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EDITORIAL COMMENT

Central Sleep Apnea in Heart Failure

Sleeping With the Wrong Enemy?*

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Sleep-disordered breathing (SDB) is very common in patients with heart failure (HF), even on optimal medical therapy, and is associated with a poor prognosis and worse functional class (1). SDB encompasses 2 disorders, obstructive (OSA) and central sleep apnea (CSA), and most HF patients have both. Important associated mechanistic links to HF include sympathetic activation, increased afterload, and recurrent hypoxemias. The targeted treatment of SDB in HF is based upon the independent association of SDB to HF outcomes, that is, a risk factor rather than just a risk marker (2,3). However, the evidence that treatment of SDB to improve HF or cardiovascular disease outcomes is predominantly observational and limited to particular cohorts. Prospective randomized studies have yet to support this hypothesis. For example, in the recent randomized SAVE (Sleep Apnea Cardiovascular Endpoints) trial, continuous positive airway pressure (CPAP) failed to improve cardiovascular outcomes in patients with moderate to severe OSA and cardiovascular or cerebrovascular disease (4).

To date, 2 prospective randomized trials of CSA in HF have been completed. In 2005, the CANPAP (Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure) trial (5) was the first randomized study to specifically target patients with predominantly CSA rather than OSA. This trial randomized 258 stable ambulatory HF with reduced ejection fraction (HFrEF) (left ventricular ejection fraction [EF] <40%) patients with severe CSA (apnea-hypopnea index [AHI] 40) to CPAP without a sham control. The study was terminated early due to an early trend in transplant-free survival favoring the control group, unanticipated low event rates, and slow enrollment. Although some surrogate endpoints were improved (e.g., EF, 6-min walk, and norepinephrine levels), there was no benefit to overall transplant-free survival.

A decade later, the SERVE-HF (Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure) trial extended these observations by using adaptive servo-ventilation (ASV), a synchronized form of positive pressure ventilation that decreases central apneas to a greater extent than CPAP (6). In the SERVE-HF trial, 1,325 chronic ambulatory HFrEF patients with predominantly CSA were randomized to ASV (AutoSet, ResMed) in addition to optimal medical therapy. Despite a clear reduction in AHI (e.g., 31.2/h to 6.6/h at 12 months), the primary endpoint of time to all-cause death, life-saving cardiovascular intervention, or HF hospitalization was not met (ASV vs. control 54.1% vs. 50.8%; hazard ratio [HR]: 1.13; 95% confidence interval [CI]: 0.97 to 1.31; p = 0.10). Importantly, all-cause (HR: 1.28; 95% CI: 1.06 to 1.55; p = 0.01) and cardiovascular mortality (HR: 1.34; 95% CI: 1.09 to 1.65; p = 0.006) were significantly higher in ASV group.

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It is with this background that, in this issue of the *Journal*, O'Connor et al. (7) now add their report of the CAT-HF (Cardiovascular Outcomes With Minute Ventilation Targeted Adaptive Servo-Ventilation Therapy in Heart Failure) trial, which evaluated the effects of ASV (ApneaLink Plus, ResMed, San Diego, California) added to optimal medical therapy on outcomes in patients *hospitalized* for HF with moderate-to-severe sleep apnea (AHI >15, predominantly CSA)

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FIGURE 1 Selected Randomized Trials of Treatment for Central Sleep Apnea in Heart Failure

Trial	#pts	LVEF	Intervention	Baseline AHI	F/u AHI	Primary Outcome	Comments
CANPAP 2005	258	25%	CPAP	40	19	Neutral	Suspended
SERVE-HF 2015	1325	32%	ASV	31.2	6.6	Neutral	↑CV and all-cause mortality
CAT-HF 2017	126 (hosp)	32%	ASV	35.7	2.1	Neutral	Suspended
ADVENT-HF 2018*	850	<45%	ASV	AHI >15	TBD	TBD	In progress

*In progress. ADVENT-HF = Effect of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure; AHI = apnea-hypopnea index; CAT-HF = Cardiovascular Outcomes With Minute Ventilation Targeted Adaptive Servo-Ventilation Therapy in Heart Failure; CANPAP = Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure; CV = cardiovascular; F/u = follow-up; LVEF = left ventricular ejection fraction; SERVE-HF = Treatment of Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients With Heart Failure; TBD = to be determined.

regardless of ejection fraction. The trial was suspended after 126 of an intended 215 patients were randomized in light of the SERVE-HF trial results. Despite falling short of the 3-h target for ASV support, the AHI fell dramatically (mean AHI 35.7/h to 2.1/h vs. 35.1/h to 19.0/h) at 6 months compared with controls. However, there was no significant difference between groups in the primary composite endpoint of death, cardiovascular hospitalizations, or percent change in 6-min walk distance. There were also no differences in secondary endpoints (cardiovascular hospitalizations, cardiovascular mortality, all-cause mortality, number of days alive or out of hospital, biomarkers, daytime sleepiness, echocardiographic parameters, and general quality of life). The authors did highlight 24 patients with HFpEF who improved their 5-min walk times and experienced decreased hospitalizations, but the CIs were wide.

