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Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne–Stokes respiration

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Background Cheyne–Stokes respiration disrupts sleep, leading to daytime somnolence and cognitive impairment. It is also an independent marker of increased mortality in heart failure. This study evaluated the effectiveness of oxygen therapy for Cheyne–Stokes respiration in heart failure.

Methods Eleven patients with stable heart failure and Cheyne–Stokes breathing were studied. Oxygen and air were administered for 4 weeks in a double-blind, cross-over study. Sleep and disordered breathing was assessed by polysomnography. Symptoms were assessed using the Epworth Sleepiness Scale, visual analogue and quality of life scores. Cognitive function was assessed by neuropsychometric testing. Overnight urinary catecholamine excretion was used as a measure of sympathetic nerve activity.

Results Ninety-seven percent of apnoeas were central in origin. Oxygen therapy reduced the central apnoea rate ($18{\cdot}4 \pm 4{\cdot}1$ vs $3{\cdot}8 \pm 2{\cdot}1$ per hour; $P=0{\cdot}05$) and periodic breathing time ($33{\cdot}6 \pm 7{\cdot}4$ vs $10{\cdot}7 \pm 3{\cdot}9\%$ of actual sleep time; $P=0{\cdot}003$). Oxygen did not improve sleep quality, patient symptoms or cognitive failure. Oxygen reduced urinary noradrenaline excretion ($8{\cdot}3 \pm 1{\cdot}5$ vs $4{\cdot}1 \pm 0{\cdot}6$ nmol . mmol^{-1} urinary creatinine; $P=0{\cdot}03$).

Conclusion Oxygen stabilized sleep disordered breathing and reduced sympathetic activity in patients with heart failure and Cheyne–Stokes respiration. We were unable to demonstrate an effect on either patient symptoms or cognitive function.

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Key Words: Heart failure, Cheyne–Stokes respiration, oxygen, sympathetic activity.

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Introduction

In 1818 Cheyne described a case of periodic respiration during sleep in a patient with terminal heart failure[1]. We now know that Cheyne–Stokes respiration is a common finding, even in patients with mild–moderate heart failure[2]. The presence of Cheyne–Stokes respiration is important since it is an independent marker of increased mortality[3]. In sleep disorders such as obstructive sleep apnoea, the repeated episodes of nocturnal desaturation and arousal from sleep leads to cognitive impairment[4,5]. Furthermore, this cognitive impairment and increased daytime somnolence has been linked with an increased risk of motor vehicle accidents[6].

A number of studies have shown that oxygen therapy stabilizes sleep-disordered breathing in patients with heart failure and Cheyne–Stokes respiration. In a well controlled and randomized study, Hanly *et al.* showed that oxygen increased total sleep time, improved sleep quality and reduced both the number of apnoeas and arousals during sleep[7]. In this study the effect of oxygen was only investigated for a single night, and no assessment of patient symptoms were made. Walsh *et al.*[8] and Andreas *et al.*[9] reported similar findings, although neither observed improvements in patient symptoms. The latter study also reported improvements in cognitive function and exercise capacity[9]. Only Franklin *et al.* have reported an improvement in patient symptoms with oxygen therapy; however, this was an

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open study in which only 8/20 of the patients had heart failure[10].

We set out to test the hypothesis that long-term overnight oxygen therapy would reduce Cheyne–Stokes respiration and by so doing produce an improvement in patient symptoms and cognitive function. The treatment of Cheyne–Stokes respiration with nasal continuous positive airway pressure has been shown to reduce sympathetic nervous activity[11]. We also investigated whether or not the treatment of Cheyne–Stokes respiration with oxygen would reduce sympathetic nervous activity.

Methods

Study population

Eleven consecutive patients with stable heart failure and documented Cheyne–Stokes respiration during sleep were studied. All patients were recruited from a specialist heart failure outpatients clinic. Sleep-disordered breathing was screened for using overnight home pulse oximetry. Patients with a desaturation index of ≥ 15 per hour were invited to take part in the study. The presence of Cheyne–Stokes respiration was confirmed using full polysomnography (see below).

