Management of central sleep apnoea: a review of non-hypercapnic causes

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Shareable abstract (@ERSpublications)
Non-hypercapnic CSA encompasses different aetiologies and pathophysiological mechanisms. Consequently, management requires an individualised approach with consideration of underlying mechanisms, comorbidities and symptoms. https://bit.ly/3B0m8W0

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Abstract

Central sleep apnoea (CSA) is characterised by recurrent episodes of airway cessation or reduction in the absence of respiratory effort. Although CSA is less common than obstructive sleep apnoea, it shares similar symptoms. CSA can be secondary to various medical conditions, high altitude and medication exposure. CSA can also emerge during obstructive sleep apnoea therapy. There are a range of treatment options and selecting the right therapy requires an understanding of the pathophysiology of CSA. This review explores the aetiology, pathophysiology and clinical management of non-hypercapnic CSA.

Introduction

Central sleep apnoea (CSA) is defined as recurrent episodes of cessation or reduction in airflow in the absence of respiratory effort. CSA is not a single disease entity but rather a manifestation of altered central respiratory control *via* different mechanisms. It is typically associated with male gender, older age and more frequently observed in those with underlying medical conditions [1]. In the general population, it is less commonly encountered than obstructive sleep apnoea (OSA) (CSA prevalence of 0.9% *versus* 47.6% for OSA in a cross-sectional analysis of the Sleep Heart Health Study). In this study, it was found that approximately half of the patients with CSA also had Cheyne–Stokes Breathing (CSB) [2].

In certain clinical populations, such as patients with heart failure, post-stroke or with chronic opioid usage, the prevalence of CSA is much higher. In the Sleep Heart Health Study, 4.1% of all patients with a reported history of heart failure had CSA. Interestingly, this occurred exclusively in males with heart failure. Conversely, in the 55 patients in this study who had CSA, 15.1% had a history of myocardial infarction, 18.2% had atrial fibrillation, 7.4% had congestive heart failure, 7.3% had a history of stroke and 5.5% had a history of opioid usage [2]. Although there is polysomnographic distinction between CSA and OSA, they can occur within the same patient as there is pathophysiological overlap [3]. This is especially the case in patients with heart failure, with 12.2% demonstrating evidence of predominant OSA with a CSA component [2].

In contrast to OSA, the clinician encounters a greater degree of complexity in the assessment and management of CSA. The diagnostic process requires investigation of underlying medical causes and effective treatment remains an area of ongoing study with evolving literature. This review explores the classification, pathophysiology, clinical aspects and management of CSA, focusing on the non-hypercapnic form.

Aetiology and classification

The International Classification of Sleep Disorders (third edition) (ICSD-3) classifies CSA based on the polysomnographic finding of central apnoeas and the presence of underlying comorbidities [4]. Table 1

TABLE 1 ICSD-3 classification of CSA subtypes

Subtype	Additional comments
CSA with CSB	Typically associated with heart failure
CSA due to medical disorder without CSB	
CSA due to high altitude periodic breathing	Typically at an altitude of 2500 m, but can occur at 1500 m
CSA due to medication or substance	Opioids, sodium oxybate, baclofen, gabapentin, valproic acid, ticagrelor
Primary CSA	
Primary CSA of infancy	
Primary CSA of prematurity	
Treatment-emergent CSA	

ICSD-3: International Classification of Sleep Disorders (third edition); CSA: central sleep apnoea; CSB: Cheyne–Stokes breathing.

outlines the subtypes of CSA as defined by ICSD-3. Terms like CSB and periodic breathing denote a crescendo–decrescendo breathing pattern characterised by alternating periods of reduced tidal volumes followed by hyperventilation.

One of the issues highlighted regarding the ICSD-3 classification of CSA is its limited correlation with underlying pathophysiological causes and the frequent coexistence of multiple comorbidities within the same individual [5]. A recently proposed classification subdivides CSA aetiologies based on their underlying pathophysiological mechanisms, such as increased controller gain, increased plant gain, failure of rhythm generation and other [6].

The hypercapnic form of CSA, which falls in the category of increased plant gain, is less common and characterised by a reduced response of the central respiratory control centres to arterial carbon dioxide (CO_2) levels. It is seen in alveolar hypoventilation syndromes, such as COPD, neuromuscular diseases and chest wall deformity. In contrast, the non-hypercapnic form of CSA is thought to be a manifestation of instability in the ventilatory control pattern, with an exaggerated response to arterial CO_2 levels causing a crescendo–decrescendo oscillation seen classically in CSB [7]. The latter category will be the focus of this review. Table 2 summarises the hypercapnic and non-hypercapnic causes of CSA.

Pathophysiology

The mechanisms leading to CSA are heterogeneous, given its different aetiologies. They may be broadly categorised as either a reduced ventilatory drive or a paradoxically excessive drive leading to increased loop gain [8]. The pathophysiology may be conceptualised by viewing the respiratory control system as a closed feedback loop. Simplistically, this loop comprises the respiratory control centre in the pons and medulla, chemoreceptors in the carotid bodies and medulla (the “controller”), the lungs (the “plant”), and the bloodstream connecting the circuit (“mixing”) [9].

There are multiple components to central respiratory control. The ventral surface of the medulla contains chemoreceptors which sense pH changes in the central nervous system in response to CO_2 levels. The pre-Bötzinger complex in the medulla functions to ensure a smooth transition between inspiration and expiration [10]. The cerebral cortex is responsible for the wakefulness drive to breathe that is independent of metabolic influences [11]. Opioids inhibit the respiratory neurons in the pre-Bötzinger complex, resulting in impairment of rhythm generation and ataxic breathing [6].

TABLE 2 Causes of central sleep apnoea (CSA) based on hypercapnic and non-hypercapnic categories

Hypercapnic	Non-hypercapnic
Neuromuscular disease	Cheyne–Stokes breathing in heart failure
COPD	Idiopathic CSA syndrome
Chest wall deformity	High altitude periodic breathing
Obesity hypoventilation syndrome	Treatment-emergent CSA
Brainstem pathology	Primary CSA

In a healthy respiratory control system, changes in arterial oxygen and CO_2 tension are swiftly detected by chemoreceptors, eliciting proportional ventilatory signals from the respiratory control centre. Subsequently, the gas exchange system responds appropriately to restore normal arterial gas tensions. Any aberrations from these responses introduce instability into the feedback loop [8].

