

Idiopathic Central Sleep Apnea



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KEYWORDS

• Idiopathic central sleep apnoea • Loop gain • Cheyne Stokes respiration

KEY POINTS

- Central sleep apnea (CSA) can be characterized as either *persistent hypoventilation* with hypercapnia (eg, motor neurone disease) or *periodic hyperventilation* followed by a central apnoea associated with normal or reduced CO₂ (eg, opioids, idiopathic, and heart failure).
- Nonhypercapnic CSA, including idiopathic central sleep apnoea (ICSA), occur due to derangements in ventilatory control.
- ICSA describes periodic, nonhypercapnic CSA that occurs in the absence of an identifiable etiology.
- Polysomnographic features in ICSA include short-cycle length central apneas. Arousals have been noted to occur at the termination of the apnoea, rather than the peak of the hyperpnea.
- The natural history of CSA, and consequently the implications of suppressive treatment, is not well-understood.
- We recommend treatment of ICSA focus on identification and reversal of any metabolic/physiologic derangement, monitoring of symptoms and consideration of referral to an expert center.

INTRODUCTION

Central sleep apnea (CSA), a form of sleep disordered breathing, in which there is a failure to drive ventilation. It can be either hypercapnic related to persistent and prolonged hypoventilation or normohypocapnia associated with periodic hyper then hypoventilation with a cycle length (ventilation and apnea periods) usually less than 90 seconds.¹

Hypercapnic CSA occurs in patients who have persistent and prolonged hypoventilation over days, weeks or years. Etiology of such include primary neuromuscular disorders (eg, motor neurone disease), obesity hypoventilation syndrome, diaphragm palsy or chest wall deformity (eg, kyphoscoliosis). Hypercapnic CSA will not be discussed further in this article.

Periodic nonhypercapnic CSA most commonly occurs in the setting of heart failure, opioid analgesic use, continuous positive airway pressure

(CPAP) therapy (treatment emergent) or at high altitude in healthy subjects.²

Idiopathic central sleep apnea (ICSA) represents a rare subset of CSA patients with no discernible etiologic factor. These patients have a distinct clinical presentation, epidemiology and natural history. The American Academy of Sleep Medicine (AASM) divides CSA into 6 categories (**Box 1**).³ The biggest group among this is Cheyne-Stokes respiration with CSA (CSR-CSA), the majority of cases of which occur in the setting of cardiac failure.

Specifically, nonhypercapnic CSA is characterized by at least 5 consecutive crescendo—decrescendo patterns of ventilation each followed by a central apnea or hypopnea lasting greater than 10 seconds duration. It is this nonhypercapnic CSA that this article will focus upon.

As will be discussed later, CSA is not a result of upper airway collapse and obstruction as seen with obstructive sleep apnoea.

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Abbreviations	
AASM	American Academy of Sleep Medicine
ASV	adaptive servoventilation
CSA	central sleep apnea
CSR-CSA	Cheyne-Stokes respiration with CSA
DLCO	diffusing capacity for carbon monoxide
ESS	Epworth Sleepiness Score
FRC	functional residual capacity
GABA	gamma-aminobutyric acid
ICSA	idiopathic central sleep apnea
NIV	noninvasive ventilation
PSG	Polysomnogram
TE-CSA	treatment-emergent CSA
TLC	total lung capacity

EPIDEMIOLOGY

The overall prevalence of nonhypercapnic CSA is significantly higher in men than in women. The reasons for this are not entirely clear. It is plausible that higher average inspiratory muscle strength in men may allow the development of hyperpneas; however, this hypothesis has not yet been tested. It is noted that altitude related periodic breathing occurs to a greater degree, and at a lower altitude, in men compared to women.^{4,5}

PATHOPHYSIOLOGY OF NONHYPERCAPNIC CENTRAL SLEEP APNEA

All forms of CSA appear to share a common underlying pathophysiology. This is mediated by 2 primary factors—the apneic threshold and loop gain.

Apnoeic Threshold

In the absence of chronic hypercapnia, ventilation is driven primarily by arterial carbon dioxide levels (P_{aCO_2}). In healthy subjects during wakefulness, profound hyperventilation results in hypocapnia and thereby apnea, due to P_{aCO_2} drifting below the *apneic threshold*.⁶

Box 1
American Academy of Sleep Medicine International Classification of Sleep Disorders for Central Sleep Apnoea
Primary CSA
CSA with Cheyne-Stokes breathing (CSR)
CSA due to a medical disorder without CSR
CSA due to high-altitude periodic breathing
CSA due to a medication or substance
Treatment-emergent CSA (TE-CSA)

During rapid eye movement (REM) sleep however, multiple factors beyond a metabolic (P_{aCO_2}) drive are responsible for the control of ventilation. This helps explain the irregular rate and tidal volume characteristic of REM sleep.

