Central sleep apnoea (CSA) is characterized by the cessation of breathing during sleep due to absent ventilatory drive and may be associated with symptoms of insomnia, excessive daytime sleepiness or frequent arousals. Central apnoeas occur through two pathophysiologic patterns, either post-hyperventilation or post-hypoventilation. The prevalence of CSA is dependent on the population being studied, the predominant risk factors being elderly age group and co-morbid conditions. Data regarding the racial distribution of this disorder are very limited. CSA may be a clinical marker of underlying medical disorders, including cardiac or neurological disease, with resultant significant morbidity and mortality. Given that the underlying pathogenesis remains poorly understood, therapeutic options are currently limited to empiric treatment with PAP devices and rudimentary attempts at pharmacologic therapy with respiratory stimulant drugs and/or oxygen/carbon dioxide gas supplementation as well as treating the underlying cause. The long-term impact of CSA on health and mortality needs further clarification. Future research should be aimed at elucidating the physiologic determinants and consequences of central breathing instability in populations of different age groups, gender and racial descent, as a prerequisite to the development of novel therapeutic interventions in the different populations.

**Key words** Central sleep apnoea - cheyne stokes breathing - neurodegenerative diseases and stroke - primary central sleep apnoea

There is a paucity of data about CSA in the different ethnic groups, including those of Asian descent. Most data on sleep apnoea in persons of Asians descent pertains to obstructive sleep apnoea (OSA). Given that craniofacial characteristics vary between Asians and whites, leading to differences in the demographics and pathogenesis of OSA in Asians, it is conceivable that the pattern and pathogenesis of central apnoeas in Asians may be unique. However, the lack of available studies precludes insight into this disorder in the different population groups.

**Epidemiology of CSA**

The prevalence of CSA varies depending on the population investigated. Epidemiologic studies...
suggest a high prevalence of both obstructive and central sleep apnoeas, in the elderly with a significant association between age and apnoea-hypopnoea index (AHI, number of apnoeas and hypopnoeas per hour of sleep). Epidemiologic studies also indicate that CSA per se is more prevalent in older adults relative to middle-aged individuals. In one of the earliest studies involving 40 elderly individuals (mean age: 72.7 yr), Carskadon & Dement found that 37.5 per cent of all subjects over the age of 62 had apnoeas or hypopnoeas, mostly central apnoeas. Large epidemiologic cohorts have also demonstrated a higher percentage of central apnoeas in the elderly population. Bixler et al. noted that the prevalence of any type of sleep apnoea (central and obstructive) was age related with central apnoeas at 1.1 per cent at age >65 yr vs. 0.4 per cent at 45-64 yr. This large community-based epidemiologic study found that the prevalence of CSA (defined as central apnoea index, CAI ≥2.5/h) increased from 1.7 per cent (0.8, 3.4) in the middle age group to 12.1 per cent (6.5, 21.6) in the older age group (OR= 8.3). Interestingly, no men in the youngest age group met the threshold of CAI ≥2.5 and all the men who met a high CAI ≥20 were in the ≥65 yr age group. The age-specific prevalence of a CAI ≥ 20 for males ≥ 65 yr was 5.2 per cent. For men, there was a prevalence of central apnoea of 0.4 per cent (0.1, 1.2). The overall prevalence of central apnoea (CAI> 0) in women was only 0.3 per cent (0.0, 0.6) compared with 7.8 per cent (5.9, 9.7) in men [RR = 0.04 (0.0, 0.05), P = 0.004]. In a separate epidemiologic study of a large population of elderly men, obstructive apnoea (OA, defined as an OAI index, OAI ≥1) was observed in 35.1 per cent, whereas, central apnoea (defined as CAI≥5) was observed in 7.5 per cent of participants.

Medical conditions like heart failure and stroke also predispose to a higher prevalence of CSA. CSA may have important clinical implications as it has been associated with adverse clinical sequelae, including increased risk for heart disease and cardiovascular mortality. Further investigations with large longitudinal studies are needed to clarify the natural history and clinical outcomes of this disorder.

**Pathophysiology of CSA**

On polysomnographic recording, CSA is characterized by the cessation of airflow and ventilatory effort lasting 10 sec or longer, with central apnoeas occurring at a rate of five or more per hour. The patient may report symptoms of excessive daytime sleepiness, insomnia or frequent arousals. A discussion regarding the pathophysiology is important as it underpins the rationale behind current and evolving therapy. Central apnoeas can occur through two broad pathophysiologic patterns, either post-hyperventilation or post-hypoventilation.

1) **Central apnoea secondary to hyperventilation**

The removal of the wakefulness drive to breathe renders ventilation dependent on the prevailing chemical stimuli and unmasks a highly sensitive hypocapnic apnoeic threshold (HAT). Central apnoea occurs if PaCO₂ (arterial CO₂) falls below a highly reproducible hypocapnic apnoeic threshold. Patients with post-hyperventilation central apnoea are typically free of neuromuscular or pulmonary disorder and have a normal or exaggerated response to hypocapnia. Thus, there is no evidence of daytime alveolar hypoventilation, implicating a transient instability of the ventilatory control system.