Central apnoeas typically occur in non-rapid eye movement (NREM) sleep. During sleep–wake transition, there is a loss of the wakefulness drive to breathe from suprapontine influences. Consequently, ventilation during sleep is primarily driven by arterial CO_2 tension. NREM sleep also unmasks the hypocapnic apnoeic threshold, the arterial CO_2 tension level below which central apnoea occurs [12]. A small drop in arterial CO_2 tension of 3–5 mmHg below baseline levels is enough to surpass the apnoeic threshold, leading to central apnoeas [6].

Following the occurrence of central apnoeas are oxygen desaturations and/or cortical arousals. Arousals from a sleep state conversely increase chemosensitivity and the ensuing ventilatory response to hypoxia, resulting in an exaggerated lowering of arterial CO_2 levels, which perpetuate further central apnoeas and ventilatory instability if below the apnoeic threshold upon resumption of sleep [6].

In disease states related to non-hypercapnic CSA, central apnoeas occur as cycles of apnoea/hypopnoea alternating with hyperpnoea due to ventilatory instability. This ventilatory instability can be based on the mathematical model of loop gain, which is calculated as the ratio of the magnitude of response to a disturbance (*i.e.* ventilatory response) to the magnitude of the disturbance itself (*i.e.* hypercapnia or hypoxia). In a healthy homeostatic process, the ratio is maintained at <1 to allow for a return to a steady state. However, when the loop gain is ⩾1 there is an overshoot in ventilatory response, leading to hypocapnia and ventilatory instability. Loop gain can further be broken down into three components: controller gain, which is the ventilatory response generated; plant gain, which is the change in arterial CO_2 tension in response to the change in ventilation; and mixing gain, which represents circulatory time [6, 13].

Congestive cardiac failure is a hallmark example of a condition leading to non-hypercapnic CSA from high loop gain (summarised in figure 1). Individuals with heart failure demonstrate increased controller gain and

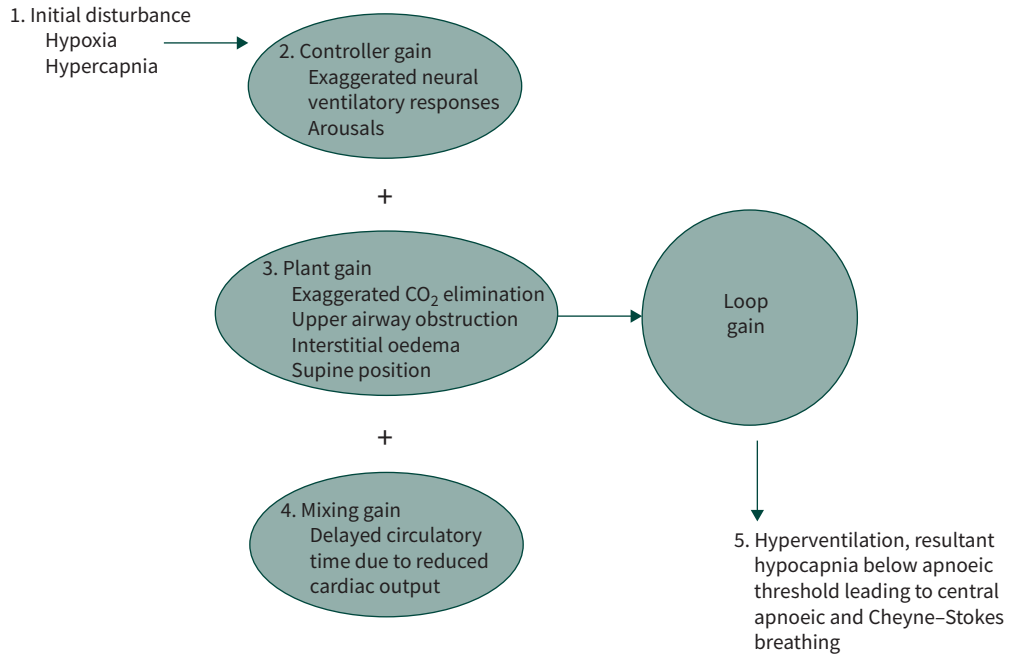

FIGURE 1 Loop gain and its components in the context of heart failure. 1) Initial disturbance such as pulmonary oedema, hypoxia in heart failure. 2) Controller gain represents sensitivity of chemoreceptors to blood gas aberrations. 3) Plant gain represents the efficiency of the lungs in clearing carbon dioxide. This may be amplified by upper airway obstruction, interstitial oedema or other factors that reduce functional residual capacity, such as supine positioning. 4) Mixing gain represents delayed circulation from reduced cardiac output leading to prolonged aberrant physiological responses. 5) Increased ventilatory responses lead to decrease of arterial carbon dioxide below the apnoeic threshold. This results in central sleep apnoea as a result of hypocapnia, leading to hypoxaemia, arousals and further ventilatory instability.

chemosensitivity [6]. This is characterised by excessive ventilation and CO_2 removal during arousals. When the CO_2 levels fall below the apnoeic threshold upon resumption of sleep, this causes central apnoeas to occur. Another important factor is a circulatory delay between the gas exchange system and central chemoreceptors due to reduced cardiac ejection fraction, leading to prolonged ventilatory instability [11]. This is termed mixing gain and the prolonged circulatory time due to reduced cardiac output causes prolonged cycles of recurrent apnoeas and hyperpnoeas known as the CSB pattern. CSB cycle length is correlated with ejection fraction measured on echocardiography [14].

Plant gain is also shown to be increased in patients with heart failure and CSB [15], and proposed mechanisms for this increased CO_2 elimination include reduced functional residual capacity from interstitial oedema and reduced metabolic rate [16]. Body position also has an impact on plant gain, and supine sleep has been associated with increased plant gain due to rostral fluid shifts into the thorax and neck causing reduced functional residual capacity of the lung and increased upper airway resistance [6].

