

EDITORIAL COMMENT

Treating Sleep Apnea in Heart Failure Patients

Promises But Still No Prizes*

Virend K. Somers, MD, PhD, FACC,
Apoor S. Gami, MD, Lyle J. Olson, MD, FACC
Rochester, Minnesota

In North American and Western European middle-age populations, the prevalence of obstructive sleep apnea (OSA), as defined by the American Academy of Sleep Medicine, is as high as 20% (1). The majority of individuals with OSA remain undiagnosed, and OSA and heart failure (HF) often coexist (2,3). They share numerous risk factors and pathophysiologic mechanisms, which together may contribute to HF progression or refractoriness to therapy. Moreover, OSA is regarded as the most common secondary and treatable cause of systemic hypertension (4). It is conceivable that OSA, acting in part through increases in blood pressure (BP), may be the primary cause of HF in some individuals. The prevalence and coexistence of both conditions will increase as the obesity epidemic continues, and it is important to clarify how OSA might contribute to the promotion or progression of HF and its associated morbidity, which remains unacceptably high.

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Sympathetic activation is characteristic of HF and is associated with disease progression and adverse prognosis (5). Therapies that attenuate sympathetic activity improve HF outcomes (5). Obstructive sleep apnea, independent of obesity and comorbid states, is characterized by sympathetic activation, tachycardia, impaired cardiovascular variability, endothelial dysfunction, and systemic inflammation (6). These homeostatic disruptions are present even in OSA patients who are awake, normoxic, and free of detectable cardiovascular disease. They are especially evident in patients with HF, for whom the disruptions may have prognostic significance. Neural and vascular dysregulation in awake, apparently healthy OSA patients led us to propose the concept that repetitive

nocturnal hypoxemia occurring during OSA may activate compensatory and/or cardiovascular disease mechanisms that carry over into the daytime (7), and that this daytime carryover effect may be attenuated by nocturnal continuous positive airway pressure (CPAP) (8).

In this issue of the *Journal*, Usui et al. (9) explore whether this concept holds true for sympathetic activation in patients with HF. They present data for eight patients with moderate to severe OSA and stable HF who were randomized to CPAP, compared to nine OSA and HF patients who received no OSA therapy. At one month, the investigators found that muscle sympathetic nerve activity (MSNA), BP, and heart rate—all measured for 15 min upon awakening—were decreased in patients who received CPAP. Although the decline in sympathetic burst frequency was modest, it nevertheless occurred with decreases in BP, which itself would be expected to raise sympathetic drive. Furthermore, the decreases in heart rate suggest that the fall in sympathetic activity with CPAP affects not only peripheral vascular sympathetic activity but also cardiac sympathetic drive.

The demonstration that CPAP significantly decreased sympathetic neural activation in patients with congestive heart failure (CHF) and OSA while awake implies that untreated OSA in such individuals may be as harmful as suboptimal treatment with beta-blockers. It is also possible that the decreases in sympathetic activation may be even greater during sleep, because nocturnal apneas and hypoxia greatly augment sympathetic activity (7) and a response to CPAP would be most marked during the night. It might also be expected that CPAP would not only attenuate sympathetic activation, but also lead to improved cardiac function. Small randomized, controlled trials (10,11) have demonstrated that patients with CHF and OSA who were provided CPAP for one to three months experienced increases of left ventricular ejection fraction similar to or higher than might be expected with pharmacologic intervention over the same time periods.

These data have clear relevance to the care of HF patients—a population with limited functional reserve and in whom interventions (both favorable and adverse) can quickly and significantly impact morbidity and mortality. However, although a non-pharmacologic approach, such as CPAP, for reducing BP, heart rate, and sympathetic activity, would also be an exciting potential strategy for reducing CHF morbidity and mortality, several considerations should temper our enthusiasm until more data are available.

