Review Article

Central sleep apnoea—a clinical review

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Abstract: Central sleep apnoea (CSA) is characterised by recurrent apnoeas during sleep with no associated respiratory effort. It mostly results from withdrawal of the wakefulness drive in sleep leaving ventilation under metabolic control. A detailed physiological understanding of the control of breathing in wakefulness and sleep is essential to the understanding of CSA. It encompasses a diverse group of conditions with differing aetiologies and pathophysiology. Likewise treatment varies according to underlying aetiology. Some of the conditions such as idiopathic (primary) CSA (ICSA) are relatively rare and benign. On the other hand Cheyne-Stokes breathing (CSB) pattern is quite common in patients with heart failure and might be a prognostic indicator of poor outcome. Unfortunately modern medical management of heart failure does not seem to have significantly reduced the prevalence of CSA in this group. Since the adoption of positive airway pressure (PAP) as a common treatment modality of obstructive sleep apnoea (OSA), complex CSA has been increasingly observed either as treatment emergent or persistent CSA. Depending on the particular condition, various treatment strategies have been tried in the past two decades which have included hypnotic therapy, respiratory stimulants, judicious administration of carbon dioxide, oxygen therapy, PAP and bi-level ventilatory support with a backup rate. In the past decade adaptive servo ventilation (ASV) has been introduced with much promise. Various studies have shown its superiority over other treatment modalities. Ongoing long term studies will hopefully shed more light on its impact on cardiovascular morbidity and mortality. Other rare forms are still poorly understood and treatments remain suboptimal.

Keywords: Apnoea; breathing control; servo-ventilation

Submitted Dec 01, 2014. Accepted for publication Feb 28, 2015.
doi: 10.3978/j.issn.2072-1439.2015.04.45
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.04.45

Introduction

Central sleep apnoea (CSA) is characterised by recurrent apnoeic episodes with no associated respiratory effort. Compared to obstructive sleep apnoea (OSA) it is not as commonly seen in sleep centres accounting for about 5-10% of clinic patients. It is, however, quite common in patients with heart failure, in patients with some neurological disorders and in those on high dose opiates. Complex CSA is now well recognised in continuous positive airway pressure (CPAP) treated OSA. Symptoms of CSA include sleep fragmentation, insomnia and daytime hypersomnolence, which is usually not as severe as in OSA. Despite a lot of research into CSA in the past two decades the condition is still poorly understood and treatment is still suboptimal perhaps owing to its aetiological and pathophysiological diversity and heterogeneity.

Definitions and classifications

CSA in adults is defined as cessation in airflow of 10 or more seconds in the absence of any inspiratory effort. CSA is diagnosed when 50% or more of the events are central. In routine practice oro-nasal thermal sensor signals are used to detect apnoeas. More accurate determination of absence of inspiratory effort would entail use of an oesophageal balloon catheter. Respiratory inductance plethysmography and strain gauges are alternative measures as is diaphragmatic electromyography. A frequency of 5 or more apnoeas per hour is considered abnormal.

The *International Classification of Sleep Disorders*, 2nd

Box 1 Central sleep apnoea (CSA) syndromes
Primary (idiopathic) CSA
Cheyne-Stokes breathing pattern
CSA due to high-altitude periodic breathing
CSA due to drug or substance
Primary sleep apnoea of infancy
From the American Academy of Sleep Medicine: ICSD-2 2005 (1). ICSD, International Classification of Sleep Disorders.

edition (ICSD-2) lists five CSA syndromes (*Box 1*) (1).

As suggested by Bradley *et al.* it is useful to divide the CSA syndromes into two broad groups: the hypocapnic and the hypercapnic groups (2). Patients in the hypocapnic group have normal or low wake $PaCO_2$ and do not develop sleep hypercapnoea. This group includes patients with ICSA, Cheyne-Stokes breathing (CSB) pattern and complex CSA. The hypercapnic group has wake high normal or elevated wake $PaCO_2$ which may rise further in sleep. This group includes patients with CSA due to drug or substance and primary CSA of infancy. This group also includes patients with obesity hypoventilation syndrome, thoracic cage disorders, neuromuscular disorders and other hypoventilation syndromes which will not be discussed further in this article.

