Sleep disordered breathing (SDB) is a common problem with adverse cardiorespiratory, endocrinological, and endothelial effects. Recent studies demonstrate an even higher prevalence of SDB in congestive heart failure (CHF) than in a randomly selected population, with up to 40% and 11% having Cheyne Stokes respiration–central sleep apnoea and obstructive sleep apnoea–hypopnoea syndromes, respectively. Randomised controlled trials of nocturnal respiratory support for SDB associated with CHF for up to three months demonstrate significant benefits in terms of improvements in left ventricular ejection fraction, markers of sympathetic system activity, and quality of life. Further randomised controlled trials of larger scale and longer duration are required to establish the role and benefit of this intervention for the treatment of this debilitating condition. The evidence for the higher prevalence of SDB in CHF, its pathogenesis, its pathophysiological consequences, and the emerging benefits of respiratory support are reviewed.

Sleep disordered breathing and its treatment in congestive heart failure

L J Cormican, A Williams

Sleep disordered breathing (SDB) is a common problem affecting up to 24% and 9% of randomly selected middle aged men and women, respectively, with 4% and 2% having obstructive sleep apnoea–hypopnoea syndrome (OSAHS). Prevalence data on CSA in the healthy adult population are lacking.

There is, however, evidence of a higher prevalence of SDB in the heart failure population than in the normal population. Obstructive sleep apnoea is also associated with increased odds of developing heart failure independent of other risk factors.

**DIAGNOSIS AND CLASSIFICATION**

The primary parameter used to quantify SDB is the apnoea–hypopnoea index (the mean number of apnoeic and hypopnoeic events an hour during a night’s sleep). Five or more an hour are regarded as significant and are classified as either obstructive or central. Table 1 outlines the diagnostic criteria for the classification of SDB.

Obstructive apnoeas and hypopnoeas result from complete or partial collapse of a narrowed pharynx, respectively. Central sleep apnoeas and hypopnoeas can result from either a reduction in central respiratory drive (as occurs in brainstem pathology or respiratory muscle weakness, thus associated with hypventilation and hypercapnia) or an instability in feedback control of the central respiratory centre (as occurs in CHF, but it is often idiopathic and not associated with hypercapnia). Cheyne-Stokes respiration (CSR) is a form of periodic breathing with oscillations in tidal volume associated with central apnoea and hypopnoea, often referred to as CSR-CSA. However, as the purpose of this review is to focus on SDB in CHF, because of the similarity in pathophysiology of CSR-CSA and CSA, they will be regarded as one.

Table 2 outlines a basic classification of sleep studies. Attended nocturnal polysomnography is considered the ideal diagnostic modality for the diagnosis of the cause of SDB, although it is clearly not widely available. However, guidelines advise that level II and III studies are acceptable for the diagnosis and assessment of treatment for SDB in the adult population. There is not yet guidance for the use of these studies on the diagnosis and assessment of SDB in the CHF population. Level IV studies, a combination of continuous pulse rate and oxyhaemoglobin saturation recording, though not recommended for the diagnosis and classification of SDB, have a role as a screening tool for SDB in an adult population. Level III studies, which can also be performed in the home, record more detailed information (pulse rate, breathing, heart rate, oxygen saturation).

**Abbreviations:** CANPAP, Canadian continuous positive airway pressure; CHF, congestive heart failure; CPAP, continuous positive airway pressure; CSA, central sleep apnoea; CSR, Cheyne-Stokes respiration; NYHA, New York Heart Association; OSAHS, obstructive sleep apnoea hypopnoea syndrome; PCO₂, partial pressure of carbon dioxide; SDB, sleep disordered breathing
Similarly in a series of 35 consecutive patients with SDB, CSA, and OSAHS was 61%, 29%, and 32%, respectively. In a population of 450 patients awaiting cardiac transplantation, 22% had CSA and 22% had OSAHS.13 In a study of consecutive patients with CHF, the prevalence of the same disorders was 65%, 37%, and 28%.13

Epidemiology of Sleep Disordered Breathing in Congestive Heart Failure

In a prospective study of 81 consecutive patients with predominantly New York Heart Association class I and II heart failure (caused by ischaemia, alcohol, and idiopathic cardiomyopathy) and a mean ejection fraction of < 30%, 51% of patients had significant evidence of SDB. Of those, 78% had CSA and 22% had OSAHS.11 In a population of 450 patients with CHF with symptoms of SDB referred for polysomnography studied retrospectively, the prevalence of SDB, CSA, and OSAHS was 61%, 29%, and 32%, respectively.12 Similarly in a series of 35 consecutive patients with CHF, the prevalence of the same disorders was 65%, 37%, and 28%.13

