Stressful Sleeping*

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Over the past 15 years, the association of sleep apnea and serious medical consequences has slowly entered mainstream medicine. From a noisy and almost comical condition to one that is now recognized to be associated with serious morbidity and mortality, investigators around the world are studying the complex relationships between sleep and the neurologic, pulmonary, endocrine, and cardiovascular systems. As the evidence has mounted, screening and treatment of sleep apnea has been incorporated into clinical practice guidelines and reports for several serious medical conditions including, among others, hypertension (Joint National Committee 7) (1), heart failure (American College of Cardiology/American Heart Association [ACC/AHA]) (2), pulmonary arterial hypertension (ACC/AHA) (3), and type 2 diabetes mellitus (International Diabetes Federation) (4). This effort has culminated in an ACC/AHA scientific statement focused exclusively on sleep apnea and cardiovascular disease. This statement reviews the known mechanisms as well as the association of various forms of sleep apnea with hypertension, heart failure, stroke, arrhythmias, myocardial infarction and ischemia, pulmonary arterial hypertension, and end-stage renal disease. It concludes with a call for more study to understand mechanisms, associations, and the impact of treatment of sleep apnea on patients with and at risk for cardiovascular disease (5).

Unfortunately, studying sleep apnea in clinical populations is a significant challenge. Obstructive sleep apnea is associated with obesity, which can mask the impact of sleep apnea on risk factors and cardiovascular disease. In addition, sleep apnea is associated with multiple comorbidities, including cardiovascular disease, diabetes, and the metabolic syndrome. Central sleep apnea is associated with the presence of heart failure and stroke. Establishing causality or even which condition came first can be elusive, requiring large populations followed up over long periods of time. It is for this reason that studies focusing on pathophysiology may help to unravel the connections and better inform the development of clinical trials.

Sleep apnea occurs primarily in 2 forms: obstructive and central. Obstructive sleep apnea results from a complete or partial collapse of the pharynx leading to respiratory effort but no airflow into the lungs (6). Central sleep apnea results from a lack of neurologic respiratory drive leading to no respiratory effort and no airflow into the lungs (7). Further complicating study in this area is that many persons display mixed apneas, having some features of both forms, and others may switch from one form of sleep apnea to another.

Heart failure, both systolic and with preserved left ventricular function, is associated with sleep apnea. Several studies have estimated that the presence of obstructive sleep apnea ranged from 11% to 37%, and central sleep apnea may be present in as many as 40% of patients with systolic heart failure (5). These findings suggest a large population at risk and a huge potential public health benefit from treating sleep apnea if treatment is shown to improve clinical outcomes.

The paper by Gottlieb et al. (8) in this issue of the Journal describes the relationship between sleep apnea and brain (B-type) natriuretic peptide (BNP) in subjects with symptomatic systolic heart failure. The population of subjects included some with obstructive sleep apnea and others with central sleep apnea. The subjects were very well treated, receiving guideline-mandated pharmacologic therapies for their systolic heart failure, with nearly everyone on both a beta-blocker and angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker. The investigators frequently measured serum BNP and correlated these measurements with measured variables during a series of overnight sleep studies.

It has been shown in both humans and animal models that obstructive sleep apnea has a significant hemodynamic impact on the heart. During an obstructive apnea event, there is inspiratory effort against the closed airway. This causes changes in intrathoracic pressure that increases left ventricular afterload, which in theory would cause increases in myocardial pressure. Simultaneously, there are surges of adrenergic activity that increase heart rate and blood pressure and may also be responsible for increased inflammatory markers. In this setting of increased afterload and adrenergic overdrive, one would expect an increase in the release of BNP (5,9). On the contrary, during a central apnea, there is no inspiratory effort and there are limited changes in

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intrathoracic pressure, although there is also a significant increase in adrenergic activity (10). In this instance, one might hypothesize that BNP levels would not change, especially if the pathway was due to the mechanical impact of pressure and volume changes in the left ventricle.

The surprising result of this investigation (8) is that instead of being correlated with mechanical events, serum BNP levels were associated with hypoxia. This finding was further validated by comparing the group of subjects with obstructive apnea against those with central apnea. In both instances, BNP correlated with hypoxia but not with the mechanical hemodynamic consequences of airway obstruction. One unifying hypothesis is that the adrenergic surges seen in both obstructive and central sleep apnea can acutely cause mechanical or neurohormonal changes leading to increased BNP levels. In this investigation, BNP levels rose despite all of the subjects being administered a beta-blocker, implying that this hypothesis may be incorrect or that beta-blockers at clinical doses are ineffective at blunting the impact of these adrenergic surges. Unfortunately, the administration of nocturnal oxygen in this study did not appear to change BNP levels, but the number of subjects evaluated was small and the population was heterogeneous.

Perhaps the most important result from this study by Gottlieb et al. (8) is the direct correlation between changes in serum BNP, a potent prognostic marker in heart failure, and hypoxia in sleep apnea. This finding should add to the evidence that sleep apnea in any form is a reasonable therapeutic target to potentially improve outcomes in people with systolic heart failure. In addition, this study suggests that beta-blockers are not completely able to protect against the impact of sleep apnea on the cardiovascular system and that more complex mechanisms may be responsible for the clinical consequences of the combination of heart failure and sleep apnea.

There is unequivocal evidence linking sleep apnea to cardiovascular disease and other chronic illnesses (5). The current investigation (8) highlights the importance of mechanistic studies to help inform the development of clinical trials in the growing population of people with sleep apnea. Assuming the results can be replicated, a potential target for treatment would be nocturnal hypoxia. In addition, differentiating between central or obstructive sleep apnea may be less important, but rather the presence of hypoxia may be enough to warrant treatment. The diagnosis and treatment of sleep apnea in any form can be challenging, but well-educated and energized clinicians can motivate patients to be successful. It is clear that large-scale multicenter clinical outcome trials evaluating sleep apnea treatments for patients with heart failure treated with modern therapies are critical to define the appropriate interventions needed to address this potential therapeutic target.

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