

LETTERS TO THE EDITOR

Effect of treatment of central sleep apnea/Cheyne-Stokes respiration on left ventricular ejection fraction in heart failure: a network meta-analysis is not the answer

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I read the article entitled “Effect of Treatment of Central Sleep Apnea/Cheyne-Stokes Respiration on Left Ventricular Ejection Fraction in Heart Failure: A Network Meta-analysis” by Schwarz et al¹ with interest. The authors state that “CPAP and ASV are effective in improving LVEF in patients with heart failure and CSA/CSR to a clinically relevant amount, whereas nocturnal O₂ is not.” However, in the meta-analysis, compared with an inactive control, both continuous positive airway pressure (CPAP) and adaptive servoventilation (ASV) significantly improved left ventricular ejection fraction (LVEF) by 4.4% and 3.8%, respectively, whereas nocturnal oxygen had no effect on LVEF. However, the interobserver variability of LVEF estimation by echocardiography and application of the modified biplane Simpson rule to quantify LVEF is of similar size and is not of clinical significance.

A network meta-analysis was performed to assess treatment effects on LVEF between different treatment comparisons (3 different active treatments and an inactive control), and multivariate random-effects meta-regression was used. However, this assumes that all interventions included in the “network” are equally applicable to all populations and contexts of the studies included and may introduce study selection bias, which is not uniformly applicable.²

However, it is not irrational to expect improvement with ASV. Because of the unexplained increased risk of mortality in the ASV arm in patients with systolic heart failure and central sleep apnea (CSA) in the Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial, the recommendation was made not to start ASV in patients with an LVEF <45%. As Javaheri et al point out, this is based on flawed methodology and analysis.³ The ASV device used in SERVE-HF allowed only fixed expiratory positive airway pressure (EPAP); the fixed EPAP might at times prove inadequate, with consequent residual sleep-disordered breathing events. The combination of the relatively low inspiratory and EPAP pressures applied by the device (values of EPAP <6 cm H₂O at baseline and at 12 months) along with the ubiquitous use of full face masks (76% of individuals; unknown in 9%) may also be detrimental. Low EPAP translates into low flow rates during exhalation when most of the intentional ventilatory leak occurs; use of a face mask may

enhance carbon dioxide rebreathing; and some patients’ excessive ventilation and/or pressure may have contributed to excess mortality. Adherence to ASV therapy was generally quite low, with an average usage of 3.7 h/night overall. Whether ASV improved survival in adherent patients in whom AHI decreased below various thresholds, such as 15, 10, or 5 events/h, is not known.

To answer the question if positive-pressure ventilation is effective in improving LVEF can only be answered by well-done randomized controlled trials (RCTs) and not by network meta-analysis and meta-regression. We must wait for Effect of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure (ADVENT-HF), with planned enrollment of ~850 patients with heart failure with reduced ejection fraction and either obstructive sleep apnea or CSA using an advanced technology ASV device including automatic end-expiratory titration.⁴ Management of these patients should be based on solid scientific evidence and not based of still evolving statistical network meta-analysis. While expensive and time consuming, RCTs are still the gold standard for studying causal relationships as randomization eliminates much of the bias inherent with other study designs.

CITATION

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ABBREVIATIONS

AHI, apnea-hypopnea index
ASV, adaptive servoventilation
CPAP, continuous positive airway pressure
CSA, central sleep apnea
EPAP, expiratory positive airway pressure
LVEF, left ventricular ejection fraction
RCT, randomized controlled trial

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DISCLOSURE STATEMENT

The author reports no conflicts of interest. The opinions expressed are the personal views of the author and do not reflect the opinions of the agency.