In contrast, in NREM sleep (especially stage NREM 1 and 2) ventilation is controlled tightly by metabolic drive, most understandably by the prevailing P_{aCO_2} level. As such, the significance of the apneic threshold is magnified in NREM sleep. During normal NREM sleep, P_{aCO_2} increases by up to 3 mm Hg. Normal subjects who are mechanically ventilated demonstrate apneas with modest increases in minute ventilation and reduction of P_{aCO_2} back to waking levels.⁷ There also appears to be a more abrupt loss of motor output below the apneic threshold in NREM sleep compared to wakefulness.⁸

These phenomena are mediated by the central and peripheral (carotid body) chemoreceptors. Animal studies suggest that while both central and carotid body chemoreceptor stimulation is required to produce apnea, the effect of hypocapnia on carotid body chemoreceptors is more potent.⁹

Loop Gain

The development of CSA is critically dependent upon a degree of instability in the ventilatory control system. The engineering concept of *loop gain* has been used to describe this, as the ratio of response to a trigger.⁹ High loop gain describes a ventilatory system where the degree of ventilatory response is greater than the preceding stimulus related to the period of hypoventilation and relative CO_2 increase, which potentiates cycles of CSA.

There are 3 major components that contribute to loop gain in ventilation (Fig. 1).

- Controller gain: ventilatory response to P_{CO_2} and a lesser extent P_{O_2}
- Plant gain: changes in pulmonary capillary blood P_{O_2} and P_{CO_2} in response to changes in ventilation
- Mixing gain: the delay between gas exchange occurring in the pulmonary circulation and feedback reaching central and peripheral chemoreceptors

Controller Gain

Controller gain describes the responses of the peripheral and central chemoreceptors to P_{CO_2}/P_{O_2} . Some circumstances—such as hypoxia or increased sympathetic activity—increase controller gain, that is, changes in P_{CO_2} result in greater

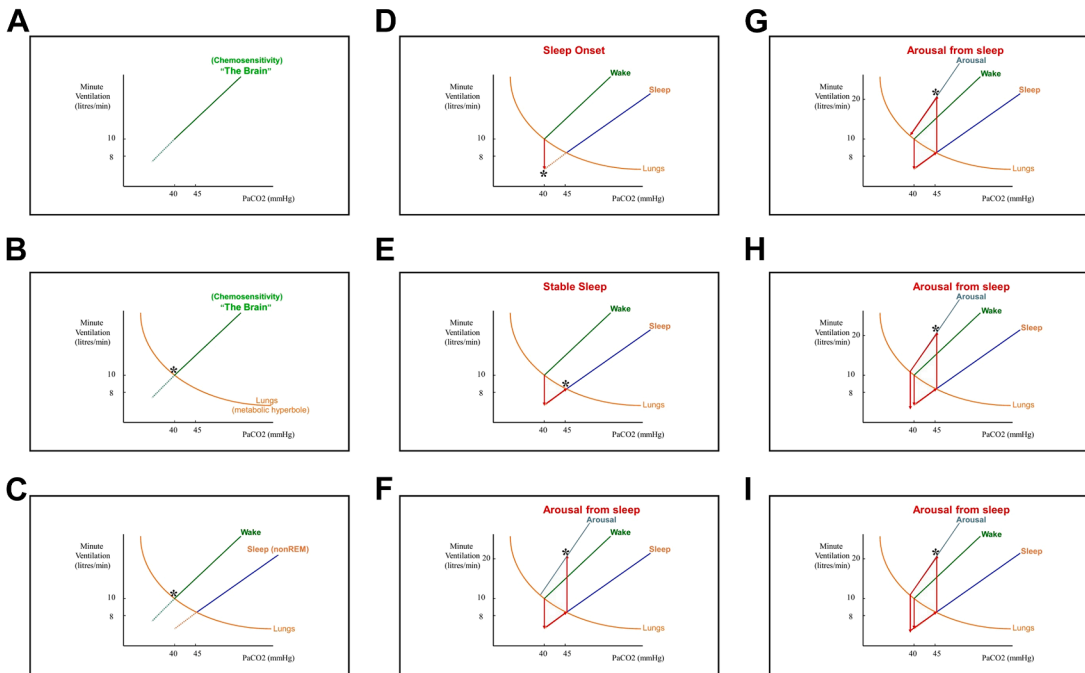


Fig. 1. (A–I) illustrates the control of ventilation. (A) illustrates the ventilatory response to CO₂ (controller gain) and (B) overlays the metabolic hyperbole illustrating the effect of ventilation on CO₂ (plant gain). (C) illustrates the change in chemosensitivity from wake to sleep and the impact upon ventilation (D, E). (F) illustrates the effect of an arousal on chemosensitivity and increase in minute ventilation, thereby reducing CO₂ (G, H) followed by a further arousal (I).

changes in minute ventilation. Conversely, hyperoxia reduces controller gain—there is a smaller degree of change in minute ventilation in response to changes in P_{CO₂}. An increased controller gain is present in many types of CSA, including ICOSA.⁹

The central and peripheral chemoreceptors have complementary roles in modulating ventilatory responses to arterial CO₂. Peripheral chemoreceptors, the most significant of which is the carotid body, exhibit a rapid response (10–30 seconds). Central chemoreceptors exhibit a greater magnitude of response, but act more slowly (60–150 seconds)^{10(p6)}.

