

## Servo-Ventilação Auto-Adaptativa e o Estudo Serve-Hf: Implicações na Insuficiência Cardíaca com Fração de Ejeção Reduzida

### *Adaptive Servo-Ventilation and the Serve-Hf Trial: Implications in Heart Failure with Reduced Ejection Fraction*

Ana Pais<sup>1</sup> (<https://orcid.org/0000-0002-0530-0358>), Luiz Menezes Falcão<sup>2,3</sup> (<https://orcid.org/0000-0003-3574-9807>)

#### Resumo:

O servo-ventilador auto-adaptativo (ASV) é um dispositivo de ventilação não invasiva, que usa pressão positiva oscilatória, para tratar fenómenos de apneia do sono central. A apneia do sono central é uma entidade frequente em doentes com insuficiência cardíaca. O SERVE-HF foi um estudo internacional, randomizado e controlado, que demonstrou os riscos deste tipo de tratamento, em doentes com insuficiência cardíaca e fração de ejeção reduzida. Algumas questões metodológicas foram levantadas acerca da consistência deste estudo. Vários ensaios clínicos encontram-se no momento em curso, e poderão ajudar, no futuro, a definir os riscos e benefícios reais do uso da servo-ventilação.

**Palavras-chave:** Apneia do Sono Central; Função Ventricular Esquerda; Insuficiência Cardíaca Sistólica; Respiração com Pressão Positiva; Respiração com Pressão Positiva Intermitente.

#### Abstract:

*Adaptive servo ventilation is a type of non-invasive ventilation device, using oscillatory positive airway pressure to treat central sleep apnoea. Central sleep apnoea is a common entity in heart failure patients. The SERVE HF trial was an international controlled and randomized study, which demonstrates the hazard effects of this device therapy in HF patients with reduced ejection fraction. Some methodological issues are being raised about the consistency of this study. Ongoing trials could help us, in the future, to definitely define the risks and the benefits of adaptive servo ventilation device therapy.*

**Keywords:** Heart Failure, Systolic; Intermittent Positive-Pressure Breathing; Positive-Pressure Respiration; Sleep Apnea, Central; Ventricular Function, Left.

#### Introduction

Sleeping disorders are highly prevalent in heart failure (HF) patients with reported prevalence of 46% - 80%.<sup>1</sup>

Two major subtypes are identified: obstructive sleep apnoea (OSA) and central sleep apnoea (CSA).

OSA is a common chronic disorder affecting about 2% - 4% of the adult population. It is characterized by anatomic and functional changes of the upper airways, associated with an increase in the central respiratory drive.<sup>2</sup>

CSA is a much less frequent condition, representing only 5% - 10% of patients in sleep clinics. It is characterized by reduction or complete cessation of airflow caused by an unstable ventilator drive, and a lack of respiratory effort.<sup>3</sup>

Cheyne-Stokes respiration (CSR) is a type of CSA characterized by a crescendo-decrescendo variation in breathing amplitude, and normocapnia. It is relatively common in heart failure patients, occurring in approximately 40% of patients with left ventricular ejection fraction inferior to 40%.<sup>4</sup>

Patients with HF and CSA have higher morbidity and mortality than their counterparts without CSA, making the diagnosis and treatment of sleeping breathing disorders (SBD) an important prognostic factor in these patients.

<sup>1</sup>Serviço de Pneumologia, Centro Hospitalar Universitário de Lisboa Norte, Hospital de Santa Maria, Lisboa, Portugal

<sup>2</sup>Serviço de Medicina I, Centro Hospitalar Universitário de Lisboa Norte, Hospital de Santa Maria, Lisboa, Portugal

<sup>3</sup>Centro Cardiovascular da Universidade de Lisboa (CCUL), Faculdade de Medicina, Lisboa, Portugal

## Pathophysiology of Sleeping Breathing Disorders (SBD)

In OSA, repeated episodes of partial or complete upper airway obstruction occur during sleep. This obstruction causes loud snoring, repeated episodes of apnoea and hypoxia, and arousals from sleep. Risk factors for OSA include obesity, advanced age, male sex or menopausal women, craniofacial abnormalities, smoking and alcohol consumption.<sup>5</sup>

