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REVIEW SERIES

Obstructive sleep apnea syndrome as a cause of resistant hypertension

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Evidence has consistently supported the association of obstructive sleep apnea syndrome (OSAS) with an increased prevalence of hypertension. It has also been shown that the severity of OSAS is directly correlated with the degree of blood pressure (BP) elevation and that hypertension occurring in subjects with OSAS is more likely to be severe, resistant to antihypertensive treatment and associated with alterations in day-to-night BP changes. Proposed mechanisms for the pathogenesis of OSAS-related hypertension include the activation of the sympathetic nervous system, alterations in autonomic cardiovascular (CV) modulation, the activation of the renin–angiotensin–aldosterone system, endothelial dysfunction, systemic and vascular inflammation, oxidative stress, metabolic abnormalities, arterial stiffness and alterations in cardiac function and structure. Given the adverse prognostic implications of OSAS-related hypertension for CV morbidity and mortality, the confirmation of resistant hypertension by using ambulatory BP monitoring (ABPM) and the identification of alterations in day-to-night BP changes is of the utmost importance to implement more aggressive strategies for achieving BP control. In turn, the proper identification and implementation of specific treatment strategies for OSAS (that is, continuous positive airway pressure) in subjects with resistant hypertension may promote BP control and optimize CV protection. The present paper will review the evidence supporting the association of OSAS with resistant hypertension and the proposed mechanisms for this association. It will also address the role of ABPM in the confirmation of resistant hypertension in subjects with OSAS and whether the proper identification and management of OSAS in subjects with resistant hypertension will improve BP control.
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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS), which combines intermittent obstruction of the upper airways at night with somnolence during the day, is one of the suggested causes of secondary hypertension[1] and has been associated with a severe and resistant hypertension.[2–4] Evidence from longitudinal studies has indicated that OSAS may also predict the development of future hypertension.[3,5–7] However, despite the wealth of epidemiological evidence supporting the association of OSAS and hypertension, there is only partial understanding of the pathophysiological mechanisms underlying this relationship. In contrast, although OSAS and resistant hypertension have been shown to be independent predictors of cardiovascular (CV) prognosis, evidence is still needed to determine the actual prognostic relevance of their interaction independently of the other CV risk factors that are often clustered in the context of OSAS. Because of the frequent association of OSAS with resistant hypertension and in recognition of their probable synergistic effects on CV risk, current guidelines for the management of arterial hypertension have included OSAS among the modifiable causes to be ruled out during the diagnostic approach to resistant hypertension.[1,8] However, whether specific treatment strategies for OSAS (that is, the implementation of continuous positive airway pressure (CPAP)) will be effective in achieving BP control in combination with antihypertensive treatment has not been consistently shown. The present paper is aimed at critically reviewing the evidence supporting OSAS as a cause of resistant hypertension as well as the proposed mechanisms of this association. It also addresses the importance of implementing ambulatory blood pressure (BP) monitoring (ABPM) and home BP monitoring to determine whether the failure to achieve OBP control in a subject with OSAS actually corresponds to true resistant hypertension. Finally, it addresses whether and to what extent the proper management of OSAS either by pharmacological or

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nonpharmacological strategies is likely to improve BP control in subjects with resistant hypertension.

OSAS AND BP LEVELS

OSAS is defined as the presence of recurrent obstructive breathing events generated by complete upper airway obstruction during sleep and is accompanied by daytime symptoms and sleep hypoventilation syndrome.[9] The alterations in breathing patterns in individuals with OSAS may influence many regulatory mechanisms involved in BP regulation. OSA events occurring at night (that is, alternating obstructive apnea and hyperventilation episodes during sleep) have been shown to be accompanied by acute changes in autonomic and hemodynamic parameters, which in turn induce marked increases in nighttime BP levels.[10] Indeed, hypertension related to OSAS is predominantly nocturnal and frequently accompanied by a nondipper profile of BP (that is, the nocturnal BP falls $<10\%$ compared with daytime BP levels).[11,12] Nonetheless, the increase in BP levels in OSA subjects is not limited to the nighttime hours when the OSA episodes occur but is also sustained during the day. Case–control studies using 24-h ABPM have provided evidence that, compared with matched control subjects, OSAS patients show significantly higher ABP levels not only during nighttime sleep but also during daytime wakefulness.[13–15]

EPIDEMIOLOGICAL EVIDENCE FOR THE ASSOCIATION BETWEEN OSAS AND HYPERTENSION

Both in the general population and in cohorts of OSAS patients, a number of studies of different natures have confirmed the association between OSAS and hypertension.[2,4,5,16–18] Overall, these studies have indicated a variable frequency of hypertension in subjects with OSAS that can range from 35 to 80%.[11,19] Conversely, when properly investigated, OSAS has been shown to be present in up to 40% of hypertensive subjects.[20] Whether the association between OSAS and hypertension is explained by other CV risk factors in addition to OSAS is still a matter of debate. For instance, OSAS is often associated with obesity, which in turn can explain $\sim$65–75% of cases of essential hypertension.[21,22] Indeed, some studies have indicated that much of the relationship between OSAS and hypertension can be explained by the associated obesity.[6] Conversely, other reports have indicated that the association between obesity and arterial hypertension can be explained by the presence of OSAS in a substantial number of subjects. In addition to body mass index (BMI), other factors such as sex and age have been shown to significantly influence the relationship between OSAS and elevated BP levels.[23] Evidence for this influence has been provided from cross-sectional[16] and longitudinal studies[6,24] indicating that OSAS is more strongly associated with hypertension and resistant hypertension in young- to middle-aged adults (<50 years of age).[23] This association is more frequently observed in men than in women.[25] It is thus clear that disentangling the independent contributions to BP elevation of OSAS, obesity and other CV risk factors is rather difficult. Despite this difficulty, several longitudinal studies have supported the association between OSAS and hypertension independently of other potential contributing factors, such as BMI, also indicating that OSAS is not only associated with an increased risk of prevalent hypertension but may also be an independent and significant predictor of the future development of hypertension, particularly if not properly treated[3,5–7] (Figure 1).

