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REVIEW

Current and future developments in the field of central sleep apnoea

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Central sleep apnoea (CSA) occurs in ~30–50% of patients with heart failure (HF) with reduced left ventricular ejection fraction (LVEF) and in as much as in 18–30% of patients with preserved LVEF. In HF patients, it is characterized by periodic breathing also known as the Cheyne–Stokes respiration followed by pauses of breathing. Central sleep apnoea remains often unrecognized due to its chronic and insidious incidences. Patients may report excessive daytime somnolence, poor sleep quality, nocturnal angina, recurrent arrhythmias, refractory HF symptoms, or demonstrate abnormal respiratory pattern or apnoeas. The pathogenesis of CSA remains incompletely understood, but changes in CO_2 above and below the apnoea threshold play a major role in its pathogenesis. The presence of CSA in patients with HF is associated with some neurohumoral and haemodynamic responses that are detrimental to the failing heart including increased morbidity and mortality. The development of successful therapies targeting CSA and its harmful downstream effects is therefore important. Several different therapies from medications to implantable devices have been tested with varying effects and primarily in small non-randomized and/or single-centre studies. Large studies to date have been disappointing, but therapeutic options targeting the physiology of the disease may herald a new era in understanding and treating CSA.

Keywords Central sleep apnoea • Cheyne–Stokes respiration • Heart failure • Sleep apnoea

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Introduction

Heart failure (HF) is a major public health issue and is a leading cause of morbidity and mortality in the developing countries. Its incidence is increasing.[1] Despite the huge advances in the management of cardiovascular diseases (CVDs), the rates of hospitalization and mortality of HF remain high and largely unchanged, and it accounts in addition for a significant economic burden.[2,3] Focusing on identifying and treating modifiable comorbidities could be of great importance in reducing the morbidity and mortality of HF.[4–9] Sleep-disordered breathing (SDB) is the most common co-morbidity in HF occurring in ~30–80% of patients with HF.[10–12] However, it is usually not part of the routine screening and management of HF and as a result remains often underdiagnosed. Sleep-disordered breathing consists primarily of two types: obstructive sleep apnoea (OSA) and central sleep apnoea (CSA):

- OSA: Excessive daytime sleepiness with at least 5 obstructive events/hour (apnoeas + hypopneas),
- CSA: Excessive daytime sleepiness OR frequent arousals with at least 5 central events/hour (apnoeas + hypopneas).

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Table 1 Prevalence of CSA in HF and cardiac device patients

	Population	No. of patients	SDB (%)	OSA (%)	CSA (%)
HF					
Ferrier, 2005[15]	HFrEF	53	68	53	15
Javaheri, 2006[16]	HFrEF	100	49	12	37
Oldenburg, 2007[12]	HFrEF	700	76	36	40
Vazir, 2007[17]	HFrEF	55	53	15	38
Schultz, 2007[18]	HFrEF	203	71	43	28
MacDonald, 2008[19]	HFrEF	108	61	30	31
Paulino, 2009[11]	HFrEF	316	81	57	24
Hagenah, 2009[20]	HFrEF	50	64	20	44
Khayat, 2009[21]	HFrEF	395	75	57	18
Bitter, 2009[22]	***HFpEF***	244	69	40	30
Device patients					
Oldenburg, 2007[23]	CRT patients	77	81	34	47
Bitter, 2013[24]	HF + ICD	638	61	30	31
Grimm, 2013[25]	ICD	204	55	14	51

While some patients have both obstructive and central events (sometimes called mixed sleep apnoea), the type of disorder is typically classified by the predominant type of event (>50% of events) as either obstructive or central.[13] Obstructive sleep apnoea is more common and occurs in both the general and HF populations, whereas the latter is more associated with HF. Obstructive sleep apnoea and the Cheyne–Stokes respiration, typically seen in CSA, are independent risk factors for malignant ventricular arrhythmias, which require appropriate cardioverter-defibrillator therapies in HF patients.[14] This article will focus on clinical presentation of CSA, its pathology, testing, as well as the current and future therapies of CSA.

Clinical presentation

Central sleep apnoea occurs in ~30–50% of patients with HF with reduced left ventricular ejection fraction (LVEF), and in as much as in 18–30% of patients with preserved LVEF (*Table 1*). In HF patients, it is characterized by periodic breathing also known as the Cheyne–Stokes respiration followed by pauses of breathing.[10,12,16,19,22,26–28] Central sleep apnoea is more common among thin males with HF, who are older than 65 years, have atrial fibrillation or other arrhythmias, and have daytime hypocapnia (PCO_2 < 38 mmHg).[26] Snoring is not as common as in patients with OSA. Sometimes, a sleep partner may report witnessed apnoeas or the unusual breathing pattern of the Cheyne–Stokes respiration. Patients with CSA typically suffer from the results of disrupted sleep including fatigue, insomnia, daytime sleepiness, and poor concentration. They may also report symptoms related to the hypoxia, as a result of the apnoea, such as paroxysmal nocturnal dyspnoea, headache, and nocturnal angina.[29] Since these are also common symptoms in HF alone, CSA could be easily overlooked if it has not been considered. Daytime sleepiness does not occur in most patients with CSA and might not be noticed because of the chronic and insidious onset of the disease. No sleep questionnaire has proved thus far to be a useful tool in screening and identifying patients with CSA in HF, and therefore, a high suspicion should be maintained in patients with HF presenting with any of the above-mentioned symptoms.[30,31] Raising the awareness of the prevalence, symptoms, risk factors, and the pathophysiology of this disease among general physicians, cardiologists, and cardiac electrophysiologists is important.

