Sleep apnoea and heart failure

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Shareable abstract (@ERSpublications)
Obstructive sleep apnoea (OSA) may result in myocardial damage. Central sleep apnoea (CSA-CSR) occurs as a consequence of heart failure (HF). There is a worse prognosis than in HF without sleep apnoea. More evidence is needed regarding treatment impact. https://bit.ly/2Xn1j3i

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Abstract

Heart failure and sleep disordered breathing (SDB) are two common conditions that frequently overlap and have been studied extensively in the past three decades. Obstructive sleep apnoea (OSA) may result in myocardial damage due to intermittent hypoxia that leads to increased sympathetic activity and transmural pressures, low-grade vascular inflammation, and oxidative stress. On the other hand, central sleep apnoea and Cheyne–Stokes respiration (CSA-CSR) occurs in heart failure, irrespective of ejection fraction, either reduced (HFrEF), preserved (HFpEF) or mildly reduced (HFmrEF). The pathophysiology of CSA-CSR relies on several mechanisms leading to hyperventilation, breathing cessation and periodic breathing. Pharyngeal collapse may result at least in part from fluid accumulation in the neck, owing to daytime fluid retention and overnight rostral fluid shift from the legs. Although both OSA and CSA-CSR occur in heart failure, the symptoms are less suggestive than in typical (non-heart failure-related) OSA. Overnight monitoring is mandatory for a proper diagnosis, with accurate measurement and scoring of central and obstructive events, since the management will be different depending on whether the sleep apnoea in heart failure is predominantly OSA or CSA-CSR. SDB in heart failure is associated with worse prognosis, including higher mortality, than in patients with heart failure but without SDB. However, there is currently no evidence that treating SDB improves clinically important outcomes in patients with heart failure, such as cardiovascular morbidity and mortality.

Introduction

Heart failure is a clinical syndrome with current or prior symptoms and/or signs caused by a structural and/or functional cardiac abnormality, corroborated by either elevated natriuretic peptide and/or objective evidence of cardiogenic pulmonary or systemic congestion [1]. A characteristic feature of heart failure is its association with neurohumoral activation and, in particular, increased sympathetic nervous system activity (SNA) [2]. The clinical manifestations of heart failure may vary from a largely asymptomatic state (with treatment) to a variable combination of symptoms of variable severity. The prevalence of heart failure ranges from ∼1% in subjects aged 45–54 years to >10% in subjects aged >75 years. Heart failure represents an important healthcare problem, especially in the elderly, because of its association with low quality of life (QoL), high healthcare costs largely due to frequent hospital admission and poor prognosis.

Sleep apnoea is associated with heart failure in several ways. Obstructive sleep apnoea (OSA) is associated with cardiovascular morbidity and mortality, largely as a result of myocardial damage due to several mechanisms. The majority are initiated by OSA-related chronic, intermittent hypoxia that leads to increased sympathetic activity, endothelial dysfunction, systemic inflammation, oxidative stress and metabolic anomalies [3]. Another important association with heart failure is central sleep apnoea and Cheyne–Stokes respiration (CSA-CSR), also called "periodic breathing in heart failure" [4]. There is a prevalence of 25–40% of periodic breathing in patients with heart failure with reduced ejection fraction (HFrEF), increasing with male sex, the severity of left ventricular impairment and the presence of atrial fibrillation [4]. CSA-CSR is not only highly prevalent in stable HFrEF patients [5, 6] but also in those with preserved ejection fraction (HFpEF) [7, 8]. The term HFmrEF (heart failure with mildly reduced ejection fraction) has been recently introduced for patients with heart failure and a left ventricular ejection fraction (LVEF) that ranges from 40% to 49% [9]. In this subgroup, the prevalence of sleep apnoea has been recently reported and seems to be also elevated with regard to CSA-CSR, particularly in patients with increased left atrial volume and increased systolic pulmonary arterial pressure [8]. While it is recognised that heart failure contributes to the development of CSA-CSR [10] and that CSA-CSR is associated with a worse prognosis in these patients, the role of specific treatments for CSA-CSR in heart failure is still debated. Indeed, in heart failure there is a paucity of evidence-based clinical guidelines to inform management of either coexisting OSA or CSA-CSR. It is thus important to review both the current evidence and to detail the research agenda.

Epidemiology of sleep apnoea and heart failure

Heart failure can be categorised based upon LVEF as significantly reduced (*i.e.* <40%; HFrEF), preserved (>50%; HFpEF) or with mildly reduced (40–49%; HFmrEF) ejection fraction [9]. Heart failure symptoms are typically classified using New York Heart Association (NYHA) Functional Classes I–IV and the objective assessment of heart failure can be graded from A (no objective evidence of cardiovascular disease and no limitations) to D (objective evidence of severe cardiovascular disease with severe limitations). The prevalence of heart failure (including both HFpEF and HFrEF) is estimated to be 1–2% of the general population, and up to 10% if aged >70 years and 30% if aged >85 years [11]. HFpEF represents up to 50% of global heart failure prevalence in the community [12]. In a recent study in a representative sample of 4 million individuals in the UK [13], heart failure incidence decreased from 2002 to 2014, by 7%. However, the estimated absolute number of incident heart failure cases increased by 12%, largely due to an increase in population size and age. The estimated absolute number of prevalent heart failure cases in the UK increased even more, by 23% (figure 1) [13]. This is in accordance with a progressive increase in frequency for each decade after 50 years of age and improved management of acute cardiac events [14, 15]. In the past 30 years, there have been more than 30 major pharmacological studies in HFrEF and 15 in HFpEF, which have resulted in at least 13 classes of medications for use in heart failure [16]. As a result, survival has improved, but more so in HFrEF than in HFpEF. Better survival, but with an ageing population and an increase in background risk factors, has led to an increased prevalence of heart failure.

In-hospital mortality for acute decompensated heart failure is 2–17% [17]; when discharged, 75% of patients require readmission within 1 year [18]. Longer-term mortality associated with heart failure remains high, and is comparable with stroke and cancer. The 5-year survival, adjusted for age and sex, is 50% for stroke, 55% for all cancers and 60% for heart failure [19]. A meta-analysis of 60 studies indicated 1-, 5- and 10-year survival in chronic heart failure to be 87%, 57% and 35% [11]. With the adoption of recent therapeutic advances, 5-year survival rates have fortunately doubled over the past 30 years [11]. Death from heart failure is either sudden (likely arrhythmic) or gradual (progressive heart failure).

The cost of managing heart failure worldwide is estimated to be 1–2% of the entire healthcare budget, which translates to around USD 108 billion annually, with the USA and Europe responsible for 28% and 7%, respectively, of this cost [20]. It has been estimated that the cost will more than double between 2012 and 2030 [21]. Greater costs are incurred in patients with comorbidities and worse functional status.

An early epidemiological sleep apnoea study, the Wisconsin Sleep Cohort Study [22], estimated habitual snoring in 28% of women and 44% of men and OSA (apnoea–hypopnoea index (AHI) >5 events·h^{-1}) in 9% of women and 24% of men aged 30–60 years in the USA. The estimated prevalence of sleep disordered breathing (SDB) in the USA represented substantial increases over the last two decades (relative increases ranging between 14% and 55% depending on age group, sex and SDB severity level) [23]. Thereafter, a European study published in 2015 using a slightly less strict hypopnoea definition indicated that 61% of women and 84% of men had AHI >5 events·h^{-1}, of which the respiratory events were mainly obstructive hypopnoeas (75%), apnoeas (19%), central apnoeas (4%) and mixed apnoeas (2%) [24]. CSA-CSR is rare in a general population.

