

# Recent Advances in Hypertension

## 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).<sup>1</sup>

### 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.<sup>2</sup> On the contrary, isolated systolic HTN, which was more commonly seen in elderly patients, was not associated with OSA in any age group.<sup>3</sup> 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).<sup>4</sup> 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).<sup>5</sup> 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,<sup>6</sup> prehypertensive subjects,<sup>7</sup> primary care patients,<sup>8</sup> patients after spinal cord injury,<sup>9</sup> and in patients after stroke.<sup>10</sup> In children, on whom fewer studies are available, the OSA-BP

relationship remains evident,<sup>11,12</sup> 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.<sup>13</sup> 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.<sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup>

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.<sup>17,18</sup>

### 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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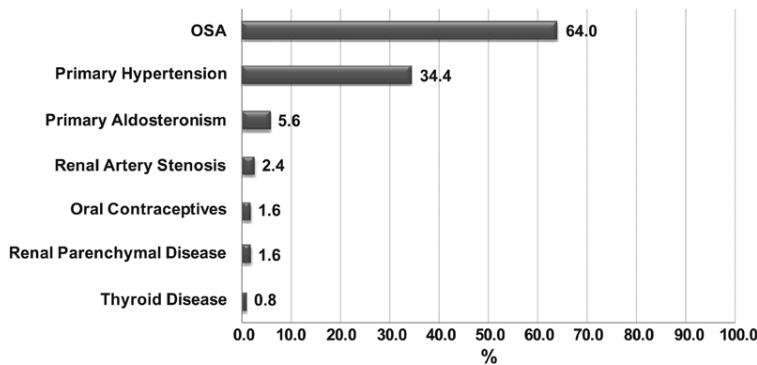
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**Figure 1.** Prevalence of secondary causes of hypertension associated with resistant hypertension in a cohort of 125 patients from Brazil. OSA indicates obstructive sleep apnea. Reproduced from Pedrosa et al<sup>1</sup> with permission of the publisher. 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.<sup>19,20</sup> These autonomic derangements, with consequent increases in catecholamine levels, persist even into the daytime and could contribute to the development of HTN.<sup>21</sup> Effective OSA treatment with continuous positive airway pressure (CPAP) reduces urinary catecholamine levels,<sup>22</sup> and this reduction seems to be especially evident in patients with more severe OSA.<sup>23</sup> Animal studies suggest that renal denervation attenuates the BP rise associated with OSA events.<sup>24</sup> 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- $\alpha$ , Rantes (Regulated

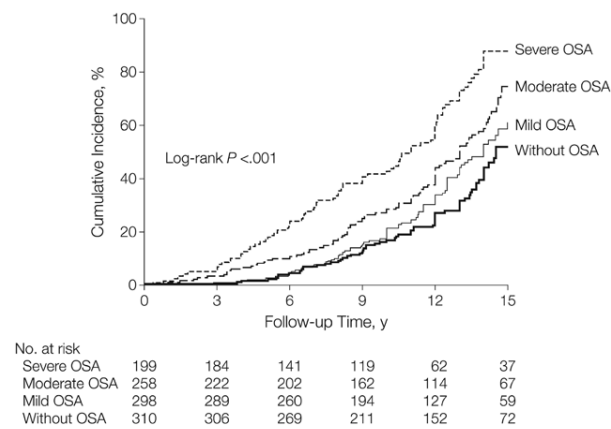
on Activation, Normal T Cell Expressed and Secreted), and sICAM (soluble intercellular adhesion molecules).<sup>25</sup> Whether these markers truly signify a worse prognosis for patients with OSA, and to what degree a potential therapeutic intervention could alter their pathogenesis remains to be determined. 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.<sup>26</sup>

