Treatment of obstructive and central sleep apnoea in heart failure: practical options

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ABSTRACT: **Sleep apnoea, both central and obstructive disordered breathing, commonly occurs in patients with heart failure.**

Obstructive sleep apnoea occurs both in systolic and diastolic heart failure and is best treated with nasal positive airway pressure devices.

Central sleep apnoea occurs primarily in systolic heart failure and therapeutic options are evolving.

Optimal therapy of systolic heart failure, nocturnal use of supplemental oxygen, theophylline, acetazolamide and positive airway pressure devices have been shown to improve central sleep apnoea. Among these therapeutic modalities only continuous positive airway pressure has been studied in a long-term trials; unfortunately, it failed to improve survival.

KEYWORDS: **Central sleep apnoea, heart failure, obstructive sleep apnoea, treatment**

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Heart failure is a highly prevalent problem associated with excess morbidity, mortality and economical impact. Multiple factors may contribute to the progressively declining course of left and right ventricular remodelling and dysfunction. One cause could be sleep apnoea and hypopnoea, which are common in patients with heart failure. The occurrences of repetitive episodes of apnoea, hypopnoea and hyperpnoea, which cause intermittent hypoxaemia re-oxygenation, hypercapnia–hypocapnia, arousals and changes in intrathoracic pressure, have deleterious effects on the cardiovascular system [1, 2]. These effects may be most pronounced in the setting of established heart failure causing further adverse remodelling of left and right ventricles. Diagnosis and treatment of sleep-related breathing disorders may therefore improve morbidity and mortality of patients with heart failure.

Several studies [3–9] have shown that both obstructive (OSA) and central sleep apnoea (CSA) are common in patients with systolic heart failure. The present author also suspects that OSA is common in patients with diastolic heart failure. Although large systematic studies are lacking, diastolic heart failure and abnormal left ventricular morphology are common in patients with OSA [10–12].

The current article will briefly review various therapeutic options for OSA and CSA in systolic and diastolic heart failure.

TREATMENT OF SLEEP-RELATED BREATHING DISORDERS IN HEART FAILURE

Systolic heart failure is a unique disorder in the sense that both OSA and CSA may commonly occur simultaneously in the same patient. Therefore, the approach to the treatment of sleep apnoea in heart failure depends upon the predominant form of sleep apnoea (table 1) [1, 2].

OSA

Treatment of OSA/hypopnoea in heart failure is similar to that in the absence of heart failure. The main therapeutic option is the use of nasal positive airway pressure devices. However, obesity is the major known risk factor for OSA in the general population and also in patients with heart failure [3–5]. Therefore, overweight and obese patients with heart failure should obtain dietary consultation and be encouraged to lose weight; this has been shown to decrease the OSA/hypopnoea index. Bariatric surgery is becoming another option for patients with morbid obesity, though there are no studies in patients with heart failure.

Noninvasive continuous positive airway pressure (CPAP) devices and bi-level pressure are the treatment of choice for OSA. However, there are limited reports on the use of nasal CPAP in heart failure [13–15]. Acute application of nasal CPAP results in the elimination of obstructive disordered breathing events [13] and the associated consequences, such as desaturation. As CPAP

TABLE 1	Potential treatment options for sleep apnoea/hypopnoea in heart failure

Obstructive sleep apnoea/hypopnoea
   Optimisation of medical therapy of heart failure
   Weight loss
   Positive airway pressure devices
      CPAP
      Bi-level pressure for CPAP noncompliance
   Mandibular advancement
   Upper airway surgery
   Oxygen for patients noncompliant with other therapeutic options
Central sleep apnoea
   Optimisation of medical therapy of heart failure (including cardiac resynchronisation when applicable)
   Nocturnal oxygen
   Positive airway pressure devices
      CPAP
      Bi-level pressure
      Pressure support servo-ventilation
   Theophylline
   Acetazloamide
   Cardiac transplantation

CPAP: continuous positive airway pressure.

eliminates OSA and the large negative swings in juxtacardiac pressure that occur during upper airway occlusion, CPAP decreases the transmural pressure and wall tension across the right and left ventricles. This results in a decrease in afterload, which should decrease myocardial oxygen consumption and increase stroke volume. As CPAP eliminates arterial oxyhaemoglobin desaturation and hypercapnia, there should also be a decrease in sympathetic activity [16], neurohormonal activation, oxidative stress and inflammation. Due to these favourable changes, treatment of OSA with CPAP has resulted in an increase in left ventricular ejection fraction (LVEF) of ~5–10% [14–15]. However, long-term studies are needed to determine whether the improvement in LVEF is translated into longevity and improved health-related quality of life of heart failure patients.

