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Pathogenesis of central and complex sleep apnoea

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ABSTRACT

Central sleep apnoea (CSA) – the temporary absence or diminution of ventilator effort during sleep – is seen in a variety of forms including periodic breathing in infancy and healthy adults at altitude and Cheyne–Stokes respiration in heart failure. In most circumstances, the cyclic absence of effort is paradoxically a consequence of hypersensitive ventilatory chemoreflex responses to oppose changes in airflow, that is elevated loop gain, leading to overshoot/undershoot ventilatory oscillations. Considerable evidence illustrates overlap between CSA and obstructive sleep apnoea (OSA), including elevated loop gain in patients with OSA and the presence of pharyngeal narrowing during central apnoeas. Indeed, treatment of OSA, whether via continuous positive airway pressure (CPAP), tracheostomy or oral appliances, can reveal CSA, an occurrence referred to as complex sleep apnoea. Factors influencing loop gain include increased chemosensitivity (increased controller gain), reduced damping of blood gas levels (increased plant gain) and increased lung to chemoreceptor circulatory delay. Sleep–wake transitions and pharyngeal dilator muscle responses effectively raise the controller gain and therefore also contribute to total loop gain and overall instability. In some circumstances, for example apnoea of infancy and central congenital hypoventilation syndrome, central apnoeas are the consequence of ventilatory depression and defective ventilatory responses, that is low loop gain. The efficacy of available treatments for CSA can be explained in terms of their effects on loop gain, for example CPAP improves lung volume (plant gain), stimulants reduce the alveolar-inspired PCO_2 difference and supplemental oxygen lowers chemosensitivity. Understanding the magnitude of loop gain and the mechanisms contributing to instability may facilitate personalized interventions for CSA.

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Key words: central apnoea, loop gain, periodic breathing, ventilatory instability.

Abbreviations: CPAP, continuous positive airway pressure; CSA, central sleep apnoea; EMG, ~~xxxx xxxx~~; NREM, non-REM; OSA, obstructive sleep apnoea; PCO_2, ~~xxxx xxxx~~; PO_2, ~~xxxx xxxx~~; REM, rapid eye movement.

INTRODUCTION AND DEFINITIONS

Central sleep apnoea (CSA) is characterized by the absence of airflow accompanying the cessation of ventilatory effort during sleep. In most forms, CSA is cyclic in nature manifesting as phases of hyperventilation alternating with apnoea: CSA can be classified into cyclic/periodic forms characterized by an oscillatory nature versus more sustained or irregular forms. CSA in periodic forms is seen commonly in preterm and term infants in the first weeks of life,[1] in adults sojourning to high altitude[2] and in about one-third of patients with heart failure.[3] CSA also occurs in ~5% of patients with obstructive sleep apnoea (OSA) when pharyngeal patency is restored with intervention, a phenomenon termed *complex sleep apnoea.*[4–7] Periodic CSA is also seen in the form of idiopathic or primary CSA.[8] CSA is a common side effect of opioids[9] and can be either periodic or 'ataxic' in nature. Finally, we note that CSA can also occur in the form of isolated or prolonged, non-periodic central apnoeas, such as those seen with apnoea of infancy/prematurity,[10] congenital central hypoventilation syndrome[11] and respiratory muscle weakness.[12]

CSA is of clinical concern as it causes arterial oxygen desaturation, hypercapnia, post-apnoeic arousals from sleep, surges in ventilatory drive and negative intrathoracic pressure, sensation of dyspnoea, swings in arterial blood pressure and sympathetic excitation.[13–15] In patients with heart failure, CSA can promote cardiac arrhythmia, reduced cardiac function and is strongly associated with mortality.[16,17] In this review, we summarize the definitions of CSA, the mechanisms contributing to this affliction and how it is transformed into stable breathing with treatment.

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Criteria used to diagnose CSA vary somewhat depending on the patient population, the suspected aetiology and whether central hypopnoeas are scored. In adults, CSA is often defined as the presence of at least five central apnoeas per hour. In patients with heart failure, CSA is typically diagnosed as at least 15 events per hour with at least 50% of these being central events, but *central hypopnoeas* are included. Central hypopnoeas are generally defined as a 30–90% reduction in airflow due to a reduction in ventilatory effort; yet since effort is not directly measured (i.e. via oesophageal pressure/diaphragm EMG), non-invasive signals are used to infer the absence of pharyngeal obstruction. Signals indicative of pharyngeal obstruction include the flattening or scooping of the inspiratory flow shape, thoracoabdominal paradox (typically inward motion of the ribcage in concert with outward motion of the abdomen indicative of raised respiratory system resistance) or the presence of snoring indicating a flow-limited upper airway. It should be noted however that American Academy of Sleep Medicine scoring rules state that distinction between central and obstructive hypopnoeas is not required and can be challenging, and thus central events may be underreported.[18]

The duration of respiratory events is also employed in the diagnosis of CSA. In adults, as with obstructive events, apnoeas/hypopnoeas need to be at least 10 s in duration (~2–3 breaths). In preterm infants, short apnoeas can yield severe desaturation or bradycardia (up to 50% reduction in saturation in 6 s), so the definition is broadened for neonates (≥20 s, or less if accompanying desaturation or bradycardia occurs), but hypopnoeas are typically ignored.

