Treating Obstructive Sleep Apnea: Is There More to the Story Than 2 Millimeters of Mercury?

John S. Floras and T. Douglas Bradley

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Obstructive sleep apnea (OSA), a common disorder, increases the 4-year risk of developing hypertension by ≈3-fold.1 In an uncontrolled trial, treatment of OSA when present in drug-resistant hypertension by nasal continuous positive airway pressure (CPAP) achieved substantial reductions in both nighttime and daytime blood pressure (BP).2 However, in controlled and uncontrolled studies involving small cohorts of patients with OSA with stage 1 hypertension, prehypertension, or normal BP, the short-term use of CPAP had less or no effect on BP. A meta-analysis in the present issue of *Hypertension*3 attempts to estimate the effect of this intervention on BP.

The authors identified all of the published trials that reported BP as a primary or a secondary end point in which adults with OSA diagnosed by polysomnography were randomly allocated to therapeutic CPAP or not for ≥2 weeks. These 16 trials involved 818 participants (86.3% men; mean age: 51 years; mean apnea-hypopnea index: 36.2 events per hour) treated for ≥24 weeks. From the 15 trials that reported systolic and diastolic BP, the authors calculated a significant mean net reduction of 2.46/1.83 mm Hg with CPAP and, from the 7 trials that reported mean arterial BP, a significant net reduction of 2.22 mm Hg. By comparison, in a previous meta-analysis restricted to 12 trials in which the primary variable of interest was 24-hour mean ambulatory BP, the calculated net decrease was still significant at 1.69 mm Hg.4 In the present analysis by Bazzano et al,3 the mean net change in systolic BP tended to correlate with the average nightly CPAP use (Figure 5 in Reference 3; P = 0.13). These authors concluded that CPAP decreases BP among those with OSA, and treating OSA with CPAP may help prevent hypertension.

There is increasing awareness of the adverse interactions between OSA and several cardiovascular conditions.5 Consequently, these 2 conclusions are certain to attract attention. However, they are based on a meta-analysis involving a small number of subjects treated briefly. Absent are long-term data confirming that any initial reduction persists, and there has been no randomized, controlled test of the hypothesis that abolition of OSA in prehypertensive patients will prevent the subsequent development of hypertension. Only 2 of these trials recruited specifically hypertensive patients, in whom hypertension was usually treated. The average BP of all 818 subjects was 131/80 mm Hg. In a subsequent subgroup analysis, significant BP reductions were identified only in those with BP ≥130/80 mm Hg. Little or no impact on BP would be anticipated from any intervention in normoten-

sive individuals. The analysis also conflates studies of people with (afterload-insensitive) normal and (afterload-sensitive) impaired ventricular systolic function. Does this meta-analysis then truly provide robust and reliable “level A” evidence for an antihypertensive or hypertension-preventative effect of CPAP? As we address this question, we will develop 2 concepts: the distinction between “effects” and “after effects” of OSA and its treatment and the impact of negative intrathoracic pressure on cardiac structure and function.

BP was obtained by ambulatory monitoring in 11 of these studies and by conventional methods in a clinic or laboratory setting in 5. Assumed is that nocturnal BP can be measured reliably by this method. However, in OSA, nocturnal BP is inherently unstable. Each obstructive apnea during sleep elicits a 10- to 90-second cycle of apnea, progressive hypoxia and hypercapnia, efferent sympathetic vasoconstrictor nerve discharge, and arousal from sleep. Each cycle terminates with a substantial surge in BP.5 CPAP, which prevents pharyngeal obstruction, eliminates these oscillations, but once CPAP is withdrawn, this acute antihypertensive effect disappears.6 The discontinuous noninvasive ambulatory method used in the studies composing the present meta-analysis will not reliably detect these recurrent BP surges or the acute damping effect of CPAP on these oscillations. Thus, the nocturnal values reported in Table 2 of Reference 3 are unlikely to be accurate and likely underestimate any hypotensive effect of CPAP during sleep.