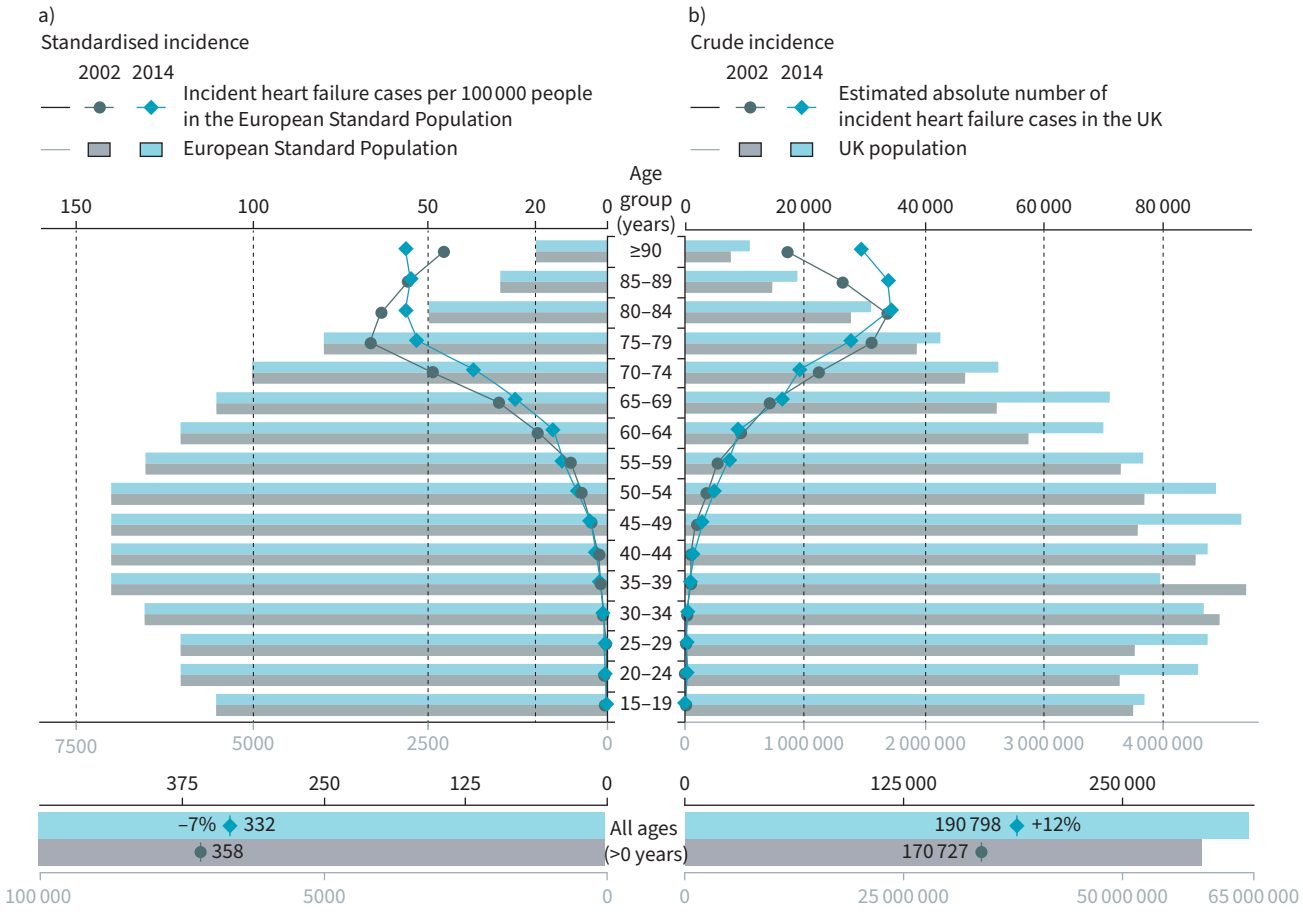

FIGURE 1 Overall and age-stratified heart failure incidence in 2002 *versus* 2014. a) Number of cases of incident heart failure per 100 000 people in the European Standard Population. b) Estimated absolute number of cases of incident heart failure in the UK population (based on census mid-year estimates). Reproduced from [13] with permission.

The Sleep Health Heart Study provides insight into the relationship between sleep apnoea and heart failure. In the USA, 4422 adults were monitored prospectively over nearly 9 years during which there was a stepwise increase in heart failure prevalence and incidence with increasing AHI quartiles [25]. In patients with AHI ⩾30 events·h^{-1}, there was a 2.38-fold increased prevalence and 1.58 increased incidence of heart failure compared with no sleep apnoea, despite controlling for most risk factors. Although not definitive, these data suggest that OSA is a risk factor for the development of heart failure.

Within heart failure populations, sleep apnoea was found to be common. In a Canadian study of 450 patients with heart failure (mean age 60 years, 85% male, body mass index (BMI) 29 kg·m^{-2}, LVEF 27%) who underwent polysomnography, OSA occurred in 37% and CSA-CSR in 33% (defined by AHI ⩾10 events·h^{-1}) [26]. The CSA-CSR group was more likely to have a lower LVEF (23% *versus* 32%) and more likely to have atrial fibrillation (23% *versus* 12%) or a pacemaker (10% *versus* 4%). This study was done prior to the widespread use of β-blockers in heart failure. In a German study of 700 patients with heart failure (mean age 65 years, 80% male, BMI 26 kg·m^{-2}, LVEF 28%) who underwent cardiopulmonary monitoring during sleep, 40% had CSA-CSR and 36% had OSA (defined by AHI ⩾5 events·h^{-1}) [27]. The groups with either OSA or CSA-CSR were older than those without SDB, with a greater proportion of males (60% *versus* 85%). The CSA-CSR population had a worse NYHA Functional Class, more atrial fibrillation (35% *versus* 21%), lower oxygen uptake (V'_{O_2}) peak and 6-min walk distance, and similar pacemaker usage (8% *versus* 11%) compared with the OSA group. β-blocker use was 85% in the German study and 0% in the Canadian study, indicating that β-blockers probably have a minimal role in changing the prevalence of sleep apnoea in heart failure. More recent and larger studies have confirmed the data of these two seminal studies, using an AHI cut-off of 15 events·h^{-1} that may be more appropriate [5, 6]. In addition, it is worth mentioning that in these large datasets (*e.g.* n=1557 [6]),

almost half (41%) of the patients had CSA-CSR for >20% of the polysomnography (PSG) recording time, which was defined as periodic breathing. This subgroup of HFrEF patients with SDB was shown to be at higher risk of experiencing a primary end-point event during treatment with adaptive servo-ventilation (ASV) in a subgroup analysis of the SERVE-HF (Adaptive Servo-Ventilation for Central Sleep Apnoea in Systolic Heart Failure) trial [28].

While all previous studies included HFrEF, there are also data regarding HFpEF published more recently. OSA prevalence was 16.8% in a large database of inpatients hospitalised with HFpEF as the primary diagnosis [29] and up to 50% in a HFpEF clinical cohort [8]. Systemic hypertension [8], male sex, obesity, diabetes and atrial fibrillation [29] were among the main predictors for OSA in HFpEF. Regarding CSA-CSR, its prevalence also seems to be very high, although decreasing from HFrEF to HFmrEF and HFpEF, *i.e.* 66% *versus* 48% *versus* 34%, respectively [8]. Interestingly, in a large observational treatment cohort [30], AHI as well as severity of CSA-CSR at baseline were higher in HFpEF when compared with HFrEF and HFmrEF [30].

Table 1 summarises the clinical features which can distinguish OSA from CSA-CSR in heart failure. As with heart failure, sleep apnoea has detrimental effects upon QoL, functional status, social independence and demands on healthcare. Sleep apnoea is associated with hypertension, atrial fibrillation, coronary artery disease and stroke [31, 32].

Pathophysiology of heart failure and sleep apnoea syndrome

Pathophysiology of OSA in heart failure

Most studies of sleep apnoea in patients with heart failure concern those with HFrEF, and consequently this section focuses on the associations between OSA and HFrEF. Although snoring is a feature of OSA among patients with HFrEF [33], compared with the general population, hypersomnolence is less common and Epworth Sleepiness Scale (ESS) scores are lower for any given AHI despite a longer sleep onset latency and mean of 1.3 h less sleep [34]. The alerting effect of excessive SNA seems to play a role in this lack of hypersomnolence [35, 36] since the superimposition of OSA on HFrEF causes an additive effect on sympathetic activity [37].

As in the general population, many factors contribute to upper airway collapse in patients with HFrEF, including smaller upper airway cross-sectional area, higher upper airway resistance and compliance [38–41]. However, OSA is far more common in fluid-retaining conditions such as end-stage renal disease and HFrEF [42, 43] than in the general population. Fluid retention and overnight rostral fluid shift from the legs may contribute to the severity of OSA by causing fluid accumulation in the neck, narrowing the pharynx and increasing its propensity to collapse during sleep. However, the relationship between OSA and HFrEF is likely to be bidirectional, with the sodium and fluid retention of HFrEF contributing to development of OSA and with OSA contributing to progression of HFrEF [44].

TABLE 1 Symptoms, signs and outcome of obstructive sleep apnoea (OSA) and central sleep apnoea and Cheyne–Stokes respiration (CSA-CSR) in heart failure [26, 27]

	No sleep apnoea	OSA	CSA-CSR
Sex ratio (male:female)	70:30	85:15	85:15
Body mass index	Normal	Normal to high	Normal to low
Heart failure severity	Less severe	Mild to moderate	Moderate to severe
Atrial fibrillation or paced (%)	14	16–33	33–43
Sleep quality	Good	Can have EDS, but uncommon	Insomnia and fatigue
Snoring	Minimal	Severe	Mild
Sleep stage of AHI predominance	Nil	REM	Non-REM
AHI responsive to PAP		Good, immediate	Variable, delayed
P_{CO_2} level	Normal	Normal–high	Low–normal
Mortality	High	Probably higher	Likely higher

EDS: excessive daytime sleepiness; REM: rapid eye movement; AHI: apnoea–hypopnoea index; PAP: positive airway pressure; P_{CO_2}: carbon dioxide tension. As with heart failure, sleep apnoea has detrimental effects upon quality of life, functional status, social independence and demands on healthcare. Sleep apnoea is associated with hypertension, atrial fibrillation, coronary artery disease and stroke [31, 32].