GENERAL BACKGROUND

Introduction to ventilatory control

The primary features of the ventilatory control feedback loop that determine ventilatory effort are described as follows: Increased PCO_2 and reduced PO_2 are sensed at the carotid bodies located at the carotid bifurcation, making up the *peripheral chemoreceptors*. These chemoreceptors are well perfused and positioned to detect fast changes in PCO_2/PO_2 levels and are generally thought to dominate the response to transient changes in these variables. Increased PCO_2 (in the form of H+) is also sensed at the medulla and pons, particularly at the retrotrapezoid nucleus in the ventrolateral medulla, making up the *central chemoreceptors*. The central chemoreceptors also typically dictate the baseline level of ventilatory effort. Both sets of inputs are integrated and act on the respiratory pattern generator to determine the strength and frequency of the efferent neural signals to the inspiratory muscles, namely the diaphragm and external intercostals. If the respiratory mechanics are normal, these efferent signals generate a level of inspiratory muscle pressure that yields a tidal volume excursion in direct proportion.

Traditionally, CSA has been considered a simple failure of this apparatus, described broadly as the *controller*, to generate ventilatory effort during sleep, akin to a severe yet temporary respiratory depression. Indeed, during normal sleep, ventilatory drive is reduced and reflex ventilatory responses to changes in PCO_2 and PO_2 are diminished[19,20] leading to the view that CSA is an extension of this diminution in ventilatory drive. Yet, as we discuss below, CSA in most ~~cases~~ is paradoxically the consequence of hypersensitivity of this chemoreceptor system.

Introduction to loop gain

To understand the negative feedback control system, we also consider the effect that ventilation has on PCO_2 in the lungs and in the pulmonary venous blood leaving the lungs (arterial PCO_2). An increase in arterial PCO_2 will act on chemoreceptors to cause a rise in ventilation that will subsequently lead to a corrective reduction in arterial PCO_2, that is as indicated by the metabolic hyperbola (the increase in ventilation is roughly proportional to the percent rise in PCO_2). Normally, an equilibrium is achieved whereby ventilation and PCO_2 levels are relatively steady. Yet on the timescale of CSA, a fluctuation in ventilation such as a temporary hyperpnoea accompanying arousal can wash CO_2 out of the lungs, leading to a temporary fall in arterial PCO_2. After a circulation time, the hypocapnic arterial blood reaches the chemoreceptors, yielding a temporary reduction in ventilatory drive. But because of time delay between this disturbance and its effect on the control system, the ventilatory drive response will typically yield a ventilatory undershoot. This reflex undershoot will, in turn, raise alveolar/arterial PCO_2 to elicit a delayed reflex ventilatory overshoot and so on.

The *loop gain* of this system, which describes the ratio of this ventilatory response (e.g. undershoot) to a prior disturbance (e.g. overshoot), ultimately determines whether the oscillation will grow into periodic central apnoeas (loop gain >1) or damp out (loop gain <1).[21,22]

It is also apparent that the ventilatory response to a disturbance has two distinct components (see Fig. 1). Consider that the temporary rise in ventilation (5 L/min) washed CO_2 out of the lungs such that PCO_2 falls by 5 mm Hg (*plant gain* of 1 mm Hg/L/min). After a lung to chemoreceptor circulatory delay, this reduction in PCO_2 elicits a temporary 6 L/min reduction in ventilation (*controller gain* is 1.2 L/min/mm Hg), such that the undershoot is larger than the initial disturbance (loop gain = 1.2) and periodic CSA will occur. CSA could be avoided if the CO_2 damping was improved (lowered plant gain via increased lung volume) or if the chemoreflexes were less sensitive. Reducing circulatory delay also lowers loop gain.