OSA also occurs in patients with diastolic heart failure [10] and may contribute to the progression of adverse remodelling of the cardiac chambers. Two recent studies [11, 12] have shown that the chronic use of CPAP may result in reverse remodelling. Further long-term studies are needed to determine the prevalence of diastolic heart failure in OSA and the impact of CPAP treatment.

Among the remaining modalities of therapeutic options for OSA in heart failure (table 1), the most systematic study has been with mandibular advancement. In 14 patients with systolic heart failure (mean LVEF ~34%), ESKAFI [17] reported that mandibular advancement resulted in a significant reduction in apnoea/hypopnoea index (AHI; 25 versus 15 events·h^{-1}, p=0.003). After 6 months of therapy, brain naturetic peptide also decreased significantly; however, there was no significant change in LVEF.

CSA
The treatment options for CSA are evolving [18, 19]. In general, however, CSA is more difficult to treat than OSA.

Optimisation of cardiopulmonary function
Early [1, 2] and more recent studies [7] show that the aggressive treatment of systolic heart failure may improve or even eliminate periodic breathing. Several mechanisms may be invoked, including decreasing wedge pressure, increasing stroke volume, decreasing arterial circulation time and normalising of functional residual capacity [1, 2, 18, 19], all of which should stabilise periodic breathing. Similarly, improvement in cardiac function by resynchronisation therapy may improve CSA [2, 18].

Nocturnal supplemental nasal oxygen
Systematic studies [20–22] of patients with systolic heart failure have shown that nocturnal administration of supplemental nasal oxygen improves CSA and desaturation [1, 2, 23]. In the largest study [21] of 36 subjects with systolic heart failure (mean LVEF about 22%), it was observed that the central apnoea index decreased significantly from ~28–10 events·h^{-1}. Administration of supplemental nasal oxygen has been shown to decrease sympathetic activity, as measured by peroneal muscle sympathetic activity [23] and overnight urinary norepinephrine excretion [22]. These findings are important in relating sleep apnoea to progressive heart failure, since increased sympathetic activity has a deleterious effect in left ventricular structure and function in patients with systolic heart failure. Furthermore, in a randomised, placebo-controlled, double-blind, crossover study, ANDREAS et al. [24] showed that 1-week administration of supplemental nocturnal oxygen improved maximum exercise capacity. This is also an important finding, as maximum oxygen uptake is an independent predictor of survival in heart failure [25] and coronary artery disease [26]. Most recently, in a randomised, parallel-design open trial of 56 patients with systolic heart failure, SASAYAMA et al. [27] reported that the use of nocturnal administration of supplemental nasal oxygen (n=25) resulted in significant improvement in LVEF and New York Heart Association functional class. Such changes were not observed in the control group.

Mechanisms of the therapeutic action of nasal oxygen on CSA are multiple [23] and include (presumably) an increase in the difference between the prevailing carbon dioxide tension and the apnoeic threshold, a reduction in the ventilatory response to carbon dioxide and increasing body tissue stores (e.g. lung and blood contents) of oxygen. Consequently, breathing during sleep should stabilise.

With regard to potential adverse effects of supplemental oxygen, it has been reported that in patients with congestive heart failure, hyperoxia may be associated with adverse haemodynamic effects [28, 29]. However, this has been shown primarily with breathing 100% oxygen, a dose which is far beyond what is necessary to treat CSA [21]. In a study of 16 patients with stable congestive heart failure, MAK et al. [28] showed that the administration of 100% oxygen, which resulted in an increase in arterial oxygen tension from 10.4–47.7 kPa (78–358 mmHg), was associated with an increase in left ventricular end-diastolic pressure and impaired relaxation.

