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Review Article

Central Sleep Apnea in Heart Failure: From Diagnosis to Therapy

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Abstract

Heart Failure is a condition that affects a significant proportion of population, being known that a big part of the patients with heart failure has a type of sleep breathing disorder. These patients have poor sleep quality which affects their quality of live and survival rates, being important to understand the ideal treatment for them. Adaptative Servo-ventilation used to be the gold standard treatment for patients with heart failure and sleep respiratory disturbs, mainly central sleep apnea. Since SERVE-HF trial the course of treatment of patients with heart failure and central sleep apnea has changed. It's fundamental to study the relationship between heart failure and central sleep apnea to understand the ideal therapeutics for these patients and improve their quality of life and survival rates.

Keywords: *Heart Failure; Central Sleep Apnea; Cheyne-Stokes Respiration; Adaptative Servo-Ventilation*

Abbreviations

HF: Heart Failure; LVEF: Left Ventricle Ejection Fraction; CSA: Central Sleep Apnea; SNS: Sympathetic Nervous System; CSR: Cheyne-Stokes Respiration; N-REM: Non-Rapid Eye Movement; REM: Rapid Eye Movement; NYHA: New York Heart Association; AF: Atrial Fibrillation; TTS: Total Time of Sleep; TIB: Time in Bed; AHI: Apnea-Hypopnea Index; ASV: Adaptative Servo-Ventilation

Heart Failure

Heart Failure (HF) is a syndrome where it's verified a low cardiac output, presenting symptoms like fatigue, dyspnea, edema and orthopnea [1]. It affects around 1 to 2% of general population [2], however, it affects 4 to 16% of population with > 55 years [3], being an growing pathology with countless comorbidities. HF is provoked by valvular heart disease, left ventricular heart block, severe decrease in left ventricle ejection fraction (LVEF), myocardial ischemia or arterial hypertension [3].

Central sleep apnea

Central Sleep Apnea (CSA) is the absence of flow in the airway and of ventilatory effort during sleep [4] due to a reduction on respiratory muscle stimulation by the respiratory drive [5]. It's a rare condition in general population, displaying a prevalence of less than 1% [5], but frequent between patients with HF.

CSA causes clinical conditions such as hypoxia, post-apnea arousals, sudden changes in intrathoracic pressure, dyspnea, variations in heart pressure and an increase on Sympathetic Nervous System (SNS) activity [4]. Frequently CSA presents under the form of Cheyne-Stokes respiration (CSR), which is a periodic and cyclic breathing, alternating periods of hyperventilation with apneas or hypopneas - crescendo-decrescendo pattern - which translates in changes in tidal volume a long time [6-8]. CSR occurs mainly during the transition of waking period to sleep period, namely during stage 1 and 2 of Non-Rapid Eye Movement (N-REM) sleep [1], but it can also occur during the waking period [8].

Physiopathology

It's known that 50 to 75% of patients with HF has sleep breathing disorders [2,4,9], 25 to 50% of these has CSA [3,10,11]. The relationship between HF and CSA is multifactorial and, in these individuals, CSA occurs frequently in the form of CSR [7]. The presence of HF is associated with a respiratory instability [5] because these individuals tend to hyperventilate due to the presence pf pulmonary congestion and augmented chemoreceptors sensitivity [8]. The pulmonary congestion is associated with pulmonary capillary pressure augmented which is aggravated by supine position due to fluid displacement from the lower limbs to the chest [7,8], stimulating the J-pulmonary receptors and provoking hyperventilation [7]. The elevated chemoreceptors sensitivity originates an exaggerated ventilatory response and floatation in CO_2 arterial blood pressure [7,8].

During the waking period the respiration is controlled by metabolic and behaviour factors. The first are due to modifications in the production of CO_2 by the metabolism which stimulates the central and peripheral chemoreceptors originating changes in frequency and tidal volume, with the purpose of correcting the CO_2 arterial pressure [7]. The behaviour factors are voluntary changes in breathing that alter the arterial blood gases levels, which triggers a ventilatory response [7]. During sleep only, the metabolic factors influence the respiratory drive. At the beginning of sleep the respiratory frequency decreases and the CO_2 arterial blood pressure increases above the apnea threshold, allowing a normal breathing during sleep [7,8]. However, in individuals with HF when sleep begins the CO_2 arterial blood pressure doesn't increase normally because these patients have chronic hyperventilation, which facilitates the occurrence of central apneas or hypopneas due to minimal changes in CO_2 arterial blood pressure [8].

The maintenance of an nocturnal hyperventilation pattern in patients with HF triggers an decrease in CO_2 arterial blood pressure below the apnea threshold, which is detected by the peripheral chemoreceptors present in the carotid body and by the central chemoreceptors present in the ventrolateral medulla and retrotrapezoid nucleus, leading the respiratory drive to not stimulate the respiratory muscles and provoking an CSA and therefore an increase in CO_2 arterial blood pressure [6]. However due to the delay in the circulatory time provoked by the low cardiac output, the hypocapnia induced by the hyperventilation and consequently the respiratory drive action is delayed [6]. The presence of this delay causes higher variations in O_2 and CO_2 arterial blood pressure and therefore worst consequences [6]. At the end of the compensatory apnea the CO_2 arterial blood pressure is going to be higher than presumed, originating a new hyperventilation which becomes a cyclic pattern of CSR [7]. When CSR is initiated it's maintained by a combination of: augmented chemoreceptors sensitivity, pulmonary congestion, arousals and hypoxia induced by apnea [12,13].

