

CORRESPONDENCE



Adaptive Servo-Ventilation for Central Sleep Apnea in Heart Failure

TO THE EDITOR: Cowie et al. (Sept. 17 issue)¹ report on the results of the Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial. They found increases in all-cause and cardiovascular mortality among patients with heart failure who received adaptive servo-ventilation therapy, and the adaptive servo-ventilation group had no improvement in quality-of-life measures.

These results contradict those of our Study of the Effects of Adaptive Servo-ventilation Therapy on Cardiac Function and Remodeling in Patients with Chronic Heart Failure (SAVIOR-C).² The majority of patients who received adaptive servo-ventilation in our study had improvements in quality of life, and the improvement from New York Heart Association (NYHA) functional class III heart failure to class II heart failure was significant.

We found that the adaptive servo-ventilation settings differed between the two studies. Cowie et al. manually increased the expiratory and inspiratory positive airway pressures from the default levels to suppress sleep apnea.¹ Because the effects of positive airway pressure on cardiac output depend on the baseline pulmonary-capillary wedge pressure,³ we were concerned that excessive increases in levels of airway pressure might diminish cardiac output and induce reflex sympathetic hyperactivity in some patients with mild pulmonary congestion. For this reason, the levels of airway pressure in patients in the SAVIOR-C were maintained at or below the default levels.^{2,4} It would be useful to know whether high-pressure adaptive servo-ventilation settings precipitated adverse events in their patients.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the article by Cowie and colleagues about the use of adaptive servo-ventilation in patients who had heart failure with reduced ejection fraction and sleep apnea, adaptive servo-ventilation was not beneficial with respect to the primary end point. In addition, all-cause and cardiovascular mortality were increased with this therapy.

Although adaptive servo-ventilation can work in the treatment of sleep apnea,¹ when sleep apnea is associated with heart failure, the background physiology may be more complicated. Sleep apnea is accompanied by mouth breathing; this leads to loss of water and, eventually, it could cause dehydration. Appropriate physiological responses to dehydration are drinking, vasopressin release, and activation of the renin-angiotensin-aldosterone system (RAAS).² Antagonists of the RAAS are mainstays of treatment for heart failure³ and are used in the majority of patients with sleep apnea.⁴ This suggests that patients with sleep apnea⁵ and patients with heart failure may both have severe dehydration.

Increased water intake to restore blood volume would reduce blood levels of angiotensin, vasopressin, and aldosterone. These decreased levels may decrease mortality among patients with heart failure who have sleep apnea.

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TO THE EDITOR: Cowie et al. report an increase in all-cause and cardiovascular mortality among patients with heart failure and predominantly central sleep apnea who received adaptive servo-ventilation. It would be interesting to know the prevalence of pulmonary hypertension, right ventricular failure, or both among patients in this study and whether these conditions were associated with an increased risk of death from any cause and death from cardiovascular causes. Pulmonary hypertension and right ventricular failure are common complications of left heart failure and are associated with a poor prognosis.¹

In addition, the presence of these conditions and the associated effect of positive pressure ventilation on the right ventricle may provide insight into the potential mechanism of the increased all-cause and cardiovascular mortality observed in the adaptive servo-ventilation group. Positive pressure ventilation imposes a burden on the right ventricle by decreasing right ventricular preload and increasing pulmonary vascular resistance because of an increase in lung volume.^{2,3} This burden could potentially lead to worsening right ventricular function, which may translate into an increase in all-cause and cardiovascular mortality in this subgroup.