There is some evidence that the prevalence of CSA is increased in CHF populations with increasing disease severity. In a study of consecutive patients presenting with acute left ventricular failure, the prevalence of SDB, CSR-CSA, and OSAHS was 82%, 75%, and 25%, respectively, within one month of presentation and treatment.21 CSR-CSA syndrome affected up to 45% in a series of consecutive patients awaiting cardiac transplantation.22 However, the strength of this relation has recently been questioned.23

On the other hand, prospective studies of consecutive patients who have OSAHS provide evidence of left ventricular dysfunction when all other causes of left ventricular dysfunction have been excluded (coronary artery disease, CHF caused by cardiomyopathy or valvar heart disease, hypertension, and hypertrophic cardiomyopathy).24–25 Therefore, SDB can occur as a consequence of CHF but may also exacerbate the disease process.

However, it must be highlighted that larger epidemiological studies are required to quantify more accurately the prevalence of SDB and its subclassifications in the CHF population. Such studies will also add to our understanding of the impact of more recently introduced treatment modalities such as β-blockade and biventricular pacemaker insertion on the prevalence of SDB, especially CSR-CSA, in CHF.

Pathogenesis

The pathogenesis of CSR-CSA in CHF has recently been elucidated.

Hyperventilation with reduction of arterial carbon dioxide pressure below a threshold is critical to the initiation of CSR-CSA independent of circulation time. However, there is a significant correlation between lung to chemoceptor circulation time and the length of the CSR-CSA cycle.10 Hyperventilation in the setting of CHF is believed to occur due to the stimulation of lung vagal irritant receptors as a consequence of pulmonary congestion as indicated by higher pulmonary capillary wedge pressure in patients with CHF associated with CSR-CSA than in those without.26

Hyperventilation may also occur due to increased ventilatory sensitivity to carbon dioxide, as patients with CHF associated with CSR-CSA have a greater ventilatory responsiveness to carbon dioxide than do those without.27 Risk factors for the occurrence of CSR-CSA in a CHF population are male sex, atrial fibrillation, age greater than 60, and daytime hypocaopia.12

The reason for the increased prevalence of OSAHS in CHF is less clear. The coexistence of both may also be a function of their respective high prevalence in the adult population.10–11 On the other hand, sleep onset is associated with loss of pharyngeal dilator muscle tone, which in the setting of normal pharyngeal anatomy is not associated with airway compromise. In patients with OSAHS, the pharynx is

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Symptoms and signs</th>
<th>Overnight monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSAHS</td>
<td>Excessive daytime sleepiness not explained by other factors or two or more of the following: choking or gasping during sleep; recurrent awakenings from sleep; unrefreshing sleep; daytime fatigue; impaired concentration</td>
<td>Five or more obstructed breathing events/hour, any combination of apnoea, hypopnoea, and respiratory effort related arousal</td>
</tr>
<tr>
<td>CSA-HS</td>
<td>One or both of excessive daytime sleepiness and frequent nocturnal arousals or awakenings</td>
<td>Five or more central apnoic and hypopnoeic events/hour and normal daytime PCO₂ (&lt;6 kPa)</td>
</tr>
<tr>
<td>CSR-CSA</td>
<td>CHF or cerebral neurological disease</td>
<td>Three or more consecutive cycles of cyclical crescendo and decrescendo change in breathing amplitude and five or more central apnoeic and hypopnoeic events/hour or a cycle of crescendo-decrescendo change in breathing amplitude lasting 10 minutes or more</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; CSA, central sleep apnoea; CSR, Cheyne Stokes respiration; HS, hypopnoea syndrome; OSAHS, obstructive sleep apnoea–hypopnoea syndrome; PCO₂, partial pressure of carbon dioxide; SDB, sleep disordered breathing.
already mentioned occurs in CHF patients as a result of carbon dioxide as reflected by \( P_{\text{CO}_2} \). Hyperventilation as that may be a determinant of apnoea type is the arterial vasoconstriction, and raised peripheral vascular resistance. The consequences are increased heart rate, tachycardia activity by simulating peripheral and central chemoreceptors. The consequences are increased heart rate, tachycardia and reduced stroke volume.34

The pathophysiological consequences of OSAHS in CHF are multiple.

