Heart failure and sleep disorders

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Abstract | Awareness of the importance of sleep-related disorders in patients with cardiovascular diseases is growing. In particular, sleep-disordered breathing, short sleep time, and low sleep quality are frequently reported by patients with heart failure (HF). Sleep-disordered breathing, which includes obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), is common in patients with HF and has been suggested to increase the morbidity and mortality in these patients. Both OSA and CSA are associated with increased sympathetic activation, vagal withdrawal, altered haemodynamic loading conditions, and hypoxaemia. Moreover, OSA is strongly associated with arterial hypertension, the most common risk factor for cardiac hypertrophy and failure. Intrathoracic pressure changes are also associated with OSA, contributing to haemodynamic alterations and potentially affecting overexpression of genes involved in ventricular remodelling. HF treatment can decrease the severity of both OSA and CSA. Indeed, furosemide and spironolactone administration, exercise training, cardiac resynchronization therapy, and eventually heart transplantation have shown a positive effect on OSA and CSA in patients with HF. At present, whether CSA should be treated and, if so, which is the optimal therapy is still debated. By contrast, more evidence is available on the beneficial effects of OSA treatment in patients with HF.

Heart failure (HF) affects an increasing number of individuals all over the world every year. Severe HF is the leading cause of hospital admissions in elderly patients[1], and mortality remains high despite the progress in treatment strategies. However, a limitation of many studies on the evaluation and management of chronic HF is their focus on the assessment of patient characteristics during daytime only, when the patient is awake. This approach assumes that the mechanisms contributing to the pathophysiology of HF, and the factors related to the clinical progression of this condition, can be satisfactorily explored during daytime hours and that no relevant information can be obtained by investigating these patients during sleep. This general belief is challenged by the growing awareness of the presence of important problems during sleep in patients with HF, among which are short sleep time and low sleep quality.

Patients with HF often complain of sleep fragmentation or nonrestorative sleep, difficulties in initiating sleep, or waking up too early in the morning. Epidemiological data show a higher prevalence of chronic insomnia in patients with HF than in the general population (33% versus 10–15%)[2], sometimes related to mood disorders and psychological stress. Many factors might affect sleep quality and duration in patients with HF. Some patients can have primary or psychophysiological insomnia that might not be caused by the HF treatment. In other cases, insomnia can be of secondary nature, possibly caused by the HF itself or by adverse effects of commonly prescribed HF medications, such as angiotensin-receptor blockers, loop diuretics, and β-blockers[3]. In these cases, the complaints that are associated with HF might cause the insomnia and the related symptoms, and could be markedly improved by appropriate HF management. Nocturia is also commonly reported by patients with HF, and is often suggested as a cause of poor sleep quality together with nocturnal dyspnoea and orthopnoea[4] (BOX 1).

Sleep-disordered breathing — also known as sleep-related breathing disorders — is highly prevalent in patients with HF. Both central and obstructive sleep apnoeas are frequently observed in these patients and are reported to have an important added prognostic value in HF. This effect on HF outcomes is a result not only of the intrinsic alterations of ventilation, but also because sleep apnoeas can have a role in other sleep alterations, for example, through the sleep fragmentation secondary to recurrent apnoeas or because concomitant sleep-disordered breathing can affect both primary and secondary insomnia, worsening the related symptoms[5].

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Key points

- Patients with heart failure (HF) are characterized by relevant problems during sleep, including short sleep time, low sleep quality, and sleep-disordered breathing
- Approximately 33% of patients with HF have insomnia, potentially related to HF features, adverse effects of medications, or to conditions that often accompany chronic diseases such as mood disorders and psychological stress
- ACC/AHA guidelines have identified sleep deprivation and poor sleep quality as barriers to self-care and treatment adherence in patients with HF
- Sleep-disordered breathing is highly prevalent in patients with HF; both central and obstructive sleep apnoeas are frequently observed in these patients, and were shown to have an important added prognostic value
- Continuous positive airway pressure has a beneficial effect on left ventricular ejection fraction and is currently the best treatment option for obstructive sleep apnoeas in patients with HF
- At present, no consensus exists on whether central sleep apnoeas should be treated and what the optimal therapy in HF might be

Finally, poor health-related quality of life is common in adult patients with HF[6], and sleep disorders (with or without daytime sleepiness) can greatly contribute to these symptoms[7,8]. Therefore, the presence of sleep disorders might be an additional risk factor for increased mortality in patients with HF. ACC/AHA guidelines[9] identify sleep deprivation and poor quality of sleep — often associated with low sustained attention, poor memory, impaired executive function, and psychomotor delay — as barriers to self-care and treatment adherence in patients with HF.

This Review addresses the complex interactions between HF and sleep alterations, in particular with sleep-disordered breathing, and describes the pathophysiology, diagnosis, and management of these sleep disorders on the background of increasing evidence from clinical studies. Importantly, the evidence from clinical trials is not yet well integrated into the current HF management guidelines, exemplified by the 2012 ESC guidelines on HF[10] in which sleep-disordered breathing is referred to only as a possible HF comorbidity and for which the possibility of treatment might be considered. Therefore, in this Review, we aim to raise the awareness among clinicians of issues related to sleep-disordered breathing in HF and their management. This Review is especially important following publication in 2015 of the interventional SERVE-HF trial[11], designed to assess the effects of adaptive servo-ventilation in patients with chronic HF and central apnoeas, and with two more trials currently ongoing: ADVENT-HF[12], which includes patients with chronic HF and obstructive and/or central apnoeas, and CAT-HF[13], which includes patients with post-acute decompensated HF.

HF and sleep-disordered breathing

The two major forms of sleep-disordered breathing are obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). OSAs result from the complete collapse of the pharynx and upper airways, whereas CSAs arise from fluctuations in the central respiratory drive. During OSA, the abdominal and thoracic efforts increase with the aim of producing airflow (FIG. 1a). By contrast, respiratory movements are absent in CSA[14] (FIG. 1b). OSA and CSA might share a common origin, as the same patient can present with predominantly obstructive apnoeas at the beginning of the night that turn into mainly central apnoeas towards the morning[15–18]. A third form of sleep-disordered breathing that is also frequent in patients with HF is mixed sleep apnoea, characterized by an initial central apnoea event followed by an obstructive component.

Respiratory patterns characterized by hyperpnoea and central hypopnoea (or apnoea) alternating during sleep were reported to occur in patients with HF more than a century ago. First Cheyne in 1818, and later Stokes in 1834, described a periodic breathing pattern that was later named after them as 'Cheyne–Stokes respiration'. This condition is a form of periodic breathing in which the ventilatory period is characterized by a prolonged waxing and waning pattern of tidal volume, followed by central apnoea or hypopnoea. Cheyne–Stokes respiration can be observed during both sleep and wakefulness, although it seems to be more common during sleep[19]. Cheyne–Stokes respiration that occurs during sleep is considered a form of CSA with a prolonged hyperpnoea. The term 'CSA' is generally used synonymously with Cheyne–Stokes respiration in patients with HF, although Cheyne–Stokes respiration is actually a special type of CSA.

