The SERVE-HF trial

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The Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure (SERVE-HF) trial tested the hypothesis, in 1325 patients with heart failure with reduced ejection fraction (HFrEF) and co-existing central sleep apnea (CSA), that adaptive servoventilation (ASV) would reduce the incidence of the primary end point: the composite of all-cause mortality, life-saving cardiovascular interventions, or unplanned hospitalizations for worsening heart failure (1). The intention-to-treat analysis showed no significant difference between individuals randomly assigned to ASV and those randomly assigned to control for the primary end point ($P=0.10$). However, the ASV group experienced significantly higher all-cause and cardiovascular mortality than the control group (HR 1.28 [$P=0.01$], and HR 1.34 [$P=0.006$], respectively), and no improvement in quality of life. The authors concluded that the ASV device used (Auto CS, ResMed, USA) increased mortality without improving quality of life and, therefore, should not be used in HFrEF patients with CSA.

Importantly, they acknowledged that different ASV devices use different algorithms to suppress CSA, and cite the Effect of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure (ADVENT-HF) trial (1) as one that may help to determine whether the results of SERVE-HF were a class effect of ASV, or were specific to the ASV device used. Both the original article (1) and the accompanying editorial (2) emphasized that the SERVE-HF results cannot be extrapolated to HFrEF patients with obstructive sleep apnea (OSA) because OSA causes more adverse cardiac loading than CSA, which are reversible by positive airway pressure devices.

As compelling as the SERVE-HF data appear, they raise a number of issues that should not preclude completion of other trials of devices for therapy of CSA or OSA in HFrEF patients.

First, the SERVE-HF publication reports only the results of a treatment strategy. This is important because there was substantial nonadherence to the study protocol: 29% of patients either discontinued or never used ASV, while 16% of patients randomly assigned to control crossed-over to positive airway pressure therapy. ASV compliance was low, averaging only 3.4 h per night one year postrandomization. This low adherence suggests that subjects remained exposed to CSA during a substantial length of time when ASV was not worn. A potential reason for low compliance was that 76% of treated subjects used a full face mask, which is generally less well tolerated than a nasal mask (3).

Second, the ASV device used has relatively high default pressures as part of its ventilation algorithm (minimum end-expiratory pressure of 5 cmH₂O and minimum inspiratory pressure support of 3 cmH₂O), making it more likely to induce hyperventilation and to lower cardiac output in those with normal or low left ventricular filling pressures than a device with lower default pressures (4).

Third, the reason for the increased mortality in the ASV group is not known. The authors speculate that it could be because CSA is an adaptive mechanism in HFrEF (5), and that its reversal may be harmful, or that ASV-induced positive intrathoracic pressure may lower cardiac output, at least in those with normal left ventricular filling pressures by impeding venous return to the heart (4). Another possibility is that inspiratory pressure support could lead to hyperventilation, alkalosis and

accompanying hypokalemia, which may increase the propensity for cardiac arrhythmias (6). If any of these were the case, one may expect a tendency for deaths to occur while using the device. However, no data regarding the time of death or whether subjects were wearing ASV at that time were reported.

The SERVE-HF data indicate that ASV should not be used to treat CSA in patients with HFrEF outside of the setting of a randomized trial (2). Any such trial would require close monitoring by an independent data and safety monitoring board (DSMB) to detect any early potential adverse effects of ASV.

The ADVENT-HF trial (7), while similar to SERVE-HF in that it includes HFrEF patients with CSA and employs ASV as the intervention, differs from SERVE-HF in several respects. First, unlike SERVE-HF, it includes non-sleepy patients with OSA (7,8). To date, 64% of patients enrolled have OSA. Second, the ASV device used is made by another company, and its algorithm has lower default end-expiratory and minimum pressure support settings (4 cmH₂O and 0 cmH₂O, respectively) than that used in SERVE-HF. Theoretically, this should reduce the risk of lowering cardiac output and of inducing hyperventilation. Third, the trial is more closely monitored than SERVE-HF: patients are seen at six-monthly intervals compared to yearly in the SERVE-HF trial; and the DSMB review data six monthly compared with only twice over the seven-year course of SERVE-HF. In fact, following the release of the SERVE-HF results, the ADVENT-HF DSMB reviewed adverse events separately for patients with CSA and those with OSA. They did not observe any safety signal in either group and recommended the trial continue without modification. Irrespective of the SERVE-HF results, ADVENT-HF will provide novel data regarding the effects of treating asymptomatic OSA in patients with heart failure, and will provide evidence as to whether the adverse effects observed in SERVE-HF were a class effect or were device specific.

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