Repeated upper respiratory obstructive events result in negative intrathoracic pressure, increased systolic transmural pressure, increased left ventricular afterload, and hence reduced stroke volume and cardiac output.35 Increased negative intrathoracic pressure results in increased venous return, which contributes to leftward shift of the interventricular septum, impaired left ventricular filling, and reduced stroke volume.36

Increased sympathetic nervous system activity is a central feature of obstructive sleep apnoea. The pulmonary stretch receptor mediated reflex, which normally suppresses central sympathetic discharge during normal breathing, ceases during apnoea, facilitating sympathetic outflow.37 The associated hypoxia and hypercapnia further augment sympathetic activity by simulating peripheral and central chemoreceptors. The consequences are increased heart rate, vasoconstriction, and raised peripheral vascular resistance.38–40

The pathophysiological impact of OSAHS extends into wakefulness, with it now being recognised as an independent risk factor for hypertension41–45 and it being associated with left ventricular hypertrophy in normotensive patients.46

Obstructive sleep apnoea syndrome is now recognised as an independent risk factor for increased insulin resistance. Furthermore, treatment with continuous positive airway pressure (CPAP) has been shown to increase insulin sensitivity in these patients.47

There is also evidence that OSAHS may have potential detrimental endothelial effects. Patients with OSAHS have higher plasma C reactive protein concentrations48 than controls, they have signs of increased oxidative stress, such as increased reactive oxygen species production in neutrophils,49 and they have increased serum concentrations of intracellular adhesion molecule 1 and vascular cell adhesion molecule 1.50

There are some reports that OSAHS alone can also act as an independent risk factor for the development of left ventricular dysfunction. In patients without a history of CHF or coronary artery disease, the presence of OSAHS is associated with evidence of left ventricular systolic41 and diastolic dysfunction.42–43 Nocturnal CPAP for six months results in the correction of these indices. Furthermore, normotensive patients with OSAHS have increased left ventricular wall thickness in comparison with controls.44

The presence of CSR-CSA additionally has an adverse prognostic impact and pathophysiological burden on patients with CHF. It is associated with a higher mortality even after adjustment for other disease severity risk factors.45–46 The adverse effects of CSR-CSA probably arise from similar factors described for OSAHS including intermittent hypoxia, frequent arousals from sleep, sympathetic system activation, and apnoea related surges in blood pressure and heart rate, but without the effects of negative intrathoracic pressure during apnoeic events.

EVIDENCE FOR THE TREATMENT OF SDB IN CHF

There is compelling evidence for the treatment of OSAHS with CPAP irrespective of whether patients have CHF.47–48

The physiological benefits are reduced frequency and severity of desaturations, heart rate variability, apnoea, hypopnoea events,49 daytime somnolence, and improved control of hypertension50 and neuropsychological symptoms.51

There is also evidence that the treatment of OSAHS in CHF with CPAP has additional positive physiological and clinical benefits by abolishing apnoea related hypoxia, lowering nocturnal blood pressure, improving sleep quality52 and ejection fraction,53–56 and reducing catecholamine production57 (table 3). Two randomised controlled trials of CPAP for OSAHS associated with CHF have confirmed that these improvements in ejection fraction are significant (5%58 and 8.8%59) and that they are associated with improvements in symptoms.56

Even in the absence of evidence of CHF or a primary cardiac disease, there is some evidence (albeit from uncontrolled trials with small numbers) that the treatment of OSAHS for six months or longer results in a significant increase in left ventricular ejection fraction.59–64

These changes are believed to be caused by the relative increase in intrathoracic pressure due to CPAP, resulting in a reduction in cardiac transmural pressure. The reduction in transmural pressure in conjunction with the reduction of nocturnal blood pressure leads to a reduction in left ventricular afterload.65

However, larger and longer term randomised controlled studies recruiting treatment naive patients with OSAHS without cardiovascular morbidity at baseline are required to determine whether OSAHS can cause CHF directly.