Fluid shift

Bio-electrical impedance can estimate fluid volumes of the entire body or of various body segments, such as the leg, thorax or neck, and has been used to investigate the role of fluid accumulation and displacement in the pathogenesis of OSA [45, 46]. When lying down, patients with HFrEF experience a greater volume of fluid moving from the interstitial spaces of the legs into the intravascular space, with more fluid redistribution into the chest and neck than in normovolaemic subjects [47, 48]. Fluid movement into the neck could lead to fluid accumulation in the pharyngeal walls and distension of the internal jugular veins that lie lateral to the pharynx. The resulting increase in peri-pharyngeal tissue pressure could therefore cause inward displacement of the lateral pharyngeal walls and impinge on the upper airway lumen [49, 50].

Among patients with HFrEF and OSA, there is an overnight reduction in leg fluid volume inversely related to both an overnight increase in neck circumference and AHI (figure 2) [47]. In addition, among patients with HFrEF, those with OSA had higher sodium intake than those without OSA and that sodium intake was directly related to the AHI [51]. Subsequently, it was demonstrated that infusing 2 L of normal saline into men aged ⩾40 years induced an increase in neck circumference that was accompanied by a tripling of the AHI (increase of 32.3±22.1, from 16 to 48 events·h^{-1}). This provided direct evidence that salt and fluid overload can induce or worsen OSA [52]. In another study of patients with HFrEF, anti-shock trousers were inflated to induce fluid displacement from the legs [53]. Among patients with OSA, neck circumference and upper airway resistance increased in association with a reduction in minute ventilation (V'_E) and an increase in carbon dioxide tension (P_{CO_2}). Thus, in these patients, rostral fluid shift from the legs induced a significant degree of upper airway obstruction.

Taken together, these findings suggest that overnight rostral fluid shift contributes to the pathogenesis of OSA in patients with HFrEF. Factors associated with a greater degree of overnight fluid shift include sedentary living, poorer physical fitness, higher sodium intake and greater degree of leg oedema. The extent to which this mechanism is involved likely varies from patient to patient and may be related to their volume status.

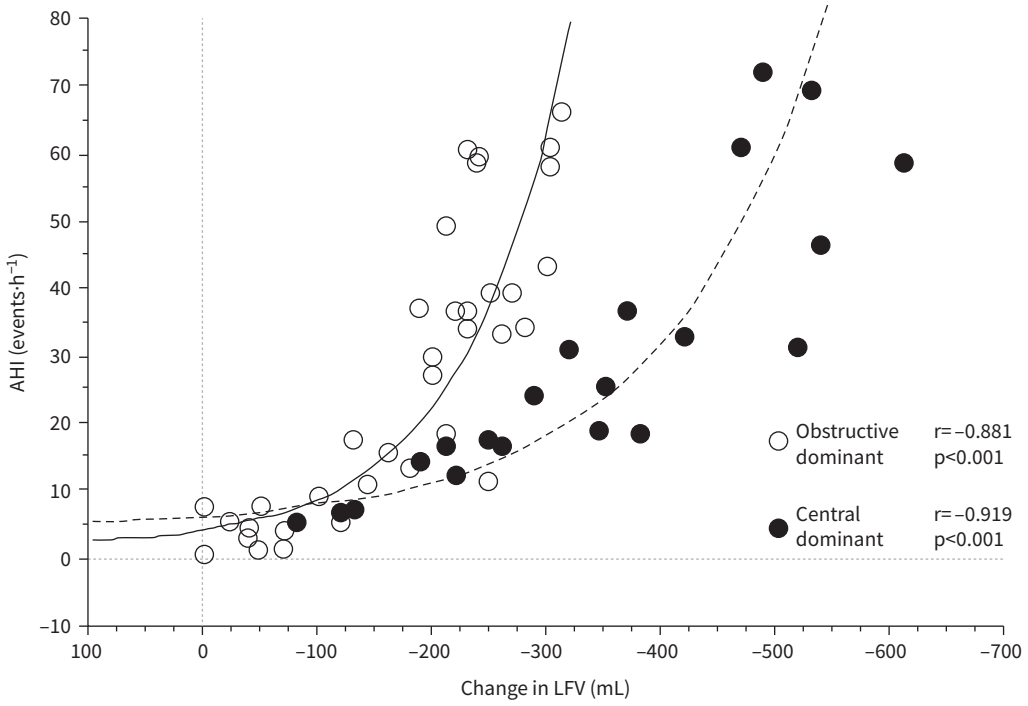

FIGURE 2 Relationship between overnight change in leg fluid volume (LFV) and apnoea–hypopnoea index (AHI) in men with heart failure. Correlation between overnight decrease in LFV and AHI in men with heart failure and either obstructive or central sleep apnoea. Central sleep apnoea was associated with greater overnight fluid shift. Reproduced from [47] with permission.

Respiratory control

In some patients with HFrEF, obstructive apnoeas and hypopnoeas display a periodic pattern resembling CSA-CSR, during which there is a prolonged crescendo–decrescendo pattern of hyperpnoea. As in CSA-CSR, the prolonged hyperpnoea is related to prolonged lung-to-chemoreceptor circulation time that is reflective of low cardiac output [54, 55]. This periodicity suggests the possibility that respiratory control system instability with high loop gain may be playing a role in its pathogenesis, but no studies have addressed this possibility directly. However, in one study involving patients with HFrEF, there was no difference in either central or peripheral chemoresponsiveness between those with and without OSA, suggesting that high loop gain was not a factor [56]. Thus, it remains unclear whether high loop gain contributes to the causation of OSA in patients with HFrEF.

Impact of OSA on heart failure

OSA could contribute to progression of heart failure through several mechanisms. During obstructive apnoeas in patients with HFrEF, intrathoracic pressure can reach as low as −80 cmH_2O during inspiratory efforts against the occluded upper airway [57, 58]. This increases left ventricular transmural pressure (the difference between intracardiac and intrapleural pressure) and hence left ventricular afterload. Venous return also increases, resulting in right ventricular distension and a leftward shift of the interventricular septum during diastole that impedes left ventricular filling [59, 60]. Together, these factors reduce stroke volume and cardiac output acutely [58, 59, 61, 62]. Furthermore, left ventricular transmural pressure increases myocardial oxygen demand and reduces coronary blood flow [62]. Coupled with apnoea-related hypoxia, these mechanisms may precipitate myocardial ischaemia and impair cardiac contractility such that stroke volume and cardiac output fall overnight [63–65]. Reversal of OSA by continuous positive airway pressure (CPAP) in patients with HFrEF prevents overnight reductions in stroke volume and cardiac output.

OSA-induced intermittent hypoxia and hypercapnia stimulate peripheral and central chemoreceptors, leading to increases in SNA [66, 67]. Arousal from sleep at apnoea termination also augments SNA and reduces cardiac vagal activity, causing post-apnoeic surges in blood pressure and heart rate [68]. These adverse autonomic effects can carry over into wakefulness through as-yet unidentified mechanisms [69]. Long-term elevations in SNA can cause cardiac myocyte necrosis and apoptosis, and worsening ventricular dysfunction [70–72]. OSA-induced intermittent hypoxia and subsequent post-apnoeic reoxygenation may lead to oxidative stress and activation of inflammatory mediators accompanied by impaired vascular endothelium-dependent flow-mediated dilation [73–76]. These abnormalities appear to be at least partially reversible by CPAP.

HFpEF is characterised by increased left ventricular filling pressure secondary to diastolic dysfunction [77]. It should be kept in mind, however, that besides this definition of a clinical syndrome, based on the presence of clinical symptoms and preserved ejection fraction (with variable cut-off points), there is substantial variation regarding the use of biomarkers, abnormal cardiac structure and function ascertained by echocardiography, and previous hospitalisations to define HFpEF [78]. Regarding cardiac structure, there is increased vascular and cardiac stiffness that affects both systolic contraction and diastolic filling of the left ventricle [77, 79]. OSA may contribute to the development of HFpEF *via* several mechanisms. For example, acute hypoxia, which occurs recurrently in patients with OSA, impairs diastolic relaxation of both ventricles that stiffens them and impairs their diastolic filling [80]. In HFpEF, fibrosis and structural changes in collagen and myocardial titin induce myocardial stiffening [79, 81]. OSA may favour changes in the extracellular matrix and development of myocardial fibrosis. Overall, there is an interaction between risk factors such as obesity, hypertension, metabolic stress, cardiac ageing and loss of cardiovascular reserve, which results in the development of symptomatic HFpEF [77]. OSA is likely to contribute to the development of HFpEF through intermittent hypoxia, hypertension, sympathetic excitation, systemic inflammation and oxidative stress [79]. Also, atrial fibrillation, a condition commonly found in OSA [82], seems to be associated with left atrial remodelling, reduced compliance and contractile function, which progressively worsens as atrial fibrillation burden increases [83]. OSA therefore appears as a common cofactor in the development of HFpEF [79].