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TO THE EDITOR: We would like more information regarding the SERVE-HF trial. Specifically, we think that the device may have provided excessive ventilation. In patients with compensated heart failure, the adaptive servo-ventilation device provided pressure support of 8.5 cm of water at respiratory rates of 20 breaths per minute or more; this amounts to a minute ventilation of 10.2 liters per minute, which is double the normal value (assuming the lower limit of normal respiratory compliance). Patients with heart failure and central sleep apnea have hypoxemia, with a consequent predilection for arrhythmias during the hyperventilation phase of Cheyne–Stokes respiration.¹

We are concerned that the device algorithms that control rate and pressure support, compounded by a minimum default pressure support of 3 cm of water, could have provided high minute ventilation (up to 26.6 liters per minute). This high minute ventilation, in turn, may have contributed to life-threatening arrhythmias and death in the adaptive servo-ventilation group. Arrhythmia information from explanted pacemakers or defibrillators from deceased patients, as well as information about minute ventilation from the adaptive servo-ventilation device, could shed more light on why there was an increased rate of deaths from cardiovascular causes with this treatment.

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Dr. Parthasarathy reports receiving grant support and personal fees from Philips Respironics, which makes products related to the adaptive servo-ventilation device. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The SERVE-HF investigators report substantial nonadherence to the study protocol: at least 28% of the patients either discontinued use of the trial device or never used it, and approximately 17% of the patients who were ran-

domly assigned to the control group crossed over to positive airway pressure therapy. Thus, without presenting an on-treatment analysis, the investigators cannot conclude definitively that use of adaptive servo-ventilation places patients with central sleep apnea at increased risk for death from any cause or death from cardiovascular causes.

Of the 666 patients who were randomly assigned to adaptive servo-ventilation, how many were adherent to adaptive servo-ventilation when they died, how many deaths occurred after patients abandoned its use, and how many deaths occurred in patients who were assigned to adaptive servo-ventilation but did not receive it? Similar data should be provided for the 659 control patients who were or were not receiving positive airway pressure ventilation when they died. Also, because any putative adverse hemodynamic effect of positive intrathoracic pressure would dissipate once the mask is removed on awakening, would the investigators comment on whether participants were actually wearing the adaptive servo-ventilation mask when they died?

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Drs. Bradley and Floras report serving as coinvestigators in a randomized trial of an adaptive servo-ventilation device (Philips Respironics) to treat sleep apnea in patients with heart failure. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In Germany, the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]) is the national authority responsible for the approval of clinical trials, collection of risk-related data, and assessment of risks associated with the use of medical devices. At BfArM, we were formally notified about the results of the SERVE-HF trial by the trial sponsor (ResMed) in May 2015. Consequently, BfArM assumed a primary role in assessing subsequent corrective actions by various manufacturers.

In almost all reported subgroups, the rates of the primary end point (the first event of the composite of death from any cause, a lifesaving cardiovascular intervention, or an unplanned hospitalization for worsening chronic heart fail-

ure) and cardiovascular death were higher in the adaptive servo-ventilation group than in the control group; we consider these increased rates to be serious concerns. Since the trial, specialist associations in Germany have recommended that adaptive servo-ventilation therapy should not be used in patients such as those enrolled in the SERVE-HF trial. The risk among all other patients remains unknown, and data from meta-analyses, further clinical trials, or both are lacking.

However, we disagree with the conclusions expressed by Magalang and Pack¹ in the editorial accompanying the article. They suggest that patients with heart failure who have predominantly central sleep apnea are suitable candidates for clinical trials. We have serious objections regarding the approval of such studies unless measures of risk reduction are identified. Ethical aspects of these studies have to be considered as well.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: In reply to Kihara et al.: in the SAVIOR-C, results from only 24 weeks of adaptive servo-ventilation therapy in 205 patients with heart failure were reported. Although there was a significant improvement in NYHA class, it was not accompanied by any difference in heart failure–related quality of life, left ventricular ejection fraction, or plasma levels of brain natriuretic peptide (BNP).¹ In marked contrast to patients in the SERVE-HF trial, patients in the SAVIOR-C received adaptive servo-ventilation therapy irrespective of the presence or severity of sleep-disordered breathing. Such data cannot be directly compared with data from our study. We reported that throughout our trial the median inspiratory positive airway pressure was 10 cm of water (95th percentile, 14) and the median expi-

ratory positive airway pressure was 6 cm of water (95th percentile, 6); these pressures were similar to those in other studies of adaptive servo-ventilation that showed improvement in left ventricular ejection fraction, symptoms, or both. An analysis of the lack of association between applied pressures and events in our study is under way, although confounding by disease severity may be problematic.

