

Pathophysiology and treatment of Cheyne-Stokes respiration

M T Naughton

Cheyne-Stokes respiration is a disorder characterised by recurrent central apnoeas during sleep alternating with a crescendo-decrescendo pattern of tidal volume.^{1,2} It is often observed in patients with congestive heart failure, usually during stages 1 and 2 non-REM sleep when ventilation is under chemical-metabolic control.² Patients with Cheyne-Stokes respiration usually present with the symptoms of orthopnoea, paroxysmal nocturnal dyspnoea, excessive daytime sleepiness and witnessed apnoeas in the setting of congestive heart failure.^{1,3} Excessive weight and snoring may be absent. Approximately 50% of patients with symptomatic congestive heart failure have sleep apnoea, mainly of the Cheyne-Stokes respiration variety.^{4–6} As congestive heart failure occurs in 1% of the adult population and doubles in prevalence for each decade beyond 60 years,⁷ Cheyne-Stokes respiration is common but often left unrecognised.

Adverse effects

Based upon small case series, patients with congestive heart failure and Cheyne-Stokes respiration have a significantly greater mortality,^{8,9} particularly if present during wakefulness,¹⁰ than those without Cheyne-Stokes respiration. Although Cheyne-Stokes respiration is likely to arise as a result of congestive heart failure, once present it is likely to have adverse effects upon cardiac function akin to a vicious cycle. Following an initial cardiac insult there is a compensatory increase in sympathetic activity^{11,12} which in susceptible patients causes hyperventilation,¹³ destabilises respiratory control, and leads to Cheyne-Stokes respiration. Once Cheyne-Stokes respiration is established, apnoea related hypoxaemia causes cardiac diastolic dysfunction.¹⁴ Hypoxaemia and arousals lead to further increases in sympathetic activity¹⁵ which contribute to potentially fatal arrhythmias^{16–18} and further cardiotoxicity.¹⁹

Hyperventilation and resultant increased work of the respiratory muscles probably play a part in the symptom of paroxysmal nocturnal dyspnoea¹ and place an increased demand upon the already reduced cardiac output.²⁰

Finally, patients with congestive heart failure and Cheyne-Stokes respiration frequently complain of fatigue and excessive daytime sleepiness which relate to reduced amounts of total, slow wave, and REM sleep in association with marked sleep fragmentation due to arousals from sleep.⁵

Pathophysiology

Instability of respiratory control underpins the development of Cheyne-Stokes respiration and

results from hyperventilation, prolonged circulation time, and reduced blood gas buffering capacity.²¹

HYPERVENTILATION

Hyperventilation, the common pathophysiological feature of all forms of periodic breathing, causes PaCO₂ levels to fall below the apnoeic threshold triggering a central apnoea. Once the peripheral chemoreceptors sense an apnoea related rise in the PaCO₂ level above the apnoea threshold, hyperventilation recurs driving the PaCO₂ level below the apnoea threshold once again.²

Increased central hypercapnic ventilatory responsiveness has been reported to occur in Cheyne-Stokes respiration with congestive heart failure²² and in other forms of periodic breathing in subjects without congestive heart failure—namely, idiopathic non-hypercapnic central sleep apnoea²³ and high altitude periodic breathing.^{24,25} A significant positive correlation between central hypercapnic ventilatory responsiveness and percentage sleep time with Cheyne-Stokes respiration has also been reported.²⁶ Taken together, it would appear that Cheyne-Stokes respiration is associated with increased central chemosensitivity and explains the low mean PaCO₂ observed during sleep and wakefulness in patients with Cheyne-Stokes respiration.^{3,27,28} As the response time of central chemoreceptors in normal subjects is of the magnitude of five minutes²⁹ and the mean cycle length of Cheyne-Stokes respiration is 60 seconds,^{3,28,30} rapidly responsive peripheral chemoreceptors are likely to play an integral part in the propagation of Cheyne-Stokes respiration.²⁹ Data in support of a significant positive relationship between increased peripheral chemosensitivity and periodic breathing, however, are limited to idiopathic non-hypercapnic central sleep apnoea²³ and high altitude periodic breathing.^{24,25}

It is likely that one or more of the following factors are likely to contribute to hyperventilation in congestive heart failure.