The Carotid Bodies

The carotid bodies have a multifaceted and central role in maintaining homeostasis. The functions of the carotid bodies are numerous, with multiple neural pathways, which act in a *ribbon cable* type fashion, that is, the individual pathways may act independently or in tandem. Stimulation of the carotid bodies results in a stimulation of afferent neurons terminating in the nucleus tractus solitarius and resulting in a peripheral chemoreflex.¹¹

Most relevant for CSA pathogenesis, the carotid bodies contain multiple chemosensory units that

detect changes in P_{CO₂} and arterial pH. Other chemical stimuli include glucose, insulin, hemoglobin and lactate in addition to changes to blood pressure. Following a 10 to 40 second period of hyperventilation, a period of hypoventilation lasting a similar period of time occurs. This hypoventilation results in an increase in P_{CO₂} and decrease in pH, thereby stimulating the carotid body in which causes an increase in respiratory rate and tidal volume.¹¹

The carotid bodies also initiate a chemoreflex in response to hypoxia—however, this only begins around a P_{O₂} of 60 mm Hg. In patients with hypoxia and hypercapnia, the additive chemoreflexes produce a large stimulus to ventilation.¹⁰

Historically, the carotid bodies have been used as a therapeutic target in cardiorespiratory disease, such as severe asthma before the advent of inhaled bronchodilators and inhaled steroids.^{12,13} More recently, carotid body resection has been trialed as a therapeutic option to reduce sympathetic drive in heart failure with reduced ejection fraction.¹⁴ Despite meeting the primary endpoint of reducing muscle sympathetic nerve activity, there was significant increase in resting P_{CO₂}.¹⁴

Central Chemoreceptors

Central chemoreceptors are present in multiple locations in the hindbrain. Unlike the carotid bodies, central chemoreceptors are not sensitive to hypoxia. Rather, they are activated by changes in cerebrospinal fluid CO_2 and pH. Along with the neural pathways from the carotid bodies, central chemoreceptors project to the dorsal respiratory group and ventral respiratory group in the medulla^{10(p6), 15}

Plant Gain

Plant gain describes the relationship between ventilation and capillary Pco_2/Po_2 . As minute ventilation falls, Pco_2 increases. Moreover, patients with a higher resting CO_2 require a smaller change in minute ventilation to reach the apneic threshold. This is termed high plant gain.

Total lung capacity (TLC) and functional residual capacity (FRC) independently influence plant gain. For patients with heart failure for example, a restrictive ventilatory defect is commonly seen and is related to cardiomegaly and pleural effusions. For individuals with a lower TLC and FRC, there is a smaller reserve of alveolar O_2 and CO_2 in the lungs. Consequently, a fixed change in minute ventilation will result in a greater degree of change in alveolar and arterial Po_2 and Pco_2 . This is supported by the observation that there is a decrease in FRC and simultaneous increase in dynamic loop gain in OSA patients during supine sleep, as compared to nonsupine sleep.¹⁶

CLASSIFICATION OF NONHYPERCAPNIC CENTRAL SLEEP APNEA

Cardiac Failure

Patients with cardiac failure, particularly those with a reduced ejection fraction, generally exhibit a specific type of CSA termed Cheyne-Stokes respiration (CSR-CSA), which is characterized by a long cycle length.¹⁷ Other causes of heart failure exhibit CSR-CSA where cardiac output is reduced due to valvular (eg, aortic stenosis or mitral regurgitation) or rhythm disturbance (eg, atrial fibrillation). A decreased cardiac output leads to an increased arterial circulation time (mixing gain).

Some patients with cardiac failure do not demonstrate normal sleep-related decreases in ventilation and increases in Pco_2 , reducing the CO_2 reserve (difference between resting CO_2 and apnoeic threshold).¹⁸

Some patients with cardiac failure demonstrate awake low Paco_2 indicative of resting hyperventilation. Despite low Paco_2 decreasing plant gain, these patients have been noted to have higher

rates of CSR-CSA, which is likely due to the severity of the underlying left ventricular dysfunction and increased stimulation of pulmonary J receptors when supine (increased controller gain). Notably however, CSR-CSA has been observed in a lung transplant patient with mechanical denervation of the pulmonary J receptors, suggesting that other triggers may also trigger hyperventilation in this population.¹⁹

Furthermore, there are numerous pathologic pulmonary changes that may occur in cardiac failure, which independently increase loop gain. Advanced cardiac failure is associated with increased pulmonary vascular resistance, interstitial edema, and increased capillary basement membrane thickness. Consequently, there is a decrease in gas transfer, measured as the diffusing capacity for carbon monoxide (DLCO),^{20,21} resulting in chronic hypoxia and increased controller gain.

