Advances in the management of sleep-disordered breathing in heart failure

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\textbf{A B S T R A C T}

Obstructive (OSA) and central sleep apnea (CSA) are very common in patients with congestive heart failure (CHF). This is clearly a risk factor for worsening the prognosis of patients. Treatment of sleep apnea in these patients may stop disease progression. Modern therapy, primarily central sleep apnea, is provided by adaptive servoventilation (ASV). Short-term randomized trials have demonstrated that treatment with ASV increased ejection fraction (EF), reduces sympathetic activity and blood pressure. Unfortunately, there is not enough data on whether there are effects on mortality and morbidity. Studies of this issue, such as SERVE-HF and ADVENT-HF, are currently in progress and results are expected. There are other forms of therapy of OSA like CPAP, oxygen, theophylline, acetazolamide, heart synchronisation therapy and transplantation. In patients with a predominance of OSA, in addition to previous methods, there are other recommended forms of therapy like appropriate weight loss, orthodontic appliances and surgical treatment.

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1. Introduction

Sleep-disordered breathing (SDB) is common in patients with congestive heart failure (CHF). SDB can be classified as 2 types: central sleep apnea (CSA), often associated with Cheyne-Stokes breathing (CSA–CSB), followed by obstructive (OSA) or mixed apnea/hypopnea. This is clearly a risk factor for worsening the prognosis of patients with heart failure, although usually not associated with daytime sleepiness. The exact etiology of these disorders in patients with heart failure is not fully understood.

One of the reasons may be wall thickening and edema of the larynx and respiratory control instability. OSA may impair cardiac function by increasing afterload, caused by an increase in ventricular transmural pressure during breathing and chronic increase in sympathetic activity. OSA is also associated with a higher incidence of hypertension, myocardial infarction, stroke and nocturnal arrhythmias [1,2]. In our article, we discuss the epidemiology, pathophysiology, diagnosis, and new trends in the treatment of SDB in heart failure.

1.1. Epidemiology of sleep-disordered breathing in congestive heart failure

Prevalence of SDB in CHF is rather difficult to diagnose. The case studies used different criterias for the evaluation of sleep apnea, hypopnea, apnea–hypopnea index (AHI) and criteria used to differentiate CSA and OSA. Also, the definition of CHF is not always the same (systolic or diastolic, different ejection fraction—EF), etc. According to the studies by Oldenburg et al. 700 patients with systolic heart failure treated according to current guidelines, a prevalence of SDB was discovered in 76% (36% with OSA and 40% with CSA) [3]. Paulino et al. noted that among 316 French patients with stable heart failure and with an ejection fraction of less than 45% found a prevalence of SDB in 81% (of which 70% had OSA and 30% had CSA) [4]. MacDonald et al. studied the prevalence of SDB in 108 patients with heart failure and an ejection fraction of less than 40%. SDB was found in 61% (including 30% with OSA and 31% of CSA) [5]. Redeker et al. discovered SDB in 51% of patients with heart failure with an ejection fraction of 32±14.6 (9% with CSA and 21% with OSA) [6]. Bitter et al. studied 244 patients with heart failures with a normal ejection fraction, (EF >55%) SDB and found in 69.3% of patients (39.8% with OSA and 29.5% with CSA) [7]. Khayat et al. tested 395 patients with acute decompensated heart failure and found SDB in 75% of patients (57% had OSA and 18% CSA) [8]. Ferreira et al. followed 103 patients with heart failure with optimal treatment. SDB was found in 72.8% of patients. (60% of those with OSA and 9.3% with CSA, mixed apnea was at 30.7% of patients) [9]. Recent studies by Damy et al. noted among 384 patients with heart failure and with an ejection fraction ≤45% SDB was discovered present in 88% of patients (62% with OSA and 26% with CSA) [10] Table 1.

2. Pathophysiology of sleep-disordered breathing in congestive heart failure

OSA in SDB may accompany central sleep apnea episodes at the end of almost a third of the cases [11]. Direct fibroscopic observation has shown episodes of the upper airway narrowing and closure during central apneas [12]. This narrowing could be the effect of a reduction in the muscle structures of the upper respiratory tract, which is combined with anatomical narrowing of the upper airway. Pure OSA may appear especially in obese patients. Obesity and fat in the neck region leads to narrowing of the upper airway. Pharyngeal edema and narrowing may develop during supine sleep with redistribution causing swelling of the legs. This observation was supported by the observed improvement in OSA by diuretic therapy in patients with diastolic heart failure [13].