Epidemiology

The prevalence of OSA in otherwise healthy adults varies widely in the literature[20] and has been reported to be 2–9% in women and 4–26% in men depending on which criteria have been considered for the diagnosis, but with a marked upsurge in prevalence in the past 2 decades[21] (BOX 2). The prevalence of CSA/Cheyne–Stokes respiration in otherwise healthy adults seems to be lower than that of OSA, but no strong evidence has been provided on this issue so far. Age, sex, sleep stage, and several medical conditions have been reported to affect susceptibility to CSA[19,22,23]. Breathing instability, which is likely to occur at sleep onset when patients can oscillate between wakefulness and various sleep stages, is also a potential trigger for CSA.

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Almost 50% of patients with HF have alterations of ventilation during sleep (central or obstructive apnoeas and hypopnoeas) that can disrupt the positive effects of physiological sleep on the cardiovascular system[24,25]. Nevertheless, most of the available evidence on sleep-disordered breathing refers to patients with HF with reduced ejection fraction, and few data are available on patients with HF with preserved ejection fraction.

In two case series, cross-sectional studies including patients with HF undergoing polysomnography, OSA was detected in 37% and 11% of patients, with the prevalence of OSA being greater in men (38%) than in women (31%)[26,27]. Risk factors for OSA in patients with HF, as in the general population, are multiple and, among them, male sex and being overweight or obese (quantified by the body mass index) have an important role. In women, menopausal status, in particular if combined with obesity and age >50 years, are the most important determinants of OSA[21,28]. The Sleep Heart Health Study[29], a perspective study comprising 6,424 men and women, indicated that the presence of OSA (defined as an apnoea–hypopnoea index (AHI) ≥10 per h) favoured the appearance of HF independently of other known risk factors, with a 2.20 relative risk.

In the largest, cross-sectional studies on sleep-disordered breathing in patients with HF with left ventricular systolic dysfunction, the frequency of CSA/Cheyne–Stokes respiration was reported to range between 28% and 82%[26–28,30–33]. This extremely wide range might depend on a number of variables, including HF aetiology and severity. The principal risk factors for CSA/Cheyne–Stokes respiration in patients with HF identified in cross-sectional studies are male sex, advanced age, hypocapnia, atrial fibrillation[34], or presence of a pacemaker, but not obesity[27]. Interestingly, women with systolic dysfunction rarely develop CSA/Cheyne–Stokes respiration[27,35]. Women are less susceptible to the development of hypocapnic central apnoea than men, and sex-related differences can also be found in the development of periodic breathing at high altitude[36,37]. This sex-related difference in the prevalence of CSA/Cheyne–Stokes respiration might contribute to the higher death rate in men with HF than in female patients with HF.

Box 1 | Key clinical terms

- Apnoea: complete cessation of breathing
- Apnoea–hypopnoea index (AHI): number of apnoea plus hypopnoea events per hour of sleep
- Capnography: noninvasive monitoring of the partial pressure of CO_2 in exhaled breath
- Dyspnoea: sudden and severe shortness of breath or difficulty in breathing
- Hypercapnia: elevated arterial partial pressure of CO_2
- Hyperpnoea: abnormally deep or rapid respiration
- Hypocapnia: low arterial partial pressure of CO_2
- Hypopnoea: episodes of transient reduction of airflow, shallow breathing, or an abnormally low respiratory rate
- Nocturia: excessive urination during the night
- Orthopnoea: shortness of breath that occurs when lying flat

Pathophysiology

Obstructive sleep apnoea

OSA is caused by the collapse of the upper airways during sleep in patients with anatomically narrowed and highly compliant airways. This collapse is caused by dysfunction of the motor neurons responsible for controlling the musculature within the pharynx[38]. In patients with HF, additional factors can favour the collapse of the upper airways, such as marked oscillations in the ventilatory drive, which lead to periodic breathing and predispose to upper airway narrowing[16,39], and fluid shift from the legs to central structures, including the upper airways, when the patient is lying down (FIG. 2).

HF can favour the appearance and severity of OSA, and OSA might, in turn, favour the progression of chronic HF through multiple mechanisms (FIG. 2). Inspiration against a closed airway determines a negative intrathoracic pressure that increases venous return to the right ventricle[40]. This increase in cardiac preload is associated with a leftward shift of the interventricular septum that further reduces left ventricular function[41,42]. The negative intrathoracic pressure during obstructive apnoea is also responsible for an increased left ventricular transmural pressure, which increases the afterload[42], further impairing the function of an already failing left ventricle. These recurrent events that accompany repeated obstructive apnoea determine a further increase of the already elevated sympathetic activity in patients with HF, documented by increased plasma catecholamines[43]. The repeated occurrence of apnoeas and hypopnoeas has been associated with deranged endothelial function, an increase in the plasma concentration of inflammatory markers, increased platelet aggregability, and increased variability in blood pressure and heart rate[44–46].

Central sleep apnoea

The arterial partial pressure of CO_2 (P_aCO_2) is the most important factor influencing ventilatory drive during both wake and sleep. Periodic breathing is characterized by central apnoea, which occurs when the P_aCO_2 is lowered below the apnoeic threshold[47,48], followed by a hyperventilation phase. Whenever the chemical drive of breathing prevails over the cortical influence on the respiratory controller — as typically occurs during sleep — the patient becomes apnoeic until the P_aCO_2 rises again above the apnoea threshold, accompanied by a reduction in the arterial partial pressure of O_2 (P_aO_2)[49–52]. The alternating pattern of apnoea and hyperpnoea continues because of the ongoing oscillations of P_aCO_2 around the apnoea threshold, associated with concomitant oscillations in P_aO_2 (REFS 49–52).

In patients with HF, the increased pulmonary venous pressure that results from left ventricular failure leads to pulmonary congestion, stimulating pulmonary stretch receptors and leading in turn to hyperventilation and hypocapnia (FIG. 3). Stimulation of the stretch receptors increases the respiratory centre sensitivity to CO_2 through their vagal afferents[31,53,54]. When patients with

HF and peripheral oedema lie flat, the increased venous return from the extremities causes rostral fluid shift with central fluid accumulation and pulmonary congestion, which further stimulates vagal receptors in the lungs to elicit reflex hyperventilation[54] (FIG. 3). Indeed, central apnoeas are more frequent in the supine position, and sleeping on one side can lead to the amelioration of the severity of CSA and Cheyne–Stokes respiration in patients with HF[55]. Patients with HF who experience respiratory difficulties during exercise testing are particularly prone to Cheyne–Stokes respiration[56].

