Sleep disordered breathing in patients with heart failure

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Abstract

Sleep disordered breathing (SDB) is a common co-morbidity in patients with heart failure (HF). Both its forms — central and obstructive sleep apnea — are highly prevalent in this population. SDB fragments sleep, impairs life quality, worsens exercise tolerance, worsens HF and is an independent predictor of poor prognosis. Therefore, early detection of SDB seems to be of primary importance, especially in the presence of new diagnostic and therapeutic methods. Treatment with continuous positive airway pressure (CPAP) increases left ventricular ejection fraction and stroke volume in virtually all HF patients with obstructive and in 50% with central sleep apnea. For those in whom central sleep apnea is not suppressed by CPAP, a trial of adaptive servoventilation is recommended. Although no randomized, controlled trials have shown improvement in mortality, several observational studies have shown that effective treatment of both forms of sleep apnea with various positive airway pressure devices improves survival of HF patients. Currently, 2 large trials with newer masked based therapies with adaptive servoventilation are in progress. This article is a brief overview of present knowledge, the pathophysiology, diagnostic approach and therapy of SDB. (Cardiol J 2013; 20, 4: 345–355)

Key words: central sleep apnea, Cheyne Stokes respiration, heart failure

Introduction

Sleep disordered breathing (SDB) is one of the most common and yet largely under-diagnosed co-morbidity in patients with heart failure (HF) [1, 2]. It leads to further deterioration of cardiac function and worsens prognosis [3–6]. SDB may be a potential therapeutic target as its effective treatment improves quality of life, exercise tolerance and, possibly, long term prognosis [5–10]. However, the importance of SDB remains unrecognized and the disorder itself is diagnosed rarely and remains untreated [5]. The availability of simple screening methods and severe clinical consequences of SDB justify routine and widespread screening and appropriate treatment.
Diagnosis and definitions

Overnight polysomnography (PSG) is the gold standard for diagnosing SDB. These studies are completed in a sleep laboratory with monitoring. During a sleep study, breathing disorders can be detected and differentiated into central (CSA) and obstructive sleep apnea (OSA), based on presence of respiratory effort. Multiple parameters are monitored including oro-nasal airflow, thoracoabdominal movements, arterial blood oxyhemoglobin saturation, electrocardiogram (ECG), at least 2 channel electroencephalogram (EEG), chin and anterior tibialis electromyogram (EMG) and electrooculogram (EOG). With this montage total recording time, total wake time, total sleep time, sleep stages, apnea/hypopnea index (AHI) and arousal index are accurately determined.

Apnea is defined as a cessation of respiratory airflow for 10 s or more. If respiratory effort, manifested by abdominal and/or chest wall movement, is present, OSA is diagnosed (Fig. 1). CSA is diagnosed when no respiratory muscles activity is detected (Fig. 2). Hypopnea is defined as the reduction in airflow by at least 50% of the preceding baseline associated with the drop in arterial blood oxygen saturation of at least 3%. An alternative definition of hypopnea is reduction of airflow by at least 30% and associated with 4% or more desaturation. The number of apnea and hypopnea episodes during 1 h of sleep, known as AHI, is a valuable tool in recognition of sleep disorders and determination of their severity. Normally AHI should not exceed 5/h. An AHI of 5 to < 15/h of sleep is considered mild, ≥ 15 to < 30/h moderate and ≥ 30/h severe SDB [11]. Disordered breathing events are also associated with arousals. The number of arousals per hour of sleep is calculated as the arousal index.

Due to low accessibility and high cost of PSG new diagnostic methods have been developed. Self-assessment questionnaires, such as the Epworth Sleepiness Scale or Berlin Questionnaire, estimating the probability of SDB presence based on subjective symptoms are in common use. These questionnaires have been successfully used in general population, but as noted below they are
virtually useless for suspicion of sleep apnea in HF patients.