Heart failure was diagnosed on the basis of a documented episode of pulmonary/pedal oedema together with impaired left ventricular systolic function on 2D echocardiography (ejection fraction <40% by Simpson's rule). All patients had controlled, stable cardiac failure without signs of fluid overload at the time of study. All patients were receiving loop diuretics and an angiotensin converting enzyme inhibitor.

None of the subjects had evidence of stroke, neuromuscular disorders, obstructive sleep apnoea or significant pulmonary disease. Lung function tests (forced expiratory volume in 1 s, forced vital capacity and lung transfer factor KCO) were performed as part of the pre-study assessment.

Study design

The study design was a double-blind, placebo-controlled cross-over. Patients were treated successively and in random order with both overnight oxygen and air at a rate of $2\,l\,.\,min^{-1}$ via nasal cannulae. Gas was delivered via 'real' and 'sham' oxygen concentrators (De Vilbiss Healthcare UK Ltd) each for periods of 4 weeks. Compliance was monitored with patient diaries and using the in-built concentrator tachometer. Neuropsychometric testing, symptom assessment and measurement of sympathetic activity was performed in both arms of the study (see below). The study protocol was approved by the Hospital Ethics Committee.

Sleep studies

All subjects retired to bed at 2300h. The MEDILOG Multiparameter Analysis System (Oxford Medical Ltd, U.K.) was used to record the polysomnographs. Surface electrodes were used to record the encephalogram, electro-oculogram and mental electromyogram. Respiratory movements were recorded by impedance. ECG was recorded with standard limb leads. Arterial oxygen saturation was measured with a pulse oximeter (Ohmeda Biox 3700, Colorado, U.S.A.) via a finger electrode. Oral and nasal airflow was detected by thermistors attached to the upper lip. The data were analysed using the MEDILOG 9000-III Replay and Display System and a SS90-III Sleep Stager (Oxford Medical Ltd, U.K.). The automated output from the computerized analysis system was then checked by inspection of the raw data by an independent EEG technician (R.S.) blinded to the patients' randomization sequence. All the polysomnograms were visually analysed in 30 s epochs for sleep stages using standard criteria according to Rechtschaffen and Kales[12].

The following definitions were used to classify abnormal breathing patterns and arousal. Central apnoeas were defined by the absence of airflow for 10 s accompanied by an absence of chest wall movement. Hypopnoea was defined as a reduction in the amplitude of respiratory movement for more than 10 s to less than 50% of the maximum amplitude recorded during the preceding breathing cycle. Periodic breathing was defined as the occurrence of at least three consecutive cycles of characteristic crescendo–decrescendo hyperpnoea–central apnoea. Arousal was defined as awakening from sleep for longer than 5 s, as evidenced by the simultaneous occurrence of α activity on the electroencephalogram, electromyogram activation, and eye movements. This definition of an arousal was used by Hanly in his original paper describing the beneficial effects of oxygen on Cheyne–Stokes respiration[7]. Desaturation events were defined as a reduction in oxygen concentration of $\geq 4\%$ from baseline.

Psychometric testing

All tests were performed in a quiet environment using standard protocols between 0900 and 1700h and were supervised by a single investigator (A.D.S.). Follow-up testing was standardized for every patient according to time of day of their original baseline test. No feedback was given to subjects on their level of performance.

The rate of information processing and level of attention was assessed using the Paced Auditory Serial Addition Test (PASAT)[13]. Both the 2 and 4 s tests are sensitive markers of impaired attention and concentration; the 4 s test is also vulnerable to defects in short-term memory. The Reitan Trailmaking Test (Part B) was used as a test of speed of visual search, attention, mental flexibility, and motor function[14]. Vigilance (the ability to maintain concentration whilst performing a tedious and repetitive task) was measured using the Four Choice Reaction Time Test[15] and the 'Steer Clear' driving simulator[16].

Patient symptoms

A visual analogue scale and the Epworth Sleepiness scale were used to assess daytime sleepiness. The latter has been validated against objective EEG based measurements of daytime sleepiness[17]. Quality of life was assessed with a disease-specific questionnaire that has been used in a number of multicentre heart failure trials[18,19].