Pathophysiology

The pathogenesis of CSA remains incompletely understood. One of the most favoured hypotheses suggests that the changes in $PaCO_2$ above and under the apnoeic threshold—a tightly regulated level of $PaCO_2$—may play the major role in the pathophysiology of CSA in HF.[32,33] There are two responsible factors for the breathing process during wakefulness (metabolic and behavioural). The latter could be divided into involuntary, for example during stress, or voluntary like holding a breath. Behaviour factors play a negligible role in controlling breathing during sleep. The metabolic factors through controlling the level of $PaCO_2$ are determinant factors in this process both during wakefulness and sleepiness. As an example, exercise-induced acidosis through the elevated level of $PaCO_2$ stimulates ventilation. On the other hand, each situation that decreases $PaCO_2$ under the apnoeic threshold like hyperventilation will cease respiration. There is a complex system operating in a negative feedback loop and regulating the level of CO_2 and O_2 through many peripheral and central receptors, which interact with the chest wall, lung, and arterial blood gas content in a continuous way.[34–36]

It is known that patients with HF tend to hyperventilate.[32,33] The exact mechanism, however, remains incompletely understood. This could be related to the pulmonary interstitial congestion as a result of the fluid redistribution in the supine position, which activates pulmonary stretch receptors that stimulate ventilation and leads to a *relative* hypocapnia. Some of these patients are not hypocapnic, but they have an elevated apnoeic threshold.[37–40] In an effort to

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correct the hypocapnia, a hypersensitive respiratory control centre initiates an apnoea. This occurs when the $PaCO_2$ is below the 'apnoeic threshold'. The $PaCO_2$ then begins to rise, resulting in another exaggerated response of hyperventilation and leading to the cyclical pattern of the Cheyne–Stokes respiration.[41,42]

Normally, at the onset of sleep, there is an increase in the upper airway resistance as a result of the normal sleep-related decrease of muscular tone.[43] In addition, as part of the normal sleep physiology, ventilation decreases and $PaCO_2$ increases. This keeps the level of $PaCO_2$ above the apnoeic threshold, allowing normal, rhythmic breathing to continue throughout the night.[44] There are normally both central (brain and brainstem) and peripheral (carotid body) chemoreceptors to detect $PaCO_2$. This in turn controls the respiratory response according to apnoeic threshold.[30] However, significant changes take place in the sleep architecture in HF leading to respiratory instability. These factors include hyperventilation, circulatory delay, and cerebrovascular reactivity. Circulatory delay, as a result of the decreased cardiac output in HF patients, plays an additional role in the respiratory instability. Lung-to-ear circulation time could be used as a surrogate measure of circulatory delay, and it is usually elevated in this group of patients due to the reduced cardiac output. This delay lengthens the time for the chemoreceptors to identify changes in CO_2 and influences as a result the cycle duration of waxing–waning pattern of periodic breathing seen with CSA.[45] Patients with HF and CSA have, in addition, a diminished cerebrovascular response to CO_2. This may be another important contributor factor to the breathing instability seen in these patients during sleep.[46] Cerebrovascular reactivity, which represents the alterations in cerebral blood flow caused by respiratory-induced changes in $PaCO_2$, is reduced in HF patients with CSA. This leads in turn to an impaired buffering action, which happens normally according to the central hydrogen ion concentration ($[H+]$), and as a result to an inappropriate reaction of $[H+]$ and $PaCO_2$ at the central chemoreceptor in both hyper- and hypocapnia.[46] This reduces the ability of the central respiratory control centre to adequately dampen ventilator undershoots or overshoots, such as those seen during apnoea or at apnoea termination.

The relationship between central sleep apnoea and heart failure and the pathophysiologic consequences

The repeated episodes of apnoea, hypoxia, reoxygenation, and arousal in HF patients with CSA have pathological consequences including sympathetic nervous system activation, oxidative stress, systemic inflammation, and endothelial dysfunction (*Figure 1*). Due to missing data in CSA population, we extrapolated the findings regarding the metabolic and cardiovascular effects of OSA to CSA.

The presence of CSA in patients with HF is associated with some neurohumoral and hemodynamic responses that are detrimental to the failing heart. Cyclical arousals provoke periodic elevations in the activity of the sympathetic nervous system,[47,48] which is already increased in HF.[49] This causes tachycardia, peripheral vasoconstriction, sodium retention, and renin–angiotensin system activation. The consequent increases in myocardial oxygen demand, blood pressure, and blood volume lead to increased myocardial ischaemia, preload, and afterload that together further stress the failing heart. Furthermore, increased sympathetic tone may contribute to ventricular irritability and arrhythmias in patients with HF.[50] The stimulated sympathetic nervous system activity is associated with increased mortality in HF patients.[51–53]

Oxidative stress represents an important factor in the pathology and the progression of HF.[53,54] Episodes of hypoxia-reoxygenation, such as those in CSA, seem to increase systemic oxidative stress.[55] The latter takes place when there is an imbalance between the production of the reactive oxygen species (ROS) and the endogenous antioxidant defences. Elevated concentrations of ROS lead to tissue damage through oxidative reactions with lipids, proteins, and deoxyribonucleic acid. Reactive oxygen species might contribute to the progression of HF through impairment of myocardial contraction, cardiac remodelling, and interfering with nitric oxide metabolism, which is important for a normal endothelial function.[54–65] It is hypothesized that during ischaemia, metabolic intermediates accumulate. During reperfusion, there will be a sudden increase in ROS. This decompensates the usual cellular antioxidant defence and as a result leads to uncontrolled oxidation of vital cellular biomolecules.[56] This could be evaluated through the elevated levels of biomarkers like lipid peroxidation products and oxidized protein and deoxyribonucleic acid.[57] Researches have shown decreased antioxidant levels in sleep apnoea[57–59] and an improvement of the oxidative stress with the application of continuous positive airway pressure (CPAP) therapy in patients with OSA.[60,61]