In reply to Thornton et al.: on exploratory analysis, we found no association between markers of decreased intravascular volume and both the primary combined end point and cardiovascular mortality. Although 85% of the patients were receiving a diuretic at baseline, the median of the furosemide-equivalent dose was only 40 mg (95% of the patients received a dose in the range of 10 to 300) per 24 hours. In addition, 56% of our patients used a humidifier with the adaptive servo-ventilation device. During the trial, we saw no difference between the two groups with respect to temporal trends in renal function (according to the estimated glomerular filtration rate) or hematocrit.

In reply to Hodges and Pilcher: although it has less power than the main study, a mechanistic substudy has not shown an association between right ventricular function and the excess mortality in our trial. There was a positive association with pulmonary-artery pressure on univariate analysis, but this effect was independent of adaptive servo-ventilation therapy and left ventricular ejection fraction.

We do not think that we provided excessive ventilation to patients, and we disagree with the calculation by Yamauchi et al., because the respiratory system is less compliant in patients with heart failure than in patients without heart failure.² Our algorithm achieves a moving target ventilation of 90% of the long-term average, thereby avoiding excessive ventilation. Elsewhere, we have shown that this algorithm is associated with only a very minor and statistically nonsignificant drift in the partial pressure of carbon dioxide overnight (0.2 mm Hg).³

We agree with Bradley and Floras that on-treatment analysis can be helpful, albeit with the challenges of the differential effects of selection and self-selection, the possibility of reverse causation, and larger random fluctuations in the data. The results of such an analysis do not

contradict the results of the intention-to-treat analysis.

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Since publication of their article, the authors report no further potential conflict of interest.

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THE EDITORIALISTS REPLY: With respect to the comments by Schäfer and colleagues: we think that further investigation in this area is required, albeit with appropriate informed consent. There are at least two major unanswered questions. First, we do not know whether the results of the

SERVE-HF trial were influenced by the specific adaptive servo-ventilation algorithm for adjustment of positive pressure. An ongoing trial (Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure [ADVENT-HF]; ClinicalTrials.gov number, NCT01128816) has different inclusion and exclusion criteria (it includes patients with both obstructive and central apneas) and uses a different adaptive servo-ventilation device with a less aggressive adjustment of positive pressure. The data and safety monitoring board for the ADVENT-HF trial has performed two interim analyses subsequent to the initial notification of the results of the SERVE-HF trial, and it has concluded that there are no safety concerns (Bradley TD: personal communication).

Second, we do not know whether the risks and benefits of adaptive servo-ventilation are different in specific subgroups of patients with sleep-disordered breathing and congestive heart failure. Thus, we continue to think that further investigation of this topic is required.

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A Randomized, Controlled Trial of Total Knee Replacement

TO THE EDITOR: In the study reported by Skou and colleagues (Oct. 22 issue),¹ patients were excluded if they had symptomatic knee osteoarthritis with pain scores higher than 60 mm on a visual-analogue scale (on which scores range from 0 to 100, with higher scores indicating worse pain). We are unclear as to the rationale for excluding patients with this level of pain, who are commonly seen in orthopedic practice. We agree with the conclusion that total knee replacement is superior to the nonsurgical regimen investigated. However, we are concerned that the exclusion of 117 of 244 otherwise eligible patients (48%) because of severity of symptoms may have

led to substantial underestimation of the effect sizes of treatments in both groups, especially in the surgical group because of potentially increased crossover rates among the more severely symptomatic patients.

Reported serious adverse events (stiffness requiring manipulation of the knee while the patient was under anesthesia and deep venous thrombosis requiring anticoagulation) both occurred among 6% of patients in the total-knee-replacement group. These rates were higher than the respective rates (1.3%² and 1.5%³) reported elsewhere for much larger cohorts. The authors did not report the time-to-event end points, care