Obstructive Sleep Apnea and Hypertension
An Update

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Obstructive sleep apnea (OSA) is highly relevant to patients with hypertension (HTN). These 2 conditions frequently coexist (an estimated 50% of patients with HTN have concomitant OSA), and recent evidence supports the notion that OSA represents the most prevalent secondary contributor to elevated blood pressure (BP) in patients with resistant HTN (Figure 1).[1]

Epidemiological Association of OSA and HTN

Previously published population-based studies identified an independent correlation between greater apnea–hypopnea index and increasing BP, both at baseline and also when measured over long-term follow-up.[2] On the contrary, isolated systolic HTN, which was more commonly seen in elderly patients, was not associated with OSA in any age group.[3] The key challenge in deciphering the OSA–HTN connection lies in appropriately accounting for the many confounding variables, particularly obesity and age. Two recent prospective longitudinal cohort studies addressed these questions in normotensive subjects and reached opposing conclusions: The first study reported that after adjusting for relevant confounders, OSA was not associated with incident systolic HTN (1180 subjects over 7.5-year mean follow-up period).[4] The second study (also from Spain, 1889 participants, 12.2 years of median follow-up) identified an increased hazard ratio for incident HTN in patients with OSA compared with control subjects, and in this second study, the OSA–HTN association remained independent of confounders including age and obesity. Furthermore, follow-up of this patient cohort revealed a dose–response relationship between the severity of OSA and the cumulative incidence of HTN (Figure 2).[5] Given the extensive follow-up period, this second study provides relatively robust epidemiological evidence implicating OSA as a factor in the development of HTN.

Focus on Unique Patient Populations

An association between OSA and elevated BP has been recently reported in various specific patient cohorts: elderly women,[6] prehypertensive subjects,[7] primary care patients,[8] patients after spinal cord injury,[9] and in patients after stroke.[10] In children, on whom fewer studies are available, the OSA–BP relationship remains evident,[11,12] but the challenge is again in separating what portion of BP elevation can be attributable to OSA, or to obesity, or to an interaction between these. Although relatively modestly powered, these studies may be helpful in identifying specific patient groups in which diagnosis and treatment of OSA would have a more pronounced effect on BP and ultimately would be able to reduce HTN-related morbidity and mortality. If such patient cohorts were identified, they would then be prime targets for cost-effective OSA treatment.

Diurnal Variation of BP

The physiological nocturnal BP decrease in normal individuals (dipping pattern) seems to be altered in patients with OSA, and more recent data confirm these findings in older adults as well.[13] Night-time BP may reflect cardiovascular risk as well as daytime BP, and a nocturnal nondipping pattern has been shown to confer an increased rate of adverse events.[14] The mechanisms underlying the nondipping pattern have received considerable attention. However, studies evaluating diurnal biomarker variation corresponding to the OSA-induced BP changes have been inconclusive.[15] This line of research nevertheless remains potentially valuable because continuous methods of 24-hour BP monitoring are becoming more affordable and readily available. Indeed, a relatively novel categorization of sleep-related HTN in OSA has been proposed: a sustained type (both nocturnal and morning HTN) and a surge type (morning HTN only without nocturnal HTN), but a validation of the variability in the effect of these 2 types of sleep-related HTN on hard clinical outcomes is needed.[16]

In children, the data on OSA and nocturnal BP dipping remain conflicted and lead us to conclude that either (1) children with OSA may not have been exposed to the pathophysiology of OSA long enough to affect their BP or (2) elevation of BP in the rapid eye movement phase of sleep may not suffice to change the overall mean nocturnal BP in children.[17,18]

Pathophysiologic Links Between OSA and HTN

Given that HTN and OSA are complex processes with multifactorial pathogeneses, it is no surprise that they seem to be

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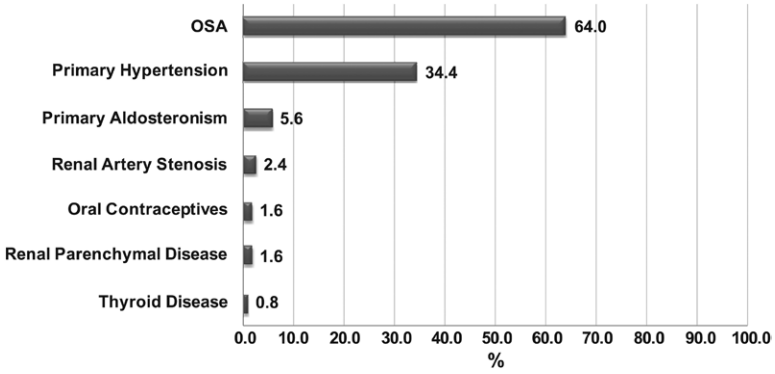

Figure 1. Prevalence of secondary causes of hypertension associated with resistant hypertension in a cohort of 125 patients from Brazil. OSA indicates obstructive sleep apnea. Reproduced from Pedrosa et al[1] with permission of the publisher. Copyright © 2011, American Heart Association, Inc.

linked by an interplay of mechanisms, schematically shown in Figure 3.

Neural Circulatory Mechanisms

Repetitive OSA-induced hypoxemia and hypercapnia elicit reflex changes in both sympathetic and parasympathetic activation.[19,20] These autonomic derangements, with consequent increases in catecholamine levels, persist even into the daytime and could contribute to the development of HTN.[21] Effective OSA treatment with continuous positive airway pressure (CPAP) reduces urinary catecholamine levels,[22] and this reduction seems to be especially evident in patients with more severe OSA.[23] Animal studies suggest that renal denervation attenuates the BP rise associated with OSA events.[24] Autonomic ganglia-mediated changes in cardiac arrhythmogenicity related to OSA are discussed in sections below.

Inflammatory and Cytokine-Mediated Effects of OSA

Preliminary data on molecular mechanisms linking OSA to cardiovascular morbidity related to HTN suggest that OSA correlates with an increased burden of systemic inflammation and higher concentrations of hs-CRP (high sensitivity C-reactive protein), interleukin-1, interleukin-8, interleukin-6, tumor necrosis factor-α, Rantes (Regulated on Activation, Normal T Cell Expressed and Secreted), and sICAM (soluble intercelular adhesion molecules).[25] Whether these markers truly signify a worse prognosis for patients with OSA, and to what degree a potential therapeutic intervention could alter their pathogenesis remains to be determined. Encouraging data have been suggested by studies in a murine model, in which atorvastatin, which is known to reduce inflammation, prevented various adverse cardiovascular processes related to intermittent hypoxia.[26]

Hemodynamic Effects of OSA

Two studies identified an OSA-associated impairment in the cardiovascular response to exercise but differ as to whether this difference remains independent after adjusting for sex, body mass index, and other comorbidities.[27,28] Decreased functional aerobic capacity in patients with OSA raises particular concern given its power to predict both overall and cardiovascular mortality.

Age-Related Modulation of OSA Pathophysiology

Several studies have reported that the effects of OSA on cardiovascular conditions, such as HTN and atrial fibrillation, are more evident in younger subjects than older subjects. The attractive hypothesis that OSA affects younger versus older patients differently was assessed in a pilot study of changes in

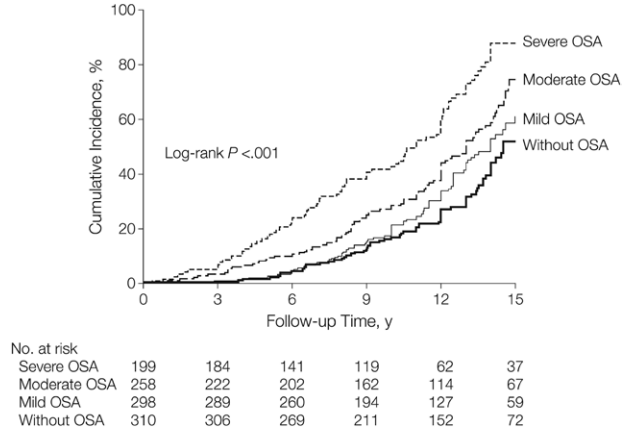

Figure 2. Cumulative incidence of hypertension in the participants of a prospective cohort study by Marin et al[5] who were not treated with continuous positive airway pressure. OSA indicates obstructive sleep apnea. Reproduced from Marin et al[5] with permission of the publisher. Copyright © 2012, American Medical Association.

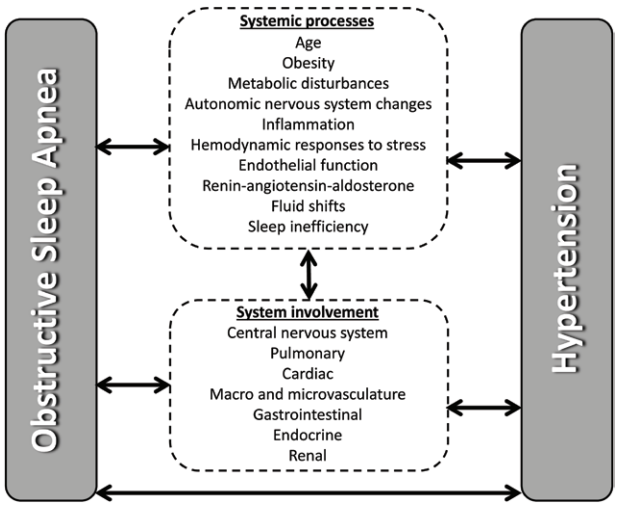

Figure 3. Schematic representation of the complex interactions between blood pressure and obstructive sleep apnea.

the renal vascular resistance index, but no substantial differences between the age categories were found.[29]

Renin–Angiotensin–Aldosterone System

Evidence relating OSA to markers of the renin–angiotensin–aldosterone system, clearly of high interest in patients with HTN, is unfortunately limited.[30] A curious observation in patients with resistant HTN attributable to hyperaldosteronism suggested that dietary salt intake was related to the severity of OSA (this was not found to be the case in hypertensive patients without hyperaldosteronism). This raises the question of whether salt intake and aldosterone levels constitute yet other variables which we need to control for when assessing the OSA–HTN relationship.[31] In a broader sense, a clearer understanding of the role of renin–angiotensin–aldosterone in the OSA–BP relationship would be of considerable clinical significance, given the ready availability of medication groups affecting such targets.

Nocturnal Fluid Redistribution

Whether nocturnal rostral fluid shift plays a significant role in patients with HTN and OSA was addressed in a recent study that examined the effects of graded lower body positive pressure on upper airway cross-sectional area (among other end points).[32] The authors reported that the subjects with HTN reduced their mean upper airway cross-sectional area in direct relationship to the amount of displaced fluid from the legs, and that this upper airway reduction was significantly more pronounced in the patients with resistant HTN compared with the patients with controlled HTN (Figure 4). These data could support the notion that HTN begets HTN in part via the OSA pathway: patients with HTN could be prone to increased rostral fluid shift which worsens their OSA (narrowed airway) subsequently further increasing BP, leading eventually to resistant HTN, a correlation where OSA has been shown consistently to be highly prevalent.

