Cheyne–Stokes respiration during sleep: mechanisms and potential interventions

Cheyne–Stokes respiration is characterized by a typical waxing and waning pattern in breathing amplitude, interspersed with central apnoeas or hypopnoeas. This article reviews current knowledge regarding Cheyne–Stokes respiration with a particular emphasis on the mechanisms and latest methods of intervention.

Cheyne–Stokes respiration is a form of central sleep-disordered breathing in which there are cyclical fluctuations in breathing. These lead to periods of central apnoeas and hypopnoeas, which alternate with periods of hyperpnoea in a gradual waxing and waning fashion. Cheyne–Stokes respiration is associated with changing arterial partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) (AlDabal and BaHammam, 2010). Cheyne–Stokes respiration is believed to mirror an underlying cardiac disease with subsequent negative consequences for the cardiac disease (Oldenburg et al, 2014a). Central sleep apnoea and Cheyne–Stokes respiration occur in 30–50% of patients with congestive heart failure (Noda et al, 2013). There is an increase in the prevalence of Cheyne–Stokes respiration when the severity of heart failure increases and cardiac function decreases (Bitter et al, 2009). At the same time, the presence of Cheyne–Stokes respiration accelerates the progression of congestive heart failure, which is associated with increased mortality and morbidity and has a significant impact on quality of life (Duning et al, 2013).

Several physiological or pathological factors influence the susceptibility to Cheyne–Stokes respiration including sex (male), age (>60 years old), $PaCO_2$ (5.0 kPa) and a history of atrial fibrillation (Noda et al, 2013). Some diseases increase susceptibility to Cheyne–Stokes respiration, including those causing a dysfunction of central respiratory control centres in the brainstem (strokes, traumatic brain injuries and brain tumours) (Duning et al, 2013; Noda et al, 2013), pulmonary hypertension (Ulrich et al, 2008) or end-stage renal failure (Perl et al, 2006).

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Mechanisms

Normal function

The pathophysiological mechanism leading to Cheyne–Stokes respiration is very complex, but the instability in respiratory drive results in fluctuation of $PaCO_2$ around the apnoeic threshold. Hyperventilation and $PaCO_2$ below the apnoeic threshold trigger a central apnoea. The crescendo–decrescendo pattern of respiration in Cheyne–Stokes respiration is a compensation for the changing levels of blood O_2 and CO_2 (AlDabal and BaHammam, 2010).

Pathological changes

When respiratory disorders develop, resulting in changes to levels of $PaCO_2$ and PaO_2, this is detected and stimulates feedback regulation, which increases or decreases ventilation accordingly. The $PaCO_2$ can be corrected gradually and active adjustment stops after this returns to the normal range, keeping ventilation at a stable level. However, changes in $PaCO_2$ may not feed back to the CNS in a timely manner, and active ventilation regulation persists which may lead to overcorrection of $PaCO_2$. At this time, if $PaCO_2$ falls below the apnoeic threshold, apnoea appears (Badr, 2009).

The normal $PaCO_2$ level during sleep is about 6.0 kPa (the eucapnic sleep $PaCO_2$ level) and the apnoeic threshold is usually 0.27–0.80 kPa lower. The sleep apnoeic threshold is equal to or marginally lower than the wakefulness eucapnic $PaCO_2$ level (Eckert et al, 2007). The difference between the eucapnic sleep $PaCO_2$ level and the apnoeic threshold is critical in the development of Cheyne–Stokes respiration: the smaller the difference, the more likely the occurrence of Cheyne–Stokes respiration (Randerath, 2009).

Factors including hypocapnia, arousal, chemoreceptor sensitivity enhancement and the prolonging of circulating time may lead to instability of the respiratory control system (*Figure 1*).