Inflammation is part of the pathology process in several CVDs including HF.[62–64] Elevated levels of pro-inflammatory mediators independently predict increased mortality in HF patients.[66,67] Many studies in the past decade showed that patients with sleep apnoea have elevated amounts of pro-inflammatory cytokines, cellular adhesion molecules, and activated circulating neutrophils.[68,69] As a result, sleep apnoea through its contribution to the increased pro-inflammatory factors and inflammatory state may lead to further progression of HF. Nuclear factor-kappa B (NF-κB) is proposed to play a central role in this process. It is one of the most important oxidation-sensitive transcription factors that activates several genes associated with CVD.[70] Studies measuring NF-κB in circulating neutrophils and monocytes showed increased activity of NF-κB in OSA patients compared with controls patients and the reduction in its concentration after application of the CPAP therapy.[71,72] One of the hypotheses that could explain the role of NF-κB in sleep apnoea patients is that the increased levels of ROS as a result of the apnoea-induced hypoxia-reoxygenation may trigger the expression of multiple pro-inflammatory genes via activation of NF-κB.[73,74]

Endothelial dysfunction, which is characterized of vasoconstriction, inflammation, and thrombosis, is a critical component of the pathophysiology of HF and many other CVDs. Endothelial dysfunction in HF patients with sleep apnoea may be as a result of both oxidative stress and the inflammation.[75–77] Apnoea-induced intermittent hypoxia-reoxygenation through increasing ROS leads to the reduced availability of nitric oxide (NO) and exacerbates the local oxidant stress by reacting with NO forming the potent oxidant peroxynitrite[78–80] and, as a result, contributes to the endothelial dysfunction. Recent research detected the presence of endothelial dysfunction in patients with OSA and its reversal after using the CPAP therapy.[81]

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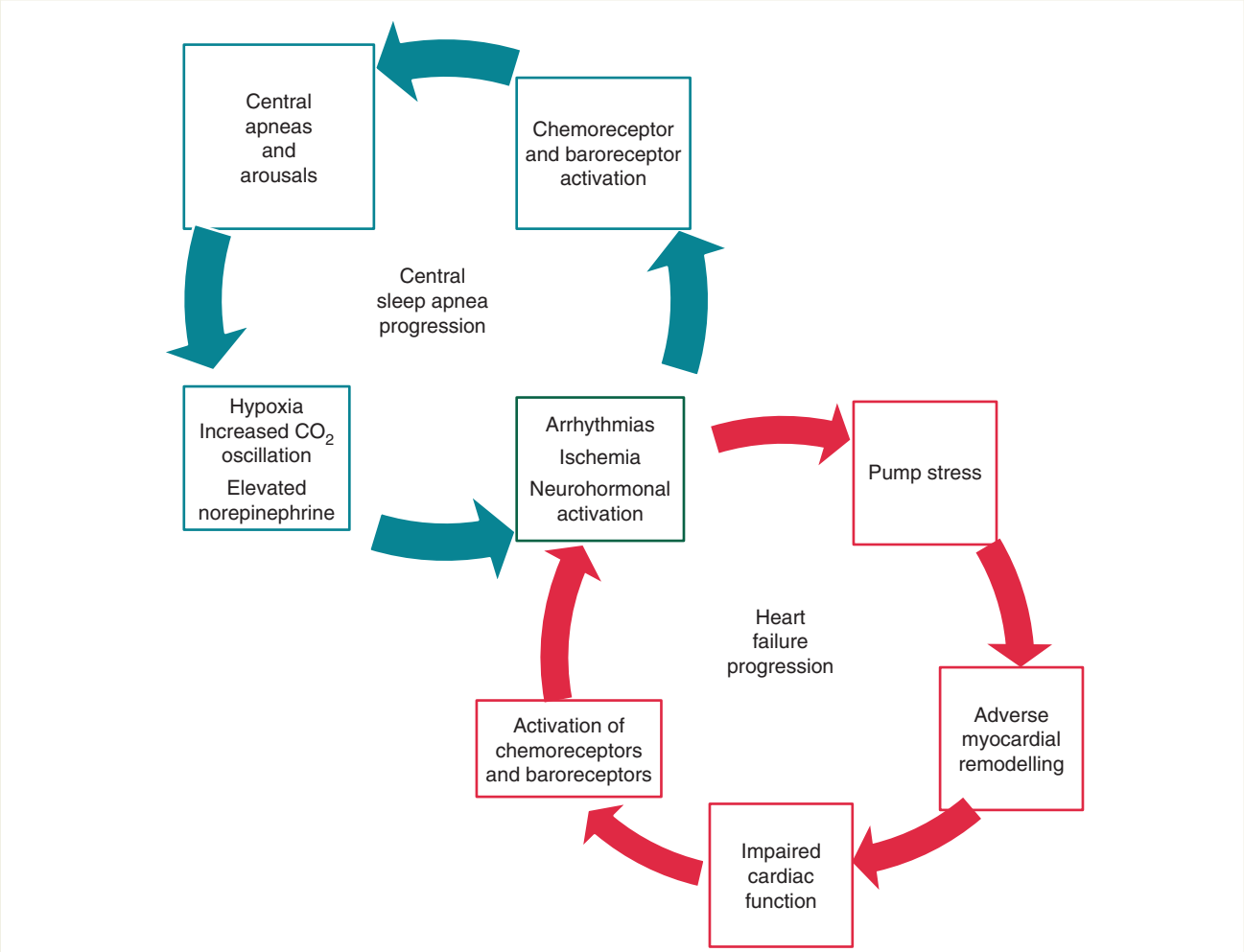

Figure 1 Pathophysiology and the relationship between HF, CSA and arrhythmias: each episode of central apnoea and arousal results in hypoxia, norepinephrine, and wide oscillations in carbon dioxide. Hypoxia results in cardiac ischaemia, plaque rupture, and dementia. Elevated norepinephrine causes atrial and ventricular arrhythmias and activates the renin–angiotensin system resulting in sodium retention and neurohormonal activation. Neurohormonal activation and ischaemia further activate central and peripheral chemoreceptors and baroreceptors further destabilizing breathing and triggering CSA. In addition to CSA, feeding back to continue the CSA cycle, ischaemia, and neurohormonal activation causes additional pump stress leading to adverse myocardial remodelling. With adverse remodelling, cardiac function is further impaired and worsens the downward progression of HF.