There may have been also some impairment in left ventricular systolic function (although the change in pressure/change in time ratio did not change significantly, the stroke volume decreased in the face of an increase in left ventricular diastolic pressure). Furthermore, systemic vascular resistance increased significantly, but arterial blood pressure did not change significantly because stroke volume decreased. As noted earlier, these adverse haemodynamic effects occurred with 100% oxygen breathing. In a previous study of 10 patients with New York Heart Association functional class III and IV, HAQUE et al. [29] also showed that breathing 100% oxygen resulted in a significant decrease in stroke volume (from 43–35 mL) and an increase in systemic vascular resistance with mean arterial blood pressure remaining essentially unchanged. The authors also showed that pulmonary capillary wedge pressure increased from ~3.9–4.3 kPa (~28–32 mmHg). HAQUE et al. [29] also studied the effects of 24 and 40% oxygen administrations on central haemodynamics. Although the authors reported ''dose-dependent'' changes in haemodynamics with increased concentration of oxygen, the effects were primarily seen at 100% oxygen breathing and to a minor degree with 40% oxygen. Specifically, with 40% oxygen breathing, stroke volume decreased by 5 mL (not significant) and heart rate decreased by about 4 beats·min^{-1} (also not significant), with the combination of the two resulting in a significant reduction in cardiac output from 3.8–3.2 L·min^{-1} (the only significant variable).

The two above-mentioned studies [28, 29], therefore, show that breathing 100% oxygen results in adverse haemodynamic effects in patients with congestive heart failure; similar changes have also been observed in patients with normal cardiac function. However, in patients with congestive heart failure with CSA, oxygen is used during sleep to overcome arterial oxyhaemoglobin desaturation and its potential adverse consequences. Therefore, these results are not applicable to patients with CSA. Furthermore, the amount of oxygen used to overcome arterial oxyhaemoglobin desaturation during sleep varies from 1–3 L. It is noteworthy that 4 L·min^{-1} of oxygen is equivalent to breathing 36% oxygen, and 5 L·min^{-1} is equivalent to 40%. In all of the studies on the use of supplemental oxygen, no investigator has used 5 L·min^{-1} to treat CSA. In the present author's study [21], most individuals were treated with 1–3 L·min^{-1} of oxygen, and the maximum amount was 4 L·min^{-1}.

In summary, short-term studies show that nocturnal oxygen improves CSA and its associated consequences. However, prospective, placebo-controlled, long-term studies are necessary to determine if nocturnal oxygen therapy has the potential to decrease morbidity and mortality of patients with systolic heart failure [23].

Nasal positive airway pressure devices

Various positive airway pressure devices have been used to treat CSA in congestive heart failure [1, 2, 30]. Nasal CPAP has been studied most extensively, and results reported from different laboratories differ [30].

The present author studied 21 heart failure patients with CSA, and nine (43%) responded to CPAP on the first night of treatment [13]. In these patients, CPAP decreased the AHI from 36 to 4 events·h^{-1} and the central apnoea index from 22 to 2 events·h^{-1}. CPAP eliminated arterial oxyhaemoglobin desaturation. In CPAP nonresponders, the AHI did not change significantly. Controlled studies of the chronic effects of CPAP by NAUGHTON et al. [31] and SIN et al. [32] showed a reduction in the AHI and an increase in LVEF.

Despite early enthusiasm, unfortunately, long-term CPAP therapy does not improve the number of hospitalisations, quality of life or survival of patients with heart failure and CSA [33]. The multi-centre study, by BRADLEY et al. [33], had to be terminated prematurely, in part due to an early high mortality in patients who were on CPAP. The increase in mortality occurred in spite of an improvement in the average AHI, desaturation and LVEF. The reasons for the early high mortality noted in CPAP users are probably multifactorial and have been discussed in detail elsewhere [34]. One likely reason could have been the adverse haemodynamic effects of CPAP. CPAP increases intrathoracic pressure and so, as a result, it could adversely affect both right and left ventricular stroke volume. For example, if right ventricular function is such that it is pre-load-dependent, any reduction in venous return (due to CPAP-induced increase in intrathoracic pressure) could decrease right ventricular stroke volume and blood return to the left ventricle. A similar mechanism operating on the left ventricle could further decrease left ventricular stroke volume, causing hypotension, diminished coronary blood flow, myocardial ischaemia and arrhythmias. These adverse haemodynamic effects could have had major deleterious effects, particularly in the CPAP nonresponders. As noted above, in the present author's study of heart failure patients [13], overnight CPAP titration did not improve CSA in ~60% of the patients. These patients continued to have arrhythmias during sleep [13], which was in contrast to those heart failure patients whose CSA was eliminated by CPAP. Continued use of CPAP in first-night CPAP nonresponders will impose additional adverse haemodynamic effects of increased intrathoracic pressure. Therefore, in the current author's opinion, CPAP use is contraindicated in such patients as it may be associated with increased mortality [34]. It must be emphasised, however, that CPAP remains the therapy of choice for treatment of OSA in patients with heart failure.