In particular, in the Wisconsin Sleep Cohort Study, a dose–response relationship between sleep-disordered breathing at baseline and the development of hypertension after 4 years of follow-up was reported independently of baseline hypertension status, BMI, neck and waist circumference, age, sex or other potential confounders, suggesting that sleep-disordered breathing is likely to be a risk factor for hypertension and resultant CV morbidity in the general population.[3]

OSAS AS A CAUSE OF RESISTANT HYPERTENSION: PROPOSED MECHANISMS

Several studies have identified OSAS as an important risk factor for resistant hypertension and have shown a dose–response relationship between OSAS severity and the degree of BP elevation.[15] It has also been shown that hypertension occurring in individuals with OSAS is more likely to be severe, resistant to treatment and associated with alterations in day-to-night BP changes (that is, nocturnal hypertension and nondipping profile of BP on 24 h ABPM).[15,26,27] Conversely, an extremely high level of OSA ($\sim$80%) has been reported among adult patients with drug-resistant hypertension.[25] It has also been shown that the rates of BP control decrease as the severity of sleep-related breathing disorders increases.[2] Although all the above evidence supports a potential role of OSAS in the pathogenesis of hypertension and drug-resistant hypertension, the mechanisms by which OSAS promotes arterial hypertension are not completely understood. Evidence provided by experimental and clinical studies has indicated that the pathogenesis of OSAS-related hypertension is likely to be multifactorial, involving alterations in several regulatory systems: the activation of the sympathetic nervous system, alterations in autonomic CV modulation, the activation of the renin–angiotensin–aldosterone system, endothelial dysfunction, systemic and vascular inflammation, oxidative stress, metabolic abnormalities, arterial stiffness and alterations in cardiac function and structure. Figure 2 outlines the main mechanisms by which OSAS contributes to resistant hypertension.

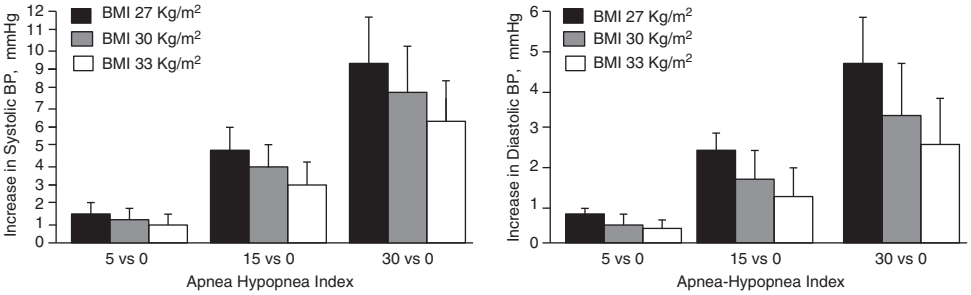

Figure 1 Predicted increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) associated with sleep-disordered breathing for three body mass index (BMI) categories in the Wisconsin Sleep Cohort Study. Modified from Young *et al*.[5] by permission.

Sympathetic nervous system activation

The activation of the sympathetic nervous system is considered a major pathophysiological mechanism underlying the alterations in BP regulation reported in OSAS (Figure 2). This has been consistently demonstrated by several studies implementing direct techniques for the assessment of the sympathetic nervous system (that is, the recording of efferent postganglionic muscle sympathetic nerve activity via microneurography and norepinephrine plasma levels) in which an increase in central sympathetic drive was positively correlated with increases in BP levels independently of other contributing factors. The sympathetic activation in OSAS is largely explained by the stimulation of the peripheral and central chemoreflexes, triggered by the reductions in arterial oxygen content and hypercapnia, respectively. Moreover, sleep fragmentation, related to repeated arousals after each apnea/hypopnea event, might have an additional role in this context. The resultant increases in sympathetic drive to the heart and peripheral vasculature lead to significant increases in heart rate and vascular tone, which in turn are responsible for the marked increases in BP levels during the resumption of ventilation after each apneic episode[28] (Figure 3a).

This increase in central sympathetic drive has also been shown to be associated with alterations in circadian BP variation (that is, the absence of nocturnal BP fall or an increase in BP at night), and nocturnal hypertension is frequently observed in OSAS patients.[29] In addition, several studies using microneurography recordings have indicated that the sympathetic activation in OSAS subjects is not only limited to nighttime but may persist even after resuming a normal breathing pattern during daytime wakefulness, despite normal arterial oxygen saturation and carbon dioxide levels[28,30] (Figure 3b). Remarkably, in several studies, the long-term implementation of CPAP resulted in marked reductions in sympathetic nerve traffic[28] and BP levels[31] during nighttime and daytime,[32] further supporting the

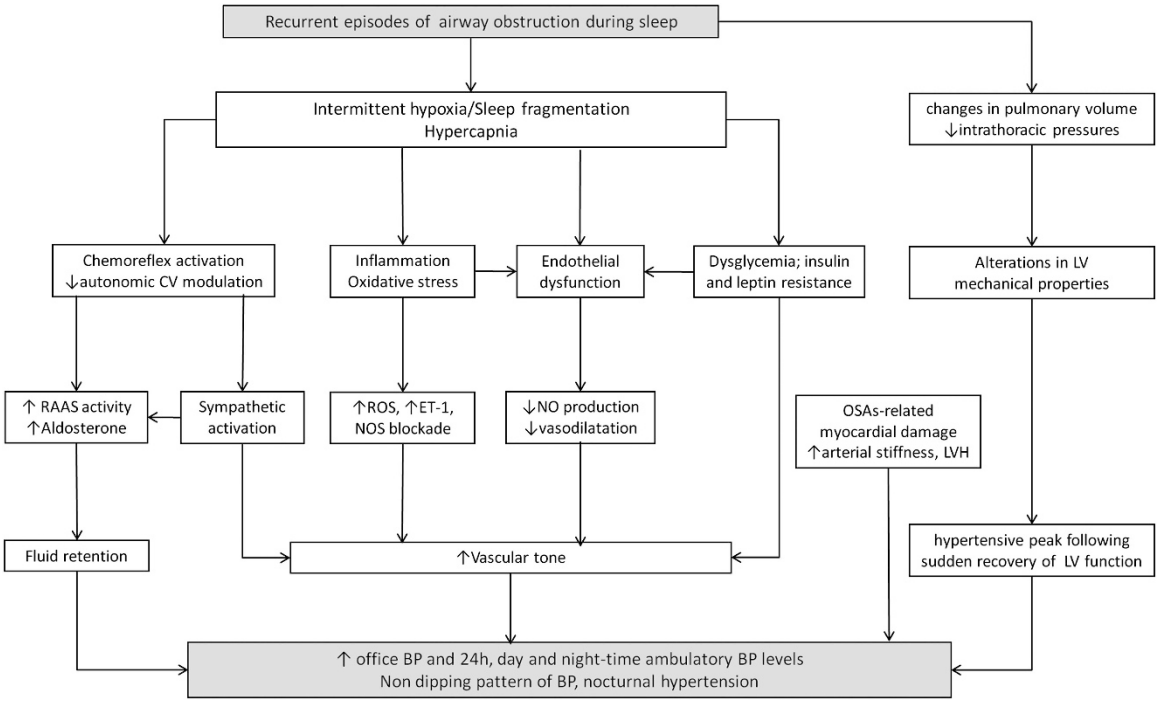

Figure 2 Mechanisms by which obstructive sleep apnea syndrome (OSAS) contributes to resistant hypertension. CV, cardiovascular; LV, left ventricular; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; ET-1, endothelin-1; NOS, nitric oxide synthase; NO, nitric oxide; LVH, left ventricular hypertrophy; BP, blood pressure.

