

Sleep apnea causes daytime hypertension.

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Editorial

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Sleep predisposes to disordered breathing (SDB) across a broad continuum ranging from periodic episodes of transient hypoventilation to full-blown obstructive sleep apnea (OSA) syndrome with markedly impaired daytime functioning. A major cause of SDB is the sleep-induced reduction in tonic neural activity to muscles of the upper airway. Thus, in persons with already compromised airway structure, sleep and changing sleep states result in intermittent airway narrowing and often closure. These episodic ventilatory insufficiencies cause intermittent asphyxia, chemoreceptor stimulation, increased respiratory efforts, and transient arousals. Cardiovascular responses are analogous to a defense homeostatic response. Cardiac output and blood pressure decline slightly and then increase transiently upon termination of each event, and muscle sympathetic nerve activity (MSNA) increases during the apneas, peaks during the early recovery period, and then shuts off abruptly. The increased MSNA is due primarily to peripheral chemoreceptor stimulation, to cortical arousal, and their interaction. In turn, increased sympathetic nerve activity is obligatory to the acute pressor responses to apnea (1).

What are the long-term consequences of these recurring periods of cardiovascular stimulation that prevent much of the normal lowering effect of sleep on nocturnal blood pressure? Systemic hypertension and cardiovascular morbidity have been linked statistically to obstructive sleep apnea; however, it is difficult to prove these associations in cross-sectional studies because of the presence of common risk factors such as age, gender, obesity, and alcohol consumption.

In this issue of *The Journal*, Brooks and colleagues (2) provide the first prospective experimental evidence showing that severe obstructive sleep apnea produced experimentally in a unique canine model by repeated, intermittent tracheal occlusions for up to 14–16 h/d can lead to persistent daytime hypertension. These apneas increased average nighttime blood pressure $\sim 10\%$ above control and caused significant increases in daytime blood pressure which were apparent as early as 2 wk, peaked at 5 wk, and recovered to normal within 3 wk of return to uninterrupted sleep.

There are several additional findings in humans and other species which are consistent with the direct evidence of Brooks et al. (2) that sleep apnea and hypertension are causally related. Treatment of OSA in many (but not all) patients reduces daytime systemic blood pressure (3); and in a large cohort of undiagnosed human subjects a significant influence of SDB alone on daytime hypertension was shown statistically (4). Furthermore, weeks of episodic hypoxia in rats led to chronic systemic and pulmonary hypertension after the hypoxemia was removed (5). In the healthy human, systemic blood pressure rises during sojourn in the hypoxia of high altitude and remains elevated for several days upon return to sea level (6).

The mechanisms responsible for the conversion of the acute pressor responses to nocturnal apnea into persistent daytime hypertension have not been elucidated. Three possible triggers include arousal, hypoxic chemoreceptor stimulation, and negative intrathoracic pressure. Again, the Brooks et al. (2) study provides important information in this regard by showing that acoustically induced arousals and sleep discontinuity per se, sufficient to increase nighttime blood pressure to the same extent as the OSA protocol, did not cause the sustained increase in daytime blood pressure. These types of non-apneic arousals have also been shown to cause small transient increases in MSNA and blood pressure in sleeping humans (7). The effects of repeated long-term negative intrathoracic pressure swings alone have not been studied. However, acute production of negative intrathoracic pressure has been shown to reduce blood pressure and MSNA; furthermore, central apneas (i.e., without inspiratory effort) elicit increases in blood pressure and MSNA similar to those with obstructive apnea (1, 5, 7).

Long-term increases in daytime blood pressure appear to require hypoxia acting via increased carotid chemoreceptor stimulation of the sympathetic nervous system. Thus, after carotid chemoreceptor denervation or chemical sympathectomy, rats did not become hypertensive in long-term, intermittent hypoxia (5). In addition, human OSA patients with hypertension have elevated levels of MSNA and circulating catecholamines and augmented responses of blood pressure and ventilation to acute hypoxia; and their MSNA is reduced with treatment of OSA (8). In normal humans, a “carry-over” effect of hypoxia-induced increases in MSNA has been demonstrated in the persistently elevated levels of MSNA after 20 min of hypoxia (7). Long-term effects on blood pressure from a variety of chemical modulators of vasomotor activity have been suggested (8); however, the negative findings obtained by Brooks et al. (2) with acoustic arousals cast doubt on the popular premise that repetitive contraction/relaxation of vascular smooth muscle, per se, is the critical factor in the release of these mediators.

The Brooks et al. study (2) has shown that OSA can cause hypertension, but the converse may also be true. Transient elevations in systemic blood pressure have been shown to depress ventilation, to reduce EMG activity of the muscles of the upper airway, and to increase pharyngeal collapsibility; whereas sustained decreases in blood pressure stimulate ventilation (5). Furthermore, some types of OSA are ameliorated after treatment of high blood pressure (9). Thus, these findings raise the intriguing possibility that the acute and chronic hypertension caused by OSA can in turn exacerbate OSA. The two diseases may be linked via positive feedback.

Several important clinical considerations are forthcoming from the mounting evidence for a causal relationship between OSA and hypertension. The proposal of Brooks et al. (2) that, “. . . the possibility of OSA should be considered in all patients with hypertension,” should also include the specific aims: (a) to realize that the usual daytime screening indicating a borderline hypertension will often underestimate the actual level of hypertension and left ventricular afterload existent over 24 h; and (b) that the decision threshold for diagnostic sleep studies

should be lowered for the hypertensive patient (3). Secondly, while most of the focus is on the very severe forms of OSA (as produced by the dog model), more moderate levels of SDB occur in a significant portion of the undiagnosed population. These events also elicit acute pressor responses and contribute independently of other risk factors to relatively small but significant daytime elevations in blood pressure (4). Accordingly, we need to define the levels of SDB that are truly significant pathophysiologically and determine the effects of early intervention. Finally, it is worth remembering that hypertension is one of the strongest predictors of cardiovascular disease morbidity and mortality. In light of the clear demonstration of a causal relationship between OSA and hypertension, accumulating evidence that cardiac failure, arrhythmias, stroke, and myocardial infarction are more common in OSA patients should receive more attention.

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