morbidity in OSA patients (27, 82, 114), but the concomitant occurrence of other cardiovascular risk factors often limits the assessment of an independent pathogenetic role for OSA. The first observational reports on cardiovascular mortality in OSA have also been confirmed by later studies. Before CPAP treatment was introduced into clinical practice, OSA patients, particularly relatively young patients (46, 74), who had been conservatively treated and only encouraged to lose weight, showed a higher morbidity and mortality for cardiovascular diseases over 5–8 yr after the diagnosis of OSA. On the other hand, patients tracheostomized because of very severe OSA showed survival outcomes similar to those of the general population. (46, 50). Other studies have shown that CPAP-treated patients who were compliant with treatment had normal mortality rates compared with the general population (82, 83, 147). Indeed, compliance with CPAP rather than severity of OSA at diagnosis was the most important determinant of long-term outcome of therapy.

OSA and coronary artery disease. Several studies have found positive associations between incidence of OSA and ischemic heart disease. Patients with known CAD and a RDI > 10 events/hour were reported to be much more likely to experience cardiovascular death over a 5-yr period than those with low RDIs (37.5 vs. 9.3%, respectively) after controlling for age, weight, and smoking (113, 135), whereas patients with CAD and OSA who accepted CPAP therapy had a better clinical course compared with those who refused treatment (90).

OSA and chronic heart failure. Animal experimental models indicate a distinct connection between obstructive apneic episodes and left ventricle dysfunction (110). Although there are conflicting data on the effect of OSA on cardiac function in humans, the majority of studies indicate a positive association between OSA and cardiac dysfunction. Patients with OSA without clinical history of heart failure may exhibit an abnormal relaxation pattern with diastolic cardiac dysfunction (87). OSA patients free of any cardiovascular disease may also develop impaired systolic cardiac function (1, 37). OSA has also been shown to be an independent risk factor for development of left-ventricular hypertrophy (68) which itself deteriorates cardiac performance. Other studies in patients with chronic heart failure and OSA have shown that short-term CPAP treatment increased left-ventricular ejection fraction (63, 81) and improved quality-of-life indicators. The effects of CPAP on chronic heart failure patient prognosis is still a debated issue (3). Although a small study by Sin et al. (138), carried out before the current wide use of beta blockers, suggested an improved survival in chronic heart failure patients treated with CPAP, a recent study by Bradley et al. (15) did not confirm this finding. These investigators reported that a group of heart failure patients with only CSA, after 3 mo of CPAP

therapy during sleep, presented no differences in transplantation-free survival, number of hospitalizations, quality of life, or atrial natriuretic peptide levels compared with the control group. However, the CPAP group, compared with the control group, had greater reductions in the frequency of episodes of apnea and hypopnea (-21 ± 16 vs. -2 ± 18/h; $P < 0.001$) and in norepinephrine levels (-1.03 ± 1.84 vs. 0.02 ± 0.99 nmol/l; $P = 0.009$) and greater increases in the mean nocturnal oxygen saturation (1.6 ± 2.8 vs. $0.4 \pm 2.5\%$; $P < 0.001$), ejection fraction (2.2 ± 5.4 vs. $0.4 \pm 5.3\%$; $P = 0.02$), and distance walked in 6 min (20.0 ± 55 vs. -0.8 ± 64.8 m; $P = 0.016$) (15) (Fig. 5*A*).

The importance of this controversial issue is further emphasized by a very recent study by Wang et al. (149), showing that in patients with chronic heart failure, untreated OSA is associated with a significantly reduced survival rate independently of confounding factors (Fig. 5*B*).

OSA and stroke. Convincing evidence of a causal relationship between OSA and stroke has been recently provided by prospective, well-designed studies in young, middle-aged, and
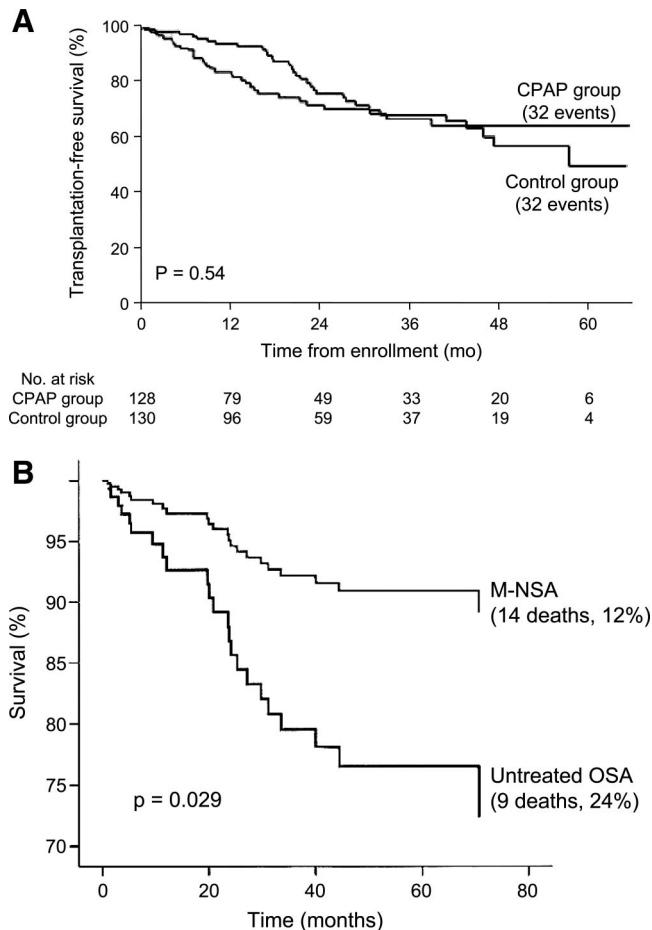