CSA, by contrast, is caused by the temporary withdrawal of central (brainstem-driven) respiratory drive resulting in cessation of respiratory muscle activity and airflow. Risk factors include chronic opioid use and a number of cardiovascular, neurological and/or renal disorders.<sup>5,6</sup>

Often the distinction between these two subtypes of SBD are not easy as they might coexist (mixed types), or lead to each other, for example, the arousal from an obstructive episode can cause hyperventilation and changes in pCO<sub>2</sub> initiating cycles of compensatory apnoeas, or a central episode can cause significant arterial deoxygenation leading to loss of airway tone and airway obstruction.<sup>7</sup>

In HF, pulmonary congestion during sleep activates pulmonary stretch receptors that stimulate ventilation, resulting in hyperventilation and lowered blood pCO<sub>2</sub>, triggering an exaggerated compensatory response, resulting in apnoea. This apnoea produces a significant increase in pCO<sub>2</sub> resulting in another exaggerated response: hyperventilation, setting up the cyclical pattern of Cheyne-Stokes respiration (CSR).<sup>7</sup>

While CSA is considered a consequence of severe HF, both types of SBD can be important risk factors for cardiovascular diseases, inducing and exacerbating heart damage by various mechanisms. Intermittent episodes of hypoxia (caused both from airway obstruction or central apnoea/hypopnoea) induce a pro-inflammatory status and sustained sympathetic stimulation with release of catecholamines, resulting in tachycardia, peripheral vasoconstriction, sodium retention and renin-angiotensin-aldosterone system (RAAS) activation, increasing the risk of hypertension, myocardial ischemia, cardiac fibrosis and remodelling. It can also induce a number of metabolic disturbances such as insulin resistance, diabetes mellitus and/or dyslipidaemia, which can further contribute to cardiovascular disease and the development of heart failure.<sup>8,9</sup>

## Clinical Features and Diagnosis of SBD

The most common symptom of OSA, present in 80% of cases, is daytime somnolence due to nocturnal sleep fragmentation. Morning headaches, cognitive and neurobehavioral disturbances with inability to concentrate, memory impairment and mood changes, such as irritability and depression, are also quite frequent.<sup>2</sup>

The clinical presentation of CSA is much less specific, and often overlaps with those with HF without sleeping breathing disorders (SBD): fatigue, dyspnoea, orthopnoea, paroxysmal

nocturnal dyspnoea and nocturia are typical. Daytime sleepiness, which is quite common in OSA, is often absent in patients with CSA. Sometimes, a sleep partner can help us with the diagnosis, reporting unusual breathing pattern.<sup>10-12</sup>

The gold standard test for diagnosing SBD is polysomnography. This nocturnal cardio-respiratory monitoring detects and measures the severity of sleeping disorders by using the apnoea/ hypopnoea index (AHI). AHI is defined by the number of abnormal respiratory events (apnoeas or hypopnoea) per hour. Apnoea is defined as a 90% reduction in the tidal volume, lasting more than 10 seconds, while hypopnoea is a reduction in the tidal volume of 50% - 90%, lasting more than 10 seconds, accompanied by, at least, 4% decrease in oxyhaemoglobin saturation. According to one study of ambulatory HF patients, the mortality rises progressively with every 5 events/hour increase in AHI, making this measurement an important prognostic factor in those patients.<sup>13</sup>

## Treatment of SBD

Treatment of SBD depends upon the underlying pathophysiology and severity of the disorder.

In mild OSA, general measures such as weight loss, cessation of smoking, and avoidance of alcohol and sedatives might be sufficient. In selected cases, oral appliances like mandibular advancement devices, or tongue retaining devices, can be offered to correct facial and cranial abnormalities.