Overall, there is a bidirectional relationship between OSA and heart failure. On the one hand, OSA can aggravate heart failure by all the previously mentioned mechanisms. On the other hand, reduced stroke volume is associated with fluid retention in patients with heart failure and impaired kidney function contributes to this phenomenon [47, 51, 84]. Thus, heart failure may contribute to the severity of OSA by generating increased fluid accumulation in the neck, narrowing the pharynx and increasing its propensity to collapse during sleep [44].

Pathophysiology of CSA-CSR in heart failure

Apnoeic threshold and carbon dioxide reserve

Several inputs that regulate breathing during wakefulness are downregulated during sleep. The wakefulness drive to breathe is removed during the transition from wakefulness to sleep. This is the reason why inputs from the central and peripheral chemoreceptors become of major importance in regulating breathing during sleep. It should be noted, however, that in healthy individuals both responsiveness of the chemoreceptors and feedback from the respiratory muscle afferents are reduced in their ability to maintain ventilation, particularly during rapid eye movement (REM) sleep [85]. These changes, as well as the increase in upper airway resistance occurring at sleep onset, result in reduced ventilation from wakefulness to sleep. This may result in significant breathing anomalies such as apnoeas and hypopnoeas since a delay is required to elicit a compensatory response from the chemoreceptors. In particular, if arterial carbon dioxide tension (P_{aCO_2}) falls below a critical threshold called the apnoeic threshold, central respiratory drive will cease. However, over time, when stable sleep is obtained, the reduction in ventilation leads to a gradual rise in P_{aCO_2} ranging from 3 to 8 mmHg and a new sleep-specific carbon dioxide set-point (close to 45 mmHg) [85]. Thus, the difference between the carbon dioxide set-point and the apnoeic threshold, *i.e.* the carbon dioxide reserve, is increased, which leads to breathing stability (figure 3) [86].

Breathing instability can arise from a reduction in the carbon dioxide set-point as seen during the transition from sleep to wake, *e.g.* from 45 to 40 mmHg, or from an increase in the apnoeic threshold. Carbon dioxide reserve is increased when ventilation is augmented, with the notable exception of hypoxia [87]. In hypoxic conditions, carbon dioxide reserve is reduced to less than normoxic, normocapnic control despite an increase in background ventilatory drive. This hypoxic effect, enhancing ventilatory inhibition in response to hypocapnia, may reflect a unique sensory input from the carotid chemoreceptors [87]. This could be specific to hypoxia or a vasodilatory effect of hypoxia on the cerebral circulation that would promote apnoea and hypopnoea by lowering medullary chemoreceptor P_{CO_2} at any given P_{aCO_2} [87]. Actually, in heart failure presenting with CSA-CSR, it has been evidenced that eupnoeic P_{CO_2} is not increased, suggesting an additional ventilatory stimulant during sleep while the apnoeic threshold is not reduced despite the additional ventilatory stimulation, thus leading to a reduced carbon dioxide reserve in a similar manner to what has been shown during hypoxia [88, 89]. Hypoxia does not seem to be a primary cause of CSA-CSR, but both conditions may have a common mechanism [89].

Role of hyperventilation

Hyperventilation plays a significant role in the genesis of periodic breathing and central apnoeas in heart failure as evidenced in a series of 24 patients with heart failure with (n=12) and without (n=12) CSA-CSR [90]. Awake P_{aCO_2} and mean nocturnal transcutaneous carbon dioxide tension (P_{tcCO_2}) were significantly lower in patients with CSA-CSR than in those without (P_{aCO_2} 33.0±1.2 *versus* 37.5±1.0 mmHg and mean P_{tcCO_2} 33.2±1.2 *versus* 42.5±1.2 mmHg, respectively), suggesting chronic hyperventilation in patients with CSA-CSR. However, subjects with and without CSA-CSR had similar LVEF, awake P_{aO_2}, mean nocturnal arterial oxygen saturation (S_{aO_2}) and lung-to-ear circulation time (an index of circulatory delay between the lungs and carotid chemoreceptors). The role of hypocapnia is also supported by the observation that increasing P_{aCO_2} during sleep *via* inhalation of carbon dioxide-enriched gas (1–3%) or the addition of an external dead-space during sleep abolishes central events both in CSA-CSR [91, 92] and in idiopathic CSA [93, 94].

Several factors could contribute to hyperventilation and ventilatory instability in patients with CSA-CSR. One such factor is increased loop gain. One aspect of loop gain is increased controller gain *via* augmented chemoresponsiveness, stimulation of pulmonary vagal C-fibres and elevated SNA. Compared with patients with HFrEF without sleep apnoea or with OSA, those with CSA-CSR have greater central and peripheral responsiveness to carbon dioxide [95, 96]. Stimulation of pulmonary vagal C-fibres by pulmonary congestion can also provoke hyperventilation [97]. This is supported by the fact that patients with CSA-CSR have a significantly higher pulmonary capillary wedge pressure (PCWP) than those without CSA-CSR [98], with a significant negative correlation between PCWP and awake P_{aCO_2} [99]. Finally, elevated SNA is an important feature in the pathogenesis of HFrEF [100, 101] and is higher among those with CSA-CSR than those without sleep apnoea or with OSA [69, 93]. Elevated SNA and circulating catecholamines could augment chemoresponsiveness in HFrEF and contribute to a self-perpetuating effect [102].

Role of arousal from sleep

Arousal from sleep can also contribute to increased loop gain and destabilise breathing in patients with HFrEF. Arousal recruits the wakefulness drive to breathe at a time when ambient P_{CO_2} during sleep is higher than during steady-state wakefulness. The wakefulness drive augments the ventilator response to elevated P_{CO_2} in order to lower it to the new, lower waking set-point. Consequently, there is a rapid

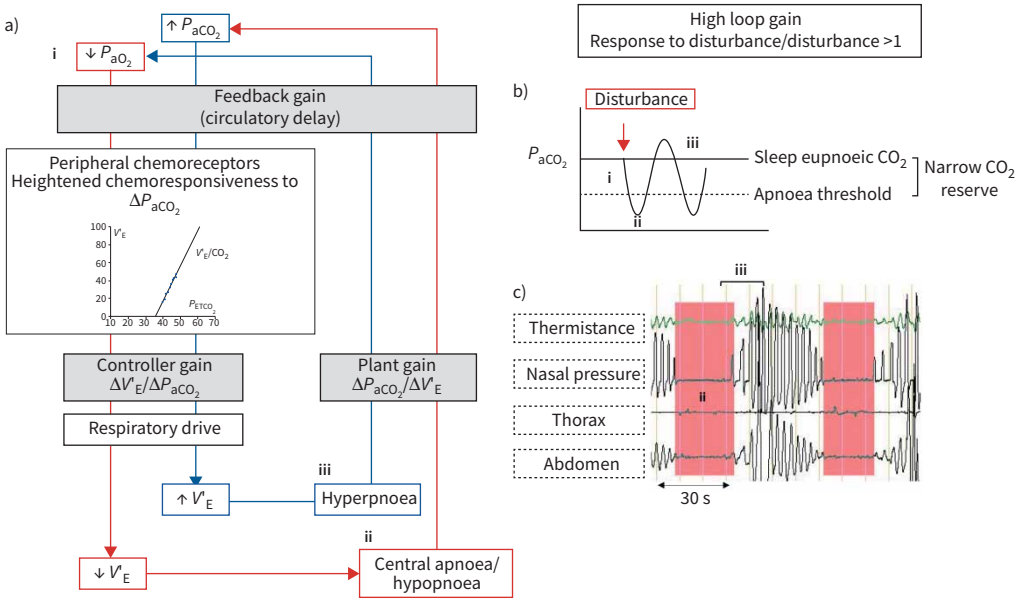

FIGURE 3 Pathophysiology of central sleep apnoea and Cheyne–Stokes respiration (CSA-CSR). a) Simplified block diagram of the respiratory control system. b) Carbon dioxide levels in a subject with ventilatory instability and a narrow carbon dioxide reserve. c) Polysomnographic trace of central sleep apnoea. In CSA-CSR, two main determinants play a role in ventilatory control instability: a high loop gain and a narrow carbon dioxide reserve (ΔP_{aCO_2} between eupnoea and apnoea thresholds, a condition in which the sleep eupnoeic P_{aCO_2} set-point is near the sleep P_{aCO_2} apnoea threshold). Loop gain can be defined as the magnitude of the response to a given disturbance and has three main components: controller gain ($\Delta V'_E/\Delta P_{aCO_2}$, *i.e.* change in V'_E in response to a change in P_{aCO_2}), plant gain ($\Delta P_{aCO_2}/\Delta V'_E$, *i.e.* blood gas response to a change in V'_E, mainly affected by baseline carbon dioxide levels and lung volume) and feedback gain (the speed of the feedback signal from plant back to the controller, mainly determined by circulation time, *i.e.* cardiac output). A high loop gain is defined as a ratio >1, *i.e.* a disproportional response to a given stimulus, promoting instability of the system. The main determinant of high loop gain is heightened chemosensitivity to carbon dioxide when measuring ventilator responses to carbon dioxide, *i.e.* a higher controller gain. When combined with a narrow carbon dioxide reserve, a cycle of hypocapnia-induced central apnoea will be initiated. A disturbance to this system (*e.g.* hyperventilation) temporarily decreases alveolar (P_{ACO_2}) and arterial (P_{aCO_2}) carbon dioxide tension levels (i). After a delay (circulatory delay, *i.e.* feedback gain), the controller detects the blood gas change and decreases its output to counter the original disturbance, leading to a central apnoea (ii), resulting in an increase in P_{aCO_2} levels (plant gain). In high loop gain, each response to a disturbance is greater than the initial disturbance, resulting in a corrective hyperpnoea (iii) that will send P_{aCO_2} levels towards the borders of the carbon dioxide reserve and, in turn, a new oscillation of the ventilatory system. The respiratory pattern is characterised by more or less prolonged breathing cycles (depending on feedback gain) with distinctive alternation between central apnoeas–hypopnoeas (waning) and hyperpnoeas (waxing). P_{aCO_2}: arterial carbon dioxide tension; V'_E: minute ventilation; P_{ACO_2}: alveolar carbon dioxide tension. Reproduced from [86] with permission.