As controller gain describes the change in ventilation due to changes in PCO_2 (or PO_2), the controller gain can be modified by sleep state transitions. During the CSA cycle, as ventilatory drive rises, there is often an accompanying arousal that provides an additional increase in ventilatory drive[20,23–26] that in turn further increases the ventilatory overshoot. The effective gain relevant for the pathogenesis of CSA now becomes the chemoreflex response plus the arousal response per change in PCO_2 throughout the cycle. Evidence that this effect plays a role includes: (i) CSA occurs more commonly at sleep onset or in light sleep (stage 1 non-

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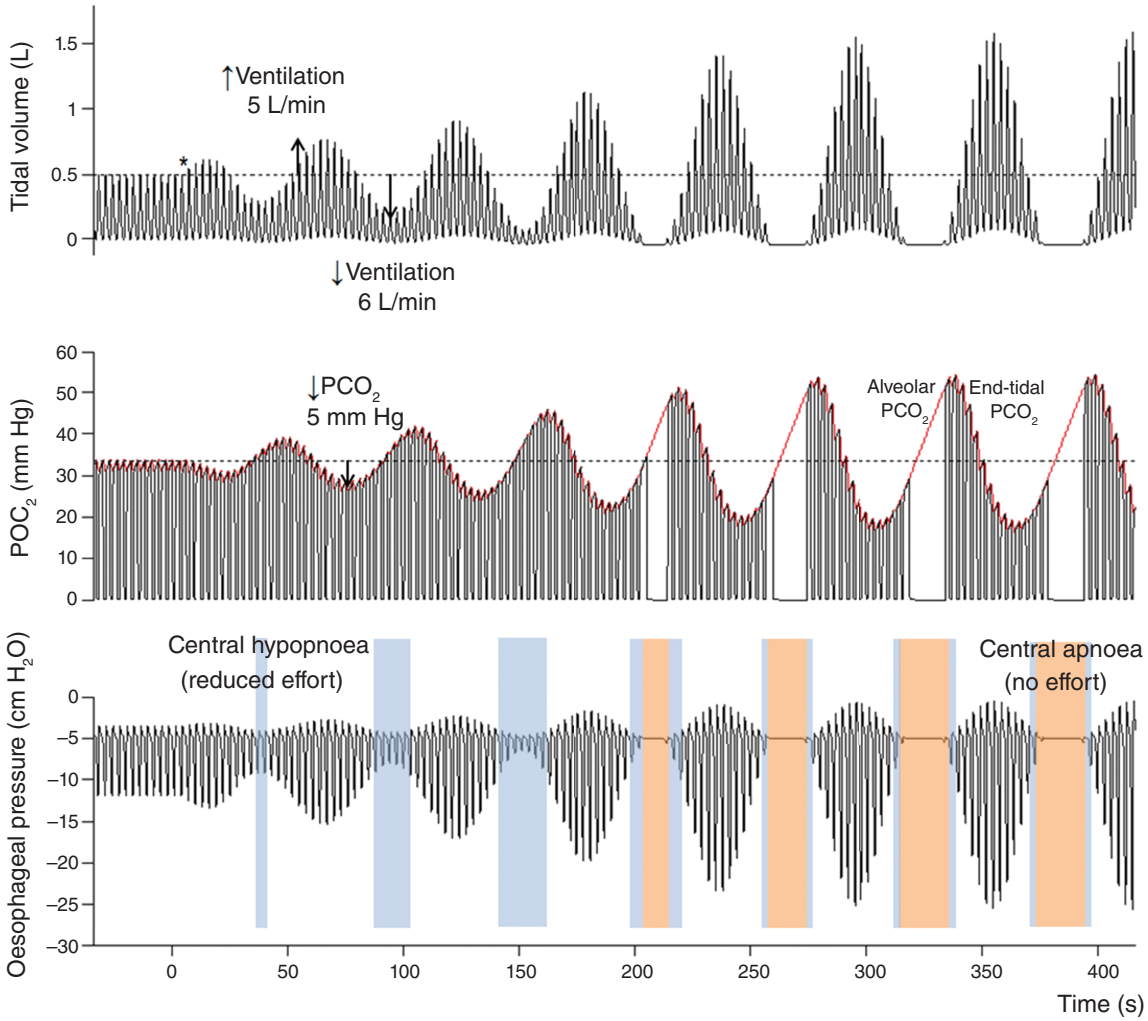

Figure 1 Computer simulation of central sleep apnoea (CSA) in heart failure illustrating the impact of loop gain >1. Loop gain was set to 1.2 at the time denoted by the asterisk. As CSA builds up, each undershoot in ventilation is ~1.2 times larger than the prior ventilatory overshoot (see text for details). The example also illustrates the spectrum of central events, from mild hypopnoeas to more severe apnoeas (left to right).

rapid eye movement (NREM)) compared with during wake or deeper NREM sleep,[27,28] and (ii) sedatives can improve CSA in some patients.[29] The increase in ventilation during arousal might relate to intrinsically greater ventilatory drive (for the same PCO_2) observed during the awake state when compared with sleep, and possibly a reflex arousal ventilation, akin to a startle response.[26]