Hypoxaemia

Hypoxaemia may contribute to hyperventilation and Cheyne-Stokes respiration in congestive heart failure through peripheral chemoreceptor stimulation. However, in contrast to high altitude periodic breathing where hypobaric hypoxia stimulation of the peripheral chemoreceptors is likely to be responsible for the periodic breathing,²⁴ hypoxia is thought not to be solely responsible for the development of Cheyne-Stokes respiration in patients with congestive heart failure for the following reasons. Hyperventilation, in the absence of

Alfred Sleep Disorders and Ventilatory Failure Service, Department of Respiratory Medicine, Alfred Hospital, Commercial Road, Prahran 3181, Victoria, Australia
M T Naughton

Correspondence to:
Dr M T Naughton.

hypoxaemia, has been shown to trigger central apnoeas during non-REM sleep induced by either mechanical hyperventilation in normal subjects³¹ or by arousal induced hyperventilation in Cheyne-Stokes respiration³ and idiopathic non-hypercapnic central sleep apnoea.³² Furthermore, supplemental oxygen has been shown to attenuate rather than abolish Cheyne-Stokes respiration in patients with congestive heart failure.³³⁻³⁶

Increased pulmonary vagal afferent traffic

Increased pulmonary vagal afferent nerve traffic related to pulmonary venous congestion and pulmonary C fibre stimulation has been shown to induce rapid shallow breathing and hyperventilation in animal studies.³⁷⁻⁴⁰ In humans with congestive heart failure, those with Cheyne-Stokes respiration have a significantly greater pulmonary artery pressure (mean 34 mm Hg) than those without Cheyne-Stokes respiration (mean 21 mm Hg).⁶ Moreover, there is a significant inverse correlation between awake pulmonary capillary wedge pressure (PCWP) and awake PaCO₂.⁶ Finally, there is a tendency for the analogous condition high altitude periodic breathing to occur in patients with associated high altitude pulmonary oedema,⁴¹ so Cheyne-Stokes respiration with congestive heart failure is associated with increased pulmonary artery pressures, but whether this is a cause and effect relationship remains to be seen.

Increased sympathetic activity

Heistad *et al* reported a 20% increase in minute ventilation 10 minutes after a six minute venous infusion of noradrenaline, an effect that could be blocked by prior treatment with propranolol.¹³ As increased circulating noradrenaline levels and hyperventilation occur in congestive heart failure,^{11,12} particularly in those with Cheyne-Stokes respiration, it is possible that peripheral chemoreceptors bathed in noradrenaline, or possibly central sympathetic activation related to spontaneous arousals, precipitates Cheyne-Stokes respiration. Upper airway collapse towards the end of the central apnoea, known to occur in Cheyne-Stokes respiration,⁴² may also cause arousal from sleep and thereby hyperventilation.^{3,32}

CIRCULATORY DELAY

The time taken for oxygenated blood leaving the pulmonary artery to reach the peripheral chemoreceptor, known as the circulation time, is increased in patients with congestive heart failure by virtue of a reduced cardiac output, increased cardiac chamber size, and increased circulating blood volume. However, circulatory delay in patients with congestive heart failure with mild Cheyne-Stokes respiration is similar to those with severe Cheyne-Stokes respiration (20.5 *vs* 25.0 seconds, respectively).³ Moreover, using canine models, artificial lengthening of the circulation times to as long as five minutes did not precipitate periodic breathing reliably.⁴³ Hence, circulatory delay is thought not to be a significant precipitant of Cheyne-Stokes respiration. However, circulatory delay

is directly related to the length of the apnoea-hyperpnoea cycle and contributes to the crescendo-decrescendo respiratory pattern.^{28,30}

REDUCED BLOOD GAS BUFFERING CAPACITY

Reduced total body oxygen and carbon dioxide stores are considered factors that amplify the blood gas oscillations in Cheyne-Stokes respiration. Pulmonary function tests of patients with severe congestive heart failure reveal a restrictive ventilatory defect, and therefore oxygen storage, which relate to cardiomegaly and pleural effusions.⁴⁴⁻⁴⁶ Carbon monoxide transfer capacity is approximately 70% of predicted normal values in patients with severe congestive heart failure and correlates inversely with PCWP.⁴⁶ Despite these findings, no significant differences in pulmonary function tests have been observed between those with and without Cheyne-Stokes respiration.^{3,9,27} As patients with Cheyne-Stokes respiration hyperventilate awake and asleep,^{3,27} total body carbon dioxide stores are likely to be reduced, hence the carbon dioxide buffering capacity will be diminished.

Treatment

Generally, patients with Cheyne-Stokes respiration sufficient to cause symptoms have more than 20 apnoeas and hypopnoeas per hour sleep and should be considered for treatment.⁵ Treatment options can be broadly divided into five groups: intensive heart failure treatment, respiratory stimulants, respiratory depressants, oxygen, and continuous positive airway pressure (CPAP).

