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Sleep-disordered breathing in heart failure

Zaburzenia oddychania w trakcie snu w niewydolności serca

Barbara Uznańska-Loch, Małgorzata Kurpesa

Chair and Department of Cardiology, Medical University of Lodz, Lodz, Poland

INTRODUCTION

Heart failure (HF) is a major and increasing public health problem. Despite advances in medicine, the disease remains common. Among Framingham Heart Study subjects, the risk of developing congestive HF was estimated as 20% [1]. The chronic and progressive character of HF is related to significantly compromised life quality, increased need for medical care and poor prognosis. Since these issues remain unsolved, great efforts have been made to identify and manage modifiable factors that might be responsible for the thus far unsatisfactory results of HF treatment. One of these factors is probably sleep-disordered breathing.

The major types of sleep-disordered breathing (SDB) in HF are shown in Table 1. They include obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) which may manifest in periodic (Cheyne-Stokes) respiratory pattern.

Apnoea is defined as cessation of airflow for ten or more seconds. Hypopnoea is usually understood as reduced airflow (> 50%) or impairment of respiratory movements of chest and abdomen with oxygen blood saturation decreased by at least 4% and/or arousal [2].

In order to assess the severity of SDB, an apnoea-hypopnoea index (AHI) is calculated. Its value represents the number of apnoea and hypopnoea episodes during an hour of sleep. According to criteria proposed for OSA, the diagnosis is confirmed when AHI is greater than 15, or greater than five in a patient with symptoms [3]. The gold standard for apnoea detection and assessment is polysomnography. However, there is evidence that Holter ECG monitoring may be a useful method of sleep apnoea diagnosis [4].

Obstructive sleep apnoea (Table 1) is characterised by a periodic collapse of the airways that prevents inhalation despite respiratory effort. During sleep, the muscles that maintain patent airways are relaxed and an obstruction may occur, especially in obese individuals with narrowed airways. Despite respiratory movements of chest and abdomen, the airflow ceases. After nervous system activation and arousal, the respiratory effort is increased and the airflow is restored. This type of SDB contributes to a number of cardiovascular (CV) problems.

Central sleep apnoea (Table 1) probably arises as a consequence of HF and is characterised by a periodic lack of central respiratory drive. When a patient lies supine, pulmonary congestion stimulates vagal irritant receptors in the lungs, causing hyperventilation. Increased ventilation results in reduction in $PaCO_2$ even below the threshold level required to stimulate breathing. Efferent activity to the respiratory pump muscles is reduced. With lack of central drive, the respiratory effort ceases. As a consequence, $PaCO_2$ rises and ventilation

Table 1. Major types of sleep-disordered breathing (SDB)

Type of SDB	Characteristics
Obstructive sleep apnoea	Collapse of airways
	Respiratory effort against obstruction during apnoea
Central sleep apnoea	Likely consequence of heart failure
	Periodic lack of central respiratory drive
	No respiratory effort during apnoea
	Cheyne-Stokes respiratory pattern
Mixed sleep apnoea	Both central and obstructive factors contribute to apnoea episode
	Possible gradual shift between predominant mechanisms of apnoea during the night

Address for correspondence:
Barbara Uznańska-Loch, MD, Chair and Department of Cardiology, Medical University of Lodz, ul. Kniaziewicza 1/5, 91–347 Łódź, Poland, e-mail: tyhe@op.pl
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Table 2. Clinical manifestations of sleep apnoea syndrome

Symptoms of apnoea	
Nocturnal	**Daytime**
Choking	Morning headaches
Snoring	Fatigue
Dyspnoea	Sleepiness
Fragmented sleep	Lack of concentration
Arousals	Falling asleep during work or
Nycturia	when driving a car, accidents
Sweating	Mood disorders
Gastro-oesophageal reflux	Sexual dysfunction
(in obstructive sleep apnoea)	

is restored. Arousals are not required for airflow initiation; they frequently occur later and stimulate hyperventilation. The length of ventilatory phase is inversely proportional to cardiac output, which reflects delay in transmission of blood gas tensions from lungs to chemoreceptors. In HF, prolonged circulation results in Cheyne-Stokes respiratory pattern. This type of SDB may be developed on the HF background and then additionally complicates a patient's status.

Mixed sleep apnoea (Table 1) is quite a common situation. In this type of apnoea, during the apnoeic event, both central and obstructive factors contribute to breathing disturbance. The episode usually begins with a reduced central respiratory drive, followed by obstruction. A gradual shift from predominantly obstructive apnoeas in the early hours of sleep to mainly central apnoeas at the end of the night has been described in such cases [5].