Sleep Inefficiency

OSA is an important cause of impaired sleep quality. Sleep inefficiency and short sleep duration have been postulated as potential contributors to elevated BP. A recent longitudinal study identified chronic insomniacs with short sleep duration as being at increased risk of incident HTN, but this effect was largely explained by controlling for obesity.[33] On the contrary, several studies showed positive correlations between sleep deprivation and various adverse cardiovascular risk factors: arterial stiffness,[34] endothelial dysfunction, sympathetic activity,[35] nondipping nocturnal BP pattern,[36] and insulin insensitivity.[37]

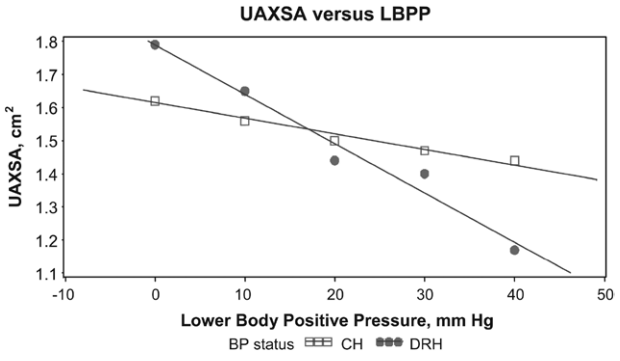

Figure 4. Relationship between mean upper airway cross-sectional area (UAXSA) in response to the graded lower body positive pressure (LBPP) in patients with controlled hypertension (CH) and drug-resistant hypertension (DRH). Adapted from Friedman et al[32] with permission of the publisher. Copyright © 2012, American Heart Association, Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Novel Drug Targets

Sudden change in altitude may adversely affect both OSA and HTN, and a recent randomized controlled trial of acetazolamide in addition to CPAP versus CPAP with placebo suggested that this carbonic anhydrase inhibitor ameliorated the BP rise seen with sleeping at high elevation in treated OSA patients.[38] Even though BP was not the primary end point of this study, the possible mechanisms behind the BP findings were intriguing because both acid–base imbalance and partial pressures of oxygen could pose possible targets for therapeutic intervention.

System-Specific Pathophysiology Related to OSA

The complexity of the influence of OSA on specific organ systems is underlined by the possible bidirectionality in the cause–effect relationships; for example, does OSA lead to altered cerebral hemodynamics resulting in HTN, or does OSA lead to HTN directly with the alterations in the cerebral perfusion as a consequence (Figure 3).

Central Nervous System

Patients with OSA had altered cerebral vasomotor reactivity when assessed by the breath-holding maneuver,[39] and prospective follow-up revealed that 2 years of CPAP attenuated this impairment.[40] Although the mechanisms of cerebral vascular damage remain unclear, several murine studies have shed light on possible mediators. In an evaluation of the topographical effects of chronic intermittent hypoxia and the interaction with BP changes, areas of the brain that regulate sympathetic outflow were pre-eminently affected.[41] Delta-FosB in the preoptic nucleus was necessary for hypoxia to induce HTN, suggesting that neural adaptation may contribute to the increase in BP.[42] These studies support a likely direct effect of OSA on the central neural vasculature and have implications for understanding the link between OSA and both HTN and stroke, as well as potential avenues for targeted intervention.[43]

Pulmonary

OSA-related hypoxemia may have a particularly deleterious effect in patients with idiopathic pulmonary fibrosis, possibly by aggravating pulmonary HTN.[44] Similarly concerning are OSA-related nocturnal hypoxemic episodes in patients with precapillary pulmonary HTN of thromboembolic or idiopathic pathogenesis, where the addition of OSA-related stress on an already burdened pulmonary vasculature and right ventricle could theoretically be avoided by the appropriate use of CPAP.[45] Whether OSA treatment provides tangible clinical benefit remains unclear.

Cardiovascular

A smaller study on cardiac morphology of OSA patients treated with 3 months of CPAP suggested that indices of both right and left ventricular function improved mildly[46] which has particular relevance to the recently recognized high prevalence of OSA in patients with ischemic and hypertrophic cardiomyopathy.[47,48] Emerging evidence also links OSA to thoracic aortic dilatation, with implications for risk of aneurysm formation. One possible mechanism could be the OSA-induced increase in aortic wall dilatory transmural pressure.[49]

Although OSA may cause structural changes in large vessels, it has also been shown to impair endothelial function. This impairment may be reversible by CPAP treatment.[50] Further work is required in identifying all the pathways involved, but recent evidence implicates the lectin-like oxidized low-density lipoprotein receptor 1 (a scavenger receptor known to be also upregulated in atherosclerosis) as playing an important role.[51]

Atrial fibrillation is a common end point of hypertensive cardiac structural changes. Provocative canine experiments suggest that atrial arrhythmogenicity is increased by simulated OSA, and that this effect is likely mediated by cardiac autonomic mechanisms.[52,53] Especially exciting are data showing that blockade of cardiac autonomic ganglia markedly attenuates the occurrence of atrial fibrillation in response to simulated OSA, suggesting a novel option for preventing atrial fibrillation in patients with OSA.[52]

Gastrointestinal/Endocrine

In patients with metabolic syndrome in whom HTN coexists with dyslipidemia, obesity, and pre-diabetes mellitus, the treatment of OSA could theoretically improve prognosis by a multifaceted beneficial effect on BP as well as on the lipid profile and glucose metabolism. Postprandial dyslipidemia, which confers significant cardiovascular risk, was shown to improve after 2 months of effective CPAP treatment.[54] In addition, improvements in obesity, caloric intake, and body composition have been reported in successfully treated OSA patients.[55] More complex mechanisms centered around altered insulin resistance may also play a role in the susceptibility of patients with OSA to HTN-related morbidity as this could be confounded by diabetes mellitus.[56]

Renal

A recent pilot study of renal sympathetic denervation in patients with resistant HTN suggested that this procedure may also attenuate the severity of sleep apnea.[57] However, much remains to be learned before renal denervation can be used clinically in this regard.

Effect of OSA Treatment on BP

Prevention and Treatment of HTN With CPAP

A possibly preventive role of CPAP in reducing incident HTN was suggested by the large prospective Zaragoza Sleep Cohort Study, which reported a lower incidence of newly diagnosed HTN in those patients with OSA who tolerated CPAP.[5] These findings were not confirmed in a recent randomized controlled study, also from Spain, possibly attributable to limited power, although the tendency to benefit from CPAP therapy was encouraging.[58] Acute decreases in BP and sympathetic traffic during sleep can be achieved with effective OSA treatment; however, the data regarding long-term, clinically meaningful BP reduction with CPAP treatment have been less clear. Meta-analyses previously conducted on this topic spoke to the modest but statistically significant beneficial effect of CPAP,[59] and congruent with these findings was the recently published meta-analysis by Montesi et al[60] which included 28 studies representing 1948 patients and reported weighted mean decrease in systolic and diastolic BP of 2.58 and 2.01 mm Hg, respectively, favoring those treated with CPAP.

Predictors of Antihypertensive Efficacy of CPAP

The knowledge of specific patient characteristics which may predispose to a more substantial BP reduction after initiation of CPAP would be of high value. A modestly powered study of 24 patients with OSA reported the following variables to be independent predictors of the CPAP-related fall in 24-hour mean BP: male sex, sleepiness, body mass index, smoking, alcohol use, and baseline BP.[61]

Studies in Unique Patient Cohorts

A pilot study of diabetic patients (type 2) with OSA showed that systolic and diastolic BP in those receiving CPAP dropped by 9 and 7 mm Hg, respectively.[62] These BP changes could not be attributed to changes in weight, waist circumference, or glycemic control, but the authors reported significant decrease in urinary noradrenaline and dopamine. These fairly substantial decreases in BP are encouraging and raise the possibility that diabetic patients may be especially responsive to CPAP therapy as an antihypertensive strategy.

Prehypertensive patients with severe OSA were the focus of a randomized study that showed that 3 months of CPAP produced a significant decrease in daytime, night-time, systolic, and diastolic BP, all of which translated into a reduction in the frequency of pre-HTN and masked HTN.[63]

In patients with coronary artery disease and OSA, CPAP treatment led to an effective reduction in diastolic BP and improvements in daytime somnolence; however, only a trend in the reduction of systolic BP was noted, possibly attributable to modest power of the study, timing of the BP checks, and relatively short CPAP treatment period (1 month).[64] In an adequately powered, randomized controlled trial of CPAP in patients with metabolic syndrome in India, 3 months of CPAP led to a decrease in both systolic and diastolic BP (3.9 and 2.5 mm Hg, respectively) and improved lipid profiles and glycohemoglobin percentages, ultimately resulting in a 13% reduction in the frequency of metabolic syndrome (compared with a 1% reduction in controls).[65]

Alternatives and Supplements to CPAP Therapy in OSA

Oral appliances may offer an important and effective alternative to CPAP therapy in patients with mild to moderate OSA, particularly in those who cannot tolerate chronic CPAP treatment.[66,67] Both OSA treatment modalities seem to result on average in similar changes in 24-hour mean BP, possibly because the greater efficacy of CPAP is offset by inferior compliance relative to oral appliances.[68]

Beneficial effects of bariatric surgery on OSA and BP have been reported in several observational studies,[69,70] but the recently published randomized, controlled trial that compared the change in apnea–hypopnea index after a bariatric surgery versus regular weight loss program showed only a trend favoring the surgical arm.[71] Nevertheless, the substantial decrease in weight in both treatment arms translated to an improvement in OSA severity (decrease in apnea–hypopnea index by 26 for surgically treated patients versus decrease by 14 for those in the regular weight loss arm), suggesting that lifestyle modification aimed at weight loss and increased activity should play a prominent role in managing patients with OSA.

Conclusion

Key Points

1. Epidemiological evidence implicates OSA as one of the modifiable and highly prevalent factors in the development of HTN. A nocturnal nondipping pattern of BP has been confirmed in older adults with OSA but not in children.
2. Patients with OSA have decreased exercise tolerance and higher diastolic BP during exercise testing.
3. Patients with resistant HTN may exhibit nocturnal rostral fluid shifts and decreased airway diameter.
4. Conflicting data exist regarding the role of CPAP in reducing incident HTN in patients with OSA.
5. Results of meta-analyses speak consistently to a modest 2-mm Hg antihypertensive effect of CPAP.

Remaining Unknowns

Given the emerging importance of individualized medicine,[72] the routine use of home BP monitoring devices could facilitate greater focus on studies of particular subsets of patients who would most profoundly benefit from OSA treatment in terms of BP reduction (responders).[73] Such studies could also reveal a predictive model for the BP response to effective OSA treatment, especially because the average BP decrease obtained with OSA treatment has been modest, yet responder patients manifest substantial BP improvements. The increased power of longitudinal trials using well-designed portable therapeutic systems could also help shed further light on the controversy regarding the degree to which age, obesity, and other comorbidities explain the increased prevalence of HTN and HTN-related adverse outcomes among patients with OSA, and how lifestyle modifications fit into the complex interactions between OSA and BP. Most important, however, is to confirm that any BP reduction is accompanied by tangible improvements in cardiovascular outcomes.