Fig. 5. *A*: lack of difference in transplantation-free survival rates between a group of patients with chronic heart failure randomized to chronic positive air pressure (CPAP) treatment and control group randomized to treatment without CPAP. Reprinted from Ref. 15, with permission. *B*: adjusted survival curves showing worse survival in heart failure patients with untreated OSA than in those with mild to no sleep apnea (M-NSA; hazard ratio = 2.81, $P = 0.029$) after adjusting for significant confounders (left-ventricular ejection fraction, New York Heart Association functional class, and age). Reprinted from Ref. 149, with permission.
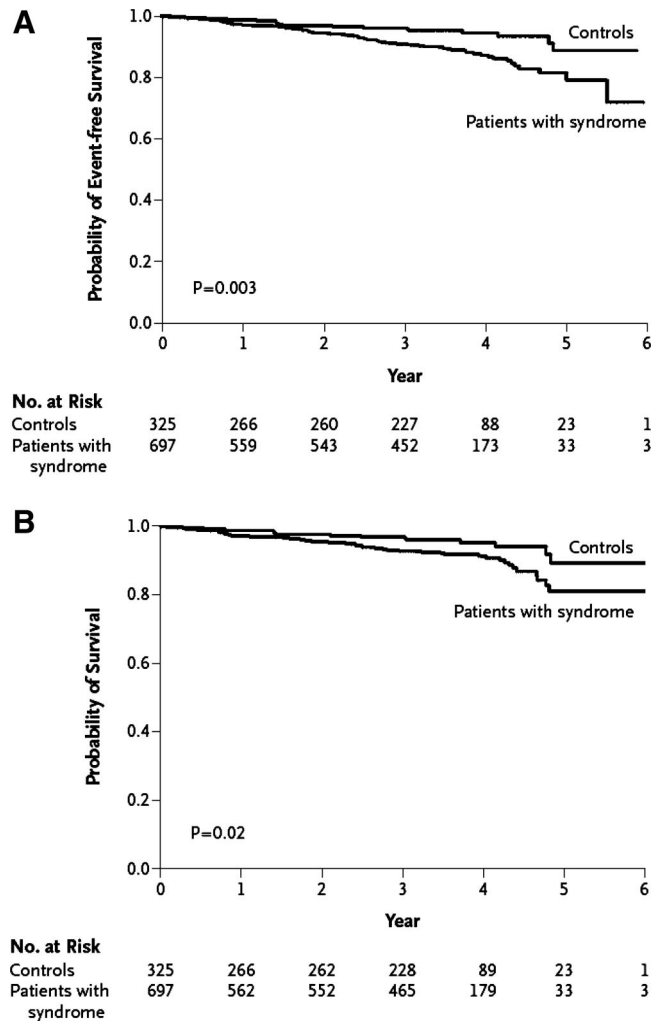

Fig. 6. *A*: Kaplan-Meier estimates of probability of event-free survival (for a combined end-point of stroke and death) among patients with OSAS and controls. *B*: Kaplan-Meier estimates of probability of overall survival among patients with OSA and controls. Reprinted from Ref. 153, with permission.