Complex sleep apnoea (complex SA) refers to patients who have primarily OSA or mixed apnoeas who develop central apnoeas on positive airway pressure (PAP) treatment (treatment-emergent central apnoeas) or have significant persistent central apnoeas on PAP treatment (treatment-persistent CSAs).

Pathophysiology of CSA

Breathing in non-rapid eye movement (NREM) sleep

An understanding of the normal physiological changes in breathing between wake and NREM sleep is essential for the understanding of CSAs. Respiratory control is quite unstable during transition from wake to sleep and with further sleep stage transitions (3,4). There is usually a 2 to 8 mmHg rise in $PaCO_2$ during NREM sleep. During NREM sleep ventilation is totally under metabolic control (5). The wakefulness drive is no longer operational, the hypercapnic and hypoxic drives are reduced and there is also increased upper airway resistance (6-8). But is it really as simple as this? Some doubt has been raised as to whether there is true loss of chemo-responsiveness and loss of drive and some have suggested that the changes in sleep might be mostly due to increased upper airway resistance.

Breathing in REM sleep

REM sleep is characterised by generalised skeletal muscle atonia leaving the diaphragm as the main active respiratory muscle. There is further reduction of the hypercapnic and hypoxic drives. There is also further inhibition of upper airway muscles and diaphragmatic activity in phasic REM which may lead to episodes of CSA and reduced tidal volumes (9-11).

Apnoeic threshold (AT)

If the $PaCO_2$ falls below an individual's set value (apnoea threshold) a CSA will ensue. Ventilation will only resume after the $PaCO_2$ has risen above that threshold. The sleeping $PaCO_2$ is normally 2 to 8 mmHg above the wake level. The AT is usually 1 to 2 mmHg lower than the waking $PaCO_2$. The important factor which determines the propensity to develop an apnoea is the difference between the individual's $PaCO_2$ and the AT. The smaller the $PaCO_2$-AT difference the more likely it is that a central apnoea will occur. It is important to note that an individual's $PaCO_2$-AT difference is not fixed and can vary with ventilatory drive (12).

Loop gain

The engineering concept of loop gain is helpful in the understanding of the pathogenesis of CSA. The loop gain is determined by the plant gain and controller gain. In this case the plant gain is the ability to increase ventilation by the lungs and respiratory muscles and the controller gain the change in ventilation induced by a change in $PaCO_2$.

Idiopathic (primary) CSA (ICSA)

The aetiology and pathogenesis of ICSA is still not clear. It is essentially a diagnosis of exclusion after excluding the known causes of CSA. Patients are usually not obese. Symptoms include fragmented/disturbed sleep, insomnia, witnessed apnoeas and some daytime sleepiness. Snoring is not as intrusive as in OSA. These patents tend to have a high hypercapnic response (2,13,14) and sleep state instability. Wake $PaCO_2$ levels tend to be low. Arousals, usually non-respiratory related, cause a transient increase in ventilation and a consequent fall in $PaCO_2$. Unlike Cheyne-

Stokes there is no waxing and waning of ventilation. Polysomnographic studies usually show frequent isolated central apnoeas or runs of central apnoeas. They occur in NREM sleep and mostly arise from stage 1 and 2. Treatments which have been tried include respiratory stimulants, hypnotics, CPAP and oxygen therapy (15). The carbonic anhydrase inhibitor acetazolamide which induces a metabolic acidosis has been shown to reduce AHI by as much as 50% but has a doubtful impact on sleep efficiency (16). Hypnotics work by suppressing the arousal response and consolidating sleep (17-19). Stage 3 NREM sleep is increased, $PaCO_2$ levels are higher and respiration is more stable. In some patients hypnotics can increase obstructive events; they should not be used in patients with hypercapnic CSA. CPAP has been used to treat ICSA (20,21). It probably works by stabilising the upper airways and abolishing the upper airway resistance related arousals. It might also minimise $PaCO_2$ overshoots after an arousal. It has also been suggested that it might slightly increase the sleeping $PaCO_2$ in patients who are hypocapnic at baseline. Xie *et al.* demonstrated elimination of apnoeas by administration of a CO_2-enriched gas mixture and addition of dead space (22). This has, however not translated into common clinical practice. Supplemental oxygen has also been used in ICSA (23). Adaptive servo ventilation (ASV) might be a reasonable treatment strategy in selected cases