A new positive airway pressure device [35–40] may prove to be more effective in the treatment of CSA than CPAP. This pressure support servo-ventilator improves (or may even eliminate) periodic breathing by performing in an opposite manor to the patient's breathing pattern. However, well-controlled, long-term studies are needed to determine if use of this device will affect quality of life and survival of heart failure patients with CSA.

Theophylline

Some open studies [41–43] and one double-blind, placebo-controlled study [44] have shown the efficacy of theophylline in the treatment of CSA in heart failure. In the randomised, double-blind, placebo-controlled, crossover study [44] of 15 patients with treated, stable systolic heart failure, theophylline (b.i.d., p.o.) at therapeutic plasma concentrations (mean 11 µg·mL^{-1}, range 7–15 µg·mL^{-1}) decreased the AHI by ~50%, and improved arterial oxyhaemoglobin saturation.

Theophylline significantly decreased CSA, but had no effect on obstructive apnoeas.

The mechanisms of action of theophylline in improving central apnoea remain unclear [44]. At therapeutic serum concentrations, theophylline increases ventilation [45]. This is probably due to competitive inhibition of adenosine, which is a respiratory depressant. Conceivably, therefore, an increase in ventilation by theophylline could decrease the likelihood of occurrence of central apnoea during sleep.

Potential arrhythmogenic effects and phosphodiesterase inhibition are common concerns with the use of theophylline in patients with heart failure, and further controlled studies are necessary to assure its long-term safety. A recent study [46] shows that theophylline does not increase sympathetic activity in patients with heart failure, which is in contrast to healthy subjects.

Acetazolamide
Acetazolamide is a mild diuretic and also a respiratory stimulant. Acetazolamide has been used effectively for treatment of CSA at high altitude [47] and idiopathic CSA [48]. In the randomised, double-blind, placebo-controlled, crossover study [49] of 12 patients with stable severe systolic heart failure and mean LVEF of ~20%, acetazolamide at a dose of ~3 mg·kg^{-1} administered 30 min before bedtime, resulted in considerable improvement in CSA and arterial oxyhaemoglobin desaturation. Comparing acetazolamide with placebo, the central apnoea index decreased from 49 to 23 events·h^{-1}. The obstructive AHI did not change significantly. As a result of improvement in CSA, the degree of arterial oxyhaemoglobin desaturation improved. While on placebo, oxyhaemoglobin saturation remained <90% for ~20% of the total sleep time; this decreased to 6% while on acetazolamide. Acetazolamide caused mild metabolic acidosis, as measured by the arterial blood gases in the morning. Therefore, acetazolamide improved CSA in spite of lowering of the arterial carbon dioxide tension. Further long-term studies are needed to determine the efficacy and side-effects of acetazolamide in patients with heart failure. However, as noted above, in the same study [49], acetazolamide was administered as a single dose at night, in the hope that long-term potential side-effects of multi-pill dosing would be minimised.

Cardiac transplantation
In the largest study of patients with systolic heart failure who received cardiac transplantation, CSA was generally eliminated [50]. Unfortunately, however, many of these patients had developed OSA; these were the transplant recipients who had gained the most weight after surgery. In these patients, OSA was associated with hypertension and poor quality of life [50]. Therefore, cardiac transplant recipients need to be monitored for development of OSA, and appropriately treated if applicable (table 1).

CONCLUSIONS
Heart failure is a highly prevalent problem associated with excess morbidity, mortality and economical impact. Multiple factors may contribute to the progressively declining course of heart failure. One such cause could be the occurrence of sleep apnoea, characterised by repetitive episodes of apnoea,

hypopnoea and hyperpnoea, which occur frequently in patients with systolic heart failure. Although sleep apnoea also occurs in diastolic heart failure, data are limited. These pathophysiological consequences of sleep-related breathing disorders have deleterious effects on cardiovascular system, particularly in the setting of established systolic and diastolic heart failure. Diagnosis and treatment of sleep-related breathing disorders may therefore be expected to improve cardiac structure and function, morbidity and mortality of patients with heart failure [18, 19, 51]. However, large-scale, carefully executed therapeutic studies are needed to determine if the treatment of sleep-related breathing disorders changes the natural history of left ventricular failure. The only long-term study so far [33] has been with continuous positive airway pressure, and it failed to show any important survival effect.

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