elderly people (91). Arzt and colleagues (4), using data from the Wisconsin Sleep Cohort Study, further demonstrated that a moderate OSA (defined as AHI > 20) was associated with a threefold increment in the risk of developing a stroke. Recent longitudinal population data support the interpretation that SDB usually precedes and increases the risk for the occurrence of stroke after OSA diagnosis (146). Moreover, the risk for stroke or death during follow-up appears to linearly increase with OSA severity, patients with OSA being characterized by a worse events rate over time when separately considering mortality and stroke (Fig. 6) (153). Despite differences in the selection of patients, methods used, and interval between onset of stroke and sleep recording, between 44 and 72% of patients with stroke were found to have an AHI >10 (8). (Fig. 7) Many uncertainties about the role of OSA in the pathogenesis of stroke are due to the fact that SDB not only can precede but also can follow a stroke episode. Stroke in fact may aggravate or even cause a sleep-related breathing disorder "de novo." This hypothesis is supported by the observation in a few studies of an improvement of SDB after the acute phase of stroke, with a normalization of the AHI in 40% of them (8).
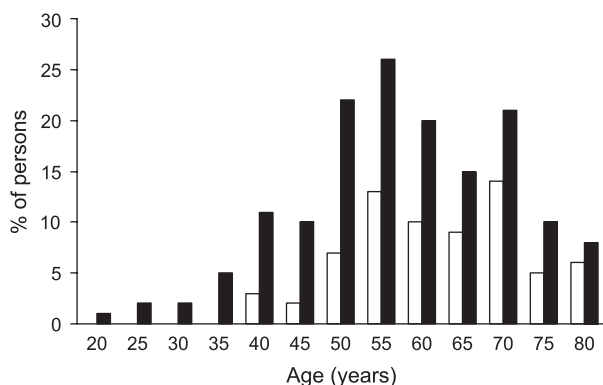
Fig. 7. Sleep-disordered breathing (SDB) in 152 patients with acute ischemic stroke. Open bars indicate stroke patients with SDB. Closed bars refer to all stroke patients regardless of occurrence of SDB. SDB was defined as AHI > 10. Reprinted from Ref. 8, with permission.

Moreover, stroke severity or topography does not predict presence or severity of SDB. This observation supports the hypothesis that SDB often precedes stroke, as demonstrated by the high frequency of SDB in transient ischemic attack patients (85). Moreover, sleep apneas secondary to stroke are more likely to be central than obstructive. OSA is also potentially associated with poor outcomes following stroke, even if only limited data are available on short-term and long-term effects of SDB on stroke outcome and mortality. Clinical data indicate a high mortality of patients with an AHI > 30 after stroke and an improvement in 18-mo survival of those OSA patients (AHI $\geq$ 20) who were able to tolerate CPAP treatment after stroke (84). Conflicting data is conversely available on the relationship between SDB and long-term outcome of stroke (8). The variable mortality rates found in these different studies probably reflect differences in the stroke population studied, including age, initial severity of stroke, and stroke etiology.

OSA, arrhythmias, and sudden cardiac death. Several observational studies indicate an association between OSA and the incidence of cardiac arrhythmias (39, 42). Recent analysis of the Sleep Heart Health Study has shown that patients with severe OSA (AHI > 30 events/h sleep) are at fourfold increased risk of occurrence of atrial fibrillation compared with matched controls without SDB (86). In patients with atrial fibrillation included in a 1-yr follow-up after cardioversion, untreated OSA was associated with a higher rate of arrhythmia recurrence compared with matched controls free of breathing disturbances (82 vs. 53%; $P = 0.009$) (62). Finally, whereas in a general population sudden cardiac death prevalence is characterized by a nadir during sleep at night, in patients with OSA this event displays a peak of frequency during sleeping hours (38).

It is hypothesized that the frequent apneic/hypopneic episodes and the resulting arterial desaturation and hypercapnia cause activation of the sympathetic nervous system. This mechanism has been suggested to be responsible for the described relationship between OSA and tachyarrhythmias, especially atrial fibrillation. In contrast, bradyarrhythmias are probably related to an increase in vagal tone due to stimulation of upper airway receptors (80).