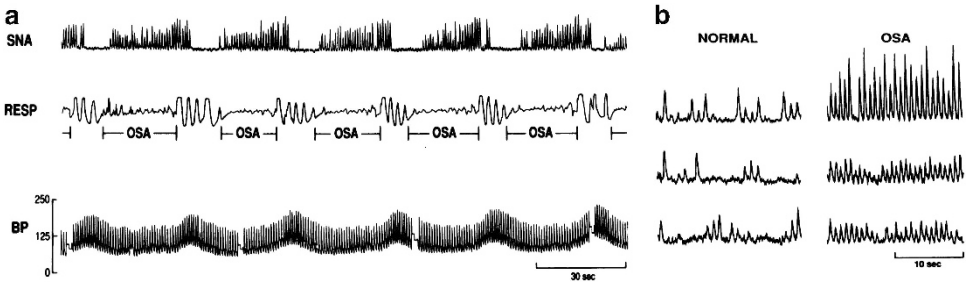

Figure 3 (**a**) Recordings of sympathetic nerve activity (SNA), respiration (RESP) and blood pressure (BP) during 3 min of stage II sleep, showing continuous oscillations in BP and SNA in response to the repetitive obstructive sleep apneas (OSAs). These oscillations occurred continuously during sleep, throughout all sleep stages. (**b**) Recordings of SNA during wakefulness in patients with OSAS and matched controls showing high levels of SNA in patients with OSA. Taken from Somers *et al*.[28] by permission.

pathogenic role of sympathetic activation in BP elevation associated with OSAS.

Alterations in autonomic CV modulation

In normal physiological conditions, the control of BP levels is achieved through a complex interplay between the central and reflex neural influences, leading to a continuous modulation of efferent sympathetic and parasympathetic nerve activity and the associated activity of neurohormonal systems primarily regulated by the hypothalamus. In OSAS, the sustained chemoreflex activation, the related adrenergic overactivity and the resulting hypertension may blunt and/or reset arterial and cardiopulmonary reflexes, which in turn may lead to chemoreflex potentiation.[33,34] In addition, the dysfunction of neural reflexogenic areas (that is, baroreflex impairment) may lead to reduced sympathoinhibition,[35,36] further contributing to adrenergic overdrive and BP elevation (Figure 2). In particular, the observation of a reduced cardiac baroreflex sensitivity (BRS; as assessed by the sequence method) and the absence of 24-h baroreflex modulation (that is, blunted increase in BRS during sleep compared with its values during wakefulness) in OSAS patients[35] has provided indirect support for the concept that baroreflex dysfunction in addition to chemoreceptor stimulation by hypoxia may contribute to the acute and long-term sympathetic activation in OSAS patients (Figure 4). The depressed BRS during sleep may in turn contribute to the pathophysiology of hypertension in OSAS patients.

This concept has been further supported by the results of interventional studies in OSAS patients showing a significant improvement in BRS after the long-term implementation of CPAP treatment.[37,38]

Other independent studies applying the spectral analysis of the variability of microneurography, BP and heart rate have provided additional evidence that the autonomic CV modulation is impaired in OSA based on the demonstration of significant increases in heart rate and sympathetic drive, reduced HRV and a marked increase in BP variability (more than double the variance in healthy controls)[39] (Figure 5).

Further evidence that sleep-related breathing disorders may induce alterations in autonomic CV modulation has been provided by a recent study in untreated subjects with sleep-related breathing disorders of differing severity, which indicated that excessive daytime sleepiness is accompanied by lower BRS and a significantly higher low-to-high-frequency power ratio of heart rate variability (which is believed to be a marker of sympathetic activity) during the different stages of nocturnal sleep[40] (Figure 6).

Activation of renin–angiotensin–aldosterone system (increase in aldosterone levels)

The frequent association of OSAS with hyperaldosteronism reported in patients with resistant hypertension has led to the suggestion that both factors may interact to contribute to BP elevation.[41–43] Although evidence is still needed to determine the cause of this association, it has been hypothesized that OSAS may contribute to the pathogenesis of resistant hypertension by stimulating aldosterone excretion[44] (Figure 2). Evidence supporting this concept has been provided by several studies showing positive and significant correlations between plasma aldosterone concentrations and OSAS severity in patients with resistant hypertension but no correlations in normotensive subjects or in hypertensive patients treated with BP controlled.[45] It is likely that aldosterone excess promotes fluid accumulation in the neck and thus increases upper airway resistance, which may increase the severity of OSA and the related increase in BP levels.[20,46] Indirect evidence favoring this concept has been provided by interventional studies in subjects with OSAS and resistant hypertension in which the addition of spironolactone to antihypertensive treatment resulted in significant reductions in the severity of OSA (that is, reductions in apnea-hypopnea index and the number of central and obstructive events) in

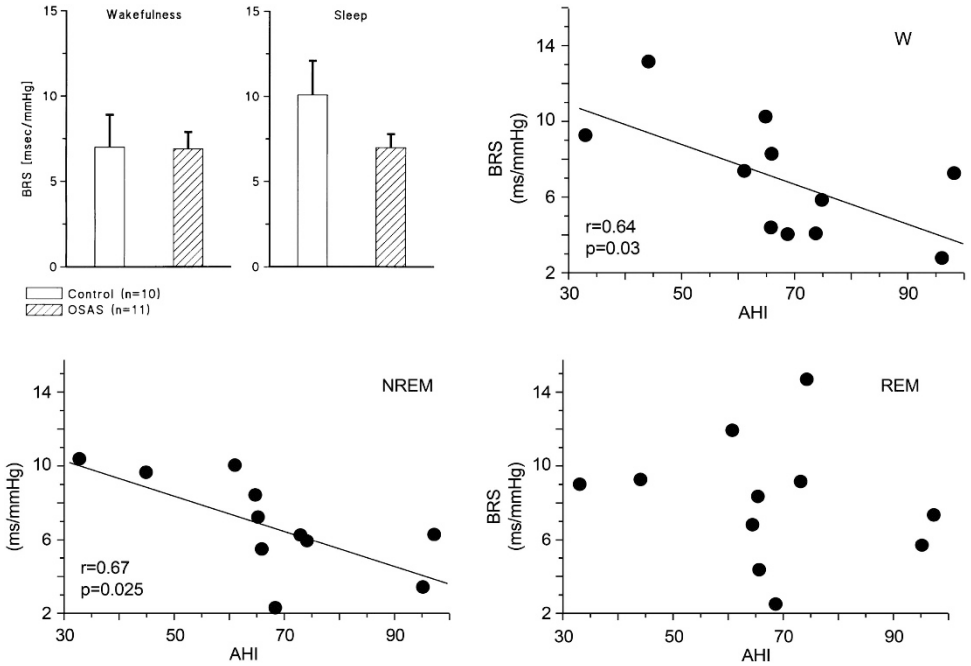

Figure 4 Relationship between spontaneous baroreflex sensitivity (BRS) and the severity of obstructive sleep apnea syndrome (OSAS), as quantified by the apnea-hypopnea index (AHI). Data are shown as individual values from 11 patients during periods of wakefulness (W), nonrapid eye movement (REM) sleep (NREM) and REM sleep (REM). Taken from Parati *et al*.[35] by permission.