In principle, upper-airway effects may also promote CSA.[30–32] For example, changes in pharyngeal patency that occur in parallel with PCO_2 will raise controller gain. In this case, the overall controller gain (chemoresponsiveness) is equal to the intrinsic gain (chemosensitivity) multiplied by the effectiveness of the upper airway. In this context, some authors make a distinction between chemosensitivity (which reflects the ventilatory drive response to PCO_2) and chemoresponsiveness (which reflects the change in actual ventilation in response to a PCO_2 stimulus). The reason that the upper airway is considered a component of controller gain is that controller gain is essentially synonymous with chemoresponsiveness. This concept has two implications: An airway that tends to collapse as drive is reduced (i.e. via loss of muscle tone) will tend to yield a greater undershoot, thereby increasing the effective loop gain. Likewise, the same individual will exhibit a greater increase in ventilation as ventilatory drive is increased and muscle tone is re-established.

PATHOGENESIS IN PATIENT POPULATIONS

Cheyne–Stokes respiration in congestive heart failure

Cheyne–Stokes respiration is perhaps the most widely recognized form of CSA, occurring in a substantial proportion of patients with heart failure (see example trace taken from a recent study[33] in Fig. 2). A reduced cardiac output and resultant increase in the circulatory

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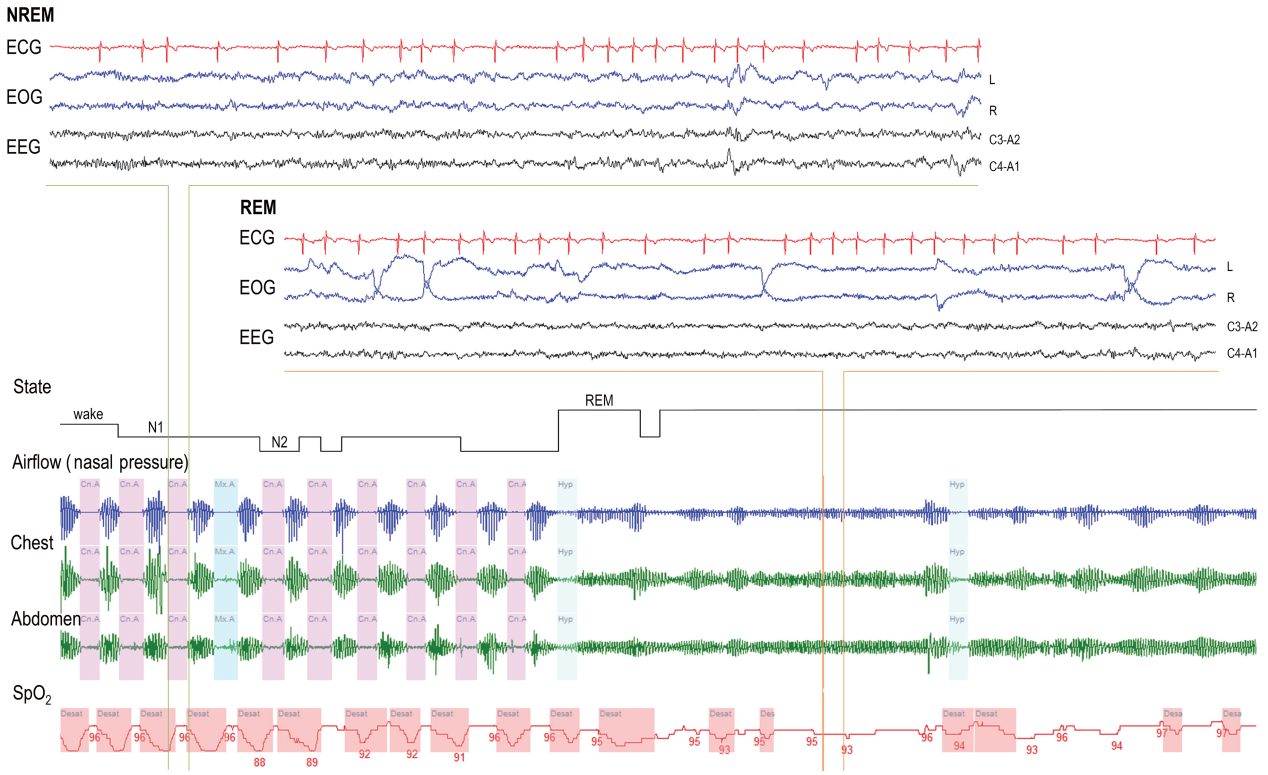