In moderate to severe OSA, continuous positive airway pressure (CPAP) is the first line treatment. In addition, nasal, facial or maxillomandibular surgery may be considered to improve the patency of the upper airways. Bariatric surgery may be offered to obese patients with body mass index (BMI) over 40, who fail to lose weight with conservative measures.<sup>14</sup>

Current treatment approaches for CSA include, as a first step, optimization of medical therapy according to the guidelines of chronic heart failure (CHF). CRT (cardiac resynchronization therapy) may be offered to symptomatic HF failure patients with LVEF ≤ 35%, in sinus rhythm with a wide QRS complex (≥ 150 ms) and left bundle branch block (LBBB), despite optimal medical treatment (Class I of recommendation, Level of evidence A-2016 ESC guidelines). In small studies of CRT-treated HF patients with documented CSA, CRT increases cardiac output and, consequently, reduces CSA and improves quality of sleep.<sup>15</sup>

Phrenic nerve stimulation (PNS) is a novel approach for the treatment of CSA. PNS consists of a stimulation electrode placed within the brachiocephalic vein or in the left pericardiophrenic vein, a sensing lead placed in the azygous vein, and an implanted pulse generator in the right pectoral area controlled by an external system programmer. It detects the hyperventilation episode and stimulates unilaterally the phrenic nerve, to reduce the breathing rate keeping the pCO<sub>2</sub> above the apnoeic threshold, thus preventing apnoea episodes. In contrast to positive airway pressure (PAP) devices, it

creates a negative intrathoracic pressure (considered safer in cases of reduced LVEF) and requires no patient intervention to function, thus eliminating patient nonadherence.<sup>16,17</sup> Fourteen international studies describing the use of transvenous PNS have been published showing statistically significant reduction in AHI, and in the central apnoea events ( $p$  value  $<0.001$ ). In October 2017, PNS was approved by the FDA to treat moderate to severe CSA.<sup>18</sup>

The positive airway pressure devices (PAP) are commonly used nowadays to treat moderate to severe sleeping disorders. Three types of PAP therapy exist: CPAP (continuous positive airway pressure), BiPAP (bilevel positive airway pressure), and ASV (adaptive servo-ventilation). They have different mechanisms of action and different indications.

- CPAP is the first therapeutic approach in OSA and the first line PAP therapy for non- hypercapnic CSA. It delivers a continuous pre-set pressure to maintain the airway open and preventing airway collapse.

- BiPAP is the first PAP option for hypercapnic respiratory failure, mainly seen in COPD (chronic obstructive pulmonary disease) patients. It provides 2 different pressure settings, one for inspiration (IPAP) and another for expiration (EPAP), with a fixed back up rate.

- ASV is the most sophisticated form of PAP therapy. It is indicated for patients with CSA after CPAP has failed to reduce AHI, or for patients with mixed sleep apnoea without response to CPAP or BiPAP. ASV devices have the capacity to provide baseline positive pressure to stabilize and maintain the patency of the airway (similar to CPAP) and are capable of delivering additional breaths when apnoeas or hypopnoeas are detected (similar to BiPAP). By contrast to BiPAP, during a hyperventilation phase, these devices do not supply the ventilator support, to prevent further exacerbation of hyperventilation, breaking up the periodic breathing cycle typical of CSA. ASV is considered to be superior to the other PAP therapies at normalizing the AHI in patients with CSA or mixed sleep disorders, as well as more comfortable to the patients because it adjusts to the patient breathing pattern, resulting in greater regulation of the amount of airflow delivered and creating a more physiological ventilation.<sup>19</sup>

The wide use of this latter device led to large randomized trials evaluating its efficacy and safety. SERVE-HF was a large randomized, controlled, international, multicentre study, designed to assess the effects of ASV on morbidity and mortality in patients with symptomatic heart failure with reduced left ventricular ejection fraction (LVEF) and predominant CSA. The results of this study were first presented at the 2015 ESC Congress in London, and have been published in the *New England Journal of Medicine* (NEJM).<sup>20</sup>

### SERVE-HF Results and Limitations of the Study

SERVE-HF trial was designed to compare the effect of stan-

dard medical treatment plus ASV, versus medical treatment alone, in patients with symptomatic chronic heart failure (NYHA class III or IV, or class II with at least one hospitalization for HF over the preceding 24 months), LVEF  $\leq 45\%$ , and predominant moderate to severe CSA (AHI  $\geq 15/h$  and  $>50\%$  central events). A total of 1325 patients were included in the study and followed for a mean of 3.5 years. The adherence to ASV therapy was considered satisfactory with an average usage of 3.7 hours/night.<sup>20</sup>