Despite these proposed pathophysiological mechanisms, the actual factors responsible for CSA/Cheyne–Stokes respiration are not fully understood. Overall, CSA/Cheyne–Stokes respiration has been considered in most studies to be more a consequence than a cause of HF. However, even if patients with HF and CSA are not affected by episodes of negative intrathoracic pressure — as is the case in patients with OSA — they are nevertheless characterized by a high sympathetic activation during both day and night. This sympathetic activation is related to the frequency of apnoeas and the

Figure 1 | **Polygraphy records of obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). a** | OSA is characterized by cessation or marked reduction of the airflow (Airflow band) in the presence of ventilatory effort (Thorax and Abdomen bands). **b** | CSA is characterized by cessation of both airflow (Airflow band) and respiratory effort (Thorax and Abdomen bands) during sleep. Snoring sounds and airflow were recorded with a nasal cannula; thoracic and abdominal muscle effort with piezoelectric strain gauges; oxygen saturation (SpO_2), heart rate, and plethysmography (Plethysm.) with a finger cuff; and body position with an accelerometer.

frequency and severity of hypoxia though chemoreflex activation, adding to the degree of sympathetic activation that results from the underlying left ventricular dysfunction. This mechanism suggests that CSA can have a causative role in worsening the clinical condition of patients with HF, emphasizing the existence of a bidirectional relationship between these two conditions[57] (FIG. 3). This bidirectional relationship has possible therapeutic implications, given the evidence that treatment of CSA can reduce sympathetic activity[58].

Sleep disorders and cardiac function

The high sympathetic activation that occurs in both OSA and CSA might negatively affect the prognosis of patients with HF, suggesting that treating these disorders can favourably affect the clinical history of these patients. Therefore, combining the treatment for sleep-disordered breathing with the currently recommended therapeutic neurohormonal modulation in patients with HF can be useful. The importance of considering the frequency and severity of sleep-disordered breathing — and the associated sympathetic activation — in patients with HF is reinforced by studies showing an increased frequency of nocturnal malignant arrhythmia in these patients, documented by an increased nocturnal discharge rate from implantable cardioverter–defibrillators[59].

Effects of obstructive sleep apnoea

Obstructive apnoeas during sleep induce a series of systemic haemodynamic, autonomic, and humoral changes with adverse consequences for the cardiovascular system in individuals with normal ventricular function. Inspiratory efforts against the occluded upper airway are associated with intrathoracic pressure oscillations[42,60] that result in increased sympathetic activity[61] (FIG. 2). The hypoxia, hypercapnia, and arousal from sleep that occur at the end of the obstructive apnoea further increase sympathetic activity[61–63]. The postapnoeic period — when a patient recovers upper airway patency — is often characterized by marked increases in blood pressure and heart rate[64]. Importantly, the adverse cardiovascular consequences of OSA are not confined to sleep. Indeed, increased daytime sympathetic nervous activity and arterial hypertension are also reported to occur in patients with OSA[65–67].

The increase in sympathetic activity observed in HF and OSA is documented by elevations in norepinephrine plasma levels[68,69], increases in muscle sympathetic nervous activity during wakefulness and sleep[70] (obtained by microneurographic recordings of efferent sympathetic fibres in peroneal nerves), and an increase in the power of spectral components of blood pressure and heart rate variability around 0.1 Hz (the so-called low-frequency band) that have been shown to be associated with baroreflex and sympathetic cardiovascular modulation[71,72]. The concomitant reduction in parasympathetic activity observed in HF and OSA is documented by the reduction in the power of high-frequency spectral components of heart rate variability, which largely reflects heart rate variations related to respiratory activity and parasympathetic cardiac modulation[72]. This reduction in high-frequency spectral components is associated with an increase in the low-frequency/high-frequency ratio of heart rate spectral components, which have been shown to reflect the balance between sympathetic and parasympathetic cardiac modulation[72]. An additional phenomenon that indicates the occurrence of a deranged autonomic cardiovascular control in HF and OSA is the reduction in cardiac baroreflex sensitivity[73–76].

Evidence from both experimental and large, prospective, epidemiological studies shows that OSA is an independent risk factor for the development of systemic hypertension[65]. In animal models, this systemic hypertension leads in turn to left ventricular hypertrophy, systolic dysfunction, and interstitial pulmonary oedema[77]. Moreover, OSA severity in patients with HF has been shown to be associated with increasing blood-pressure values during the day[78]. The mechanisms by which OSA promotes chronic hypertension are similar in patients with HF and in individuals with normal cardiac function[66,79], including sympathetic overactivity, intrathoracic pressure changes, inflammation, oxidative stress, and vascular endothelial dysfunction[66,79–83] (FIG. 2). Systemic hypertension is the most common risk factor for cardiac hypertrophy and failure in longitudinal studies, in particular when high blood-pressure values are observed during sleep[84–86]. Sympathetic activation promotes renin–angiotensin–aldosterone system activation and sodium and fluid retention[87] that contribute, together with the accompanying increase in blood-pressure levels, to worsen the clinical course of HF. The impaired baroreflex and tonic vagal heart-rate control and the sympathetic overactivity in patients with HF and OSA are additional markers of adverse outcome in these patients, in part as a result of an increased risk of sudden death[88,89].

OSA might also promote myocardial dysfunction by favouring coronary diseases and ischaemic heart disease, conditions that are often associated with hypertension. Patients with HF and OSA show increased myocardial oxygen demand during sleep in the setting of recurrent hypoxia, reduced cardiac output, and coronary perfusion, leading to an increased risk of recurrent nocturnal ischaemia and arrhythmias[90]. An increased risk of developing HF or coronary heart disease has been shown in patients with severe elevation of AHI[91]. Moreover, the sympathetic overactivity associated with OSA can induce myocyte necrosis and apoptosis, adrenoceptor downregulation and desensitization, and increased mortality[87].

Box 2 | Epidemiology of sleep-disordered breathing

Prevalence of sleep disorders in patients with heart failure compared with the general population

Obstructive sleep apnoea[20,21,26,27]:
11–38% versus 2–26%

Central sleep apnoea/Cheyne–Stokes respiration[26–28,30–33,194]:
28–82% versus <5%