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References

1. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, Amodeo C, Bortolotto LA, Krieger EM, Bradley TD, Lorenzi-Filho G. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension*. 2011;58:811–817.
2. Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, Skatrud J. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med*. 1997;157:1746–1752.
3. Haas DC, Foster GL, Nieto FJ, Redline S, Resnick HE, Robbins JA, Young T, Pickering TG. Age-dependent associations between sleep-disordered breathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study. *Circulation*. 2005;111:614–621.
4. Cano-Pumarega I, Durán-Cantolla J, Aizpuru F, Miranda-Serrano E, Rubio R, Martínez-Null C, de Miguel J, Egea C, Cancelo L, Alvarez A, Fernández-Bolaños M, Barbé F. Obstructive sleep apnea and systemic hypertension: longitudinal study in the general population: the Vitoria Sleep Cohort. *Am J Respir Crit Care Med*. 2011;184:1299–1304.
5. Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ, Barbé F, Vicente E, Wei Y, Nieto FJ, Jelic S. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012;307:2169–2176.
6. Sforza E, Chouchou F, Collet P, Pichot V, Barthélémy JC, Roche F. Sex differences in obstructive sleep apnoea in an elderly French population. *Eur Respir J*. 2011;37:1137–1143.
7. Roche F, Pépin JL, Achour-Crawford E, Tamisier R, Pichot V, Celle S, Maudoux D, Chouchou F, Ntougou-Assoumou HG, Lévy P, Barthélémy JC; PROOF Study Group. At 68 years, unrecognised sleep apnoea is associated with elevated ambulatory blood pressure. *Eur Respir J*. 2012;40:649–656.
8. Broström A, Sunnergren O, Johansson P, Svensson E, Ulander M, Nilsen P, Svanborg E. Symptom profile of undiagnosed obstructive sleep apnoea in hypertensive outpatients in primary care: a structural equation model analysis. *Qual Prim Care*. 2012;20:287–298.
9. LaVela SL, Burns SP, Goldstein B, Miskevics S, Smith B, Weaver FM. Dysfunctional sleep in persons with spinal cord injuries and disorders. *Spinal Cord*. 2012;50:682–685.
10. Cereda CW, Tamisier R, Manconi M, Andreotti J, Frangi J, Pifferini V, Bassetti CL. Endothelial dysfunction and arterial stiffness in ischemic stroke: the role of sleep-disordered breathing. *Stroke*. 2013;44:1175–1178.
11. Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Fedok F, Vlasic V, Graff G. Blood pressure associated with sleep-disordered breathing in a population sample of children. *Hypertension*. 2008;52:841–846.
12. Archbold KH, Vasquez MM, Goodwin JL, Quan SF. Effects of sleep patterns and obesity on increases in blood pressure in a 5-year period: report from the Tucson Children's Assessment of Sleep Apnea Study. *J Pediatr.* 2012;161:26–30.
13. Endeshaw YW, White WB, Kutner M, Ouslander JG, Bliwise DL. Sleep-disordered breathing and 24-hour blood pressure pattern among older adults. *J Gerontol A Biol Sci Med Sci*. 2009;64:280–285.
14. Waeber B, Mourad JJ, O'Brien E. Nighttime blood pressure: a target for therapy? *Curr Hypertens Rep*. 2010;12:474–479.
15. von Känel R, Natarajan L, Ancoli-Israel S, Mills PJ, Loredo JS, Dimsdale JE. Day/night rhythm of hemostatic factors in obstructive sleep apnea. *Sleep*. 2010;33:371–377.
16. Sasaki N, Ozono R, Yamauchi R, Teramen K, Edahiro Y, Ishii K, Seto A, Kihara Y. The relationship between morning hypertension and sleep quality in patients with obstructive sleep apnea syndrome. *Clin Exp Hypertens*. 2013;35:250–256.
17. Horne RS, Yang JS, Walter LM, Richardson HL, O'Driscoll DM, Foster AM, Wong S, Ng ML, Bashir F, Patterson R, Jolley D, Walker AM, Anderson V, Davey MJ, Nixon GM. Nocturnal dipping is preserved in children with sleep disordered breathing regardless of its severity. *Pediatr Pulmonol*. 2013;48:1127–1134.
18. Nisbet LC, Yiallourou SR, Biggs SN, Nixon GM, Davey MJ, Trinder JA, Walter LM, Horne RS. Preschool children with obstructive sleep apnea: the beginnings of elevated blood pressure? *Sleep*. 2013;36:1219–1226.
19. Konecny T, Somers VK. Chapter 112: Sleep apnea. In: RobertsonD, Biaggioni I, Burnstock G, Low PA, Paton JFR, eds. *Primer on the Autonomic Nervous System.* 3rd ed. San Diego, CA: Elsevier; 2012.

20. Parati G, Lombardi C, Hedner J, Bonsignore MR, Grote L, Tkacova R, Levy P, Riha R, Bassetti C, Narkiewicz K, Mancia G, McNicholas WT. Position paper on the management of patients with obstructive sleep apnea and hypertension: Joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific and Technological Research) ACTION B26 on obstructive sleep apnea. *J Hypertens*. 2012;30:633–646.
21. Freet CS, Stoner JF, Tang X. Baroreflex and chemoreflex controls of sympathetic activity following intermittent hypoxia. *Auton Neurosci*. 2013;174:8–14.
22. Leung RS. Sleep-disordered breathing: autonomic mechanisms and arrhythmias. *Prog Cardiovasc Dis*. 2009;51:324–338.
23. Pinto P, Bárbara C, Montserrat JM, Patarrão RS, Guarino MP, Carmo MM, Macedo MP, Martinho C, Dias R, Gomes MJ. Effects of CPAP on nitrate and norepinephrine levels in severe and mild-moderate sleep apnea. *BMC Pulm Med*. 2013;13:13.
24. Linz D, Mahfoud F, Schotten U, Ukena C, Neuberger HR, Wirth K, Böhm M. Renal sympathetic denervation suppresses postapneic blood pressure rises and atrial fibrillation in a model for sleep apnea. *Hypertension*. 2012;60:172–178.
25. Testelmans D, Tamisier R, Barone-Rochette G, Baguet JP, Roux-Lombard P, Pépin JL, Lévy P. Profile of circulating cytokines: impact of OSA, obesity and acute cardiovascular events. *Cytokine*. 2013;62:210–216.
26. Totoson P, Fhayli W, Faury G, Korichneva I, Cachot S, Baldazza M, Ribuot C, Pépin JL, Lévy P, Joyeux-Faure M. Atorvastatin protects against deleterious cardiovascular consequences induced by chronic intermittent hypoxia. *Exp Biol Med (Maywood)*. 2013;238:223–232.
27. Rizzi CF, Cintra F, Mello-Fujita L, Rios LF, Mendonca ET, Feres MC, Tufik S, Poyares D. Does obstructive sleep apnea impair the cardiopulmonary response to exercise? *Sleep*. 2013;36:547–553.
28. Mansukhani MP, Allison TG, Lopez-Jimenez F, Somers VK, Caples SM. Functional aerobic capacity in patients with sleep-disordered breathing. *Am J Cardiol*. 2013;111:1650–1654.
29. Patel HM, Mast JL, Sinoway LI, Muller MD. Effect of healthy aging on renal vascular responses to local cooling and apnea. *J Appl Physiol (1985)*. 2013;115:90–96.
30. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest*. 2007;131:453–459.
31. Pimenta E, Stowasser M, Gordon RD, Harding SM, Batlouni M, Zhang B, Oparil S, Calhoun DA. Increased dietary sodium is related to severity of obstructive sleep apnea in patients with resistant hypertension and hyperaldosteronism. *Chest*. 2013;143:978–983.
32. Friedman O, Bradley TD, Logan AG. Influence of lower body positive pressure on upper airway cross-sectional area in drug-resistant hypertension. *Hypertension*. 2013;61:240–245.
33. Fernandez-Mendoza J, Vgontzas AN, Liao D, Shaffer ML, Vela-Bueno A, Basta M, Bixler EO. Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension*. 2012;60:929–935.
34. Sunbul M, Kanar BG, Durmus E, Kivrak T, Sari I. Acute sleep deprivation is associated with increased arterial stiffness in healthy young adults. *Sleep Breath*. 2013 Jul 14 [Epub ahead of print].
35. Dettoni JL, Consolim-Colombo FM, Drager LF, Rubira MC, Souza SB, Irigoyen MC, Mostarda C, Borile S, Krieger EM, Moreno H Jr, Lorenzi-Filho G. Cardiovascular effects of partial sleep deprivation in healthy volunteers. *J Appl Physiol (1985)*. 2012;113:232–236.
36. Carev M, Karanović N, Bagatin J, Matulić NB, Pecotić R, Valić M, Marinović-Terzić I, Karanović S, Dogas Z. Blood pressure dipping and salivary cortisol as markers of fatigue and sleep deprivation in staff anesthesiologists. *Coll Antropol*. 2011;35(suppl 1):133–138.
37. Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes*. 2010;59:2126–2133.
38. Latshang TD, Nussbaumer-Ochsner Y, Henn RM, Ulrich S, Lo Cascio CM, Ledergerber B, Kohler M, Bloch KE. Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude: a randomized controlled trial. *JAMA*. 2012;308:2390–2398.
39. Jimenez Caballero PE, Coloma Navarro R, Segura Martn T, Ayo Martn O. Cerebral hemodynamic changes at basilar artery in patients with obstructive sleep apnea syndrome. A case-control study. *Acta Neurol Scand*. 2013 Jun 13 [Epub ahead of print].
40. Jiménez Caballero PE, Coloma Navarro R, Ayo Martín O, Segura Martín T. Cerebral hemodynamic changes in obstructive sleep apnea syndrome after continuous positive airway pressure treatment. *Sleep Breath*. 2013;17:1103–1108.
41. Knight WD, Little JT, Carreno FR, Toney GM, Mifflin SW, Cunningham JT. Chronic intermittent hypoxia increases blood pressure and expression of FosB/DeltaFosB in central autonomic regions. *Am J Physiol Regul Integr Comp Physiol*. 2011;301:R131–R139.
42. Cunningham JT, Knight WD, Mifflin SW, Nestler EJ. An Essential role for DeltaFosB in the median preoptic nucleus in the sustained hypertensive effects of chronic intermittent hypoxia. *Hypertension*. 2012;60:179–187.
43. Capone C, Faraco G, Coleman C, Young CN, Pickel VM, Anrather J, Davisson RL, Iadecola C. Endothelin 1-dependent neurovascular dysfunction in chronic intermittent hypoxia. *Hypertension*. 2012;60:106–113.
44. Kolilekas L, Manali E, Vlami KA, Lyberopoulos P, Triantafillidou C, Kagouridis K, Baou K, Gyftopoulos S, Vougas KN, Karakatsani A, Alchanatis M, Papiris S. Sleep oxygen desaturation predicts survival in idiopathic pulmonary fibrosis. *J Clin Sleep Med*. 2013;9:593–601.
45. Jilwan FN, Escourrou P, Garcia G, Jaïs X, Humbert M, Roisman G. High occurrence of hypoxemic sleep respiratory disorders in precapillary pulmonary hypertension and mechanisms. *Chest*. 2013;143:47–55.
46. Colish J, Walker JR, Elmayergi N, Almutairi S, Alharbi F, Lytwyn M, Francis A, Bohonis S, Zeglinski M, Kirkpatrick ID, Sharma S, Jassal DS. Obstructive sleep apnea: effects of continuous positive airway pressure on cardiac remodeling as assessed by cardiac biomarkers, echocardiography, and cardiac MRI. *Chest*. 2012;141:674–681.
47. Konecny T, Kuniyoshi FH, Orban M, Pressman GS, Kara T, Gami A, Caples SM, Lopez-Jimenez F, Somers VK. Under-diagnosis of sleep apnea in patients after acute myocardial infarction. *J Am Coll Cardiol*. 2010;56:742–743.
48. Konecny T, Brady PA, Orban M, Lin G, Pressman GS, Lehar F, Tomas K, Gersh BJ, Tajik AJ, Ommen SR, Somers VK. Interactions between sleep disordered breathing and atrial fibrillation in patients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2010;105:1597–1602.
49. Clarenbach CF, Camen G, Sievi NA, Wyss C, Stradling JR, Kohler M. Effect of simulated obstructive hypopnea and apnea on thoracic aortic wall transmural pressures. *J Appl Physiol (1985)*. 2013;115:613–617.
50. Kohler M, Craig S, Pepperell JC, Nicoll D, Bratton DJ, Nunn AJ, Leeson P, Stradling JR. CPAP improves endothelial function in patients with minimally symptomatic OSA: results from a subset study of the MOSAIC trial. *Chest*. 2013;144:896–902.
51. Akinnusi ME, Laporta R, El-Solh AA. Lectin-like oxidized low-density lipoprotein receptor-1 modulates endothelial apoptosis in obstructive sleep apnea. *Chest*. 2011;140:1503–1510.
52. Ghias M, Scherlag BJ, Lu Z, Niu G, Moers A, Jackman WM, Lazzara R, Po SS. The role of ganglionated plexi in apnea-related atrial fibrillation. *J Am Coll Cardiol*. 2009;54:2075–2083.
53. Lu Z, Nie L, He B, Yu L, Salim M, Huang B, Cui B, He W, Wu W, Jiang H. Increase in vulnerability of atrial fibrillation in an acute intermittent hypoxia model: importance of autonomic imbalance. *Auton Neurosci*. 2013;177:148–153.
54. Phillips CL, Yee BJ, Marshall NS, Liu PY, Sullivan DR, Grunstein RR. Continuous positive airway pressure reduces postprandial lipidemia in obstructive sleep apnea: a randomized, placebo-controlled crossover trial. *Am J Respir Crit Care Med*. 2011;184:355–361.
55. Tuomilehto H, Gylling H, Peltonen M, Martikainen T, Sahlman J, Kokkarinen J, Randell J, Tukiainen H, Vanninen E, Partinen M, Tuomilehto J, Uusitupa M, Seppä J; Kuopio Sleep Apnea Group. Sustained improvement in mild obstructive sleep apnea after a diet- and physical activity-based lifestyle intervention: postinterventional follow-up. *Am J Clin Nutr*. 2010;92:688–696.
56. Lindberg E, Theorell-Haglöw J, Svensson M, Gislason T, Berne C, Janson C. Sleep apnea and glucose metabolism: a long-term follow-up in a community-based sample. *Chest*. 2012;142:935–942.
57. Witkowski A, Prejbisz A, Florczak E, Kądziela J, Śliwiński P, Bieleń P, Michałowska I, Kabat M, Warchoł E, Januszewicz M, Narkiewicz K, Somers VK, Sobotka PA, Januszewicz A. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension*. 2011;58:559–565.
58. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, et al; Spanish Sleep And Breathing Network. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA*. 2012;307:2161–2168.

59. Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension*. 2007;50:417–423.
60. Montesi SB, Edwards BA, Malhotra A, Bakker JP. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J Clin Sleep Med*. 2012;8:587–596.
61. Yorgun H, Kabakci G, Canpolat U, Kirmizigul E, Sahiner L, Ates AH, Sendur MA, Kaya EB, Demir AU, Aytemir K, Tokgozoglu L, Oto A. Predictors of blood pressure reduction with nocturnal continuous positive airway pressure therapy in patients with obstructive sleep apnea and prehypertension. *Angiology*. 2013 Feb 20 [Epub ahead of print].
62. Myhill PC, Davis WA, Peters KE, Chubb SA, Hillman D, Davis TM. Effect of continuous positive airway pressure therapy on cardiovascular risk factors in patients with type 2 diabetes and obstructive sleep apnea. *J Clin Endocrinol Metab*. 2012;97:4212–4218.
63. Drager LF, Pedrosa RP, Diniz PM, Diegues-Silva L, Marcondes B, Couto RB, Giorgi DM, Krieger EM, Lorenzi-Filho G. The effects of continuous positive airway pressure on prehypertension and masked hypertension in men with severe obstructive sleep apnea. *Hypertension*. 2011;57:549–555.
64. Zhao Q, Liu ZH, Luo Q, Zhao ZH, Zhang HL, Wang Y. Effects of continuous positive airway pressure on blood pressure and daytime sleepiness in obstructive sleep apnea patients with coronary heart diseases under optimal medications. *Sleep Breath*. 2012;16:341–347.
65. Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhiravan T, Lakshmy R, Jagia P, Kumar A. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. *N Engl J Med*. 2011;365:2277–2286.
66. Li W, Xiao L, Hu J. The comparison of CPAP and oral appliances in treatment of patients with OSA: a systematic review and meta-analysis. *Respir Care*. 2013;58:1184–1195.
67. Iftikhar IH, Hays ER, Iverson MA, Magalang UJ, Maas AK. Effect of oral appliances on blood pressure in obstructive sleep apnea: a systematic review and meta-analysis. *J Clin Sleep Med*. 2013;9:165–174.
68. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, Marks GB, Cistulli PA. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med*. 2013;187:879–887.
69. Hady HR, Dadan J, Gołaszewski P. 100 obese patients after laparoscopic adjustable gastric banding - the influence on BMI, gherlin and insulin concentration, parameters of lipid balance and co-morbidities. *Adv Med Sci*. 2012;57:58–64.
70. Woodman G, Cywes R, Billy H, Montgomery K, Cornell C, Okerson T; APEX Study Group. Effect of adjustable gastric banding on changes in gastroesophageal reflux disease (GERD) and quality of life. *Curr Med Res Opin*. 2012;28:581–589.
71. Dixon JB, Schachter LM, O'Brien PE, Jones K, Grima M, Lambert G, Brown W, Bailey M, Naughton MT. Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. *JAMA*. 2012;308:1142–1149.
72. Bejan-Angoulvant T, Baguet JP, Erpeldinger S, Boivin JM, Mercier A, Leftheriotis G, Gagnol JP, Fauvel JP, Giraud C, Bricca G, Gueyffier F. The IDEAL study: Towards personalized drug treatment of hypertension. *Therapie*. 2012;67:195–204.
73. Bravata DM, Ferguson J, Miech EJ, et al. Diagnosis and treatment of sleep apnea in patients' homes: the rationale and methods of the "GoToSleep" randomized-controlled trial. *J Clin Sleep Med*. 2012;8:27–35.

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Obstructive Sleep Apnea and Hypertension: An Update

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Apnea obstructiva del sueño e hipertensión
Una actualización

Tomas Konecny, Tomas Kara, Virend K. Somers

La apnea obstructiva del sueño (AOS) es de gran relevancia en los pacientes con hipertensión arterial (HTA). Estos dos trastornos coexisten con frecuencia (se estima que el 50% de los pacientes con HTA presentan concomitantemente AOS), y existe evidencia reciente que respalda la noción de que la AOS representa la contribución secundaria más prevalente para la presión arterial (PA) elevada en pacientes con HTA resistente (Figura 1).[1]

Asociación epidemiológica entre AOS e HTA

Estudios basados en la población publicados previamente identificaron una correlación independiente entre un mayor índice de apnea-hipopnea y el aumento de la PA, tanto en niveles basales como así también en las mediciones durante el seguimiento a largo plazo.[2] Al contrario, la HTA sistólica aislada, observada con mayor frecuencia en pacientesde edad avanzada, no se asoció a AOS en ningún grupo etáreo.[3] El principal desafío para descifrar la conexión entre AOS-HTA se encuentra en comprender adecuadamente las múltiples variables de confusión, particularmente obesidad y edad. Dos estudios de cohorte longitudinales prospectivos recientes trataron estas interrogantes en sujetos normotensos y llegaron a conclusiones opuestas: el primer estudio informó que luego de ajustar las variables de confusión relevantes, la AOS no estaba asociada a la aparición de HTA sistólica (1180 sujetos a lo largo de un período de seguimiento promedio de 7,5 años).[4] El segundo estudio (también de España, 1889 participantes, media de 12,2 años de seguimiento) identificó un índice de riesgo aumentado para la incidencia de HTA en pacientes con AOS en comparación con sujetos control, y en este segundo estudio, la asociación entre AOS-HTA se mantuvo independiente de las variables de confusión incluyendo edad y obesidad. Además, el seguimiento de esta cohorte de pacientes reveló una relación dosis-respuesta entre la gravedad de la AOS y la incidencia acumulativa de HTA (Figura 2).[5] Dado el extenso período de seguimiento, este segundo estudio proporciona evidencia epidemiológica relativamente sólida que implica a la AOS como un factor para el desarrollo de la HTA.

Enfoque en poblaciones específicas de pacientes

Se ha informado recientemente una asociación entre AOS y PA elevada en varias cohortes específicas de pacientes: mujeres de edad avanzada,[6] sujetos pre-hipertensos,[7] pacientes de atención primaria,[8] pacientes que han sufrido lesiones de médula espinal,[9] y en pacientes que han sufrido accidentes cerebro-vasculares.[10] En niños, sobre los cuales hay menor cantidad de estudios disponibles, la relación entre AOS-HTA permanece evidente,[11,12] pero el desafío se encuentra nuevamente en separar la proporción de elevación de PA que puede ser atribuida a la AOS, obesidad, o a una interacción entre ambas. Aunque posean una potencia relativamente modesta, estos estudios pueden ser útiles para identificar grupos específicos de pacientes en los cuales el diagnóstico y tratamiento de la AOS tendría un efecto más pronunciado sobre la PA y finalmente podrían ayudar a reducir la morbilidad y mortalidad asociada a la HTA. Si estas cohortes de pacientes fueran identificadas, serían entonces objetivos ideales para el tratamiento costo-efectivo de la AOS.