**How does the first apnoea begin?** Oscillation in sleep state, transient hypoxia possibly due to retention of secretions or reduced lung volumes in obese supine patients may be primary precipitating events. For example, hypoxia stimulates ventilation, subsequently leading to hypocapnia, and subsequently, apnoea. The occurrence of apnoea initiates the repetitive process of apnoea-hypopnoea and leads to sustained breathing instability, manifested as periodic breathing. Post-hyperventilation central apnoea is a heterogeneous entity that may be an idiopathic phenomenon or a secondary condition, as described below. The pathogenesis may vary depending upon the clinical condition.

**How is central sleep apnoea related to obstructive sleep apnoea?** CSA may also induce OSA. There is evidence that patients with sleep apnoea and snorers with evidence of inspiratory flow limitation are dependent on ventilatory motor output to preserve upper airway patency. In these individuals, pharyngeal obstruction occurs when ventilatory drive reaches a nadir during induced periodic breathing. Likewise, using fiberoptic nasopharyngoscopy, Badr et al. have shown, that central apnoea is associated with pharyngeal narrowing or occlusion early (<10 sec) during the central apnoeic period and even in the absence of inspiratory efforts. In addition, many OSA patients display an enhanced controller gain during sleep, which would predispose to periodic breathing. Furthermore, the ability of the patient with severe OSA to effectively compensate (via effective neural
control of the respiratory muscles of both the upper airway and the pump, without EEG arousal) for airway narrowing and increased mechanical load was shown, by correlational analysis, to be a more important determinant of the degree of cycling behaviour of airway patency and ventilation than was the inherent passive collapsibility of the airway. An implication of these clinical data is that although an inherently collapsible airway may allow for significant airway narrowing and even obstruction during sleep, any repetitive cycling behaviour in airway patency and ventilation is critically dependent upon neurochemical control mechanisms.

In summary, differences in ventilatory control stability during sleep may contribute to CSA; however, the few available investigations that have described age-related changes in ventilatory control during sleep have reported conflicting findings. In addition, increased prevalence of co-morbid conditions such as thyroid disease, congestive heart failure, atrial fibrillation, and cerebrovascular disease may also contribute to increased susceptibility to develop central apnoea in older adults. Increased sleep state oscillations may also precipitate central apnoeas in older adults. Therapy is aimed at treating the underlying condition, and often, addition of nasal continuous positive airway pressure (CPAP) and/or supplemental oxygen and carbon dioxide (Fig.).

(ii) Central sleep apnoea secondary to hypoventilation

The transition from wakefulness to sleep is associated with decreased ventilatory motor output, a fall in ventilation and increased \( \text{PCO}_2 \), likely due to the combination of decreased ventilatory motor output and increased upper airway resistance. Therefore, increased \( \text{PCO}_2 \) by 3-6 mmHg during sleep is a physiologic event. Similarly, rapid eye movement (REM) sleep, especially phasic REM is associated with hypventilation and hence increased \( \text{PCO}_2 \). Hypoventilation during sleep may be inconsequential in a healthy individual but leads to significant reduction in alveolar ventilation. However, in patients with chronic ventilatory failure, neuromuscular disease or chest wall disease, these changes may manifest as central apnoea or hypopnoea. This is particularly noted in patients who suffer from central nervous system disease (e.g., encephalitis), neuromuscular disease or severe abnormalities in pulmonary mechanics (e.g., kyphoscoliosis). Thus, central apnoea due to hypoventilation is due to the removal of the wakefulness stimulus to breathe or to phasic REM-related hypoventilation. This type of central apnoea does not necessarily meet the strict definition of “apnoea”; as ventilatory motor output is severely reduced and therefore insufficient to preserve alveolar ventilation. Likewise, it may not meet the definition of “central” in patients with respiratory muscle disease or skeletal deformities. The figure summarizes an algorithm for the management of central sleep apnoea based on pathogenesis.

Elderly patients may be at high risk for developing episodic hypoventilation and related apnoea/hypopnoea given the high prevalence of neurological disease in older adults. The clinical presentation may be of nocturnal ventilatory failure, particularly in patients with marginal ventilatory status, or worsening of existing chronic ventilatory failure. Arousal from sleep restores alveolar ventilation to a variable degree, while resumption of sleep reduces ventilation in a cyclical fashion. Consequently, the presenting clinical picture includes both features of the underlying ventilatory insufficiency (e.g., morning headache, cor pulmonale, peripheral oedema, polycythemia, and abnormal pulmonary function tests) and features of the sleep apnoea/hypopnoea syndrome (e.g., poornighturnal sleep, snoring, and daytime sleepiness). The mechanism(s) responsible for CSA in a given patient influence(s) the management strategy aimed at restoration of effective alveolar ventilation during sleep. Treatment of choice in such patients is assisted ventilation. Nasal CPAP and supplemental oxygen are unlikely to alleviate the condition (Fig.).