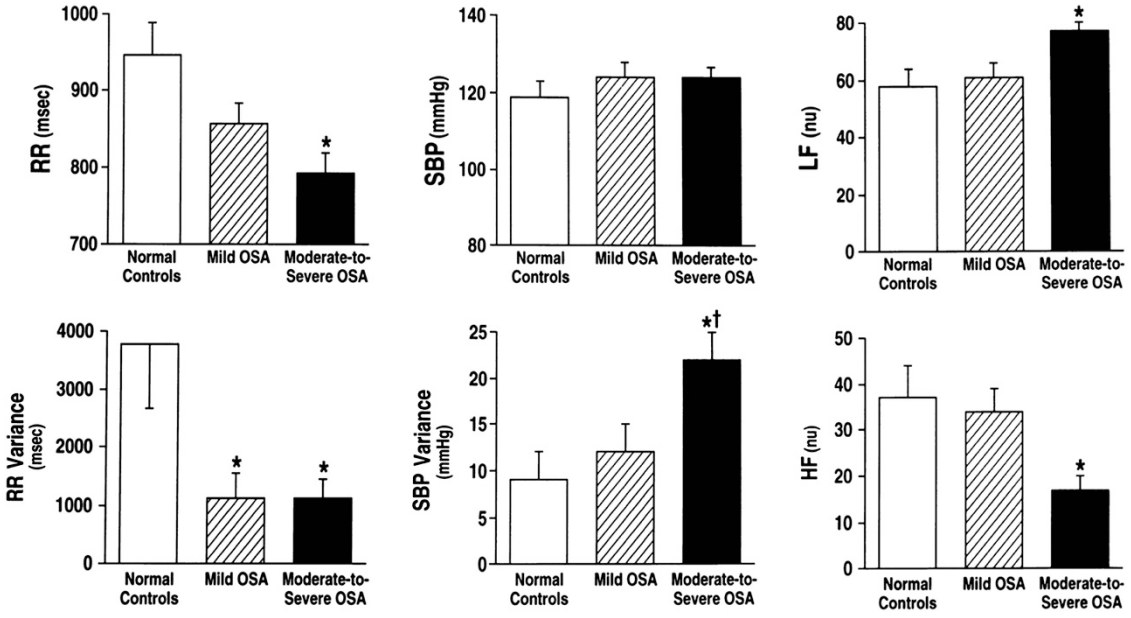

Figure 5 RR interval, systolic blood pressure (SBP) and their variances, and normalized low-frequency (LF) and high-frequency (HF) components of RR interval in control subjects, patients with mild OSA and patients with moderate-to-severe OSA. *$P<0.05$ versus control subjects. †$P<0.05$ versus mild OSA. Data are the means ± s.e.m. Modified from Narkiewicz *et al.*[39] by permission.

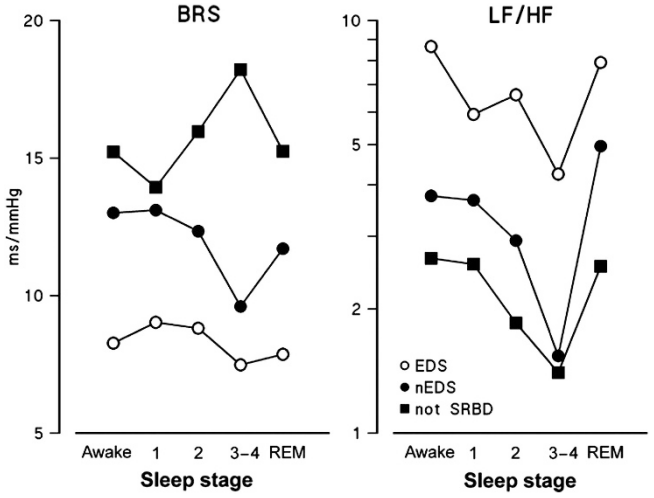

Figure 6 Trends of baroreflex sensitivity (BRS) and of the ratio between low- and high-frequency powers of RRI (LF/HF) in healthy controls without sleep-related breathing disorders (square symbols), in patients with excessive daytime sleepiness (EDS, open circles) and in subjects not affected by EDS (nEDS, solid circles). Taken from Lombardi *et al.*[40] by permission.

addition to the BP-lowering effects.[47] Despite this finding, evidence is still needed to convincingly demonstrate a causal relationship between excess aldosterone in OSAS and resistant hypertension.

Endothelial dysfunction

Intermittent hypoxia and the associated neural and humoral alterations and recurring BP surges during OSA episodes may contribute to endothelial function impairment. In turn, the inhibition of nitric oxide (NO) production, decreased vasodilatation and increased vasoconstriction associated with endothelial dysfunction may substantially contribute to BP elevation (Figure 2). Several studies assessing brachial artery endothelium-dependent flow-mediated dilation (FMD, an indirect marker of endothelial NO-mediated reactivity) and forearm blood flow responses to different stimuli (that is, the infusion of acetylcholine, sodium nitroprusside or nitroglycerin) have shown that compared with healthy controls, patients with OSAS often exhibit an impairment of resistance-vessel endothelium-dependent vasodilation.[48,49] Even when accounting for important confounding factors, such as body weight, brachial artery flow-mediated dilation has been shown to be significantly lower in normal-weight OSAS patients than in OSAS-free controls.[50] Additional evidence that OSAS may significantly influence both indices of macrovascular and microvascular endothelial function was provided by a recent study showing abnormal myocardial perfusion, attenuated brachial artery reactivity and reduced cutaneous perfusion response in OSAS patients compared with healthy controls.[51] Remarkably, several interventional studies have shown substantial improvements in different indices of endothelial function following the implementation of regular CPAP use in subjects with hypertension and OSAS,[49–51] which indirectly supports a role for endothelial dysfunction in the pathogenesis of arterial hypertension in OSAS.