Neuroendocrine assessment

Urinary noradrenaline, adrenaline and immuno-reactive brain natriuretic peptide excretion were determined from 8 h overnight urine collections obtained during sleep studies. The urine was collected in containers acidified with 20 ml of 6 molar hydrochloric acid. Venous blood specimens were obtained between 0700 and 0800h on the morning following sleep study, for measurement of plasma adrenaline, noradrenaline, brain natriuretic peptide, atrial natriuretic peptide and N-terminal atrial natriuretic peptide. All subjects were kept supine for 20 min prior to venesection. The urine catecholamine and immuno-reactive brain natriuretic peptide results were normalized to urinary creatinine concentration[20]. Urine and serum catecholamine assays were performed by HPLC with electrochemical detection[21]. Serum brain natriuretic peptide, atrial natriuretic peptide, N-terminal atrial natriuretic peptide, and urine immuno-reactive brain natriuretic peptide measurements were performed by radioimmunoassay after extraction[22]. All biochemical assays were performed by a single investigator blinded to the treatment allocation (D.J.H.).

Statistical analysis

All sleep and neuropsychometric variables showed non-parametric distributions. The presence of a treatment effect between baseline (room air), air (sham concentrator) and oxygen (oxygen concentrator) was examined using Friedman's two way analysis of variance.

Results

Patient characteristics

Twelve patients were identified from screening overnight home pulse oximetry, one of whom declined polysomnography. Table 1 shows that our patients had moderate–severe heart failure of predominantly ischaemic aetiology. Six patients were randomized to initial oxygen treatment, the remaining five received air.

The mean (SEM) duration of treatment with oxygen was 25 (3) days whilst that with air was 28 (3) days. The mean number of treatment hours per night with oxygen was 7·9 (0·5), compared with 7·7 (0·6) for air. There was no difference in subject compliance as assessed by either patient diary or concentrator tachometers. Six patients expressed a verbal preference for overnight oxygen, whereas no patient preferred air over oxygen. Two subjects underwent clinical decompensation requiring an increase in diuretic dose on crossing-over from oxygen to air. One patient requested early cross-over from air to oxygen after two weeks. No patient was withdrawn from the study.

Table 1 Demographic characteristics of 11 consecutive patients with heart failure and Cheyne–Stokes respiration

	Mean
Age (years)	68 (7)
Symptom duration (months)	45 (39)
Body mass index ($kg \cdot m^{-2}$)	25 (3·2)
Frusemide dose (mg)	198 (120)
Captopril dose (mg)*	134 (74)
Cardiothoracic ratio	0·59 (0·07)
Ejection fraction	0·19 (0·06)
LVEDV (ml)	196 (64)
PaO_2 (kPa)	10·7 (1·1)
$PaCO_2$ (kPa)	4·4 (0·6)
FEV_1 (% predicted)	83 (17)
FVC (% predicted)	84 (15)
Lung transfer factor KCO	125 (31)

All results given as mean (SD). *All ACE inhibitor doses converted to equivalent doses of captopril.
LVEDV=left ventricular end-diastolic volume; FEV_1=forced expiratory volume in 1 s; FVC=forced vital capacity.
PaO_2=partial pressure of O_2 in arterial blood.
$PaCO_2$=partial pressure of CO_2 in arterial blood.

Sleep studies

A total of 863 apnoeas were recorded at baseline, 835 of which (97%) were central in origin. Table 2 shows that supplemental oxygen significantly improved overnight oxygenation and reduced disordered breathing. The stabilizing effect of oxygen on Cheyne–Stokes respiration is shown in Fig. 1. Oxygen reduced the central apnoea index ($18·4 \pm 4·1$ vs $3·8 \pm 2·1$ apnoeas/hour actual sleep time; $P=0·05$) and the periodic breathing time ($33·6 \pm 7·4$ vs $10·7 \pm 3·9$% of actual sleep time; $P=0·003$). Oxygen had no effect on the obstructive apnoea index ($2·0 \pm 1·2$ vs $2·1 \pm 1·2$ apnoeas/hour with oxygen and air respectively). There was no beneficial effect on sleep quality or arousal index.

Patient symptoms and cognitive function

Table 3 shows that overnight oxygen had no effect on either patient symptoms or cognitive function.