Hypocapnia

In normal conditions, a certain concentration of CO_2 can stimulate chemoreceptors and is necessary for maintenance of normal breathing. When $PaCO_2$ decreases

excessively, the CO_2-dependent stimulation of respiratory drive will be reduced or even eliminated, leading to Cheyne–Stokes respiration. In patients with Cheyne–Stokes respiration, the $PaCO_2$ level is close to the eucapnic sleep $PaCO_2$ level. Therefore, the respiratory control system in these patients is not stable and a slightly increase in ventilation may cause $PaCO_2$ to be less than the threshold. In patients with chronic heart failure, left ventricular volume and perfusion pressure increases, which worsens pulmonary congestion and pulmonary oedema, elevates pulmonary capillary wedge pressure, enhances J-receptor and C fibre sensor stimulation and ultimately leads to excitation of respiratory drive (AlDabal and BaHammam, 2010). The increased sympathetic activity in patients with chronic heart failure as a compensation for cardiac pump failure, together with hypoxaemia resulting from obstructive apnoea often as a comorbidity of heart failure, can also lead to hyperventilation and hypocapnia.

Arousal

Arousal from sleep is an important protective response in order to restore gas exchange, but it can lead to respiratory control instability. A low arousal threshold may be more likely to lead to a repetitive Cheyne–Stokes respiration cycle as the individual oscillates between wakefulness and sleep. Some respiratory events, hypoxaemia, periodic leg movements in sleep, spontaneous awakening, pain, gastro-oesophageal reflux disease and insomnia can all lead to arousals. Sleep state conversion and lower arousal threshold may be sufficient to promote Cheyne–Stokes respiration.

A CO_2 level which has reached the threshold during sleep can lead to hypercapnia compared to a relatively lower CO_2 level which would trigger this during arousal, thus triggering hyperventilation, and ultimately leading to Cheyne–Stokes respiration. If patients immediately go into the sleep stage after arousals, and this is followed by hyperventilation which may persist for a while, the $PaCO_2$ will rapidly fall below the sleep apnoeic threshold, causing Cheyne–Stokes respiration again and leading to a series of Cheyne–Stokes respiration cycles (Malhotra and Owens, 2010). So arousals may play a key role in maintenance of hyperventilation in Cheyne–Stokes respiration. Pinna et al (2012) showed that fluctuations in sleep/wake state are an important mechanism contributing to the development of oscillatory breathing patterns in patients with congestive heart failure. Domenico Pinna et al (2014) also found that transitions between wakefulness and non-rapid eye movement sleep paralleled apnoeic events during Cheyne–Stokes respiration in patients with heart failure. They concluded that the relationships between state changes and respiratory events are consistent with the notion that state fluctuations promote ventilatory instability.

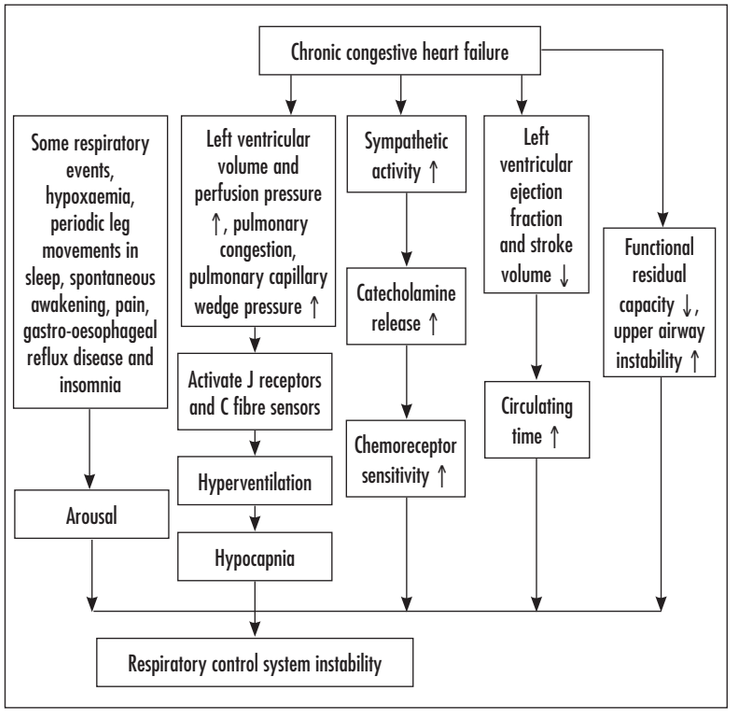
Chemoreceptor sensitivity enhancement

The pathophysiological role of enhanced chemosensitivity to CO_2 and/or hypoxia has been emphasized in patients with heart failure. In the early stages of congestive heart failure, the chemoreflex acts as a compensatory mechanism. Later, however, it helps to sustain the sympathetic activation, with detrimental effects on cardiovascular function and prognosis (Passino et al, 2010).