lowering of P_{CO_2}, and if the subject falls back to sleep at that point, P_{CO_2} will now be lower than the higher sleep set-point and central apnoea will ensue. Evidence in favour of this mechanism is that the great majority of central events in patients with HFrEF are triggered by augmented ventilation following an arousal from sleep [85]. In addition, among patients with HFrEF randomised to CPAP in the CANPAP (Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnoea and Heart Failure) trial, alleviation of CSA-CSR had no effect on arousal frequency. This suggested that arousal did not act as a protective mechanism to terminate apnoeas, as it does in OSA, but rather, contributed to the causation of CSA-CSR [103].

A second aspect of loop gain is plant gain. In the case of HFrEF, reduced lung volumes related to pulmonary congestion should increase plant gain by reducing the lung carbon dioxide and oxygen reservoirs, impairing the ability of the lung to damp large swings in P_{aO_2} and P_{CO_2} in response to changes

in ventilation, *e.g.* following arousal at apnoea termination [104]. Such an effect should destabilise breathing and predispose to CSA-CSR. While there is evidence that lung volumes are reduced in chronic heart failure, there is little direct evidence that this contributes to CSA-CSR pathogenesis or severity.

Increased circulation time from the lungs to the chemoreceptors could contribute to the pathogenesis of CSA-CSR. Indeed, an early study reported increased circulation time in patients with heart failure with CSA-CSR [105]. However, to induce CSA-CSR in dogs, GUYTON *et al.* [106] had to artificially lengthen heart-to-brain circulation time far beyond physiological values of up to several minutes and even then induced CSA-CSR in only approximately one-third of the animals. Although increased circulatory delay does not seem to act as a primary cause of CSA-CSR [107], it does affect periodicity of the phenomenon. The durations of the hyperpnoeic phases of CSA-CSR are directly proportional to lung-to-peripheral chemoreceptor circulation time. However, there is no relation between lung-to-peripheral chemoreceptor circulation time and apnoea duration [55].

Role of fluid shift in CSA-CSR

Lying down at night provokes fluid displacement from the legs into the thorax that can increase PCWP and lung water [108–110]. In men with HFrEF, among those with CSA-CSR, the greater the amount of fluid displaced from the legs overnight, the lower the nocturnal P_{aCO_2} and the higher the AHI (figure 2) [47]. This suggests that fluid accumulation in the lungs stimulates pulmonary vagal irritant receptors that provoke hyperventilation and a fall in P_{aCO_2} below the apnoea threshold. Furthermore, severity of CSA-CSR is reduced by raising the head of the bed, presumably by reducing pulmonary congestion and ventilation, and increasing P_{aCO_2} [111, 112].

Alterations in sleep apnoea type

In a study of patients with HFrEF and a combination of OSA and CSA-CSR, sleep apnoea type shifted from predominantly obstructive to central from the beginning to the end of the night in association with increases in CSA-CSR cycle duration and circulation time, and a decrease in P_{aCO_2} [113]. These findings suggest that this shift occurred due to a decrease in cardiac output and an increase in pulmonary congestion [55, 99]. Furthermore, among patients with HFrEF who underwent two sleep studies months apart, conversion from predominantly OSA to CSA-CSR was associated with a decrease in nocturnal P_{CO_2} and an increase in CSA-CSR cycle duration, and *vice versa* [114]. Moreover, in the CANPAP trial, among the control group of patients with HFrEF and CSA-CSR, 18% converted to mainly OSA several months after randomisation in association with an increase in LVEF and a decrease in circulation time [115].

In patients with HFrEF and CSA-CSR, inflation of anti-shock trousers to induce fluid displacement from the legs reduced upper airway resistance, increased V'_E and reduced P_{aCO_2} [53]. Similar overnight rostral fluid shift might therefore provoke hyperventilation and a fall in P_{CO_2} below the apnoea threshold that could trigger CSA-CSR. These observations are in keeping with the concept that in some patients with HFrEF, OSA and CSA-CSR are part of a spectrum of SDB whose predominant type can shift over time in response to alterations in cardiac function and fluid status, and according to where fluid accumulates. Proposed means by which cardiac function, fluid retention and overnight fluid shift interact to influence the type and severity of SDB in patients with HFrEF are shown in figure 4 [48]. The potential for the predominant apnoea type to alter over time is something one should take into account when considering options for treating SDB in patients with HFrEF.

Diagnosis of SDB in heart failure

As previously described, although snoring is a feature of OSA among patients with heart failure [33], compared with the general population, hypersomnolence is less common and ESS scores are lower for any given AHI despite a longer sleep onset latency and a reduced total sleep time [34].

Symptoms suggestive of CSA-CSR include delayed sleep onset and maintenance insomnia, nocturia, orthopnoea, paroxysmal nocturnal dyspnoea and hyperpnoea during periodic breathing, perception of not feeling refreshed upon awakening, and daytime fatigue, but usually not hypersomnolence [116]. Diagnosis of CSA-CSR in heart failure patients should be particularly prompted by male predominance, worse NYHA Functional Class, frequent heart failure hospitalisations, low P_{aCO_2}, atrial fibrillation and complaint of daytime fatigue rather than sleepiness.

Questionnaires have not been found very useful in pre-screening heart failure patients for SDB, because they have been validated mainly for OSA in the general population, but not for OSA or CSA-CSR in patients with heart failure, who often do not present with similar symptoms and risk factors [34, 117]. This might, in part, account for why SDB is underdiagnosed in patients with heart failure [118].

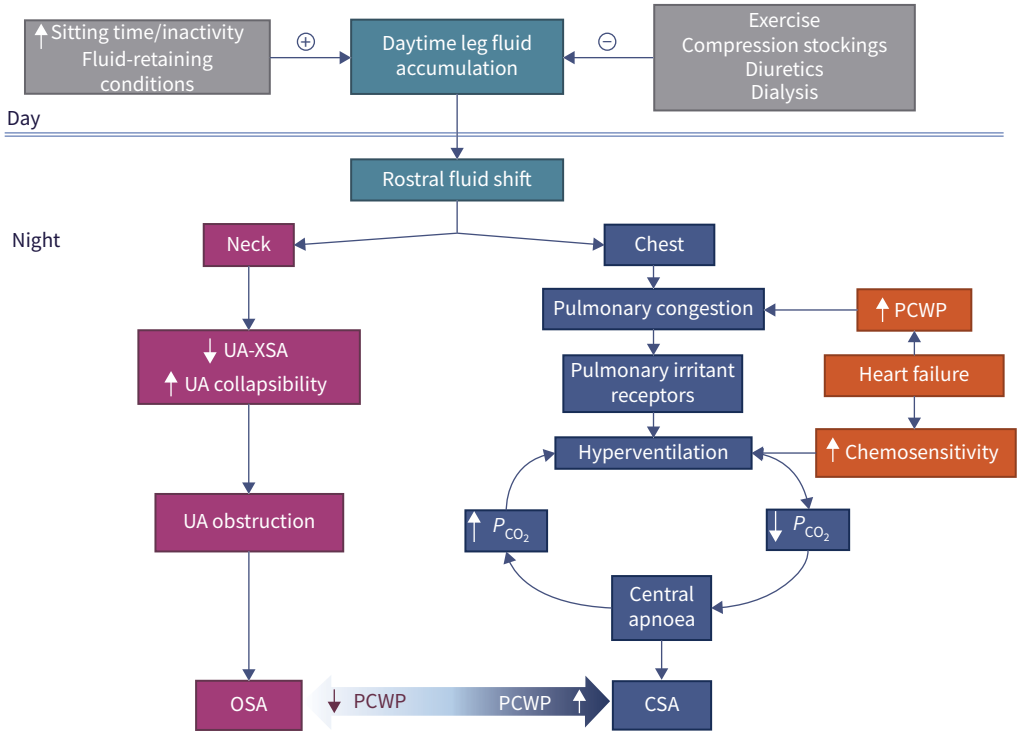

FIGURE 4 The role of overnight rostral fluid shift in the pathogenesis of obstructive sleep apnoea (OSA) and central sleep apnoea and Cheyne–Stokes respiration (CSA-CSR). Overnight fluid shift from the legs to the neck can affect upper airway (UA) mechanics and lead to OSA, whereas fluid shift to the lungs can provoke hyperventilation, hypocapnia and CSA-CSR. XSA: cross-sectional area; PCWP: pulmonary capillary wedge pressure; P_{CO_2}: carbon dioxide tension. Reproduced from [48] with permission.