Neuroendocrine function

Table 4 shows that overnight oxygen therapy had no effect on early morning adrenaline, noradrenaline, atrial

Table 2 Effect of overnight oxygen therapy on sleep quality and disordered breathing in patients with heart failure and Cheyne–Stokes respiration

	Study period			*P*
	Baseline	Oxygen	Air	
Total sleep time (min)	305 (37)	302 (30)	275 (37)	0·07
Total stage 1 & 2 sleep (% of AST)	55 (3)	51 (3)	58 (4)	ns
Total stage 3 & 4 sleep (% of AST)	31 (3)	33 (3)	29·5 (3)	ns
Total REM sleep (% of AST)	14 (2)	16 (3)	13 (3)	ns
Arousal index (per hour TST)	9·8 (2·2)	5·8 (1·4)	7·6 (1·3)	ns
Desaturation index (per hour TRT)	22·4 (4·1)	2·9 (1·1)	23·7 (4·1)	0·001
Min SaO_2 %	84·5 (0·8)	91·0 (1·3)	82·3 (1·6)	0·001
AHI (per hour AST)	37·8 (3·9)	24·9 (3·7)	38 (5)	0·01
Central apnoea index (per hour AST)	13·4 (4·5)	3·8 (2·1)	18·4 (4·1)	0·04
Periodic breathing time (% of AST)	23·6 (8)	10·7 (3·9)	33·6 (7·4)	0·003

All data shown as mean (SEM). Total sleep time (TST) defined as time from sleep onset to end of final sleep epoch; actual sleep time (AST), defined as time from sleep onset to end of final sleep epoch minus time awake (*a* activity on EEG); total recording time (TRT) defined as time from switching on to switching off of all transducers. AHI=apnoea hypopnoea index.

natriuretic peptide, brain natriuretic peptide or N-terminal atrial natriuretic peptide venous blood concentrations. Urinary immuno-reactive brain natriuretic peptide concentrations also remained unchanged. Figure 2 shows that oxygen therapy reduced overnight urinary noradrenaline excretion (4·1 ± 0·5 vs 8·3 ± 1·3 nmol/mmol urinary creatinine for oxygen and air respectively; $P=0·03$).

Discussion

In this paper we report that long-term nocturnal oxygen therapy is an effective treatment for Cheyne–Stokes respiration in heart failure. Our results extend the findings of earlier investigators, the majority of whom administered oxygen therapy for one night only[7,8,10]. Using three separate tools, and in agreement with other investigators[8,9], we were unable to demonstrate a beneficial effect on symptoms. One earlier study has reported a beneficial effect on cognitive function measured using the Reitan trailmaking test only[9]; we were unable to demonstrate a treatment effect using a battery of neuropsychometric tests.

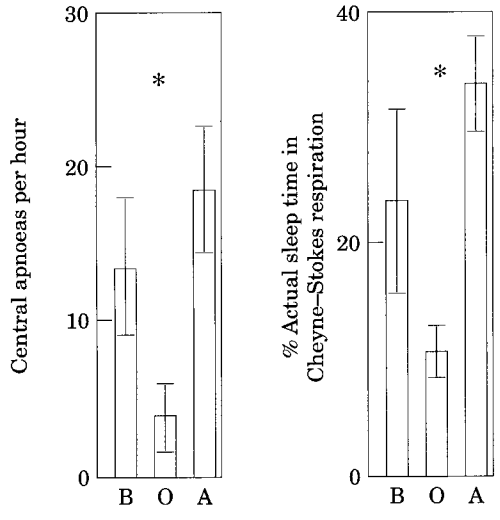

***Figure 1* Effect of overnight oxygen therapy on disordered breathing in patients with heart failure and Cheyne–Stokes respiration. B=baseline; O=oxygen; A=air: *indicates $P<0·05$ by Friedmans two-way analysis of variance.**

Oxygen stabilized breathing during sleep, although the reductions in periodic breathing time and central apnoea index were proportionately greater than those in the apnoea–hypopnoea index. This was because the overall hypopnoea index remained unchanged, rather than because the obstructive apnoea index increased.