Risk factors for CSA

Age: While CSA is more prevalent in older adults relative to middle aged individuals, the effect of ageing on sleep-related decrease in ventilatory drive...
in humans is unclear. We know that sleep eliminates the wakefulness drive to breathe\textsuperscript{23} leading to reduced ventilatory motor output. Findings from a canine model suggest that ageing is associated with decreased minute ventilation and increased PaCO\textsubscript{2} during slow wave sleep\textsuperscript{24}. However, the effect of ageing on sleep-related decrease in ventilatory drive and on chemosensitivity during wakefulness in humans is uncertain. Available studies have reached conflicting conclusions regarding the effect of age on chemosensitivity. A few have shown a difference\textsuperscript{25,26} or decreased responsiveness\textsuperscript{27} to hypercapnia during wakefulness or sleep\textsuperscript{28}. The response to hypoxia is also variable. While one study\textsuperscript{27} demonstrated a lower initial increase in minute ventilation in response to acute mild hypoxia in men>70 yr, others\textsuperscript{29-31} reported that the ventilatory response to sustained hypoxia declined in elderly men but was the same as in younger men.

The effect of age on susceptibility to periodic breathing is also unclear. The available limited evidence does not indicate a higher susceptibility to developing periodic breathing\textsuperscript{32}. In fact, a recent study\textsuperscript{33} found no difference in loop gain in the elderly OSA group upon using proportional assist ventilation. However, the application of proportional assist ventilation may alter some of the components of the loop gain, namely plant gain and mixing factors and hence obscure real differences among subjects\textsuperscript{34}. The HAT is a measure of a robust marker of susceptibility to post-hyperventilation apnoea and possibly to periodic breathing. Nasal mechanical ventilation is used to induce hypocapnia and hence central apnoea. It is sensitive to the changes in the background drive to breathe (‘plant gain’)\textsuperscript{34,35} as well as to the slope of the reduction in ventilation below eupnoea in response to induced hypocapnia (‘controller gain’)\textsuperscript{35}.

Ageing also has an important influence on respiratory plasticity in animals. One example of respiratory plasticity is the long-term facilitation (LTF) phenomenon. LTF is a physiologic response noted in animal models and humans, in response to episodic hypoxia (EH)\textsuperscript{36-42} and is characterized by prolonged increase in ventilation up to hours, demonstrating a form of respiratory neuroplasticity. A decline in LTF in humans may attenuate a significant protective mechanism that maintains upper airway patency\textsuperscript{43}. A recent study reported a significant negative correlation between age and the genioglossus muscle LTF in normal humans\textsuperscript{44}. LTF of genioglossus was present in healthy non-flow limited humans (n=12) during NREM sleep and that this was inversely correlated with age. However, this study only investigated a narrow age range and similar investigations in older age groups are lacking. Thus, further explorations of the basic mechanisms of an increased occurrence of central apnoeas in the elderly (in turn leading to obstructive apnoeas), examining the factors modulating ventilatory control stability with well-designed experiments are needed.

In addition to age, several physiologic and pathologic factors may modulate the susceptibility of the elderly to developing central apnoea. These include gender, sex hormones, sleep state and medical conditions.

Gender is a significant modifier of the effects of age on the susceptibility to central apnoea. There is epidemiologic and empiric evidence that central apnoea is less common in pre-menopausal women relative to men or post-menopausal women. One large population study\textsuperscript{2} demonstrated paucity of central apnoea in pre-menopausal women. Likewise, there is experimental evidence that the hypocapnic central apnoea sleep is higher in men relative to women. Using nasal mechanical ventilation during stable NREM sleep, Zhou et al\textsuperscript{45} have shown that the apnoeic threshold was -3.5 vs. -4.7 mmHg below room air level in men and women respectively. This difference was not due to progesterone. Rowley et al\textsuperscript{46} explored the determinants of the apnoeic threshold in normal individuals. Interestingly, age, \textit{per se}, was not an independent determinant of the apnoeic threshold in men or post-menopausal women. Only pre-menopausal women demonstrated narrowing between apnoeic and apnoeic PCO\textsubscript{2} with ageing, indicative of ventilatory instability.

Sex hormones also influence the susceptibility to central apnoeas. Male sex hormones are important determinants of the apnoeic threshold. Administration of testosterone to healthy pre-menopausal women for 12 days elevates the apnoeic threshold closer to eupnoea, narrowing the magnitude of hypocapnic required for induction of central apnoea during NREM sleep\textsuperscript{47}. Conversely, suppression of testosterone with leuprolide acetate in healthy males decreases the hypocapnic apnoeic threshold\textsuperscript{48}. Finally, administration of hormone replacement therapy to post-menopausal women lowered their apnoeic threshold to the level of pre-menopausal women\textsuperscript{49}. The complex interactions between age, gender, sex hormones, and menopausal
status render broad notions generalizations difficult to uphold. In addition, the proportion of participants in studies declines with advancing age, whether because of substantial co-morbidity or as a survival effect.

Sleep state oscillations may precipitate central apnoea in older adults. Transient breathing instability and central apnoea often occurs during the transition from wakefulness to NREM sleep. As sleep state oscillates between wakefulness and light sleep, the level of PaCO₂ is at or below the hypocapnic level required to maintain rhythmic breathing during sleep (i.e., the “apnoeic threshold”), resulting in central apnoea; recovery from apnoea is associated with transient wakefulness and hyperventilation. The subsequent hypocapnia elicits apnoea upon resumption of sleep. Consolidation of sleep alleviates the oscillation in sleep and respiration and stabilizes PaCO₂ at a higher set point above the apnoeic threshold. Interestingly, central apnoea may occur without preceding hyperventilation at the transition from alpha to theta in normal subjects and is associated with prolongation of breath duration.