Clinical features and diagnosis

Clinically, CSA is thought to present with similar symptoms to OSA, namely excessive daytime sleepiness, sleep disruption, insomnia and poor concentration. Few studies have quantified the prevalence of these symptoms in CSA. In the Sleep Heart Health study, sleep symptoms were generally less common in the CSA group when compared to the OSA group [2]. In another study, the most common symptoms were daytime sleepiness (43%), snoring (35%) and insomnia (23%), but a significant association between the apnoea–hypopnoea index (AHI) and symptom frequency was not confirmed [17].

Overnight level 1 polysomnography with nasal cannula, thermistor for measuring oronasal flow, and thoracoabdominal bands are required to accurately detect central apnoeas [5]. In a polysomnogram, a central apnoea is scored if the following criteria are met: 1) reduction in peak signal excursion by ⩾90% of pre-event baseline using an oronasal thermal sensor, 2) Duration of ⩾90% drop in sensor signal is ⩾10 s and 3) absence of respiratory effort on thoraco-abdominal bands (as observed in figure 2). Polysomnographic diagnosis of CSA requires an AHI of ⩾5 events per hour, with central events accounting for >50% of all respiratory events. For CSB to be diagnosed, the polysomnogram must demonstrate crescendo–decrescendo events for ⩾3 central apnoeas with a cycle length of ⩾40 s [4] (figure 3). In patients with heart failure, cycle length duration averages ∼60 s and is inversely proportional to cardiac output/left ventricular ejection fraction. This contrasts with other forms of CSA with periodic breathing (idiopathic or high altitude), where the cycle length is shorter [18]. In cases of failure of respiratory rhythm generation (such as in opioid use or brainstem injury), a Biot's breathing pattern (figure 4) can be observed.

CSA management

General management principle

The heterogeneity in pathophysiological mechanisms means no single effective therapy exists for all patients. Hence, treatment strategy requires an individualised approach, taking into consideration the

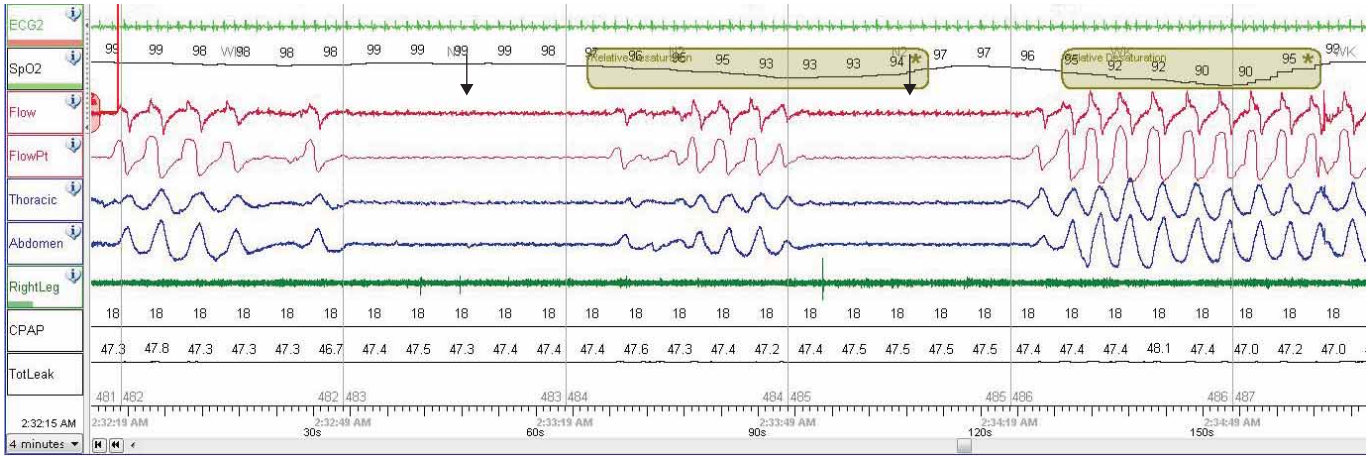

FIGURE 2 4-minute view of polysomnogram demonstrating two episodes of central sleep apnoea during positive airway pressure titration study (black arrows indicate episodes of central apnoea). CPAP: continuous positive airway pressure; Flow: flow measured from CPAP; FlowPt: flow from pressure transducer; S_{pO_2}: peripheral oxygen saturation in %; TotLeak: total leak in L·min^{-1}.