In some patients with OSA, after introducing treatment with CPAP/BiPAP (i.e. types of mechanical ventilation: continuous positive airway pressure/bi-level positive airway pressure), there is the persisting or newly arising component of CSA. Before treatment, SDB consists of entirely or predominantly obstructive apnoeas which then convert to entirely or predominantly central apnoeas. In such cases, complex sleep apnoea (CompSA) may be diagnosed.

Clinical manifestations of obstructive sleep apnoea include not only disturbed sleep but also all the consequences for everyday life quality; thus the symptoms can be divided into nocturnal and daytime (Table 2). In patients with SDB, arrhythmia such as atrial fibrillation (AF) or ventricular extrasystoles is more common.

As shown in Table 2, some of the symptoms of SDB are similar to those of HF or the effects of medicines, which may be misleading for the physician. Simple tools designed to assess symptoms of apnoea may be helpful, for example the Epworth Sleepiness Scale or the Berlin Questionnaire. Methods using Holter ECG monitoring to calculate risk of apnoea may be used in further examination. The awareness of apnoea prevalence and risk factors or indicators of sleep-disordered breathing allows early diagnosis.

In a large study on a representative sample of the Bangkok population [6], based on 4,680 interviews, 4% of subjects (5.3% of men and 3.5% of women) complained of habitual snoring (> 3 nights/week) and excessive daytime sleepiness (> 3 days/week) over the course of at least three months. Individuals reporting SDB were older, had greater body mass index (BMI), neck size, and waist circumference. They complained of shorter nocturnal sleep, awakenings, unrefreshing sleep, choking, night sweats, nycturia, and bruxism. Regarding a Western population, there is evidence from the Sleep Heart Health study [7] conducted on 5,615 community-dwelling men and women aged between 40 and 98. The authors clearly defined SDB according to AHI. In the total sample, 53% of subjects had AHI < 5, 29% had AHI from 5 to 14, and 18% had AHI ≥ 15. The authors of the Wisconsin Sleep Cohort study [8], which involved 602 employed men and women aged 30 to 60, estimated the prevalence of SDB (AHI ≥ 5) to be 9% for women and 24% for men.

The prevalence of OSA syndrome in the general population aged 30–60 is assessed as 2–4%. Apnoea is 2–3 times more common in men than in women. In middle-aged individuals, the prevalence is 5% for females and 15% for males. In a population aged 65–95, AHI ≥ 10 is found in 56% of women and 70% of men [9]. In adults with diabetes, the prevalence of AHI ≥ 10 is 48% and AHI ≥ 20 is 29%. The OSA is diagnosed in 30–40% of obese individuals with BMI > 40.

The data concerning HF patients is even more bothering, since many reports indicate a very high prevalence of SDB in this group. According to the literature, most of this population experience different forms of the problem. For example, Javaheri et al. [10] found CSA in 40% and OSA in 11% of HF patients. In another study, Sin et al. [11] examined 450 patients with ejection fraction (EF) of 27.3 ± 15.6%. Using an AHI cut-off of 10, 15 and 20 per hour of sleep, the overall occurrences of SBD were 72%, 61% and 53%, respectively; of CSA they were 33%, 29% and 25%, respectively; and of OSA they were 38%, 32% and 27%, respectively. Oldenburg et al. [12] screened 700 patients with congestive HF (NYHA ≥ ≥ II class, EF ≤ 40%) using cardiorespiratory polygraphy. The SDB was present in as much as 76% of patients (40% CSA, 36% OSA). As regards the severity of SDB in these patients, a mild (AHI = 6–14/h) form of CSA was present in 8% and mild OSA in 17%. More than 50% of the subjects had moderate to severe SDB with AHI of ≥ 15/h (specifically CSA 32%, OSA 19%). The authors suggest that CSA may be a marker of HF severity.

It should be noted that Cheyne-Stokes respiratory pattern may also be present during the daytime in patients with severe congestive HF. Brack et al. [13] monitored 60 patients during 24 h of routine activities with a portable respiratory inductive plethysmograph. During the night, 62% of patients

had ≥ 15 periodic breathing cycles per hour, and during the day the prevalence was 16%! The authors determined that Cheyne-Stokes respiration during ≥ 10% of the daytime was an independent predictor of mortality.