Table 1 – Prevalence of SDB in heart failure.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Ejection fraction (EF) (%)</th>
<th>SDB definition</th>
<th>SDB Prevalence (OSA, CSA) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oldenburg</td>
<td>2007</td>
<td>700</td>
<td>≤40</td>
<td>AHI≥5</td>
<td>76 (36, 40)</td>
</tr>
<tr>
<td>Paulino</td>
<td>2009</td>
<td>316</td>
<td>≤45</td>
<td>AHI≥10</td>
<td>81 (from which 70 a 30)</td>
</tr>
<tr>
<td>MacDonald</td>
<td>2008</td>
<td>108</td>
<td>≤40</td>
<td>AHI≥15</td>
<td>61 (30, 31)</td>
</tr>
<tr>
<td>Redeker</td>
<td>2010</td>
<td>170</td>
<td>–</td>
<td>AHI≥5</td>
<td>51 (22, 9)</td>
</tr>
<tr>
<td>Bitter</td>
<td>2009</td>
<td>244</td>
<td>≤55</td>
<td>AHI≥5</td>
<td>69 (40,29)</td>
</tr>
<tr>
<td>Khayat</td>
<td>2009</td>
<td>395</td>
<td>ADHF</td>
<td>AHI≥15</td>
<td>75 (57,18)</td>
</tr>
<tr>
<td>Ferreira</td>
<td>2010</td>
<td>103</td>
<td>–</td>
<td>AHI≥5</td>
<td>73 (60,9)</td>
</tr>
<tr>
<td>Damy</td>
<td>2012</td>
<td>384</td>
<td>≤45</td>
<td>AHI≥5</td>
<td>88 (62,26)</td>
</tr>
</tbody>
</table>
OSA in heart failure is caused, as in other cases of laryngeal closure during sleep. Obstructive apnea and hypopnea increases negative intrathoracic pressure that increase left ventricular transmural pressure and afterload. It also increases venous return and causes right ventricular distention. There is a deterioration of the left ventricular filling and a decreased ejection fraction [14]. Intermittent hypoxemia during OSA leads to an increase in pressure in the pulmonary arteries and the sympathetic activation with a consequent increase in blood pressure [15]. OSA also leads to the formation of oxidative stress, vascular endothelial dysfunction and progression of atherosclerosis [16,17] Fig. 1.

It is suspected, that CSA in heart failure is mainly caused by the instability of the ventilatory control system. Patients with CSA–CSB have increased response of peripheral and central chemoreceptors, leading to hyperventilation and hypocapnia. Patients with CSA–CSB in CHF usually have chronic respiratory acalasis from hyperventilation. Hyperventilation often drives the PCO₂ below the apneic threshold, leading to decreased central respiratory drive. An important factor contributing to hyperventilation is vagal irritant J-receptor stimulation by pulmonary venous congestion. This mechanism creates a typical crescendo–decrescendo type of Cheyne–Stokes breathing [18,19] Fig. 2.

3. Diagnosis of sleep-disordered breathing in congestive heart failure

OSA affects more men than women. The typical patients with OSA are obese, snoring men who can be sleepy during the day. They are usually tired in the morning, with sleepless behavioral changes, poor concentration, fatigue and headaches. They can acquire erectile dysfunction. Patients with CSA may develop different symptoms. Patients are not often overweight and do not snore. They are even less prone to early fatigue and sleepiness. They can often be subjected to periodic breathing whilst awake, during exercise and hyperventilation and subsequent hypocapnia. SDB is associated with a higher incidence of associated diseases—hypertension, heart failure, arrhythmias, stroke, myocardial infarction, chronic renal insufficiency and sudden cardiac death.

The gold standard in laboratory diagnosis is the nocturnal polysomnographic examination rated by an experienced sleep technician. During polysomnography EEG, ECG, EMG of the chin muscle, electro-oculogram (EOG), the air flow during breathing, breathing movements of the chest and abdomen, breathing sounds, oxygen saturation of hemoglobin, the movements of the legs and body positions are all monitored. The patient is monitored by a video camera. Beforehand, we ask patients for prior history with the presence of snoring, fatigue, increased daytime sleepiness or poor sleep quality. Also, a history of nocturnal angina pectoris, dyspnea, arrhythmia apnea during sleep should be prescribed for a departure to the sleep laboratory. We can also use questionnaires such as the Epworth Sleepiness Scale for the evaluation of sleep [20]. A variety of different kinds of portable polysomnography devices are also available to diagnose SDB. In-home respiratory telemonitoring can reduce costs compared to traditional polysomnography [21]. It is suspected that CSA–CSB may also result in the absence of a drop in pressure during sleep within 24-h monitoring cycle.