The large and statistically significant improvements we observed in disordered breathing did not translate into improvements in either symptoms or cognitive function. Studies in sleep deprived volunteers[23] and in obstructive sleep apnoea[5] show that sleep fragmentation is more important than nocturnal hypoxaemia in the development of cognitive impairment. We believe that oxygen failed to improve symptoms and cognitive function because it did not stabilize breathing sufficiently to produce either an improvement in sleep quality or a reduction in arousal index. The size of our study raises the possibility that some of our negative findings may have arisen from a type II error. Our study had a power of 80–95% to detect a 20% change in the results of the Reitan trailmaking, PASAT (4 second), reaction time and quality of life scores at a significance level of $P\leq0·05$. The interpretation of the PASAT (2 second), Steer Clear and sleepiness scores requires more caution, however, since for these tests we only had a power of 45–60% to detect a 20% change at a significant level of $P\leq0·05$.

The pathogenesis of Cheyne–Stokes respiration in heart failure has been well described[24]. Although

Table 3 Effect of overnight oxygen therapy on symptoms in patients with heart failure and Cheyne–Stokes respiration

Test	Study period		*P*
	Air	Oxygen	
Patient symptoms			
Epworth Sleepiness Scale	10 (2·1)	9·4 (1·9)	ns
Daytime somnolence, VAS	3·6 (0·9)	4·1 (0·9)	ns
Quality of life score (max 240)	113 (10)	115 (9)	ns
Cognitive function			
Reitan trailmaking B (s)	197 (43)	196 (44)	ns
PASAT, 2 s	26 (6)	28 (6)	ns
PASAT, 4 s	43 (7)	48 (6)	ns
Four choice reaction time (s)	0·82 (0·1)	0·86 (0·1)	ns
Steer Cleer (objects hit)	69 (33)	103 (40)	ns

All data given as mean (SEM); VAS=visual analogue score, max 10; PASAT=Paced Auditory Serial Addition Test; Steer Clear=Steer Clear driving simulator.

Table 4 Effect of overnight oxygen therapy on neuroendocrine function in patients with heart failure and Cheyne–Stokes respiration

Air	Oxygen	*P*	
Serum noradrenaline (nmol . l^{-1})	3·5 (0·8)	2·3 (0·3)	ns
Serum adrenaline (nmol . l^{-1})	0·15 (0·02)	0·13 (0·03)	ns
Serum ANP (pmol . l^{-1})	73·2 (8·2)	76·7 (12·9)	ns
Serum N-ANP (pmol . l^{-1})	1353 (153)	1366 (134)	ns
Serum BNP (pmol . l^{-1})	24·5 (2·3)	21·1 (2·4)	ns
Urine BNP (pmol . $mmol^{-1}$)	3·9 (0·4)	3·3 (0·4)	ns

All data given as mean (SEM). N-ANP=N-terminal atrial natriuretic peptide; BNP=brain natriuretic peptide.
Urinary immuno-reactive BNP concentration is normalized for mmol creatinine excretion.

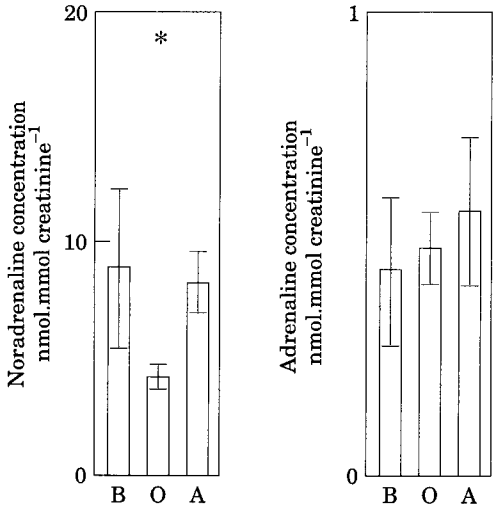

***Figure 2* Effect of overnight oxygen therapy on sympathetic activity in patients with heart failure and Cheyne–Stokes respiration. Abbreviations as for Fig. 1.**

