Sleep Apnea in Hypertension: When, How, and Why Should We Treat?

Fatima H. Sert Kuniyoshi and Virend K. Somers

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Editorial Commentary

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Hypertension is a notoriously complex disease, with a mosaic of potential interactive etiologies. Age, gender, nutrition, environment, stress, obesity, and genetics have been cited as causal factors, as has been dysfunction in renal, endocrine, and neural circulatory control mechanisms. More recently, the epidemic of obesity has prompted recognition of an interaction between obstructive sleep apnea and increased blood pressure. This has, in turn, provided an exciting opportunity for more comprehensive understanding of the pathophysiological mechanisms and potential treatment strategies for hypertensive patients.

Both hypertension and obstructive sleep apnea (OSA) are each increasingly common. Hypertension is present in well over a third of middle-aged subjects, and sleep apnea is reported to be present in 25% of middle-aged men and 10% of middle-aged women.[1] Other common characteristics of hypertension and OSA include their association with obesity and male gender. Furthermore, both conditions are often clinically undiagnosed and may be accompanied by increased risk of cardiac and vascular damage.

Although hypertension and OSA are common in the general population, epidemiological studies suggest that their comorbid prevalence exceeds strikingly that which would be anticipated to occur by chance alone. These observations, based on cross-sectional data, have been further strengthened by prospective studies demonstrating that increasing severity of OSA is a risk factor for the development of incident hypertension over 4 years.[2] This etiologic interaction is independent of traditional risk factors for hypertension, such as alcohol, body mass index, and gender. Also impressive is that an apnea-hypopnea index of $\geq$15 (indicating that breathing decreases or stops $\geq$15 times for each hour of sleep) is accompanied by a 3-fold increased risk for the development of what we generally assume to be essential hypertension. Further confirmation of a likely etiologic role for sleep apnea in higher blood pressures has been provided by several small randomized, controlled trials demonstrating that effective treatment of OSA in hypertensive subjects was accompanied by significant decreases not only in the nighttime but also in daytime blood pressures.[3–5]

Why should a disorder occurring exclusively during sleep elicit sustained increases in blood pressure during wakefulness? Mechanisms that are potentially activated during nocturnal apneas and which could chronically raise blood pressure include increases in central sympathetic outflow, endothelial dysfunction, increased endothelin, and activation of systemic inflammation, among others.[6] It is generally believed that it is the hypoxemia during apnea that is the primary offending agent, although other nocturnal stresses, such as repeated arousals and chronic sleep deprivation, may be implicated. Animal studies suggest that it is indeed the nocturnal hypoxemia rather than the arousals alone that is important in the development of higher daytime blood pressures.[7]

Norman et al[8] extend their prior work and address this question further in the context of human hypertension. In a randomized, double-blind study, patients with hypertension were assigned to 3 groups: continuous positive airway pressure (CPAP), sham-CPAP, and sham-CPAP plus supplemental oxygen therapy. They found that whereas 2 weeks of CPAP therapy was effective in lowering nighttime and daytime blood pressures, neither sham-CPAP nor sham-CPAP combined with oxygen therapy lowered blood pressure. Indeed, evidence of any blood pressure–lowering effect from oxygen therapy was absent, although nocturnal oxygen saturation was significantly improved.

One interpretation of these data is that it is not the nocturnal hypoxemia alone but the constellation of stresses resulting from obstructive apneic episodes that raises blood pressure. However, an unexpected consequence of randomization in this study was that the pretreatment blood pressure in the sham-CPAP group was substantially lower than either of the other 2 patient groups. Hence, the influence of regression to the mean cannot be excluded. Furthermore, trials of CPAP in normotensive and hypertensive subjects suggest that it is primarily in hypertensive subjects in whom CPAP effectively lowers daytime blood pressure.[9] Pretreatment blood pressure in the sham CPAP group was, on average, well within normal limits.

A more important question relates to the absence of any blood pressure–lowering effect of improved nocturnal oxygen saturation, placing into question the role of hypoxemia as a primary trigger of daytime hypertension; however, potential unexpected effects of sham-CPAP need to be recognized. It is possible, as the authors note, that disturbed sleep resulting from sham-CPAP may have mitigated any blood pressure–lowering effect of oxygen supplementation. Furthermore, the possibility of increased work of breathing in the sham-CPAP group needs to be taken into consideration, because breathing through a closed circuit with even low levels of positive

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From the Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, 200 First St, SW, Rochester, Minn.

Correspondence to Virend K. Somers, Mayo Clinic, 200 First St, SW, Rochester, MN 55902. E-mail somers.virend@mayo.edu

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pressure could increase airway resistance. Indeed, the tendency toward higher blood pressures with sham-CPAP was much less evident when sham-CPAP was combined with nasal oxygen supplementation, speaking to a potential interaction between these interventions. Perhaps an oxygen supplementation group, without simultaneous administration of sham-CPAP, may speak more clearly to the potential role of oxygen desaturation in blood pressure changes with sleep apnea.

The study from Norman et al,[8] nevertheless, constitutes an important step in confirming that effective prevention of nocturnal apneas results not only in decreased nighttime blood pressures but also in modest but significant decreases in blood pressures measured during the day. That the fall in nighttime blood pressures was more substantial is itself relevant to preventing the consequences of hypertension, because high nocturnal blood pressures have been increasingly linked to adverse cardiac and vascular events.[10] The small change in daytime blood pressure complements further the overall reduction in "blood pressure burden." It is quite possible that daytime blood pressures might have been even more strikingly lower had these investigators chosen to study patients with more severe hypertension.

Whereas hypertension may be one mechanism leading to increased cardiovascular risk in sleep apnea patients, cross-sectional data and longitudinal observational studies suggest that a component of the cardiovascular risk associated with OSA is independent of blood pressure levels. Thus, an important aspect of being able to lower blood pressures, however modestly, by preventing apneic events may be that overall cardiovascular risk reduction exceeds that which would be expected based on blood pressure lowering alone. However, this remains to be demonstrated and underscores an important caveat in our understanding of the indications and benefits of treating sleep apnea. Namely, there are no longitudinal randomized interventional studies that have been conducted so as to demonstrate conclusively whether or not treatment of sleep apnea, regardless of the presence of absence of hypertension, results in decreased likelihood of cardiovascular end points, such as stroke, myocardial infarction, or cardiovascular death.

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