Variación diurna de la PA

La disminución fisiológica nocturna de la PA en individuos normales (patrón *dipper*) parecería estar alterado en pacientes con AOS, y los datos más recientes confirman también estos hallazgos en adultos mayores.[13] La PA nocturna podría reflejar el riesgo cardiovascular tan adecuadamente como la PA diurna, y se ha demostrado que un patrón nocturno *non dipper* confiere un riesgo aumentado de eventos adversos.[14] Los mecanismos subyacentes al patrón *non dipper* han recibido una atención considerable. Sin embargo, los estudios realizados que evalúan la variación diurna de biomarcadores correspondientes a los cambios en la PA inducidos por AOS no han sido concluyentes.[15] Sin embargo, esta línea de investigación continúa siendo potencialmente valiosa debido a que los métodos continuos de medición de PA durante 24 horas se están volviendo cada vez más accesibles y fácilmente disponibles. De hecho, se ha propuesto una categorización relativamente novedosa de HTA asociada al sueño en la AOS: una forma sostenida (HTA tanto nocturna como diurna) y una forma con picos (HTA diurna solamente, sin HTA nocturna), pero se requiere una validación de la variabilidad del efecto de estos dos tipos de HTA asociada al sueño sobre resultados clínicos firmes.[16]

En niños, los datos acerca deAOS y PA nocturna *dipper* continúan siendo conflictivos y nos llevan a concluir que (1)

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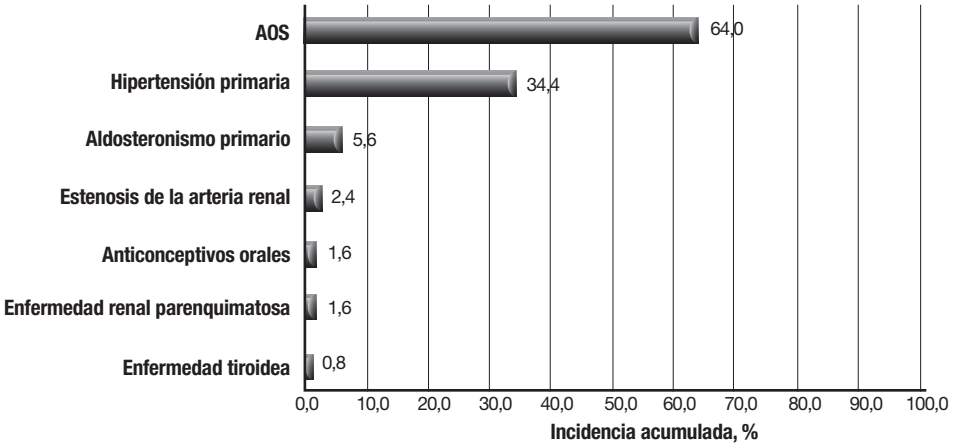

Figura 1. Prevalencia de causas secundarias de hipertensión asociadas a hipertensión resistente en una cohorte de 125 pacientes en Brasil. AOS significa apnea obstructiva del sueño. Reproducido de Pedrosa *et al*[1] con permiso del editor. Copyright © 2011, American Heart Association, Inc.

los niños con AOS pueden no haber estado expuestos a la fisiopatología de la AOS durante suficiente tiempo como para afectar su PA, o que (2) la elevación de la PA durante la fase de movimientos oculares rápidos del sueño puede no ser suficiente para cambiar la PA nocturna global en niños.[17,18]

Vínculos fisiopatológicos entre AOS e HTA

Dado que la HTA y la AOS son procesos complejos con patogenias multifactoriales, no es sorprendente que parecerían estar vinculadas por una interacción de mecanismos, mostrado de forma esquemática en la Figura 3.

Mecanismos circulatorios neuronales

La hipoxemia e hipercapnia repetidas inducidas por AOS producen cambios reflejos tanto en la activación simpática como parasimpática.[19,20] Estas alteraciones autonómicas, con aumentos concomitantes en los niveles de catecolaminas, persisten incluso durante el día y podrían contribuir al desarrollo de la HTA.[21] El tratamiento efectivo de la AOS con presión positiva continua en la vía aérea (CPAP) reduce los niveles de catecolaminas urinarios,[22] y esta reducción parecería ser particularmente evidente en paciente con AOS más severa.[23] Estudios realizados en animales sugieren que la denervación renal atenúa el aumento de PA asociada a eventos de AOS.[24] En las secciones siguientes se analizan los cambios mediados por ganglios autonómicos en los trastornos del ritmo cardíaco asociados a AOS.

Efectos inflamatorios y mediados por citoquinas de la AOS

Los datos preliminares acerca de los mecanismos moleculares que vinculan la AOS con la morbilidad cardiovascular asociada a la HTA sugieren que la AOS se correlaciona con un aumento de la carga de inflamación sistémica y mayores concentraciones de PCR-as (proteína C reactiva de alta sensibilidad), interleuquina-1, interleuquina-8, interleuquina-6, factor de necrosis tumoral-α, Rantes (Regulado por Activación, Expresado y Secretado por Linfocitos T Normales) y sICAM (moléculas solubles de adhesión intercelular).[25] Aún debe ser determinado si estos marcadores realmente implican un peor pronóstico para los pacientes con AOS, y el grado en que una potencial intervención terapéutica podría alterar su patogenia. Se han sugerido datos alentadores en estudios realizados con

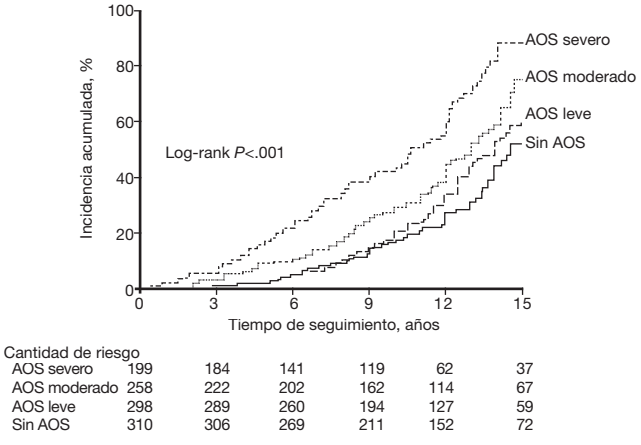

Figura 2. Incidencia acumulativa de hipertensión en participantes de un estudio prospectivo de cohortes realizado por Marin et al5 que no fueron tratados con presión positiva continua en la vía aérea. AOS significa apnea obstructiva del sueño. Reproducido de Marin *et al.*[5] con permiso del editor. Copyright © 2012, American Medical Association.

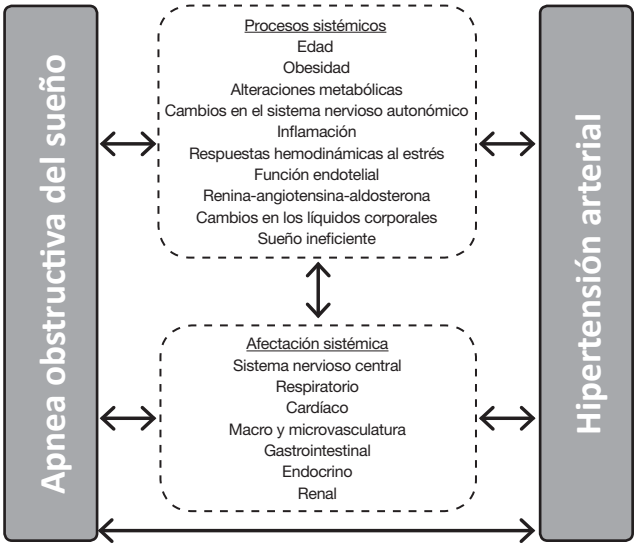

Figura 3. Representación esquemática de las complejas interacciones entre presión arterial y apnea obstructiva del sueño.

un modelo murino en los cuales el uso de atorvastatina, conocido por disminuir la inflamación, previno varios procesos cardiovasculares adversos relacionados con la hipoxia intermitente.[26]

Efectos hemodinámicos de la AOS

Dos estudios identificaron una alteración asociada a la AOS en la respuesta cardiovascular al ejercicio, pero difieren en cuanto a si esta diferencia se mantiene independiente luego de ser ajustada según sexo, índice de masa corporal, y otras comorbilidades.[27,28] La disminución de la capacidad funcional aeróbica en pacientes con AOS genera preocupación dada su capacidad para predecir mortalidad global y cardiovascular.

Modulación relacionada con la edad de la fisiopatología de la AOS

Varios estudios han informado que los efectos de la AOS sobre los trastornos cardiovasculares, tales como HTA y fibrilación auricular, son más evidentes en sujetos de menor edad que en aquellos de mayor edad. La hipótesis atractiva de que la AOS afecta de forma diferente a pacientes más jóvenes en comparación con los de mayor edad fue evaluada en un estudio piloto sobre cambios en el índice de resistencia vascular renal, pero no se hallaron diferencias sustanciales entre las categorías de edad.[29]

Sistema Renina-Angiotensina-Aldosterona

Lamentablemente es limitada la evidencia que relaciona la AOS con los marcadores del sistema renina-angiotensina-aldosterona, claramente de gran interés en pacientes con HTA.[30] Una observación llamativa en pacientes con HTA resistente atribuible a hiperaldosteronismo sugiere que la ingesta dietaria de sal está relacionada con la gravedad de la AOS (esto no se halló en pacientes hipertensos sin hiperaldosteronismo). Esto genera el interrogante acerca de si la ingesta de sal y los niveles de aldosterona constituyen otras variables adicionales que debemos controlar al evaluar la relación entre AOS-HTA.[31] En un sentido amplio, la mejor comprensión del rol del sistema renina-angiotensina-aldosterona en la relación entre AOS-HTA sería de particular importancia clínica, dada la fácil disponibilidad de grupos de medicación que afectan a dichos objetivos.

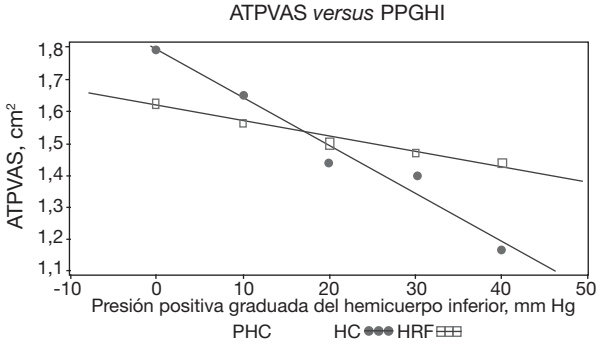

Figura 4. Relación entre el área transversal promedio de la vía aérea superior (ATPVAS) en respuesta a la presión positiva graduada del hemicuerpo inferior (PPGHI) en pacientes con hipertensión controlada (HC) e hipertensión resistente a fármacos (HRF). Adaptado de Friedman *et al.*[32] con permiso del editor. Copyright © 2012, American Heart Association, Inc. La autorización para esta adaptación se obtuvo tanto del titular de los derechos de autor del trabajo original como del titular de los derechos de autor de la traducción o adaptación.