There are numerous clinical findings that may suggest OSA in general population, such as snoring, interrupted sleep, increased daytime sleepiness, morning headaches, nocturia, chronic fatigue, arterial hypertension, and arrhythmias. A number of these symptoms such as interrupted sleep, nocturia, fatigue and arrhythmias are non-specific, being present in HF itself. Furthermore, in patients with HF, the prevalence of excessive daytime sleepiness is similar between those with or without sleep apnea [12, 13]. For all these aforementioned reasons, sleep apnea remains under diagnosed in HF [5]. Snoring, however, remains a predictor of OSA in patients with HF as it is, in general population. Similarly, hand in hand with snoring, obesity remains a major risk factor for OSA in HF, and its prevalence is on the rise in this population.

Diagnosis of CSA in patients with HF is most problematic as HF patients with CSA are generally thin and do not snore much [12]. Major predictors of CSA are atrial fibrillation, very low left ventricular ejection fraction (LVEF less than 20%), presence of nocturnal ventricular arrhythmias and a low steady state arterial PCO₂ [13].

Recently, new methods which seem to be useful in identifying patients with SDB have appeared. One of them utilizes heart rate variability (HRV) assessment. A typical pattern of HRV with very low frequency rhythms has been found in patients with HF and SDB, especially with CSA (for review see reference [14]). This can be measured at home with a Holter monitor, but is not diagnostic for the type or severity of SDB. Another method that can be applied in patients with implanted pacemakers, relies on the assessment of minute ventilation by evaluation of changes in transthoracic impedance between the pacemaker case and the electrode tip. It enables detection of decreased ventilation episodes. However, it cannot differentiate between obstructive and central episodes. Importantly, this method showed high sensitivity in identifying severe SDB when compared to traditional PSG, suggesting its potential application as a screening tool in patients with implantable cardiac devices [15].

Home sleep-studies with cardiorespiratory polygraphy have been utilized for diagnosis of sleep apnea both in general population and in patients with HF. A major the difference with in laboratory PSG is lack of EEG. There are several portable devices available: Embletta, ApneaLink, Stardust, Venla, to name a few. Typically, they consist of nasal pressure detector, belts detecting thoraco-abdominal movement and finger pulse oximeter. They have some potential advantages over PSG, such as lower cost, better sleep quality in home environment than in sleep laboratory, portability and broad accessibility. However, home sleep-studies cannot replace full PSG as for lack of EEG, total sleep time cannot be determined. As a result, the true AHI (AHI/h of sleep) is underestimated, as the denominator used for the calculation is the total recording time, and not the hours of sleep. This is an important consideration, since patients with HF...
have curtailed sleep time even after spending 2 consecutive nights in sleep laboratory for habituation [12, 13]. Therefore, a number of HF patients with SDB may go unrecognized as a negative polygraphy does not rule out significant sleep apnea.

### Epidemiology of SDB in HF

The prevalence of SDB has been extensively studied both in patients with reduced as well as preserved LVEF. In the population of patients with HF and reduced left ventricular ejection fraction, SDB occurs frequently. Multiple studies (Table 1) show a high prevalence of sleep apnea both central and obstructive in this population [13, 16–20]. One important difference is the variability in the distribution of central vs. obstructive disordered breathing events. This difficulty stems from accurately differentiating obstructive and central sleep hypopneas from each other. Combining the results of multiple studies from various countries, the overall prevalence of sleep apnea in patients with HF with a threshold of an AHI of 15 or more per hour is 52%. Central apnea accounts for 32% and obstructive apnea for 20% (Table 1). It is important to emphasize that the subjects enrolled in most recent studies were consecutive patients with stable HF on contemporary therapy. Therefore, the results of these studies are consistent with those of early studies in which only 10% of the patients were on a beta-blocker (Table 1). We therefore conclude that introduction of beta-blockers for treatment of HF has had no major impact on the prevalence of sleep apnea in this population.

There is growing evidence that sleep apnea is also highly prevalent in patients with HF and preserved ejection fraction. Bitter et al. [21] used echocardiography and right and left heart catheterization to characterize sleep apnea in 244 consecutive patients with HF and preserved ejection fraction. In this study, 33% had coronary artery disease, 44% had systemic hypertension and 23% had hypertrophic/restrictive cardiac disease. Using polygraphy without EEG, 48% of the patients had an AHI ≥ 15 h of recording time. As noted earlier, polygraphy may underestimate the severity of sleep apnea, therefore the data from patients with HF and preserved ejection fraction are virtually similar to those in patients with HF and reduced ejection fraction. Twenty-five percent of the 244 patients had OSA and 23% had CSA.