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Figure 2 Illustrative example trace of central sleep apnoea (CSA) during non-rapid eye movement (NREM) sleep in a male patient with heart failure and atrial fibrillation. Note the resolution of CSA with the transition to rapid eye movement (REM).

delay between the lungs and chemoreceptors is believed to play an important role in the pathogenesis of CSA. Indeed, patients with a reduced cardiac output, worsened systolic function, atrial fibrillation and prolonged lung to chemoreceptor delays are more likely to exhibit CSA.[34–37] Furthermore, heart failure therapies such as cardiac resynchronization and afterload reduction improve ventilatory stability.[38,39] While many patients with CSA have prolonged circulatory delays, the presence of prolonged delay alone does not appear sufficient to generate CSA, highlighting the importance of increased chemosensitivity.[40–43]

The specific causes of increased chemosensitivity in CSA are unclear, and may differ between individuals.[40,43] Elevated pulmonary capillary pressures are associated with the presence of CSA and its severity, while diuresis improves CSA within individual patients.[34,39,44–47] Overnight shifts in fluid from the legs may provide another source of pulmonary congestion, with ventilatory instability more likely with increasing volume of mobilized fluid.[48] Left atrial distension may also drive increased chemosensitivity and CSA irrespective of pulmonary vascular congestion.[49] Notably, a few studies have called into question the role of pulmonary congestion in development of CSA.[50,51] Recent evidence from animal models suggests that abnormalities at the level of the carotid body may play an important role, leading to both enhanced chemosensitivity and sympathetic hypertonia, which might propagate CSA and worsen heart failure.[52,53] Identifying the precise sources of enhanced chemosensitivity will likely provide for new therapeutic targets for CSA. For example, pharmacological reversal of the signalling mechanisms causing carotid chemoreflex hyperactivity (e.g. purinergic)[54] might help suppress CSA.

Idiopathic CSA

The presence of CSA in patients without any identifiable cardiac or neurological cause is termed idiopathic CSA. The cycling period in idiopathic CSA is ~30–40 s and appears to be driven largely by elevated chemosensitivity to PCO_2.[8,40] Arousals typically occur at the peak of hyperventilation and likely contribute to ventilatory overshoot, enhancing chemoresponsiveness.[55] Circulatory delay is by definition normal in these patients and therefore unlikely to contribute to CSA.

Periodic breathing at altitude

At high altitude, low total barometric pressure with a relatively stable fraction of oxygen results in a decreased PO_2, leading to CSA of a periodic nature.[56,57] Although there is variation in the altitude at which CSA will develop, CSA occurs in virtually all lowlanders at arrival to altitude.[58] Hypoxia promotes instability via hypoxic augmentation of the chemoreflex response to CO_2 and via an increase in hypoxic chemoresponsiveness while on a steeper portion of the hypoxic ventilatory response curve.[59] In contrast to sojourners, highlanders are less susceptible to CSA, suggesting that genetic or adaptive factors likely play an important role

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in these responses.[56] Interestingly, the hypoxic chemosensitivity increases over days-to-weeks after arrival at altitude, facilitating an increase in ventilation and improvement in PO_2, but further increasing loop gain[58,60,61] (i.e. differences in instability are typically attributable to differences in the hypoxic ventilatory response rather than those in the magnitude of arterial hypoxaemia). This instability appears to persist in lowlanders living at altitude beyond 1 year.[62] Adaptive increases in the hypoxic ventilatory response with acclimatization appear to improve symptoms of acute mountain sickness (via raising PO_2) but come at the cost of exacerbating CSA.[63] CSA is also linked with hypoxaemia and pulmonary hypertension accompanying chronic mountain sickness, likely acting via hypoxaemic effects on chemosensitivity ~~in such cases~~.[64]

Other factors beyond chemosensitivity may play some role in CSA at altitude. Decreases in plant gain due to hyperventilation with resulting hypocapnia, and increases in cardiac output with short circulatory delays would act as compensatory mechanisms to stabilize breathing[61,65] and thus individuals with less strong compensatory mechanisms may have more severe CSA. Subclinical pulmonary oedema appears to occur relatively frequently in sojourners and might lower lung volumes which would exacerbate CSA.[66] Recent research has suggested that cerebral blood flow reactivity may be important in ventilatory instability at altitude via regulation (damping) of cerebral PCO_2 levels.[58]

