

Expert Opinion

Should We Let Sleeping Dogs Lie? Controversies of Treating Central Sleep Apnoea in HFrEF Following the SERVE-HF Study

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Abstract

Central sleep apnoea (CSA) is common in patients with heart failure (HF), with a prevalence of 20–45 %. It is a marker of severity of HF and is independently associated with increased morbidity and mortality rates in patients with HF. Targeting CSA with adaptive servo-ventilation (ASV) was postulated to improve outcomes; however, the results of the recent SERVE-HF (Treatment of Sleep-disordered Breathing by Adaptive Servo-ventilation in Heart Failure Patients) trial showed that in patients with CSA and HF with reduced ejection fraction (HFrEF), ASV, despite successfully treating CSA, was associated with increased risk of cardiovascular death compared with medical therapy. In this expert opinion we discuss the controversies of treating CSA in HFrEF following the SERVE-HF study.

Keywords

Central sleep apnoea, heart failure, adaptive servo-ventilation

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Central sleep apnoea (CSA) is characterised by cycles of apnoea, hypopnoea and hyperpnoea during sleep due to abnormalities in the regulation of breathing within the respiratory centre in the brainstem. CSA, defined as an apnoea–hypopnoea index (AHI) of ≥ 15 events/h, is common in patients with heart failure (HF), with a prevalence of 20–45 %.^{1,2} Its presence is reported to be a marker of severity of HF. It is also described in some studies to be independently associated with increased morbidity and mortality rates in patients with HF.³

Improving the underlying HF has often resulted in resolution of CSA. Cardiac resynchronisation therapy,⁴ ventricular assist device implantation⁵ and cardiac transplantation⁶ have led to reduction of AHI to normal levels (i.e. < 5 events/h). During CSA, the recurrent cycles of oxygen desaturations and autonomic arousals (elevation in sympathetic activity with rise in heart rate and blood pressure) may contribute to worsening HF, thus targeting CSA may be a potential treatment option that could slow the progression of HF and improve outcomes. Treatment modalities targeting CSA have included drugs such as theophyllines, opiates, carbonic anhydrase inhibitors, oxygen and various forms of positive pressure ventilation.

To date, the most extensively studied modalities of positive pressure treatments are continuous positive airway pressure (CPAP) support and adaptive servo-ventilation (ASV). CPAP delivers constant and continuous pressure throughout both inspiration and expiration through a nasal or face mask. ASV is a form of positive pressure ventilation with variable pressure algorithm that delivers back-up breaths and high pressures during apnoea and lower pressure during

hyperpnoea, resulting in resolution of AHI to normal levels in most cases. ASV has been shown to treat CSA more effectively than CPAP. In small studies, both CPAP and ASV have shown a fall in AHI levels coinciding with improvement in surrogate markers of HF,^{7–9} such as biomarkers (e.g. brain natriuretic peptide), exercise capacity, ejection fraction and symptoms.

The enthusiasm generated by these small studies of CPAP and ASV for the treatment of CSA in patients with HF with reduced ejection fraction (HFrEF), led to larger outcome studies. The first outcome study, the CANPAP (Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure) trial (N=203), assessed the effectiveness of CPAP versus medical therapy on transplant-free survival in patients with HFrEF with CSA.¹⁰ The findings from this study showed that the use of CPAP, which resulted in a drop in mean AHI level from 40 ± 16 events/h to approximately 19 ± 16 events/h, did not improve survival rates. However, a post hoc analysis of this trial suggested that those patients who had their CSA suppressed by CPAP (to an AHI level < 15 events/h) had a significantly better survival rate compared with those in whom CPAP did not suppress CSA effectively. However, the number of events in this analysis were low – five in the CPAP-suppressed versus 13 in the CPAP-unsuppressed group;¹¹ thus interpretation of these data, as with most post hoc analyses, requires cautious interpretation.

Subsequently, the SERVE-HF (Treatment of Sleep-disordered Breathing by Adaptive Servo-ventilation in Heart Failure Patients) study (N=1325) assessed the effectiveness of ASV versus optimal medical therapy

on survival in patients with HF with CSA.¹² This trial unexpectedly demonstrated that ASV, despite effectively treating CSA (with a drop in mean AHI levels from 31.2 events/h at baseline to 6.6 events/h at 12 months), had no impact on the primary endpoint of the trial, which was a composite endpoint of time-to-event analysis of first event of death from any cause, lifesaving cardiovascular intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock) or unplanned hospitalisation for worsening HF (54.1 % in the ASV group versus 50.8 % in the medical group; hazard ratio 1.13; 95 % CI [0.97–1.31]; P=0.10). Surprisingly, ASV was associated with harm with increased all-cause mortality rate (hazard ratio 1.28; 95 % CI [1.06–1.55]; P=0.01), predominantly due to an increased risk of cardiovascular death (hazard ratio 1.34; 95 % CI [1.09–1.65]; P=0.006). The latter was driven by an increased number of sudden cardiac death events; the mechanism by which this occurred is unclear. Results for further analyses from SERVE-HF study are eagerly awaited.