Although CSA was effectively controlled in the ASV group, confirmed by significant reductions in AHI from 31.2/h at baseline to 6.7/h at 12 months ( $p < 0.001$ ), it did not improve the outcome in this group of patients. There was, surprisingly, a statistically significant increased risk for cardiovascular events in patients treated with ASV compared with the control group. The risk of cardiovascular death was increased by 34%, which was sustained throughout the trial ( $p < 0.006$ ).<sup>20</sup>

Two main explanations have been postulated for these results: the first is that CSA may be a compensatory mechanism in HFrEF population, with hyperventilation-related increases in end-expiratory volumes, and decrease work of breathing, with periodic rest of the respiratory muscles; and secondly that the positive airway pressure applied by the ASV device may further reduce the cardiac output in patients with lower ejection fraction.<sup>21-23</sup>

Based on these results, the AASM (American Academy of Sleep Medicine) released a statement, in May 2015, recommending doctors to stop prescribing ASV to treat CSA in patients with LVEF  $\leq 45\%$ , and to warn all those patients who are already on this kind of treatment for the possible risks. It is also recommended, before starting on ASV therapy, echocardiographically assess ejection fraction, to exclude those who are in the higher risk group.

SERVE-HF findings are not generalized to: HF patients with LVEF  $> 45\%$ , patients with predominant OSA regardless of LVEF, patients treated with ASV for other reasons than HF (for example, in opioid abusers or after acute ischemic stroke) or to other PAP devices different from ASV (for example, CPAP).<sup>21-23</sup>

Methodological issues within this trial have recently been raised.

The first issue is whether the settings utilized and/or the specific ASV device used might be the cause of the increased cardiovascular mortality. SERVE-HF utilized an old fashioned device that is no longer in clinical use, a device that was set to deliver fixed and mandatory pressure. The pressure utilized could be too low or too high, resulting in inappropriate treatment of CSA, or harmful excessive positive pressure.<sup>24</sup>

It shouldn't be forgotten, the changing of the SBD phenotype during time. For example, in a fluid overload state such as heart failure, the shift of fluids can cause airway obstruction leading to obstructive events. That is why a fixed EPAP might at times prove inadequate and ineffective,

and the checking up of the device should be frequent. In the SERVE-HF study, after the first 12 months, the revision of the settings was done only annually. These long intervals without assessment raise the possibility that the negative results were partially attributable to SDB, even if the last download showed adequate control of sleep apnoea.<sup>25</sup>

Other issue raised is whether the use of a full face mask is actually beneficial. In SERVE HF study, a full face mask was used. Some authors speculate that a face mask may enhance CO<sub>2</sub> rebreathing, leading to elevated levels of CO<sub>2</sub> and renal bicarbonate retention. During the day, the CO<sub>2</sub> elimination is faster than the renal response, which may result in an inappropriate elevation of bicarbonate, and consequently in a state of sustained metabolic alkalosis. Metabolic alkalosis is known to induce cardiac arrhythmias and other adverse cardiovascular events.<sup>26-30</sup>

The fourth issue is whether the study have included patients that were, actually, sicker at a baseline, than the patients on previous studies. In SERVE-HF, more than 70% of patients were NYHA class III or IV, with a mean LVEF of 32%. These patients have an initial worse prognosis, and may be more prone to the hemodynamic adverse effects of the increased positive intrathoracic pressure induced by the device.<sup>20</sup>

### ASV Usage in HF Patients with Preserved Ejection Fraction (HFpEF)

In a randomized prospective study realized at Fukushima Medical University in Japan, 36 HFpEF patients with LVEF  $\geq$  50% and predominant CSA with an AHI of, at least, 15 events/hour, were followed up by a mean of 543 days. The cardiac event rate was compared between patients on optimized medical treatment alone, versus optimized medical treatment plus ASV. Over 6 months of treatment, the ASV group had a higher event-free rate (94.4%) compared with those on the control group (61.1%, *p* value < 0.05), as well as greater improvements from baseline in B-type natriuretic peptide (BNP) levels and New York Heart Association (NYHA) functional class.<sup>31,32</sup>