Periodic breathing in newborn infants

Periodic breathing is almost ubiquitous in term infants and those born prematurely in the first weeks of life and its high prevalence has led to the assumption that it is non-pathological.[67] However, ~~in some cases,~~ periodic breathing ~~in~~ preterm infants can lead to profound oxygen desaturation[14] that may have serious consequences. Treatment of periodic breathing in such ~~cases~~ is warranted in light of the associations between reduced oxygen levels and mortality in neonatal intensive care.[68] Periodic breathing is rare in the first days after birth but becomes progressively more prevalent over the next 2–4 weeks before a steady decline over the first year.[1,69] The increased CSA prevalence likely results from the raised hypoxic chemosensitivity that accompanies chemoreceptor 'resetting' in the days after birth,[70] followed later by a reduced chemosensitivity with development. CSA is also thought to be due partly to hypoxaemia[71,72] consequent to ventilation-perfusion heterogeneity in the developing lungs. Lower lung volumes (relative to body weight/metabolic rate) especially in preterm infants are also expected to play a role in some infants.[73]

Opioid-induced CSA

Use of opioids has become a major public health issue that has garnered considerable media attention. Studies suggest that roughly one-third of chronic opioid-administered patients have some form of CSA.[74] This breathing pattern has several important characteristics: First, opioids are sometimes associated with bradypnoea, that is very low respiratory rates and attendant hypoventilation, hypercapnia and hypoxaemia.[75] Second, breathing is often erratic in nature, often described as 'ataxic',[9] attributable to effects at the central respiratory pattern generator.[76] Third, severe CSA in opioid users often exhibits a periodic pattern remarkably similar to CSA at altitude, with a cycle period similar to idiopathic CSA (~30–40 s)[75] suggesting that elevated loop gain is responsible. Detailed mechanistic studies in chronic opioid patients are relatively sparse but possible causes of elevated loop gain include: (i) an elevated alveolar PCO_2 which would be expected to reduce CO_2 damping (elevated plant gain), (ii) severe hypoventilation and concomitant hypoxaemia[75] that will presumably raise hypoxic chemosensitivity and (iii) a doubling of the slope of the hypoxic ventilatory response independent of the prevailing hypoxaemia.[77] These factors likely combine to yield an elevated loop gain and promote CSA. An increased loop gain with opioids appears paradoxical given that ventilatory drive is typically reduced, highlighting the important distinction between baseline ventilatory drive and the responsiveness to changes in drive.

Treatment of opioid-induced CSA is challenging. Continuous positive airway pressure (CPAP) may improve sleep apnoea in some patients, but often fails to improve it in others.[75,78] Opioid effects on CSA are thought to be dose dependent such that breathing pattern may actually normalize with reduced doses.[79] Adaptive servo-controlled ventilation has been used effectively in small studies, but the use of this therapy clinically in this context remains to be defined.[75,78] There is a mechanistic basis for use of ventilatory stimulants (acetazolamide) or oxygen but the efficacy of such therapies is unproven. Of particular interest is a case study illustrating that acetazolamide improved opioid-induced CSA in a patient on CPAP therapy, but oxygen was ineffective.[80]

Overlap between and OSA and CSA

OSA is a very common condition affecting roughly 10% of the US population. The details of OSA are covered elsewhere in this *Review Series*, but we review important concepts to give a more complete view of central apnoea pathogenesis. OSA is known to be due to multiple underlying mechanisms: While some patients have primarily an anatomical problem, others have issues with control of upper airway dilator muscles while still others have unstable ventilatory control (high loop gain).[81,82] Some patients have multiple mechanisms underlying apnoea. In theory, treatment directed at the underlying mechanism is likely to yield improvement in apnoea using a personalized approach.

Among OSA patients with high loop gain, the question arises as to why they develop OSA rather than CSA. In reality, many patients have features of both OSA and CSA or can change features during the course of an overnight recording, emphasizing that the distinction between these two conditions can be challenging. A number of lines of evidence suggest considerable overlap between OSA and CSA:

- Patients with more severe OSA have been shown to have higher loop gain than milder OSA or controls using multiple different measurement techniques.[81,82]

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Presumably, the fluctuations in output from the central pattern generator lead to upper airway collapse when output to the upper airway dilator muscles is at its nadir in those who are anatomically predisposed.
- Agents which lower loop gain such as oxygen and acetazolamide improve OSA in some individuals, particularly those with high loop gain.[83–85]
- Tracheostomy in patients with OSA can transform OSA into CSA, that is complex sleep apnoea (see below).
- In patients with CSA, the forced oscillatory technique and direct visualization of the airway have shown evidence of upper airway narrowing/closure during central apnoeas and hypopnoeas.[31,32]
- Some patients have mixed apnoeas with features of both OSA and CSA, for example patients can have minimal respiratory effort during a portion of a respiratory event but evidence of obstructive physiology during the same respiratory event. Thus, some patients are difficult to classify as strictly OSA or CSA.
- Rapid eye movement (REM) sleep is a period of blunted chemosensitivity that is often associated with improvements in CSA including Cheyne–Stokes breathing or periodic breathing at high altitude. Similarly, some OSA patients have worse breathing disturbance in NREM, presumably driven by a higher loop gain in this sleep stage.