IMPLICATIONS FOR TREATMENT

Therapeutic strategies for OSA include sleep postural changes, focusing on avoidance of sleeping in the supine position, weight loss, avoidance of alcohol and sedative hypnotics intake, and upper airway surgical procedures (104). However, the current treatment of choice in OSA is the nocturnal application of nasal CPAP. CPAP treatment prevents airway collapse during respiration at night, and this is associated with acute and marked reduction in nocturnal sympathetic nerve traffic and in the related blood pressure surges during sleep (93) Indeed, effective long-term treatment of OSA by CPAP treatment has been shown to improve systolic and diastolic blood pressure control in hypertensive patients, particularly when blood pressure is monitored over 24 h (32, 150) (Fig.8). The benefit is larger in patients with more severe sleep apnea, may be independent of the baseline blood pressure levels (9, 26, 117), and is especially evident in patients already under drug treatment for hypertension. Interestingly, faster heart rate also predicts a greater CPAP effect on blood pressure (132). Long-term CPAP treatment decreases MSNA in other-
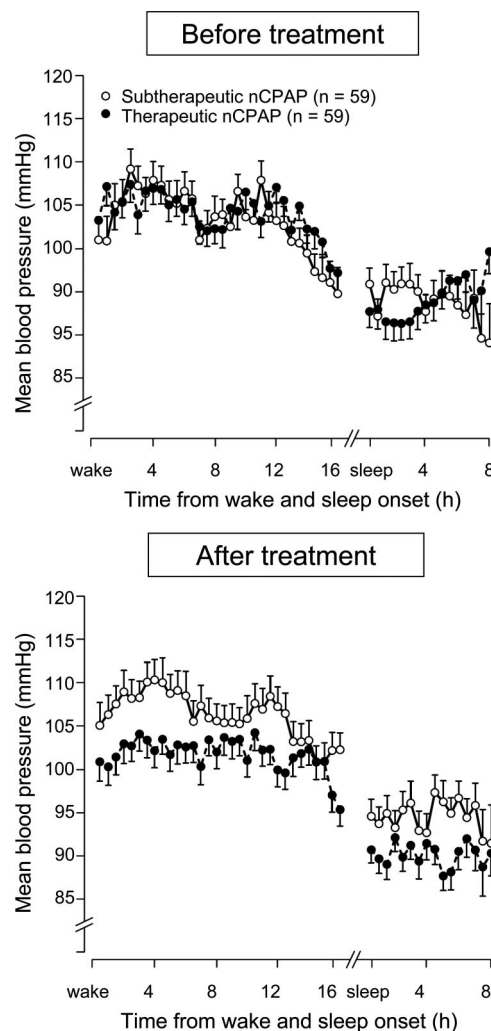

Fig. 8. 24-h mean ambulatory blood pressure profiles in patients before (*top*) and after treatment (*bottom*) with subtherapeutic (level of pressure lower than needed to correct obstructive events) CPAP (○) and with therapeutic CPAP (●). Reprinted from Ref. 117, with permission.

wise healthy OSA patients (93), improves baroreflex sensitivity (14), and improves glycemic control in type 2 diabetics, the effect of CPAP on insulin sensitivity being greater in nonobese than in obese OSA patients (45).

Other strategies for treating OSAS include oral appliances (22) or surgical procedures (the most popular one being uvulopalatoplasty), but their efficacy is questionable and their effects on blood pressure have not been adequately studied.

An issue of great practical importance is the choice of the most suitable antihypertensive drugs to be administered to OSA patients with high blood pressure. Because increased sympathetic activity appears to be one of the key mechanisms involved, a possible benefit from the administration of adrenergic blocking agents was hypothesized (67). Although some data are available to support this hypothesis, they do not appear sufficient to allow a definite recommendation of this class of drugs in treating OSAS-related hypertension, especially in the light of a possible aggravation of metabolic changes frequently present in OSA patients. Other suggestions focus on use of drugs interfering with the renin-angiotensin-aldosterone system (67), given the pathophysiological mechanisms relating OSA to hypertension, or on use of long-acting calcium-channel blockers belonging to the dihydropyridine class (67).

Surgical treatment of obesity may have striking effects on OSA. A recent systematic review and meta-analysis of articles on bariatric surgery has shown that up to 85% of OSA patients experience complete resolution of SDB after surgery (17). This may conceivably serve as a potential option in markedly obese patients with OSA who cannot tolerate CPAP therapy. Limited evidence is available, however, on the effects of these interventions on blood pressure levels or on the rate of cardiovascular complications.

CONCLUSIONS

The evidence reviewed in this paper emphasizes the association between SDB, in particular OSA, and cardiovascular problems, in particular arterial hypertension, and provides some insight into the mechanisms potentially involved in determining this association (Fig. 2).

The clinical implications of the demonstrated link between hypertension and OSA include the need for a more systematic search for SDB among hypertensive patients at the time of their diagnostic evaluation, ranging from an accurate sleep history to performance of full polysomnography whenever appropriate. They also include, however, the need for a more systematic search of blood pressure elevation in OSA patients, in particular in case of severe OSA, mainly if associated with obesity.

Despite the rapidly expanding knowledge on this issue, a number of important aspects still need to be further assessed. They include the interrelation between OSA, energy metabolism, and sleep deprivation; the role of genetic mechanisms in predisposing to SDB at different ages; and the identification of early markers of OSA-associated cardiovascular risk to pursue effective preventive programs rather than just concentrating on treatment of an established disease.

In general terms, there is a clear need for large-scale studies of carefully defined patient populations with OSA, adequately controlling for potential confounders that might increase cardiovascular risk, such as diabetes and dyslipidemia. It should be acknowledged, however, that the recognized efficacy of

CPAP in treating the breathing disorder makes long-term randomized studies difficult to design because of the inability, for ethical reasons, to withdraw an effective therapy in severely affected patients.

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