Vascular inflammation and oxidative stress

Recurring episodes of hypoxia/reoxygenation during the transient cessation of breathing in OSA may also reduce NO availability, promoting vascular endothelial inflammation and elevated oxidative stress[48,49,52–54] (Figure 2). When compared with OSAS-free controls and regardless of the presence of obesity, OSAS patients have been shown to have reduced expression of endothelial NO synthase and phosphorylated endothelial NO synthase (proteins that regulate basal NO production and activity) as well as increased levels of nitrotyrosine (a marker of oxidative stress) and nuclear factor κ-light-chain enhancer of activated B cells (a marker of inflammation).[50] Most importantly, after 1 month of regular treatment with CPAP, flow-mediated dilation, the expression of endothelial NO synthase and phosphorylated endothelial NO synthase were significantly increased,

whereas the levels of nitrotyrosine and nuclear factor κ-light-chain enhancer of activated B cells were decreased.[50] It has also been proposed that intermittent hypoxia/hypercapnia associated with OSAS may contribute to the pathogenesis of hypertension by increasing endothelin-1 production. This hypothesis has been supported by experimental studies in rats showing significant increases in the plasma levels of endothelin-1 (a potent vasoconstrictor) and higher BP levels in rats exposed to intermittent hypoxia (that is, cycles of hypoxia/hypercapnia for 8 h a day over 11 days) compared with those breathing normoxic air.[55]

Data from several studies have indicated that the selective activation of inflammatory pathways may be an additional important molecular mechanism for the pathogenesis of arterial hypertension in OSAS. This concept has been supported by translational studies showing a selective activation of the proinflammatory transcription nuclear factor κ-light-chain enhancer of activated B cells in HeLa cells exposed to intermittent hypoxia/reoxygenation cycles.[56] In addition, compared with healthy controls, subjects with OSAS showed significantly higher levels of circulating proinflammatory cytokines (that is, tumor necrosis factor-α and the adaptive factor erythropoietin) and higher levels of circulating neutrophils. Interestingly, the levels of tumor necrosis factor-α normalized after 6 weeks of continuous treatment with CPAP.[56] Other studies have shown that compared with healthy controls, the serum levels of inflammatory markers (that is, C-reactive protein) are significantly higher in OSAS patients and independently associated with OSAS severity.[57] Interestingly, interventional studies have shown significant reductions in serum levels of C-reactive protein and interleukin-6 following the implementation of regular CPAP treatment.[58] Finally, evidence has also been provided that OSAS may induce the activation of adhesion molecules participating in inflammation. These data have been supported by case–control studies showing significantly higher levels of intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and L-selectin in OSA patients compared with healthy controls.[59]

Arterial stiffness

Increased arterial stiffness is a recognized risk factor contributing to the pathogenesis of arterial hypertension.[60–62] A recent systematic review of relevant studies indicated an independent effect of OSAS on arterial stiffness, which in turn may contribute to BP elevation and resistant hypertension[63] (Figure 2). A number of studies have consistently reported significantly higher values of carotid-femoral pulse wave velocity, which is considered the 'gold-standard' measure of aortic stiffness, in patients with OSAS compared with healthy controls.[63,64] Of note, the increase in carotid-femoral pulse wave velocity has been shown to be directly related to the severity of the disease and to be even higher in subjects with OSAS and associated hypertension or in the presence of other CV risk factors.[65] In the Asian population, several studies implementing brachial-ankle PWV have also reported significant associations between OSAS and increased arterial stiffness.[66] Even when comparisons have been performed between individuals with or without OSAS entirely free from other CV risk factors, an independent effect of OSAS on arterial stiffening has been reported.[67] Remarkably, in randomized interventional studies, the effective treatment of OSAS with CPAP has been associated with significant decreases in arterial stiffness.[68,69] In one of these studies, CPAP was also associated with significant reductions in sympathetic nerve activity and ambulatory BP and with significant improvements in arterial BRS.[68]

Metabolic factors

In addition to the hemodynamic changes, OSAS has been frequently associated with metabolic alterations (that is, alterations in glucose metabolism, insulin resistance and leptin resistance), which in turn may contribute to the pathogenesis of arterial hypertension (Figure 2). Although altered glucose metabolism is thought to be a consequence of other conditions associated with OSAS (that is, an increased BMI, metabolic syndrome and/or type 2 diabetes) rather than a consequence of OSAS, evidence has shown that OSAS, independently of the presence of confounding factors, is associated with alterations in glucose metabolism that may promote the development of type 2 diabetes.[70] In addition, interventional studies have shown the efficacy of regular CPAP treatment in improving glucose metabolism in OSAS patients.[70] Compared with healthy controls, OSAS patients have also been shown to have greater insulin and leptin resistance[71–73] even after accounting for body fat content.[74] Although the aforementioned metabolic alterations should theoretically contribute to the pathogenesis of hypertension in OSAS, their relative contribution to BP elevation still needs to be further explored independently of other concomitant factors.

Contribution of genetic variation to OSAS-related hypertension

Hypertension and OSAS represent complex polygenic disorders. The pathophysiology for both implies joint actions of different genes acting at different levels and their interactions with intrinsic and extrinsic environmental factors. Although genetic variation may explain ~30–40% of BP variation, identifying a genetic etiology for OSAS-related hypertension is difficult.[75] Genome-wide association studies have yielded inconsistent results, and identified associations with some candidate genes have not always been replicated. The limited amount of data, the small sample size of the studies and the failure to properly phenotype the clinical characteristics of OSAS patients have prevented the identification of a genetic etiology of OSAS-related hypertension.

PROGNOSTIC RELEVANCE OF THE COMBINATION OF OSAS AND HYPERTENSION

Evidence from several studies has supported an independent association between OSAS and CV disease.[76] OSAS, particularly if severe, has been linked to fatal and nonfatal CV events,[77–81] the development and progression of congestive heart failure[79] and with all-cause mortality.[82,83] However, because the link between OSAS and CV disease may be related to age, obesity and visceral adiposity, in some of these studies the associations have loose strength when adjusting for these factors. With regard to subclinical organ damage, evidence has also been provided that OSAS is independently associated with cardiac (that is, left ventricular hypertrophy and dysfunction),[69,84,85] vascular (that is, increased carotid intima-media thickness, increased arterial stiffness),[63] renal organ damage (that is, increased urinary albumin excretion)[86,87] and with endothelial dysfunction (that is, blunted endothelium-dependent dilatation).[63] Evidence has also shown that patients with drug-resistant hypertension are at a considerably greater risk of CV complications, including myocardial infarction, stroke, congestive heart failure and chronic kidney disease than patients whose BP is pharmacologically well controlled.[88–90] In consideration of the increased CV risk associated with OSAS and resistant hypertension, current guidelines for the management of arterial hypertension include OSAS among the modifiable causes to be addressed in subjects with resistant hypertension to properly manage both conditions.[1,8] It should be mentioned, however, that no studies have specifically addressed how and to what extent the

coincidence of hypertension with OSAS increases the risk of CV disease independently of other CV risk factors that are often clustered in the context of OSAS. Evidence from longitudinal interventional studies in OSAS controlling for potential confounders (that is, visceral obesity, increased BMI) are thus needed not only to determine the prognostic relevance of the interaction between OSAS and hypertension but also to determine whether treating OSAS in resistant hypertension confers significant benefits in terms of CV protection.