Chronic insomnia[2]:
33% versus 10–15%

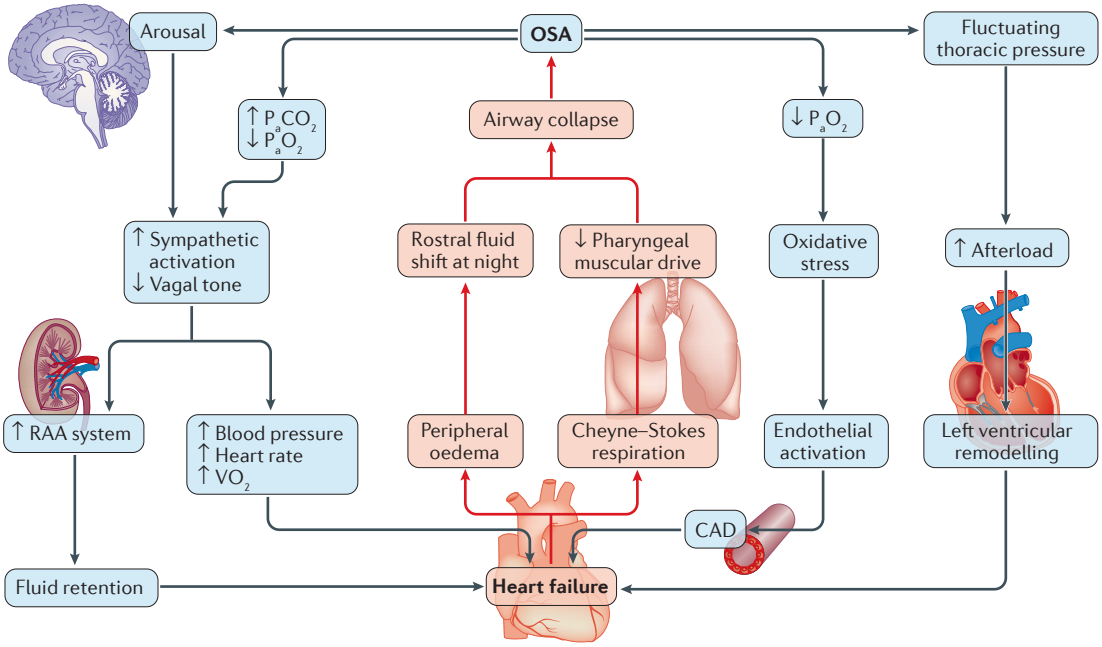

Figure 2 | **Relationship between obstructive sleep apnoea (OSA) and heart failure.** Schematic representation of the mutual interactions between OSA and heart failure. CAD, coronary artery disease; P_aCO_2, arterial partial pressure of CO_2; P_aO_2, arterial partial pressure of O_2; RAA, renin–angiotensin–aldosterone; VO_2, oxygen consumption rate.

Accumulating evidence indicates that plasma levels of inflammatory mediators, such as C-reactive protein, IL-6, and TNF, are elevated in patients with OSA proportionally to the frequency of apnoeas and hypopnoeas[92]. Patients with OSA also show signs of increased oxidative stress, for example, high production of reactive oxygen species in neutrophils and monocytes[80,81], and have elevated levels of circulating adhesion molecules, such as intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin[93,94]. Patients with OSA have low plasma nitrite concentrations and altered endothelial-mediated vasodilatation[94,95], confirmed by a reduced expression and activity of endothelial nitric oxide synthase (eNOS) and phosphorylated eNOS[96]. Moreover, OSA increases the concentration of endothelial microparticles (a marker of endothelial apoptosis), reduces the circulating levels of endothelial progenitor cells (a marker of endothelial repair capacity)[97], and might impair the protection against complement attack[98]. Obstructive events during sleep can also have long-term effects, for example by the induction of genes involved in ventricular remodelling caused by the repetitive increases in wall stress, and by inducing myocyte slippage and contractile dysfunction[99] (FIG. 2).

All these observations support the suggestion that the pathophysiology of OSA and HF has several aspects in common such as the adverse effects of the sympathetic overactivity that is associated with the heightened chemoreflex sensitivity typical of these conditions[45,100,101]. Other common factors are the vagal withdrawal that accompanies the reduced arterial baroreflex sensitivity associated with heightened chemoreflex sensitivity, and the inflammation, hypoxia, and intermittent intrathoracic pressure changes[102,103]. In view of these findings, the role for OSA in determining or favouring the occurrence or progression of HF should merit greater attention than it has received in the past 15 years.

Effects of central sleep apnoea

The clinical relevance of CSA in HF is emphasized by studies showing that the presence of CSA is associated with increased mortality in patients with HF[104]. Although knowledge of the pathophysiology of CSA/Cheyne–Stokes respiration has been growing in the past 2 centuries, whether CSA/Cheyne–Stokes respiration is merely a marker of the severity of the underlying disease or an important risk factor that independently worsens the prognosis of patients with HF — and, therefore, requires treatment — is still widely debated. Indeed, when multivariate analyses were performed to control for potential confounders involved in determining outcome in patients with HF, CSA was an independent risk factor for death or cardiac transplantation in these patients[105,106]. CSA, unlike OSA, is not associated with negative intrathoracic pressure changes; therefore, the effects of CSA on the outcome of patients with HF might depend on the marked neurohumoral activation associated with this sleep disorder[58]. In particular, the effect on outcomes might depend on the increased sympathetic activity, the surges in blood pressure and heart rate, and the greater propensity towards lethal arrhythmias induced by CSA[58,105–110]. Patients with HF and CSA have higher concentrations of urinary and plasma norepinephrine during sleep and wakefulness than patients with HF matched for ejection fraction and other clinical characteristics

but without CSA[58]. This periodic respiratory pattern causes additional sympathetic stimulation in patients who already have sympathetic activation because of the HF, adding further load at night on an already stressed myocardium[110].

The respiratory oscillations characterizing CSA also influence other physiological systems, with the result that end-expiratory lung volume, blood pressure, heart rate, cerebral perfusion, pupillary size, and electroencephalographic activity start to oscillate at the same frequency[107,108,111–113]. In particular, very low frequency oscillations in ventilation during periodic breathing induce concomitant very low frequency oscillations in heart rate[108,114,115]. Similarly to the mechanisms described for OSA, hypoxia, arousals from sleep, and adrenergic activation are involved in determining the cyclical oscillations in heart rate and blood pressure in patients with CSA[108]. Additionally, a direct cyclic activation of cardiovascular sympathetic neurons by respiratory neurons in the brain stem is probably involved[116]. Such oscillations of heart rate synchronized with ventilation can be associated with both positive and detrimental effects. Heart-rate oscillations can optimize ventilation–perfusion matching and maintain efficient gas exchange even in patients with HF. Nevertheless, these oscillations can also be repetitive, stressful phenomena that worsen ventricular dysfunction, favouring arrhythmias and reducing survival.

Cheyne–Stokes respiration occurs not only during the night, but also during the day. Patients with severe HF were found to breathe periodically during 10% of daytime, with Cheyne–Stokes respiration peaks at 04:00, 14:00, and 18:00 (REF. 117). Patients with Cheyne–Stokes respiration can also present with exercise oscillatory ventilation (that is, cyclic fluctuations of ventilation during exercise), generally unravelled by cardiopulmonary exercise testing, that can disappear early or persist during the entire exercise protocol. In this context, up to 80% of patients with exercise oscillatory ventilation can present a severe sleep-disordered breathing (AHI >30). This combination of exercise oscillatory ventilation and sleep-disordered breathing has been associated with a worse prognosis[32,118,119]. Beyond their possible association in the same patient, exercise oscillatory ventilation and CSA/Cheyne–Stokes respiration are thought to share a common pathophysiology, in which a variable combination of impaired cardiac output and increased filling pressures, along with neurohumoral activation and altered chemoreflex/metaboreflex control, might have a role.

A higher mortality in patients with HF has been associated with the combined presence of periodic breathing, very low frequency oscillations in heart rate, and enhanced peripheral chemoreceptor sensitivity[120]. Patients with congestive HF and Cheyne–Stokes respiration showed increased mortality (86%) during a 2-year follow-up compared with patients with congestive HF but without Cheyne–Stokes respiration (56%)[121]. Lanfranchi *et al.* found that the prevalence of Cheyne–Stokes respiration combined with the cross-sectional area of the left atrium could be used to predict mortality in patients with HF[105]. The association between Cheyne–Stokes respiration and a twofold to threefold increase in mortality in patients with HF has raised the question whether treatment of Cheyne–Stokes respiration would decrease mortality in HF. However, some reports question the independent association between Cheyne–Stokes respiration and mortality in HF[122–124].