### Pathomechanisms of SDB

#### Central sleep apnea

Central sleep apnea occurs in the background of a specific respiratory pattern known as Hunter-Cheyne-Stokes breathing (HCSB). It had first been described by John Hunter [22], 37 years before it was described by Cheyne in 1818 [23] (see references [1] and [2] for more details). HCSB is characterized by recurrent episodes of apnea/hypopnea in the context of long crescendo-decrescendo breathing cycles. The length of the cycle reflects the prolonged circulation time, the pathologic feature of HF. HCSB occurs in patients with HF both during the day and at night, but CSA occurs only during sleep or when the patient is dozing. Pathological mechanisms underlying CSA have been widely investigated within last decade and explained in detail in a recent monograph [24]. The important factors involved in pathophysiology of CSA are: diminished PCO2 reserve (difference between eupneic PCO2 and apnea threshold) [24,

### Table 1. Prevalence of sleep apnea (AHI ≥ 15/h), central (CSA) and obstructive (OSA) sleep apnea in recent prospective studies in patients with heart failure with reduced ejection fraction; NA — not available. Modified from: [2].

<table>
<thead>
<tr>
<th>Country [year] Author N</th>
<th>AHI ≥ 15/h</th>
<th>CSA</th>
<th>OSA</th>
<th>β-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>*USA [2006] Javaheri</td>
<td>100</td>
<td>49%</td>
<td>37%</td>
<td>12%</td>
</tr>
<tr>
<td>USA [2008] MacDonald</td>
<td>108</td>
<td>61%</td>
<td>31%</td>
<td>30%</td>
</tr>
<tr>
<td>*Canada [2007] Wang</td>
<td>287</td>
<td>47%</td>
<td>21%</td>
<td>26%</td>
</tr>
<tr>
<td>*UK [2007] Vazir</td>
<td>55</td>
<td>53%</td>
<td>38%</td>
<td>15%</td>
</tr>
<tr>
<td>Germany [2007] Oldenburg</td>
<td>700</td>
<td>52%</td>
<td>33%</td>
<td>19%</td>
</tr>
<tr>
<td>*Germany [2009] Hagenah</td>
<td>50</td>
<td>64%</td>
<td>44%</td>
<td>20%</td>
</tr>
<tr>
<td>*Germany [2010] Jilek</td>
<td>273</td>
<td>64%</td>
<td>50%</td>
<td>14%</td>
</tr>
<tr>
<td>*Portugal [2010] Ferreira</td>
<td>103</td>
<td>46%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>1676</td>
<td>54%</td>
<td>34%</td>
<td>20%</td>
</tr>
</tbody>
</table>

* Asterisk indicates studies using polysomnography.
Hyperventilation is a consequence of chronic pulmonary congestion and interstitial pulmonary edema. In response to pulmonary congestion vagus nerve becomes activated (by non-myelinated type C nerve fibers in parenchyma of the lungs, in alveolar bronchioles, alveolar capillaries and distention-sensitive receptors), that leads to central activation of breathing. Meanwhile, pulmonary congestion also decreases the PCO2 reserve and predisposes to central apnea [24], this by mechanisms not fully explained. Therefore, during sleep, even a slight increase in ventilation caused by arousal or changes in position may lead to a drop in PCO2 below the apnea threshold and results in occurrence of apnea episode. Cessation of breathing leads to accumulation of CO2 which is the chemical stimulus for resumption of ventilation. Enhanced chemoreceptor sensitivity propagates excessive ventilation and subsequent drop in PCO2 below apnea threshold and the next apnea [1, 2, 24, 26]. The duration of the cycle of periodic breathing is proportional to circulation time from lung to chemoreceptors.

In HF patients with CSA, PCO2 does not increase at sleep onset which narrows PCO2 reserve increasing the likelihood of developing CSA. It has been suggested [2, 24] that lack of increase in PCO2 results from inability to decrease ventilation that normally occurs at sleep onset. Patients with HF, particularly those with severely impaired diastolic function, may develop an increase in pulmonary capillary pressure due to increased venous return, which in turn reflexively increases respiratory rate and ventilation at sleep onset. Therefore, nocturnal rostral shift of fluid into the lung causing pulmonary congestion enhances CSA [28].