On the basis of many studies, several risk factors particularly indicative of the probability of significant SDB have been identified. These features, especially several of them coexisting in one patient, should encourage further examination. Obese hypertensive men aged ≥ 60 years reporting snoring probably suffer from SDB. Sometimes the family may provide information about witnessed apnoea. The patient would complain of fatigue after awakening and excessive daytime sleepiness, morning headaches, and insomnia. The SDB may be suspected [11] in patients with episodes of angina and during sleep, paroxysmal nocturnal dyspnoea, low $PaCO_2$, AF or ventricular arrhythmia, worsening systolic or diastolic dysfunction of left ventricle (LV), implantable cardioverter-defibrillator, patients complaining of restless sleep and candidates for cardiac transplantation.

PATHOPHYSIOLOGY

In patients with SDB, physiological variability patterns of sympathetic nervous system activity dependent on sleep phases is disturbed by recurring episodes of apnoea. Apnoeas cause hypoxia and hypercapnia and these stimulate chemoreceptors to activate the sympathetic nervous system, including nerves in the walls of blood vessels. In patients with congestive HF, blood pressure fluctuations during Cheyne-Stokes respiration related to oscillations in ventilation have been observed [14]. In OSA at the end of each apnoea episode, sympathetic activation reaches a maximum level. Blood pressure, even in normotensive individuals, may rise as high as 250/110 mm Hg [15]. Recurrent hypoxemic stress seems to increase endothelin secretion and induces vasoconstriction. Catecholamines levels are elevated. Impairment of autonomic regulation extends to daytime, which is reflected by greater variations in blood pressure levels but diminished heart rate variability. Similarly, it has been demonstrated that in HF, CSA is associated with elevated sympathoneural activity, measured as nocturnal urinary and daytime plasma norepinephrine concentrations. After using nasal CPAP, norepinephrine concentrations were significantly reduced [16].

INFLUENCE OF SDB ON CLINICAL COURSE AND PROGNOSIS IN HEART FAILURE

As mentioned before, SDB is related to decreased quality of life [17]. Besides subjective complaints of the patients, there are many consequences of long-term negative impact of apnoea on the CV system. According to a prospective study on 6,441 men and women participating in the Sleep Heart Health study [18], SDB was associated with all-cause mortality. This relationship was particularly noted in men aged 40–70, and the authors suggested a connection to mechanisms involving intermittent hypoxemia and coronary artery disease (CAD).

OSA

The OSA is nowadays considered to be an important background of some cases of arterial hypertension previously recognised as idiopathic. The OSA is a common finding in hypertensive individuals, especially those who are obese, difficult to treat and who have a non-dipper profile (lack of normal fall of blood pressure during the night). The ESH/ESC guidelines from 2007 [19] advise exclusion of OSA with secondary hypertension in such cases. Rising blood pressure is a direct mechanism by which OSA might induce LV systolic dysfunction. Hypertension is the risk factor for ventricular hypertrophy and failure, and OSA has been shown to be related to hypertrophy of the myocardium, increased LV mass and impaired function. This influence increases with higher AHI and could be reversible with effective CPAP therapy.

The prevalence of insulin resistance and metabolic syndrome rises with the severity of OSA. Increased levels of inflammation markers were also observed. The presence of OSA is related to higher prothrombotic activity, with increased markers of thrombotic risk. It has been shown that excretion of urine albumins may be related to the presence and severity of apnoea [20]. This might be a sign of underlying endothelium dysfunction in patients with OSA. Patients with OSA (with or without CV disease) have been shown to report more premature deaths of CV causes in their family history. The OSA causes repetitive forced inspiration, with substantial negative pressures in the chest cavity, to levels approaching 65 mm Hg. Pressure changes cause increased transmural gradients across the atria, ventricles and aorta, and may disrupt ventricular function.

Arrhythmias are frequent in OSA (nocturnal arrhythmias in up to 50% patients) and the prevalence of rhythm disturbances rises with AHI and the severity of the associated hypoxemia. Different forms of arrhythmia have been described: ventricular beats with nonsustained ventricular tachycardia, bradyarrhythmia-like sinus arrest or second-degree atrioventricular conduction block and AF [21]. Untreated OSA greatly increases the risk for recurrence of AF after successful cardioversion. A recent study in a large cohort of older men showed that increasing severity of SDB was associated with a progressive increase in the likelihood of AF and complex ventricular ectopy. As regards central or obstructive types of SDB, complex ventricular arrhythmia was associated most strongly with OSA and hypoxia, whereas AF was associated with CSA. These findings suggest that different forms of sleep-related stresses may contribute to atrial and ventricular arrhythmogenesis in older men [22].