Given the high prevalence of SDB in the heart failure population and the poor specificity of screening questionnaires, there should be a low threshold for performing a sleep study to make this diagnosis. PSG is the preferred type of sleep study since the multiple variables it monitors provide detailed information for detecting and quantifying SDB and differentiating between obstructive and central events. It also has the advantage over level 2 and 3 portable monitoring of providing information about sleep time, efficiency, staging and fragmentation by arousals and periodic leg movements. Consequently, whenever possible, full overnight PSG should be employed to detect SDB in patients with heart failure [119]. However, this may prove difficult in routine practice owing to the lack of access to PSG and the high prevalence of SDB in patients with heart failure. SDB can be reliably diagnosed with simplified diagnostic methods. There are several signals that can be used in combination in order to detect breathing anomalies during sleep. The simplified devices are classified into type 3 and type 4 [120]. Type 3 devices, also called respiratory polygraphs, record a minimum of four channels, including ventilation or airflow (at least two channels of respiratory movement, or respiratory movement and airflow), heart rate or ECG and oxygen saturation [112–114]. Type 4 devices use one or two respiratory signals, such as airflow or oximetry. Since most type 3 and 4 devices do not assess sleep time, but instead use recording time as the denominator to calculate the AHI, the actual AHI, and thus disease severity, may be underestimated. Devices that estimate sleep time using either actigraphy or another indirect measure of sleep may be useful in this regard [121, 122]. The potential added value of using such devices [121], particularly in subgroups like heart failure patients, has yet to be determined. However, it must be kept in mind that portable monitoring has not been validated for detecting and classifying SDB in patients with heart failure. Finally, certain cardiac pacemakers have the ability to screen for SDB by analysing changes in intrathoracic impedance [123], although their clinical usefulness remains limited

Overall, scoring of the respiratory events either in OSA or CSA-CSR is critical, including separating between central and obstructive events. However, the AHI may not sufficiently reflect characteristics of SDB like nocturnal hypoxaemic burden, subclassification of respiratory events, long-term night-to-night SDB variability (SDB burden) as well as variable occurrence of respiratory events and arousals during different sleep stages and sleeping position [124].

Treatment of OSA in heart failure

Alleviation of OSA by CPAP in patients with HFrEF abolishes negative intrathoracic pressure swings, reduces blood pressure and left ventricular afterload [125], and prevents OSA-induced overnight falls in stroke volume and cardiac output [65]. In a randomised trial involving 24 patients with HFrEF and OSA, but normal ESS scores (⩽10), CPAP increased LVEF by 9% [126] and reduced sympathetic vasoconstrictor activity and daytime blood pressure [37]. CPAP also improved baroreceptor sensitivity and myocardial oxidative metabolism [127, 128]. Among patients with HFrEF and mainly OSA and normal ESS scores (⩽10), CPAP improved LVEF, but had no effect on ESS scores, QoL, NYHA Functional Class or 6-min walk distance [129]. In another trial of 55 similar patients, but with an elevated ESS score (>10), CPAP reduced SNA and improved LVEF and QoL, but not blood pressure [130]. However, in another trial of 26 patients, auto-PAP had no effect on LVEF [131]. Differences in trial design, patient characteristics and the type of PAP employed may explain discrepancies in the results of the aforementioned studies.

OSA is associated with both left ventricular hypertrophy and left and right ventricular diastolic dysfunction [3, 132]. Several studies were limited by study cohorts with comorbidities such as obesity, coronary artery disease and hypertension that can independently affect left ventricular systolic and diastolic function [133]. However, it appears that left ventricular mass/end-diastolic volume ratio, a measure of concentricity, is significantly higher in both nonobese and obese participants with OSA compared with participants without OSA [134]. Posterior wall thickness and left ventricular mass index are significantly higher in OSA and hypertensive groups compared with healthy subjects. Systolic *S* velocity (mitral annular systolic velocity) is reduced in patients with OSA or hypertension compared with healthy control subjects, while diastolic function *E*/*A* (mitral early inflow peak velocity/mitral late inflow peak velocity), intraventricular relaxation time and *E*/*e′* (early diastolic transmitral flow velocity/early diastolic mitral annular velocity) are also impaired in both OSA and hypertensive groups [133]. PAP effects have been assessed in various observational studies and randomised controlled trials (RCTs) [133–139]. The results are variable according to patient selection, sample size, study design and the imaging techniques used to detect early changes in diastolic function. While some RCTs were negative [136, 138], others evidenced a significant improvement in diastolic function [135, 137]. It should be noted that the latest studies used new imaging techniques, *i.e.* diastolic stress echocardiography, Doppler imaging or magnetic resonance imaging [134], in order to detect early diastolic dysfunction and its changes after CPAP treatment [137].

An observational trial involving patients with HFrEF and OSA reported a trend to lower mortality in 14 patients who accepted CPAP than in 37 patients who did not (p=0.07) [140]. In another observational trial, involving 88 similar patients, hospitalisation-free survival was significantly greater in the 65 CPAP-treated patients than in the 23 untreated patients [141]. In contrast, another observational study did not find a difference in mortality rates between patients with HFrEF, with or without OSA. However, patients with OSA were not divided into those who were treated or untreated [142]. Owing to their nonrandomised nature and small sample sizes, results of these trials are not conclusive. Regarding other therapies for OSA in patients with HFrEF, such as mandibular advancement devices and hypoglossal nerve stimulation, no conclusions can be drawn about their efficacy because of the paucity of such studies.

The aforementioned evidence suggests that, just as in the general population, the main indication for treating OSA in patients with HFrEF is hypersomnolence, where treating OSA reduces sleepiness and improves QoL and LVEF [130]. However, most patients with HFrEF and OSA are not hypersomnolent [34]. In such patients, adequately powered randomised trials are required to assess whether treating OSA in nonsleepy patients with HFrEF improves morbidity and mortality or other clinical outcomes.

Treatment of CSA-CSR in heart failure

The first approach to therapy of CSA-CSR should be optimisation of medical management of heart failure, which may improve the condition [143]. The goals of treatment in patients with heart failure are to improve their clinical status, functional capacity and QoL, prevent hospital admission, and reduce mortality [9]. Neuro-hormonal antagonists (angiotensin converting enzyme inhibitors (ACEIs) and β-blockers as well as mineralocorticoid receptor antagonists in the case of patients remaining symptomatic despite ACEIs and β-blockers) have been shown to improve survival in patients with HFrEF. They are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated [9]. This should include the appropriate use of diuretics (which also may reduce the nocturnal rostral fluid shift that can worsen both OSA and CSA-CSR) and disease-modifying drug therapy for HFrEF [9]. Cardiac resynchronisation therapy for patients with reduced ejection fraction and a broad QRS complex may lead to a modest but significant reduction in severity of CSA-CSR (but not OSA) [144].

Positive airway pressure

In the CANPAP trial involving patients with HFrEF and CSA-CSR, CPAP caused a 55% reduction in the AHI that was accompanied by increases in LVEF and 6-min walk distance, and a reduction in plasma norepinephrine concentrations, but did not improve heart transplant-free survival over a mean 2 years of follow-up in 258 patients [145]. *Post hoc* subgroup analysis suggested that there was a survival advantage in those in whom AHI was suppressed to <15 events·h^{-1} by CPAP [146].

In small RCTs, beneficial effects of treating CSA-CSR with ASV in patients with HFrEF included significant reductions in AHI, plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), urinary catecholamine concentration and left ventricular end-systolic diameter along with increases in 6-min walk distance and LVEF, and improved NYHA Functional Class [147, 148]. However, in a large RCT (SERVE-HF) involving 1325 patients with HFrEF and CSA-CSR, there was no difference between those in the control group who received no therapy for CSA-CSR and those randomised to ASV in the primary composite end-point of death from any cause, lifesaving cardiovascular intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest or appropriate lifesaving shock) or unplanned hospitalisation for worsening heart failure despite a marked lowering of the AHI by ASV [28]. In addition, contrary to the small trials [147, 148], ASV did not cause any improvements in QoL, NYHA Functional Class, LVEF, left ventricular dimensions or plasma NT-proBNP and actually reduced 6-min walk distance. Most importantly, however, there was a significantly higher all-cause and cardiovascular mortality in those treated with ASV, largely driven by an increase in sudden death (figure 5) [28]. Various explanations have been proposed including a direct toxic effect of ASV on patients with poor left ventricular function, possibly lowering cardiac output due to impedance to venous return, or causing hyperventilation, alkalosis and hypokalaemia predisposing to arrhythmias; or that CSA-CSR may be at least partially adaptive for patients with severe heart failure [149]. It is important to note that different ASV algorithms may have different effects on V'_E and sleep architecture that might influence outcomes [150]. In the meantime, the use of ASV (and perhaps other PAP therapies) for the treatment of predominantly CSA-CSR in HFrEF cannot be recommended.