Another factor which may increase the likelihood of developing central apnea is cerebrovascular response to PCO2 which may result in reduced PCO2 reserve. To this end Xie et al. [31] used indomethacin to reduce cerebral blood flow response to PCO2 and using a mechanical ventilator in pressure support mode gradually reduced PCO2 until apnea occurred. They observed that in conditions of decreased cerebrovascular reactivity, PCO2 reserve needed to produce an apnea dropped from 6.3 to 4.4 mm Hg [31]. This is an important observation as cerebral blood vessels reactivity to CO2 is diminished in patients with HF [32], which may lead to a significant decrease in PCO2 reserve and consequently promote breathing instability.

Obstructive sleep apnea

The pathomechanisms of OSA are complex and their detailed description remains beyond the goal of this article, however they have been discussed in detail elsewhere [33]. The main underlying mechanism of OSA is partial or complete occlusion of upper airway, mainly due to genioglossus muscle relaxation in the face of altered mechanical properties of the upper airway. With this background, negative pressure within airways generated by diaphragm contraction during inspiration results in pharyngeal collapse and obstruction.

Factors that impair upper airway patency relate to upper airway anatomical abnormalities such as micrognathia, retrognathia, hypertrophy of palatine tonsils, macroglossia and increased adipose tissue deposition. In patients with HF, rostral fluid shift in supine position causing venous congestion and upper airway edema may further predispose to upper airway collapse [28].

We must emphasize however, that most frequently both types of apnea occur together during one night. This was recognized early on for which reason we used arbitrary criteria to define whether the breathing disorder is predominantly central or obstructive in nature [12, 13, 34]. Presence of a hybrid disordered breathing and the predominant form of sleep apnea depends on a number of factors such as use of alcohol, medications, changes in position and body weight and fluid shifts.

Clinical consequences

Normally, about 80% of the sleep period is non-rapid eye movement sleep (NREM), when increased parasympathetic activity and decreased sympathetic activity is observed. This is associated with a drop in heart rate, cardiac output and
blood pressure, therefore, there is cardiovascular quiescence. However, in the face of sleep apnea, NREM sleep is fragmented with arousals, and along with other consequences of sleep apnea, a hyperadrenergic state is created [1, 2].

We must emphasize that the biological consequences of sleep apnea which adversely affect cardiovascular function are qualitatively similar in both forms of apnea although such adverse effects are more severe in OSA than CSA (Fig. 1).

Consequences of sleep apnea in HF

The SDB events are characterized by cycles of apnea/hypopnea followed by recovery. The 3 main consequences of SDB are hypoxia/hypercapnia, negative swing in intrathoracic pressure and arousals (Fig. 1–3). During recovery following apneas or hypopneas, ventilation increases and reoxygenation/hypocapnia ensue. These consequences of sleep apnea are qualitatively similar when the 2 forms of apnea are compared; however, they are more pronounced in OSA than CSA (Fig. 3).

A major adverse consequence of apneas/hypopneas is elevated sympathetic nervous system activation induced by repetitive arousals and hypoxia/hypercapnia (Fig. 3) through enhanced peripheral and central chemoreceptors [1, 24, 26, 27, 35]. Increased sympathetic activity leads to vasoconstriction and subsequently to a surge in blood pressure, heart rate and left ventricular afterload — changes that are particularly unfavorable in patients with HF. As a consequence of elevated sympathetic activation nocturnal arrhythmias may also occur [11, 13, 29, 34]. Most recently [36], it has been shown that in HF patients with sleep apnea, current smoking further increases the odds ratio for nocturnal arrhythmias considerably; nicotine, via activation of the peripheral chemoreceptors, a shared pathway with hypoxia, increases sympathetic activity and this hand in hand, with other consequences of sleep apnea contribute to excess nocturnal arrhythmias in HF [39], creating the substrate for sudden cardiac death, a major mode of mortality in these patients. Cessation of smoking should have a major impact on prevention of sudden cardiac death in HF patients, particularly those with sleep apnea as it does in patients with coronary artery disease.