The surprising results of the SERVE-HF study have caused a reassessment of the way we construe CSA, such that this adaptation may in fact be favourable in HF and perhaps treating it may not be beneficial, as was argued by Naughton in 2012.¹³ The cycles of apnoea and hyperventilation may in fact have several benefits. An apnoea may prevent respiratory muscle fatigue that develops with continuous tachypnoea in the context of pulmonary congestion.

Stroke volume and circulation may increase in the presence of swings in intrathoracic pressure with alternating hyper- and hypoventilation. Furthermore, the hyperventilation phase may reduce sympathetic and increase vagal activity, and the development of hypocapnia and respiratory alkalosis may aid cardiac function during hypoxaemia by improving oxygen delivery (via Bohr and Haldane effects). In addition, hyperventilation leads to a larger end-tidal volume that may act as a reservoir of oxygen-counteracting hypoxaemia in the context of pulmonary oedema. Thus correcting CSA and the loss of these protective mechanisms may in part explain the increased cardiovascular mortality rates observed in the SERVE-HF study. Another factor that should be considered as a potential mechanism of increased cardiovascular mortality rates in the SERVE-HF study is the impact of positive pressure ventilation in patients with HF who have low left ventricular (LV) filling pressures and poor LV systolic function, considering that positive pressure may reduce both the LV preload and afterload, predisposing such patients to the development of haemodynamic instability.¹⁴

In light of the unexpected results of the SERVE-HF study, the optimal treatment of CSA remains controversial. Whether CSA should be interpreted merely as a marker of severity of HF or as a target for treatment remains unknown. Further adequately powered studies are required to determine whether ventilatory or non-ventilatory therapies (e.g. phrenic nerve stimulation, acetazolamide) are beneficial before we can conclude that we should let sleeping dogs lie. ■

- Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation* 1998;**97**:2154–9. PMID: 9626176.
- Vazir A, Hastings PC, Dayer M, et al. A high prevalence of sleep disordered breathing in men with mild symptomatic chronic heart failure due to left ventricular systolic dysfunction. *Eur J Heart Fail* 2007;**9**:243–50. DOI: 10.1016/j.ejheart.2006.08.001; PMID: 17030014.
- Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol* 2007;**49**:2028–34. DOI: 10.1016/j.jacc.2007.01.084; PMID: 17512359
- Sinha AM, Skobel EC, Breithardt OA, et al. Cardiac resynchronization therapy improves central sleep apnea and Cheyne-Stokes respiration in patients with chronic heart failure. *J Am Coll Cardiol* 2004;**44**:68–71. DOI: 10.1016/j.jacc.2004.03.040; PMID: 15234409
- Vazir A, Hastings PC, Morrell MJ, et al. Resolution of central sleep apnoea following implantation of a left ventricular assist device. *Int J Cardiol* 2010;**138**:317–9. DOI: 10.1016/j.ijcard.2008.06.072; PMID: 18752859
- Mansfield DR, Solin P, Roebuck T, et al. The effect of successful heart transplant treatment of heart failure on central sleep apnea. *Chest* 2003;**124**:1675–81. PMID: 14605034.
- Pepperell JC, Maskell NA, Jones DR, et al. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. *Am J Respir Crit Care Med* 2003;**168**:1109–14. DOI: 10.1164/rccm.200212-1476OC; PMID: 12928310.
- Sin DD, Logan AG, Fitzgerald FS, et al. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. *Circulation* 2000;**102**:61–6. PMID: 10880416.
- Tkacova R, Liu PP, Naughton MT, Bradley TD. Effect of continuous positive airway pressure on mitral regurgitant fraction and atrial natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 1997;**30**:739–45. PMID: 9283534.
- Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005;**353**:2025–33. DOI: 10.1056/NEJMoa051001; PMID: 16282177.
- Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation* 2007;**115**:3173–80. DOI: 10.1161/CIRCULATIONAHA.106.683482; PMID: 17562959.
- Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;**373**:1095–105. DOI: 10.1056/NEJMoa1506459; PMID: 26323938.
- Naughton MT. Cheyne-Stokes respiration: friend or foe? *Thorax* 2012;**67**:357–60. DOI: 10.1136/thoraxjnl-2011-200927; PMID: 22318163.
- SpieBhöfer J, Fox H, Lehmann R, et al. Heterogenous haemodynamic effects of adaptive servoventilation therapy in sleeping patients with heart failure and Cheyne-Stokes respiration compared to healthy volunteers. *Heart Vessels* 2015;**31**:1117–30. DOI: 10.1007/s00380-015-0717-6; PMID: 26296413.