Although OSA and CSA clearly have some similar features, this overlap is particularly evident in people with congestive heart failure. In some patients, investigators have observed an overnight conversion of OSA to CSA in conjunction with a reduction in PCO_2 and an increase in circulatory delay suggesting an overnight deterioration of cardiac function and rise in chemosensitivity.[86] CSA can also convert to OSA with improvement in cardiac function and circulatory delay over time,[87] and can also revert to OSA with cardiac transplant.[88] CSA and OSA can both be improved with heart failure treatment in the form of cardiac resynchronization therapy.[89] Given the evidence of considerable overlap, the use of strict cut-off values based on percentage of central events (e.g. >50%) to define CSA may be inappropriate. We therefore favour the use of the more general term sleep apnoea to encompass both CSA and OSA manifestations of disordered ventilatory control.

Treatment emergent CSA: 'complex sleep apnoea'

The overlap between CSA and OSA is particularly relevant for patients with OSA who exhibit CSA when the upper airway is made patent with therapies. This phenomenon has been labelled complex sleep apnoea. The conversion from OSA to CSA was reported in classic studies in the context of tracheostomy. Likewise, during CPAP titrations, removal of upper airway obstruction results in CSA in some patients. This form of CSA often resolves over time with ongoing CPAP treatment, although in individuals with higher loop gain, complex sleep apnoea may persist. Oral appliance therapy can also yield CSA in patients treated for OSA.[4–7]

Although unproven, a likely mechanism of complex sleep apnoea involves the relief of inspiratory flow limitation. In some patients with pharyngeal compromise, increasing ventilatory drive with increasing CO_2 may not yield increased airflow due to the prevailing upper airway mechanics (i.e. ineffective muscle responses). That is, the presence of flow limitation can markedly reduce the controller gain (i.e. no rise in airflow for increasing effort). When inspiratory flow limitation is then relieved with treatment, a high chemosensitivity can be unmasked to yield CSA. In this context, application of CPAP would increase chemoresponsiveness without changing chemosensitivity *per se*.

Depressed ventilatory drive and chemoresponsiveness as a mechanism of CSA

In contrast to the elevated loop gain mechanism of periodic breathing, prolonged apnoeas consequent to reduced ventilatory drive and depressed chemoresponsiveness (i.e. extremely low loop gain) occur in some ~~cases,~~ highlighting the importance of having an intact chemoreflex control system. Infants with prolonged apnoeas (apnoea of prematurity, apnoea of infancy and apparent life-threatening events) – as opposed to periodic breathing – have been found to have a reduced chemosensitivity and a depressed ventilatory drive[10] consistent with a reduced or less robust ventilatory drive response to apnoea/hypoventilation. The neonatal tendency to respond to hypoxia with further ventilatory depression (i.e. negative chemoresponsiveness) may serve to further reinforce an event once initiated. Patients with central congenital hypoventilation syndrome exhibit profound hypoventilation and hypoxaemia during sleep consequent to reduced ventilatory drive and virtually non-existent sleep-related ventilatory responses to CO_2 and hypoxia.[11] In patients with neuromuscular weakness, apnoeas may be seen particularly during REM sleep due to a combination of low chemosensitivity and severe muscle weakness during REM atonia.[12] While the absence of effort during these events classifies them as central, some have advocated for the terminology 'pseudo-central' or 'diaphragmatic' to emphasize the primary role of muscle weakness.

PERSONALIZING TREATMENTS

The loop gain concept integrates several different components into a combined parameter which is helpful in determining overall stability and the likelihood of CSA. Several individual components (chemosensitivity, plant gain and circulatory delay) interact in a multiplicative manner to yield the overall loop gain. Thus, ~~in many cases,~~ the improvement of any given component, strictly speaking, does not require knowledge of the particular mechanism of CSA. For example, instability caused by elevated circulatory delay could be resolved with CPAP/or lateral positioning to improve lung volume (plant gain).

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However, we emphasize that identification of the underlying mechanism may help to guide therapy for a number of reasons. The isolation of an underlying abnormality is critical as such abnormalities may well be the most amenable to improvement with therapy. For instance, a normal circulatory delay may be difficult to improve, but a markedly elevated chemosensitivity may well respond to appropriate interventions (oxygen/pharmacological agents). In addition, the potential for toxicity of an intervention might be heightened if a normal value is being manipulated. For example, a patient with a normal chemosensitivity (but high plant gain and increased delays) may be more likely to exhibit hypoventilation in certain circumstances (e.g. REM) if efforts to suppress chemosensitivity are successful.

