Sleep-disordered breathing and heart failure

Sleep-disordered breathing is a spectrum of disorders. As our knowledge of sleep medicine is improving, the strong association of sleep-disordered breathing with cardiac disorders is being recognized. This article discusses the association of sleep-disordered breathing and heart failure.

Human beings spend one third of their lives asleep. Rechtschaffen (1970) rightly observed: 'If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made.'

Research has proven that sleep fulfils essential needs: it serves to restore the body functions and hence body health. Sleep-disordered breathing is a spectrum of disorders from simple snoring to severe sleep apnoea (both obstructive and central). As our knowledge of sleep medicine is improving, the strong association of sleep-disordered breathing with cardiac disorders is being recognized. Although sleep-disordered breathing is associated with hypertension, atrial fibrillation (Gami et al, 2004) and ischaemic heart disease this article discusses the association of sleep-disordered breathing and heart failure.

Normal sleep

The discovery of rapid eye movement (REM) sleep by Nathaniel Kleitman and Eugene Aserinsky in 1953 divided normal sleep into two stages:

1. Non-rapid eye movement sleep, which is further divided into stages 1–4, depending on the predominant rhythm in the electroencephalogram
2. Rapid eye movement sleep, characterized by rapid eye movements in the electrooculogram, loss of muscle tone (recorded in the electromyogram) and the typical low amplitude mixed frequency waves in the electroencephalogram.

Non-rapid eye movement sleep

Humans enter sleep via the non-rapid eye movement sleep and later on in the night non-rapid eye movement sleep alternates with rapid eye movement sleep. The physiology of every organ is altered during sleep.

Non-rapid eye movement sleep is a placid stage. During this phase, increased parasympathetic tone and decreased sympathetic tone lead to bradycardia and decreased cardiac output. The associated vasodilatation leads to a reduction in systemic vascular resistance. This, combined with a reduced cardiac output, reduces the systemic blood pressure by 5–15%. This reduces myocardial workload and allows time for replenishment of cardiac metabolic stores.

Rapid eye movement sleep

During rapid eye movement sleep, increased sympathetic tone results in significant heart rate variability, leading to episodes of bradycardia and tachycardia. In addition, the cardiac vagal tone is suppressed during rapid eye movement sleep. In animal models Vatner et al (1971) showed that rapid eye movement sleep was associated with an increase in coronary blood flow. Interestingly, in patients with severe coronary artery stenosis, phasic decreases in coronary arterial flow were observed during rapid eye movement sleep.

Sleep-disordered breathing

Sleep-disordered breathing is a spectrum of disorder with snoring at one end and severe sleep apnoea (central or obstructive) at the other end. Sleep-disordered breathing is one of the most common sleep disorders seen in sleep clinics. Its presence also affects cardiac function adversely.

Sleep apnoea is characterized by repetitive episodes of apnoea and hypopnoea during sleep. In obstructive sleep apnoea, apnoeas occur as a result of intermittent upper airway obstruction causing negative intrathoracic pressure. Large negative swings in intrathoracic pressure can affect left ventricular function (Buda et al, 1979) by increasing left ventricular transmural pressures and thus afterload. Dursunoglu et al (2005) found that patients with severe and moderate obstructive sleep apnoea had higher left ventricular mass, left ventricular mass index and also left ventricular global dysfunction. The intermittent hypoxia that accompanies apnoea results in arousal and sympathetic activation causing acute surges in blood pressure and heart rate, further increasing left ventricular afterload. Patients are more likely to have elevated daytime sympathetic activity and blood pressure, which may further perpetuate cardiac failure. Obstructive sleep apnoea can adversely affect left ventricular function in a patient with an already failing heart.

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Central sleep apnoea is characterized by absence of respiratory effort leading to apnoea or hypopnoea. Unlike obstructive sleep apnoea, there is no upper airway obstruction. John Cheyne and William Stokes described a unique pattern of breathing in heart failure known as Cheyne–Stokes respiration. This is characterized by crescendo-decrescendo changes in tidal volume with an intervening central apnoea.

During sleep the voluntary control of breathing is lost and ventilation depends on chemical stimuli and on the chemoreceptors, respiratory muscles and the respiratory centre. Carbon dioxide levels in the body are regulated within a narrow range. During sleep, the level of partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) that inhibits ventilation leading to apnoea (apnoeic threshold) may be only 1–2 mmHg lower than the $PaCO_2$ during wakefulness. The hypoxia induced during sleep leads to hyperventilation and consequently hypocapnia leading to apnoea.

Poor left ventricular function leads to a reduced cardiac output and to increased circulation time. As a result, chemoreceptors receive delayed information regarding gas exchange and acid–base balance so the reduction in ventilation that occurs in response to hypocapnia is delayed, leading to further hypocapnia and apnoea if the apnoeic threshold is reached.

Hyperventilation with reduction of arterial carbon dioxide pressure below the apnoeic threshold is critical to the initiation of Cheyne–Stokes respiration–central sleep apnoea irrespective of the circulation time. Hyperventilation in heart failure is believed to occur as a result of the stimulation of lung vagal irritant receptors as a consequence of pulmonary congestion as indicated by higher pulmonary capillary wedge pressure in patients with congestive heart failure associated with Cheyne–Stokes respiration–central sleep apnoea than in those without (Solin et al, 1999).