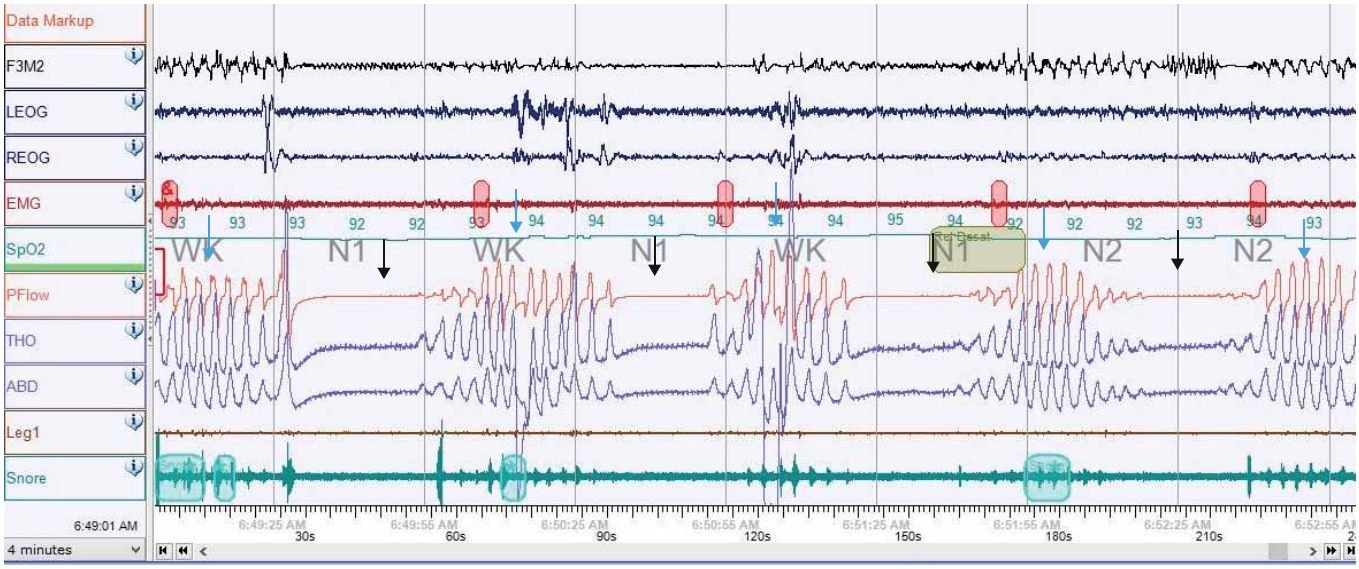

FIGURE 3 4-minute view of polysomnogram demonstrating central sleep apnoea with Cheyne–Stokes breathing (crescendo–decrescendo flow pattern) in a patient with reduced ejection fraction heart failure (black arrows: central apnoeas; blue arrows: crescendo–decrescendo pattern of hyperventilation). F3M2: frontal to mastoid EEG; LEOG: left eye oculogram; REOG: right eye oculogram; EMG: electromyogram; S_{pO_2}: peripheral oxygen saturation in %; PFlow: pressure transducer flow; THO: thoracic; ABD: abdominal; Leg1: anterior tibialis EMG.

patient's underlying aetiology, polysomnographic features, comorbidities and therapeutic goals [3]. An integral component of CSA management in all patients is addressing their underlying cause, including optimising their cardiac failure management and discontinuation/dose reduction of offending medications. In some cases, this may resolve their CSA without further intervention.

There are several CSA-specific therapies available, both pharmacological and non-pharmacological, that target one or more of the CSA pathophysiologies (figure 5). This review will explore treatment options and algorithms for different aetiologies, summarised in figure 6.

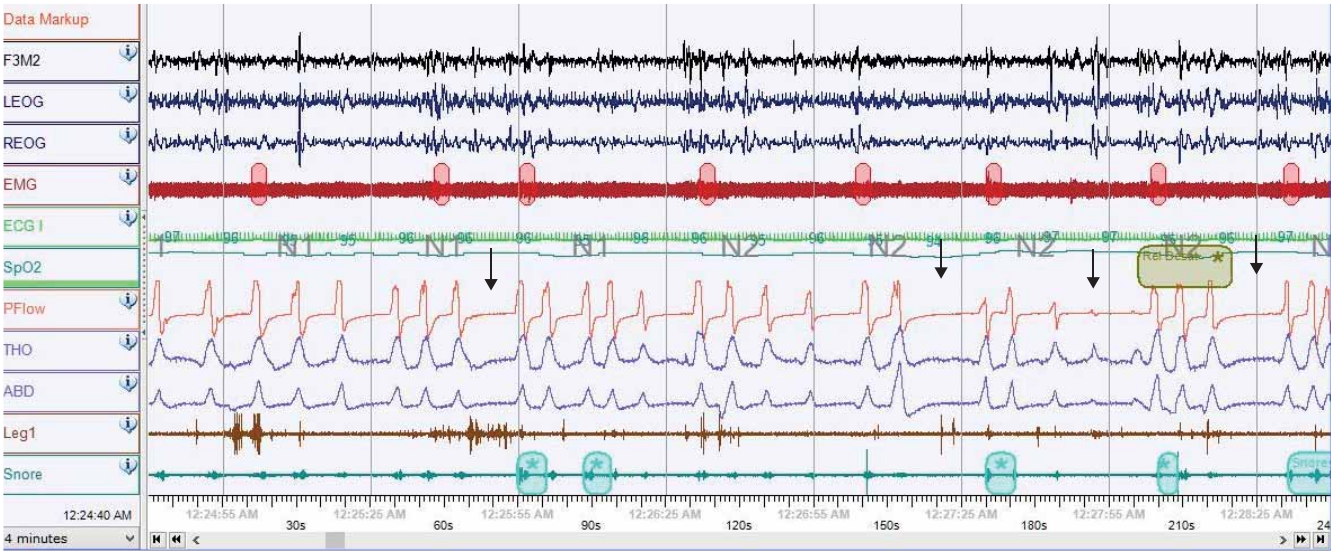

FIGURE 4 4-minute view of polysomnogram demonstrating Biot's breathing with a pattern of random apnoea, variable flow/tidal volume in a patient on long-term opioids (black arrows: central apnoeas; note the irregular breathing rhythm and amplitude between apnoeic episodes). F3M2: frontal to mastoid EEG; LEOG: left eye oculogram; REOG: right eye oculogram; EMG: electromyogram; S_{pO_2}: peripheral oxygen saturation; PFlow: pressure transducer flow; THO: thoracic; ABD: abdominal; Leg1: anterior tibialis EMG.

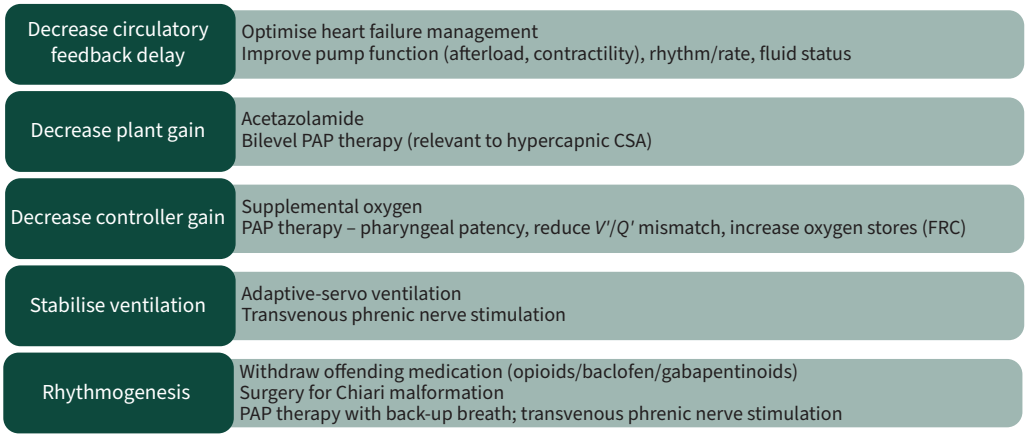

FIGURE 5 CSA therapy options targeting different pathophysiology mechanisms. PAP: positive airway pressure; CSA: central sleep apnoea; *V′*/*Q′*: ventilation/perfusion ratio; FRC: functional residual capacity.