In a randomized retrospective analysis at two medical centres in Germany, 114 patients with the same inclusion criteria as the study above were followed up by 27 months. The patients treated with ASV had a significant reduction in AHI from a mean of 54 events/hour to less than 10 events/hour (*p* value < 0.001).<sup>33</sup> There were also reports of improvement on cardiac diastolic function and cardiopulmonary exercise capacity (*p* value < 0.01) in the patients on ASV therapy, versus those on medical treatment alone.<sup>34</sup>

Considering these results, we expect that the effect of the ASV device on HFpEF patients may be different from the effect of this therapy on HFrEF patients, and that its use may be safe. However, the provided evidence is not sufficient for a general treatment recommendation, and larger long term studies are required to definitely answer this question.<sup>31-33</sup>

### Ongoing Studies and Registries

Three major randomized controlled trials concerning this problematic are ongoing at the moment.

The ADVENT-HF is a multicentre, multinational and randomized Canadian trial, with the main goal to investigate the effect of ASV therapy in patients with HFrEF with either predominant OSA or CSA (differing from the SERVE-HF study which was concerning HFrEF patients with predominant CSA). This trial employs an ASV device that uses peak flow to trigger pressure support (peak flow ASV), with relatively low minimum expiratory (EPAP) and inspiratory pressure support (minimum expiratory positive airway pressure of 4 cmH<sub>2</sub>O and minimum inspiratory pressure support of 0 cmH<sub>2</sub>O), different from the ASV device used in the SERVE HF trial that uses minute volume of ventilation (minute ventilation ASV) to trigger pressure support, and has higher minimum default pressures (minimum EPAP of 5 cmH<sub>2</sub>O and minimum inspiratory pressure support of 3 cmH<sub>2</sub>O). In addition, unlike the ASV device used in the previous studies, this device has an automatic algorithm to titrate EPAP, controlling the obstructive events, and may give us some data about the benefit of this therapy in OSA. Unlike the SERVE HF trial, the ADVENT trial is preferential using the nasal interface, rather than the full face mask.<sup>35</sup>

The FACE study is a French prospective, observational trial that concerns the use of ASV in different subgroups of patients. The goal is to provide complementary data to SERVE HF, by characterizing CHF populations that are eligible for ASV. This trial has included 361 chronic heart failure (CHF) patients, enrolled by 30 centres. The results appear to be consistent with those of the SERVE HF trial, and HFrEF patients with predominant central sleep apnoea (CSA) may have a poorer prognosis under ASV therapy, than the other CHF populations, like those with predominant obstructive sleep apnoea and/or those with preserved ejection fraction.<sup>36,37</sup>

The CAT HF study is an American trial evaluating the cardiovascular outcomes of minute ventilation ASV therapy in hospitalized patients with acute decompensated heart failure, rather than in chronic stable HF patients, like in the SERVE HF study. Both HFrEF and HFpEF patients were, initially, eligible for the study, as long as they had signs and symptoms of acute HF (dyspnoea at rest or with minimal exertion, orthopnoea, elevated natriuretic peptide levels, rales on physical examination, congestion on chest radiograph, and/or pulmonary capillary wedge pressure  $\geq$  25 mmHg) and either obstructive and/or central sleep apnoea. By the time the results of the SERVE HF trial got available, the subgroup of patients with HFrEF was withdrawn from the study, reducing the sample size, and limiting the statistical power. However, the preliminary findings favour the use of minute ventilation ASV in patients with acute heart failure and preserved ejection fraction with moderate to severe sleep apnoea, showing improvement at the six month outcome, with lower rates of cardiovascular

hospitalization, and higher functional capacity assessed by the six minute walk distance (6 MWD).<sup>38</sup>

The changing of terminology of HF groups presented in the newer ESC guidelines of May 2016, defining three subgroups of HF patients (HFpEF with ejection fraction (EF)  $\geq$  50%, HFrEF with EF < 40% and the newer entity, with EF 40% - 49%, called heart failure midrange ejection fraction (HFmrEF), may lead to conflicting results in these ongoing trials, which are still using the older HF terminology.<sup>15</sup>

## Conclusion

Since the publication of the SERVE-HF trial, all patients should be assessed echocardiographically before starting on ASV therapy, and it should not be prescribed if LVEF is equal or inferior to 45%.

Ongoing studies are trying to confirm these data and to evaluate the effect of this PAP therapy in patients with LVEF > 45%.