Race: Unlike in OSA, the effect of racial characteristics on the prevalence and pathogenesis of CSA has not been studied. Recently, a cross-sectional analysis of the MrOS sleep study (Osteoporotic Fractures in Men Sleep Study) reported on the prevalence and distribution of sleep-disordered breathing (SDB) in a large cohort of predominantly Caucasian (90%) older men (age 76.4±5.5 yr) from six US communities (n=2911). Asians comprised 2.9 per cent of the cohort. The prevalence of moderate–severe SDB (including obstructive apnoeas, hypopnoeas and central apnoeas) with respiratory disturbance index >15, was estimated to be 21.4 to 26.4 per cent. Multivariable logistic regression models, after adjusting for age and obesity, demonstrated that Asians had an increased risk for SDB compared to Caucasians, adjusted odds ratio, 2.14 (1.33, 3.45). In unadjusted and age-, race-, and obesity adjusted models, CA was associated only with age and heart failure and not with race. Analyses performed including only participants with a CAI of 5 or greater without a concomitant OAI of 5 or greater revealed a significant association with age, however, there was not enough power to detect a significant association with congestive heart failure (OR was reduced from 1.47 to 1.29).

REM sleep: Post-hyperventilation CSA is uncommon during REM sleep raising the possibility that breathing during REM sleep is impervious to chemical influences, possibly due to increased ventilatory motor output relative to NREM sleep. This question is further confounded by the difficulty in conducting such experiments without disrupting REM sleep. Nevertheless, central apnoea due to hypoventilation may be seen in REM sleep, triggered by the loss of intercostal muscle activity during phasic REM sleep and subsequent hypoventilation. This may manifest as apparent central apnoea or hypopnoea in patients with neuromuscular disease diaphragmatic dysfunction or compromised pulmonary mechanics. If severe impairment is present, nadir tidal volume may be negligible and the event may appear as central apnoea. Thus, central apnoea during REM sleep represents transient hypoventilation rather than post-hyperventilation hypocapnia.

Medical conditions may increase the propensity to central apnoea. Congestive heart failure (CHF) is associated with high prevalence of central apnoea. Sleep apnoea is common in patients with CHF. Javaheri et al demonstrated that 51 per cent of male patients with CHF had sleep-disordered breathing; 40 per cent had CSA and 11 per cent obstructive apnoea. Risk factors for CSA in this group of patients included age > 60 yr, male gender, atrial fibrillation and daytime hypocapnia (PCO₂ < 38 mm Hg during). However, risk factors for CSA differed by gender; the only independent determinant in men was body mass index (BMI), whereas age over 60 was the only independent determinant in women. Patients with central apnoea and CHF demonstrate pulmonary vascular congestion leading to hyperventilation and hypocapnia; hence, there is an absence of a rise in PCO₂ from wakefulness to sleep.

Sleep apnoea is common after a cerebrovascular accident (CVA); with central apnoea being the predominant type in 40 per cent of patients of sleep apnoea after a CVA. Likewise, central apnoea occurs in 30 per cent of patients stable methadone maintenance treatment. Finally, several medical conditions, in addition to CHF and atrial fibrillation, predispose to the development of central apnoea including hypothyroidism, acromegaly, and renal failure. Notably, nocturnal haemodialysis has been associated with improvement in sleep apnoea indices.

Etiologic classification of CSA

Based on aetiology, CSA can be broadly divided into 3 categories: Primary central sleep apnoea, Cheyne stokes breathing pattern, and central sleep apnoea in stroke and neurodegenerative diseases.
Primary central sleep apnoea

By definition, primary CSA is of unknown aetiology and comprises five or more central apnoeas per hour of sleep associated with one or more of the following symptoms: daytime sleepiness, frequent awakenings with complaints of insomnia or awakening with shortness of breath, and in the absence of another concurrent sleep disorder, medical or neurological disorders or medication/substance use. Thus, it is a diagnosis of exclusion. Typically these patients demonstrate increased chemoresponsiveness and sleep state instability. Frequent oscillation between wakefulness and stage 1 NREM sleep may cause sleep fragmentation and poor nocturnal sleep as the presenting symptoms. Other symptoms like snoring and witnessed apnoeas may be present. Patients with primary CSA have a high hypoxic response. Hypocapnia leads to central apnoea if end-tidal CO$_{2}$ (P$_{ET}$CO$_{2}$) is reduced below a threshold, the HAT. These patients have significantly lower mean transcutaneous and P$_{ET}$CO$_{2}$ during sleep and lower arterial PaCO$_{2}$ levels while awake, typically a 2 to 3 mm Hg difference from controls, and have increased wake ventilatory responses to CO$_{2}$. The onset of central apnoea may initiate several processes that perpetuate breathing instability including inertia of the ventilatory control system, hypoxia and transient arousal as described above. These combined factors produce ventilatory overshoot, hypocapnia and recurrent central apnoeas and perpetuates further breathing instability.