CSA-CSR is found in the majority of patients with acute decompensated heart failure, is usually severe, and is associated with an increased risk of readmission and mortality [151]. A randomised trial of ASV in this patient group was initiated, but was terminated after the results of SERVE-HF became available [152].

There is some evidence to suggest that ASV can improve cardiac diastolic function, improve symptoms and decrease plasma BNP concentrations in patients with HFpEF and CSA-CSR [153] or coexisting OSA and CSA-CSR [154]. However, no adequately powered randomised trial assessing cardiovascular outcomes has been undertaken.

Overall, it is of interest to mention the conclusions of the most recently published meta-analysis [155]. As stated by the authors of the meta-analysis, the findings were limited by low or very low quality of evidence. The effects of PAP therapy on all-cause mortality were uncertain. In addition, although PAP therapy did not reduce the risk of cardiac-related mortality and re-hospitalisation, there was some indication of an improvement in QoL for heart failure patients with CSA-CSR, although not confirmed in the largest available study [28].

Oxygen

Small randomised trials from 1 night to 1 month duration have demonstrated that in patients with HFrEF and CSA-CSR, nocturnal oxygen reduces AHI by ~50% [156, 157] and overnight urinary norepinephrine excretion, but had no effect on daytime plasma norepinephrine, plasma BNP, neurocognitive function, sleepiness or QoL [157–160]. In the CHF-HOT (Congestive Heart Failure-Home Oxygen Therapy) randomised trial, low-flow oxygen caused a modest reduction in AHI, and an improvement in LVEF and NYHA Functional Class after 12 weeks [161]. However, there is no consistent evidence that it improves cardiovascular function or clinical outcomes in such patients. Indeed, there is good evidence that administration of oxygen to patients with coronary artery disease or heart failure may cause hyperoxia and increase the generation of oxygen free radicals and, hence, oxidative stress. This can exert adverse haemodynamic effects, such as raising vascular resistance, blood pressure and left ventricular filling pressure, and lowering cardiac output [162, 163]. In addition, administration of oxygen following acute myocardial infarction or resuscitation from cardiac arrest increased myocardial damage and tended to increase the mortality rate [164]. Consequently, the evidence does not currently support the use of supplemental oxygen for therapy of CSA-CSR in patients with HFrEF. Therefore, large trials are required to determine whether oxygen improves clinical outcomes in such patients (*e.g.* LOFT-HF; ClinicalTrials.gov: NCT 03745898).

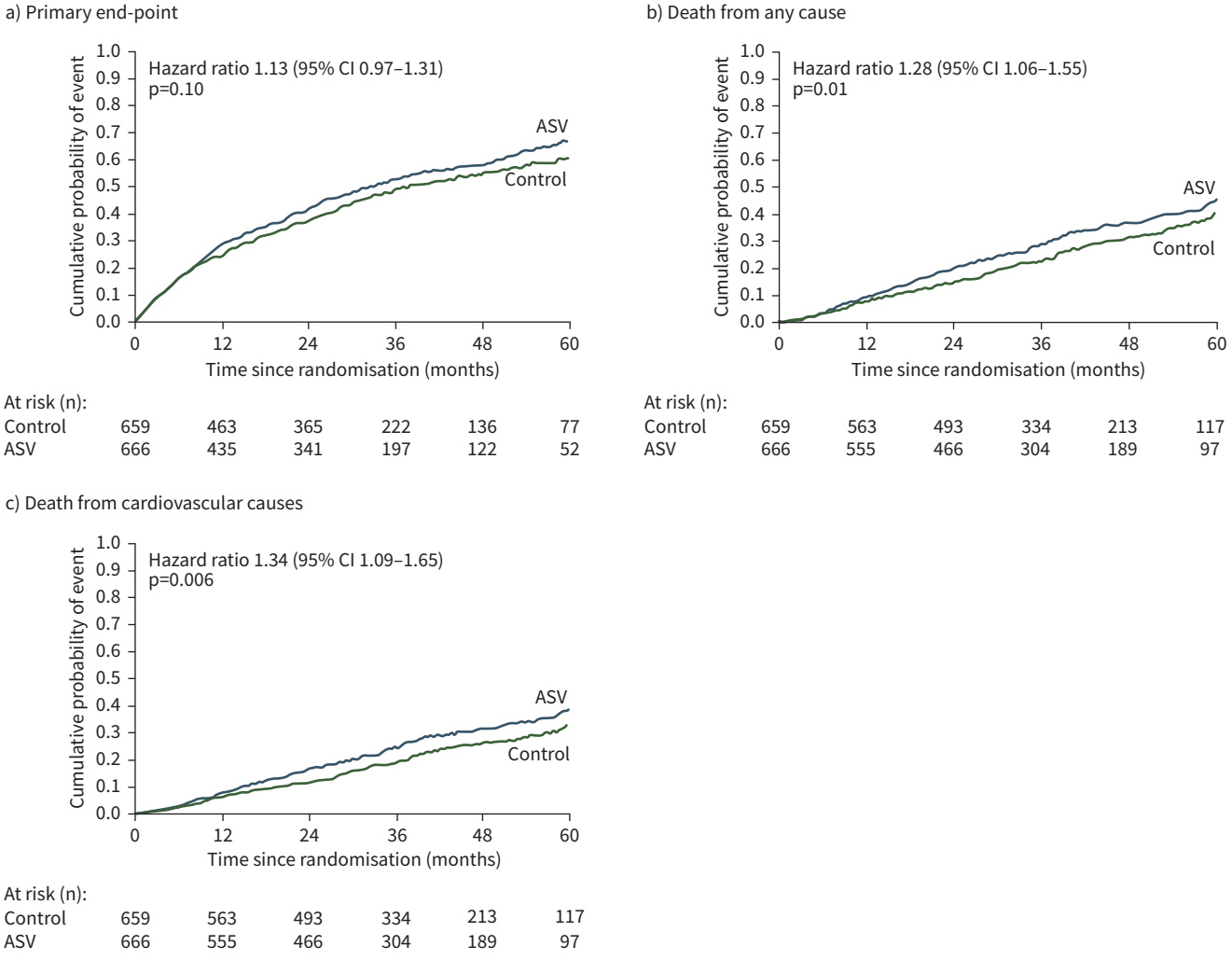

FIGURE 5 Cumulative incidence curves for the a) primary end-point, b) death from any cause and c) cardiovascular death in the SERVE-HF study [28]. The primary end-point was a composite of death from any cause, lifesaving cardiovascular intervention (cardiac transplantation, implantation of a long-term ventricular assist device, resuscitation after sudden cardiac arrest or appropriate shock for ventricular arrhythmia in patients with an implantable cardioverter defibrillator) or unplanned hospitalisation for worsening chronic heart failure. ASV: adaptive servo-ventilation. Reproduced from [28] with permission.

Phrenic nerve stimulation

Transvenous unilateral phrenic nerve stimulation has been studied in a randomised trial of 151 patients with predominantly CSA-CSR [165], only 64% of whom had heart failure [166]. At the end of the 6-month trial periods, AHI fell ~50% in the paced group (from 49.7 to 25.9 events·h^{-1}) and most of the residual events were obstructive. AHI did not change in the control group. Oxygen desaturation improved, as did daytime sleepiness and QoL. The trial was not powered for cardiovascular events. Further analysis of the per-protocol population demonstrated a significant reduction of the hypoxic burden [167]. However, further studies will be required to determine whether this therapy will improve cardiovascular outcomes.

Respiratory stimulants

Theophylline stimulates central respiratory drive and augments cardiac contractility by antagonism of adenosine. In a randomised trial involving 15 patients with stable heart failure and CSA-CSR, theophylline administered for 5 days reduced the AHI, but did not improve LVEF [168]. However, theophylline, once widely used for therapy of acute heart failure, is no longer used for this purpose because it increased the incidence of cardiac arrhythmias and sudden death [169]. The carbonic anhydrase inhibitor, acetazolamide, stimulates respiration by causing metabolic acidosis. In a short-term randomised trial in patients with HFrEF and CSA-CSR, acetazolamide caused modest reductions in the AHI and improvements in nocturnal

oxygenation as well as daytime sleepiness and fatigue [170]. However, it cannot be recommended for therapy of CSA-CSR in HFrEF at present as the long-term effects of acidosis and hyperventilation on safety and effectiveness have not been assessed.

Overall, there is increasing interest in developing integrated models of care among specialists and between specialists and primary care practitioners. There are fertile opportunities for sleep medicine and cardiology to develop co-management practices given the high co-aggregation of SDB and cardiovascular disease and the potential for bidirectional associations [171]. A multidisciplinary and integrated care approach model for heart failure patients presenting with SDB may allow accurate diagnosis, timely treatment and careful follow-up of both sleep apnoea and heart failure.