Peripheral chemoreceptors include the carotid body and the aortic body. Central chemoreceptors are located on the surface of the medulla oblongata. They regulate respiration through changes in PaO_2 and hydrogen ion (H+) concentration. In patients with congestive heart failure, carotid body chemoreceptor activity is enhanced and is associated with oscillatory breathing (Cheyne–Stokes respiration) patterns, increased sympathetic nerve activity and increased arrhythmia incidence. Yumino and Bradley (2008) showed that the central and peripheral chemoreceptor excitability in patients who have heart failure and Cheyne–Stokes respiration, whether during waking or sleeping, is higher than those without any sleep-disordered breathing or only with obstructive sleep apnoea. Chemoreceptor sensitivity enhancement means that these patients may suffer drastic reactions to tiny blood $PaCO_2$ changes, leading to apnoea or hypoventilation.

Some hormones and drugs affect chemoreceptor sensitivity. Adrenaline or noradrenaline can excite carotid body chemoreceptors because they cause local vasoconstriction and reduce the blood flow to the carotid body, leading to hypoxia and then ischaemia. Circulating concentrations of catecholamine increase in patients with congestive heart failure and the peripheral chemoreceptor sensitivity will increase as well (Brack et al, 2012). In a

Figure 1. The main mechanisms and interrelation of Cheyne–Stokes respiration.



study on rabbits with pacing-induced congestive heart failure Marcus et al (2014) demonstrated that denervation of the carotid body reduces renal sympathetic nerve activity, sympatho-respiratory coupling and arrhythmia incidence, while improving breathing stability and cardiac function.

Prolonged circulation time

The circulation time is inversely proportional to stroke volume and cardiac output. Patients with chronic congestive heart failure have decreased left ventricular ejection fraction (McGee, 2013) and stroke volume, so their circulation time increases. This delays delivery of information on blood gases to the chemoreceptors which thus delays feedback input to the respiratory centre (Momomura, 2012). The respiratory control system will be instable, which may change negative feedback to positive feedback and cause hyperventilation, thus causing the crescendo–decrescendo respiratory pattern (Lorenzi et al, 2005).

Others

Patients with congestive heart failure have a low functional residual capacity as a result of pulmonary congestion, cardiomegaly, pleural effusion or the fluid shift from a standing to supine position (Wilcox et al, 2015). Thus the lung O_2 and CO_2 reservoir is decreased, which may contribute to instability of the respiratory control system (Lorenzi et al, 2005). In addition, muscle tone decreases when sleeping, rendering the upper airway prone to collapse and thus causing hypoventilation. During arousals, the upper airway patency is reestablished, resistance is reduced and hyperventilation occurs (Lorenzi et al, 2005; Badr, 2009). This results from sleep-awake transitions and may also lead to respiratory control instability and fluctuations of $PaCO_2$ above or below the apnoeic threshold.

Clinical manifestation and diagnosis

The signs of Cheyne–Stokes respiration are similar to those of obstructive sleep apnoea such as excessive daytime sleepiness, frequent arousals during sleep with choking, morning fatigue and headaches, and complaints of sleeplessness. These may be partially masked by the manifestations of congestive heart failure (Kazimierczak et al, 2013). Patients with severe Cheyne–Stokes respiration have a significantly increased prevalence of non-sustained ventricular tachycardia and other arrhythmias compared to patients with mild or no Cheyne–Stokes respiration (Lanfranchi et al, 2003) as a result of increased sympathetic activity during the hyperpnoeic phase of Cheyne–Stokes respiration. In addition, patients with severe Cheyne–Stokes respiration have reduced heart rate variability, which suggests autonomic dysfunction (Leung et al, 2003).

As many symptoms are also common in patients with obstructive sleep apnoea, diagnosis of Cheyne–Stokes respiration requires nocturnal polysomnography and accurate detection of flow, measurement of oxyhaemoglobin saturation and detection of respiratory effort (Farré et al, 2004), which is regarded as a 'gold' standard. Features of Cheyne–Stokes respiration seen on polysomnography include:

- The typical crescendo–decrescendo model of central apnoea or hypopnoea, which predominantly occurs in stage 1 and 2 of non-rapid eye movement sleep
- O_2 desaturation is usually mild (<80–85%)
- Arousal usually appears at the strong peak of breathing
- The respiratory cycle is generally >45 s (proportional to lung–chemoreceptor cycle time, but inversely proportional to cardiac output)
- Apnoeas are worse in the supine position during sleep.

