Rev Port Cardiol. 2017;36(11):859–867

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

REVIEW ARTICLE

Sleep-disordered breathing in heart failure: The state of the art after the SERVE-HF trial☆

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KEYWORDS
Heart failure;
Sleep-disordered breathing;
Treatment;
Non-invasive ventilation;
Adaptive servo-ventilation;
Prognosis

Abstract Heart failure (HF) is one of the most prevalent conditions worldwide and despite therapeutic advances, its prognosis remains poor. Among the multiple comorbidities in HF, sleep-disordered breathing (SDB) is frequent and worsens the prognosis. Preliminary observational studies suggested that treatment of SDB could modify the prognosis of HF, and the issue has gained importance in recent years. The diagnosis of SDB is expensive, slow and suboptimal, and there is thus a need for screening devices that are easier to use and validated in this population. The first-line treatment involves optimization of medical therapy for heart failure. Continuous positive airway pressure (CPAP) is used in patients who mainly suffer from obstructive sleep apnea. In patients with predominantly central sleep apnea, CPAP is not sufficient and adaptive servo-ventilation (ASV), despite promising results in observational studies, showed no benefit in patients with symptomatic HF and reduced ejection fraction in the SERVE-HF randomized trial; on the contrary, there was unexpectedly increased mortality in the ASV group compared to controls, and so ASV is contraindicated in these patients, calling into question the definition and pathogenesis of SDB and risk stratification in these patients. There are many gaps in the evidence, and so further research is needed to better understand this issue: definitions, simple screening methods, and whether and how to treat SDB in patients with HF.

☆ Please cite this article as: Carmo J, Araújo I, Marques F, et al. Distúrbios respiratórios do sono na insuficiência cardíaca: o estado da arte depois do estudo SERVE-HF. Rev Port Cardiol. 2017;36:859–867.

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PALAVRAS-CHAVE
Insuficiência cardíaca;
Distúrbios respiratórios do sono;
Tratamento;
Ventilação não invasiva;
Servo-ventilação adaptativa;
Prognóstico

Distúrbios respiratórios do sono na insuficiência cardíaca: o estado da arte depois do estudo SERVE-HF

Resumo A insuficiência cardíaca (IC) é uma das entidades mais prevalentes em todo o mundo e o seu prognóstico, apesar dos avanços terapêuticos, continua reservado. De entre as múltiplas comorbilidades, os distúrbios respiratórios do sono (DRS) são frequentes na IC e agravam o seu prognóstico. Estudos preliminares observacionais sugeriam que o tratamento dos DRS poderia modificar o prognóstico da IC, motivo pelo qual o tema tem ganho importância nos últimos anos. O diagnóstico dos DRS é caro e moroso, pelo que subótimo, com necessidade de dispositivos de rastreio mais fáceis de usar e validados nesta população de doentes. O tratamento em primeira linha passa pela otimização da terapêutica médica da IC. A pressão positiva contínua na via aérea (CPAP) é utilizada em doentes com predomínio de apneia obstrutiva. Já nos doentes com predomínio de apneia central, o CPAP não é suficiente e a servo-ventilação adaptativa (SVA), apesar de ter mostrado resultados promissores em estudos observacionais, não mostrou benefício nos doentes com IC sintomática e fração de ejeção deprimida no estudo aleatorizado SERVE-HF; pelo contrário, registou-se, inesperadamente, um aumento da mortalidade no grupo do SVA em relação ao grupo controlo, razão pela qual está contraindicada nestes doentes, pondo em causa a definição e etiopatogenia dos DRS e estratificação de risco destes doentes. Existem muitas lacunas na evidência, pelo que será necessária mais investigação para um melhor entendimento deste tema: definição, métodos simples de rastreio, bem como da necessidade ou não, e melhor forma de tratar os DRS nos doentes com IC.

Introduction

Heart failure (HF) is recognized as a worldwide epidemic, with high morbidity and mortality. Its prevalence is around 1-2% and can exceed 10% in those aged 70 years or over.[1] In Portugal, it ranges from 1.36% in those aged over 25 years to 16% in those over 80; the prevalence of HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) is 1.3% and 1.7%, respectively.[2] Despite therapeutic advances, the short- and long-term prognosis of HF remains poor, which has prompted an ongoing search for risk modifiers and treatments that can demonstrably improve prognosis. In this context, in recent years there has been considerable interest in sleep-disordered breathing (SDB), a condition that is frequently associated with worse prognosis in HF patients. The main form of treatment for SDB in HF is non-invasive ventilation, either by continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP) for patients who mainly suffer from obstructive sleep apnea (OSA), or by adaptive servo-ventilation (ASV) for those with predominantly central sleep apnea (CSA). It has been hypothesized that in addition to optimal HF therapy, such treatment could bring added benefits for HF patients.

Preliminary observational studies suggested that treatment of SDB could modify the prognosis of HF, reducing hospitalizations and long-term mortality.[3] However, these expectations were frustrated by the recently published results of the SERVE-HF trial,[4] in which treatment of SDB by ASV in fact increased mortality in patients with symptomatic HFrEF. The discrepancy between the results of observational studies and those of SERVE-HF call into question the pathogenesis of SDB in HF, challenging clinicians and researchers to improve their knowledge in this area. To this end, we present a review of the subject.

Concepts

Sleep apnea syndrome is characterized by repeated pauses in breathing resulting in sleep fragmentation, daytime sleepiness and blood oxygen desaturation. According to the American Academy of Sleep Medicine, apnea is defined as a drop of $\geq$90% in respiratory flow from baseline lasting for $\geq$10 s, and hypopnea as a drop of $\geq$30% in respiratory flow from baseline lasting for $\geq$10 s in association with either $\geq$3% arterial oxygen desaturation or an arousal.[5]

Patients with HF can suffer from CSA, OSA, or both. The prevalence of CSA increases with increasing severity of HF. OSA is caused by upper airway collapse with increased reflex respiratory effort. Predisposing factors include obesity and unfavorable craniofacial structure.

In CSA, there is no strengthening of the respiratory reflex during episodes of apnea or hypopnea. The underlying mechanism is increased sensitivity of chemoreceptors in the brainstem and the carotid bodies to small variations in partial pressure of carbon dioxide ($PaCO_2$), leading to inappropriate hyperventilation.[6,7] The resulting reduction in $PaCO_2$ weakens the respiratory stimulus and apnea or hypopnea occurs; when $PaCO_2$ rises, the cycle repeats. In addition to this excessive respiratory response to CO_2 levels, another mechanism at play in hyperventilation is stimulation of vagal mechanoreceptors (J receptors) due to pulmonary congestion via vagal afferents.[8–11] CSA with a cyclic pattern of hyperventilation-apnea-hyperventilation is known as Cheyne-Stokes respiration.