Table 2 A comparison between the different characteristics of the testing devices

	Class I	Class II	Class III	Class IV
Example	EMBLA (PSG)	Embletta MPR ST+ proxy	NOX-T3	MIR Spirodoc Oxi
Site of test	In sleep lab	In sleep lab or at home	Home	Home
Measure oxygenation	X	X	X	X
Measure respiratory events (e.g. AHI)	X	X	X	Available in some devices
Monitor ECG/arrhythmias and position	X	X	Available in some devices	Available in some devices
Measure sleep (EEG)	X	Fewer measurements than in sleep lab studies	Simple measurements available on some devices	
Diagnose additional sleep disorders (e.g. periodic leg movements, parasomnias)	X	X		

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Patient identification and sleep testing devices

According to the recommendation from the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the diagnosis and treatment of chronic HF,[82] clinical judgement should be used to screen for SDB in patients with HF such as those who report excessive daytime somnolence, poor sleep quality, nocturnal angina, recurrent arrhythmias, refractory HF symptoms, and those by whom abnormal respiratory pattern or apnoeas were witnessed. Though it is unfortunately not common yet, sleep studies are being done in some hospitals as routine clinical care. All patients who are hospitalized with an admission diagnosis of acute HF have a high likelihood (>50%)[21,83] of testing positive for SDB. Ideally, the hospital should have trained night shift nurses, who note the patient's visual sleep and wakefulness and any interruptions to sleep or desaturations in an inpatient setting.[21,83] Identification of patients could be done as well in ambulatory setting with more stable patients with chronic HF both with reduced or preserved left ejection fraction. There are four types of sleep study monitoring devices (*Table 2*).

A SDB index derived from home sleep apnoea testing (HSAT) device differs from the apnoea hypopnea index (AHI) during polysomnography (PSG). The AHI is calculated by dividing the number of apnoeas and hypopneas by total sleep time, whereas the HSAT index divides by total recording time. This leads usually to lower index derived from HSAT than an AHI derived by PSG.

There is a new classification schema of HSAT devices summarized in the word SCOPER.[84] SCOPER stands for Sleep, Cardiovascular, Oximetry, Position, Effort, and Respiration. The SCOPER categorization system provides a more detailed description of the type of physiologic parameters that are being measured and how they are being measured than traditional classification schemes.

Recently, several recently introduced cardiac devices have parameters indicating the presence of SDB. These devices are not currently able to distinguish between central and obstructive episodes. The REPLY 200 SR and DR devices (LivaNova) detect changes in thoracic impedance and translate this into a respiratory disturbance index, which demonstrated 89% sensitivity and 85% specificity for detecting SDB.[85] Boston Scientific has developed a parameter (ApneaScan) with the ability to identify changes in thoracic impedance and heart rate to predict SDB with a high negative predictive value of 88%, but slightly lower sensitivity and specificity (83 and 70%, respectively).[86] As this technology continues to develop, implanted cardiac devices will help identify patients with SDB or those who develop SDB over time.

Scoring a sleep study

Many sleep studies now have automated software that can be used to aid in scoring, but it is important that trained personnel review the study as the software may misinterpret the signal in some patients (*Figure 2*). Here are some definitions:

Apnoea: This is the cessation, or near cessation, of airflow. It exists when airflow is <10% of pre-event baseline for at least 10 s in adults.87 Apnoea can be associated with arousals from sleep, increased arterial carbon dioxide, and decreased oxygen levels. Inspiratory airflow or nasal pressure is typically used to identify an apnoea, although both inspiratory and expiratory airflows