First, in this relatively small group of subjects (only eight patients received intervention), the drop in sympathetic activity was measured only for 15 min in the morning after waking. Whether attenuation of sympathetic activity in HF patients persists for the remainder of the day remains to be established. This distinction is important, because sympathetic activity likely exerts its pathophysiologic effects on HF throughout the day.

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota. The authors are supported by NIH grants HL61560, HL65176, HL73211, and M01-RR00585, and the Mayo Clinic College of Medicine. Dr. Olson's funding sources: NIH-R01 HL71478; AHA 04-50103Z; Medtronic; NIH-HL63747-01A2. Dr. Somers funding sources: NIH-R01 HL/NS70302-01; NIH-R01 HL73211; NIH-R01 HL65176-05; M01-RR00585; consultant: Respironics.

Second, whereas a randomized design is reported as a salient aspect of this study, the researchers present data only for patients with adequate MSNA recordings at both time points. Not reported are how many patients initially underwent randomization and whether assessments of MSNA recording quality (and thus patient inclusion or exclusion from the statistical analysis) were made systematically and in a blinded fashion. This approach detracts from the randomized design of the study and also, with the small number of selected patients, from the reliability of the results.

Third, criteria for subject selection deserve comment. Although Usui et al. (9) report that subjects had been on optimal pharmacotherapy at highest tolerated dose for three months before enrollment, the subjects actually had suboptimally controlled BP. The subjects in the control group were hypertensive (mean systolic BP 141 mm Hg), and those in the CPAP group had a mean systolic BP (135 mm Hg) that is not typical of well-treated HF patients. As a comparison, the mean systolic BP of participants in the Carvedilol Or Metoprolol European Trial (COMET) prior to receiving beta-blocker therapy was 126 mm Hg and decreased further with therapy (12). Also, the resting heart rates in both groups were higher than that which is encouraged and often achievable with optimal beta-blockade in HF patients. In patients with OSA without HF, treatment with CPAP consistently has been demonstrated to lower daytime BP, primarily in hypertensive patients but not normotensive individuals (13). Thus, the CPAP treatment effect in the study by Usui et al. (9) may very well be due to comorbid hypertension in their HF study sample. It would be necessary to study patients who are truly receiving optimal pharmacotherapy, with normal BP levels and controlled heart rates, to identify the adjuvant therapeutic effects of CPAP on HF per se.

Fourth, no specific data are provided regarding beta-blocker use for the two treatment groups. Knowing about concomitant therapies is relevant because, as noted in work by the same laboratory (14), beta blockers in CHF would be expected to directly affect the primary outcome of the study (i.e., sympathetic burst activity) as would digitalis. It also would be useful to know whether patients who were treated with CPAP were more likely to be on different doses or types of beta blockers, because the pharmacologic properties of various beta blockers differentially affect muscle sympathetic nerve activity (15).

Finally, whether surrogate end points, such as changes in peripheral sympathetic nerve traffic, translate into improvements in important cardiovascular outcomes remains unknown. Also not known is whether OSA adversely affects mortality of HF patients (16). While treatment with CPAP in HF patients is often systematically beneficial and well received by patients, some data suggest that it is not always necessarily benign (17,18). These issues speak to the need for carefully designed, adequately powered, randomized trials of sufficient duration to clarify the effects of CPAP

therapy on important outcomes in patients with OSA and HF.

Nevertheless, although preliminary, the findings of Usui et al. (9) are of interest and raise a number of important questions. They add to our growing understanding of the mechanisms by which OSA may contribute to (and its therapy may prevent) HF progression and adverse outcomes. Their work provides impetus for development of larger, more definitive studies that address the efficacy and benefit of CPAP in the management of HF with coexistent OSA.

Reprint requests and correspondence: Dr. Virend K. Somers, Mayo Clinic, Rochester, Internal Medicine, St. Mary's Hospital, DO-4-350, 1216 Second Street SW, Rochester, Minnesota 55902. E-mail address: somers.virend@mayo.edu.

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