One of the sleep periods predisposed to the occurrence of respiratory instability is the transition between wake and sleep period, mainly the phase 1 and 2 of N-REM sleep, because the respiratory drive activity is only dependent of metabolic factors [5,8,14], 92% of CSA occur in this period [9]. In Rapid Eye Movement (REM) sleep the respiratory drive response to CO_2 arterial blood pressure variations is minor, occurring rarely CSA [5].

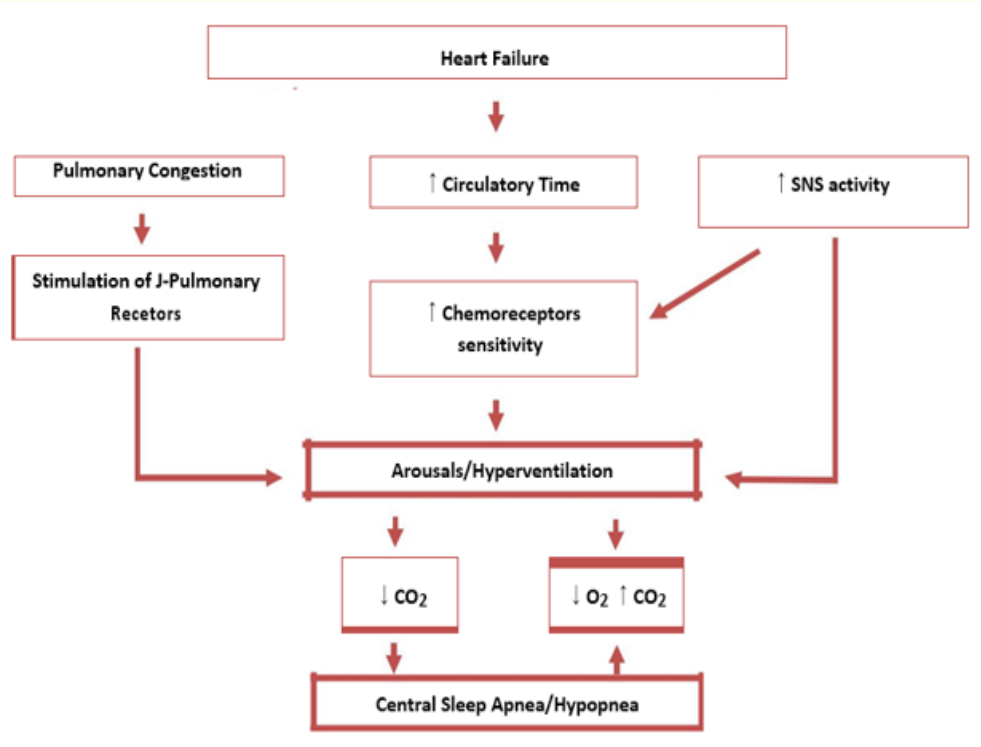
In healthy individuals the metabolic rate, SNS activity, blood pressure and heart rate diminish, and the vagal activity rises during N-REM sleep. In REM sleep it's verified intermittent variations in SNS activity, blood pressure and heart rate [13], the CSA interrupts this process.

There exist risk factors to the presence of CSA in patients with HF namely: being make; elevated New York Heart Association (NYHA) score; reduced LVEF; frequent presence of ventricular arrythmias [7]; atrial fibrillation (AF) [1,7,9,12]; hypocapnia at waking up; elevated levels of type-B natriuretic peptide [7,9,12]; elevated pulmonary capillary pressure; ventricular dilation; pulmonary restrictive pattern [9,12] and frequent hospital admissions for HF exacerbation [1].

Calvin., *et al.* [2] studied the hypothesis that left atrial volume is a predictor factor of the augmented chemoreceptors sensitivity to CO_2 in patients with HF, verifying that the chemoreceptors sensitivity to CO_2 is superior in individuals with HF and CSA comparatively to those without CSA. Simultaneously it was found that left atrial volume correlates with the chemoreceptor's sensitivity, and a volume ≥ 53 ml/m2 indicates a risk of 92% of having CSA. This demonstrates that left atrial volume is strongly related with the presence of CSA and augmented chemoreceptors sensitivity to CO_2.

The presence of CSR during the vigil period was evaluated by Grimm., *et al.* [15], it was verified that its presence is associated with: advanced age; AF; reduced LVEF; augmented left ventricular diastolic diameter; type-B natriuretic peptide augmented levels e elevated NYHA class. They have concluded that the presence of CSR during vigil period is a marker of the HF severity but not a marker of the survival rate.

