

## Pneumologia

# Sleep apnea syndrome and heart failure—mechanisms and consequences

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## Abstract

### English:

*Heart failure (HF) remains a major public health issue despite advances in treatment, being associated with increased morbidity and mortality, multiple hospitalization and, implicitly, very high economic costs. Therefore, it becomes increasingly important to identify and treat factors or comorbidities that contribute to the progression of HF. Breathing disorders during sleep (sleep-disordered breathing), especially sleep apnea syndrome, obstructive or central form, may be one of these factors.*

## Keywords

*sleep apnea • comorbidities • heart failure*

# Sindromul de apnee în somn și insuficiența cardiacă – mecanisme și consecințe

## Rezumat

### Romanian:

*Insuficiența cardiacă (IC) rămâne în continuare o problemă majoră de sănătate în ciuda noilor tratamente, fiind asociată cu creșterea mortalității și morbidității, multiple spitalizări și implicit costuri economice ridicate. A devenit astfel deosebit de important identificarea și tratarea factorilor de risc sau a comorbidităților ce contribuie la progresia IC. Tulburările de respirație în timpul somnului, în special sindromul de apnee în somn în formă obstructivă sau centrală pot fi unul din acești factori.*

## Cuvinte-cheie

*apnee în somn • comorbidități • insuficiența cardiacă*

## Introduction


Sleep-disordered breathing (SDB) are more frequent in patients with heart failure (HF) and its prevalence can exceed 50% (1), than in general population, which is ~10% (2). Even if patients with HF are on optimal therapy, association with sleep apnea is linked with poor prognosis and worse functional class (3).

Considering that in Europe are estimated over 14 million of patients cu HF, three million new cases annually diagnosed (4) and the mortality at 5 years for this patients of 40–60% (5), identifying treatable risk factors that might contribute to the progression of HF, may lead to reduction of morbidity

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and mortality (6). One of this risk factor can be sleep apnea syndrome (SAS) (7).

Thus, the significance of identifying and managing sleep apnea should be more emphasized to prevent the development or progression of HF.

### Definition of HF

According to the European Society of Cardiology (ESC) guidelines, HF is a clinical syndrome caused by cardiac abnormality manifested by symptoms (breathlessness, orthopnea, paroxysmal nocturnal dyspnea, reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, ankle swelling) and signs (elevated jugular venous pressure, pulmonary crackles and peripheral edema, hepatojugular reflux, third heart sound—gallop rhythm, laterally displaced apical impulse) and leading to a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress (8).

New classification of HF based on measurement of the ejection fraction (EF) of left ventricle (LVEF), defined three classes: HF with preserved EF (HFpEF), with LVEF  $\geq 50\%$ ; HF with reduced EF (HFrEF) with LVEF  $< 40\%$  and HF with mid-range EF (HFmrEF), LVEF in the range of 40–49%. (8) This new classification aims to better differentiate patients with HF based on LVEF, considering that there are different underlying etiologies, demographics, comorbidities, and response to treatments applied (9).

### Definition of SAS

According to American Academy of Sleep Medicine, sleep apnea is characterized by partial or complete cessation of breathing during nighttime sleep, with duration of minimum 10 seconds (s) and leads to sleep fragmentation with repeated arousal from sleep, oxyhemoglobin desaturation, and daytime sleepiness.

Apnea is defined as complete cessation of airflow for at least 10 s (10), whereas hypopnea is a partial cessation of airflow, with a reduction  $\geq 30\%$  of pre-event baseline in airflow for at least 10 s, accompanied by either 3% decreases in oxyhemoglobin saturation (SaO<sub>2</sub>) or a cortical arousal (11). There are three types of sleep apnea: obstructive, central, and mixed. Obstructive sleep apnea (OSA) is characterized by absence of naso-oral airflow caused by pharyngeal collapse due to decrease in muscle tone but with the presence of thoracoabdominal excursions, because the thoracic inspiratory muscles, including the diaphragm, are active. In contrast, central sleep apnea (CSA) is characterized by a complete withdrawal of central

respiratory drive to the inspiratory muscles and results in both absence of naso-oral airflow and thoracoabdominal excursions. Mixed apnea begins as a central apnea and ends as an obstructive apnea.