There is also evidence from randomised controlled trials that CPAP has a significant beneficial effect on CSR-CSA caused by CHF when applied for at least 1–3 months67–71 (table 4). The benefits were a reduced apnoea–hypopnoea index and improved ejection fraction (6.5% to 8.6%), New York Heart Association (NYHA) functional status, and symptom score. This is postulated to be caused by reduced minute ventilation, with an increase in arterial carbon dioxide pressure (possibly above the apnoeic threshold) during sleep as a consequence of reduced lung vagal irritant

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Table 3  Randomised controlled trials of nocturnal respiratory support in patients with OSAHS associated with CHF

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Duration of treatment</th>
<th>No of patients</th>
<th>Cardiovascular outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko et al55</td>
<td>ICM, DCM</td>
<td>CPAP</td>
<td>1 month</td>
<td>24</td>
<td>8.8% increase in LVEF, reduced LVESD, reduced heart rate and SBP</td>
</tr>
<tr>
<td>Mansfield et al56</td>
<td>Not stated</td>
<td>CPAP</td>
<td>3 months</td>
<td>55</td>
<td>5% increase in LVEF, reduced fatigue and overnight urinary noradrenaline excretion, increased disease mastery and emotional wellbeing (CHFQ)</td>
</tr>
</tbody>
</table>

CHFQ, Guyatt chronic heart failure questionnaire; CPAP, continuous positive airway pressure; DCM, dilated cardiomyopathy; ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; NYHA, New York Heart Association; SBP, systolic blood pressure.

Furthermore, mean daytime systolic blood pressure (126 to 116 mm Hg), heart rate (68 to 64 beats/min), and left ventricular end systolic dimension (54.5 to 51.7 mm) changed significantly. Sympathetic nervous system activity as measured by overnight urinary noradrenaline (norepinephrine) excretion was reduced in the treatment group and indices of quality of life were improved (fatigue, disease mastery, and emotional wellbeing as measured by the chronic heart failure questionnaire).56

This treatment for this specific CHF patient population compares favourably with the effects of β blockade and angiotensin converting enzyme inhibition in CHF as shown by randomised controlled trials.63 However, as mentioned above, this evidence is limited by a lack of a demonstrable impact on mortality, possibly as a result of sample size and the duration of follow up.

Larger prospective trials such as the ongoing CANPAP (Canadian continuous positive airway pressure) trial are required to delineate the precise benefit and roles of CPAP in the treatment of SDB in CHF.

**OTHER TREATMENTS**

Nocturnal supplemental oxygen in the context of CSR-CSA associated with CHF, though abolishing apnoea related hypoxia and alleviating CSR-CSA does not cause improvements in cardiac function or quality of life over a period of one month.71

Oral theophylline treatment of patients with SDB associated with CHF reduces the apnoea–hypopnoea index and duration of arterial oxygen desaturation during sleep but has
not been shown to cause improvements in ventricular function, quality of life, or clinical outcomes. Atrial
overdrive pacing has recently been shown by one group to reduce the number of episodes of central and obstructive
apnoea in a cohort of patients with SDB without CHF. The mechanism by which this occurs is a matter of debate. It may
be related to the effect of an augmentation in cardiac output reducing pulmonary congestion, a stimulus for hyperventila-
tion, and to a reduction in circulation time. Further studies are awaited to determine whether this effect can be reproduced.
Lifestyle modification resulting in weight loss reduces the severity of OSAHS, possibly through a decrement in upper
airway collapsibility in an obese non-CHF population. Though there is no such evidence for an obese CHF
population, presumably the same should occur.

CONCLUSION
The presence of SDB presents another treatment opportunity in CHF. There is now a burgeoning field of evidence that
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IMAGES IN CARDIOLOGY

Cardiac angiosarcoma: diagnosis by coronary angiography

A 55 year old man was admitted to hospital after collapsing while playing golf. During assessment in the emergency department the patient became unconscious and lost cardiac output associated with a sinus bradycardia of 40 beats/min, some non-specific changes in the inferior ECG leads, and normal myocardial injury markers. Coronary angiography demonstrated normal coronary arteries; however, a branch of the right coronary artery (RCA) supplying the right atrium (RA) was associated with a tissue blush (panel A). Transosophageal echocardiography (TTE) confirmed a mass in the RA and a global pericardial effusion (panel B). Transosophageal echocardiography (TOE) showed a localised 3.5 x 3.5 cm tumour of the RA anterior wall (panel C). A computed tomographic (CT) scan of the chest showed no evidence of metastasis. Operative findings showed extension of the tumour to the surface of the RA and involvement of the RCA. The tumour was resected and a saphenous vein graft was anastomosed to the distal RCA. Histology confirmed angiosarcoma with a high mitotic rate and incomplete resection at the margin. A repeat operation with wider excision was performed with a clear histological margin. Five cycles of doxorubicin and ifosfamide chemotherapy were administered. Adjunct radiotherapy to the site of the primary tumour was given. The patient died 11 months after primary diagnosis from CT proven metastatic disease.

This case demonstrates the unusual angiographic findings of a cardiac malignancy and its correlation with TTE and TOE echocardiographic images.
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