Patients with advanced cardiac failure also commonly have pulmonary restriction due to increased cardiac size,^{22,23} which may increase plant gain.

Opiates

Sleep disordered breathing occurs in approximately 60% of chronic methadone users.²⁴ Within the sleep disordered breathing (SDB) group, about 20% have CSA and the balance obstructive sleep apnea (OSA). Those with CSA have a lower resting SpO_2 yet maintain or elevate their SpO_2 levels with sleep, compared with OSA and no apnea groups in whom there is a decrease in SpO_2 .²⁵ The relative increase in SpO_2 with sleep is likely due to underlying periodic hyperventilation.

Opiates mediate central sleep apnea primarily through stimulation of mu receptors in the pre-Botzinger complex and parabrachial/Kolliker-Fuse nucleus.²⁶ Opiate use reduces resting minute ventilation (resulting in a mild increase in Paco_2) due to a suppressed central ventilatory response. Of interest is the elevated peripheral ventilatory response with opioids, which results in the periodic hyperventilation followed by apnea characteristic of opioid induced CSA.^{27,28} During sleep, this manifests as hypercapnic periodic CSA. However, patients with opiate induced CSA often display an irregular, periodic ventilation pattern termed *ataxic breathing* on PSG.²⁹ This phenomenon is not seen in other causes of hypercapnic CSA.

CPAP Emergent Central Sleep Apnea

This condition is defined by a residual central AHI of greater than 5 events per hour on CPAP. It occurs in about 5% of patients with significant OSA

who initiate CPAP.³⁰ It self-resolves in the majority of patients within 30 days.

The mechanism responsible may be related to a readjustment of chemosensitivity—chronic intermittent hypoxia and hypercapnia due to OSA are abolished with CPAP, such that triggers for chemosensitivity are changed. An alternative theory relates to excessive CPAP pressures, greater stretch receptor activation via the afferent vagal nerve (Hering-Breuer reflex).^{31,32} If there is persistent CSA on CPAP after 30 days despite readjusting pressures, it would be wise to exclude cardiac or opioid related causes. Uncommonly, patients could be trialled on alternative flow generators such as adaptive servoventilation.

In another group, patients with OSA who have been stable on long term CPAP with apnea hypopnea index (AHI) less than 5 events per hour suddenly—over a few days—develop quite a variable residual AHI often between 5 to 30 events per hour. Commonly this is due to the development of atrial fibrillation and carries with it an 14-fold increased risk of a serious cardiac event.^{33,34}

Although poorly described in the literature, patients with SDB on auto CPAP who also have periodic limb movements may have a high residual AHI identified from some flow generator devices. It is possible this occurs as a result of the periodic increase in motor activity of intercostal as well as limb skeletal muscles. The transient increase in intercostal activity can change the tidal volume and thereby interfere with the feedback the auto CPAP devices require to set their pressure.

High Altitude

Periodic breathing occurs almost universally at high altitude, even in healthy subjects. As altitude increases Fio_2 decreases, increasing controller gain, and the risk of CO_2 falling less than the apnoeic threshold.³⁵

Cerebrovascular Disease

Although obstructive sleep apnea is the most common form of sleep disordered breathing in patients post stroke, a significant number demonstrate CSA. Two distinct patterns have been observed—a CSR-CSA pattern, which occurs in patients with subclinical left ventricular dysfunction³⁶ and a short cycle length pattern.^{9,37} Short cycle length CSA post stroke is likely to be due to changes in ventilatory response to CO_2 (controller gain).³⁸

Pulmonary Hypertension

Patients with idiopathic group 1 pulmonary hypertension, by definition, have pulmonary vascular

and right ventricular dysfunction but preserved left ventricular function. However, in advanced or decompensated disease there is a diminished cardiac output due to right ventricular failure. This leads to increased mixing gain.³⁹

Chronic Renal Failure

Similarly to the cardiac failure population, patients with renal failure are likely to have volume overload and pulmonary edema, which increases controller gain. In keeping with this, the severity of sleep disordered breathing in a population of dialysis patients (including both OSA and CSA) has been shown to improve postfluid removal.⁴⁰

Iatrogenic—Vagal Nerve Stimulators

Vagal nerve stimulation has emerged as a therapeutic option for refractory epilepsy, for which sleep disordered breathing has been reported as a potential complication. Numerous mechanisms have been reported, including in some cases reduction/termination of respiratory effort⁴¹ and hyperventilation with postevent apnea.⁴² As the use of vagal nerve stimulators increases, this phenomenon may be observed on a larger scale.

