Does the Altered Cardiovascular Variability Associated With Obstructive Sleep Apnea Contribute to Development of Cardiovascular Disease in Patients With Obstructive Sleep Apnea Syndrome?

To the Editor:

In a recent issue of Circulation, Narkiewicz et al1 demonstrated that cardiovascular variability is altered in patients with obstructive sleep apnea (OSA). The authors concluded that abnormalities in cardiovascular variability might be implicated in the subsequent development of overt cardiovascular disease in patients with OSA. We basically agree with the authors that patients with OSA in the absence of hypertension (HT) or heart failure have an altered cardiovascular variability. However, the role of altered cardiovascular variability in the development of cardiovascular disease has not been determined. Although an association of OSA with HT has been documented, this association may also be affected by confounding factors such as age and obesity, which commonly occur along with both OSA and HT.2–4 Because OSA is associated with repetitive arousals, hypoxia, and a rise in catecholamine and sympathetic nervous system activity, all of which can lead to HT, there is no doubt that OSA is a risk factor for HT and other cardiovascular diseases.2 A recent experimental study also suggests that apnea, but not hypoxia or arousal, is responsible for the development of HT.3 However, similar conditions have also been observed in patients who snore in the absence of OSA, ie, upper-airway resistance syndrome (UARS).

Thus, although there is a significant link between OSA and the altered cardiovascular variability, the association between OSA/UARS and HT/cardiovascular disease may depend on repetitive arousals, repetitive hypoxia, and increased sympathetic nervous system activity rather than the impaired cardiovascular variability.2–4 Furthermore, it has been reported that treatment of OSA with prosthetic mandibular advancement does not yield changes in the frequencies of heart rate variability, such as high-, low-, and ultra-low-frequency component values.5 Because the treatment of OSA with nasal continuous positive airway pressure reverses HT,6 it is evident in time domain analysis, showing reduced RR variability and increased blood pressure variability in sleep apnea. Teramoto et al focus exclusively on variability measurements in the frequency domain. Fifth, Teramoto et al make the categorical but unreferenced assertion that “the treatment of OSA with nasal continuous positive airway pressure reverses HT.” This is at odds with a number of actual studies that do not demonstrate reversal of hypertension after continuous positive airway pressure (CPAP).5,6 The effects of nasal CPAP on blood pressure are hence less clear than Teramoto et al would have us believe. Last, our studies were conducted exclusively in normotensive sleep apneic patients. Extrapolations from studies of hypertensive patients are, at best, only indirectly relevant.

Sleep apnea patients had markedly decreased RR variability and increased blood pressure variability. These variability abnormalities characterize patients with hypertension, but in our study they were manifest in normotensive sleep apneics. Thus, our findings suggest a potential link between normotensive sleep apnea, abnormalities in cardiovascular variability, and hypertension. We state clearly that we “speculate [emphasis added] that abnormalities in cardiovascular variability may precede, and possibly predispose to, the development of hypertension in patients with sleep apnea.”

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Response

We appreciate the interest of Teramoto et al in our work. It is important, however, to correct the record on several issues they address. First, Teramoto et al erroneously conclude from the study by Brooks et al1 “that apnea, but not hypoxia or arousal, is responsible for the development of HT [hypertension].” For technical reasons, oxygen saturation was not measured in the first study by Brooks et al. However, in a subsequent study in the same animals,7 apneas similar to those induced in the first study elicited significant decreases in oxygen saturation. Thus, hypoxia would likely be a key contributor to apnea-related increased blood pressures. Second, Teramoto et al suggest that “a direct causal relationship between altered cardiovascular variability and cardiovascular disease may not exist.” They base this statement on their assertion that treatment of OSA does not change measurements of heart rate variability but reverses hypertension. A fatal problem in their reasoning is that they ignore one of the key measures in their equation, namely, blood pressure. While it is true that Shiomi et al6 did not detect changes in heart rate variability measurements, they also did not detect changes in blood pressure. While we fully accept, now and in our original article, that their underlying premise may be true, their reasoning contradicts rather than supports their premise. Third, Teramoto et al refer to “change in the frequencies of heart rate variability.” We remind them that the article they cite7 focuses on changes in power for a given frequency band rather than changes in the frequency itself. Fourth, the most compelling of our findings was evident in time domain analysis, showing reduced RR variability and increased blood pressure variability in sleep apnea. Teramoto et al focus exclusively on variability measurements in the frequency domain. Fifth, Teramoto et al make the categorical but unreferenced assertion that “the treatment of OSA with nasal continuous positive airway pressure reverses HT.” This is at odds with a number of actual studies that do not demonstrate reversal of hypertension after continuous positive airway pressure (CPAP).5,6 The effects of nasal CPAP on blood pressure are hence less clear than Teramoto et al would have us believe. Last, our studies were conducted exclusively in normotensive sleep apneic patients. Extrapolations from studies of hypertensive patients are, at best, only indirectly relevant.

Chronic sleep apnea patients had markedly decreased RR variability and increased blood pressure variability. These variability abnormalities characterize patients with hypertension, but it is not clear if these abnormalities exist in normotensive sleep apneics. Thus, our findings suggest a potential link between normotensive sleep apnea, abnormalities in cardiovascular variability, and hypertension. We state clearly that we “speculate [emphasis added] that abnormalities in cardiovascular variability may precede, and possibly predispose to, the development of hypertension in patients with sleep apnea.”

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_Circulation_. 1999;100:e136-e137
doi: 10.1161/01.CIR.100.25.e136

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/100/25/e136

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