Redistribución nocturna de líquidos

En un estudio reciente que evaluó los efectos de la presión positiva graduada del hemicuerpo inferior sobre el área transversal de la vía aérea superior (entre otras metas), se analizó si la redistribución nocturna de líquidos en sentido cefálico desempeña un papel significativo en pacientes con HTA y AOS.[32] Los autores informaron que los sujetos con HTA redujeron el área transversal promedio de su vía aérea superior en relación directa con la cantidad de líquidos redistribuidos desde los miembros inferiores, y que esta reducción de la vía aérea superior fue significativamente más pronunciada en los pacientes con HTA resistente en comparación con los pacientes con HTA controlada (Figura 4). Estos datos podrían respaldar la noción que la HTA conduce a HTA en parte mediante la vía de la AOS: los pacientes con HTA podrían manifestar una tendencia hacia una mayor redistribución cefálica de líquidos, lo cual empeora su AOS (estrechamiento de la vía aérea) con el posterior incremento adicional en la PA, conduciendo eventualmente a HTA resistente, una correlación en la cual la AOS ha demostrada ser altamente prevalente de forma consistente.

Sueño ineficiente

La AOS es una causa importante de alteración de la calidad del sueño. Se ha postulado que el sueño ineficiente y la corta duración del sueño son posibles factores que contribuyen a la elevación de la PA. Un estudio longitudinal reciente identificó que los pacientes con insomnio crónico con corta duración del sueño poseen un riesgo aumentado de aparición de HTA, pero este efecto fue explicado en gran parte al controlar la obesidad.[33] Al contrario, varios estudios mostraron correlaciones positivas entre la deprivación de sueño y varios factores de riesgo cardiovasculares: rigidez arterial,[34] disfunción endotelial, actividad simpática,[35] patrón *non dipper* de PA nocturna,[36] y resistencia a la insulina.[37]

Objetivos farmacológicos novedosos

Un cambio súbito en la altitud puede afectar de forma adversa tanto la AOS como la HTA, y un ensayo aleatorizado controlado reciente de acetazolamida en conjunto con CPAP *versus* CPAP con placebo sugirió que este inhibidor de la anhidrasa carbónica mejoró el aumento de la PA observado al dormir con gran elevación en pacientes con AOS tratados.[38] A pesar de que la PA no fue una meta primaria en este estudio, los posibles mecanismos detrás de los hallazgos relacionados con la PA fueron intrigantes dado que tanto el desequilibrio ácido-base como las presiones parciales de oxígeno podrían ser potenciales objetivos de intervención terapéutica.

Fisiopatología de sistemas específicos relacionados con AOS

La complejidad de la influencia de la AOS sobre sistemas de órganos específicos se encuentra resaltada por la posible bidireccionalidad de las relaciones causa-efecto; por ejemplo, si la AOS conduce a la alteración de la hemodinamia cerebral que resulta en HTA, o si la AOS conduce directamente a HTA con las alteraciones en la perfusión cerebral como consecuencia (Figura 3).

Sistema nervioso central

Los pacientes con AOS presentaron alteraciones en la reactividad vasomotora cerebral al ser evaluados mediante la maniobra de retención de la respiración,[39] y el seguimiento prospectivo reveló que dos años de CPAP atenuaban esta alteración.[40] Aunque los mecanismos del daño vascular cerebral aún permanecen inciertos, varios estudios murinos han proporcionado información acerca de posibles mediadores. En una evaluación de los efectos topográficosde la hipoxia intermitente crónica y la interacción con los cambios en la PA, se observó que las áreas del cerebro que regulan el flujo simpático eran afectados de forma preferencial.[41] La presencia de delta-FosB en el núcleo preóptico era necesario para que la hipoxia indujera HTA, lo cual sugiere que la adaptación nerviosa podría contribuir al aumento de la PA.[42] Estos estudios respaldan un probable efecto directo de la AOS sobre la vascularización del sistema nervioso central y presentan implicancias para la comprensión de la relación entre AOS, HTA y accidente cerebro-vascular, como así también potenciales caminos para intervenciones dirigidas. [43]

Respiratorio

La hipoxemia asociada a la AOS podría tener un efecto particularmente deletéreo en pacientes con fibrosis pulmonar idiopática, posiblemente por empeoramiento de la hipertensión pulmonar.[44] También generan preocupación los episodios de hipoxemia nocturna asociados a AOS en pacientes con hipertensión pulmonar precapilar de patogenia trombo-embólica o idiopática, donde el agregado del estrés asociado a AOS sobre la ya recargada vasculatura pulmonar y el ventrículo derecho podría ser evitada teóricamente mediante el uso apropiado de CPAP.[45] Aún continua siendo poco claro si el tratamiento de la AOS brinda beneficios clínicos tangibles.

Cardiovascular

Un estudio de menor tamaño acerca de la morfología cardíaca en pacientes con AOS tratados con 3 meses de CPAP sugirió que los índices de función ventricular derecha e izquierda mejoraron levemente,[46] lo cual es deimportancia particular para la alta prevalencia recientemente reconocida de AOS en pacientes con cardiomiopatía isquémica e hipertrófica.[47,48] Existe evidencia emergente que también vincula la AOS con dilatación de la aorta torácica, con implicancias de riesgo de formación de aneurismas. Un potencial mecanismo podría ser el aumento de la presión transmural dilatoria de la pared aórticainducido por la AOS.[49]

Aunque la AOS puede causar cambios estructurales en vasos de gran tamaño, también se ha demostrado que altera la función endotelial. Esta alteración podría ser reversible mediante el tratamiento con CPAP.[50] Se requieren estudios adicionales para identificar todas las vías involucradas, pero existe evidencia reciente que sugiere que el receptor 1 de lipoproteínas de baja densidad oxidadas símil lectina (un receptor scavenger que también presenta expresión aumentada en la ateroesclerosis) desempeña un rol importante.[51]

La fibrilación auricular es una consecuencia habitual de los cambios estructurales cardíacos causados por lahipertensión. Experimentos provocativos en perros sugieren que las alteraciones del ritmo auricular cardíaco se encuentra aumentado por la estimulación de la AOS, y que este efecto probablemente se encuentra mediado por mecanismos cardíacos autonómicos.[52,53] Son particularmente alentadores los datos que muestran que el bloqueo de los ganglios autonómicos cardíacos disminuye de forma marcada la aparición de fibrilación auricular en respuesta a la estimulación de la AOS, lo cual sugiere una opción novedosa para la prevención de la fibrilación auricular en pacientes con AOS.[52]

Gastrointestinal/endocrino

En los pacientes con síndrome metabólico en los cuales la HTA coexiste con dislipemia, obesidad, y pre-diabetes mellitus, el tratamiento de la AOS podría teóricamente mejorar el pronóstico mediante un efecto beneficioso multifacético sobre la PA como así también sobre el perfil lipídico y el metabolismo de la glucosa. Se demostró que la dislipemia posprandial, que conlleva un riesgo cardiovascular significativo, mejora luego de 2 meses de tratamiento efectivo con CPAP.[54] Además, se han informado mejorías con relación a la obesidad, ingesta calórica, y composición corporal en pacientes con AOS tratados existosamente.[55] Existen mecanismos más complejos centrados en la alteración de la resistencia a la insulina que también podrían desempeñar un papel en la susceptibilidad de los pacientes con AOS para las morbilidades asociadas a HTA, ya que esto podría ser confundido por la diabetes mellitus.[56]

Renal

Un estudio piloto reciente acerca de denervación simpática renal en pacientes con HTA resistente sugirió que este procedimiento podría también disminuir la severidad de la apnea del sueño.[57] Sin embargo, aún queda mucho por conocer previo a que la denervación renal pueda ser utilizada clínicamente con este propósito.

Efecto del tratamiento de la AOS sobre la PA

Prevención y tratamiento de la HTA con CPAP

El posible rol preventivo del CPAP sobre la reducción de la incidencia de HTA fue sugerido por el Estudio Cohorte de Sueño Zaragoza, un estudio prospectivo de gran tamaño que informó una menor incidencia de HTA recientemente diagnosticada en aquellos pacientes con AOS que toleraron el CPAP.[5] Estos hallazgos no fueron confirmados en un estudio controlado aleatorizado reciente, también de España, posiblemente debido a su potencia limitada, aunque la tendencia a obtener beneficios mediante el tratamiento con CPAP era alentadora.[58] Se pueden lograr reducciones agudas de la PA y la actividad simpática durante el sueño con el tratamiento efectivo de la AOS; sin embargo, los datos referidos a la reducción clínicamente significativa a largo plazo de la PA con el tratamiento con CPAP han sido menos claros. Los meta-análisis realizados previamente acerca de este tema hicieron referencia sobre el efecto beneficioso modesto pero estadísticamente significativo del CPAP,[59] y el meta-análisis publicado recientemente por Montesi et al[60] que incluyó 1948 pacientes e informóuna disminución media de la PA sistólica y diastólica de 2,58 y 2,01 mmHg, respectivamente, fue congruente con estos hallazgos favoreciendo a aquellos tratados con CPAP.

Predictores de la eficacia antihipertensiva del CPAP

El conocimiento acerca de las características de pacientes específicos que podrían tener predisposición a una mayor reducción de la PA luego del inicio del CPAP podría ser de gran valor. Un estudio de potencia moderada con 24 pacientes con AOS informó que las siguientes variables eran predictores independientes de disminución de la PA promedio de 24 hs asociado al CPAP: sexo masculino, sueño, índice de masa corporal, tabaquismo, uso de alcohol, y PA basal.[61]

Estudios en cohortes de pacientes específicos

Un estudio piloto de pacientes diabéticos (tipo 2) con AOS demostró que la PA sistólica y diastólica en aquellos que recibían CPAP disminuyó en 9 y 7 mmHg, respectivamente.[62] Estos cambios en la PA no pudieron ser atribuidos a cambios en el peso, circunferencia de cintura, o control glucémico, pero los autores informaron una reducción significativa en la noradrenalina y dopamina urinarias. Estas importantes reducciones de la PA son alentadoras y surge la posibilidad que los pacientes diabéticos puedan ser especialmente respondedores al tratamiento con CPAP como estrategia antihipertensiva.

Los pacientes con pre-hipertensión con AOS severa fueron el objetivo de un estudio aleatorizado que mostró que 3 meses de tratamiento con CPAP condujo a una disminución significativa de la PA diurna, nocturna, sistólica, y diastólica, traduciéndose todas en una reducción de la frecuencia de pre-HTA e HTA enmascarada.[63]

En pacientes con enfermedad coronaria y AOS, el tratamiento con CPAP condujo a una reducción efectiva de la PA diastólica y mejorías en la somnolencia diurna; sin embargo, solamente se observó una tendencia hacia la reducción de la PA sistólica, posiblemente atribuible a la modesta potencia del estudio, el momento de los controles de PA, y el período de tratamiento con CPAP relativamente corto (1 mes).[64] En un ensayo controlado aleatorizado con potencia adecuada de CPAP en pacientes con síndrome metabólico en India, 3 meses de CPAP condujeron a una disminución tanto en la PA sistólica como diastólica (3,9 y 2,5 mmHg, respectivamente) y mejoría del perfil lipídico y porcentajes de hemoglobina glicosilada, resultando finalmente en una reducción del 13% de la frecuencia del síndrome metabólico (en comparación con una reducción del 1% en controles).[65]

Alternativas y complementos para el tratamiento con CPAP de la AOS

Los aparatos orales pueden ofrecer una alternativa importante y efectiva al tratamiento con CPAP en pacientes con AOS leve a moderada, en particular en aquellos que no pueden tolerar el tratamiento crónico con CPAP.[66,67] Ambas modalidades de tratamiento de la AOS parecerían resultar por lo general en cambios similares en la PA media de 24 hs, posiblemente debido a que la mayor eficacia del CPAP es contrarrestada por una menor adherencia en relación a los aparatos orales.[68]

Se han informado efectos beneficiosos de la cirugía bariátrica sobre la AOS y PA en varios estudios observacionales,[69,70] pero el ensayo controlado aleatorizado recientemente publicado que comparó el cambio en el índice de apnea-hipopnea luego de una cirugía bariátrica en comparación con un programa común de pérdida de peso solamente mostró una tendencia a favor del grupo quirúrgico.[71] Sin embargo, la disminución significativa de peso en ambos grupos de tratamiento se tradujo en una mejoría de la severidad de la AOS (disminución del índice de apnea-hipopnea en 26 para los pacientes tratados quirúrgicamente *versus* una disminución en 14 para aquellos en el grupo de pérdida de peso común), lo cual sugiere que las modificaciones del estilo de vida centradas en la pérdida de peso y el aumento de la actividad deberían desempeñar un papel prominente en el manejo de pacientes con AOS.