MEDICATIONS

Although opiates are the most commonly implicated medication class, CSA has also been noted with gamma-aminobutyric acid (GABA) receptor agonists and P2Y₁₂ inhibitor ticagrelor.

Gamma-Aminobutyric Acid Agonists

Although less frequently recognized, GABA agonists such as gabapentin, sodium oxybate and valproic acid have been noted to produce CSA with an ataxic breathing pattern. It is likely that the pathophysiology is similar to that of opiate-induced CSA.⁴³ CSA has also been previously reported in the context of long-term benzodiazepine use.⁴⁴

Ticagrelor

Ticagrelor is an antiplatelet agent that has become widely used in the treatment of acute coronary syndrome. A high prevalence of CSA has been noted in patients taking ticagrelor, which is likely due to an increased hypercapnic ventilatory response.^{45,46} Consequently, patients taking ticagrelor may demonstrate polysomnographic findings similar to patients with ICOSA. CSA generally normalizes with ticagrelor discontinuation.⁴⁶

The following table outlines the patterns of non-hypercapnic CSA in adults (**Table 1**).

Table 1
Clinical and polysomnographic features of central sleep apnea, grouped by underlying etiology

	Clinical	Cycle Length (sec)	Paco ₂ (mm Hg)	Central Chemoreceptor Sensitivity	Peripheral Chemoreceptor Sensitivity
CSA due to opiates	Positive drug screen	15–45	<50	Reduced	increased
CSA without opiates	Negative drug screen	15–45	<40	Increased	increased
CSA due to heart failure	Low EF, arrhythmia, or valvular disorder	45–75	< 40	Increased	Increased
CSA due to high altitude	Healthy mountain climbers	10–20	<30	Likely increased	Increased
CPAP emergent CSA	Seen with CPAP initiation for OSA	10–20	<40	N/A	N/A

NATURAL HISTORY/PROGNOSIS

As we have outlined, CSA occurs due to a disturbance in normal ventilatory physiology. Unlike OSA, the sequelae of long-term, controlled CSA has not been established. Although CSR-CSA is a negative prognostic marker in cardiac failure, this likely reflects that CSR-CSA becomes more prevalent as severity of cardiac failure increases. For other forms of CSA, its prognostic significance is uncertain.

CSA may in fact be a compensatory mechanism in some contexts. Patients with advanced cardiac failure exhibit resting hyperventilation and increased work of breathing. However, CSR-CSA may improve efficiency of breathing by interspersing hyperpneas with periods of rest (apneas). Further to this, the modest swings in intrathoracic pressure without upper airway obstruction (as with obstructive sleep apnea), which occur during the hyperpnea may improve cardiac output.⁴⁷ Also during the periods of hyperventilation, the end expiratory lung volume increases by as much as 1 L. Moreover, the prolonged central apnea is in reality a prolonged exhalation as seen with end tidal Pco₂ measurements during CSA. About half way during this *central apnea* the upper airway closes passively, yet pulmonary elastic recoil continues and creates a small amount of PEEP (~5 cmH₂O), which may be sufficient to prevent alveolar collapse.^{47,48}

IDIOPATHIC CENTRAL SLEEP APNEA: A CLINICAL APPROACH

CSA is an uncommon and clinically heterogenous condition. The majority of patients with CSA have an identifiable physiologic etiology, such as cardiac failure, neurologic deficit, or medications. Workup of patients with CSA requires careful evaluation to accurately classify etiology. An estimate

of cycle length (from the beginning of hyperventilation to the next is an important guide (Fig. 2).

For patients with a reversible physiologic disturbance, treatment should focus on reversal of the specific disturbance where possible. For example, CSR-CSA has been shown to improve with treatment of underlying cardiac failure. These treatments have included pharmacologic,⁴⁹ left ventricular assist device,⁵⁰ and transplant.⁵¹

Patients with no discernible etiology and compatible clinical features may have ICSA, for which a uniform management approach has not yet been established. We describe our approach to ICSA here.