In the 'Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events' (Berry et al, 2012), Cheyne–Stokes respiration in adults is scored when both of the following are met:

1. There are episodes of three or more consecutive central apnoeas and/or central hypopnoeas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of at least 40 s (typically 45–90 s)
2. There are five or more central apnoeas and/or central hypopnoeas per hour associated with the crescendo–decrescendo breathing pattern recorded over a minimum of 2 hours' monitoring.

Potential interventions

Since Cheyne–Stokes respiration occurs as a consequence of heart failure, optimization of heart failure is essential to treat this – improving cardiac function may ameliorate Cheyne–Stokes respiration. Diuretics and angiotensin-converting enzyme inhibitors can ease pulmonary vascular congestion, decrease preload and afterload, improve oxygenation and minimize overshoot. Beta blockers can lessen sympathetic overstimulation and decrease afterload. Besides drugs, methods such as electrical stimulation, atrial overdrive pacing and cardiac resynchronization with biventricular pacemakers have all been reported to reduce Cheyne–Stokes respiration in patients with heart failure, and improve their sleep quality, life quality and cardiac pump function as well as prognosis (Brack et al, 2012).

In addition, many other methods including oxygen therapy, positive airway pressure, sedative-hypnotic medications, theophylline and exogenous CO_2 can smooth Cheyne–Stokes respiration (*Table 1*). However, the therapeutic effect on Cheyne–Stokes respiration is not generally hopeful. A meta-analysis by Aurora et al (2012) showed that the main treatments for Cheyne–Stokes respiration caused by congestive heart failure are continuous positive airway pressure, adaptive servo ventilation and nocturnal oxygen therapy, while bi-level positive airway pressure, acetazolamide and theophylline are options.

Continuous positive airway pressure

Mechanisms by which continuous positive airway pressure reduces Cheyne–Stokes respiration may include preventing pharyngeal narrowing during central apnoea,

stabilizing respiratory drive, reducing respiratory events, improving oxygenation by increasing lung volume, improving cardiac function, decreasing preload by reducing venous blood backflow to the right atrium and afterload by increasing intrathoracic pressure, improving left ventricular ejection fraction and mitral regurgitation. The Canadian Continuous Positive Airway Pressure for patients with Central Sleep Apnea and Heart Failure Trial (CANPAP) was a multicentre randomized controlled clinical trial in 258 patients who had heart failure and central sleep apnoea and were receiving optimal medical therapy. The trial showed that continuous positive airway pressure could improve nocturnal oxygenation, left ventricular ejection fraction and 6-minute walking distance, and lower plasma noradrenaline concentrations, but it had no effect on survival without a heart transplant (Arzt et al, 2007).

In a post-hoc stratified analysis, transplant-free survival and left ventricular ejection fraction were improved in patients in whom continuous positive airway pressure suppressed the apnoea–hypopnoea index to less than 15/h, but were not improved in patients without this level of suppression. Therefore polysomnography should be repeated within 1–3 months of beginning continuous positive airway pressure to assess its effect on the apnoea–hypopnoea index. Repeated titration of continuous positive airway pressure is also important, which may determine any benefits of long-term treatment (Arzt et al, 2007).

Adaptive servo ventilation

Adaptive servo ventilation is the most effective treatment for Cheyne–Stokes respiration and is well tolerated. While continuous positive airway pressure reduces Cheyne–Stokes respiration by 50% on average, adaptive servo ventilation normalizes it in most patients. In a multinational, multicentre, randomized, parallel group study, use of adaptive servo ventilation improved multiple intermediate cardiorespiratory end points, including the time to first event of all-cause death, unplanned hospitalization (or unplanned prolongation of a planned hospitalization) for worsening congestive heart failure, cardiac transplantation, resuscitation of sudden cardiac arrest, or appropriate life-saving shock for ventricular fibrillation or fast ventricular tachycardia in patients who have an implantable cardioverter defibrillator (Cowie et al, 2013).