PROGNOSTIC RELEVANCE OF ALTERATIONS IN DAY-TO-NIGHT BP PROFILES AND NOCTURNAL HYPERTENSION IN OSAS

As mentioned above, nocturnal sympathetic activation during OSAS episodes significantly contributes to increases in BP during sleep, thus attenuating the physiologic nocturnal dipping of BP (average 10–20% decrease from daytime BP values) or even increasing nocturnal BP levels. It is thus not surprising that a nondipping BP profile (that is, nocturnal BP falls $<10\%$ compared with daytime BP levels) is often seen in OSA patients independently of the presence of hypertension.[91] Remarkably, the degree of impairment in the nocturnal BP decrease has been found to be related to the severity of OSAS.[92] In contrast, an increased incidence of alterations in day-to-night BP profiles and nocturnal hypertension has been reported in subjects with resistant hypertension regardless of the presence of OSAS.[90,93,94] It is thus expected that alterations in day-to-night BP changes might be even more pronounced in subjects with OSAS and resistant hypertension. From a prognostic point of view, the identification of nocturnal hypertension and alterations in day-to-night BP changes in subjects with OSAS-related hypertension is of utmost relevance, considering the evidence showing the superior prognostic value of nocturnal BP compared with awake or 24 h average BP in predicting CV morbidity and mortality,[95–100] the development of CV events[95,96,101–103] and overall mortality.[95–97,102,104,105] The identification of a 'nondipping' BP pattern in OSAS patients is also important if we consider that subjects whose nocturnal BP decrease is blunted have been reported to have a higher prevalence of subclinical organ damage,[106,107] and an increased risk of CV events[108] and mortality,[100] which is even higher in patients whose BP increases rather than decreases at night (often referred to as risers or 'inverted dippers'). Despite the very high prevalence of nocturnal hypertension and alterations in day-to-night BP changes in OSAS patients, these morbidities are often undiagnosed (that is, masked resistant hypertension) because BP measurements are usually measured during the day at a clinical visit. Given their relevant prognostic value, alterations in circadian BP should be properly investigated in patients with OSAS-resistant hypertension through the use of 24-h ABPM to guide antihypertensive treatment toward the normalization and optimization of CV protection.

DIAGNOSTIC APPROACH TO OSAS-RELATED RESISTANT HYPERTENSION

Confirming the diagnosis of OSAS in subjects with resistant hypertension is relevant to implement specific treatment strategies (that is, CPAP, weight reduction). This confirmation might allow the achievement of BP control and reduce the CV risk of these subjects. Polysomnography is currently considered the standard technique for the diagnosis of OSAS and requires the simultaneous monitoring of several CV and respiratory variables during nocturnal sleep (that is, sleep, air flow, respiratory effort, oxygen saturation and brain activity through electroencephalogram). On the basis of the number of apneas and hypopneas lasting >10 s during each hour of recording, the severity of the disease is graded using the apnea-hypopnea index.[109] Whether polysomnography should be employed systematically in individuals with resistant hypertension is still a matter of debate in the absence of cost-effectiveness studies supporting this suggestion. According to a recent position paper of the European Respiratory Society/European Society of Hypertension,[110] polysomnography should be performed in all subjects with a high pretest probability of OSA based on structured questionnaires (for example, Epworth and Berlin questionnaires).

Considering the extremely high frequency of alterations in ambulatory BP profiles during the nighttime in subjects with resistant hypertension and OSAS, the task force of the European Respiratory Society/European Society of Hypertension also recommends performing ABPM to identify alterations in day-to-night BP changes in subjects with resistant hypertension to guide the decision to perform polysomnography in subjects with a low probability of OSA based on questionnaires. Indeed, in subjects with a low pretest probability of OSAS, polysomnography is only recommended for those who present alterations in day-to-night BP changes (that is, nondipping pattern of BP; Figure 7).

It is worth mentioning that before starting the instrumental tests to rule out OSAS, a first step in the diagnostic approach of the patient with resistant hypertension consists of confirming whether resistance to antihypertensive treatment is real or false. Current guidelines for the management of arterial hypertension define resistant hypertension as the persistence of elevated BP (that is, $\geqslant 140/90$ mm Hg for diastolic/systolic BP) despite the concomitant use of three optimally dosed antihypertensive medications from different classes, one of which should ideally be a diuretic, at near-maximal doses.[1,8] However, this definition is based on office (clinically obtained) BP measurements, which have acknowledged limitations, including the inherent inaccuracy of the technique, the observer's bias and digit preference, variable interference as a result of the 'white-coat effect' and the inability of this approach to collect information on BP during subjects' usual activities or over an extended time.[111] Thus, for the confirmation of truly resistant hypertension, out-of-office BP measuring techniques, such as ABPM and/or home BP monitoring (which are not affected by the limitations of OBP), should be performed in addition to OBP. On the basis of measurements obtained with these methods, a substantial and sometimes larger than expected number of subjects initially diagnosed with resistant hypertension or with BP control based on OBP may actually have false resistant hypertension or white-coat resistant hypertension (that is, elevated OBP but normal out-of-office BP values) or masked resistant hypertension (that is, normal OBP but elevated out-of-office BP values).[90,112,113]

From a prognostic point of view, the identification of OSAS patients with true resistant hypertension in addition to those with masked resistant hypertension (normal OBP and elevated ABP or HBP)[114,115] is of the greatest relevance, considering the evidence showing these conditions to be associated with a higher incidence of target organ damage,[116,117] a higher risk of future CV and renal events,[103,118,119] and ultimately higher health-care costs.[27,120,121]

EFFECTS OF DIFFERENT THERAPEUTIC STRATEGIES ON OSAS-RELATED RESISTANT HYPERTENSION

Effects of lifestyle changes and weight loss on OSAS-related hypertension

Obesity is the single most important cause of OSAS and BP elevation. It is thus expected that weight loss will reduce the severity of OSAS and reduce BP levels. Indeed, in subjects who achieve significant