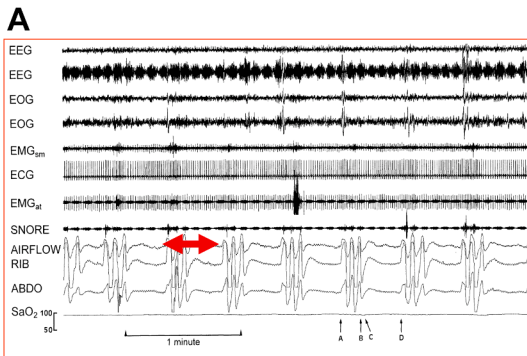
Background

ICSA is a rare condition that represents less than 5% of CSA cases.^{2,52} ICSA patients present with a unique clinical phenotype, the etiology for which has not yet been described. ICSA patients are more commonly male, and have a median age of between 58.6 and 66.7 in previously described cohorts.^{52,53} Although by definition these patients do not have established cardiovascular or cerebrovascular disease, ICSA patients have been shown to have a strikingly high rate of atrial fibrillation,⁵³ as well as high rates of hyperlipidemia, systemic hypertension⁵² and carotid stenosis.⁵⁴

On polysomnography, patients with ICSA demonstrate numerous short cycle length (20–40 second) central apneas, which generally occur in N1 and N2 sleep. Arousals have been observed to occur at the termination of the apnea²—in contrast to CSR-CSA, where arousals occur at the peak of ventilation.⁵⁵ It has also been noted that the time from sleep onset to stable N3 sleep is increased.²

Although the etiology is not completely understood, it has been demonstrated that patients

Short Cycle Length



Long Cycle Length

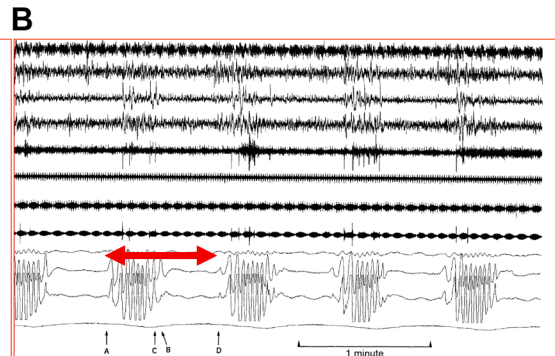


Fig. 2. Two PSGs (4 minute epoch) illustrating the difference between short and long cycle length CSA. Arrows A–B indicate ventilation period and arrows C–D indicate the central apnea. (A) represents short CL of 35 seconds: this patient having a normal systolic (LVEF 60%) and diastolic function, in sinus rhythm without valvular heart disease or pulmonary hypertension. In addition absence of diabetes or neurologic impairment. (B) illustrates a typical patients with heart failure and CSA-CSR with a long cycle length of 70 sec associated with LVEF 19%.

with ICSA demonstrate increased hypercapnic ventilatory responses, indicative of increased controller gain.^{56,57}

Unlike CSR-CSA, which is a negative prognostic marker (in the context of cardiac failure), the prognosis of ICSA are likely relatively benign.¹ However, due to the minority of patients presenting with this condition, further study is required to understand its natural history.

Clinical Presentation

Compared to patients with obstructive sleep apnea, patients with ICSA generally have a lower body mass index (BMI) and are less likely to snore. Both insomnia and hypersomnolence are possible presenting symptoms.²

As noted previously, true ICSA is rare. As such, for patients with suspected ICSA we would suggest a robust pathway of investigations to rule out subclinical cardiac or neurologic disease.

Evaluation: a Suggested Approach

A detailed clinical history, including any recent medications, is crucial in patients presenting with suspected ICSA. A urinary drug screen may be considered.

Diagnosis of Central Sleep Apnea

For patients presenting with sleep related symptoms, the initial investigation of choice is an in-lab polysomnogram (PSG). Typically, patients with ICSA will demonstrate sleep state instability, which occurs on the background of multiple central apneas with a short cycle length.

Typically, these patients do not have a high burden of obstructive events. However, note that gold-standard measurement of respiratory effort requires esophageal pressure monitoring, which is seldom performed in routine clinical practice.

Many patients with CSA, including those with ICSA, may demonstrate frequent hypopnoeas on PSG. Identifying central hypopnoeas, as opposed to obstructive, is challenging and not routinely performed by all sleep laboratories. AASM scoring guidelines recommend the use of three metrics to subclassify hypopnoeas, all of which should be absent during a central event.⁵⁸

1. Snoring during the event
2. An increased flattening of the nasal pressure signal compared to baseline
3. Presence of a thoracoabdominal paradox

Supplemental arterial blood gases, which may be accompanied by transcutaneous CO₂ measurements during PSG, may be helpful to demonstrate the presence of hyperventilation rather than hypoventilation.

Exclusion of Identifiable Etiologies

For patients with findings consistent with CSA on PSG, it is then prudent to evaluate for potential underlying etiologies. Given the relatively high prevalence of cardiac failure, particularly among all-comers presenting with CSA, we would suggest measurement of serum natriuretic peptides and an initial transthoracic echocardiogram. Patients with subtle abnormalities on these initial investigations may be subsequently referred for

cardiac magnetic resonance imaging or invasive right heart catheterization.