**Hemodynamic Effects of OSA**

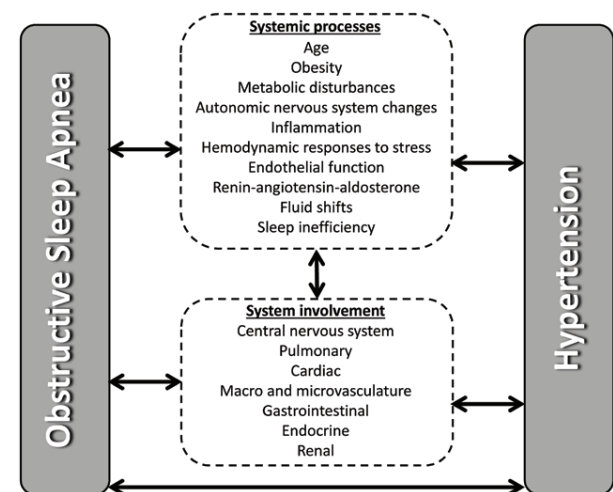
Two studies identified an OSA-associated impairment in the cardiovascular response to exercise but differ as to whether this difference remains independent after adjusting for sex, body mass index, and other comorbidities.<sup>27,28</sup> Decreased functional aerobic capacity in patients with OSA raises 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<sup>5</sup> who were not treated with continuous positive airway pressure. OSA indicates obstructive sleep apnea. Reproduced from Marin et al<sup>5</sup> 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.<sup>29</sup>

### Renin–Angiotensin–Aldosterone System

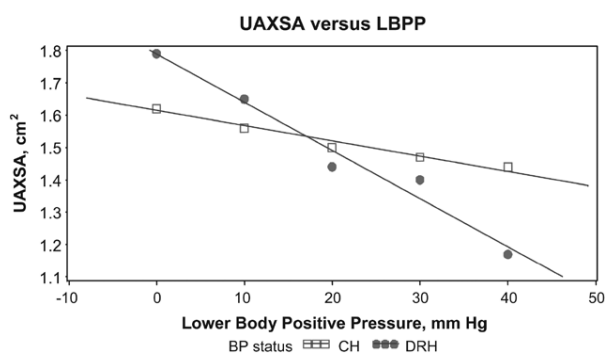
Evidence relating OSA to markers of the renin–angiotensin–aldosterone system, clearly of high interest in patients with HTN, is unfortunately limited.<sup>30</sup> A curious observation in patients with resistant HTN attributable to hyperaldosteronism suggested that dietary salt intake was related to 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.<sup>31</sup> 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).<sup>32</sup> 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



**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<sup>32</sup> 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.

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.<sup>33</sup> On the contrary, several studies showed positive correlations between sleep deprivation and various adverse cardiovascular risk factors: arterial stiffness,<sup>34</sup> endothelial dysfunction, sympathetic activity,<sup>35</sup> nondipping nocturnal BP pattern,<sup>36</sup> and insulin insensitivity.<sup>37</sup>

### 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.<sup>38</sup> 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,<sup>39</sup> and prospective follow-up revealed that 2 years of CPAP attenuated this impairment.<sup>40</sup> 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.<sup>41</sup> Delta-FosB in the pre-optic nucleus was necessary for hypoxia to induce HTN, suggesting that neural adaptation may contribute to the increase in BP.<sup>42</sup> 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.<sup>43</sup>

### Pulmonary

OSA-related hypoxemia may have a particularly deleterious effect in patients with idiopathic pulmonary fibrosis, possibly by aggravating pulmonary HTN.<sup>44</sup> 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.<sup>45</sup> 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<sup>46</sup> which has particular relevance to the recently recognized high prevalence of OSA in patients with ischemic and hypertrophic cardiomyopathy.<sup>47,48</sup> 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 dilatatory transmural pressure.<sup>49</sup>

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.<sup>50</sup> 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.<sup>51</sup>

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.<sup>52,53</sup> 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.<sup>52</sup>

### 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.<sup>54</sup> In addition, improvements in obesity, caloric intake, and body composition have been reported in successfully treated OSA patients.<sup>55</sup> 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.<sup>56</sup>

### 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.<sup>57</sup> 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.<sup>5</sup> 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.<sup>58</sup> 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,<sup>59</sup> and congruent with these findings was the recently published meta-analysis by Montesi et al<sup>60</sup> which included 28 studies representing 1948 patients and reported weighted mean decrease in systolic and diastolic BP of 2.58 and 2.01 mmHg, 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.<sup>61</sup>

### 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 mmHg, respectively.<sup>62</sup> 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.<sup>63</sup>

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).<sup>64</sup> 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 mmHg, 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).<sup>65</sup>

### 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.<sup>66,67</sup> 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.<sup>68</sup>

Beneficial effects of bariatric surgery on OSA and BP have been reported in several observational studies,<sup>69,70</sup> 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.<sup>71</sup> 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-mmHg antihypertensive effect of CPAP.

### Remaining Unknowns

Given the emerging importance of individualized medicine,<sup>72</sup> 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).<sup>73</sup> 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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