The prevalence of primary CSA in persons of Asian descent is not known. It is also not clear whether gender or genetics modify the prevalence. White et al. and Bradley et al. reported a strong male predominance, while Roehrs et al. observed central apnoeas more commonly in women. While there are no prospective studies evaluating the course and long-term outcomes, it is believed that the chemoresponsiveness of the respiratory system is high so that significant hypoxia and hypocapnia rarely develop during the course of the disease. It is distinguished from CSR in that there is no crescendo-decrescendo pattern and the cycle times are shorter. In primary CSA, the apnoeas are terminated with an abrupt, large breath, not with a gradual increment in ventilation. Unlike sleep related hypoventilation syndromes, the hypoxaemia in primary CSA is less pronounced and there is absence of hypocapnia on waking arterial blood gases.

In primary CSA, daytime hypersomnolence is less common than with OSA, although such daytime sleepiness has been commonly described in patients with central apnoea. As the proportion of obstructive or mixed events increases in these patients hypersomnolence may become more frequent. The primary complaint of many patients with central apnoea tends to be insomnia, restless sleep, or frequent awakenings during the night that may be accompanied by shortness of breath. Patients with these central apnoeas also tend to have a normal body habitus, unlike the characteristically obese patient with obstructive apnoea. Arousals from apnoeas disrupt normal sleep architecture. There was a reduction in the normal percentage of stage 3 or 4 sleep and an increase in stage 1 or 2 sleep in a group of patients with about 50 per cent central apnoeas. Frequent arousals and awakenings generally associated with the hypocapnia after an apnoea can lead to disruption of the normal distribution of sleep stages.

Cheyne Stokes breathing pattern in heart failure

On polysomnography, Cheyne-Stokes breathing pattern is the presence of at least 10 central apnoeas and hypopnoeas per hour of sleep in which the hypopnoea has a crescendo-decrescendo pattern of tidal volume accompanied by frequent arousals from sleep and occurs in association with a serious medical illness such as heart failure, stroke or renal failure. In this section, Cheyne-Stokes respiration (CSR) occurring in the context of heart failure is discussed. Patients with central apnoea and CHF demonstrate pulmonary vascular congestion leading to hyperventilation and hypocapnia; hence, there is an absence of rise in P$_{ET}$CO$_{2}$ from wakefulness to sleep. Increased ventilation and reduced P$_{ET}$CO$_{2}$ indicate decreased plant gain, which should be stabilizing. In other words, steady-state reduction of PaCO$_{2}$ is potentially stabilizing rather than destabilizing as is commonly thought. However, the apnoeic threshold in CHF patients with central apnoea is precariously close to the eupnoeic PaCO$_{2}$, owing to increased controller gain. Those with CSA have a significantly larger ventilatory response to carbon dioxide than those without (5.1±3.1 vs. 2.1±1.0 liters per minute per millimeter of mercury, $P$=0.007), with a significant positive correlation between ventilatory response and the number of episodes of apnoea and hypopnoea per hour during sleep ($r$=0.6, $P$=0.01). Consequently, small decrements in PaCO$_{2}$ cause central apnoea.

Given that CHF is a major public health problem, the association between sleep-disordered breathing (SDB) and CHF has important clinical significance.
Central sleep apnoea in stroke and neurodegenerative diseases

Central apnoeas and periodic breathing occur with increased frequency either in subjects with neurological disorders such as infarction, tumour, or diffuse encephalopathies. Patients with cerebrovascular disease (stroke, or transient ischaemic attacks) have a high prevalence of SDB, mainly OSA. Whether stroke is a cause or a result of SDB is not clear. In one study, there was no change in the frequency of obstructive apnoeas 3 months after the stroke compared with that at 48 h. However, central apnoeas decreased at 3 months, leading the authors to conclude that the obstructive events probably occurred before the stroke and were a risk factor for stroke, whereas the CSA developed after stroke. More recent data from a prospective series of first ever stroke, suggest that central periodic breathing during sleep may develop in strokes involving autonomic (insula) and volitional (cingulated cortex, thalamus) respiratory networks and that this seems to resolve within 3 months.

CSA may also be present in neurodegenerative disorders, e.g., Parkinson's disease and multisystem atrophy, where it may be the presenting feature or may develop in the late stages of the disorder. In CSA related to central degenerative disorder, concomitant symptoms of the underlying disorder may be present; these may include ataxia, dementia, cogwheel rigidity or dysautonomia. Multisystem atrophy (MSA) is a sporadic, progressive, adult onset disorder characterized by autonomic dysfunction, parkinsonism and ataxia in various combinations. Damage to the brainstem, particularly the medullary area, may lead to hypoventilation during wakefulness but more commonly affects ventilation during sleep early in the disease. The autonomic manifestations include orthostatic hypotension, impaired vagal regulation of heart rate (cardiovagal failure), anhidrosis, impotence, and urinary incontinence or retention, which may precede the motor symptoms. Respiratory dysfunction, including sleep-related breathing disorders, may be a serious manifestation of MSA. Although OSA is an important manifestation of this disorder, CSA may also occur as the presenting feature of MSA where CSA developed 4 yr prior to the onset of MSA or develop in later stages of the disease. In a case series of six patients, SDB was present as an early finding of MSA. Three of these patients presented with acute respiratory distress before the ultimate diagnosis of MSA was made; the other three had OSA due to bilateral vocal cord paralysis and presented with stridor.