Hypoxia and hypercapnia lead to vasoconstriction not only in systemic but also in pulmonary circulation resulting in augmented right ventricle afterload (Fig. 3). Hypoxia along with reoxygenation which occurs with increased ventilation consequent to apnea, similar to ischemia-reperfusion, results in oxidative stress, inflammation and eventually endothelial dysfunction contributing to progression of HF as detailed elsewhere [1, 2]. Activation of redox–sensitive genes via transcription factors such NFκb are involved in these processes.

As noted above, the consequences of CSA and OSA are qualitatively similar, though there are quantitative differences. One such difference is the large negative intrathoracic pressure drops during upper airway occlusion which defines obstructive apnea (Figs. 1, 2). These pressure
changes are reflected in the surrounding of all intrathoracic structures and have significant hemodynamic consequences. Augmented gradient between intraventricular pressure and intrathoracic (juxtacardiac) pressure, which determines left ventricular transmural pressure, causes increased ventricular wall tension and oxygen consumption. Negative intrathoracic pressure increases venous return and right ventricular preload [1, 2] which may cause septal deviation impairing left ventricular stroke volume. The negative pressure in the lung interstitial compartment promotes pulmonary edema (Fig. 3) [1, 2]. The described changes have unfavorable impact on left ventricular function and may cause or worsen existing HF.

Not only left ventricular, but also atrial function and structure may be affected by repetitive negative shifts in intrathoracic pressure. Augmented negative pressure gradient between intra-atrial cavities and juxtacardiac space causes atrial chamber distension and fibrosis resulting in structural atrial remodeling as well as increased P-wave duration in ECG recognized as electrical atrial remodeling. These pathophysiological changes along with increased sympathetic activity and myocardial hypoxia are believed to be the substrate for atrial fibrillation [37].

Regarding negative pressure swings associated with CSA, these will be noted during the hyperventilation which follows the apnea; the magnitude of the negative pressure changes depend on stiffness of the lung and also the depth of inhalation.

**Treatment of sleep apnea in HF and its impact on cardiovascular function and mortality**

The various therapeutic approaches for both OSA and CSA have been reviewed extensively elsewhere [1, 2, 38] and will only be briefly reviewed below.

**Obstructive sleep apnea**

In OSA, general recommendations include lifestyle changes such as exercise, cessation of smoking and weight loss when applicable, avoidance of alcohol, hypnotics, opioids, phosphodiesterase inhibitors, and supine position during sleep. Pharmacological approaches to treat OSA in general have not proven effective [39]. However, fluid overload should be treated aggressively. Phosphodiesterase inhibitors [40] and opioids [41] at bed time could worsen sleep apnea and should be avoided. Phosphodiesterase inhibitors perhaps via vasodilatation and vascular congestion in the nasal cavity and upper airway could promote OSA, and opioids via central mechanisms could cause central and obstructive apneas [41].

Continuous positive airway pressure (CPAP) ventilation is the treatment of choice. It provides upper airway patency (pneumatic splint) and at appropriate airway pressure keeps the upper airway open preventing development of obstructive apnea and hypopnea. In patients with OSA and HF with reduced ejection fraction, 3 randomized clinical trials have shown variable [42–44] but significant increases in LVEF following 1 to 3 month therapy with CPAP. In a fourth randomized study [45], ejection fraction did not change significantly; in this regard, perhaps the most important issue is adherence to CPAP [1, 2, 38, 46].

There is only one double-blind placebo-controlled (sham CPAP, a CPAP device with minimal pressure) trial in HF with preserved ejection fraction [47]. In this study of 12 weeks duration, effective CPAP therapy resulted in a significant increase in E/A ratio and a significant decrease in isovolumic relaxation and mitral deceleration time [47].

In regards to mortality, observational studies [4, 5, 48, 49] suggest that HF patients with OSA have a shorter survival compared to matched patients without OSA, and that effective treatment of OSA with CPAP [5, 48, 49] improves survival, but only in those who remain adherent to CPAP. This observation that adherence to CPAP is critical for survival, is similar to that noted above for improved LVEF. The reason why many HF patients are not compliant with CPAP is that they commonly do not suffer from excessive day time sleepiness and therefore do not see any immediate improvement. This is in contrast to garden variety OSA patients whose day time sleepiness is eliminated by CPAP and therefore they remain CPAP-compliant. Adherence is the Achilles tendon of CPAP.