In individuals with no history of CAD who underwent computed tomography, coronary artery calcification score was

Table 3. Treatment of sleep-disordered breathing

Therapeutic interventions	
Obstructive sleep apnoea	**Central sleep apnoea**
GOLD STANDARD: Continuous positive airway pressure	IMPORTANT: Optimal treatment of heart failure
Reducing body weight	Adaptive pressure support servoventilation
Avoiding alcohol, smoking, sedatives	Continuous positive airway pressure
Surgical correction of airways	Cardiac resynchronisation therapy
Oxygen supplementation	Oxygen supplementation
Adjusting body position during sleep	Drugs?

shown to be related to OSA. Patients with CAD significantly more often have coexisting OSA than the controls. The relationship between ischaemic heart disease and OSA is independent of gender, age, BMI, arterial hypertension and diabetes [23, 24].

Shahar et al. [25] studied a subgroup consisting of 6,424 individuals selected from the Sleep Heart Health study population. They found an inverse correlation between AHI and HDL-cholesterol level. There was a positive relationship between AHI and diabetes, arterial hypertension and CV diseases (all, CAD, stroke). The correlation between AHI and HF or stroke was even stronger than with CAD.

Via all these mechanisms, SDB contributes to increased mortality [26] and morbidity. The OSA is a risk factor of developing HF [27] as well as coronary events (myocardial infarction, coronary artery revascularisation procedures) or death from CV causes [28]. Untreated OSA may, through sympathetic nervous system activation, lead to an elevated risk of arrhythmia. It has been demonstrated that in OSA a peak in sudden death from cardiac causes is shifted in comparison with the general population towards the period of sleeping hours (in the general population the risk of sudden death peaks between 6am and noon, with its nadir from midnight to 6am) [29].

CSA

The CSA may also contribute to cardiac electric instability [30] and impair the quality of life in HF patients. There is evidence that treatment of CSA in HF patients may improve further clinical course. In a trial on 66 patients (29 with and 37 without CSA), the subjects were randomised to either a group that received CPAP or to a control group. In patients with CSA, using CPAP resulted in both a significant improvement in EF at three months and a relative risk reduction of 81% in the mortality — cardiac transplantation rate [31]. Nocturnal Cheyne-Stokes respiration is known to be an independent predictor of cardiac death in patients with EF $\leq$ 35% [32]. An early, small study [33] on 16 male patients with chronic, stable congestive HF, nine with Cheyne-Stokes respiration and seven without, showed a significant difference between the number of deaths in each subgroup over the next few years of follow-up. In the Cheyne-Stokes respiration subgroup, five patients died and two received a heart transplant, whereas only one patient died in the other subgroup. A recently published study on 283 patients [34] with congestive HF with EF $<$ 40%, after implantation of a cardiac resynchronisation device with cardioverter-defibrillator (CRT-D), confirmed the high prevalence of SDB (AHI $\geq$ 5) in this population. It also proved that both subgroups with OSA and CSA had shorter times to appropriate CRT-D intervention and higher risks of ventricular tachyarrhythmia. Importantly, the hazard ratio was even higher in patients with CSA than with OSA. Generally, the CSA subgroup tended to have a worse profile of several parameters used for HF assessment, including serum concentration of NT-proBNP, EF, and VE/VCO_2 slope in cardiopulmonary exercise testing. The CSA has been reported to be correlated with poor survival in systolic HF, alongside severity of right ventricular systolic dysfunction and low diastolic blood pressure [35].

TREATMENT

Therapeutic methods are summarised in Table 3. In some patients, body position during sleep has a great impact on the severity of SDB, and avoiding sleeping on one's back results in reduction of AHI. Small studies regarding possible benefits from exercise training in SDB have resulted in contradictory results. An initial study proposed overdrive atrial pacing as a way of reducing apnoeas, but further research did not support these findings.

Treatment of obstructive sleep apnoea

Obese patients with OSA are advised to reduce body weight. Alcohol, smoking and sedative drugs should be avoided.

In some cases, surgical correction of airways (for example nasal septum correction, tonsillectomy, uvulopalatopharyngoplasty) may be beneficial. There are also less invasive strategies of opening airways by using a dental appliance (oral appliance therapy) such as a mandibular repositioner, tongue-retaining device or palatal lifting appliance.

The gold standard in OSA treatment is CPAP. The device maintains positive pressure in the airways, thus preventing

obstruction. There are different protocols for pressure regulation: stable pressure on exhalation and inhalation (CPAP); two different pressure levels with lower value for exhalation (BiPAP); low pressure during exhalation and changing pressure during inhalation (ASV, adaptive pressure support servoventilation). The choice of protocol depends on the patient's tolerance of the treatment. Nasal mask CPAP may be used alongside an oral appliance therapy method. Oxygen supplementation may be considered in patients intolerant of mechanical devices [36].