Management of specific CSA syndromes

CSA with CSB

CSA, often with concurrent CSB (a form of periodic breathing with waxing and waning amplitude of flow/tidal volume), can be observed in low cardiac output states including heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF; impaired cardiac filling/relaxation) and cardiac arrhythmia. Heart failure is the most associated condition among patients with CSA. The rates of CSA are higher among patients with worse cardiac function as well as during acute exacerbation of their heart failure. CSA is associated with worse outcomes among the heart failure population [19]. It is unclear if CSA is an independent pathological factor (increased sympathetic drive from repeated arousals and nocturnal hypoxaemia) or merely reflects a marker of poor cardiac function.

Optimisation of heart failure therapy should be incorporated in all patients with cardiac dysfunction as it has been shown to improve CSA among other clinical outcomes, such as cardiac function, cardiovascular-related mortality and overall quality of life. This includes β-blockers to reduce sympathetic nervous activity, angiotensin-converting enzyme-inhibitor to reduce ventricular afterload and blockade of the renin–angiotensin system, diuretics to reduce pulmonary venous congestion and appropriate rate/rhythm control of atrial fibrillation. Heart failure patients with ventricular conduction delay can also benefit from cardiac resynchronisation therapy, which has improved cardiac function and reduced CSA–CSB severity. In patients who are appropriate for heart transplantation, CSA–CSB improves after transplantation.

In patients who have had inadequate response to heart failure optimisation, the next line of therapy is continuous positive airway pressure (CPAP) therapy. Potential beneficial mechanisms of CPAP therapy in this group of patients include prevention of pharyngeal narrowing, dampening of ventilatory overshoot (addressing the co-occurrence of CSA and OSA), improved functional residual capacity and oxygenation, reduction of pulmonary congestions and vagal receptor activation. Bradley *et al.* [20] randomised heart failure patients with CSA to CPAP or usual care with a mean follow-up of 2 years. There was a small improvement in left ventricular ejection fraction (LVEF), exercise tolerance and catecholamine levels in the CPAP arm relative to control. However, there was no statistical difference in transplant-free survival, the primary endpoint. The CPAP therapy was not titrated (10 cmH_2O or maximum pressure tolerated), and although the mean AHI improved in the CPAP arm, it did not normalise [20]. A subsequent *post hoc* analysis showed that among subjects of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP) with CSA syndrome that were adequately controlled with CPAP therapy (AHI <15 events per h), the transplant-free survival and LVEF were better than in non-suppressed and control subjects [21].

Adaptive servo ventilation (ASV) initially offered an effective therapeutic option in CSA with or without CSB in heart failure patients as it was specifically designed to treat people with CSA and is shown to be more effective than CPAP in reducing AHI [22]. Using computer-controlled algorithms, it provides variable ventilation/pressure support that is anti-cyclic to the patient's respiratory drive – it delivers minimal support during the hyperventilatory phase and increases ventilation during the apnoeic phase.

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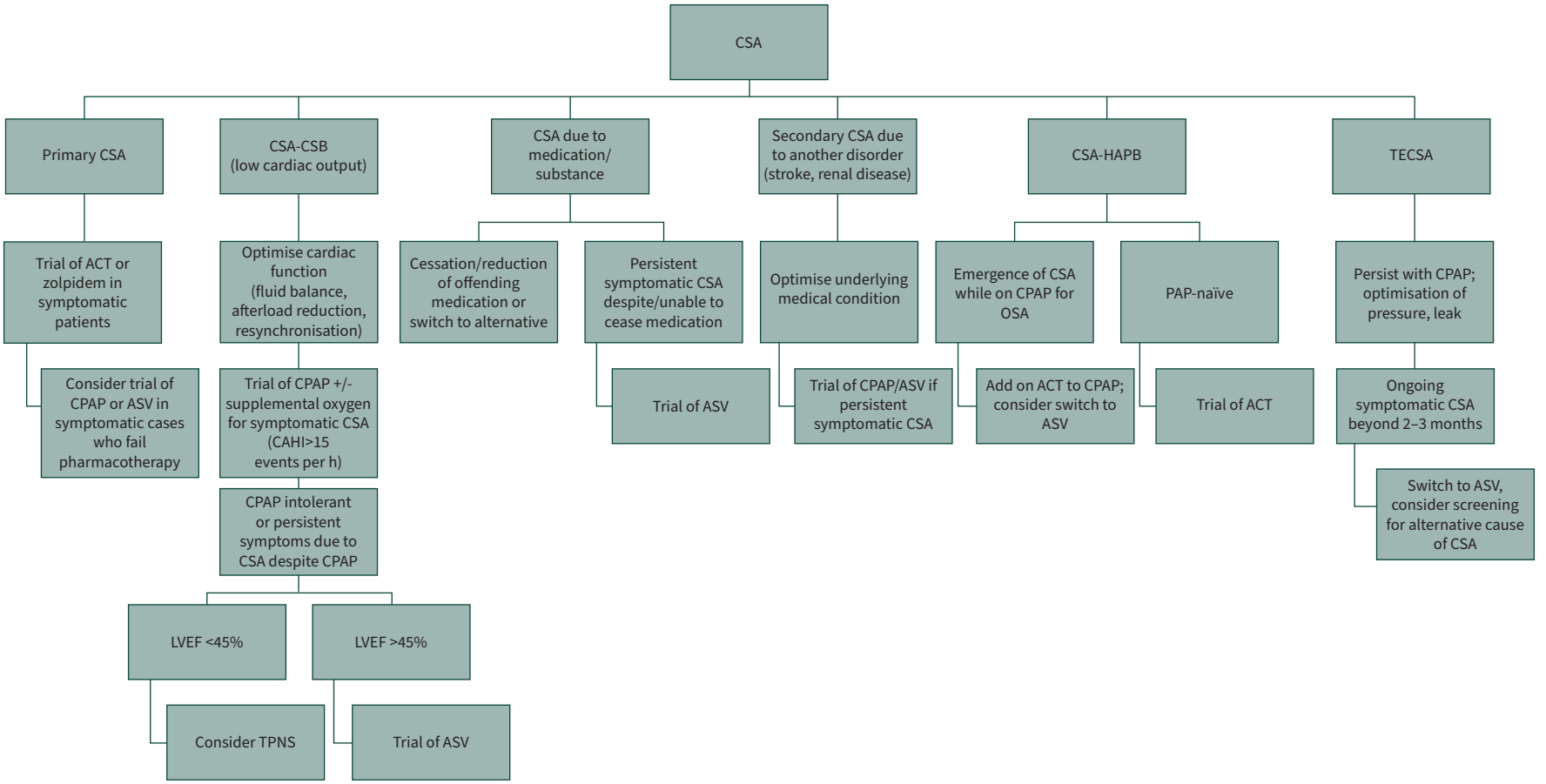