Clinicians should also have a low threshold to consider central nervous system (CNS) imaging (eg, MRI brain), particularly if any signs are detected on bedside neurologic examination. Aside from ischemic insults, structural lesions that affect brainstem function may also result in CSA. This has been previously described in the context of a Chiari malformation, which is often associated with secondary syringomyelia.^{59,60}

Although a clear etiologic link has not been identified, screening for systemic illnesses that may affect carotid body responses could be considered. For example, hyperglycaemia (as may occur in diabetes) and raised serum catecholamines (as may be seen in pheochromocytoma) may impact carotid body signaling.¹¹

MANAGEMENT OF IDIOPATHIC CENTRAL SLEEP APNEA

The management of nonhypercapnic CSA, including ICSA, is not well elucidated. Several management options have been trialed, which are detailed further. To date, there have been no large randomized clinical trials of therapy in ICSA. Some management options have been studied more extensively in the CSR-CSA population.

CO₂

Given the fundamental role of hypocapnia in initiating CSA, it has been hypothesized that administration of exogenous CO₂ may increase alveolar CO₂ and subsequently terminate central apnea. This approach has been shown to be effective in reducing AHI, however at the expense of a continuous high respiratory rate and greater arousals in patients with ICSA.⁶¹ In a similar vein, addition of anatomic dead space, which consequently raises arterial CO₂, has been shown to decrease AHI in patients with ICSA.⁶¹

Despite decreasing AHI, raising arterial CO₂ may independently cause cortical arousals and increase sympathetic tone, which may counteract the improvement in sleep consolidation that occurs with abolition of central apneas.⁶² As such, inhaled CO₂ and increasing dead space have not been widely studied, nor have they been adopted as a treatment approaches. In summary, CO₂ therapy is experimental and not used clinically.

Oxygen Therapy

Hyperoxia decreases controller gain, which reduces the magnitude of ventilatory changes relative to changes in arterial CO₂. Several

nonrandomized studies have demonstrated decreased central apnea frequency in patients with CSA with the use of nocturnal home oxygen therapy.^{63–65} While the majority of patients enrolled in these studies had alternative etiologies for CSA (eg, cardiac failure, stroke), this approach may plausibly benefit patients with ICSA. However supplemental oxygen is not a benign gas. Hyperoxia is associated with reduced cardiac output⁶⁶ and coronary artery vasoconstriction.⁶⁷ Accordingly, international guidelines do not recommend long term home oxygen therapy for normoxic patients with CHF.⁶⁸

Respiratory Stimulants

Acetazolamide is a carbonic anhydrase inhibitor, which increases renal bicarbonate excretion and results in a mild metabolic acidosis, stimulating respiratory drive. A small nonrandomized study has shown improvement in burden of central apneas as well as clinical symptoms with use of acetazolamide in ICSA patients.⁶⁹ Use should be avoided in patients with liver disease or in pregnancy.

Hypnotics

GABAergic hypnotic medications have been trialed in CSA to combat sleep fragmentation. A small trial of 5 patients with ICSA demonstrated that triazolam decreased AHI compared to placebo. However this study was limited by a small sample size, lack of standard deviation measures and lack of quality of life measurements.⁷⁰ Two studies have examined the use of zolpidem in CSA (including ICSA), demonstrating a variable reduction in AHI.^{71,72} It should also be noted that GABAergic medications, including benzodiazepines, may cause CSA in rare cases.⁴⁴

Continuous Positive Airway Pressure

Continuous positive airway pressure has been shown in select cases to improve central apneas in ICSA.^{73,74} It has been postulated that pharyngeal collapse may be implicated in either the initiation and/or propagation of central apneas, which may account for the therapeutic effect of CPAP.¹ Furthermore, some patients classified as ICSA may in fact have subclinical cardiac disease, and may plausibly have a favorable hemodynamic response from CPAP.

Theoretically, CPAP may increase minute ventilation and therefore increase the chance of P_{CO₂} falling less than the apnoeic threshold, potentiating central apneas—this has been observed in the context of bilevel noninvasive ventilation (NIV).⁷⁵ However we are not aware of any

documented cases of this in the context of CPAP. Given the potentially heterogeneous response to CPAP, in-laboratory titration is suggested to allow retitration to overcome upper airway instability (ie, snoring and obstructive hypopneas) yet avoiding over-zealous over titration.

Noninvasive Ventilation

Typical bilevel fixed pressure NIV is well established as a treatment of disorders of hypoventilation (including hypercapnic CSA) but does not have a role in nonhypercapnic CSA (including ICOSA).