Severity of SAS is measured depending on apnea–hypopnea index (AHI), defined as the number of apnea–hypopnea that occur during sleep divided by the number of hours of sleep, and is represented in events per hour. Thus, there are three classes of SAS: mild with 5–15 apnea/h, moderate with 15–30 apnea/h, and severe with  $> 30$  apnea/h.

SAS is usually confirmed by overnight polysomnography in a sleep laboratory during which sleep architecture, cardiac rhythm, SaO<sub>2</sub>, airflow, and thoracoabdominal movements are recorded (12,13).

### Consequences of SAS

The consequences of untreated SAS are multiple and can be related, on the one hand, to sleep fragmentation, patients often feeling unrested, fatigued, and sleepy during the daytime, with the impairments in vigilance, concentration, cognitive function, social interactions, and quality of life (QOL) (14). On the other hand, disordered breathing during sleep are related to intermittent hypoxia, intrathoracic pressure swings, and increased sympathetic nervous activity that can increase risk of developing cardiovascular disease, including uncontrolled hypertension, coronary artery disease, congestive HF, arrhythmias, stroke, and impairment of metabolic regulation with increased risk for diabetes (15–17).

Association of SAS and comorbidities may magnify the cardiometabolic risk, aggravating morbidity and mortality (18,19). SAS is very common in HF patients, with an estimated prevalence between 47% and 76%. SAS causes a number of disorders that may lead to the development of the HF or the exacerbation of HF symptomatology (20).

### OSA in patients with HF

In different studies, the prevalence of OSA in patients with HF varies from 12% to 53%, higher than in the general population (2, 21–23).

Data from the Sleep Heart Health Study (SHH) showed that the presence of OSA with an AHI  $> 11/h$  may be associated with a relative incidence of 2.38 for HF, independent of other known risk factors, including hypertension, coronary artery disease, or stroke (24). The prevalence of OSA in HF patients with altered systolic function exceeds with 5–10% the prevalence of OSA in healthy adults.

Longitudinal studies of the same cohorts after adjusting for risk factors have shown that the severity of OSA has been an important predictor for the incidence of HF in men only (25). Observational study of Wang et al., revealed that untreated OSA, with AHI  $> 15/h$ , in HF patients is associated with an increase in mortality regardless of other risk factors (2,21).

SAS in HF patients causes two major changes that lead to progression of HF and premature death. The first is the negative impact of sympathetic nervous system activation on the cardiovascular system and the second is the negative effect of left ventricular load and the presence of hypoxia (19). The consequence of sympathetic nervous system activation is necrosis and apoptosis of myocytes that predisposes to arrhythmias and an increase in mortality rate. The sympathetic stimulation causes activation of the renin–angiotensin–aldosterone system, which has the negative effect of fluid retention (7). On the other hand, hydrosaline retention due to HF can contribute to the pathogenesis of SAS. These data suggest a bidirectional relationship between HF and SAS (26).

OSA can be more frequent in patients with HF and fluid retention, regardless of body weight, due to increase in mucosal fluid volume around the pharynx that can reduce pharyngeal cross-sectional area and increase transpharyngeal resistance (27). Some studies demonstrate that a reduction in overnight rostral fluid redistribution from the legs into the neck due to compression stockings during the daytime can attenuate OSA (28).

The presence of OSA aggravates other HF risk factors such as hypertension or diabetes and also induces increased sympathetic tone and heart rate. Several studies have shown that an increase in sympathetic tone causes worsening of HF (20,29).

Also, diastolic dysfunction is correlated with SAS and nocturnal hypoxemia. The prevalence of SAS in patients with HF with preserved EF is >70%, but with the predominance of obstructive apnea (20).

SAS, regardless of form, obstructive or central, increases mortality in patients with ischemic HF (30) because the oxidative, mechanical, and autonomic stress that occurs in SAS leads to worsening of myocardial ischemia and thus to increased mortality.

### **CSA in patients with HF**

CSA, which is more common in patients with HF (21–37%), is an important independent predictor of HF mortality (31,32).