Treatment of central sleep apnoea

According to the AHA/ACC statement from 2008 [37], given the lack of evidence from randomised trials showing a significant benefit with respect to hospitalisation or mortality, there is no consensus as to whether CSA in HF should be treated or what the best therapy may be.

Optimal treatment of HF may normalise $PaCO_2$, reduce congestion and thus reduce the tendency to periodic breathing. Carvedilol, like other beta-blockers, reduces sympathetic activation but doesn't share their negative effect on melatonin secretion. Theophylline has been proved to reduce the severity of CSA in a five day trial. In patients with HF, long-term treatment with theophylline is questionable because of possible adverse effects (for example arrhythmogenic). In a small study, administration of a single dose of acetazolamide before sleep improved CSA and its related daytime symptoms [38].

Cardiac resynchronisation therapy (CRT) has been reported to have a beneficial impact on CSA severity in patients with HF. The CRT reduced AHI and also improved EF and exercise capacity, and reduced NYHA functional class.

In patients with CSA undergoing heart transplantation, CSA may subside, though in such cases OSA may arise.

Nocturnal supplemental oxygen has been shown to have promising effects in short period studies. Oxygen therapy may improve maximal exercise capacity. The beneficial effect was also reflected by decreased overnight urinary noradrenaline excretion.

If, for patients with OSA, CPAP is considered the optimal treatment, for patients with CSA, the evidence is not so clear. In patients with CSA in whom CPAP caused improvement of SDB, reduction of ventricular arrhythmia, AHI, desaturation, blood and urinary noradrenaline levels and increased LVEF was observed. However, the CANPAP study [39], a multi-centre randomised controlled trial, showed no survival benefit in a group of 258 patients with HF and CSA. This surprising result provoked further analysis of the data from this study. There were concerns that in the subgroup receiving CPAP, mean AHI remained as high as 19. That might explain unsatisfying effectiveness of treatment in the whole CPAP subgroup. In post-hoc analysis, the study population was divided into three groups: those not receiving CPAP (control), those who were treated with CPAP and reached AHI < 15 in polysomnography three months after enrollment (CPAP-CSA–suppressed, 57%), and finally those whose AHI remained ≥ 15 despite CPAP (CPAP-CSA–unsuppressed, 43%). CPAP-CSA–suppressed subjects experienced a greater increase in LVEF at three months and significantly better transplant-free survival than control subjects, whereas the CPAP-CSA–unsuppressed group did not [40].

In some patients unresponsive to CPAP, adaptive pressure support servoventilation may be effective. This method allows different degrees of support in different phases of periodic breathing and smoothes out periodic breathing. Improvement during this treatment was described as more pronounced than that obtained with CPAP or oxygen supplementation.

SLEEP-DISORDERED BREATHING IN HEART FAILURE WITH PRESERVED LVEF

The data regarding SDB in HF with preserved EF (HFPEF) is limited in comparison with many studies conducted in congestive HF. There are a few reports suggesting that in HFPEF the prevalence of sleep-disordered breathing is considerably high. For example, in a small early study on 20 individuals with symptomatic HFPEF, Chan et al. [41] found significant SDB (defined as AHI > 10) in 55% of the patients and its presence seemed to be related to worse diastolic dysfunction. Consistent findings were presented by Bitter et al. [42]. In 244 patients, SDB (defined as AHI ≥ 5/h) was present in 69.3% of all subjects; 97 (39.8%) patients had OSA and 72 (29.5%) patients had CSA. Increasing impairment of diastolic function was related to more severe SDB, particularly CSA. Patients with SDB had worse exercise capacity.

As to the possible pathophysiology of obstructive apnoea in HFPEF patients, Bucca et al. [43] studied 15 individuals with severe OSA, hypertension, and diastolic HF. The patients underwent therapy consisting of i.v. furosemide 20 mg and spironolactone 100 mg, bid for three days. Such diuretic treatment caused a significant decrease in body weight, blood pressure and AHI (from 74.89 ± 6.95 to 57.17 ± 5.40/h, $p < 0.001$). The authors suggest that this treatment reduced pharyngeal oedema, which may contribute to SDB.

CONCLUSIONS

Sleep-disordered breathing in HF is very common and is related to a worsened prognosis. The prevalence of apnoea will increase with the growing population of HF patients. Further studies are needed to identify optimal diagnostic and therapeutic strategies and address the question of SDB in a large group of patients with HF with preserved ejection fraction.

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