Cheyne-Stokes breathing-central sleep apnoea (CSB-CSA)

CSB pattern's association with congestive heart failure is well known. Javaheri et al., MacDonald *et al.* and Oldenburg *et al.* have all reported on the high prevalence of CSB-CSA in stable heart failure patients (24-26). It is commonly associated with left ventricular systolic dysfunction but has also been described with diastolic dysfunction (27). CBS pattern is also seen in some neurological disorders such as cerebrovascular diseases and some neurodegenerative conditions. In heart failure associated CSB patients might report disturbed sleep. The majority of patients do not complain of subjective daytime sleepiness. Reduced survival rates in patients with heart failure and CSB pattern highlights its importance (28,29). Transplant free survival in patients with heart failure and CSB-CSA was significantly reduced compared to those without CSB-CSA independent of CPAP use (28,30).

Patients with CSB-CSA have a long circulation time. They tend to have relative daytime hypocapnia and the sleeping $PaCO_2$-AT difference is small. The ventilatory drive is high due to a high sympathetic tone and stimulation of respiration from pulmonary congestion. The supine position which worsens pulmonary congestion has been noted to increase the incidence of CSA. Polysomnographic studies demonstrate the typical crescendo-decrescendo morphology. There is a long delay in the nadir in the oxygen saturation tracing after event termination due to a prolonged circulation time. The typical CSB cycle time is long at 60-90 seconds. Risk factors for CSB-CSA include male gender, an older age, atrial fibrillation and daytime hypocapnia.

As with ICSA respiratory stimulants, hypnotics, oxygen therapy and PAP treatments have been tried in the treatment of CSB-CSA (23,31-33). Optimisation of the medical treatment of heart failure is the logical first step in the treatment of CSB-CSA. Respiratory stimulants such as theophylline and acetazolamide are not commonly used. Hypnotics are not in common use either. Krachman *et al.* compared oxygen therapy to CPAP and observed that both oxygen therapy and CPAP were equally effective at reducing the apnoea hypopnea index (AHI) in patients with heart failure and CSB (34). CPAP therapy has been noted to improve cardiac function (ejection fraction) reduce sympathetic activity and improve sleep continuity (35-37). However, it has not yet been fully shown to confer a survival benefit. The Canadian Continuous Positive Airway Pressure for Patients with CSA and Heart Failure (CANPAP) trial failed to show a survival benefit (38). The study also showed that only 50% of the patients responded to CPAP therapy after a 3-month period. A post hoc analysis of the responders showed improvement in survival and ejection fraction compared to controls. BiPAP with a backup rate has been shown to improve breathing in patient with CSB-CSA (25,39). In the past decade ASV has emerged as a promising treatment option for patients with CSB-CSA (25,40,41). It has been shown to be effective at reducing the AHI, oxyhaemoglobin desaturation index and at improving sleep quality. Some recent randomised controlled trials have also shown an improvement in cardiac function with ASV use. Kourouklis *et al.* treated nine patients with NYHA class II-III heart failure and at 6 months demonstrated significant improvement in left ventricular end diastolic volume and left ventricular ejection fraction compared to baseline parameters (42). Koyama *et al.* studied ten patients with heart failure who had CSA treated with ASV and compared to nine on conventional treatment (43). There was no improvement in echocardiographic parameters or plasma brain natriuretic peptide (BNP) levels in the conventional treatment group.

In those who used ASV, improvements were noted in left ventricular ejection fraction, left ventricular and systolic volume, and BNP. These researches also demonstrated that cardiac sympathetic nerve activity is associated with the severity of CSA.