Conclusión

Puntos clave

1. La evidencia epidemiológica implica que la AOS es uno de los factores modificables y altamente prevalentes en el desarrollo de la HTA. Se ha confirmado un patrón nocturno *non dipper* de PA en adultos mayores con AOS pero no en niños.
2. Los pacientes con AOS presentan una disminución de la tolerancia al ejercicio y mayor PA diastólica durante las pruebas de ejercicio.
3. Los pacientes con HTA resistente pueden presentar una redistribución nocturna de líquidos en sentido cefálico y disminución del diámetro de la vía aérea.
4. Existen datos controvertidos con respecto al rol del CPAP en la reducción de la aparición de HTA en pacientes con AOS.
5. Los resultados de los metaanálisis reflejan de forma concordante un efecto antihipertensivo modesto de 2 mmHg del CPAP.

Futuras áreas de estudio

Dada la importancia emergente de la medicina individualizada,[72] el uso rutinario de aparatos de monitoreo hogareño de PA podría facilitar un mayor enfoque de los estudios en subconjuntos específicos de pacientes que podrían obtener mayores beneficios a partir del tratamiento de la AOS en términos de reducción de la PA (respondedores).[73] Dichos estudios también podrían revelar un modelo predictivo para la respuesta de la PA al tratamiento efectivo de la AOS, debido especialmente a que la reducción promedio de PA obtenida con el tratamiento de la AOS ha sido modesta, pero aún así los pacientes respondedores manifiestan mejorías sustanciales de la PA. La mayor potencia de los ensayos longitudinales que utilizan sistemas terapéuticos portátiles bien diseñados también podría ayudar a aclarar la controversia acerca del grado en el que la edad, obesidad, y otras comorbilidades explican la prevalencia aumentada de HTA y eventos adversos relacionados a la HTA en pacientes con AOS, y cómo las modificaciones del estilo de vida encajan en las complejas interacciones entre AOS y PA. Sin embargo, es más importante aún confirmar que toda disminución en la PA se acompaña de mejorías tangibles en los eventos cardiovasculares.

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Declaración de conflictos de interés

V.K. Somers recibió apoyo para la investigación de la Fundación Philips Respironics (donación a la Fundación Mayo), es consultor para Respicardia, ResMed, Medtronic, y NeuPro, y trabaja con Mayo Health Solutions y sus socios industriales sobre propiedad intelectual relacionada con trastornos del sueño y enfermedad cardiovascular. Los demás autores no presentan conflictos de interés.

Referencias

1. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, Amodeo C, Bortolotto LA, Krieger EM, Bradley TD, Lorenzi-Filho G. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension*. 2011;58:811–817.
2. Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, Skatrud J. Population-based study of sleep-disordered breathing as a risk factor forhypertension. *Arch Intern Med*. 1997;157:1746–1752.
3. Haas DC, Foster GL, Nieto FJ, Redline S, Resnick HE, Robbins JA, YoungT, Pickering TG. Age-dependent associations between sleep-disorderedbreathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study. *Circulation*. 2005;111:614–621.
4. Cano-Pumarega I, Duran-Cantolla J, Aizpuru F, Miranda-Serrano E, Rubio R, Martinez-Null C, de Miguel J, Egea C, Cancelo L, Alvarez A, Fernandez-Bolanos M, Barbe F. Obstructive sleep apnea and systemic hypertension: longitudinal study in the general population: the Vitoria Sleep Cohort. *Am J Respir Crit Care Med*. 2011;184:1299–1304.
5. Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ, Barbe F, Vicente E, Wei Y, Nieto FJ, Jelic S. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012;307:2169–2176.
6. Sforza E, Chouchou F, Collet P, Pichot V, Barthelemy JC, Roche F. Sex differences in obstructive sleep apnoea in an elderly French population. *Eur Respir J*. 2011;37:1137–1143.
7. Roche F, Pepin JL, Achour-Crawford E, Tamisier R, Pichot V, Celle S, Maudoux D, Chouchou F, Ntougou-Assoumou HG, Levy P, Barthelemy JC; PROOF Study Group. At 68 years, unrecognised sleep apnoea is associated with elevated ambulatory blood pressure. *Eur Respir J*. 2012;40:649–656.
8. Brostrom A, Sunnergren O, Johansson P, Svensson E, Ulander M, Nilsen P, Svanborg E. Symptom profile of undiagnosed obstructive sleep apnoea in hypertensive outpatients in primary care: a structural equation model analysis. *Qual Prim Care*. 2012;20:287–298.
9. LaVela SL, Burns SP, Goldstein B, Miskevics S, Smith B, Weaver FM. Dysfunctional sleep in persons with spinal cord injuries and disorders. *Spinal Cord*. 2012;50:682–685.
10. Cereda CW, Tamisier R, Manconi M, Andreotti J, Frangi J, Pifferini V,Bassetti CL. Endothelial dysfunction and arterial stiffness in ischemic stroke: the role of sleep-disordered breathing. *Stroke*. 2013;44:1175–1178.
11. Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Fedok F, Vlasic V, Graff G. Blood pressure associated with sleep-disordered breathing in a population sample of children. *Hypertension*. 2008;52:841–846.
12. Archbold KH, Vasquez MM, Goodwin JL, Quan SF. Effects of sleep patterns and obesity on increases in blood pressure in a 5-year period: report from the Tucson Children's Assessment of Sleep Apnea Study. *J Pediatr*. 2012;161:26–30.
13. Endeshaw YW, White WB, Kutner M, Ouslander JG, Bliwise DL. Sleep-disordered breathing and 24-hour blood pressure pattern amongolder adults. *J Gerontol A Biol Sci Med Sci*. 2009;64:280–285.
14. Waeber B, Mourad JJ, O'Brien E. Nighttime blood pressure: a target for therapy? *Curr Hypertens Rep*. 2010;12:474–479.
15. von Kanel R, Natarajan L, Ancoli-Israel S, Mills PJ, Loredo JS, Dimsdale JE. Day/night rhythm of hemostatic factors in obstructive sleep apnea. *Sleep*. 2010;33:371–377.
16. Sasaki N, Ozono R, Yamauchi R, Teramen K, Edahiro Y, Ishii K, SetoA, Kihara Y. The relationship between morning hypertension and sleep quality in patients with obstructive sleep apnea syndrome. *Clin ExpHypertens*. 2013;35:250–256.
17. Horne RS, Yang JS, Walter LM, Richardson HL, O'Driscoll DM, Foster AM, Wong S, Ng ML, Bashir F, Patterson R, Jolley D, Walker AM, Anderson V, Davey MJ, Nixon GM. Nocturnal dipping is preserved in children with sleep disordered breathing regardless of its severity. *PediatrPulmonol*. 2013;48:1127–1134.
18. Nisbet LC, Yiallourou SR, Biggs SN, Nixon GM, Davey MJ, Trinder JA, Walter LM, Horne RS. Preschool children with obstructive sleep apnea: the beginnings of elevated blood pressure? *Sleep*. 2013;36:1219–1226.
19. Konecny T, Somers VK. Chapter 112: Sleep apnea. In: RobertsonD, Biaggioni I, Burnstock G, Low PA, Paton JFR, eds. *Primer on theAutonomic Nervous System*. 3rd ed. San Diego, CA: Elsevier; 2012.
20. Parati G, Lombardi C, Hedner J, Bonsignore MR, Grote L, Tkacova R, Levy P, Riha R, Bassetti C, Narkiewicz K, Mancia G, McNicholas WT. Position paper on the management of patients with obstructive sleep apnea and hypertension: Joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific and Technological Research) ACTION B26 on obstructive sleep apnea. *J Hypertens*.2012;30:633–646.
21. Freet CS, Stoner JF, Tang X. Baroreflex and chemoreflex controls of sympathetic activity following intermittent hypoxia. *Auton Neurosci*. 2013;174:8–14.
22. Leung RS. Sleep-disordered breathing: autonomic mechanisms and arrhythmias. *Prog Cardiovasc Dis*. 2009;51:324–338.
23. Pinto P, Barbara C, Montserrat JM, Patarrao RS, Guarino MP, Carmo MM, Macedo MP, Martinho C, Dias R, Gomes MJ. Effects of CPAP on nitrate and norepinephrine levels in severe and mild-moderate sleep apnea. *BMC Pulm Med*. 2013;13:13.
24. Linz D, Mahfoud F, Schotten U, Ukena C, Neuberger HR, Wirth K, Bohm M. Renal sympathetic denervation suppresses postapneic blood pressure rises and atrial fibrillation in a model for sleep apnea. *Hypertension*.2012;60:172–178.
25. Testelmans D, Tamisier R, Barone-Rochette G, Baguet JP, Roux-Lombard P, Pepin JL, Levy P. Profile of circulating cytokines: impact of OSA, obesityand acute cardiovascular events. *Cytokine*. 2013;62:210–216.
26. Totoson P, Fhayli W, Faury G, Korichneva I, Cachot S, Baldazza M, Ribuot C, Pepin JL, Levy P, Joyeux-Faure M. Atorvastatin protects against deleterious cardiovascular consequences induced by chronic intermittent hypoxia. *Exp Biol Med (Maywood)*. 2013;238:223–232.
27. Rizzi CF, Cintra F, Mello-Fujita L, Rios LF, Mendonca ET, Feres MC, Tufik S, Poyares D. Does obstructive sleep apnea impair the cardiopulmonary response to exercise? *Sleep*. 2013;36:547–553.
28. Mansukhani MP, Allison TG, Lopez-Jimenez F, Somers VK, Caples SM. Functional aerobic capacity in patients with sleep-disordered breathing. *Am J Cardiol*. 2013;111:1650–1654.
29. Patel HM, Mast JL, Sinoway LI, Muller MD. Effect of healthy agingon renal vascular responses to local cooling and apnea. *J Appl Physiol(1985)*. 2013;115:90–96.
30. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest*. 2007;131:453–459.
31. Pimenta E, Stowasser M, Gordon RD, Harding SM, Batlouni M, Zhang B, Oparil S, Calhoun DA. Increased dietary sodium is related to severity of obstructive sleep apnea in patients with resistant hypertension and hyperaldosteronism. *Chest*. 2013;143:978–983.
32. Friedman O, Bradley TD, Logan AG. Influence of lower body positive-pressure on upper airway cross-sectional area in drug-resistant hypertension. *Hypertension*. 2013;61:240–245.
33. Fernandez-Mendoza J, Vgontzas AN, Liao D, Shaffer ML, Vela-BuenoA, Basta M, Bixler EO. Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension*. 2012;60:929–935.
34. Sunbul M, Kanar BG, Durmus E, Kivrak T, Sari I. Acute sleep deprivation is associated with increased arterial stiffness in healthy young adults. *Sleep Breath*. 2013 Jul 14 [Epub ahead of print].
35. Dettoni JL, Consolim-Colombo FM, Drager LF, Rubira MC, Souza SB, Irigoyen MC, Mostarda C, Borile S, Krieger EM, Moreno H Jr, Lorenzi-Filho G. Cardiovascular effects of partial sleep deprivation in healthy volunteers. *J Appl Physiol (1985)*. 2012;113:232–236.
36. Carev M, Karanović N, Bagatin J, Matulić NB, Pecotić R, Valić M,Marinović-Terzić I, Karanović S, Dogas Z. Blood pressure dipping and salivary cortisol as markers of fatigue and sleep deprivation in staff anesthesiologists. *Coll Antropol*. 2011;35(suppl 1):133–138.
37. Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men.