Until new data are available, patients with LVEF > 45% may still use the ASV device, under great caution and regular evaluation. ■

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

*Conflicts of interest: The authors have no conflicts of interest to declare.*

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

*Financing Support: This work has not received any contribution, grant or scholarship.*

Proveniência e revisão por pares: Não comissionado; revisão externa por pares.

*Provenance and peer review. Not Commissioned; externally peer reviewed.*

Correspondence/Correspondência:

Ana Pais – anafspais@gmail.com  
1Serviço de Pneumologia, Centro Hospitalar Universitário de Lisboa Norte, Hospital de Santa Maria, Lisboa, Portugal  
Avenida Professor Egas Moniz  
1649-035 Lisboa

Recebido/Received: 09/07/2018

Aceite/Accepted: 04/11/2018

## REFERÊNCIAS

- Artz M, Woehrle H, Oldenburg O, Graml A, Suling A, Erdmann E, et al. Prevalence and predictors of sleep disorder breathing in patients with stable chronic heart failure: the SchlaHF registry. *JACC Heart Fail.* 2016;4:116-25. doi: 10.1016/j.jchf.2015.09.014
- Spicuzza L, Caruso D, Maria G. Obstructive Sleep apnea syndrome and its management. *Ther Adv Chronic Dis.* 2015;6:273-83.
- Muza R. Central Sleep Apnea- a clinical review. *J Thorac Dis.* 2015;7:930-7. doi: 10.3978/j.issn.2072-1439.2015.04.45.
- Nicholas WT. Sleep related breathing disorders- Nosological classification, definition, epidemiology. Regensburg: European Sleep Research Society; 2014.
- Sin DD, Fitzgerald F, Parker JD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med.* 1999; 160:1101-06.
- Javaheri S, Dempsey JA. Central sleep apnea. *Compr Physiol.* 2013; 3:141-63
- Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hypoventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. *Am Rev Respir Dis.* 1993; 148:330-8.
- Naughton MT, Liu PP, Bernard DC, Goldstein RS, Bradley TD. Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure. *Am J Respir Crit Care Med.* 1995;151:92-7.
- Javaheri S, Shukula R, Ziegler 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
- Javaheri S. A mechanism of central sleep apnea in patients with heart failure. *N Engl J Med.* 1999; 341: 949-54.
- Leung RS, Bradley TD. Sleep apnea and cardiovascular disease. *Am J Respir Crit Care Med.* 2001; 164: 2147-65.
- Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010;90:47-112.
- Costanzo MR, Khayat R, Ponikowski P, Augostini R, Stellbrink C, Mianulli M, et al. Mechanisms and clinical consequences of untreated central sleep apnea in heart failure. *J Am Coll Cardiol.* 2015;65:72-84. doi: 10.1016/j.jacc.2014.10.025.
- Pevernagie D, Sastry M, Vanderveken O. Treatment of respiratory sleep disorders. Regensburg: European Sleep Research Society; 2014.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Rev Esp Cardiol.* 2016;69:1167. doi: 10.1016/j.rec.2016.11.005.
- Ponikowski P, Javaheri S, Michalkiewicz D, Bart BA, Czarnecka D, Jastrzebski M, et al. Transvenous phrenic nerve stimulation for the treatment of central sleep apnoea in heart failure. *Eur Heart J.* 2012 ;33:889-94. doi: 10.1093/eurheartj/ehr298.
- Costanzo MR, Augostini R, Goldberg LR, Ponikowski P, Stellbrink C, Javaheri S. Design of the remed<sup>®</sup> System Pivotal Trial: a prospective, randomized study in the use of respiratory rhythm management to treat central sleep apnea. *J Card Fail.* 2015;21: 892-902.
- Ding N, Zhang X. Transvenous phrenic nerve stimulation, a novel therapeutic approach for central sleep apnea. *J Thoracic Dis.* 2018;10:2005-10. doi: 10.21037/jtd.2018.03.59.
- Javaheri S, Brown LK, Randerath WJ. Clinical applications of positive airway pressure therapy with adaptive servo-ventilation: part 2. *Chest* 2014;146:855-86.
- Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, 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.
- Brown LK, Javaheri S. Adaptive servo-ventilation for the treatment of central sleep apnea in congestive heart failure: What have we learned? *Curr Opin Pulm Med.* 2014;20:550-7. doi: 10.1097/MCP.000000000000108.
- Khayat R, Jarjoura D, Porter K, Sow A, Wannemacher J, Dohar R, et al. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. *Eur Heart J.* 2015;36:1463-9. doi: 10.1093/eurheartj/ehu522.
- Javaheri S. CPAP should not be used for central sleep apnea in congestive heart failure patients. *J Clin Sleep Med.* 2006;2:399-402.
- Javaheri S, Brown LK, Randerath WJ. Positive airway pressure therapy with adaptive servoventilation: part 1: operational algorithms. *Chest.* 2014;146:514-23
- Yumino D, Redolfi S, Ruttanaumpawan P, Su MC, Smith S, Newton GE, et al. Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. *Circulation.* 2010;121:1598-605. doi: 10.1161/CIRCULATIONAHA.109.902452.
- Ferguson GT, Gilmartin M. CO2 rebreathing during BiPAP ventilatory assistance. *Am J Respir Crit Care Med.* 1995;151:1126-35.
- Schettino GP, Chatmongkolchart S, Hess DR, Kacmarek R.M. Position of exhalation port and mask design affect CO2 rebreathing during noninvasive positive pressure ventilation. *Crit Care Med.* 2003;31:2178-82.
- Holanda MA, Reis RC, Winkeler GF, Fortaleza SC, Lima J.W. Pereira E. D. Influence of total face, facial and nasal masks on short-term adverse effects during noninvasive ventilation. *J Bras Pneumol.* 2009;35:164-73.
- Javaheri S, Kazemi H. Metabolic alkalosis and hypoventilation in humans. *Am Rev Respir Dis.* 1987;136:1011-16
- Anderson LE, Henrich WL. Alkalemia-associated morbidity and mortality in medical and surgical patients. *South Med J.* 1987;80:729-33.
- Yoshihisa A, Suzuki S, Yamaki T, Sugimoto K, Kunii H, Nakazato K, et al. Impact of adaptive servo-ventilation on cardiovascular function and prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep-disordered breathing. *Eur J Heart Fail.* 2013;15:543-50. doi: 10.1093/eurjhf/hfs197.

