EDITORIAL COMMENT

Does What Happens During Sleep Matter for the Failing Heart?*

Martin R. Cowie, MD, MSc

In this issue of JACC: Heart Failure, Arzt et al. (1) describe the prevalence of sleep-disordered breathing (SDB) in a registry of more than 6,800 patients with chronic stable systolic heart failure (HF) (heart failure with reduced ejection fraction [HFREF]) in Germany. Breathing is moderately or severely abnormal during sleep (apnea-hypopnea index $>15$) in almost one-half of such patients. Importantly, the patients are less selected than in previous reports, being recruited from a wide variety of cardiology practices, and were treated to current guidelines—with high usage of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and aldosterone antagonists.

Which patients appear to be at highest risk of developing SDB? They report independent effects of increasing age, being male (almost twice the risk of females), and increased body mass index. The risk is 19% higher in those with atrial fibrillation, and goes up by 10% for every 5% drop in left ventricular ejection fraction. If we are screening for SDB (which is straightforward to do with modern technology), we know where to look hardest. It will be interesting to see whether these risk factors are the same for both obstructive (OSA) and central (CSA) sleep apnea, and whether both phenotypes are independently associated with mortality, in future reports from this registry.

The therapeutic objectives in the treatment of SDB can vary. If a patient has daytime somnolence due to OSA, then treatment with positive airway pressure (such as continuous positive airway pressure [CPAP] therapy via a mask or nasal pillow) may improve symptoms, quality of life, and increase (driving) safety. HF patients are much less likely to be sleepy even if they have moderate or severe SDB (2), perhaps related to increased sympathetic activation. So, the main objectives in treating SDB in HF are likely to be to slow the progression of disease, reduce the need for hospitalization, and increase the length or quality of life. The evidence for this, until recently, has largely been confined to observational data or small, short-term randomized trials with surrogate endpoints such as ejection fraction, plasma B-type natriuretic peptide concentration, and quality-of-life assessments.

The CANPAP (Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial), published 10 years ago, was the first larger randomized trial to assess the effect of treating CSA in systolic HF (3). Recruitment proved challenging, and it was stopped early for a number of reasons after randomizing only 258 patients. The intention-to-treat analysis showed no difference in the survival rate without heart transplantation but a post hoc analysis suggested that if the SDB could be controlled (Apnea-Hypopnea Index [AHI] $<15$) then there was a low risk of death (4). For some this was sufficient evidence to start treating CSA in HFREF, although this was not endorsed in international HF guidelines.

Technology moves on apace, and a more intelligent form of positive airway pressure support, servo-assisted ventilation (ASV) was developed, which adjusts pressure support to the patient’s breathing pattern. This can very effectively control CSA (as well as OSA) (5). ASV was thus an obvious candidate for robust assessment in a large randomized trial with the...
hard endpoints of mortality and HF hospitalization. This trial—SERVE-HF (Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure)—has been recently reported (6). The results took everyone by surprise. Despite good control of the CSA, and reasonable long-term compliance with the therapy, there was no difference in the primary combined endpoint of mortality, life-saving cardiovascular intervention or hospitalization for worsening HF. However, cardiovascular, and total, mortality were significantly increased (hazard ratio: 1.34 [p = 0.006] and 1.28 [p = 0.01], respectively), and this effect appeared early and continued throughout the trial. There was no increase in HF hospitalizations, or deaths from progressive pump failure, but there was a substantial increase in the risk of deaths occurring without a preceding hospitalization—presumably related to sudden (cardiac) death. Such a mechanism of harm was supported by the risk being substantially reduced—although not absent—in those with an implanted defibrillator. Further, more detailed analyses are awaited.

Why should effective treatment of a clearly abnormal physiology (SDB) that is associated with increased risk be associated with increased mortality? Chance appears an unlikely explanation, although the results of another randomized trial, the ADVENT-HF trial (Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure), recruiting HFREF patients with either predominantly central or predominantly obstructive SDB, may be able to provide more data in due course (NCT01128816). Could pressure support per se be harmful in patients with stable chronic systolic HF? Although possible, we know that such treatment in the acute phase of HF (with CPAP) is not harmful overall (7), although the effect may be deleterious in patients with very poor systolic function and intravascular volume depletion. However, subgroup analyses of the SERVE-HF data do not support such an explanation. Perhaps CSA, and particularly Cheyne-Stokes Respiration (CSR), is (at least to some degree) adaptive in systolic HF. This has been suggested previously (8). Certainly, in SERVE-HF, the increased mortality was greater in those with more marked CSR. More detailed analyses of sleep parameters in the SERVE-HF substudy may provide further clues.

If CSR is indeed at least partially adaptive, and acts to reduce the risk of (sudden) death, then other technologies targeting CSR specifically may also run into problems. One such technology is phrenic nerve stimulation using an implantable technology. A pilot study has reported (9), and a larger study with respiratory endpoints has completed recruitment, but is underpowered to exclude a harmful effect on mortality (NCT01816776). Interestingly, not all of the patients enrolled in this trial have HF as the trigger for their CSA.

What about OSA in systolic HF? SERVE-HF did not enroll such patients. The current evidence base is not strong—being limited to registry data and small short-term trials in selected populations (10). Lack of daytime sleepiness reduces the therapeutic imperative to intervene. However, the hemodynamic effects of OSA are much more marked than that of CSA, and it may well be that intervention to control OSA long term may improve outcomes for such patients—the ADVENT-HF trial will address this issue.

What about acute decompensated HF? A large randomized trial of a systematic strategy of using CPAP therapy in acute pulmonary edema did not show any hard outcome benefit (7), but in clinical practice it is used for those who are becoming hypoxemic or acidicemic, or tired. Whether assessing SDB in such patients in the acute phase (before discharge from hospital) is helpful is unknown, but we know from SERVE-HF that once they have stabilized and are on good HF treatment, targeting those with predominantly CSA with ASV does not improve outcome, and may increase mortality.

So, is SDB merely a bystander comorbidity common in patients with HFREF? Is it an epiphenomenon that should only be treated for those with OSA and symp-toms directly related to that? How safe is such therapy? And what do the results of randomized hard outcome studies tell us, not only about appropriate therapy, but also about the underlying pathophysiology? Once again, HF has proven itself more complex than we thought.

Using surrogate outcomes, or the results of observational data, are not a reliable way to build the evidence base in HF. The difficulty, and expense, of conducting large outcome studies is very high—but appears to be the necessary hurdle to safely change practice. Further dialogue between the key stakeholders (patients, cardiologists and sleep/respiratory physicians, trialists, regulators, reimbursement authorities, and industry) is essential to navigate a safe and worthwhile route forward.

Arzt et al. (1) should be congratulated for showing us that SDB is very common in our HF patients. What this means for them, and for the cardiologists optimizing their therapy, remains to be seen.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Martin R. Cowie, Clinical Cardiology, National Heart and Lung Institute, Imperial College London, Dovehouse Street, London SW3 6LY, United Kingdom. E-mail: m.cowie@imperial.ac.uk.
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