Pathogenesis in neurodegenerative diseases: CSA may reflect impaired ventilatory chemosensitivity in MSA, as these patients have been shown to have impaired ventilatory responses to hypercapnia or hypoxia. CSA associated with neurodegenerative disorders in the elderly may be the manifestation of ageing process and may arise because the neuropathologic changes of MSA are prominent in the brainstem regions where the respiratory centers are located. The central pathological process in MSA involves neuronal cell loss and gliosis throughout the central nervous system (CNS), especially in the putamen, caudate, substantia nigra, locus coeruleus, pontine nucleus, inferior olivary nucleus, purkinje cells and the intermediolateral cell columns of the thoracic spinal cord. The pathological hallmarks of MSA are argyrophyllic cellular inclusions in oligodendrocytes throughout the involved regions of...
the CNS. In MSA, oligodendrocyte apoptosis occurs in a distribution similar to the finding of these cellular inclusions. Specifically, there is loss of pre-Botzinger complex (preBöC) neurons in of the medulla, which are thought to be responsible for respiratory rhythmogenesis. In addition, the ventral medullary arcuate nucleus degenerates in MSA with severe depletion of putative chemosensitive glutamatergic and serotonergic neurons in the ArcN of the ventral medullary surface in MSA. It is postulated that involvement of any or both of these neurons may contribute to impaired ventilatory responses to hypercapnia and hypoxia in this disorder. In addition, the neurokinin 1-expressing (NK1R) neurons of the preBöC in the ventrolateral medulla are depleted by 60 per cent in Parkinson’s disease and by 89 per cent in individuals with MSA, suggesting substantial damage to the preBöC. Similarly, preBot NK1R neuron ablation in adult rats lead to an ataxic breathing when 80 per cent of the neurons were ablated, indicating the importance of this area in respiration. Multiple system atrophy should probably be considered in the differential diagnosis of the neurogenic causes of late-onset CSA and progressive alveolar hypoventilation. Case reports of CSA in Parkinson’s disease have also been reported. Assessment of respiratory function, when both awake and asleep, maybe diagnostically helpful in patients with atypical Parkinsonism, ataxia, or dysautonomia. There is a need for longitudinal studies in larger populations to determine the frequency and spectrum of neurodegenerative diseases in the elderly population with CSA. Although an association between OSA and APOE epsilon-4 genotype (a marker of Alzheimer’s disease) has been reported, it has specifically not been related to CSA.

Finally, chronic neuromuscular diseases, such as amyotrophic lateral sclerosis, muscular dystrophy or myasthenia gravis, may lead to waking alveolar hypoventilation with further hypoventilation during sleep. These may occasionally be associated with central apnoeas, although hypoventilation is the more prominent disorder. The treatment of the nocturnal hypoventilation with noninvasive nasal ventilation may delay frank waking respiratory failure.

**Diagnosis**

Nocturnal polysomnography is the standard diagnostic method, including measurements of sleep and respiration. The latter includes detection of flow, measurement of oxyhaemoglobin saturation and detection of respiratory effort. Detection of respiratory effort is important to distinguish central from obstructive apnoea. This requires measurement of oesophageal pressure, as a reflection of pleural pressure changes. However, the complexity and invasiveness of the procedure have precluded widespread use. Instead, most clinical sleep laboratories utilize surface recording of effort, to detect displacement of the abdominal and thoracic compartments and dysynchrony during episodes of upper airway obstruction. Respiratory inductive plethysmography (RIP), calibrated or uncalibrated, can adequately assess respiratory effort. A complete absence of thoracoabdominal motion (RIP or strain gauges) throughout an apnoea suggests the event is central in origin. Measurement of the lapsed time for a pulse signal to reach the periphery; or pulse transit time (PTT) can also serve as a non invasive index of respiratory effort. The technique measures the elapsed time between R wave on the ECG and the arrival of the pulse wave to the finger. The underlying physiologic principle is that blood pressure influences vessel stiffness and hence the speed of the pulse wave. When blood pressure increases during an apnoea owing to increased intrathoracic pressure swings, the PTT displays parallel swings.

**Treatment**

Despite its potential morbidity and mortality, a lack of knowledge about the specific underlying pathogenic mechanisms hinders the development of novel pharmacologic therapies. Current principal therapies remain limited to mechanical devices while there have been rudimentary attempts at pharmacologic therapy with respiratory stimulant drugs and O₂ and CO₂ gas supplementation.

1. **Positive pressure therapy**

Central apnoea may respond to nasal CPAP therapy, especially if in combination with episodes of obstructive or mixed apnoea. Moreover, primary CSA may respond to nasal CPAP therapy by preventing pharyngeal narrowing during central apnoea and hence mitigating the ensuing ventilatory overshoot and perpetuation of ventilatory instability. Many patients with idiopathic CSA receive a trial of nasal CPAP, which has been shown to reverse CSA, even in the absence of obstructive respiratory events. Nasal CPAP has been shown to result in significant improvement in sleeping functional status compared to controls.
for 1 month in patients with central apnoea and CHF resulting in a decrease in the frequency of apnoeas and hypopnoeas, an increase in mean transcutaneous PCO$_2$, a reduction in mean minute ventilation and an increase in mean oxyhaemoglobin saturation (O$_2$ Sat) during sleep$^{106}$. The combination of increased PCO$_2$ and increased O$_2$ Sat readily explains the amelioration of central apnoea. Hence, nasal CPAP is the initial option during a therapeutic titration study, despite the lack of systematic studies on nasal CPAP therapy in patients with primary central sleep apnoea. Older individuals probably utilize CPAP as well as younger patients. CPAP should be used throughout the sleep duration every night.