In their prospective study of 81 patients with a left ventricular ejection fraction <45%, Javaheri et al (1998) reported that:

1. A total of 51% of the patients had severe sleep-disordered breathing with an average apnoea–hypopnoea index of 44 per hour
2. Central sleep apnoea occurred in 40% of patients while obstructive sleep apnoea occurred in 11%
3. Both forms of sleep apnoea caused sleep disruption and oxyhaemoglobin desaturation
4. Patients with sleep apnoea and heart failure were more likely to have a higher incidence of atrial fibrillation, ventricular arrhythmias and lower left ventricular ejection fraction.

Other studies have confirmed the high prevalence of sleep apnoea in patients with heart failure (Sin et al, 1999; Tremel et al, 1999).

Patients with obstructive sleep apnoea and heart failure are usually obese, give a history of snoring and have higher systemic blood pressure than patients with central sleep apnoea and heart failure. In their study of 450 patients with heart failure, Sin et al (1999) concluded that male sex and a raised body mass index significantly increased the risk of obstructive sleep apnoea in patients with heart failure, whereas low $PaCO_2$ is a key factor predicting presence of central sleep apnoea in patients with heart failure.

The prevalence of obstructive sleep apnoea in the general population is significantly higher in men than in women. Similarly in heart failure, the prevalence of sleep apnoea is higher in men. Progesterone is a known respiratory stimulant and also increases the tone of the dilator muscles of the upper airway thus conferring some protection.

Effects on morbidity and mortality

It is clear that sleep-disordered breathing is associated with heart failure, but does that affect morbidity and mortality?

In the study by Hanly and Zuberi-Khokhar (1996), 16 men with chronic stable heart failure underwent polysomnography. Of these nine had Cheyne–Stokes respiration during sleep, while seven did not. All patients were on standard medical treatment for heart failure. Over a period of 3.1–4.5 years, five patients in the Cheyne–Stokes respiration group had died and two had received cardiac transplants, while only one patient had died in the non-Cheyne–Stokes respiration group. In another study by Lanfranchi et al (1999), the risk of cardiac death in patients with heart failure and Cheyne–Stokes respiration increased progressively with the value of apnoea–hypopnoea index and left atrium area. In this study the risk of cardiac death increased progressively with the value of apnoea–hypopnoea index as well as left atrial area. Patients at high risk of a fatal outcome can be identified by an apnoea–hypopnoea index ≥30/hour and a left atrial area ≥25cm^2.

Javaheri et al (2007) followed 88 patients with heart failure (left ventricular ejection fraction ≤45%) with (n=56) or without central sleep apnoea (n=32) for 51 months. The median survival of patients with central sleep apnoea was 45 months compared to 90 months for patients without central sleep apnoea.

The prevalence of sleep-disordered breathing is high in patients awaiting cardiac transplantation (Lofaso et al, 1994). A large number of patients succumb to the disorder while awaiting cardiac transplant.

Overnight polysomnography can help diagnose and differentiate between central sleep apnoea and obstructive sleep apnoea. Obstructive sleep apnoea should be suspected in obese patients with increased neck size, habitual snoring, witnessed apnoea spells as well as choking and grunting sounds during the night, waking up tired and complaining of excessive daytime somnolence as per the Epworth Sleepiness Scale. Patients with these symptoms should be offered overnight polysomnography to confirm or exclude the presence of obstructive sleep apnoea.

Patients with central sleep apnoea do not normally have the classical features of obstructive sleep apnoea (snoring, nocturnal choking sounds, excessive daytime sleepiness). However, heart failure patients with low arterial $PaCO_2$ (<35 mmHg) and atrial fibrillation (Javaheri and Corbett, 1998) have a high prevalence of central sleep apnoea.

In all cases treatment of heart failure should be optimized. All obese patients should be advised to lose weight. If, despite these measures, sleep-disordered breathing persists, then additional treatment should be considered.

Non-pharmacological treatment

Patients with obstructive sleep apnoea should be assessed for any upper airway blockage (e.g. enlarged tonsils) and these should be corrected. Nasal continuous positive airway pressure is the cornerstone of treatment. By blowing at a fixed pressure, it prevents upper airway collapse and the resulting apnoea and hypopnoea. In their study of patients with obstructive sleep apnoea and heart failure, Mansfield et al (2004) concluded that treatment with nasal continuous positive airway pressure was associated with significant improvements in left ventricular ejection fraction, reductions in overnight urinary noradrenaline excretion (a function of reduced sympathetic activity) and improvements in quality of life.

In another study by Kaneko et al (2003), the use of nasal continuous positive airway pressure in obstructive sleep apnoea with heart failure reduced the episodes of obstructive sleep apnoea, daytime systolic blood pressure, heart rate, left ventricular end-systolic dimension and improved the left ventricular ejection fraction. In an observational study by Marin et al (2005), patients with untreated severe obstructive sleep apnoea had a higher incidence of both fatal (death from myocardial infarction or stroke) and non-fatal (non-fatal myocardial infarction, non-fatal stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography) cardiovascular events than untreated patients with mild to moderate disease, simple snorers and healthy participants.