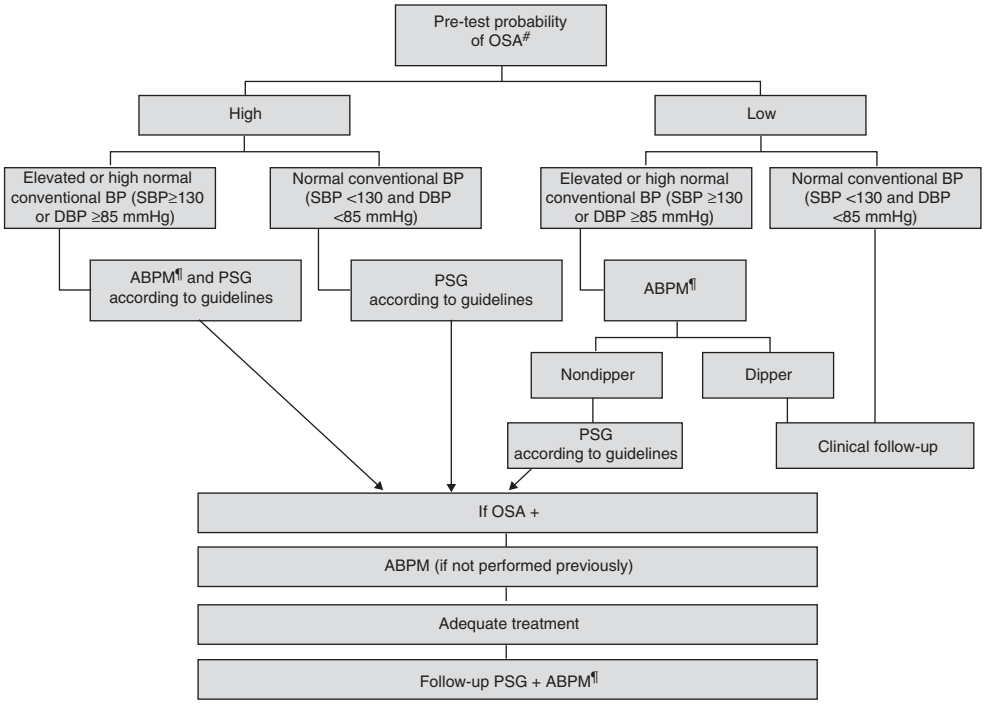

Figure 7 Proposed algorithm for the diagnostic management of patients with hypertension associated with obstructive sleep apnea (OSA). BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; ABPM, ambulatory BP monitoring; PSG, polysomnography. # denotes according to clinical evaluation and questionnaires, for example, Epworth and Berlin; ¶ indicates hypertension guidelines recommend the use of home BP monitoring in most hypertensive patients. Reproduced by permission from Parati *et al.*[110]

reductions in body weight either through dietary,[122] pharmacological[123] or surgical[124] measures, considerable reductions have been reported for various indices of OSA severity (that is, apnea-hypopnea index) and for BP levels. In particular, bariatric surgery has been shown to be a highly effective measure to achieve OSAS improvement and BP control, as supported by a large meta-analysis of 136 randomized controlled trials.[125] Of note, reductions in BP levels were mainly related to weight loss (that is, each 1% reduction in body weight decreased the SBP by 1 mm Hg and the DBP by 2 mm Hg).[125] However, despite its efficacy, bariatric surgery is reserved for selected patient groups (that is, patients with type 2 diabetes mellitus and severe obesity (BMI $>35\,kg/m^2$) and moderately obese patients (BMI: 30–35 kg/m^2) who are inadequately controlling their body weights by conventional medical and behavioral therapies).

Effects of CPAP treatment on OSAS-related hypertension

Nasal CPAP is currently considered the optimal treatment for OSA.[126] When properly implemented, CPAP not only provides relatively instant relief of clinical symptoms[127] and reduction in the severity of OSA but also improves many of the acute and chronic pathophysiological alterations induced by OSAS. Of note, CPAP use has been shown to induce marked and acute reductions in microneurography not only during nighttime sleep but also during daytime wakefulness if maintained over a long term[28] (Figure 8). Several studies have also shown the effectiveness of CPAP in improving baroreflex impairment,[68] systemic inflammation,[50,56,58] endothelial dysfunction,[49–51] RAAS activation,[128] arterial stiffness[68,69] and metabolic alterations.[70]

Although improvements in these pathophysiological alterations should theoretically translate into substantial BP reductions, most interventional trials in OSAS and subsequent meta-analyses have indicated that, although CPAP has a significant effect on BP levels, the overall effect on 24 h, daytime and nighttime systolic and diastolic ambulatory BP levels is rather small (of the order of 1–2 mm Hg).[129–131] Notably, one of these meta-analyses showed that CPAP therapy may have substantial effects in selected groups of OSAS patients.[130] Effective CPAP treatment in patients with moderate-to-severe OSAS has been shown to induce important reductions in both daytime and nighttime BP levels.[132] This has also been the case for subjects with resistant hypertension for whom regular CPAP implementation has resulted in marked reductions in ambulatory BP levels not only during the night but also during the day.[133] In a recent study addressing the effects of a 1-year treatment with CPAP, no effects on BP levels were observed in patients with BP controlled at baseline, but marked and significant reductions in BP levels were observed in subjects with resistant hypertension.[134]

A critical aspect when assessing the clinical effects of CPAP is guaranteeing patients adhere to therapy. Given the mechanical nature of CPAP (that is, facial interface mask and the pressure required to prevent airway collapse), it is not always well accepted by patients, especially those free of OSA-related symptoms. Indeed, CPAP compliance has been shown to be directly related to the severity of OSAS.[135] However, several studies have indicated that to observe an effect of CPAP on BP, this treatment should be for months and for a sufficient number of hours per night, and the BP levels should be ideally assessed by ABPM. Proof of this has been provided by several studies of OSAS in which the benefits of CPAP are evident only for subjects who have confirmed resistant hypertension (that is, persistent elevation in both the office and the out-of-office BP levels) and have used CPAP for at least 3 months and for more than 5.8 h per night.[136] For nonsleepy hypertensive patients with OSA, the most significant reductions in BP have been observed when using CPAP for more than