Adaptive servo ventilation devices apply different levels of pressure support: during periods of hypoventilation the inspiratory pressure is increased and during hyperventilation it is reduced to the lowest possible level.

Table 1. Treatment suggestions for Cheyne–Stokes respiration

Study	Recommended	Alternative	Not recommended
Eckert et al (2007)	CPAP	Larger trials are required to determine its long-term efficacy and safety of O_2 therapy and inhalation of CO_2	Acetazolamide, theophylline
Badr (2009)	CPAP, ASV, O_2	BiPAP may aggravate the severity of central apnoea, acetazolamide and theophylline remain uncommon, additional studies are needed	Inhalation of CO_2
AlDabal and BaHamman (2010)	ASV	BiPAP is a good alternative treatment in patients who are unresponsive or cannot tolerate CPAP. Large, multicentre controlled studies are needed to further investigate potential benefits of CPAP and theophylline	O_2, acetazolamide, temazepam, inhalation of CO_2
Brack et al (2012)	CPAP, ASV	O_2 may be reserved for patients who can not tolerate non-invasive ventilation, acetazolamide only be tried in selected patients under careful supervision	BiPAP, theophylline, pentobarbital, inhalation of CO_2
Momomura (2012)	CPAP, ASV, O_2	BiPAP is more effective than CPAP in treating Cheyne–Stokes respiration, but has low compliance, and cannot replace CPAP. The effect of chronic phrenic nerve stimulation (which requires surgery) is not known. Dynamic CO_2 administration might be developed to treat central sleep apnoea	Acetazolamide, furosemide, theophylline, atrial overdrive pacing
Aurora et al (2012)	CPAP, ASV, O_2	To be considered for BiPAP only if there is no response to adequate trials of CPAP, ASV and O_2. Acetazolamide and theophylline are considered if positive airway pressure therapy is not tolerated, or accompanied by close clinical follow-up	
Oldenburg (2012)	ASV, O_2	Unilateral phrenic nerve stimulation is a relatively new treatment method, but further studies are needed to confirm its long-term efficacy	Acetazolamide, theophylline, inhalation of CO_2
Selim et al (2012)	CPAP, ASV	O_2 may be an effective therapy, but less reliably effective than positive airway pressure. Acetazolamide and theophylline are considered if positive airway pressure or O_2 is not effective	
Noda et al (2013)	CPAP, O_2, ASV	BiPAP could be effective in patients with cardiac dysfunction or heart failure complicated with sleep-disordered breathing and should be considered as a non-pharmacological adjunct to conventional drug therapy	
Kazimierczak et al (2013)	CPAP, ASV	BiPAP is intended for patients who do not tolerate CPAP well. Phrenic nerve stimulation is the most recently developed method, but further studies are ongoing to assess the outcomes and safety of long-term treatment	O_2, acetazolamide, theophylline

ASV = adaptive servo ventilation; BiPAP = bi-level positive airway pressure; CO_2 = carbon dioxide; CPAP = continuous positive airway pressure; O_2 = oxygen

The devices deliver an expiratory pressure to overcome upper airways obstruction. Pressure support is defined by the difference between expiratory and inspiratory pressure (Randerath, 2009). Spontaneous inspiration is supported with varying amounts of inspiratory positive airway pressure (a relatively higher level). If spontaneous inspiration ceases, adaptive servo ventilation will increase inspiratory support (pressure) or provide back-up ventilation using an adjusted back-up respiration rate. If spontaneous inspiration then increases, support will gradually reduce, to an expiratory positive airway pressure level if necessary. This reduces nocturnal hyperventilation as shown by normalization of $PaCO_2$ (Carnevale et al, 2011).

Effects of adaptive servo ventilation in patients with congestive heart failure include reducing heart rate and blood pressure during the initial 30 minutes of treatment, and increasing cardiac output in patients with elevated filling pressures as a long-term effect (Haruki et al, 2011). Adaptive servo ventilation can also suppress respiratory events more effectively than oxygen therapy, continuous positive airway pressure or bi-level positive airway pressure. It can also improve respiratory control, New York Heart Association functional class (Hetland et al, 2013), quality of life, cardiac function, symptoms, exercise capacity and N-terminal pro-brain natriuretic peptide concentrations (Bitter et al, 2010), and reduce the risk of life-threatening arrhythmias.