Sin et al (2000) conducted a randomized controlled trial comparing use of nasal continuous positive airway pressure in patients with heart failure, with and without central sleep apnoea. They concluded that nasal continuous positive airway pressure improved cardiac function in heart failure patients with central sleep apnoea but not in patients with heart failure only. In patients with coronary artery disease, caution should be exercised with the use of nasal continuous positive airway pressure, as the raised intrathoracic pressure that it generates may result in a decrease in cardiac output and coronary blood flow.

A new method of ventilation, adaptive pressure support servo-ventilation, has been used in patients with heart failure and central sleep apnoea. This monitors the patient's breathing and supports breathing whenever it detects pauses. It also provides enough pressure support to maintain airway patency and helps reduce the work of breathing. In a small study (Teschler et al, 2001) it fared better than nasal continuous positive airway pressure or oxygen. In a Japanese study (Kasai et al, 2006), adaptive pressure support servo-ventilation improved central sleep apnoea in patients with heart failure who had not responded to conventional nasal continuous positive airway pressure.

In patients who cannot tolerate mechanical devices, oxygen is an alternative. It improves hypoxaemia and periodic breathing, decreases arousals and helps increase time spent in deep sleep. Nocturnal oxygen decreases overnight urinary noradrenaline excretion (Staniforth et al, 1998), but it does not improve left ventricle function or quality of life.

In patients with ventilatory failure (raised $PaCO_2$ leading to a decrease in arterial pH), bilevel positive airway pressure is a better therapeutic modality. This helps with exhalation of CO_2 and hence normalizes the arterial pH.

Garrigue et al (2002) used atrial overdrive pacing in 15 patients with an implanted pacemaker for symptomatic bradycardia and mild to moderate sleep apnoea (apnoea–hypopnoea index >15/hour). The patients had a relatively equal distribution of central sleep apnoea and obstructive sleep apnoea. They observed that raising the nocturnal heart rate from 57 to 72 beats per minute reduced the apnoea–hypopnoea index by 60%. In another study by Simantirakis et al (2005) atrial overdrive pacing had no significant effect in patients with obstructive sleep apnoea and normal left ventricular systolic function.

Milleron et al (2004) studied the effect of nasal continuous positive airway pressure on 54 patients with obstructive sleep apnoea and coronary artery disease. The main finding of their study was that the treatment of obstructive sleep apnoea in patients with coronary artery disease was associated with a significant decrease in cardiovascular events, defined as cardiovascular death, acute coronary syndrome, hospitalization for heart failure or need for coronary revascularization. Their data strongly suggest that obstructive sleep apnoea has a deleterious effect on coronary artery disease outcomes and that this effect can be abolished by specific treatment.

Pharmacological treatment

Javaheri et al (1996) demonstrated that, in patients with stable heart failure, oral theophylline reduced the number of episodes of apnoea and hypoponea and the duration of arterial oxyhaemoglobin desaturation during sleep. It is postulated that theophylline competes with adenosine at its receptors. Adenosine is somnogenic and accumulates in the body while people are awake. It is also a res-

piratory depressant and theophylline thus stimulates respiration. Theophylline can, however, precipitate arrhythmias and its interactions with other common drugs should not be forgotten.

Acetazolamide inhibits carbonic anhydrase leading to acidosis and stimulation of breathing. It has been used to treat high altitude-related periodic breathing and idiopathic central sleep apnoea. In a small number of patients with heart failure and central sleep apnoea, a single bedtime dose of acetazolamide improved central sleep apnoea and day-time symptoms (Javaheri, 2006).

Following cardiac transplantation, central sleep apnoea is eliminated. However, the weight gain with the use of steroids can lead to obstructive sleep apnoea.

In addition to its association with heart failure, sleep-disordered breathing has been associated with coronary artery disease. Recurrent hypoxia and reoxygenation can trigger endothelial dysfunction. Endothelial dysfunction has been detected in disease states characterized by atherosclerosis.

Mooe et al (2001) followed up 408 patients with verified coronary artery disease for a median period of 5.1 years. They concluded that sleep-disordered breathing in patients with coronary artery disease was associated with a worse prognosis.

In addition to the worse prognosis that sleep-disordered breathing has when associated with heart failure and coronary artery disease, it has been strongly associated with development of hypertension and cardiac arrhythmias.

Conclusions

There is ample proof that sleep-disordered breathing is associated with major cardiac failure and that treatment of sleep-disordered breathing can improve outcome. The authors suggest that cardiologists and sleep specialists should manage patients with heart failure jointly. BJHM

Conflict of interest: none.

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KEY POINTS

- Sleep-disordered breathing is commonly seen in patients with congestive failure.
- Patients with sleep disordered breathing and congestive heart failure have a worse prognosis than heart failure patients without sleep-disordered breathing.
- Patients with congestive heart failure should be assessed for underlying sleep-disordered breathing.