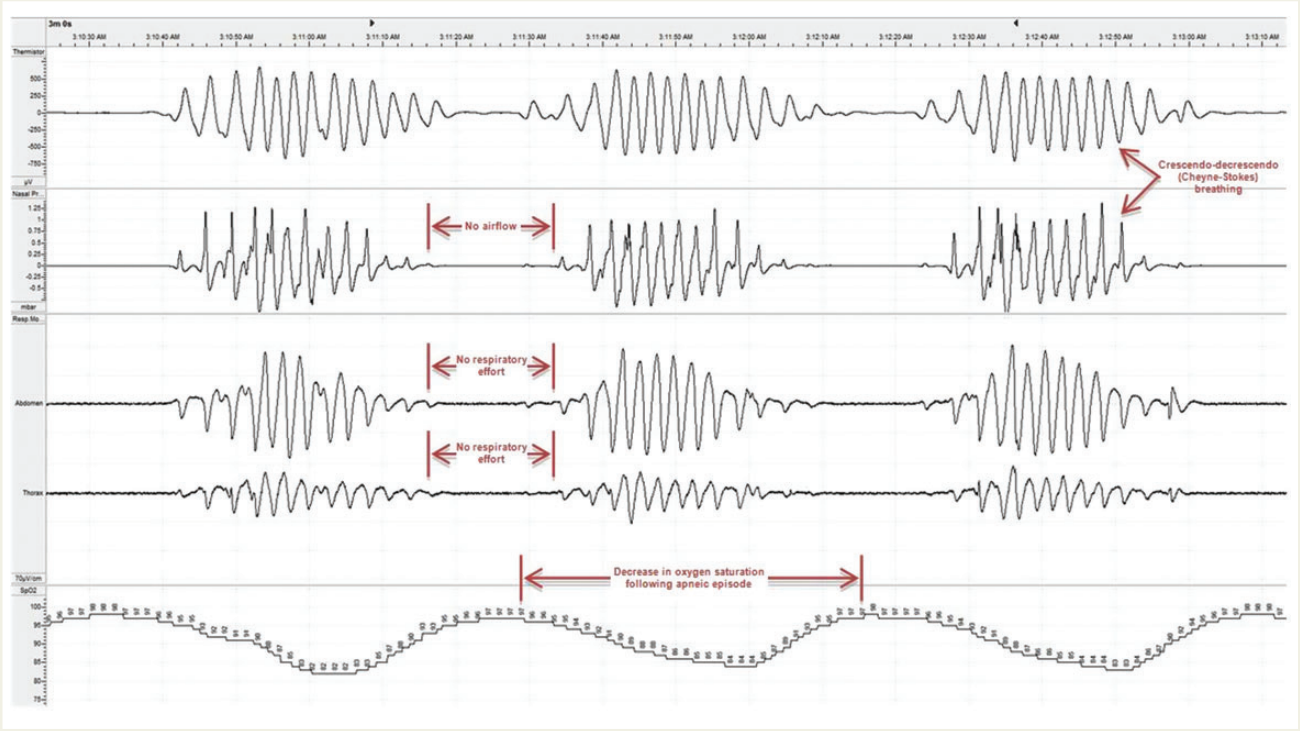

Figure 2 Selected channels of a polysomnogram of a patient with CSA with Cheyne–Stokes breathing.

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are usually abnormal. In the absence of a good airflow signal, chest wall and abdominal expansion can be used as a surrogate measure. Apnoea during sleep can be categorized as three types: obstructive apnoea, central apnoea, and mixed apnoea.

Obstructive apnoea: This occurs when airflow is absent or nearly absent, but ventilatory effort persists (as seen by the chest and abdominal belts). It is caused by complete, or near complete, upper airway obstruction.

Central apnoea: This occurs when ventilatory effort is absent leading to no airflow. This could be proved by an absence of the ventilatory signal on the chest and abdomen belts in the polygram (PG) or by the absence of diaphragmatic activation, measured by electromyography (EMG).

Mixed apnoea: There is an interval during which there is no respiratory effort (i.e. central apnoea pattern) followed by an interval during which there is obstructed respiratory efforts.

Hypopnea: This is a reduction of airflow to a degree that is insufficient to meet the criteria for an apnoea. Hypopnea should be scored when all of the following three criteria are met:

- Airflow decreases at least 30% from pre-event baseline,
- The diminished airflow lasts at least 10 s,
- The decreased airflow is accompanied by at least 3% oxyhaemoglobin desaturation from pre-event baseline, or an arousal.

Like apnoea, hypopnea is detected using sensors, such as chest wall expansion. Inspiratory airflow is typically used to identify a hypopnea, although both inspiratory and expiratory airflows are usually abnormal.

Apnoea index (AI): This is the total number of apnoeas per hour of sleep.

Apnoea hypopnea index (AHI): This is the total number of apnoeas and hypopneas per hour of sleep. The AHI is the primary parameter used to report PSG results.

Oxygen desaturation index (ODI): This is a frequent consequence of apnoea and hypopnea, and it represents the number of times that the oxygen saturation drops from baseline by >3 percentage points (ODI 3%) or, more commonly, 4 percentage points (ODI 4%) per hour of sleep.[87]

Arousal index (ArI): This is the total number of arousals per hour of sleep. Arousal index is usually lower than the AHI because not all of apnoeas or hypopneas are being followed by documented arousals on PSG. However, when arousals occur as a result to other causes like periodic limb movement, the ArI can be greater than the AHI.

Current and future treatment options

Several studies showed that improving HF through optimizing the HF therapy is followed by an improvement in CSA.[88–90] However, even with current guideline-directed medical therapies, the prevalence of CSA remains unchanged and CSA has been shown to persist despite the optimal HF therapy. Thus, the development of successful therapies targeting CSA and its harmful downstream effects is important. Several different therapies from medications to implantable devices have been tested with varying effects and primarily in small non-randomized and/or single-centre studies.

Previous and current trials in central sleep apnoea

Acetazolamide

Acetazolamide is a mild diuretic agent causing metabolic acidosis. It was hypothesized to reduce the likelihood of developing CSA due to the resulting decrease in the $PaCO_2$, and therefore, the increase in the amount of $PaCO_2$ needed to reach the apnoeic threshold.[91] In a single, double-blind study, acetazolamide showed improvement in subjective sleep quality and decreased both the respiratory events and nocturnal oxygen desaturation. However, it did not show any improvement in LVEF or in the objective measurement of sleep quality.[91] In addition, the use of acetazolamide was complicated with urinary potassium wasting, which could lead to arrhythmias. Therefore, the use of acetazolamide in treating patients with HF and CSA is not recommended currently.

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) has been evaluated for its effect on CSA in patients with HF. Cardiac resynchronization therapy demonstrates a clear reduction in morbidity and mortality associated with symptomatic HF, and it is currently indicated in patients with an LVEF of $<35\%$ and a QRS complex of >120 ms.[82] In small studies of CRT patients, CRT reduced CSA and improved sleep quality.[23,92–96] It has been proposed that the increase in cardiac output is responsible for its beneficial effects in HF patients with CSA. However, further long-term, prospective, randomized trials are needed to confirm these results. In addition, CRT is currently only indicated in a subset of HF patients. These indications limit the potential applicability of CRT as a primary treatment for CSA in HF patients with either a short QRS duration or LVEF $>$ 35%.