FIGURE 6 Summary of therapeutic algorithm based on European Respiratory Society taskforce [5]. CSA: central sleep apnoea; CSB: Cheyne–Stokes breathing; HAPB: high altitude periodic breathing; TECSA: treatment-emergent CSA; ACT: acetazolamide; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea; PAP: positive airway pressure; ASV: adaptive servo ventilation; CAHI: central apnoea–central hypopnoea index; LVEF: left ventricular ejection fraction; TPNS: transvenous phrenic nerve stimulators.

Overall, it dampens respiratory drive oscillation that leads to CSA and CSB, allowing ventilatory stability. ASV was considered as an alternative to CPAP therapy or as a second-line option in patients who did not respond to (high residual events or symptoms) or could not tolerate CPAP therapy.

However, a subsequent study sponsored by ResMed using one of the earlier models of ASV (fixed expiratory positive airway pressure (EPAP)) identified increased mortality when used in CSA patients with symptomatic heart failure with reduced LVEF (<45%) [23]. Around 1300 subjects were randomised to either ASV or usual medical therapy. Both intention-to-treat and on-treatment analyses showed similar outcomes of increased cardiovascular and all-cause mortality in the ASV arm. Mortality rates were higher among those with lower LVEF and patients who previously had not been hospitalised. The study also did not show improvements in LVEF or symptoms with ASV therapy [23].

Although there are various proposed explanations for the increased mortality risk associated with ASV, it is not clear whether the unanticipated finding is due to the specific device/algorithm (whether fixed EPAP and mandatory pressure support lead to over-ventilation, alkalosis or undertreated OSA) or related to the general design of ASV (suppressing CSA is harmful in HFrEF, deleterious effects of preload reduction) or unintended differences in study arms (higher use of antiarrhythmics in the ASV arm).

Nonetheless, after the SERVE-HF (Treatment of Predominant Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure) trial, ASV is no longer recommended in CSA–CSB among heart failure patients with LVEF <45% [24]. ASV devices were recalled in patients with HFrEF, but some opted to continue with ASV therapy due to symptomatic benefits. The decision to persist with ASV in this cohort of patients needs to be balanced with symptom benefits and the severity of systolic dysfunction (subgroup analysis suggests high mortality among those with LVEF <30%) in shared decision-making between the clinician and patient.

In CSA patients secondary to low cardiac output but with preserved ejection fraction, the impact of ASV on mortality is less clear. Subjects with preserved LVEF appear to have better outcomes in subgroup analysis from the CAT-HF (Cardiovascular Improvements With MV ASV Therapy in Heart Failure) trial [25], which recruited hospitalised patients with heart failure (including HFrEF and HFpEF patients). The trial was stopped early as the SERVE-HF trial results were released during recruitment. There was no difference in the combined primary endpoint. In HFpEF, ASV can still be considered in instances of CPAP failure to treat CSA–CSB.

Recently, another ASV (with variable EPAP) trial included HFrEF patients (LVEF <45%) with sleep disordered breathing (AHI ⩾15 events per h, combination of OSA and CSA) randomised to either standard optimal treatment or with the addition of ASV [26]. The participants were stratified by sleep apnoea type, and the primary endpoint was a composite of all-cause mortality, cardiovascular hospitalisation, new-onset atrial arrhythmia and delivery of defibrillator shock. Unfortunately, enrolments were terminated prematurely due to a combination of factors (coronavirus disease 2019, poor recruitment rates/site withdrawal after the outcome of SERVE-HF, and device recalls due to sound-ablation material). ASV improved mean AHI but did not influence the primary composite outcome. However, at least no safety concerns or increased harm were observed in the CSA subgroup [26].

The partial efficacy of CPAP therapy and mortality concerns from ASV have left a treatment gap in CSA–CSB in the setting of HFrEF. Transvenous phrenic nerve stimulator (TPNS) offers an alternative method to regulate breathing and stabilise CO_2 levels while bypassing the surgical risk seen in intrathoracic stimulator implantation. TPNS are implantable devices designed to treat moderate-to-severe CSA [22]. The devices have three components: a pulse generator/battery implanted below the clavicle; a stimulation lead placed in the left pericardiophrenic or right brachiocephalic vein that drives inspiration by activating the diaphragm *via* the phrenic nerve; and a sensing lead in the azygous system near the diaphragm to help titrate the amplitude of the stimulation. The device can be programmed to turn on during sleeping hours with additional activation criteria of the patient being in a reclined position and not moving [22]. The *post hoc* analysis of the CSA subgroup with heart failure from the remedé System Pivotal Trial (CSA with AHI >20 events per h, 1:1 randomisation to stimulation or no stimulation post TPNS implantation) showed improvement in sleep metrics from baseline (55% reduction in AHI after 3 months of therapy) and trends towards improved LVEF and time to first hospitalisation with no increased mortality [27]. Improvements in sleep metrics (CSA severity, arousals, hypoxaemia) and quality of life assessments (including Patient Global Assessment and Epworth Sleepiness Score) were sustained at 12 months [28]. The treatment was generally well tolerated, with a reported serious adverse event rate of 6%. Currently, TPNS is considered an option for symptomatic CSA in patients who fail or do not tolerate CPAP therapy.