32. Ortho M, Woehrle H. Current and future use of adaptive servo-ventilation. *Eur Resp Pulm Dis.* 2016;2:18-22.
33. Heider K, Arzt M, Lerzer C, Kolb L, Pfeifer M, Maier LS, et al. Adaptive servo-ventilation and sleep quality in treatment emergent central sleep apnea and central sleep apnea in patients with heart disease and preserved ejection fraction. *Clin Res Cardiol.* 2018;107:421-9. doi: 10.1007/s00392-018-1203-9.
34. Bitter T, Westerheide N, Faber L, Hering D, Prinz C, Langer C, et al. Adaptive servoventilation in diastolic heart failure and Cheyne Stokes respiration. *Eur Respir J.* 2010;36:385-92. doi: 10.1183/09031936.00045609.
35. Lyons OD, Floras JS, Logan AG, Beanlands R, Cantolla JD, Fitzpatrick M, et al. Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. *Eur J Heart Fail.* 2017;19:579-87. doi: 10.1002/ejhf.790.
36. Tamisier R, Damy T, Davy J.M. Adaptive servoventilation (ASV) decreases unplanned hospitalizations in chronic heart failure (CHF) patients with central sleep apnoea (CSA): the French multicentre, prospective FACE cohort study. *European Respiratory Society Congress 2015.*
37. Davy JM, Tamisier R. Morbidity and mortality of Chronic Heart Failure (CHF) patients with Central Sleep Apnoea (CSA) treated by adaptive servoventilation (ASV): Interim results of FACE cohort study. *Eur Heart J.* 2017; 38:1.
38. O'Connor CM, Whellan DJ, Fiuzat M, Punjabi NM, Tasissa G, Anstrom KJ, et al. Cardiovascular outcomes with minute ventilation- targeted adaptive servo-ventilation therapy in heart failure- The CAT-HF Trial. *J J Am Coll Cardiol.* 2017;69:1577-87. doi: 10.1016/j.jacc.2017.01.041