INTENSIVE HEART FAILURE TREATMENT

Although it would seem prudent to ensure that patients with Cheyne-Stokes respiration are on optimal medical treatment for congestive heart failure, and as a result the severity of Cheyne-Stokes respiration would diminish, there are only limited supportive data. In patients with congestive heart failure a raised PCWP is associated with greater mortality.⁴⁷ Moreover, intensive medical treatment can reduce both PCWP and mortality in a subset of patients with severe congestive heart failure patients⁴⁷ so, as patients with Cheyne-Stokes respiration have raised PCWP, one would expect the Cheyne-Stokes respiration in a subset of patients to diminish in severity with intensive medical therapy. Limited evidence in support is provided by a single small short term non-randomised study in which a 50% reduction in the severity of Cheyne-Stokes respiration was observed with captopril over a four week period.⁴⁸ Similar case series have reported reductions in Cheyne-Stokes respiration following intensive medical treatment,^{49,50} cardiac valve surgery,⁵¹ and cardiac transplantation,^{52,53} but conversion of Cheyne-Stokes respiration to obstructive sleep apnoea has also been reported following cardiac transplantation.⁵⁴

RESPIRATORY STIMULANTS

Although respiratory stimulants (theophylline, carbon dioxide and acetazolamide) have been reported to reduce the severity of Cheyne-Stokes respiration, they should be used with great caution. Javaheri *et al*⁵⁵ reported a reduction in central apnoea and arousal frequency with five days theophylline treatment in 15 men with congestive heart failure for five days, although there was no significant improvement in cardiac function and quality of life data were not presented. Moreover, nocturnal supplemental oxygen therapy was also started without rationale at the same time as theophylline and placebo and was discontinued on the follow up sleep study. Theophylline and related drugs are well known for their arrhythmogenic⁵⁶⁻⁵⁸ and hyperventilation properties⁵⁹ and thereby the requirements of cardiac output for respiratory muscles.²⁰

Carbon dioxide inhalation has been shown to reduce the frequency of central apnoeas and hypopnoeas in patients with periodic breathing,⁶⁰⁻⁶⁴ but the chronic use of carbon dioxide inhalation as treatment for Cheyne-Stokes respiration may not be feasible. In patients without congestive heart failure who demonstrate periodic breathing (idiopathic non-hypercapnic central sleep apnoea and high altitude periodic breathing), an increase of carbon dioxide levels via carbon dioxide inhalation,⁶⁰⁻⁶² oxygen inhalation,⁶⁴ or added dead space⁶³ have resulted in stabilisation of respiration at the expense of increasing overall minute ventilation.⁶⁴

The effects of other respiratory stimulants such as acetazolamide on Cheyne-Stokes respiration have not been systematically evaluated in patients with congestive heart failure.⁶⁵⁻⁶⁶ Although reductions in central apnoea indices are reported with acetazolamide in the two available uncontrolled studies, both reported a significant fall in awake PaCO₂ and an increase in hypercapnic ventilatory responsiveness indicating a greater degree of hyperventilation.⁶⁵⁻⁶⁶

Hence, at the present time there is little evidence in favour of the use of respiratory stimulants in Cheyne-Stokes respiration. Moreover, since patients with congestive heart failure who have Cheyne-Stokes respiration are already hyperventilating³ and have weak respiratory muscles,⁶⁷ there is no strong rationale for the use of these drugs in the chronic treatment of this disorder.

RESPIRATORY DEPRESSANTS

The effects of central nervous system respiratory depressants on Cheyne-Stokes respiration in patients with congestive heart failure have been tested in short term trials. The rationale for these trials was that suppression of arousal and ventilatory overshoot would prevent post-hyperventilatory apnoeas. Although various benzodiazepines did reduce the frequency of arousals, they failed to reduce the frequency of central apnoeas.⁶⁸⁻⁶⁹

OXYGEN

A number of studies have shown that the short term application of supplemental oxygen during sleep can attenuate Cheyne-Stokes respiration.^{33-35, 36, 48} It is likely that oxygen reduces the peripheral chemoresponsiveness and allows PaCO₂ levels to rise above the apnoea threshold.⁶⁴ Hanly *et al*³³ observed a significant fall in Cheyne-Stokes respiration (30 to 19 events per hour) with treatment for a single night of 2-3 l/min intranasal oxygen in a randomised single blind study. Andreas *et al*³⁵ reported a fall in Cheyne-Stokes respiration (26 to 10 events per hour) in 22 patients given 4 l/min intranasal oxygen for seven days in a randomised double blind crossover study. While on oxygen, patients also experienced a slight but statistically significant increase in peak oxygen consumption during exercise but no change in duration of exercise, peak heart rate, nor quality of life.³⁵ Cardiac function has been found not to improve with six months oxygen treatment.³⁴ Franklin reported that levels of up to 60% inspired oxygen were required to attenuate Cheyne-Stokes respiration.³⁶ Longer term trials of oxygen to examine these issues in more detail are warranted. Gold *et al* have warned that central apnoeas may convert to mixed and obstructive apnoeas with supplemental oxygen.⁷⁰