Some patients suffer co-existing obstructive sleep apnoea and Cheyne–Stokes respiration rather than pure Cheyne–Stokes respiration, and adaptive servo ventilation effectively suppresses most types of respiratory disturbances and improves sleep and life quality. Adaptive servo ventilation also improves prognosis in patients with congestive heart failure who have a cardiac resynchronization therapy defibrillator. Patients with Cheyne–Stokes respiration who have had a cardiac resynchronization therapy defibrillator implanted will benefit from adaptive servo ventilation (Miyata et al, 2012).

The latest generation enhanced adaptive servo ventilation device (AirCurve 10 CS PaceWave, ResMed Company, Australia) has a new feature – auto-adjustment of expiratory positive airway pressure. Oldenburg et al (2014b) showed that enhanced adaptive servo ventilation is non-inferior to adaptive servo ventilation with fixed expiratory positive airway pressure in patients with congestive heart failure and Cheyne–Stokes respiration, with a trend towards better control of respiratory events. But adaptive servo ventilation is relatively expensive, which restricts its wide application. Moreover, the variability in response to adaptive servo ventilation in a given patient along with the myriad choices of specific models and settings requires a high degree of expertise from the clinician. Randomized controlled studies are needed to determine the long-term clinical efficacy of these devices (Javaheri et al, 2014).

Bi-level positive airway pressure

Bi-level positive airway pressure can provide appropriate alveolar ventilation when apnoea occurs, thus reducing hyperventilation and secondary apnoea, but may lower blood $PaCO_2$, which can increase the risk of Cheyne–Stokes respiration (Badr, 2009). The S/T mode is used more frequently but the evidence is limited and results are conflicting. S/T mode bi-level positive airway pressure should only be considered to treat Cheyne–Stokes respiration in those who fail continuous positive airway pressure, adaptive servo ventilation and oxygen therapy, as there is more evidence supporting the use of these options.

Nocturnal oxygen therapy

Oxygen therapy may increase the O_2 supply to the left ventricle, reduce reflex activation of the peripheral chemoreceptors (Yumino et al, 2009), ameliorate hypoxaemia, minimize the subsequent ventilation overshoot and alleviate central apnoea by increasing cerebral partial pressure of CO_2 through the Haldane effect (Solin et al, 1999). However, oxygen therapy may cause hyperoxia and increase the generation of oxygen free radicals and, hence, induce oxidative stress. This can exert adverse haemodynamic effects such as raising vascular resistance, blood pressure and left ventricular filling pressure and lowering cardiac output (Haruki et al, 2011). In general, the advantages of O_2 supplementation in treating Cheyne–Stokes respiration may outweigh these potential disadvantages (Aurora et al, 2012). While oxygen therapy does not confer outcome advantages over continuous positive airway pressure according to available evidence, supplemental O_2 can be easily given to individuals with Cheyne–Stokes respiration who are unable to comply with continuous positive airway pressure.

Carbon dioxide inhalation

Delivery of constant CO_2 is effective in eliminating Cheyne–Stokes respiration by raising $PaCO_2$, but there are serious concerns about the potential side effects, such as unwanted elevations in ventilation, work of breathing, and sympathetic nerve activity, and thus CO_2 inhalation therapy has not been recommended as a routine option for therapy. However, studies into CO_2 inhalation therapy may reshape its role (Wan et al, 2013). Approaches like inhalation of supplemental CO_2 to elevate $PaCO_2$ above the apnoeic threshold remain experimental because it may cause sympathetic stimulation and long-term clinical trials are lacking (Brack et al, 2012).

Phrenic nerve stimulation

To date, treatment of Cheyne–Stokes respiration with adaptive servo ventilation is recommended as the gold standard. However, 15–20% of patients with congestive heart failure do not tolerate or do not want any positive airway pressure therapy. In these patients, phrenic nerve stimulation might be an alternative (Oldenburg et al,

2014c). The initial study suggested that after transcutaneous phrenic nerve stimulation, the apnoea–hypopnoea index decreased in patients with heart failure who have Cheyne–Stokes respiration and oxygenation was also improved (Zhang et al, 2012). Zhang et al (2012) showed that in a small group of patients with congestive heart failure and Cheyne–Stokes respiration, one night of unilateral transvenous phrenic nerve stimulation improved indices of Cheyne–Stokes respiration and was not associated with adverse events. Its short-term application is obvious but further studies are needed to confirm its long-term safety and efficacy.