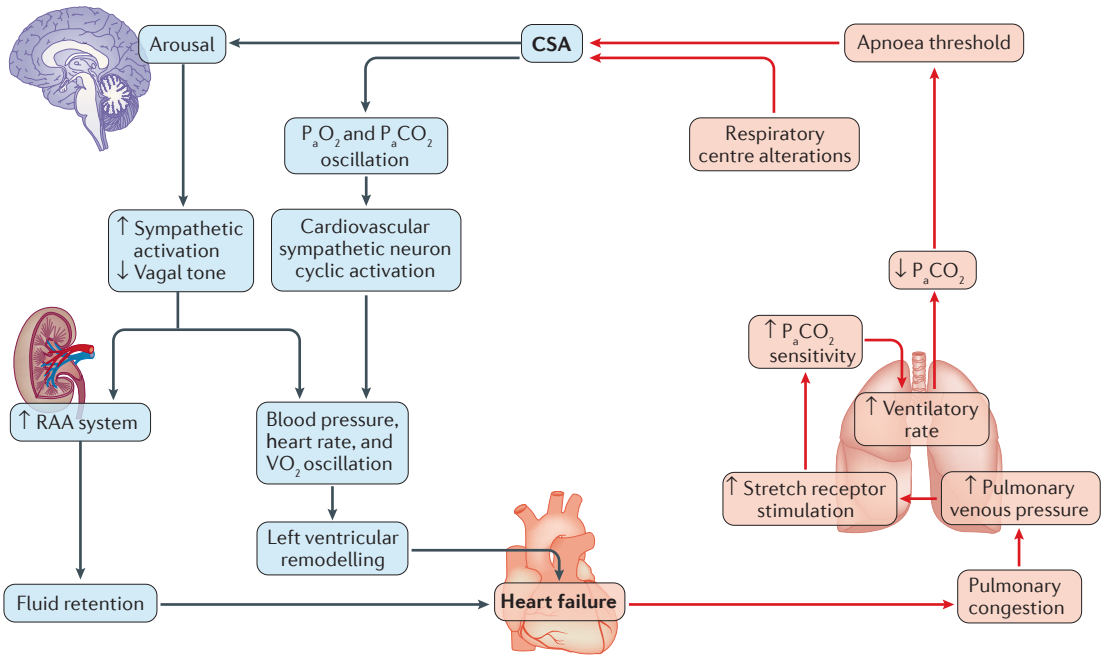

Figure 3 | **Relationship between central sleep apnoea (CSA) and heart failure.** Schematic representation of the mutual interaction between CSA and heart failure. P_aCO_2, arterial partial pressure of CO_2; P_aO_2, arterial pressure partial of O_2; RAA, renin–angiotensin–aldosterone; VO_2, oxygen consumption rate.

Effect of disrupted sleep

Very few data are available on the effect of sleep disruption on cardiac function, but improvement of sleep stability seems to have a beneficial effect on blood pressure[45], arrhythmogenesis[125], and mortality[126]. The negative cardiac effects of sleep disruption might be related to the increase in sympathetic tone induced by sleep fragmentation and sleep deprivation[127].

Clinical features and diagnosis

Most patients with HF and OSA or CSA do not complain of daytime sleepiness, probably because of the high sympathetic tone in HF[128,129], nor do they complain of other common symptoms of sleep apnoea, such as sweating and choking. Conversely, patients with HF and with sleep apnoea are commonly affected by insomnia and poor nocturnal sleep quality as prevalent symptoms[5]. However, the occurrence of sleep-disordered breathing might not be identified unless a patient's bed partner is also interviewed (TABLE 1). The HF management guideline update from the Canadian Cardiovascular Society[130] recommends considering OSA in patients with HF presenting with paroxysmal or recurrent atrial fibrillation, hypertension refractory to optimal HF therapy, increased body mass index, and unanticipated pulmonary hypertension or right ventricular dysfunction. Moreover, sleep-disordered breathing should also be considered in patients with HF when malignant ventricular arrhythmias are detected, particularly at night[130,131].

Diagnosis of sleep apnoea in patients with HF requires nocturnal monitoring of specific signals during sleep to identify the peculiar mechanical characteristics of sleep breathing typical of OSA and CSA[132], and to quantify the AHI (TABLE 1). A formal diagnosis of OSA is made in instances when AHI >15, or when AHI >5 with concomitant presence of at least one of the following symptoms: sleepiness; nonrestorative sleep; fatigue or insomnia; waking up with breath holding, gasping, or choking; habitual snoring, breathing interruptions, or both noted by a bed partner or other observer; hypertension; mood disorder; cognitive dysfunction; coronary artery disease; stroke; congestive HF; atrial fibrillation; or type 2 diabetes mellitus (TABLE 1). Similarly, a generic diagnosis of CSA is suspected in the case of a predominant component of central apnoeas and/or central hypopnoeas and more than five apnoeas and/or central hypopnoeas per hour of sleep, with additional criteria for specific subtypes of CSA[133] (TABLE 1).

Current standards for overnight full polysomnography — the typical diagnostic tool for sleep-disordered breathing — require the simultaneous monitoring of sleep electroencephalogram, eye movement, chin electromyogram, cardiac rhythm, body position, oxyhaemoglobin saturation, oronasal flow, and detection of respiratory effort with noninvasive methods that can discriminate between obstructive and central events. Another measurement of respiratory effort that is less commonly performed than polysomnography is intraoesophageal pressure assessment. The effect of

Table 1 | **Common clinical characteristics and diagnosis of obstructive sleep apnoea and central sleep apnoea**

Obstructive sleep apnoea	Central sleep apnoea
Clinical characteristics	
• Unexplained daytime somnolence[195] • Abnormal sleep noises[196] (gasping, choking, loud apnoeas) with respiratory effort witnessed by bed partners • Fatigue[195] • Resistant arterial hypertension[45] • Cardiac rhythm abnormalities[197] • Obesity/high waist and neck circumference[198] • Narrow oropharynx[199] • Heart failure symptoms, in particular peripheral oedema[200]	• Rarely daytime somnolence[129] • Repetitive sleep apnoeas without abnormal noises, and without respiratory effort[193] • Poor quality of sleep[201] • Possible association with periodic breathing during exercise[118] • Cardiac rhythm abnormalities[197] • Heart failure symptoms, in particular peripheral oedema[200]
Diagnosis[133]	
• ≥5 predominantly obstructive respiratory events (obstructive and mixed apnoeas, hypopnoeas, or respiratory effort related arousals) per hour of sleep, and at least one of the following: • Sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms • Waking up with breath holding, gasping, or choking • Habitual snoring, breathing interruptions, or both noted by a bed partner • Presence of hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus Or: • ≥15 predominantly obstructive respiratory events (apnoeas, hypopnoeas, or respiratory effort related arousals) per hour of sleep — even in absence of the associated symptoms or comorbidities	• ≥5 central apnoeas and/or central hypopnoeas per hour of sleep; the number of central apnoeas and/or central hypopnoeas needs to be >50% of the total number of apnoeas and hypopnoeas • Cheyne–Stokes breathing ventilation pattern; in the absence of this element and of daytime or nocturnal hypoventilation, the disorder is considered primary central sleep apnoea And: • At least one of the following: sleepiness, difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep; awakening with shortness of breath; snoring, witnessed apnoea Or: • Presence of atrial fibrillation or flutter, congestive heart failure, or a neurological disorder And: • The disorder is not better explained by another current sleep disorder, medication use, or substance use disorder

sleep-disordered breathing on cardiovascular function can also be assessed through measurement of the time required for pulse waves to reach peripheral arteries, defined as pulse transit time[134]. Pulse transit time can also be used in the assessment of patients with HF and sleep-disordered breathing, with better results when combined with capnography[135].