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

Considerable clinical evidence exists of beneficial short term effects of CPAP in acute cardiogenic pulmonary oedema⁷¹⁻⁷⁸ and in stable congestive heart failure patients with PCWP > 12 mm Hg,⁷⁹⁻⁸⁰ an effect thought by some to be limited to patients in sinus rhythm.⁸¹ These clinical effects are thought to arise from a reduction in left ventricular afterload and heart rate (indicating reduced cardiac work) and assistance of inspiratory muscles, an increase in functional residual volume, improved ventilation perfusion matching, and reduced work of breathing.⁸²⁻⁸⁴ Abolition of upper airway obstruction and large subatmospheric pressures have been proposed as additional factors responsible for the longer term improvements in cardiac function reported particularly in subjects with obstructive sleep apnoea.⁸⁵⁻⁸⁸

A before and after trial of CPAP at 8-12.5 cm H₂O applied at night for one month in five patients with Cheyne-Stokes respiration and congestive heart failure revealed a reduction in Cheyne-Stokes respiration and arousal frequency, an increase in nocturnal SaO₂, and an improvement in symptoms and LVEF measured when awake (from 31% to 38%).⁸⁹ Thereafter, a randomised controlled study confirmed the findings in 24 patients over a three month period.⁵ CPAP was initiated at 5 cm H₂O and then increased to 10-12.5 cm H₂O over 2-3 nights and used for an average of six hours at a pressure of at least 10 cm H₂O.⁵ Additional findings were a reduction in overnight minute ventilation, a 6.4 mm Hg rise in mean overnight transcutaneous Pco₂⁹⁰ associated with an increase in inspiratory muscle strength,⁹¹ suggesting that CPAP provided inspiratory assistance. Alleviation of

Cheyne-Stokes respiration was most probably due to the rise in Paco_2 above the apnoea threshold secondary to the decrease in minute ventilation. Moreover, the rise in LVEF was associated with a reduction in mitral regurgitant fraction⁹² and sympathetic activity,¹⁵ suggesting a remodelling of the left ventricle and improved cardiac efficiency. Improvements in LVEF and mitral regurgitation probably occurred secondary to increases in intrathoracic pressure which have been shown to reduce left ventricular afterload by decreasing left ventricle transmural pressure during systole, to which the failing heart is sensitive, and by reducing heart size.^{82, 93} The mechanism of the fall in ventilation and increase in Paco_2 is likely to reflect an improvement in cardiac function, less pulmonary oedema, improved oxygenation, and lower circulating catecholamine levels.

There is controversy as to the effectiveness of CPAP for the treatment of congestive heart failure and Cheyne-Stokes respiration. Buckle *et al*⁶⁴ found that application of CPAP of 5–7.5 cm H_2O for a single night did not affect the frequency of central apnoeas in eight patients with congestive heart failure and Cheyne-Stokes respiration. Guilleminault *et al*⁶⁹ reported similar results with a one night application of CPAP. Davies *et al*⁶⁵ studied the effects of CPAP of 5–7.5 cm H_2O over two weeks to a group of similar patients. Although full polysomnography was not performed on the follow up night, they concluded that CPAP had no effect on Cheyne-Stokes respiration.⁹⁵ However, in none of these studies was cardiac function systematically assessed. Differences between these studies^{69, 94, 95} and that of Naughton *et al*⁵ are probably related to differences in the technique for initiating CPAP and in the study designs.⁹⁶ In the studies from the other groups^{69, 94, 95} CPAP was not titrated over a period of several days, pressures used were lower, and the duration of treatment was much shorter than in the study of Naughton *et al*.⁵ Since it is well recognised that the beneficial cardiovascular effects of pharmacological afterload reducing agents such as angiotensin converting enzyme inhibitors require several months to be detected, and that they are dose related,⁹⁷ the same is likely to be true of CPAP.

Conclusion

Patients with congestive heart failure and Cheyne-Stokes respiration have increased sympathetic activity, pulmonary vascular pressures, and greater mortality than patients without Cheyne-Stokes respiration. Whether identification of such patients and treatment alters prognosis remains to be determined. However, based upon current evidence, medical therapy directed at congestive heart failure, followed by CPAP (commenced gradually under supervision) and/or supplemental oxygen should be considered. The role of respiratory stimulants or suppressants in Cheyne-Stokes respiration needs further study.

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