Pharmacological treatment

Correct pharmacological treatment of congestive heart failure decreases the severity of Cheyne–Stokes respiration. Acetazolamide is a mild diuretic and respiratory stimulant. It can inhibit carbonic anhydrase activity, increase urinary excretion of HCO_3-, increase the blood concentration of H+, stimulate the respiratory centre and reduce the peripheral and central chemoreceptor sensitivity, to treat Cheyne–Stokes respiration. However, it cannot improve haemodynamic parameters or the quality of sleep. In addition, it may also cause hypokalaemia, which has a proarrhythmic effect (Kazimierczak et al, 2013).

Theophylline, a stimulant of the respiratory centre that increases its sensitivity to hypercapnia, has been considered a potentially beneficial agent because it can increase cardiac contractility, dilate coronary arteries, loosen bronchial smooth muscle and increase respiratory drive in patients with heart failure (AlDabal and BaHammam, 2010). However, the use of theophylline is limited by its adverse effects, mainly cardiac arrhythmias that may increase the risk of sudden death, making the long-term effect not clear (Kazimierczak et al, 2013).

Sedative-hypnotic medications such as zolpidem and triazolam may stabilize ventilation through suppressing arousals, but they cannot reduce the frequency of Cheyne–Stokes respiration. They should only be considered for the treatment of primary central sleep apnoea if the patient does not have underlying risk factors for respiratory depression (Aurora et al, 2012).

Haack et al (2014) found that simvastatin treatment ameliorated carotid body chemoreflex sensitivity as well as increased respiratory variability, apnoea–hypopnoea index and arrhythmia index in a rodent model of congestive heart failure. Their findings suggest that statins may be an effective treatment for Cheyne–Stokes respiration. However, none of these medications has yet been recommended as a first-line treatment.

Prognosis

Most available studies show a higher mortality in patients with heart failure and Cheyne–Stokes respiration compared to those without Cheyne–Stokes respiration. A number of pathophysiological changes, such as sleep disruption, arousals, hypoxaemia-reoxygenation, hypercapnia/hypocapnia, and changes in intrathoracic pressure, have harmful effects on the cardiovascular system, and the presence of Cheyne–Stokes respiration is associated with increased mortality and morbidity in subjects with variable degrees of heart failure (AlDabal and BaHammam, 2010). Severe central sleep apnoea in patients with congestive heart failure is associated with elevated levels of C-reactive protein, a systemic marker of inflammation and cardiovascular risk. This might partly explain the negative prognostic impact of Cheyne–Stokes respiration in these patients (Schmalgemeier et al, 2014). In short, Cheyne–Stokes respiration is an independent marker of poor prognosis and may ultimately increase the mortality in patients with heart failure.

Conclusions

Cheyne–Stokes respiration has a high prevalence in patients with chronic congestive heart failure. The presence and severity of Cheyne–Stokes respiration is a mirror for heart function and affects the overall prognosis of patients with chronic congestive heart failure. Although the potential mechanisms of Cheyne–Stokes respiration are still under debate, it is important to understand these mechanisms and provide effective clinical interventions where possible. More research is necessary to further evaluate the effectiveness of all interventions. **BJHM**

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KEY POINTS

- Cheyne–Stokes respiration is characterized by a typical waxing and waning pattern in breathing amplitude, interspersed with central apnoeas or hypopnoeas.
- Chronic congestive heart failure is the main risk factor for Cheyne–Stokes respiration and the severity of heart failure increases its incidence. However, the presence and severity of Cheyne–Stokes respiration 'mirrors' heart function and affects the overall prognosis.
- Although the pathogenesis of Cheyne–Stokes respiration is a very complex process involving multiple factors, the key point is the instability in the respiratory control system occurring in patients with heart failure.
- The mainstay of treatment is to improve cardiac function, with continuous positive airway pressure, adaptive servo ventilation and oxygen therapy as standards, and bi-level positive airway pressure, acetazolamide and theophylline as options.

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