In the largest study from US [5] of medicare beneficiaries with newly diagnosed HF, the survival of the 258 patients who were diagnosed with sleep apnea and were treated for it, was far superior to the other 30,065 HF patients who were not tested for sleep apnea (Fig. 4).

**Central sleep apnea**

Multiple studies have shown that CSA is an independent predictor of mortality in HF ([3], [6], [7]; for reviews see [1], [2]) (Fig. 4). In one of the studies with a large number of variables as confounders, high AHI, low diastolic blood pressure
and right ventricular ejection fraction were the 3 variables which independently were associated with excess mortality [6].

Meanwhile, there are multiple options for treatment of CSA in HF. The severity of CSA is related to degree of left ventricular dysfunction and therefore optimization of medications and resynchronization therapy when applicable are of primary importance in management before performing a sleep study [1, 2]. Optimal medical therapy decreases pulmonary congestion, hyperventilation, and circulation time all of which may stabilize breathing during sleep. Improvement of CSA during therapy with beta-adrenolytics has been demonstrated [50]. However, HF is a progressive disorder, and overall introduction of beta-blockers has not changed the prevalence of sleep apnea in HF (Table 1).

Meanwhile, resynchronization therapy improves CSA, which is in contrast to OSA. A recent meta-analysis [51] of 9 studies (170 patients) revealed that in patients with CSA resynchronization therapy reduced AHI significantly — mean reduction in AHI was about 13 events/h whereas in OSA it was only 3 events/h.

Currently, a few options for pharmacotherapy of CSA have been studied [52–54]. Nocturnal oxygen therapy eliminates nocturnal oxyhemoglobin desaturation, improves VO2 max (see [2] and [52]), and also in randomized clinical trials increases LVEF and quality of life [55–57].

In small randomized clinical trials, theophylline [53] and acetazolamide [54] have been shown effective. However, their safety and long-term benefits require large trials. Theophylline stimulates breathing by competitive inhibition of adenosine from its receptors. However its pro-arrhythmogenic properties limit its use in patients with HF. Acetazolamide induces mild metabolic acidosis and increases the difference between resting PCO2 and apnea threshold (PCO2 reserve).

Several investigators have used CPAP to treat central apnea (see [38]). Whereas OSA is initially eliminated with overnight CPAP titration only in about 50% of patients, CPAP suppresses CSA [58]. The mechanisms include decreasing venous return and unloading the left ventricle both decreasing pulmonary capillary wedge pressure, decreasing circulation time, and increasing functional residual capacity all of which contribute to stabilization of breathing [1, 2, 24]. In addition, in some patients with CSA, upper airway closure occurs which is reversed by CPAP.

Regarding effects of CPAP on mortality, Bradley et al. [59] carried out a large prospective study with the use of CPAP in patients with HF and co-morbid CSA (The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure, CANPAP study). Two hundred fifty eight eligible patients were randomized to either control group with optimal medical therapy or to CPAP group with optimal medical therapy and CPAP. The average follow up time was 2 years. The study was terminated prematurely after an interim analysis, for several reasons including an early excess mortality in the CPAP arm. The reason for this excess mortality in the CPAP arm has been analyzed in detail elsewhere [60]. The major reason was that in almost 50% of the patients

\[
\text{Hazard ratio} = 0.33 \ (95\% \ CI = 0.21–0.51), \ p < 0.0001
\]
CSA was not suppressed by CPAP (these patients are considered CPAP non responders). Indeed, in a post hoc analysis, longer survival without heart transplant was reported in patients in whom CPAP effectively suppressed CSA (drop in AHI < 15/h, mean = 6/h from a baseline of about 40/h) in comparison to the control group [7].