However, the key clinical question is not, “what is the acute effect of CPAP on BP during sleep in subjects with OSA?” Because CPAP eliminates acutely the obstructive pressor stimulus, the finding that its therapeutic application lowers BP during sleep is obvious. If comparison is made between 2 sequences of ambulatory BP recordings in the same individual, 1 obtained during sustained running exercise and 1 during rest, one might choose to conclude that rest lowers systolic BP, but it would be difficult to argue that inactivity is more effective than regular exercise in preventing the development of hypertension.

If the goal is to treat or prevent hypertension, then this question should be reframed as, “what are the after effects of obstructive apnea during sleep and therapeutic CPAP on BP
during wakefulness?" The first randomized trial of CPAP in OSA with sympathetic vasoconstrictor nerve traffic as its primary end point demonstrated a significant reduction during wakefulness in all of the treated subjects and a parallel decrease in concurrently measured systolic BP.7 Thus, an important after effect of OSA is its chronic facilitation of sympathetically mediated vasoconstriction during wakefulness.8 It is, therefore, noteworthy that the trial in which CPAP caused the greatest fall in systolic BP involved patients with OSA with advanced heart failure, individuals with the highest daytime sympathetic nerve traffic of all of those represented in this meta-analysis,8 and measured BP shortly after waking.9

The after effects of therapeutic CPAP are, therefore, critical to the authors’ conclusions, and here the data presented are ambiguous. In Figure 2 of Reference 3, they present mean net changes in systolic BP for 15 studies without indicating whether these represent daytime, nighttime, or 24-hour average measurements, yet their subgroup analyses according to acquisition time (Table 2 of Reference 3) reports changes in daytime systolic BP for only 9 trials. We, therefore, assume that their pooled data represent a combination of values obtained during wakefulness, sleep, or both. If so, these data do not reveal the actual after effects of CPAP. As well, none of the mean net reductions in daytime systolic, diastolic, or mean BP reported in Table 2 of Reference 3 were in and of themselves significant, a finding that at first glance appears to contradict both the authors’ first conclusion and also their speculation that CPAP might be a useful nonpharmacological method of preventing the development of hypertension. However, this apparent lack of efficacy is likely an issue of statistical power. Had the authors calculated mean arterial BP from systolic and diastolic changes provided (approximately −2.07 mm Hg) and added these data to those from trials that reported only mean BP, a significant reduction might well have emerged. On the other hand, the authors also inform us that, in subgroup analysis, the BP-lowering effects of therapeutic CPAP were restricted to trials in which sham CPAP was administered as control. Because sham CPAP is not inert and can raise BP,10 therapeutic CPAP may itself have no clinically relevant BP-lowering effect in a primarily nonhypertensive study population.

OSA might well be the most common cause of preventable and treatable secondary hypertension, but from the limited information available to and generated by this meta-analysis, it is premature to recommend, on the basis of level A evidence, therapeutic CPAP either for the specific treatment of hypertension or for its prevention in those at risk. The importance of the present statistical exercise is that it highlights the need for adequately powered, randomized, long-term clinical trials of therapeutic CPAP involving hypertensive and prehypertensive subjects.

An equally or more important long-term adverse hemodynamic consequence of OSA may be its effect on left-ventricular (LV) transmural pressure, a major component of afterload (Figure). The heart of a patient with OSA will be subjected to acute increases in LV transmural pressure several hundred times each night during 6 to 8 hours of sleep over many years.5 Abrupt increases in negative intrathoracic pressure induced by obstructive apneas have the potential to acutely trigger myocardial ischemia, atrial fibrillation, and ventricular arrhythmias, and over time impair tonic and reflex vagal heart rate modulation and stimulate sepsia and LV hypertrophy, ventricular remodeling, and thoracic aortic dilation. Therapeutic CPAP abolishes these negative intrathoracic pressure swings and reduces LV and intrathoracic aortic transmural pressures.6 In a heart failure cohort, 1 month of therapeutic CPAP reduced daytime sympathetic vasoconstrictor discharge7 and BP8 and improved LV systolic function.9 Thus, abolition of negative intrathoracic swings is a key mechanism by which treatment of OSA could reduce adverse stimuli to the heart and intrathoracic vessels, yet one that cannot be detected by systemic BP recordings. Accordingly, the very modest BP lowering reported by Bazzano et al11 may not be the only or even the most important beneficial effect on cardiovascular risk of treating OSA with CPAP.

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Disclosures
None.

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