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Treatment of Central Sleep Apnea with Adaptive Servoventilation in Chronic Heart Failure

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Treatment of Central Sleep Apnea with Adaptive Servoventilation in Chronic Heart Failure

Patients with chronic heart failure and systolic dysfunction are at increased risk of having central sleep apnea (CSA) and Cheyne-Stokes respiration, which are associated with hypoxemia, sleep fragmentation, and mortality (1). Positive pressure devices (adaptive servoventilation or autoservoventilation [ASV]) have been designed to treat CSA and are often used in this patient population. These devices provide ventilatory support during periods of central apneas and hypopneas. ASV has been shown to be effective in improving sleep apnea severity, sleep quality, and cardiac function in short-term clinical trials (2). Given these short-term benefits, long-term treatment was hypothesized to result in improvements in robust clinical endpoints in patients with CHF.

The SERVE-HF study was designed to address this hypothesis. The rationale and design of this study are described elsewhere (3, ClinicalTrials.gov NCT00733343). In brief, patients with chronic (>12 wk) symptomatic heart failure (New York Heart Association Class III or IV at enrollment, or II with at least one hospitalization for CHF in the last 24 mo) due to systolic dysfunction (left ventricular ejection fraction ⩽ 45%) with primarily central sleep apnea (central apnea–hypopnea index ⩾ 10/h, apnea–hypopnea index ⩾ 15/h, and >50% central events) were enrolled. Participants were randomized to either standard medical therapy without treatment of CSA, or standard medical therapy with the addition of ASV.

The trial completed enrollment with over 1,300 patients recruited and with preliminary results reported (4). No significant difference in the primary composite outcome of all-cause mortality or unplanned hospitalizations was identified (hazard ratio = 1.14, 0.97–1.33; $P = 0.10$); however, cardiovascular mortality was increased in patients in the ASV arm compared with participants in the control arm with an absolute annual mortality rate of 10% versus 7.5% (HR = 1.34, 1.07–1.67; $P = 0.010$). Although final and more in-depth analyses are still pending, the excess risk appears to be driven by outpatient deaths (likely sudden cardiac deaths). The increased risk of death seemed to be independent of perceived benefit from the device, with no worsening of clinical symptoms or need for hospitalization prior to the event.

The results of SERVE-HF are surprising and contrary to the preliminary data showing short-term benefits in symptoms and physiology. More insight into the potential mechanisms for the increased mortality in the ASV arm will hopefully be available once the final results of the study are published; though open for speculation, potential explanations could include imbalances in randomization, hemodynamic effects of positive pressure, potential benefits of CSA (5), or a proarrhythmogenic effect through metabolic/electrolyte abnormalities. At this point, it is unknown whether certain subgroups might be at greater risk (e.g., lower ejection fraction, patients without an implantable defibrillator), but more insight into these issues will likely be available once the final results are published.

Field Safety Notice

Because of the results, a field safety notice was issued by ResMed, Inc., on May 13, 2015, that provided a number of recommendations (4). Specifically, they recommended that ASV should not be started in patients with symptomatic CHF and left ventricular ejection fraction ⩽ 45%, that is, heart failure with reduced ejection fraction (HFrEF), who have predominantly central sleep apnea. Similarly, before considering placing patients on ASV to treat central sleep apnea, a clinical evaluation for the presence of CHF should be done. Patients with suggestive signs and symptoms should be sent for further evaluation for HFrEF, and patients with HFrEF should not be initiated on ASV. Patients with symptomatic HFrEF currently using an ASV machine should be identified and contacted urgently to discuss discontinuation of the device. Ultimately, the decision on whether to continue ASV should be a joint one between the patient and physician balancing risks and benefits, but stopping ASV should be strongly considered given the increased cardiovascular mortality observed in this group.

There are, however, a number of additional questions related to clinical management that should be considered in the context of these trial results.

How Should ASV Be Discontinued?

Given that positive airway pressure reduces ventricular preload and afterload, abrupt discontinuation may result in an exacerbation of heart failure. We would recommend careful assessment of volume status at the time of discontinuation, as this information may help with the timing of positive airway pressure discontinuation and optimization of medical therapy.