For CPAP nonresponders, adaptive servventilator (ASV) devices are the treatment of choice. The operation algorithm of these devices is quite unique and different from CPAP or bi-level devices [61]. There are 3 specific features: first, these devices stabilize the upper airway by applying a fixed (old generations) or variable expiratory positive airway pressure (automatic, like autoCPAP, new generations) to eliminate obstructive disordered breathing. Second, they act as a ventilator and deliver a mandated breath, if spontaneous breathing ceases for just few seconds. Third, they counter-balance ventilatory instability by modulating the degree of inspiratory pressure support (defined as inspiratory pressure minus expiratory pressure). In this regard, based on unique algorithms, the inspiratory positive airway pressure, and therefore the inspiratory support, varies in an anti-cyclic manner opposite to the prevailing flow or minute ventilation of the patient. Thus, tidal volume increases during hypoventilation and decreases during hyperventilation. This component of ventilation that is anti-cyclic to the periodicity of the patient’s own breathing, acts to dampen the oscillations in the ventilatory drive that underlie periodic breathing.

Teschler et al. [62] are credited with the first ASV study showing that in a 5 arm overnight study, ASV was more effective than oxygen, CPAP and bi-level therapy. In a meta-analysis of multiple studies using ASV as a contrast group (O2, CPAP, or continued medical therapy), will show that ASV improves AHI and LVEF significantly [63]. Two observational long-term studies [8, 10] have demonstrated improved survival in those who used the ASV device compared to those who refused. Currently, 2 large prospective trials are ongoing — SERVE-HF and ADVENT-HF. Patients with HF and coexisting sleep apnea (in the first study CSA, in the second CSA or OSA) are randomized into 2 groups: the first group on optimal medical therapy for HF or the second group treated additionally with ASV. The results of these studies should answer the question whether ventilation by means of ASV influences long term prognosis and frequency of hospital re-admissions.

Despite proven beneficial effects of CPAP and also ASV therapy, a number of patients cannot tolerate mask/positive pressure device therapy; as noted before, most HF patients with sleep apnea do not see immediate improvement with the use of these devices. We believe this is the major factor influencing non-adherence. Therefore new therapeutic methods are currently a subject of research. An important advancement is transvenous phrenic nerve stimulation, which is easily placed by an electrophysiologist. This acts like a pacemaker stimulating the phrenic nerve during sleep. In a preliminary study [64] a temporary transvenous lead was placed in either the right brachiocephalic or left pericardiophrenic vein in 13 patients with HF and confirmed CSA. During PSG on therapy night, when phrenic nerve stimulation was applied, a significant decrease in AHI and central apnea index was observed when compared to control night without phrenic nerve stimulation. Simultaneously, arousal index related to periodic breathing significantly decreased. This novel method is important for a variety of reasons including the ease of use by the patient which should improve adherence, an important drawback of mask/positive airway therapy. Long-term studies with phrenic nerve stimulation are pending. Finally we note that cardiac transplantation virtually eliminates CSA indicating that CSA is the consequence of HF [65]. Un fortunately, however, a large number of cardiac-transplant recipients gain weight and develop OSA.

Conclusions

Despite recent advances in HF management, quality of life, hospital readmissions and mortality remain unacceptably high. Therefore, an increasing focus on treating co-morbidities which could change such grim prognosis is clinically relevant. SDB is reported to be among most common co-morbidities affecting HF patients. It occurs in at least half of HF population and is associated with more severe HF symptoms, lower ejection fraction and higher prevalence of arrhythmia. SDB has also been proven to be an independent risk factor of poor outcome. There are documented treatment options based on positive airway pressure ventilation, which successfully reduce number of apnea episodes, but also improve left ventricular systolic function, exercise tolerance and possibly long term prognosis. Due to low recognition of SBD it seems necessary to introduce routine investigations in patients with HF, especially with new promising treatment methods such as phrenic nerve stimulation.
Conflict of interest: Prof. P. Ponikowski is a member of speaker’s bureau and a consultant for Respica-
dria. Prof. S. Javaheri is a consultant for Respirdcia, receives honoraria for lectures from Res-Med, Phi-
lips-Respirdics, Respirdcia, and received a grant from Philips-Respirdics. Dr R. Germany is Chief
Medical Officer at Respirdcia. Respirdcia supported the research study on prevalence of sleep
disordered breathing in patients with heart failure conducted by I. Flinta, M. Krawczyk, P. Ponikowski.

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