Although in-hospital, full polysomnography is still the gold-standard diagnostic test for sleep-disordered breathing, attended polysomnography is a complex test that is expensive and not easily available. For these reasons, cardiorespiratory sleep polygraphy has been proposed as a better solution for screening sleep-disordered breathing in patients with a cardiac condition. The simplified approach of cardiorespiratory sleep polygraphy enables recording of sleep breathing patterns — chest and abdominal movements, nasal airflow, and oxygen saturation (SpO_2) combined with electrocardiogram (ECG) and body position — at the patient's home and is, therefore, more easily accepted by the patient than an in-hospital recording. Furthermore, cardiorespiratory sleep polygraphy is suggested to be as sensitive as full polysomnography in diagnosing sleep-disordered breathing[136]. Some cardiorespiratory recorders also offer the possibility of remote data transmission, which is a further advantage in monitoring patients with HF.

A frequently asked question in a cardiology environment is whether easier and simpler tools to screen for sleep-disordered breathing are available. Several approaches have been proposed, ranging from a simple recording of heart rate variability or nocturnal SpO_2 via a finger probe, to a combination of SpO_2, ECG, and peripheral pulse wave recordings. The simple SpO_2 recording was shown reliably to identify the occurrence of marked nocturnal oxygen desaturations in patients with HF, leading to a more accurate screening of sleep-disordered breathing than other tools, such as heart rate variability estimates[137]. However, SpO_2 recording might not help to detect apnoea and hypopnoea events without marked desaturations, that is, whenever desaturations are <3%. Sleep-disordered breathing management guidelines[132] clearly state that, although SpO_2 monitoring might be a simple and clinically useful screening tool, this recording cannot be used to make a diagnosis because SpO_2 monitoring cannot be used to determine the type of sleep-disordered breathing, for which a polygraphic recording is required.

A novel approach for the identification of sleep-disordered breathing comes from pacemaker technology. In patients with implanted pacemakers, the changes in thoracic impedance associated with ventilation can be assessed through the pacemaker electrodes using an *ad hoc* algorithm. These devices, through the analysis of thoracic impedance changes, can identify moderate-to-severe sleep-disordered breathing with a sensitivity of up to 88.9%, and a specificity of up to 84.6%[138]. Nevertheless, additional studies are needed to define more precisely the actual clinical role of this technology.

The diagnosis of sleep-disordered breathing and the identification of the most suitable indices for their quantification are important steps towards more accurate risk stratification of patients with HF. Sleep-disordered breathing, by reducing nocturnal oxygen and inducing oxygen desaturation, can substantially affect outcomes in patients with HF, as shown by the largest clinical study on this issue[139].

Treatment perspectives

Obstructive sleep apnoea

In contrast to CSA, OSA does not seem to be a compensatory mechanism in patients with HF and might, therefore, be a target for treatment (TABLE 2). No strong evidence is available showing that drugs used for the treatment of HF influence the severity of OSA. However, interesting preliminary data show, for example, that treatment with furosemide and spironolactone in patients with severe OSA and diastolic HF is associated with a significant reduction in AHI (from 75 to 57; $P<0.001$) and a significant increase in upper airway patency[140]. Other general therapeutic considerations for patients with HF and OSA include weight reduction and abstinence from smoke, alcohol, and sedatives (which predispose to pharyngeal collapse during sleep).

Ventilation during sleep. Continuous positive airway pressure (CPAP) treatment in patients with HF and OSA prevents recurrent hypoxia, reduces nocturnal blood pressure and heart rate[90], and increases arterial baroreflex sensitivity[141]. In the first study to examine the effects of treating OSA in patients with HF, CPAP treatment was associated with a significant increase in mean left ventricular ejection fraction and a reduction in dyspnoea[102]. A small cohort study showed that adequate diagnosis and CPAP adherence reduced both hospital readmission rate and emergency department visits of patients with HF over a 30-day observation period[142]. Moreover, randomized trials involving patients with HF and OSA treated with CPAP showed an improvement in left ventricular systolic function and reductions in blood pressure, heart rate, and sympathetic nerve activity[143,144]. Accordingly, a meta-analysis also showed that CPAP might improve left ventricular ejection fraction among patients with OSA[145]. In terms of long-term clinical outcomes, two observational studies have encouraging results, showing that CPAP treatment lowers mortality[146] and improves hospitalization-free survival[147] in patients with HF, particularly in more compliant patients whose average nightly usage of CPAP was higher than the median group use (4.9 h). However, we acknowledge that no randomized, controlled trials to evaluate the effects on mortality of CPAP treatment for OSA in patients with HF have been published. In addition, the scientific statement on sleep apnoea and cardiovascular disease from the AHA/ACC Foundation[148] considers CPAP treatment in patients with HF as being investigational because this treatment option is not supported by randomized trial data.

A preliminary pilot trial suggested a possible beneficial effect of bilevel positive airway pressure ventilation in improving left ventricular ejection fraction in patients with HF and concomitant OSA[149]. Nevertheless, larger trials are required to confirm these initial findings.

Table 2 | **Current and potential treatments for sleep-disordered breathing**

Treatment	Evidence	Refs
Obstructive sleep apnoea		
Noninvasive positive airway pressure: • Continuous positive airway pressure • Bilevel positive airway pressure	Strong evidence	55,78
Weight loss	Strong evidence provided by large interventional and observational studies	45,101
Mandibular advancement devices	Small studies, controversial evidence	150
Uvulopalatopharyngoplasty and laser assisted uvulopalatoplasty	Small studies	153
Furosemide and spironolactone	Preliminary results	140
Hypoglossal nerve stimulation	Preliminary results	152
Cardiac pacing	Potential treatment, but negative results have been obtained	185,186
Central sleep apnoea		
Noninvasive positive airway pressure: • Continuous positive airway pressure • Bilevel positive airway pressure • Adaptive pressure support servo-ventilation	 • Partly controversial evidence from small studies • Partly controversial evidence from small studies • Still under investigation	 58,170 178,179 165
Acetazolamide and theophylline	Small observational studies	154–156
Supplemental O_2	Controversial evidence	163–165
Phrenic nerve stimulation	Pilot studies, efficacy to be proven	191
Cardiac pacing	Small studies, more evidence needed	185,186

Other approaches. Other treatments proposed for patients with OSA include mandibular advancement devices, which have been shown in randomized trials to improve OSA and its symptoms, especially in mild-to-moderate OSA[150]. Nevertheless, mandibular advancement devices are generally not as effective as CPAP[151]. Hypoglossal nerve stimulation has also been suggested as a possible treatment for patients with OSA[152]. Several ear, nose, and throat surgical procedures have been proposed to increase the size of the upper airway, but they are effective in <50% of patients and have not been assessed in randomized trials[153]. Moreover, no data are available on the effects of any of these treatments on OSA in patients with HF.