Fig. 1 - Obstructive sleep apnea.
(non-dipping), a high variability in heart rate and a reduction in the oxygen saturation of hemoglobin [22].

4. Treatment of sleep-disordered breathing in congestive heart failure

The first condition is the optimal treatment for CHF. As already mentioned, diuretics may improve OSA in heart failure. The same has been shown for captopril and carvedilol [23,24].

4.1. Continuous positive airway pressure (CPAP)

Continuous positive airway pressure (CPAP) has been successfully used to treat OSA in stable CHF. This method was used in the treatment of OSA for the first time in 1981 by Sullivan et al. [25]. This ventilation unit generates continuous pressure to which the patient is connected by a nasal or facial mask. The mask has a spontaneous expiratory valve allowing exhalation. Apnea, hypopnea and awakenings should disappear when the surface pressure is properly adjusted [26]. Setting the correct level of CPAP is done via diagnostic titration. This is usually done in a sleep laboratory under the supervision of an experienced sleep technician. According to the American Academy of Sleep Medicine, the minimum recommended pressure is 4 cm H₂O. The maximum recommended pressure is 20 cm H₂O. CPAP should be increased by at least 1 cm H₂O with an interval of at least 5 min in order to eliminate respiratory problems. CPAP should be increased after two or three obstructive apnea hypopnea. CPAP should be increased by at least 1 min of continuous snoring [27]. We can also use AutoCPAP to perform CPAP titration. AutoCPAP airflow automatically evaluates and adjusts the amount of pressure. It is used for diagnostic titration. The data downloaded from the device can determine the optimal level of CPAP pressure [28,29]. CPAP therapy has been successfully used in the treatment of OSA in heart failure. CPAP use has been shown to improved EF in some studies [30,31]. Some studies have not shown this effect [32]. Negative results in this study may be explained by the low inspiratory pressure. A meta-analysis of randomized controlled trials comparing studies with nocturnal CPAP therapy in patients with heart failure and CSA-CSF decreased AHI and increased EF (16 studies). There was also an increased EF, AHI and heart transplant free survival [32]. The Canadian Continuous Positive Airway Pressure Trial for Congestive Heart Failure Patients with Central Sleep Apnea (CANPAP) studied 258 CHF patients with CHF and nocturnal CPAP. They compared 128 patients with and 130 patients without CPAP. The CPAP group had the expected decrease in AHI, increase in EF and a walking distance in 6 min compared to the branch without CPAP. There was no difference in the number of hospitalizations, quality of life or transplant-free survival. There was actually an increase in early mortality in patients with CPAP. The main discovery of this study was that there was not an adequate reduction in AHI (AHI was 19 events/h) [33]. Suboptimal treatments were the main limitations of this study. In a post trial analysis by Arzt et al., it was found that patients who were ventilated effectively achieved AHI <15 (about 57% of patients). These patients had a longer transplant-free survival rate than those of the sub-optimally treated group [34].
4.2 Biphasic positive pressure ventilation (BIPAP)

Bi-level positive pressure ventilation (BIPAP) is another option to use. When this method is adjusted, inspiratory and expiratory pressure levels are adjusted during the BIPAP set up. Inspiratory pressure (IPAP) is always higher than the expiratory pressure (EPAP). BIPAP is indicated in patients who require more than the inspiratory pressure CPAP or positive pressure at the end of expirium (PEEP). BIPAP can be used in two modes (S—spontaneous) and (ST—spontaneous-timed). BIPAP reduces the OSA AHI more than CPAP or untreated patients [35]. BIPAP in patients with nonhypercapnic CSA can cause hyperventilation (especially at high difference between IPAP and EPAP) and thereby decreasing blood pCO₂ reduction below a certain trigger level may deteriorate CSA [36].