Some study demonstrates that CSA is more prevalent in male patients with HF but the reasons are not very clearly defined (33,34).

Central apneas and hypopneas occur in HF patients with CSA while awake as part of Cheyne-Stokes respiration (35,36).

Cheyne-Stokes respiration with central sleep apnea (CSR–CSA) is commonly observed in HF patients and represent a periodic breathing in which central apneas alternate with hyperpnoea that have a waxing–waning pattern of tidal volume (37). The apnea phase of CSR–CSA causes arterial

hypoxemia, and the hyperventilation phase produces surges in blood pressure, arousal from sleep, and dyspnea (36). Usually, CSR–CSA occurs during nonrapid eye movement (NREM) sleep stages 1 and 2 and has a periodicity of about 60 seconds (11).

CSR–CSA appears when partial pressure of carbon dioxide ( $PCO_2$ ) decreased below the apnea threshold caused by hyperventilation (38) due to either stimulation of pulmonary juxta capillary receptors by pulmonary congestion, increased peripheral and central chemo responsiveness, or arousals from sleep (37,39,40). Also, decreased cardiac output may generate ventilatory instability because of increased lung-to-chemoreceptor circulation delay, which is directly proportional with the duration of an apnea–hyperpnea cycle (37,39,40).

Fluid retention may also have a significant impact in the pathogenesis of CSA due to stimulation of pulmonary irritant receptor, which can lead to hyperventilation and hypocapnia (41,42).

CSR–CSA is characterized by two patterns of hyperpnea. In positive pattern, end-expiratory lung volume remains at level or above functional residual capacity, whereas in negative pattern, end-expiratory lung volume decreases below functional residual capacity.

A recent study of Perger *et al.* (43) found that there may be several CSR–CSA subtypes that explain the differences in HF prognosis.

This small study on 33 patients with CSR–CSA showed that patients with negative hyperpnea pattern are more likely to have increased hyperpnea and CSR–CSA cycle durations due to improper cardiac output, higher value of NT-proBNP linked to increased wall tension of left ventricle. Therefore, these patients may have a poor prognosis.

In patients with worse cardiac function, the negative hyperpnea pattern may generate a higher positive expiratory pressure, which act as an adaptive mechanism to maintain stroke volume and cardiac output. Also, in the first part of inspiration, negative pattern may decrease the load of already weakened inspiratory muscles. All these data suggest that CSR–CSA may play a compensatory role in HF with reduced EF. (44)

Although there are many studies in this regard, it is still unclear whether CSR–CSA occurs due to worsening of HF, is it the one who promote progression of HF, or it functions as a compensating mechanism in severe HF to maintain stroke volume (44).

Other risk factors for CSR–CSA are male gender, older age, atrial fibrillation with left atrial enlargement, nocturnal ventricular arrhythmias, New York Heart Association (NYHA) class  $\geq$ II, nocturnal dyspnea,  $EF < 20\%$ , and increased level of Plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (2,45–48).

Also some studies found a high prevalence (40%) of CSR–CSA in patients with systolic HF (49), there are studies who demonstrate that CSR–CSA is common in patients with symptomatic HF with diastolic dysfunction (50) and in patients with asymptomatic systolic dysfunction (32). CSR–CSA seems to be more prevalent in patients with decompensated HF (19).

### **Treatment of SAS in HF patients**

Due to high prevalence in general population but also in HF patients, OSA has been extensively studied and effective therapies have been developed (51). Several studies demonstrated that therapy with continuous positive airway pressure (CPAP) is associated with a reduction of daytime symptoms (52–54), of blood pressure and mortality related to OSA (55,56). A constant positive pressure to the airways is applied through a nasal or facial mask attached to an electric ventilator, to maintain airways patency (57).

SAVE (Sleep Apnea Cardiovascular Endpoints) clinical trial, an international, multicenter, randomized, parallel-group, open-label trial, with blinded endpoint assessment, showed that the risk of serious cardiovascular events was not improved in patients who received treatment with CPAP, supplementary to usual care than in patients who received only usual care. Significantly decreased of snoring and daytime sleepiness and increase of health-related QOL and mood was observed in patients with CPAP therapy (58).