Sleep breathing disorders disturb normal sleep provoking: abnormalities in arterial blood gas concentrations; arousals; decrease in paratympanic nervous system activity; increase in SNS activity; elevated variation in intra-thoracic pressure [5]; oxidative stress; systemic inflammation; endothelial disfunction [7] and cardiac arrythmias [6]. Several authors defend that CSA is secondary to HF and that participates in the deterioration of cardiac health [13], CSA is also associated with a worse prognosis [16]. On the contrary, some authors defend that CSA with CSR is a compensatory mechanism in cases of severe HF and that it can't affect the cardiovascular system, presenting benefits in these individuals such as: increase in gas volume at the end of inspiration and protection of respiratory muscles from fatigue [9].



Sleep structure

Patients with HF present reduced Total Time of Sleep (TTS) and sleep efficiency [3]. Atalla., et al. [17] verified that individuals with HF, LVEF ≤ 45% and CSA presented a superior Time in Bed (TIB), staying a superior period in phase 1 comparatively with individuals without CSA. Türoff., et al. [18] found that patients with HF or with CSA or with obstructive sleep apnea have a reduced proportion of N-REM sleep, and that the time in phase 3 is between 3,5 to 4,8% but this value should be between 15 to 25% of TTS, which can originate an increase in SNS activity.

Diagnostic criteria in polysomnography

The gold standard exam to diagnose CSA is polysomnography [7].

Diagnostic Criteria of CSA (A or B)+C+D [19]
A. Presence of 1 or more of the following: 1. Daytime somnolence; 2. Difficulty at initiating or maintaining sleep, presence of frequent arousals or not restorative sleep; 3. Waking up with dyspnea; 4. Snoring; 5. Witnessed apneas.
B. Presence of AF, HF or Neurologic disease
C. Polysomnography: 1. Apnea-Hypopnea Index (AHI) ≥ 5; 2. Number of central apnea/hypopnea is > 50 and then the total number of respiratory events; 3. Presence of crescendo-decrescendo respiratory pattern.
D. The disturbance can't be explained by another sleep disturbance or medication.

Treatment

The most supported position is that CSA is a consequence of HF, being fundamental to optimize the HF therapeutic for improving the severity of CSA [5,7]. The optimal HF therapy consists on: diuretics; beta blockers and angiotensin converting enzyme inhibitors [20]. In patients with HF and respiratory sleep disturbance, the CSA is treated to: improve the quality of life; decrease the probability of accidents and reduce the hypersomnolence [21].

Night-time oxygen is one of the therapeutic options for CSA in patients with HF, it was verified that the use of this therapy improves: AHI; exercise capacity [5,7]; LVEF; reduces type-B natriuretic peptide levels; reduces SNS activity [7]; decrease norepinephrine nocturnal levels and ventricular arrythmias [5], on the other hand it doesn't influence daytime sleepiness and quality of sleep [7].

Adaptative Servo-Ventilation (ASV) is a therapy of CSA that administers a continuous positive pressure and has sensors that detect apneas and hyperventilation's, allowing the device to adjust the support pressure and tidal volume to maintain a steady breathing [7,16,21]. The study SERVE-HF [4] investigated the effects of ASV in general and cardiovascular mortality in patients with HF and reduced LVEF, having these fundamentally CSA. The adhesion rate of 60% of patients with ASV was of ≥ 3h/night. They concluded that the general and cardiovascular mortality is superior in the group with CSA (general mortality 34,8% vs 29,3%; cardiovascular mortality 29,9% vs 24%) [4]. Symptomatically the two groups didn't present significant differences, and this fact supports the theory that CSA is an adaptative mechanism of HF [9].

One possible explanation for the SERVE-HF [4] results is that CSA has protective effects that are masked by using ASV. Another hypothesis is that some of these individuals have daytime periodic breathing and treating it during night-time provokes a pathologic exacerbation during daytime [22]. On the other hand, the recommended time for a good therapy adhesion is ≥ 4h/night, and that isn't verified in the SERVE-HF study.

After the SERVE-HF [4] study, the American Academy of Sleep Medicine reshaped the guidelines for using ASV in patients with HF [23]:

1. ASV targeted to normalize the AHI shouldn't be used for the treatment of CSA related to HF in adults with an LVEF ≤ 45% and moderate or severe CSA.
2. ASV targeted to normalize the AHI can be used for the treatment of CSA related to HF in adults with an LVEF > 45% or mild HF related CSA.

Hetzenecker., *et al*. [3] verified that on the group treated with ASV it was observed a reduction of time in phase 1 and an increase of time in phase 2 of N-REM sleep, comparatively with the group without ASV. Several studies showed that ASV improves: AHI; quality of sleep and life; LVEF; NYHA class; type-B natriuretic peptide levels; inflammatory indicators and exercise capacity [16].

Conclusion

To conclude is fundamental to study the relationship between HF and CSA with the purpose of understanding the ideal therapeutics to improve quality of life and survival rates of these patients. At this moment is being conducted another trial - ADVENT-HF - to study the effects of ASV in patients with HF and their survival rate.

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