SDB and cardiac arrhythmia in heart failure

Ventricular arrhythmia

Among the different changes occurring during OSAs, the abrupt changes in negative intrathoracic pressure may contribute to alterations in ventricular repolarisation. This in addition with sympathetic activation may represent critical mechanisms for the increased risk of sudden cardiac death evidenced in OSA [172]. Accordingly, a mechanistic study using a pig model of obstructive respiratory events simulated by intermittent negative upper airway pressure showed a transient dissociation of ventricular electro-mechanical coupling during simulated obstructive respiratory events. It created a dynamic ventricular arrhythmogenic substrate, which was sympathetically mediated and aggravated by drug-induced long QT interval [173]. Coexisting heart failure and sleep apnoea increase the risk of developing malignant ventricular arrhythmia [174]. A real-word data registry evidenced that treating CSA-CSR with ASV in heart failure patients with implantable cardioverter defibrillator devices (ICDs) reduces the need for ICD therapies [175]. It should be kept in mind, however, that cardiovascular and all-cause mortality were increased in the SERVE-HF trial among those randomised to ASV [28].

Atrial fibrillation

Atrial fibrillation favours CSA-CSR through mechanisms similar to those in heart failure. There is an augmented pulmonary vascular pressure that triggers hyperventilation and hypocapnia owing to stimulation of pulmonary vagal irritant receptors. This contributes to respiratory system instability [98, 99]. CSA-CSR may conversely increase atrial fibrillation occurrence through hypocapnia, increased autonomic imbalance and electrical instability [176]. Alternatively, autonomic dysfunction may favour both CSA-CSR and atrial fibrillation, as evidenced in idiopathic CSA [177].

OSA patients often exhibit severe atrial structural changes and conduction abnormalities, while atrial refractoriness remains unchanged [178]. Sleep apnoea may also increase atrial fibrillation trigger formation in the pulmonary veins and elsewhere. In addition, OSA may result in transient electrophysiological changes, which by their arrhythmogenic consequences may explain the increased risk of nocturnal atrial fibrillation. Interestingly, atrial fibrillation paroxysms are temporally related to these electrophysiological changes [179, 180]. It has also been evidenced from pacemaker data simultaneously monitoring SDB and atrial fibrillation burden that the night-to-night variability in SDB severity contributes to a dynamic atrial fibrillation substrate. The nights with the highest SDB conferred an increased risk of having atrial fibrillation during the same day compared with the nights with less SDB [181].

The presence of severe OSA is associated with an impaired response to anti-arrhythmic drug therapy for atrial fibrillation [182]. In addition, meta-analyses of observational studies show that compared with subjects free of OSA, sleep apnoea patients have a 30% greater atrial fibrillation recurrence rate after pulmonary vein isolation [183]. Data from nonrandomised studies of OSA patients with atrial fibrillation suggest that treatment by CPAP may help maintain sinus rhythm after electrical cardioversion and improve catheter ablation success rates [82]. For instance, in meta-analyses of nonrandomised studies, using CPAP was associated with a 42% decreased risk of atrial fibrillation recurrence after cardioversion or pulmonary vein isolation [184]. However, there remains a need to determine, in appropriately powered randomised trials, whether treatment of OSA reduces atrial fibrillation burden and to assess whether routine OSA screening and treatment among patients with atrial fibrillation is cost-effective [82]. In the first such RCT, CPAP therapy for moderate to severe OSA in subjects with paroxysmal atrial fibrillation but without heart failure had no effect on the burden of atrial fibrillation [185]. Other RCTs are ongoing, including SLEEP-AF (Australian New Zealand Clinical Trials Registry: 12616000088448).

Several interventions for OSA, apart from CPAP treatment, have been shown to be effective in reducing atrial fibrillation recurrence. Weight loss by behavioural changes or bariatric surgery, as well as alcohol abstinence, that may have beneficial effects on OSA, favour the maintenance of sinus rhythm, albeit not

specifically in heart failure [186]. This should be specifically tested in the context of heart failure and SDB.

Future challenges regarding heart failure and sleep apnoea

The main future clinical and research challenges regarding sleep apnoea and heart failure are summarised in table 2.

Conclusions

Heart failure is an important healthcare problem associated with low QoL, high cost of medical care and poor prognosis. SDB, another frequent chronic condition, is more common among the heart failure population than the general population, either because it predisposes to heart failure and its complications or because heart failure predisposes to OSA and CSA-CSR, as discussed earlier. The most important clinical consequence of SDB in heart failure is that it is associated with worse prognosis, including higher mortality than in patients with heart failure but without SDB.

Regarding treatment, with respect to OSA, the major reason to treat in patients with heart failure is the same as in the non-heart failure population: to alleviate symptoms of OSA such as nocturnal dyspnoea or choking, morning headaches and excessive daytime sleepiness. In the absence of such symptoms, there have been no randomised trials demonstrating that treating asymptomatic OSA improves clinically important outcomes in patients with heart failure, such as cardiovascular morbidity and mortality. With respect to CSA-CSR in patients with heart failure, such patients seldom have symptoms suggestive of SDB, so in most instances there is no compelling reason to treat this breathing disorder. Indeed, the largest randomised trial in this field, SERVE-HF, demonstrated that treating CSA-CSR with ASV in patients with HFrEF increased mortality [28]. Accordingly, the greatest challenge facing this field is to determine, in randomised trials, whether treating SDB, either OSA or CSA-CSR, improves clinically important outcomes. Part of this challenge is not only to test PAP devices, but to come up with new treatment approaches, including devices and possibly pharmaceutical agents, that have a beneficial effect on SDB. Finally, there is a need to critically evaluate efficacy, potential harm and positioning of novel strategies, such as phenic nerve stimulation, in current treatment algorithms.

Until it can be demonstrated that treating asymptomatic SDB in patients with heart failure improves clinically important outcomes, it will be difficult to formulate evidence-based recommendations to guide therapy. With respect to patients with asymptomatic OSA, one could provide a trial period of CPAP to

TABLE 2 Future clinical and research challenges regarding sleep apnoea and heart failure

Main challenges	OSA in heart failure	CSA-CSR in heart failure
Sleep apnoea clinical diagnosis	Improve sensitivity and specificity of dedicated questionnaires	Improve sensitivity and specificity of dedicated questionnaires
Sleep apnoea monitoring	Assess the clinical value of simplified sleep assessment during overnight monitoring, *i.e.* PG *versus* PSG Include additional markers, *e.g.* sleep fragmentation, hypoxaemic burden and autonomic dysfunction Assess night-to-night variability and change in SDB type (OSA *versus* CSA-CSR) across time, *e.g.* in relation to changes in heart failure severity	Assess the clinical value of simplified sleep assessment during overnight monitoring, *i.e.* PG *versus* PSG Include additional markers, *e.g.* sleep fragmentation, hypoxaemic burden and autonomic dysfunction Assess night-to-night variability and change in SDB type (OSA *versus* CSA-CSR) across time, *e.g.* in relation to changes in heart failure severity
Sleep apnoea management	Assess the clinical usefulness in heart failure of remote monitoring of cardiovascular and sleep and breathing variables	Assess the clinical usefulness in heart failure of remote monitoring of cardiovascular and sleep and breathing variables
Sleep apnoea treatment	Large-scale RCTs of SDB treatment in heart failure, in order to determine whether this improves cardiovascular outcomes or not Assess cardiovascular outcomes in RCTs using PAP and alternative treatment options (*e.g.* positional therapy, oral appliances, hypoglossal nerve stimulation)	Large-scale RCTs of SDB treatment in heart failure, in order to determine whether this improves cardiovascular outcomes or not Assess cardiovascular outcomes in RCTs evaluating safety and efficacy of transvenous phrenic stimulation

OSA: obstructive sleep apnoea; CSA: central sleep apnoea; CSR: Cheyne–Stokes respiration; PG: polygraphy; PSG: polysomnography; SDB: sleep disordered breathing; RCT: randomised controlled trial; PAP: positive airway pressure.

determine if there is any subjective improvement, since patients may not realise that they have symptoms until they are relieved. If there is symptomatic improvement, treatment could be continued; if not, then treatment could be discontinued.

With respect to CSA-CSR, no randomised trials of any intervention have demonstrated improvements in either symptoms or cardiovascular morbidity and mortality. Accordingly, other than optimising medical heart failure therapy, there is presently no compelling evidence to recommend treating CSA-CSR *per se* in patents with heart failure. In addition, there was a significantly higher all-cause and cardiovascular mortality in SERVE-HF in the ASV limb, which was largely driven by an increase in sudden death [28]. Thus, we have to await the results of current or further randomised trials with more definitive results, in order to guide therapeutic recommendations in the future. In the meantime, the use of ASV (and perhaps other PAP therapies) for the treatment of predominantly CSA-CSR in HFrEF cannot be recommended.

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