Central sleep apnoea

At present, whether CSA should be treated, or what the optimal therapy of CSA in HF might be, is uncertain (TABLE 2). First-line therapy for patients with CSA should be the optimization of HF treatment, which can reduce systemic and pulmonary congestion and, thereby, reduce CSA[110]. In patients with HF, reducing the intravascular volume and venous congestion with diuretic agents might promote the reduction of OSA and CSA severities by decreasing fluid retention and rostral fluid shift at night.

Pharmacological therapy. Small studies suggest that acetazolamide and theophylline are beneficial for the treatment of CSA in patients with HF[154]. In symptomatic patients with CSA, acetazolamide — a carbonic anhydrase inhibitor that induces mild metabolic acidosis —ameliorates CSA when administered in a single, 250 mg dose before bedtime[155]. Similarly, theophylline reduces CSA in patients with HF[156] without adverse effects on sleep architecture. However, another trial showed that theophylline did not improve right or left ventricular ejection fraction, quality of life, or clinical outcomes[156]. Additionally, theophylline is associated with important adverse effects in patients with advanced HF, including inotropic and arrhythmogenic effects, precluding the long-term use of this drug[157].

Several pharmacological agents might influence the breathing pattern during sleep, in particular CSA. Therefore, ongoing drug treatments should be carefully evaluated in the management of patients with HF and CSA. An aggressive diuretic therapy combined with angiotensin-converting-enzyme inhibitors and β-blockers can reduce the severity of CSA and the associated sympathetic overactivity[158–160]. However, the metabolic alkalosis that results from the use of diuretic therapies might predispose to CSA by narrowing the difference between the circulating P_aCO_2 and apnoeic threshold. Conversely, narcotics can worsen central apnoea. Therefore, when patients with HF need analgesia, a change in the pain-control regimen might ameliorate the severity of their central apnoea.

On the basis of the available data, we might conclude that the potential usefulness of pharmacological therapy for CSA is still a debated issue, and that further research is needed in this area. In addition, the potential interference with respiratory patterns by drugs used for the treatment of other conditions should be carefully considered to avoid iatrogenic worsening of central apnoeas.

Supplemental O_2 and CO_2. Accumulating evidence indicates that chemosensitivity might have an important role in patients with HF. Increased chemosensitivity to both hypoxia and hypercapnia are suggested as serious adverse prognostic markers in HF, inducing neurohormonal derangement, ventilation instability, and ventricular arrhythmias[161]. From a pathogenic point of view, a study in healthy individuals that were tested under exercise, hypoxia, hyperoxia, hyperoxic hypercapnia, and with or without acetazolamide treatment, showed that exercise, hypoxia, and hypercapnia increased ventilatory oscillations by increasing cardiac output and breath-by-breath ventilation[162]. By contrast, acetazolamide decreased ventilatory instability, in part by a contrasting action on O_2 and CO_2 sensing[162].

Supplemental O_2 therapy in patients with HF might have beneficial effects on CSA by ameliorating the hypoxaemia, increasing cerebral PCO_2 through the Haldane effect, and decreasing nocturnal norepinephrine levels[163,164]. However, supplemental O_2 did not induce significant improvements in cardiac function or quality of life in patients with HF[163–165], and the effects of supplemental O_2 on cardiovascular end points in patients with HF and concomitant CSA over prolonged periods have not been assessed. Furthermore, O_2 supplementation in patients with ST-segment elevation myocardial infarction but with normoxia might have deleterious effects[166]. Although chemosensitivity is increased in patients with HF compared with healthy individuals[167], growing evidence also shows a major role of central afferent sympathetic fibres in modulating chemoreflex sensitivity and medullary autonomic centres[168,169]. Therefore, altered chemosensitivity and increased sympathetic drive seem to be associated in a vicious cycle, and might be causally linked in both directions in patients with HF and concomitant CSA.

Ventilation during sleep. Randomized clinical trials suggest that noninvasive positive airway pressure such as CPAP, bilevel positive airway pressure, and adaptive pressure support servo-ventilation alleviate CSA in patients with HF during periods of 1 day to 3 months[165,170]. The beneficial effects of nasal CPAP on CSA, especially if it occurs in combination with OSA, can be explained by a number of mechanisms, such as the improvement in oxygenation by inducing an increase in lung volume, and the improvement of cardiac function by decreasing preload and after load. The combination of these changes would modulate the ventilatory overshoot in CSA, thereby antagonizing the perpetuation of ventilatory instability, which is also suggested by the increase in P_aCO_2 after CPAP[171,172]. Preliminary studies showed that nasal CPAP treatment in patients with HF and CSA was associated with an increase in left ventricular ejection fraction and a reduction of the combined mortality–cardiac transplantation rate[106]. Nasal CPAP treatment also decreased the frequency of ventricular ectopic beats[173] and nocturnal and daytime sympathetic nervous system activity, resulting in improved quality of life[58,170,174]. Nevertheless, this combination of beneficial effects has not been confirmed in subsequent studies such as the CANPAP trial[175]. Investigators enrolled 258 patients with HF and CSA into this trial, which was designed to assess whether CPAP would improve the survival without heart transplantation in these patients during a 2-year follow-up. At 3 months, the CPAP group showed a reduction in the AHI, an increase in ejection fraction and mean nocturnal oxyhaemoglobin saturation, a reduction in the plasma levels of norepinephrine, and an improved 6-min walking distance compared with the placebo group. No differences were found in the overall death and heart transplantation rates between the two groups. However, the first data analysis had some limitations, acknowledged by the researchers[176], and a *post-hoc* analysis showed a decrease in mortality in patients in whom CPAP therapy resulted in amelioration of CSA[176]. Interestingly, the responder group (CPAP-CSA-suppressed) had a significant increase in left ventricular ejection fraction at 3 months ($P = 0.001$) and a higher transplantation-free survival than control individuals. No differences in any of these variables were found in the nonresponder group (CPAP-CSA-unsuppressed). Despite this *post-hoc* analysis, current evidence does not support the use of CPAP to extend life in patients with HF and CSA, in particular in the absence of ventilatory response to treatment demonstrated by polysomnography[175].

Bilevel nasal positive pressure, a noninvasive positive pressure ventilation with pressure support mode, is another therapeutic option in patients with both CSA and OSA. However, little evidence supports the use of bilevel positive pressure in nonhypercapnic central apnoea, including chronic HF[177]. Preliminary studies have investigated the beneficial effect of bilevel positive airway pressure ventilation in patients with HF and CSA[178,179], but the results strongly emphasize the need for larger trials to confirm the efficacy.