Oxygen

Therapy with 2–4 L/min oxygen by nasal cannula during the night was tested in the treatment of patients with CSA and HF. Studies showed that this method improved exercise capacity,[97] AHI,[98–102] and LVEF.[103,104] At the same time, there was a reduction in the sympathetic nervous system activity[105] and in serum B-type natriuretic peptide levels[100]; however, there was no change in the sleep quality or in the quality of life (QoL) in these patients.[106,107] It is also clear that with oxygen it is not possible to reduce the upper airway obstruction which could accompany CSA.

Carbon dioxide

Aiming to raise the concentration of $PaCO_2$, inhaled carbon dioxide has been tested as a therapy for patients with CSA. It improved the AHI, but did not improve the sleep quality in these patients.[108,109] Due to safety issues arising from using CO_2 inhalation therapy without medical supervision in outpatient setting, this therapy is not currently recommended.

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Continuous positive airway pressure

Continuous positive airway pressure is standard of choice therapy in patients with OSA[110] and has been used as well in treating patients with CSA. However, there is less evidence that this method is effective in patients with CSA. It requires a tight nasal or facial mask connected to an air blower, which gives a steady positive pressure to push air past into the lungs. Initial small trials in CSA patients showed that CPAP could improve the LVEF and the QoL. This method of treatment was associated with a reduction in AHI, nocturnal urinary and daytime plasma norepinephrine levels, and in ventricular ectopic beats.[111–113]

However, due to the increased intrathoracic pressure resulted from applying CPAP, adverse effects on the preload and afterload of both the right and left ventricles may arise. This in turn could worsen ultimately cardiac function rather than improving it.[114] Specifically, increased pressure on the right ventricle could further weaken an impaired right ventricle inhibiting forward flow or triggering arrhythmias. It was suggested in the Canadian study (CANPAP) that the early increased mortality noted in patients on CPAP therapy could have been due to these detrimental haemodynamic effects.[113,114]

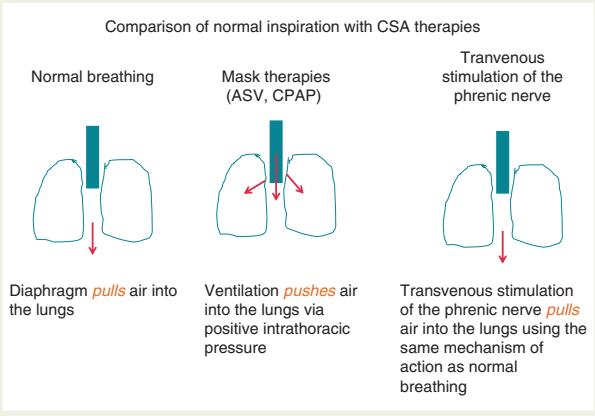

Figure 3 A comparison between the different mechanisms of therapies in patients with CSA.

Adaptive pressure support servo-ventilation

A new generation of positive pressure therapies was developed to adapt to the breathing rate and tidal volume of each patient and to match at the end the minute ventilation during rest condition. By adapting to the individual patient, it was thought that lower pressure would be delivered and this could prevent any negative consequence of positive pressure. This device supplies a small steady positive air pressure and has a sensor to detect the CSA and push air into the lungs at the tidal volume and respiratory rate set by the device. The goal of adaptive servo-ventilation (ASV) is to prevent