Treatment of CSR usually consists of optimization of medical management for CHF. Nasal CPAP may have significant salutary effects on patients with CHF and CSA. Several lines of evidence, both theoretical and empiric, underpin the use of CPAP in this setting. For example, one study has demonstrated increased LVEF and a reduction of combined mortality- cardiac transplantation risk by 81 per cent, but only in patients with CSA$^{107}$. The exuberance regarding nasal CPAP therapy in patients with central apnoea and CHF did not withstand the rigors of controlled clinical trials. The Canadian Continuous Positive Airway Pressure trial, or CAnPAP$^{103}$, tested the hypothesis that CPAP would improve the survival rate without heart transplantation in patients with heart failure and CSA. The study enrolled 258 patients who had heart failure and CSA; participants were randomly assigned to the nasal CPAP treatment group (n=128) or no CPAP (130 patients). Duration of follow up was for a mean of 2 yr. There was greater improvement in the CPAP group at 3 months relative to the placebo group as evidenced by greater reductions in AHI, ejection fraction, mean nocturnal oxyhaemoglobin saturation, plasma norepinephrine levels, and the distance walked in 6 min at 3 months. Nevertheless, there was no difference in the overall event rates (death and heart transplantation) between the two groups. Thus, nasal CPAP had no effect on survival, despite the effect on the “severity” of central apnoea and several intermediate outcome variables. Therefore, current evidence does not support the use of CPAP to extend life in patients who have heart failure and CSA. In a post-hoc analysis of the CAnPAP$^{108}$, of the 258 heart failure patients with CSA, 110 of the 130 randomized to the control group and 100 of the 128 randomized to CPAP had sleep studies 3 months later. CPAP patients were divided post-hoc into those whose AHI was or was not reduced below 15 at this time (CPAP-CSA suppressed, n=57, and CPAP-CSA unsuppressed, n=43, respectively). Despite similar CPAP pressure and hours of use in the 2 groups, CPAP-CSA–suppressed subjects experienced a greater increase in LVEF at 3 months (P=0.001) and significantly better transplant-free survival [hazard ratio (95% confidence interval) 0.371 (0.142 to 0.967), P=0.043] than control subjects, whereas the CPAP-CSA–unsuppressed group did not [for LVEF, P=0.984, and for transplant-free survival, hazard ratio 1.463 (95% confidence interval 0.751 to 2.850), P=0.260]. These results suggest that CPAP might improve both left ventricular ejection fraction and heart transplant–free survival in heart failure patients if CSA is suppressed soon after its initiation$^{108-109}$.

Non invasive positive pressure ventilation (NIPPV) using pressure support mode (bi-level nasal positive pressure) is effective in restoring alveolar ventilation during sleep$^{110}$. Clinical indications include nocturnal ventilatory failure and central apnoea secondary to hypoventilation. There is evidence that NIPPV exerts a salutary effect on survival in patients with ventilatory failure secondary to amyotrophic lateral sclerosis$^{111-112}$. It is unclear whether NIPPV exerts a similar effect in other neuromuscular conditions associated with nocturnal ventilatory failure. However, the overall evidence supports the use of NIPPV in a pressure support mode to treat CSA secondary to hypoventilation, such as neuromuscular or chest wall related nocturnal hypoventilation. If the ventilatory motor output is insufficient to “trigger” the mechanical inspiration, adding a backup rate ensures adequate ventilation.

Most patients with ventilatory failure tolerate non-invasive positive pressure ventilation well. However, there are a few specific drawbacks. The use of NIPPV in the controlled mode results in laryngeal aperture narrowing and may decrease the delivered tidal volume during NIPPV$^{113}$. Alleviating this problem is feasible with appropriate adjustments of volume, flow, and inspiratory time$^{114}$. The potential role of NIPPV in the treatment of non-hypercapnic, post-hyperventilation central apnoea is uncertain. The addition of a backup rate renders NIPPV controlled mechanical ventilation. However, NIPPV in the pressure support, bi-level mode augments tidal volume; the ensuing hyperventilation results in hypocapnia and possible worsening of central apnoea and periodic breathing during sleep$^{115}$. Recent technological advances allowed for variations in the mode of delivering positive pressure ventilation.
One such method is Adaptive Servo Ventilation (ASV) that provides a small but varying amount of ventilatory support, against a background of low level of CPAP. Contrary to bi-level pressure support devices, changes in respiratory effort result in reciprocal changes in the magnitude of ventilatory support. Thus, ventilation remains slightly below the baseline, eupneic average. There is evidence that ASV is more effective than CPAP, bi-level pressure support ventilation, or increased dead space in alleviating central sleep apnoea\textsuperscript{116}. However, this needs to be confirmed in a systematic fashion in long-term studies in larger populations.