4.3 Treatment using adaptive servoventilation (ASV)

ASV is made up of bi-level ventilation, which leads to the automatic adjustments in support pressure with every breath by the patient’s own respiratory effort. ASV is a relatively new method in the treatment of SDB. ASV provides fixed EPAP that is manually titrated from 4 cm H₂O and the IPAP variable, which allows variations in pressure between 5–30 cm H₂O. Fixed EPAP and IPAP removes OSA and CSA hyperventilation. The initial setting is EPAP 4 cm H₂O and maximum Pressure Support 9–10 cm H₂O. If the patient’s own respiratory effort is reduced, the device adds inspiratory pressure, so as to ensure a 90% baseline ventilation. The maximum pressure limit for IPAP is 30 cm H₂O. This system is especially suitable for patients with CSA and CSB–CSA mainly because it does not cause hyperventilation and a subsequent reduction in pCO₂. ResMed ASV (AutoSet CS, CS2, VPAP Adapt, AdaptSV) produces expiratory pressure, which is set to open upper airway obstruction. This device is trying to set the 90% calculated ventilatory support in a 3-min window, ensuring minimization of hypo- and hyperventilation. ResMed ASV provides pressure support between 3 and 15 cm H₂O, and if that is not sufficient, it increases respiratory rate. Respironics ASV (BIPAP autoSV) calculates pressure support in a 4-min window and minimizes hypo-and hyperventilation. Like ResMed ASV EPAP serves to stabilize the upper airway obstruction and inspiratory pressure is increased if spontaneous inspiratory pressure is below the target value [37]. In a study of Hastings et al., eleven patients were studied with stable heart failure and sleep apnea. Patients were treated with ASV for six months, and compared to eight patients without ASV. Patients with ASV achieved a reduction in sleep apnea, an improved EF and quality of life [38]. Bitter et al. conducted a study with 60 patients with heart failure and normal EF. A total of 39 patients agreed to treatment by ASV. The control group consisted of 21 patients who refused ASV. ASV improved AHI, diastolic function and loading capacity [39]. Carnevale et al. retrospectively studied 74 patients with heart failure and CSA treated with ASV for 36±18 months. There was an improvement in NYHA scores, Epworth sleepiness scale and blood gases. ASV was well tolerated and very effective [40]. A meta-analysis has shown that the ASV improved EF by 6%, decreased the AHI to 12–23 events/h compared to CPAP [37]. The SERVE-HF study is a large, multicenter, randomized trial which began recruitment in 2008. This study is actively involved in our workplace. The primary objective of the study is to demonstrate the long-term effect of ASV on morbidity and mortality in patients with heart failure and CSA [41]. ADVENT-HF study is another ongoing study. It monitors ASV effects on mortality and hospitalizations in patients with heart failure and sleep apnea (OSA and CSA). The earliest results will be expected in 2015 [37].

4.4 Cardiac resynchronization therapy (CRT)

Cardiac resynchronization therapy improves cardiac output contraction by the coordination of the right and left ventricle. This leads to a reduction in AHI and improves SDB in patients with heart failure and SDB. Gabor et al. studied 28 patients eligible for CRT. CSA–CSB was found in 12 (43%) patients. CRT was started in 10 patients. Six patients were found to have reduced the severity of CSA–CSB. Improvements in heart failure reduced hypoventilation and hypoxemia [42]. Another study by Oldenburg et al. studied 77 patients with heart failure suitable for CRT. CSA–CSB was detected in 36 (47%). CRT improved AHI and satO₂ only in patients with CSA–CSB [43]. Kara et al. studied 12 patients with CSR. They compared the AHI in patients with CSR on and off for 3 nights. There was a reduction of AHI in patients with activated CSR [44].

4.5 Cardiac transplantation

Thirteen patients with heart failure and CSA were studied before and after heart transplantation. It has been found to improve the SDB, but CSA persisted in 3 patients and OSA in 4 patients [45]. Similarly, 36% of patients with heart failure who have had a heart transplant developed OSA. It was probably due to the accumulation of fat due to steroids intake after transplantation [46].