Yoshihisa *et al.* randomised 36 patients with heart failure and preserved ejection and predominantly CSA to receive treatment with ASV plus conventional pharmacotherapy or pharmacotherapy alone (44). After 6 months of follow-up NYHA class, BNP, and diastolic function improved in the ASV group. High sensitivity troponin T was unchanged. Promisingly the event-free survival was higher in the ASV treated group compared to those receiving pharmacotherapy alone. Kasai *et al.* studied patients with moderate to severe CSB-CSA who had been on CPAP for 3 months but had failed to suppress AHI to below 15/hour (45). They then randomised them into a CPAP group and an ASV group and re-evaluated them after a further 3 months. Patients were assessed by echocardiography, polysomnography, plasma BNP, arterial blood gases, 24-hour urinary noradrenaline excretion, a 6-minute walk distance (6MWD) and the 36-item short form survey (SF36) quality of life tool at baseline and after 3 months. Of 12 patients completed the ASV arm and 11 patients completed the CPAP arm. AHI was significantly lower in the ASV group. Device compliance was better in the ASV group. Plasma BNP, LVEF, mitral regurgitation area and left ventricular end-systolic diameter were better with ASV compared to CPAP. Urinary noradrenaline excretion and 6MWD were not significantly different within group comparisons. Quality of life score as determined by the SF-36 was also better with ASV. In another randomised controlled trial comparing standard pharmacotherapy to pharmacotherapy plus ASV in patients with systolic heart failure and CSA/HCSB, Hetland and co-workers demonstrated that after 3 months of treatment, ASV patients had significant increases in LVEF, improved NYHA class, and longer 6MWD as well as a possible trend toward reduced congestive heart failure mortality but this was only at 3 months and the numbers were small (30 patients) (46). In another randomised controlled trial comparing standard pharmacotherapy with pharmacotherapy plus ASV in patients with systolic heart failure and sleep disordered breathing that was either OSA and/or CSA, LVEF increased slightly after 12 weeks in both groups by intention-to-treat and per-protocol analysis, whereas N-terminal pro-BNP remained significantly higher in the control group (47). The outcome of the ongoing multinational and multicentre trial on The Effects of Adaptive Servo Ventilation on Survival and Frequency of Cardiovascular (ADVENT-HF) will be eagerly awaited. Another multinational and multicentre randomised study looking at the treatment of sleep-disordered breathing with predominant CSA with adoptive servo-ventilation in patients with chronic heart failure (the SERVE-HF study) which is also currently in progress is hoped to provide data on the effect of treatment with ASV on morbidity and mortality as well as cost effectiveness of this treatment.

Complex SA

Complex SA is identified by emergence or persistence of central apnoea upon exposure to CPAP treatment. PAP treatments eliminate the upper airway obstruction but do not correct the ventilatory control instability or the sleep state instability (48). Relieving the upper airway resistance might result in lower $PaCO_2$. The reasons for the emergence of central apnoeas remain obscure. It is likely that a high loop gain could be responsible for its persistence. Sleep disturbance due to failure to acclimatise to CPAP might also cause frequent arousals leading to CSA. CPAP induced expansion of lung volumes might lead to prolonged expiration to the point of central apnoea in some patients. The prevalence of complex SA has been reported to be between 7% and 20% of patients put on CPAP therapy with a male preponderance being also noted (24,48-50). Symptoms include persistence of day time sleepiness despite CPAP treatment and disturbed non refreshing sleep. Polysomnographic studies usually reveal obstruction or mixed apnoeas during the diagnostic studies. During CPAP titration the AHI remains elevated. A number of studies have shown that complex SA will spontaneously resolve with chronic CPAP use. If a patient is tolerating CPAP well they might therefore be no need to change treatment. BiPAB with a backup rate can be an effective alternative (51). ASV can be used for those who do not improve. A number of studies have demonstrated its effectiveness in patients with complex SA (51-53).

High altitude periodic breathing

High altitude breathing occurs following recent ascent to altitude of at least 4,000 metres. It is a normal physiological adaptation to hypoxia at hypobaric altitudes. Hypoxia at altitude increases ventilatory drive which then leads to periodic breathing (54). Polysomnographic studies demonstrate recurrent central apnoeas primarily during NREM sleep at a frequency of >5/hour. The cycle length