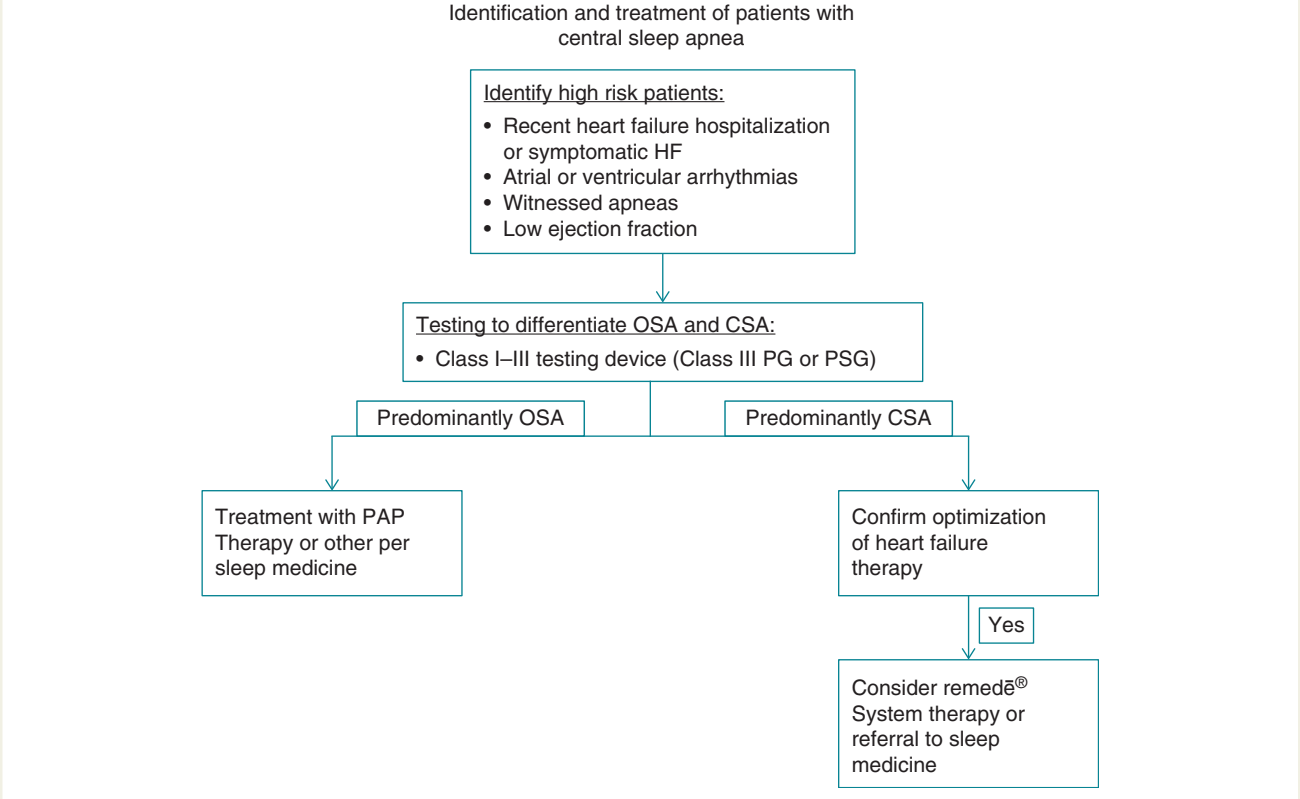

Figure 4 Pathway for the identification and treatment of patients with CSA.

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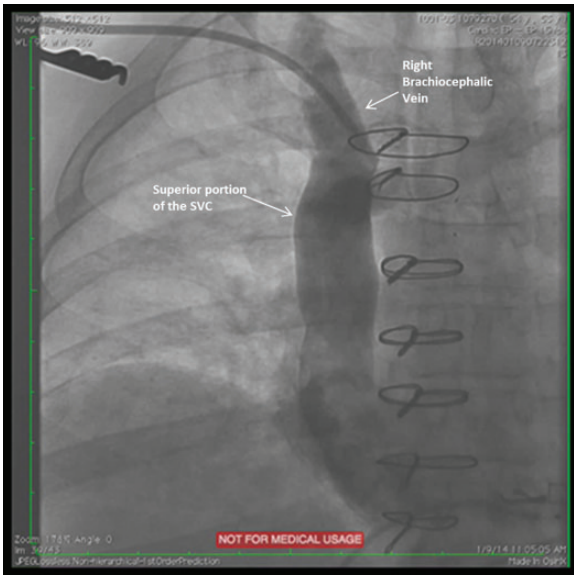

Figure 5 Right brachiocephalic vein venogram.

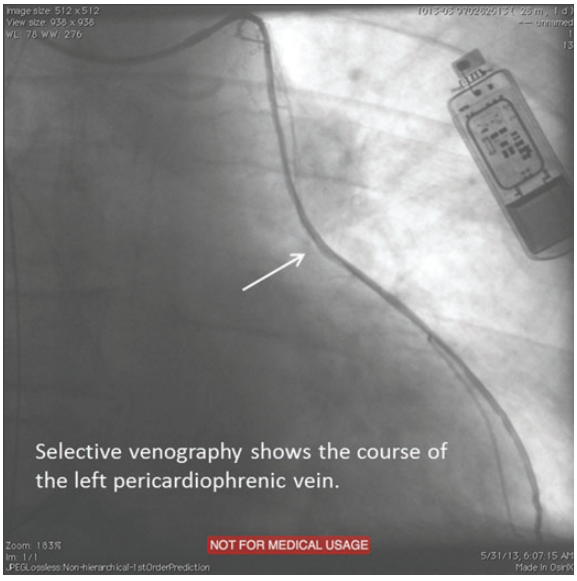

Figure 6 Left pericardiophrenic venogram.

ventilatory overshoot and undershoot and, through regulating the $PaCO_2$, to break the periodic breathing cycle. Early research suggested that ASV could be better tolerated than CPAP and showed that ASV improves LVEF, QoL, and sleep quality.[115,116]

SERVE-HF, a multinational, multicentre, randomized controlled Phase III trial, was designed to assess whether the treatment of moderate to severe predominant CSA (central AHI $\geq$ 10) with ASV therapy could reduce mortality and morbidity in patients with symptomatic chronic HF (LVEF $\leq$ 45%) in addition to optimized medical care.[117] The study failed to meet its primary endpoint of a reduction in cardiovascular morbidity and mortality. Furthermore, cardiovascular mortality was increased in patients in the ASV arm compared with those in the control arm with an absolute annual mortality rate of 10 vs. 7.5%.[118] Two possible causes for failure of the study were postulated in the manuscript: (1) CSA is beneficial or compensatory and (2) a possible detrimental effect of positive pressure on haemodynamics. The SERVE-HF results temporarily affected two other large, ongoing randomized studies: effect of ASV on survival and hospital admissions in heart failure (ADVENT-HF), which is using ASV in HF patients with both OSA and CSA and CAT-HF (Cardiovascular Improvements with MV ASV Therapy in Heart Failure), which is enrolling patients hospitalized with HF and sleep apnoea (OSA or CSA). Both of these studies have resumed enrolment in patients with EF $<$45% and CSA in most geographies and will hopefully provide additional insight regarding the treatment of CSA with positive pressure therapies.

Phrenic nerve stimulation (remede® system)

A new implantable device was developed to treat CSA in a physiologic manner. This therapeutic approach is designed to treat the underlying pathophysiology of the disease—a lack of signalling from the brain to breathe when needed. In normal breathing, a signal is sent from the brain via the phrenic nerve to move the diaphragm. The **rem**ede® system activates when the patient sleeps at night and provides therapy during the entire sleeping period without patient interaction.