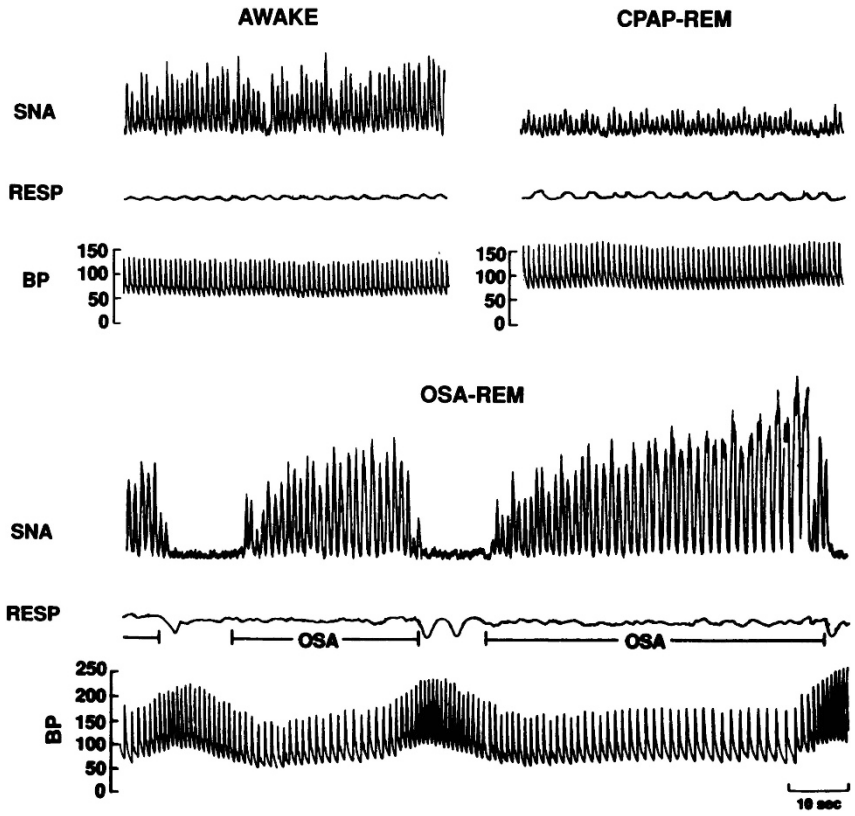

Figure 8 Elimination of apneas by continuous positive airway pressure (CPAP) reduces muscle sympathetic nerve activity (SNA) and prevents blood pressure (BP) surge during rapid eye movement (REM) sleep. Taken from Somers *et al*.[28] by permission.

5.6 h per night.[135] Further studies are needed to better determine whether CPAP implementation in OSAS patients with hypertension is associated with better BP control or a reduction in the number of antihypertensive medications needed to achieve BP control.

Finally, oral appliance therapy has been proposed as an alternative to CPAP in patients with mild-to-moderate OSA. Although a recent meta-analysis showed a favorable effect of oral appliances on BP levels,[137] most of the studies reporting the BP-lowering effects of this technique have been limited by small sample sizes, observational nature and short follow-up periods. Thus, evidence from randomized controlled trials is still needed to confirm the effects of oral appliances on BP levels (especially ambulatory BP) in OSAS patients.

EFFECTS OF RENAL DENERVATION IN OSAS-RELATED RESISTANT HYPERTENSION

Sympathetic activation in OSAS causes an increase in sympathetic drive to the heart, the peripheral vasculature and the kidneys. With respect to kidneys, the sympathetic nerves arriving in the renal area have been identified as a major contributing factor to the pathophysiology of hypertension both in experimental models and in human studies.[138] This has been the basis for the development of interventional strategies aimed at modulating renal sympathetic nerve activity through radiofrequency catheter-based renal sympathetic denervation (RDN).[139] In subjects with uncontrolled hypertension, RDN has been shown to induce significant reductions in renal sympathetic efferent-nerve activity, whole-body sympathetic-nerve activity, norepinephrine spillover and substantial and sustained reductions in BP levels.[140] A small interventional study in OSAS patients who were refractory to lifestyle modifications, weight loss, pharmacological treatment and CPAP has also suggested that RDN may represent an effective strategy for the management of resistant hypertension, as it induced significant and sustained changes in BP levels at 3 and 6 months of follow-up.[141] Remarkably, the changes in BP levels reported in this study have also been accompanied by improvements in OSAS severity as indicated by the significant reductions in apnea-hypopnea index 3 and 6 months after denervation.[141] Potential mechanisms for improving OSAS severity following RDN might include reducing salt retention and total body fluid (which in turn might reduce peripharyngeal fluid accumulation and upper airway obstruction), as well as reducing insulin resistance and improving the metabolic profile. RDN may thus represent a potentially useful option for the management of resistant hypertension in OSAS patients who are refractory to lifestyle modifications, weight loss, pharmacological treatment and CPAP. Nonetheless, given the very small sample size in this report, adequately powered longitudinal studies are needed to confirm the long-term impact of RDN on hypertension control and its benefits in terms of organ damage and the incidence of CV morbid-mortality in subjects with OSAS.

DO DIFFERENT ANTIHYPERTENSIVE DRUG CLASSES HAVE DIFFERENT EFFECTS ON OSAS-RELATED HYPERTENSION?

Different antihypertensive drug classes may have different effects on the pathophysiological mechanisms involved in the pathogenesis of OSAS-related hypertension. However, the few studies that have comparatively assessed the BP-lowering effects of different drug classes in OSAS have had small sample sizes, and their statistical power has limited consistent conclusions. In a randomized study

assessing the effects of different classes of antihypertensive drugs (that is, β-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and thiazidic diuretics) on office and ambulatory BP levels in patients with hypertension and OSAS, no significant differences between drug classes were observed in their ability to reduce office and daytime ambulatory BP levels. However, treatment with β-blockers was more effective at reducing nighttime ambulatory BP than the administration of other compounds, most likely because of their effects on sympathetic activation. In general, however, no consistent evidence has shown superior antihypertensive efficacy for any antihypertensive drug in OSA patients.[142] The long-term effects of treatment with different antihypertensive agents on hypertension severity in OSAS have not been systematically addressed in clinical trials. Evidence is therefore still needed to identify preferred compounds for an adequate BP control in this group of high-risk patients.

Recent studies in resistant hypertension have suggested that spironolactone should be considered in all patients with uncontrolled hypertension on three or more antihypertensive agents.[143] In some studies, the addition of spironolactone at doses of 25–50 mg per day to the current antihypertensive treatment in resistant hypertensive patients was shown to reduce the severity of OSAS in addition to lowering the BP.[47] This finding is in line with the concept that aldosterone-mediated chronic fluid retention may influence the severity of OSA.

CONCLUSIONS

Evidence has consistently supported the association between OSAS and hypertension;[2,4,5,16–18] showing the occurrence of a dose–response relationship between OSAS severity and the degree of BP elevation.[2,26,27] It has also been shown that hypertension in individuals with OSAS is more likely to be severe, resistant to treatment and associated with alterations in day-night BP changes.[2,26,27] The pathogenesis of OSAS-related hypertension is likely to be multifactorial, involving alterations in several regulatory systems. However, the mechanisms by which OSAS promotes arterial hypertension still need to be better understood. Although OSAS and drug-resistant hypertension are independent predictors of CV morbidity and mortality, evidence from longitudinal studies is needed to determine the actual prognostic relevance of OSAS-related hypertension. In a subject with resistant hypertension and suspected OSAS, ABPM should be performed whenever possible for the confirmation of resistant hypertension, to identify alterations in day-to-night BP changes, and to determine the need for additional diagnostic procedures (that is, polysomnography) and/or the implementation of more aggressive pharmacological or interventional strategies for the management of resistant hypertension. In turn, the identification of OSAS and the proper implementation of specific treatment strategies (that is, CPAP) in subjects with resistant hypertension may promote the achievement of BP control and improve CV protection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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