The technological progress in the past decade has led to the development of devices for adaptive servo-ventilation, which provide varying amounts of ventilatory support against a background of low-level CPAP. Several studies suggest that adaptive servo-ventilation is more effective than CPAP, bilevel pressure support ventilation, or increased dead space in alleviating central sleep apnoea[165,180–182]. However, the large, randomized, controlled SERVE-HF trial[11] has shown that adaptive servo-ventilation has no significant positive effect in patients with HF with reduced ejection fraction and predominantly with CSA, but rather increases both all-cause and cardiovascular mortality. All-cause mortality was 34.8% in the adaptive servo-ventilation group and 29.3% in the control group (HR 1.28, 95% CI 1.06–1.55, $P = 0.01$), and cardiovascular mortality was 29.9% and 24.0%, respectively (HR 1.34, 95% CI 1.09–1.65, $P = 0.006$). Two studies on the use of adaptive servo-ventilation in patients with HF, the ADVENT-HF[12] and CAT-HF[13] trials, are currently being performed. The ADVENT-HF trial was designed to assess whether survival improves when adaptive servo-ventilation is added to optimal medical therapy in patients with chronic HF affected by both CSA and OSA. The results from this trial should be available in a few years. Severe CSA is also

found in a high number of patients with acutely decompensated HF, and is associated with an increased risk of readmission and death[183,184]; CAT-HF[13] is a randomized trial on the usefulness of adaptive servo-ventilation in this patient group.

Overall, while waiting for the results of the ongoing trials, we have to conclude that no indication exists for the use of ventilatory adaptive servo-ventilation in the treatment of CSA in patients with HF with reduced ejection fraction, at least not in the frame of randomized, controlled, prospective trials. Conversely, optimization of available HF therapies is still the gold standard for the management of patients with HF, and all other treatment options need to be proved safe and of any benefit in HF with reduced ejection fraction before being considered.

Other approaches. In the past 14 years, a few studies have explored the effects of atrial overdrive pacing on sleep apnoea in patients with symptomatic sinus bradycardia. In these patients, an increase of pacing rate led to a reduction in the frequency of both central and obstructive apnoeas[185,186]. However, these effects were analysed over a single night recording, with no clinical outcome assessment, and without determining the pathogenic mechanisms[185,186].

Additional therapeutic strategies for CSA in patients with HF include physical exercise, which has been proposed as a possible effective therapy both for CSA and OSA[187,188]. Cardiac resynchronization therapy might also be useful in this setting, because this intervention was found to reduce the AHI in patients with HF and CSA[189]. However, none of the available studies on this issue had a randomized, controlled design. Finally, in 2015 phrenic nerve stimulation through a device (Remede©; Respicardia, USA) similar to a pacemaker with a stimulating electrode was proposed for the treatment of CSA, and is currently under evaluation in a randomized trial[190]. This device can be implanted percutaneously without general anaesthesia in a catheter laboratory. A nonrandomized, pilot study including 57 patients with HF showed that this technique induced a 55% reduction in the mean AHI in 3 months[191]. Phrenic nerve stimulation also reduced arousals and oxygen desaturation index, and improved quality-of-life indices, with treatment-related adverse events occurring in 26% of patients[191].

In conclusion, the following clinical indications for the management of patients with HF and CSA seem to be supported by evidence. First, optimization of the treatment for the underlying condition (that is, chronic HF) is of fundamental importance. Second, titration of CPAP in the sleep laboratory, aimed at identifying optimal ventilation pressure settings through polysomnography, is necessary to ascertain response to nasal positive airway pressure therapy and to determine any long-term benefit. Third, the use of bilevel positive airway pressure in a pressure support mode might aggravate the severity of central apnoea. By contrast, adaptive servo-ventilation is a questionable therapeutic modality for HF and CSA/Cheyne–Stokes respiration, and before suggesting the use of this technique, the results of ongoing randomized trials need to be awaited and compared. Fourth, supplemental O_2 might be beneficial, particularly in patients with HF and CSA/Cheyne–Stokes respiration. Fifth, the use of pharmacological agents remains of questionable efficacy. Additional studies are needed to provide a clearer indication on the management of CSA in patients with HF, also with the perspective of the available novel devices and techniques.

Insomnia

Guaranteeing sufficient sleep quality and duration in HF is important; therefore, in patients with HF, emphasis should be placed on treating chronic insomnia with cognitive behaviour therapy, medication, or both. However, the effects of treating insomnia in patients with HF have not been widely explored, and no randomized, controlled trials to assess this issue have been published.

As in the general population, treatment of comorbid insomnia in patients with HF can be implemented by starting with the collection of detailed patient history and sleep habits. In patients with HF, nonpharmacological approaches for insomnia, including sleep hygiene education, cognitive therapy, relaxation therapy, stimulus control therapy, and sleep restriction therapy, often seem to be preferable. In the case of concomitant sleep-disordered breathing, which can worsen the symptoms of primary and secondary insomnia, CPAP treatment can help to reduce secondary insomnia symptoms[192]. However, in patients with comorbid primary insomnia, CPAP treatment might be much less tolerated and, therefore, less effective in improving sleep duration and quality.

Pharmacological therapies for sleep might be clinically important, but should have minimal interactions with the drugs used for treating HF. Patients with HF often require a complex medication regimen and these patients are often characterized by prolonged drug-elimination times. Therefore, in these patients sleep agents can lead to an increased risk of daytime sleepiness, in particular when drugs with a long half-life are used. In this context, ramelteon — a melatonin receptor agonist with both high affinity for melatonin MT_1 and MT_2 receptors and selectivity over the MT_3 receptor — has been suggested as a safe drug to ameliorate sleep in patients with HF[193]. Other possible drugs are phytopharmacological drugs such as valerians, melissa, and L-tryptophan as mild medications, and antihistamines, antidepressants, and benzodiazepine-receptor agonists as more effective hypnotics. Benzodiazepines should be strictly avoided owing to the sedative effect on the respiratory centre.

Conclusions

The frequent occurrence of sleep alterations and sleep-disordered breathing in patients with HF, and the evidence of their influence in the HF clinical course, symptoms, and prognosis, strongly indicate that sleep alterations should receive more attention in the management of patients with HF, promoting interactive collaborations between sleep medicine centres and HF clinics. Nevertheless, more studies are needed,

in particular randomized, controlled trials, to explore whether treatment of sleep-disordered breathing and sleep improvement might have a positive effect not only on symptoms but also on outcome in patients with HF. In turn, evidence on whether treating HF can improve respiratory problems at night is also needed. As already mentioned, the SERVE-HF trial[11] has shown no benefit, or even a negative effect, of adaptive servo-ventilation in patients with CSA and concomitant HF. This finding has raised an increasing interest towards the results of the ADVENT-HF trial[12], an ongoing trial that is specifically aimed at assessing the effects of adaptive servo-ventilation on morbidity and mortality in medically treated patients with HF and OSA, CSA, or both. Finally, we have to emphasize that these conclusions apply only to sleep-disordered breathing occurring in patients with HF and reduced ejection fraction. More evidence is needed to understand whether these conclusions also apply to patients with HF with preserved ejection fraction.

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Competing interests statement
The authors declare no competing interests.