Diabetes. 2010;59:2126–2133.
38. Latshang TD, Nussbaumer-Ochsner Y, Henn RM, Ulrich S, Lo CascioCM, Ledergerber B, Kohler M, Bloch KE. Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude: a randomized controlled trial. *JAMA*. 2012;308:2390–2398.
39. Jimenez Caballero PE, Coloma Navarro R, Segura Martn T, Ayo Martn O. Cerebral hemodynamic changes at basilar artery in patients with obstructivesleep apnea syndrome. A case-control study. *Acta Neurol Scand*. 2013 Jun 13 [Epub ahead of print].
40. Jimenez Caballero PE, Coloma Navarro R, Ayo Martin O, Segura Martin T. Cerebral hemodynamic changes in obstructive sleep apnea syndrome after continuous positive airway pressure treatment. *Sleep Breath*. 2013;17:1103–1108.
41. Knight WD, Little JT, Carreno FR, Toney GM, Mifflin SW, Cunningham JT. Chronic intermittent hypoxia increases blood pressure and expression of FosB/DeltaFosB in central autonomic regions. *Am J Physiol RegulIntegr Comp Physiol*. 2011;301:R131–R139.
42. Cunningham JT, Knight WD, Mifflin SW, Nestler EJ. An Essential role for DeltaFosB in the median preoptic nucleus in the sustained hypertensive effects of chronic intermittent hypoxia. *Hypertension*. 2012;60:179–187.
43. Capone C, Faraco G, Coleman C, Young CN, Pickel VM, Anrather J, Davisson RL, Iadecola C. Endothelin 1-dependent neurovascular dysfunction in chronic intermittent hypoxia. *Hypertension*. 2012;60:106–113.
44. Kolilekas L, Manali E, Vlami KA, Lyberopoulos P, Triantafillidou C, Kagouridis K, Baou K, Gyftopoulos S, Vougas KN, Karakatsani A, Alchanatis M, Papiris S. Sleep oxygen desaturation predicts survival in idiopathic pulmonary fibrosis. *J Clin Sleep Med*. 2013;9:593–601.
45. Jilwan FN, Escourrou P, Garcia G, Jais X, Humbert M, Roisman G. High occurrence of hypoxemic sleep respiratory disorders in precapillary pulmonary hypertension and mechanisms. *Chest*. 2013;143:47–55.
46. Colish J, Walker JR, Elmayergi N, Almutairi S, Alharbi F, Lytwyn M, Francis A, Bohonis S, Zeglinski M, Kirkpatrick ID, Sharma S, Jassal DS. Obstructive sleep apnea: effects of continuous positive airway pressure on cardiac remodeling as assessed by cardiac biomarkers, echocardiography, and cardiac MRI. *Chest*. 2012;141:674–681.
47. Konecny T, Kuniyoshi FH, Orban M, Pressman GS, Kara T, Gami A, Caples SM, Lopez-Jimenez F, Somers VK. Under-diagnosis of sleepapnea in patients after acute myocardial infarction. *J Am Coll Cardiol*. 2010;56:742–743.
48. Konecny T, Brady PA, Orban M, Lin G, Pressman GS, Lehar F, Tomas K, Gersh BJ, Tajik AJ, Ommen SR, Somers VK. Interactions between sleep disordered breathing and atrial fibrillation in patients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2010;105:1597–1602.
49. Clarenbach CF, Camen G, Sievi NA, Wyss C, Stradling JR, Kohler M. Effect of simulated obstructive hypopnea and apnea on thoracic aortic wall transmural pressures. *J Appl Physiol (1985)*. 2013;115:613–617.
50. Kohler M, Craig S, Pepperell JC, Nicoll D, Bratton DJ, Nunn AJ, Leeson P, Stradling JR. CPAP improves endothelial function in patients with minimally symptomatic OSA: results from a subset study of the MOSAIC trial. *Chest*. 2013;144:896–902.
51. Akinnusi ME, Laporta R, El-Solh AA. Lectin-like oxidized low-density lipoprotein receptor-1 modulates endothelial apoptosis in obstructive sleep apnea. *Chest*. 2011;140:1503–1510.
52. Ghias M, Scherlag BJ, Lu Z, Niu G, Moers A, Jackman WM, Lazzara R, Po SS. The role of ganglionated plexi in apnea-related atrial fibrillation. *J Am Coll Cardiol*. 2009;54:2075–2083.
53. Lu Z, Nie L, He B, Yu L, Salim M, Huang B, Cui B, He W, Wu W, Jiang H. Increase in vulnerability of atrial fibrillation in an acute intermittent hypoxia model: importance of autonomic imbalance. *Auton Neurosci*. 2013;177:148–153.
54. Phillips CL, Yee BJ, Marshall NS, Liu PY, Sullivan DR, Grunstein RR. Continuous positive airway pressure reduces postprandial lipidemia in obstructive sleep apnea: a randomized, placebo-controlled crossover trial. *Am J Respir Crit Care Med*. 2011;184:355–361.
55. Tuomilehto H, Gylling H, Peltonen M, Martikainen T, Sahlman J, Kokkarinen J, Randell J, Tukiainen H, Vanninen E, Partinen M, Tuomilehto J, Uusitupa M, Seppa J; Kuopio Sleep Apnea Group. S staine-dimprovement in mild obstructive sleep apnea after a diet and physical activity- based lifestyle intervention: postinterventional follow-up. *Am J Clin Nutr*. 2010;92:688–696.
56. Lindberg E, Theorell-Haglow J, Svensson M, Gislason T, Berne C, Janson C. Sleep apnea and glucose metabolism: a long-term follow-up in a communitybased sample. *Chest*. 2012;142:935–942.
57. Witkowski A, Prejbisz A, Florczak E, Kądziela J, Śliwiński P, Bieleń P, Michałowska I, Kabat M, Warchoł E, Januszewicz M, Narkiewicz K,Somers VK, Sobotka PA, Januszewicz A. Effects of renal sympatheticdenervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension*.2011;58:559–565.
58. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, et al; Spanish Sleep And Breathing Network. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA*. 2012;307:2161–2168.
59. Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuouspositive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension*. 2007;50:417–423.
60. Montesi SB, Edwards BA, Malhotra A, Bakker JP. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J Clin SleepMed*. 2012;8:587–596.
61. Yorgun H, Kabakci G, Canpolat U, Kirmizigul E, Sahiner L, Ates AH, Sendur MA, Kaya EB, Demir AU, Aytemir K, Tokgozoglu L, Oto A. Predictors of blood pressure reduction with nocturnal continuous positive airway pressure therapy in patients with obstructive sleep apnea and prehypertension. *Angiology*. 2013 Feb 20 [Epub ahead of print].
62. Myhill PC, Davis WA, Peters KE, Chubb SA, Hillman D, Davis TM. Effect of continuous positive airway pressure therapy on cardiovascular risk factors in patients with type 2 diabetes and obstructive sleep apnea. *J Clin Endocrinol Metab*. 2012;97:4212–4218.
63. Drager LF, Pedrosa RP, Diniz PM, Diegues-Silva L, Marcondes B, Couto RB, Giorgi DM, Krieger EM, Lorenzi-Filho G. The effects of continuous positive airway pressure on prehypertension and masked hypertension in men with severe obstructive sleep apnea. *Hypertension*. 2011;57:549–555.
64. Zhao Q, Liu ZH, Luo Q, Zhao ZH, Zhang HL, Wang Y. Effects of continuous positive airway pressure on blood pressure and daytime sleepiness in obstructive sleep apnea patients with coronary heart diseases under optimal medications. *Sleep Breath*. 2012;16:341–347.
65. Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhiravan T, Lakshmy R, Jagia P, Kumar A. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. *N Engl J Med*. 2011;365:2277–2286.
66. Li W, Xiao L, Hu J. The comparison of CPAP and oral appliances in treatment of patients with OSA: a systematic review and meta-analysis. *RespirCare*. 2013;58:1184–1195.
67. Iftikhar IH, Hays ER, Iverson MA, Magalang UJ, Maas AK. Effect of oral appliances on blood pressure in obstructive sleep apnea: a systematic review and meta-analysis. *J Clin Sleep Med*. 2013;9:165–174.
68. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, Marks GB, Cistulli PA. Health outcomes of continuous positive airway pressure *versus* oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med*. 2013;187:879–887.
69. Hady HR, Dadan J, Gołaszewski P. 100 obese patients after laparoscopic adjustable gastric banding - the influence on BMI, gherlin and insulin concentration, parameters of lipid balance and co-morbidities. *Adv Med Sci*. 2012;57:58–64.
70. Woodman G, Cywes R, Billy H, Montgomery K, Cornell C, Okerson T; APEX Study Group. Effect of adjustable gastric banding on changes in gastroesophageal reflux disease (GERD) and quality of life. *Curr Med Res Opin*. 2012;28:581–589.
71. Dixon JB, Schachter LM, O'Brien PE, Jones K, Grima M, Lambert G, Brown W, Bailey M, Naughton MT. Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. *JAMA*. 2012;308:1142–1149.
72. Bejan-Angoulvant T, Baguet JP, Erpeldinger S, Boivin JM, Mercier A,Leftheriotis G, Gagnol JP, Fauvel JP, Giraud C, Bricca G, Gueyffier F. The IDEAL study: Towards personalized drug treatment of hypertension. *Therapie*. 2012;67:195–204.
73. Bravata DM, Ferguson J, Miech EJ, et al. Diagnosis and treatment of sleepapnea in patients' homes: the rationale and methods of the "GoToSleep" randomized-controlled trial. *J Clin Sleep Med*. 2012;8:27–35.