Nocturnal oxygen therapy (NOT) is also an alternative in HFrEF with CSA, and may be better accepted in patients who cannot tolerate positive airway pressure (PAP) mask interfaces. Supplemental oxygen can mitigate the severity of hypoxaemia, decrease ventilatory response to CO_2 and reduce post-apnoeic ventilatory overshoot [3]. The data on NOT is limited and from heterogeneous study designs. It appears to, on average, reduce AHI by 50% (range: −28% to −84%). Long-term safety data on NOT use in heart failure patients is lacking. As upper airway obstruction is a triggering factor in generating CSA episodes, other methods to reduce upper airway collapsibility, such as positioning devices or elevating the head of the patient's bed, can also be considered as non-PAP alternatives.

Primary CSA

As most CSA is secondary to other medical conditions, there is a paucity of evidence to guide best practice. Only five studies address therapeutic interventions for primary CSA. Most of these studies are small, non-randomised trials examining four therapeutic options (acetazolamide, zolpidem, triazolam and CO_2) [29].

Acetazolamide induces metabolic acidosis through inhibition of renal carbonic anhydrase. The increased ventilation drive lowers blood CO_2 and causes a left shift of the hypercapnic ventilatory response (lowering plant gain). Acetazolamide reduces oscillations of corrective breathing actions post-apnoea, potentially widening the difference between eupnoeic and apnoeic threshold arterial CO_2 tension. Serious adverse events are rare, while common side-effects such as paraesthesia, taste disturbance and fatigue appear dose-dependent [30]. Acetazolamide at 250 mg·day^{-1} significantly reduced AHI and improved daytime sleepiness. A separate study using a higher dose of acetazolamide (1000 mg·day^{-1}) also demonstrated a decrease in the central apnoea index. Both studies only reported short-term outcomes (1 month and 1 week of therapy, respectively) [29].

Although zolpidem and triazolam demonstrated reductions in central AHI in patients with primary CSA syndrome, the underlying therapeutic mechanism is not answered. Their actions on the γ-aminobutyric acid-A receptors, which may be relevant to CSA, include elevating baseline CO_2 tension, diminishing arousals and modifying ventilatory responsiveness [29].

A small study of six patients demonstrated a significant reduction in AHI by increasing CO_2 (administered gas or adding dead space) and dampening breath-to-breath oscillations of end-tidal CO_2. However, for reasons mentioned earlier, supplemental CO_2 is not an available treatment for clinical use [29].

There are limited data on PAP therapy in primary CSA with only case reports published. Both CPAP and ASV can be considered in symptomatic patients [5].

CSA due to medication or substance use

Recognition of medication-induced CSA, which is sometimes misclassified as primary CSA, is an important first step in its management, as withdrawal of the offending medication will reverse the disorder. The effects of opioids are among the best-known class of medication that can cause CSA, with respiratory depression mediated *via* the μ-receptors in the pontomedullary respiratory centre. It leads to a unique pattern of ataxic breathing where there is intermittent failure of impulse transmission from central pattern generators to the phrenic and intercostal nerves. Several non-opioid medications can contribute to CSA (listed in table 1), often *via* γ-aminobutyric acid-B receptors in the brainstem. The pattern and mechanism probably resemble that of opioid effects on the μ-receptors and likely also reduce hypercapnic ventilatory response. Ticagrelor has an entirely separate mechanism. It raises the tissue-level adenosine, which increases the slope of the hypercapnic ventilatory response, resulting in a CSA pattern similar to heart failure (*i.e.* with CSB) [5].

Treatment involves cessation of the offending drug and switching to an alternative (*i.e.* an alternative anti-platelet or anti-epileptic drug). When this is not possible, treatment with ASV devices has shown success in case studies. There are also proof of concept pharmacology studies that have shown improvements in CSA severity with changing methadone to buprenorphine/naltrexone (more κ-selective and less effect on μ-receptors) [31] and theophylline (competes for adenosine receptors with ticagrelor) [5].

CSA due to high altitude periodic breathing

High altitude can promote respiratory instability during sleep (also known as high altitude periodic breathing (HAPB)). Hypoxaemia and respiratory alkalosis are the primary factors leading to increased loop gain [32]. HAPB may be observed in altitudes >1600 m in healthy subjects, and the rates increase with

increasing altitude. Although acclimatisation will reduce the risk of other altitude-related illnesses, it does not necessarily improve HAPB [5], even among healthy individuals born at high altitudes.

Several studies have investigated the effectiveness of acetazolamide, which is already indicated to assist with altitude acclimatisation and address HAPB in healthy subjects and those with OSA [33]. Meta-analysis data indicates the beneficial effects of acetazolamide in nocturnal hypoxaemia, periodic breathing time and AHI, potentially more apparent in healthy subjects and even at relatively small oral doses of 250 mg per day [33]. There are also limited data regarding dexamethasone (which can reduce high-altitude pulmonary oedema) and oxygen enrichment [5]. ASV, however, was not demonstrated to significantly improve HAPB in one study [34].

In patients with OSA, central events not addressed by their CPAP device can emerge. Adding acetazolamide (750 $mg \cdot day^{-1}$) to auto-titrating CPAP improved nocturnal oxygen saturation and better controlled sleep disordered breathing than auto-titrating CPAP alone [35].