4.6 Oxygen therapy

The administration of oxygen can reduce the CSA in patients with heart failure. Oxygen administration in patients with heart failure and CSA were observed in several studies. Sasayama et al. studied nocturnal home oxygen administration for a period of one year in patients with heart failure and CSA. There was a reduction of AHI, increased nocturnal saturation, an improvement in the quality of life, NYHA reduction and increased EF [47]. Toyama et al. watched the effect of nocturnal home oxygen administration in patients with heart failure and CSA. AHI, peak VO₂ and the increase in EF was improved [48]. Krachman et al. studied the influence of nocturnal oxygen administration for one month to improve EF. They found that despite improvements of AHI, there were no improvements in EF [49]. Oxygen improves EF and the quality of life in patients with heart failure. The mechanism of action is not clear. Each patient with significant hypoxemia should be a candidate for the oxygen test. The optimal quantity of the oxygen should be titrated during polysomnography.
4.7. Submission of CO₂

It has been shown that increased levels of CO₂ during inspiration reduces the amount of CSA and CSB-CSA and reduces the AHI. This can be achieved either by increasing dead space connecting the plastic bag or by the direct administration of CO₂ via facial masks. It keeps the CO₂ level above the level that leads to the starting of apnea. The desired effect can last longer by a minimal increase in CO₂ (about 2 mmHg). Szollosi et al. tested the administration of 100% CO₂ in patients with heart failure and CSA. Administration of CO₂ led to a reduction in CSA, but did nothing to reduce the number of arousals [50]. Lorenzo-Filho et al. watched the effect of inhaled CO₂ and oxygen on Cheyne-Stokes respiration in patients with heart failure. They found a decrease in AHI and an increase in satO₂ after the administration of CO₂. Oxygen only increased satO₂ and did not decrease AHI [51]. It has been shown that increased levels of CO₂ during inspiration reduces the amount of CSA and CSB-CSA and reduces the AHI. Treatment with CO₂ is not currently available due to the inability to monitor the levels of exhaled and rebreathed CO₂. An unimproved number of arousals leading to sympathetic activation were detected which is a risk factor for cardiovascular disease.

4.8. Drug treatment

Theophylline and acetazolamide can be used as therapy for sleep apnea. Oral theophylline administered for 5 days improved SDB in patients with stable heart failure [52,53]. The mechanism of how theophylline affects sleep apnea is not known. Since they are not long-term controlled studies, theophylline is not used in the treatment of OSA. Theophylline also has a pro-arrhythmic potential which is not recommended for heart failure. Acetazolamide administered every evening for 6 days resulted in a significant reduction in AHI and sleep quality [54]. Acetazolamide is a mild diuretic and can lessen heart failure. It also causes metabolic acidosis, which stimulates breathing. This reduces levels of pCO₂ and leads to a reduction in CSA [55].

5. Further treatment of patients with OSA prevalence

Other methods to improve OSA are reductions in the weight of obese patients, avoiding sleeping on your back (tennis balls sewn into the back of pajamas), smoking prevention, alcohol and the use of benzodiazepines before bedtime.

5.1. Oral appliance therapy

Oral appliances therapy is using a removable protractor—the orthodontic appliance, which is attached only at night. They are suggested for mild to moderate degrees of OSA in patients who cannot tolerate CPAP.

5.2. Surgical therapy

Surgical therapy is recommended for the removing of anatomical obstacles. In childhood, it is tonsillectomy and adenoidectomy. Septoplasty is indicated in the adult age then patient has a deviation of the nasal septum. It is mainly used before CPAP. Uvulopalatopharyngoplasty (UPPP) reduces pharyngeal tissue and further strengthens the scar. Greater achievements are observed in patients with mild to moderate OSA who are not obese. Laser uvuloplasty (laser assisted uvuloplasty—LAUP) is used to remove parts of the soft palate and scarring. It is effective in the treatment of rhonchopathy. Other possibilities are reconstructive operations of the lower and upper jaw: (1) advancement of the m.genioglossus (genioglossus advancement—GA) (2) mandibular movement (3) maxillomandibular movement another method is radioblation to the base of the tongue and soft palate. A definitive solution to OSA is tracheostomy. However, it significantly reduces the quality of life and therefore is not used for OSA anymore [56].

6. Conclusion

Heart failure and SDB are common diseases which often occur simultaneously. The simultaneous occurrence of both
diseases has a worse prognosis and may worsen mortality. Optimal treatment of heart failure, according to international treatment recommendations is basic for SDB. CPAP can improve AHI and increase EF in patients with heart failure and SDB. A new treatment using adaptive servoventilation is a promising method that can be more successful than conventional treatment with CPAP. The results of the new long-term studies are expected to evaluate the effect of ASV on long-term survival.

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