Notable limitations of trial acknowledged by the authors include small sample size, early termination of the study, decreased adherence to the therapy, lack of blinding, and the presence of both CSA and OSA (although predominantly CSA) in most patients. The generalizability is also questionable; almost 10,000 patients were assessed for eligibility. So what went wrong?

The most obvious concern is the early study termination. Sponsors, investigators, and monitoring boards have a tremendous responsibility in this regard and continuously track multiple issues. In the case of CAT-HF, the authors note in the supplement that 3 issues were considered: overlapping treatment periods with the SERVE-HF trial, an adverse effect was not likely detectable with the small sample size, and the trial intent as a Phase II, not Phase III, study. Although no adverse safety signal was noted by the monitoring board in this trial, the data from the SERVE-HF trial were compelling. Many are likely to challenge the decision, particularly in regard to the populations studied (HFrEF vs. all HF) and when they were enrolled (ambulatory vs. hospitalized).

The CAT-HF trial was designed to study the impact of ASV on hospitalized HF patients with CSA, in contrast to SERVE-HF, which enrolled stable ambulatory HFrEF patients. However, the inclusion criteria would place CAT-HF patients in the treatment period of the SERVE-HF protocol, which could begin as early as 4 weeks following a HF admission (although with ASV initiated as an inpatient rather than as an outpatient). Treatment of CSA initiated during HF hospitalization and extending into the early post-discharge period would have to significantly attenuate the SERVE-HF treatment mortality risk to justify continuation of the study. To date, few interventions, if any, have had such a mortality impact. Moreover, the neutral CAT-HF outcomes were associated with wide confidence intervals that could include harm.

Is targeting CSA distinct from OSA worthwhile (8,9)? Both are common in patients with HF and associated with increased adrenergic activity as well as increased inspiratory transmural wall stress (due to the large negative intrapleural pressures needed to ventilate

stiff, wet lungs with or without an obstructed upper airway). However, OSA is a comorbidity to HF and commonly occurs independent of HF; CSA is a consequence of HF and is uncommon in the absence of underlying disorders. In fact, risk factors for OSA (e.g., obesity) substantially differ from CSA (e.g., male sex, advanced age, atrial fibrillation, and hypocapnia). Finally, central apneas are mechanistically distinct from obstructive apneas. OSA results from pharyngeal obstruction of airflow from a combination of factors, including anatomically narrowed airways, decreased pharyngeal muscle tone, and changes in ventilatory control leading to ineffective respiratory efforts. CPAP in this regard addresses the fundamental disorder of obstruction without a signal for harm.

By contrast, CSA is more complex. It is an oscillation between apneas and hyperpneas that is set up by low arterial carbon dioxide tension that is "overcompensated" by an apnea from a hypersensitive respiratory control center. The resulting increase in tension from the apnea then stimulates a hyperpnea from the hypersensitive control center, leading to hypocapnia that perpetuates the cycle. This overshoot can be exacerbated by a prolonged circulation time, which delays the detection of the changing CO_2 tension by the respiratory control center and places the respiratory response out of phase with the CO_2 tension. Inhaled CO_2, CPAP, and oxygen all attenuate CSA (presumably by decreasing the hypocapnia), but not by directly addressing the perturbed central control of respiration in CSA. Furthermore, the changes in central respiratory control may be compensatory. As outlined by Naughton (10), CSA may be protective in HFrEF through increased end-expiratory lung volumes, intrinsic positive airway pressure, improved vagal tone, rest of fatigued respiratory muscles, and prevention of respiratory acidosis.

Where do we go from here? Although the publication of this suspended trial provides incremental information about the relationship between CSA and HF, the limitations of this small study significantly restrict potential conclusions. The observed benefits of ASV for HFpEF patients is interesting, but a subgroup involving 24 patients in a trial with neutral findings is at best hypothesis generating. More importantly, despite differences in the CSA in HF trials to date, the totality of the current evidence reasonably calls into question the specific treatment of CSA in HF as a routine practice (**Figure 1**). Other approaches with different devices and strategies, for example, BiPAP autoSV Advanced ASV (Respironics) (ADVENT-HF [Effect of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure]; NCT01128816), phrenic nerve stimulation (2), and supplemental nasal cannula oxygen (11), are actively being pursued by seasoned investigators who are particularly vigilant of these issues. Getting these trials completed is an imperative.

We have been here before. Many will recall the broad enthusiasm for suppressing premature ventricular beats in the CAST trial (Cardiac Arrhythmia Suppression Trial) (12) to prevent sudden cardiac death, surgical ventricular remodeling in STICH (Surgical Treatment for Ischemic Heart Failure-Surgical Ventricular Reconstruction)-Hypothesis 2 (13) to slow HF progression, and lowering filling pressures in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial (14) to improve survival in acute decompensated HF. Although the associative and putative mechanistic links were strong, the outcomes of these prospective randomized trials were either neutral or even harmful; but these trials were necessary and informed later studies (e.g., CHAMPION [CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients] trial). In the meantime, providers should not forget that the most urgent therapeutic intervention to make in patients with heart failure and SDB is to optimize guideline-directed therapy and encourage lifestyle changes. When central sleep apnea complicates HF, it would appear the real enemy is the HF.

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