Box 2 Primary sleep apnoea of infancy—diagnostic criteria

Apnoea of prematurity
One of the following is recorded in an infant <37 weeks conceptional age:
Prolonged central respiratory pauses of The mechanisms by which oxygen therapy works is not entirely clear, but it is hypothesized that is has an effect on reducing peripheral chemoreceptor sensitivity to carbon dioxide which allows $PaCO_2$ to elevate above the apnoeic threshold and reduces likelihood of instability ≥20 seconds in duration
Shorter-duration events include obstructive or mixed respiratory patterns and are associated with a significant physiologic compromise, including decrease in heart rate, hypoxia, clinical symptoms or the need for nursing intervention
Apnoea of infancy
One of the following is recorded in an infant of conceptional age ≥37 weeks
Prolonged central respiratory pauses of ≥20 seconds in duration
Shorter duration events including obstructive or mixed respiratory patterns and are associated with bradycardia, cyanosis, pallor, or marked hypotonia
For either diagnosis, the disorder is not better explained by another current sleep disorder, medical or neurologic disorder, or medication

From the American Academy of Sleep Medicine: ICSD-2 2005 (1). ICSD, International Classification of Sleep Disorders.

should be 12-34 seconds. Symptoms include disturbed poor quality sleep or a sense of suffocation. Most people will gradually acclimatize to altitude. Sleep disturbance can be helped by benzodiazepines. Nickol *et al.* demonstrated that at high altitude temazepam is effective in reducing periodic breathing, and is safe to use, without adverse effect upon next day performance (55). Acetazolamide also helps sleep disturbances (56). In a randomised three way cross over study by Hackett *et al.* Acetazolamide was noted to be superior to almitrine at ameliorating periodic breathing (54). Almitrine and acetazolamide both increased saturations during sleep but it was only the acetazolamide that decreased periodic breathing. An earlier randomised double blind placebo controlled study by Fischer *et al.* demonstrated that both theophylline and acetazolamide improved sleep disordered breathing and reduced oxhaemoglobin desaturation during sleep, with acetazolamide significantly improving basal oxyhaemoglobin saturation during sleep (57). Tanner *et al.* performed a randomized, double-blind trial of temazepam and acetazolamide at an altitude of 3,540 meters on 34 healthy trekkers with self-reports of high-altitude sleep disturbance (56). They concluded that treatment of high-altitude sleep disturbance with temazepam is associated with increased subjective sleep quality compared to acetazolamide.

CSA due to medication (opiate/narcotic induced CSA)

Drugs in common use for pain control include morphine, fentanyl and methadone. Patients on high doses of these medications may have a slow sleeping respiratory rate. They may develop long obstructive apnoeas. Ataxic breathing is commonly observed with variation in respiratory rate and tidal volume. Relatively few arousals are noted and stage N3 can be increased. Periodic breathing and intermittent central apnoeas are seen and these may even occur in stage N3. Treatment emergent central apnoeas are also common even if the diagnostic study might have shown mainly obstructive events. Reduction in opiate dose is a logical first step if this were possible. Patients with mostly obstructive events respond to CPAP but then central apnoeas may emerge or persist (58). Javaheri *et al.* reported on ASV being effective treatment for both central and obstructive apnoea in opiate induced complex SA (40). It is essential to increase EPAP sufficiently to eliminate upper airway obstructive events in these situations.

Primary sleep apnoea of infancy

Primary sleep apnoea of infancy is due to immaturity of the respiratory control system. It is deemed pathological only if the duration of apnoea is greater than 20 seconds or if the events are associated with desaturation or other physiological compromise. The ICSD-2 diagnostic criteria are outlined in *Box 2*. Therapy is often mostly just supportive management. The primary pharmacologic agents used to treat apnoea of prematurity are caffeine and theophylline (59).

Conclusions

Of the CSA syndromes CSB in heart failure is the most common and most important. There is mounting evidence that its presence can adversely affect outcome in affected individuals. In the past decade ASV has emerged as a promising treatment modality which might improve cardiac function, improve sleep quality and possibly confer a survival benefit. Outcomes of the studies looking into the beneficial effects of its long term use are eagerly awaited. Complex SA has also been increasingly recognised with the widespread use of CPAP for OSA. With the more liberal administration of strong opiates to treat pain syndromes central apnoea due to drug or substance is also now being increasingly encountered. A back to basics physiological approach helps in the understanding of central apnoea syndromes. Further physiological and clinical research is still required into this field.

Acknowledgements

Disclosure: The author declares no conflict of interest.

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Cite this article as: Muza RT. Central sleep apnoea—a clinical review. J Thorac Dis 2015;7(5):930-937. doi: 10.3978/j.issn.2072-1439.2015.04.45