How Should CSA Be Managed in Patients in Whom ASV Is Discontinued?

Certainly, therapies such as supplemental oxygen, acetazolamide, or continuous positive airway pressure (CPAP) can be useful to correct hypoxemia and improve sleep apnea (6). However, the long-term effects of these therapies are unknown and may not be beneficial; for example, in a recent trial, oxygen was found to be potentially detrimental in nonhypoxemic patients with myocardial infarction (7). Clearly, the priority is to ensure that patients have their heart failure medical management optimized.

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Should These Recommendations Be Applicable to All Types of ASV Machines?

It is also unclear whether this is a class effect of ASV or specific to the ResMed device used in the SERVE-HF trial. Although there are differences in algorithms and targets of positive pressure delivery between ResMed and Philips Respironics devices, their overall mechanisms are similar. At this point, it would be prudent to use similar recommendations for all ASV devices. Philips Respironics has issued a press release advising physicians to adhere to the recommendations published by ResMed with regards to Philips ASV devices (8).

What Should We Do with Patients Being Treated with ASV for Other Indications?

It is important to note that the SERVE-HF study only included patients with HFrEF and predominantly central events, and the findings should not be extrapolated beyond the study population. Patients who have been given ASV for other indications such as narcotic-induced central apnea, heart failure with preserved ejection fraction, or complex sleep apnea (treatment-emergent central apnea) can likely continue ASV safely as we see no compelling reason to withdraw it, especially if there is a beneficial impact on symptoms.

What Should We Do with HFrEF Patients with Predominantly Obstructive Sleep Apnea?

Patients with HFrEF but with predominantly obstructive sleep apnea (OSA) were not enrolled in the study, and it is difficult to make recommendations for these patients. Although both obstructive and central forms of sleep apnea may coexist in the same patient and on the same night, the physiology of OSA is somewhat different from CSA, and the effects of positive airway pressure will likely be different as well. The results of the ongoing ADVENT-HF trial may provide information on the safety and effectiveness of ASV in these patients in the future (ClinicalTrials.gov NCT01128816).

We believe that newly diagnosed patients should be started on CPAP as first-line treatment of OSA if clinically indicated, as there is also no compelling reason to believe that CPAP is harmful in patients with HFrEF (9). If these patients subsequently develop central apneas on CPAP, one could consider ASV balancing potential risks and possible symptomatic benefits. For patients already on ASV, we would recommend that patients be switched to CPAP, especially if they have not been tried on CPAP in the past, as this approach should adequately treat obstructive events. However, we recognize that some of these patients may find CPAP more uncomfortable than ASV, especially in the context of treatment-emergent CSA. The decision on whether to switch back to ASV in this context needs to carefully discussed with the patient, again balancing potential risks and benefits.

We believe the issue of sleep-disordered breathing in the context of CHF is important. The results of this study should alert us to the complexity of treating this patient group and should spur us to more studies to understand better the pathophysiology of sleep-disordered breathing in chronic heart failure and design better treatment approaches for these patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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AUTHOR QUERIES

1 AU: Please define CHF at first use.

2 AU: Please clarify the meaning of "0.97–1.33" (e.g., "95% confidence interval"?) and "1.07–1.67" at the end of the same sentence.

3 AU: Please verify change from "or **a** proarrhythmogenic effect**s**" to "or a proarrhythmogenic effect"; alternatively, should it read "or proarrhythmogenic effects"?

4 AU: Please provide academic/medical degrees (M.D., Ph.D., etc. [but not fellowships, memberships, or honorary degrees]) for all authors.

5 AU: Please check authors and affiliations carefully. In particular, please verify addition of "Department of" with several affiliations and added locations.

6 AU: Please verify edits to references 4 and 8 or correct as necessary.

7 AU: Reference 7 was a duplicate of reference 5; it has been deleted and subsequent references renumbered. Also, the clinicaltrials.org references have been cited in text rather than as references. Please verify accuracy.

8 AU: Please update reference 7 if possible.