Effects of CPAP therapy in CSA and HF patients was first evaluated in CANPAP study (Canadian Positive Airway Pressure Trial for Patients with Congestive Heart Failure and Central Sleep Apnea) (59), a large, prospective, multicenter study. Because of poor patients' compliance (about 3.6 h/night) and variable effects with CPAP therapy (60), a newer therapy was developed, called adaptive pressure support servo-ventilation (ASV), a synchronized form of positive pressure ventilation. Compliance and efficiency of this therapy was followed in several multicenter studies.

SERVE-HF trial (Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients with Heart Failure) included ambulatory patients with HF with reduced ejection fraction (HFrEF) and CSA, who were randomly assigned to minute ventilation ASV (ASVmv) (AutoSet, ResMed) in addition to optimal medical therapy (61). All-cause mortality was increased and no better change in QOL was observed in ASV group. But this study had important limitations due to low compliance—only 3.4 h/night, 76% of patients used a full-faced mask, the ASV device used a high default pressures, which induced hyperventilation and decreased cardiac output. It was assumed that increased mortality was due either to the fact that suppression of CSA had a negative effect by loss of the adaptive mechanism (44) or increased intrathoracic pressure by ASV may obstruct

venous return to the heart and lower cardiac output (62), or hyperventilation induced by inspiratory pressure support may lead to alkalosis and hypokalemia, which may increase the risk for cardiac arrhythmias (63).

CAT-HF (Cardiovascular Outcomes with Minute Ventilation Targeted Adaptive Servo-Ventilation Therapy in Heart Failure) trial included patients hospitalized for HF, either reduced or preserved EF, with moderate-to-severe SAS (AHI >15 event/h, predominantly CSA) and were followed for the effects of ASV (ResMed) added to optimal medical therapy (64).

Also trial was suspended in light of the SERVE-HF trial results and the primary endpoint of death, cardiovascular hospitalizations, or change in 6-minute walk distance was not achieved, an improved outcome was observed in patients with HF and preserved EF (HFpEF). Data are supported by an ongoing analysis from SERVE-HF reporting that patients with HFrEF have the highest cardiovascular risk, and the response to ASV may depend on EF.

In a population-based study using the Rochester Epidemiology Project database, patients with CSA were followed 2 years pre-ASV and post-ASV initiation and after accounting for adherence to ASV, CSA subtype and comorbidities, no significant differences were observed in terms of rates of hospitalizations, emergency department visits, outpatient visits, and changes of medications prescribed per year (65).

ADVENT-HF (The Effect of Adaptive Servo-ventilation on Survival and Cardiovascular Hospital Admissions in Patients with Heart Failure and Sleep Apnoea) trial, an ongoing randomized multicenter study, included patients with HFrEF and SDB and assesses the effect of using peak flow targeted adaptive servo ventilation (ASVpf) for treating SDB on morbidity and mortality, at 1 and 12 months post randomization (66).

Short- and long-term ASVpf compliance in ADVENT-HF trial were good in patients with HF with either CSA or OSA, possible because of use of lower default pressures with a minimum end-expiratory positive airway pressure (EPAP) of 4 cm H<sub>2</sub>O and a minimum pressure support of 0 cm H<sub>2</sub>O, compared to compliance of ASVmv with high default pressures with EPAP of 5 cm H<sub>2</sub>O and minimum inspiratory pressure support of 3 cm H<sub>2</sub>O on SERVE-HF trial and CAT-HF trial. Also, more frequent interactions with patients were important in increased compliance to ASV therapy. Until the end of the trial, it is unknown if this increased compliance to ASV use, is associated with positive changes in clinical outcome (67).

## **Conclusions**

Undiagnosed and untreated SAS increase morbidity and mortality in HF patients and represent a significant burden

on the healthcare system, with more costs and resources utilization, emphasizing the importance of early diagnosis of this disease.

This might require introduction of SAS screening as a routine method in the management of patients with HF.

### Ethics approval and consent to participate

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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