Adaptive servoventilation (ASV) is a specific type of bilevel NIV, which has been designed to stabilize breathing pattern in CSA. The ASV algorithm delivers a fixed expiratory pressure, variable pressure support and backup rate.⁷⁶ ASV was initially adopted for the management of CSA, particularly CSR-CSA. However, there has been significant controversy regarding its ongoing use in the context of the SERVE-HF trial, which indicated an increased risk of cardiovascular death and all-cause mortality in patients with ASV for patients with heart failure and reduced ejection fraction.⁷⁷ This ASV device was triggered by minute ventilation with high pressures.

More recently, the ADVENT-HF trial, which used an alternative ASV algorithm triggered by peak flow with lower pressures, did not reproduce this mortality signal. However, the study may have been underpowered due to the COVID-19 pandemic and Phillips device recall. Another important difference was that the ADVENT-HT trial included a variety of sleep disordered breathing types (obstructive and central).

The use of ASV for CSA is highly variable. The European Respiratory Society and European Sleep Research Society recently published a statement promoting the use of ASV, including in patients with an left ventricular ejection fraction (LVEF) between 30% and 45% (but only when initiation is performed in an expert center).⁷⁸

Phrenic Nerve Stimulation

Phrenic nerve stimulation is a novel and emerging therapy for CSA, including ICOSA. Akin to cardiac pacing, phrenic nerve stimulation uses a generator and transvenous lead to stimulate unilateral diaphragmatic contraction. The largest studies of phrenic nerve stimulation in CSA are the pivotal study and follow-up postapproval study, which enrolled patients with CSA of any cause except opiates. 11% of initial patients had idiopathic CSA. Phrenic nerve stimulation was highly effective in reducing AHI and reducing Epworth

Sleepiness Score (ESS).⁷⁹ However, it should be noted that baseline ESS was in the *high normal* rather than *abnormal range*, likely reflecting the fact that CSA patients often present with insomnia rather than pathologic sleepiness.

Despite significant improvement in AHI and reduction index, patients demonstrated persistently minimal proportions of N3 sleep at 5 year follow-up (1% of total sleep time, compared to 2% at baseline). This may suggest that phrenic nerve stimulation independently influences sleep architecture. Furthermore, there was no monitoring of respiratory symptoms or lung function.

MANAGEMENT: OUR SUGGESTED APPROACH

ICOSA is an uncommon condition. Although respiratory effort is routinely quantified during PSG using thoracic and abdominal movement, studies with esophageal manometry demonstrate that respiratory events are often misclassified. Further to this, some patients with true ICOSA appear to respond to CPAP, which plausibly may play a role in reversing the underlying physiologic derangement (as in CSR-CSA). As such, we would suggest an initial trial of CPAP for all patients with a suspected diagnosis of ICOSA, preferably with an in-lab CPAP implementation study.

For patients who do not respond to CPAP, we would suggest referral to a specialist center for consideration of further management. Quite often in the absence of snoring or any underlying cause (as listed earlier)—observation may be all that is required. Feasible options that may be trialed in this setting with close monitoring include low flow oxygen, acetazolamide, ASV and phrenic nerve stimulation.

In the setting of ICOSA, we would suggest reserving phrenic nerve stimulation for carefully selected patients.

FUTURE DIRECTIONS

The clinical entity of ICOSA is likely to evolve significantly in the future. Although there is currently no clearly defined etiology, the epidemiologic profile of ICOSA suggests that this may be a largely acquired, rather than genetic illness. There may also be heterogeneity within this patient group, which has not yet been described.

Patients with ICOSA have high rates of metabolic and cardiovascular comorbidities. As our diagnostic tools improve—or example, use of cardiac MRI (cMRI) over echocardiography in appropriate cases—it is likely that our understanding and classification of this condition will change.

Both current therapeutic options and our understanding of the underlying pathogenesis in ICSA are relatively rudimentary. CSA syndromes may in part reflect an adaptive response to physiologic dysregulation, and the natural history of untreated CSA is not well understood in any context. As our understanding of this condition evolves, evaluation of potential therapies on a broader scale is also warranted. Given that we do not understand the prognostic implications of suppressing CSA, treatments should improve quality of life in addition to reducing the burden of respiratory events.

SUMMARY

ICSA is a rare condition characterized by short-cycle central apneas, which usually occur in transitional sleep. ICSA occurs in the absence of known cardiac failure or established cerebrovascular disease. Data on therapeutic options for ICSA remain relatively sparse; however, there has been significant interest recently in ASV and phrenic nerve stimulation. An evolving understanding of this condition and therapeutic options will serve to improve care for ICSA patients in the future.

CLINICS CARE POINTS

- When CSA appears consider the cycle length: short (<45 seconds indicates opioid induced; long (>45 seconds) indicates heart failure related.
- The pathogenesis of CSA differs significantly from OSA and may not carry the same adverse pathophysiological consequences.
- Evidence suggests treatment of CSA is best directed at the cause (eg opioids, heart failure) rather than the downstream AHI.

DISCLOSURE

None.

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