There is limited evidence about the efficacies of PAP in the Asian population. The use of bi-level PAP and ASV for CSA with Cheyne-Stokes respiration (CSA-CSR) in CHF has been reported in a few case series\textsuperscript{49,117,118}. Both bi-level PAP and ASV improved CSA-CSR. These studies noted significant improvements in left ventricular EF, plasma brain natriuretic peptide and NYHA functional class after 3 months of treatment with bi-level PAP\textsuperscript{117}.

More research is needed on the use of PAP treatment. Evaluations of immediate and long-term benefits of PAP treatment including evaluation for cardiovascular, cognitive, psychological, and functional outcomes are required. Research also needs to investigate which patients should receive treatment.

2. Pharmacologic agents

Certain pharmacologic agents may influence the propensity to develop central apnoea. Therapy of the underlying condition that is predisposing to CSA should be initiated. For example, the use of beta-blockers in patients with CSA and CHF is associated with reduced apnoea index\textsuperscript{119}. Conversely, narcotics may worsen central apnoea; a change in the pain control regimen may ameliorate the severity of CSA\textsuperscript{120}. If a concomitant clinical condition is present, such as congestive heart failure, hypothyroidism, or acromegaly, optimization of medical therapy is also required and may ameliorate the severity of central apnoea. The role of pharmacological therapy for primary central apnoeas is very modest, and there are no controlled clinical trials demarcating the outcomes. There is evidence derived from small studies, but no large clinical trials, to support the use of acetazolamide and theophylline in the treatment of central apnoea\textsuperscript{121}. Acetazolamide is a carbonic anhydrase inhibitor and a weak diuretic that causes mild metabolic acidosis and enhances the respiratory drive. In a few studies acetazolamide ameliorated CSA when administered as a single dose of 250 mg before bedtime\textsuperscript{122}. In a study by White \textit{et al}\textsuperscript{123}, there was a reduction in central apnoeas, an increase in $O_2$ saturation and improvement in symptoms. However, in another study an improvement was not consistently observed\textsuperscript{124}. In patients with heart failure, Cheyne-Stokes breathing with an AH\textsubscript{1} of more than 15/h, administration of a single dose of acetazolamide before sleep improved central sleep apnoea and related daytime symptoms; mean age of patients was $66 \pm 6$ yr\textsuperscript{125}.

Theophylline ameliorates the severity of Cheyne-Stokes respiration in patients with CHF\textsuperscript{121,126}. The short-term administration of oral theophylline improved SDB and reduced associated arterial-blood oxyhaemoglobin desaturation in patients with stable heart failure\textsuperscript{126}, without adverse effect on sleep architecture. Nevertheless, theophylline is rarely used for the treatment of central apnoea owing to the narrow therapeutic margin, interaction with other medications and the risks of toxicity.

3. Supplemental oxygen and carbon dioxide

Several studies have demonstrated a salutary effect of supplemental $O_2$ in patients with idiopathic CSA and patients with CHF-CSR\textsuperscript{81,127}. The mechanism of action is by ameliorating hypoxaemia and minimizing the subsequent ventilatory overshoot. Thus, oxygen may improve CSA by the suppression of the hypercapnic and the hypoxic ventilatory drives. Conversely, supplemental $O_2$ may elevate cerebral PCO$_2$ by the Haldane effect. Likewise, supplemental CO$_2$ eliminates central apnoea in patients with pure central sleep apnoea. In one study of 6 patients with primary CSA\textsuperscript{128}, mild reduction of end-tidal CO$_2$ during sleep that was associated with uncontrollable mixed disease, a single night of increasing PCO$_2$ by 2 to 3 mm Hg, to the low normal level, as an adjunct to CPAP or bi-level PAP therapy, resulted in complete abolition of central apnoeas. The mechanism of action is by raising PCO$_2$ above the apnoeic threshold. However, this therapy is not practical given the need for a closed circuit to deliver supplemental CO$_2$\textsuperscript{128,129}.

Subjects with CSA have enhanced CO$_2$ chemosensitivity. During arousals, enhanced CO$_2$ (and hypoxic) chemosensitivity above eucapnia will tend to lower the prevailing PCO$_2$ and increase the likelihood of the occurrence of apnoea during subsequent sleep. There was a considerable reduction in the number of central apnoeas present in a patient with central alveolar hypoventilation after oxygen therapy was begun\textsuperscript{130}. The
addition of low levels of CO₂ to the CPAP circuit has been reported as an effective treatment of refractory mixed or central sleep apnoea and is a promising solution for some individuals. However, there are very few large-scale studies assessing treatment efficacy with either O₂ or CO₂ in subjects with CSA and without CHF.

**Conclusion**

CSA is a prevalent disorder and may be a clinical marker of underlying cardiac or neurological disease, with resultant serious morbidity and mortality. Studies on pathophysiology and long-term impact of CSA on health and mortality in the Asian population are absent. Further research in this field will help clarify the physiologic determinants of central breathing instability in populations of different age groups, gender and racial descent, as a prerequisite to the development of novel therapeutic interventions for central sleep apnoea in different populations.

**References**


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