Treatment-emergent CSA/complex sleep apnoea

Patients with primarily OSA can go on to demonstrate CSA during CPAP titration studies, reported rates range from 0.5 to 20% [36]. The emergence or persistence of CSA during therapy for upper airway obstruction (often associated with CPAP, but can also occur with non-PAP OSA treatment modalities) is termed complex sleep apnoea or treatment-emergent CSA (TECSA). The underlying mechanism is likely due to unmasking or enhancing a high chemoreflex sensitivity upon relief of inspiratory flow limitation activation of pulmonary stretch receptors. This results in increased ventilation and lowers the CO_2 below the apnoeic threshold. This phenomenon is associated with reduced adherence and observed more frequently in comorbid cardiac disease, male gender, OSA severity, and mixed apnoeas in the initial study [37]. There is a possibility that there may be an alternative cause that was revealed by CPAP therapy, and further clinical assessment should be considered.

In most instances, the frequency of central events improves with time without the need to switch out CPAP therapy, while avoiding excessive titration, mask leak minimisation and optimising other sleep disorders contributing to arousals (insomnia, sleep insufficiency). In ∼30% of patients with persistent CSA at 90 days, CPAP can be switched to ASV or bilevel PAP spontaneous/timed modes to reduce AHI and improve adherence (ASV appears superior to bilevel PAP due to sustained response). There is no randomised control trial in this area, and further research is needed to identify patients likely to benefit from early switching to ASV. Enhanced expiratory rebreathing space may also be a solution as it prevents all the exhaled air from being vented through the CPAP mask. The rebreathing of air with higher CO_2 content can reduce plant gain and the patient's risk of reaching the apnoeic threshold [38].

Summary

Although non-hypercapnic CSA has shared polysomnographic features, it encompasses multiple aetiologies with differing contributing pathophysiological mechanisms. Understanding the underlying pathophysiology leading to the development of CSA in each case is vital in tailoring appropriate therapy. The general principle of treating the underlying cause applies to all cases, but beyond that, deciding on further CSA-specific therapy is more nuanced. In addition to considering the driving pathophysiology, patient symptoms, treatment goals, comorbidities (in particular cardiac function), and disease trajectory are important factors in determining optimal management.

Key points

- CSA is not a single disease entity but encompasses a range of aetiologies with different underlying pathological mechanisms.
- Treatment should be individualised, taking into account a patient's symptoms, contributing comorbidities, likely mechanism of CSA, polysomnographic features and therapeutic goals.
- An integral component of CSA management in all patients is addressing their underlying cause.
- There are a range of pharmacotherapy, PAP and implantable device options available. Although they may improve sleep parameters and symptoms, none have demonstrated a mortality benefit.

Recommended reading

- Donovan LM, Kapur VK. Prevalence and characteristics of central compared to obstructive sleep apnea: analyses from the Sleep Heart Health Study cohort. *Sleep* 2016; 39: 1353–1359.

- Randerath W, Verbraecken J, Andreas S, *et al*. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. *Eur Respir J* 2017; 49: 1600959.
- Javaheri S, Badr MS. Central sleep apnea: pathophysiologic classification. *Sleep* 2023; 46: zsac113.
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Self-evaluation questions

1. Which of the following is true regarding CSA management in heart failure?
    a) ASV is contraindicated in heart failure with preserved ejection fraction (LVEF >45%).
    b) TPNS improves sleep metrics, quality of life and reduces hospitalisation at the cost of increases in mortality in the CSA subgroup with heart failure.
    c) Spontaneous mode bilevel PAP therapy is the preferred next option in CSA patients with heart failure who fail to improve or tolerate CPAP therapy.
    d) Optimising cardiac function is paramount and should be first-line therapy in all patients with CSA in the setting of heart failure.
2. Which of the following is correct with respect to management options for CSA?
    a) Bilevel PAP is an effective treatment modality in both hypercapnic and non-hypercapnic CSA.
    b) CPAP can improve CSA in a portion of patients, mechanisms of action include improving upper airway patency, hypoxia and reducing plant gain.
    c) Pharmacotherapy options such as acetazolamide, theophylline and sedatives improve CSA by increasing ventilatory threshold and are effective options for most types of CSA.
    d) TPNS stimulate the phrenic nerve and is an effective option in TECSA patients who cannot tolerate PAP therapy.
3. Which of the following is correct regarding CSA aetiology?
    a) A secondary cause is only identified in 50% of CSA cases.
    b) Only CPAP, not other OSA treatment modalities, leads to TECSA.
    c) Concurrent CSB suggests a non-cardiogenic cause of CSA.
    d) Medication induced CSA often involves the inhibition of rhythmogenesis in the pre-Bötzinger complex.
4. CSA is more likely to be observed in which of the following scenarios?
    a) Supine position more than non-supine position
    b) REM sleep more than NREM sleep
    c) Pre-menopausal females more than males
    d) Sea level more than high altitude

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Suggested answers

1. d) is correct as improving cardiac function may also reduce CSA burden. a) is incorrect as ASV is contraindicated in heart failure with reduced ejection fraction and may still be considered an option in

those with preserved ejection fraction. b) is incorrect as no increase in mortality was demonstrated in TPNS data thus far. c) is incorrect as spontaneous mode bilevel will worsen CSA.

2. b) is correct. Bilevel is generally not favoured in non-hypercapnic CSA (a) is incorrect). Pharmacotherapies have different mechanisms and in most CSA scenarios, only acetazolamide is considered a PAP alternative or adjunct treatment option (c) is incorrect). TPNS may worsen OSA and is contraindicated in patients with significant OSA (d) is incorrect).
3. d) is correct, most medications other than ticagrelor have a shared mechanism (*via* pre-Bötzinger complex in the medulla). a) is incorrect as most CSA is secondary. b) is incorrect as other OSA therapy modalities can also lead to TECSA. c) is incorrect as CSB suggests a cardiogenic cause of CSA.
4. a) is correct. CSA is more common in men, older age, comorbidities, at higher altitudes and more frequent in NREM sleep (stages 1 and 2) in the supine position (consequences of upper airway narrowing).