The **rem**ede® system is a small neurostimulator implanted in the right or left pectoral region with a transvenous lead, implanted in the left pericardiophrenic vein or in the right brachiocephalic vein, and designed to stimulate the nearby phrenic nerve, resulting in diaphragmatic contraction and restoring normal breathing. The implantation techniques required by the device will be familiar to implanters of cardiac devices and utilizes techniques and catheters similar to those used in CRT. The device is able to stimulate the phrenic nerve next to the vein it is implanted in, resulting in movement of the diaphragm and a breath similar to a normal breath. This allows stabilization of oxygen and CO_2 levels and therefore prevents the next cycle of apnoea/hypopnea from occurring. By stimulating the diaphragm, air is pulled into the lungs similar to normal breathing and avoids the detrimental haemodynamic changes possible with positive airway pressure (*Figure 3*).[119]

In the initial multicentre pilot study of 47 patients with documented CSA, this therapy was found to be safe and effective. There was an improvement in central apnoea index, oxygenation, arousal index, and QoL. The improvement in sleep parameters remained through the 6-month follow-up.[120] Compliance with this therapy is not an issue since the device is implanted, and it initiates and terminates the therapy automatically without patient intervention. Currently, a multicentre, randomized study (The **rem**ede® System Pivotal Trial) is ongoing. Results are expected to be available in 2016.

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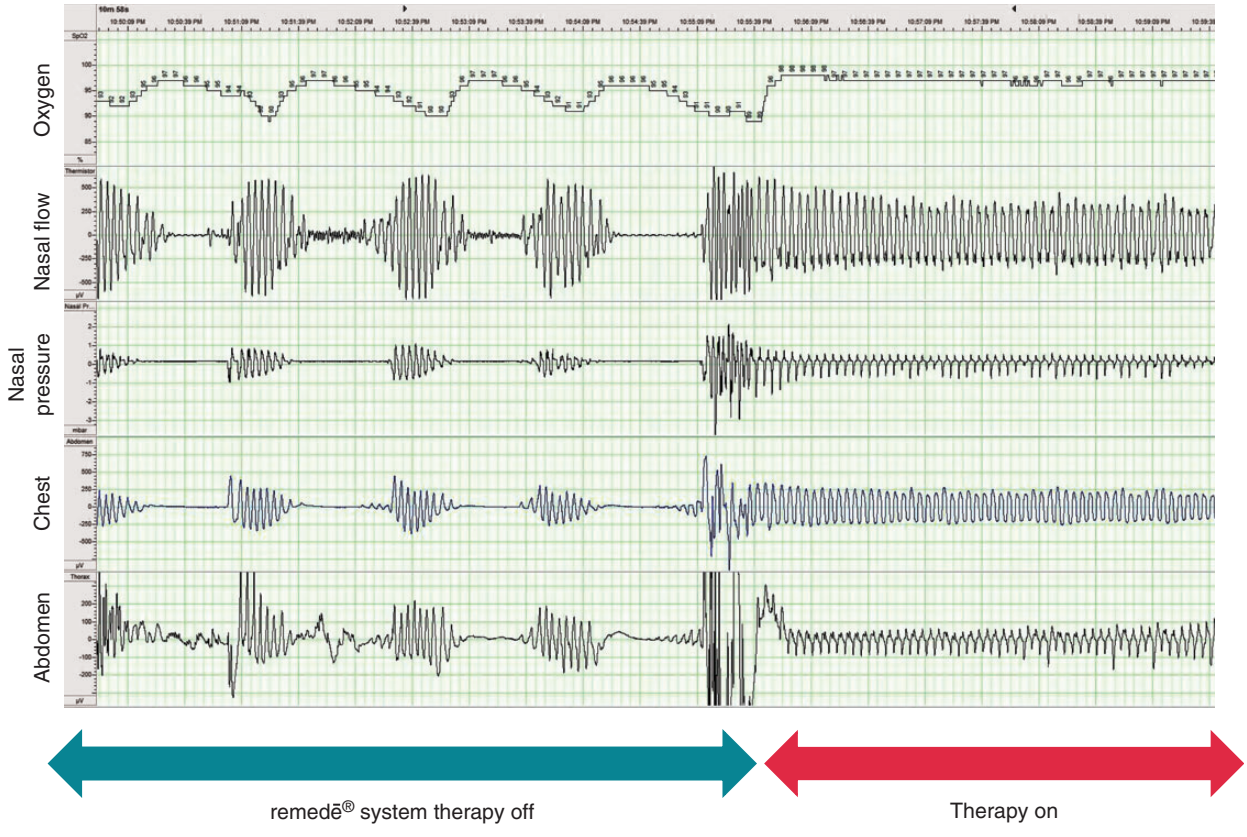

Figure 7 The **rem**ede® system therapy.

Conclusion

Central sleep apnoea is a very common co-morbidity in HF. The Cheyne–Stokes respiration, which is characteristic for CSA in patients with HF, is an independent risk factor for malignant arrhythmias. Unfortunately, CSA often remains unrecognized due to its chronic and insidious nature. A high suspicion of CSA should exist when patients with HF present with symptoms or risk factors of CSA. Recommendations for identifying, testing, and treating patients presenting to the cardiology clinic are shown in *Figure 4*. There is a strong interaction between the mechanisms of HF and CSA leading to the progression and worsening of both diseases. Central sleep apnoea leads to increased morbidity and mortality in HF. Raising the awareness of the prevalence, symptoms, risk factors, and the pathophysiology of this disease among general physicians and cardiologists is important. Identifying and testing for these patients could be done in an outpatient setting. However, PSG, done only in a sleep laboratory, remains the gold standard for identifying patients with CSA. Several studies have been performed in the past aiming to find a therapy for this group of patients. None of these studies thus far have demonstrated reduced mortality or morbidity in HF patients with CSA. As a result, there is currently no recommended therapy for CSA in HF patients. There are currently a few continuing studies in HF patients with positive airway pressure therapies. Transvenous stimulation of the phrenic nerve through the implantation of a pacemaker-like device and an intravenous lead could be the most promising method for treating patients with CSA due to its similar mechanism of action to the physiology of normal breathing (*Figures 5–7*). Results of the Remede® System Pivotal Trial are expected to be available later this year. This could create a new era in treating CSA similar to the one that accompanied the discovery of CRT.

Conflict of interest: Dr. Abraham has received consulting fees from Respicardia, Inc.

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