The overall loop gain can also be considered the sum of the separate feedback loops for PO_2 and PCO_2.[21] Thus, identifying whether increased chemosensitivity is driven by hypoxic versus hypercapnic hyperreflexia may have important implications for therapy. For example, CSA driven by hypoxic feedback (e.g. infants/altitude) is expected to be readily resolved with supplemental oxygen administration. However, supplemental oxygen is effective in some heart failure patients with CSA but not in others,[90] consistent with findings that some patients with heart failure have increased responses to PO_2 whereas others have increased responses to PCO_2.[43] Thus, we view a mechanistic understanding of control of breathing critical for meaningful progress towards individualized therapies to occur.

Finally, the magnitude of loop gain is also important, regardless of the particular factor destabilizing breathing. For example, it is harder to lower loop gain to below 1 and resolve CSA in a patient with a loop gain of 1.9 at baseline than if it is 1.1. Recognizing the magnitude of instability may inform which treatments have the scope to resolve CSA.[22,33] Clinicians could combine interventions if an individual intervention does not have sufficient potential, for example CPAP plus acetazolamide, or bed elevation plus oxygen. Further investigation along these lines is needed.

PHYSIOLOGICAL MECHANISMS OF TREATMENTS

The following interventions are considered in terms of their mechanistic effects on ventilatory control:

- *CPAP* undoubtedly increases lung volume and consequently improves CO_2 damping (reducing plant gain).[22] There is little direct evidence that CPAP improves circulatory delay, but cardiac function can be improved and a preferential benefit may occur in those with increased filling pressures in whom there is a mechanistic basis for improved cardiac output.[20]
- *Supplemental oxygen* has a profound impact on CSA in infants[91] and at altitude, and improves CSA in some patients with heart failure.[90] Increased arterial PO_2 is known to lower carotid body chemosensitivity.[92] Other beneficial effects on stability are unlikely, as supplemental oxygen is expected to increase plant gain (for feedback control of PO_2) and circulatory delay.
- *Respiratory stimulants* (e.g. inhaled carbon dioxide, rebreathing, acetazolamide and theophylline) act to increase CO_2 damping (reduce 'plant gain') by making alveolar PCO_2 less susceptible to changes due to fluctuations in ventilation.[33] This phenomenon is encapsulated by a reduction in the difference between alveolar and inspired PCO_2. For patients with CSA due to ventilatory depression rather than high loop gain, respiratory stimulants may act to prevent apnoea by restoring baseline ventilatory drive.
- *Sleeping position* can have as profound an impact on CSA as CPAP. Sleeping lateral or with bed elevation can improve CSA and is likely to act in part by raising lung volume.[27,93] Improvements in upper airway collapsibility may also contribute in some individuals.
- *Bi-level positive airway pressure with a backup rate and phrenic nerve stimulation* seek to provide an additional non-chemical source of actual ventilation independent of a subject's own ventilatory drive. The expected effect on loop gain is complex: Loop gain will be reduced by increasing ventilation and lowering the alveolar-inspired PCO_2 gradient. A baseline source of ventilation will minimize the possible amplitude of hypopnoea for any reduction in ventilatory drive, thereby effectively lowering controller gain.[94,95] For patients with CSA due to ventilatory depression, these interventions act to prevent apnoea by providing an additional source of ventilatory effort.
- *Dynamic interventions*, including adaptive servo-controlled ventilation[95] and dynamic inspired CO_2 delivery,[96] seek to clamp ventilation or PCO_2 levels to resolve CSA. If these interventions were completely effective, loop gain would be lowered to zero.

In treating CSA that is secondary to heart failure or opioids, we note that the primary focus must be on resolving the underlying pathophysiology causing CSA.

CONCLUSIONS

CSA, defined as the temporary absence of ventilatory effort during sleep, is seen in a variety of forms across the life span. Paradoxically, in most ~~cases~~, the reduction in ventilatory effort is a consequence of hypersensitive ventilatory effort responses to changes in PCO_2/PO_2, that is elevated loop gain (overshoot/undershoot). In other patients, central apnoeas are the consequence of depressed/absent ventilatory effort responses, that is extremely low loop gain. Treatments for CSA can be explained in terms of effects on loop gain, for example CPAP improves lung volume (plant gain), stimulants reduce the alveolar-inspired CO_2 difference and supplemental oxygen lowers chemosensitivity. A greater understanding of the pathophysiology in subgroups of patients may provide insight into which interventions will have the greatest beneficial impact.

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