Cheyne–Stokes respiration in heart failure is caused by left ventricular dysfunction (circulatory delay), other factors are important: increased chemoresponsiveness ('controller gain') to hypercapnia and hypoxia, reduced intrapulmonary gas stores of oxygen and carbon dioxide ('under-damping') and an increase in the apnoeic threshold. Transient periods of even mild nocturnal hypoxia will increase the already elevated peripheral chemoreceptor response to carbon dioxide. The arousal stimulus in patients with Cheyne–Stokes respiration is unclear, but arousal in obstructive sleep apnoea is due to mechanoreceptor rather than chemoreceptor stimulation[25]. It is likely that the arousal stimulus in Cheyne–Stokes respiration are the negative swings in intrathoracic pressure seen during periods of hyperpnoea, rather than the mild degree of hypoxia associated with central apnoeas (the average minimum Sao_2 was 83% in our patients). Although oxygen improves Cheyne–Stokes respiration by reducing 'under-damping' and offsetting the detrimental effects of periods of hypoxia on CO_2 hyper-responsiveness, it cannot restore the underlying level of damping and controller gain back to normal. We believe that it was therefore unable to stabilize breathing sufficiently to reduce the number of arousals to below that critical level at which sleep architecture is normalized.

It was unsurprising that oxygen therapy had no effect on early morning serum catecholamines since these have a short half life and would not be expected to remain elevated once disordered breathing had ceased.

We hypothesized that Cheyne–Stokes respiration would be associated with increased activation of the sympathetic nervous system, and that the effective treatment of Cheyne–Stokes respiration would reduce sympathetic activity. This was confirmed by using urinary noradrenaline excretion as an integrated measurement of overnight serum noradrenaline concentration. This result is important because increased neurohormonal activation is causally linked to death heart failure, and may underpin the further increase in mortality described in patients with Cheyne–Stokes respiration. The mechanism by which oxygen therapy reduced urinary noradrenaline excretion was unclear, since in our study there was only a non-significant trend towards reduced arousals with oxygen therapy. Two recent studies have shown that the increase in sympathetic activity seen in Cheyne–Stokes respiration is not wholly attributable to the response of the autonomic nervous system to arousal from sleep. In these reports, Cheyne–Stokes respiration in awake subjects with heart failure was associated with increased muscle sympathetic activity[26], and oxygen therapy in awake patients reduced muscle sympathetic activity during periods of simulated central apnoea[27].

Natriuretic peptide levels are increased in patients with obstructive sleep apnoea, and normalized following treatment with continuous positive airway pressure[28]. We reasoned that the negative swings in intrathoracic pressure during periods of Cheyne–Stokes respiration would be associated with the release of atrial natriuretic peptide, and that treatment of Cheyne–Stokes respiration with oxygen would be accompanied by a fall in atrial natriuretic peptide levels. Oxygen had no effect on either early morning serum natriuretic peptides or urinary immuno-reactive brain natriuretic peptide. This may be because the negative swings in intrathoracic pressure at end-apnoea in obstructive sleep apnoea are far greater than those observed during the hyperpnoeic phase of Cheyne–Stokes respiration.

Oxygen has been reported to produce an acute deterioration in central haemodynamics in heart failure[29]. These reports do not detract from our results, they merely highlight the need for a mortality study of oxygen therapy in patients with heart failure and Cheyne–Stokes respiration. We now know that treatments that reduce mortality in chronic heart failure modulate neuroendocrine activation, and do not necessarily produce acute improvements in central haemodynamics; indeed beta-blockers, which improve survival in chronic heart failure, actually have an acute adverse effect on central haemodynamics.

The rationale for treating Cheyne–Stokes respiration has yet to be determined. If Cheyne–Stokes respiration is a marker of poor prognosis in heart failure[3], then oxygen may be of benefit since it reduces periodic breathing and sympathetic activity. If the only indication for treating Cheyne–Stokes respiration is to improve symptoms, then we feel that our results have raised important questions over the value of oxygen therapy that require further investigation.

Alternative treatment strategies for Cheyne–Stokes respiration are sedatives, theophylline, carbon dioxide and continuous positive airway pressure. Sedatives prevent arousal from sleep without addressing the underlying disordered breathing pattern[30]. Although theophylline reduces Cheyne–Stokes respiration[31], this is probably related to its action as an inotrope, in which case doubts must exist over its safety. Continuous positive airway pressure augments left ventricular systolic function[32] by reducing left ventricular afterload[33], and directly treats Cheyne–Stokes respiration by mechanically loading breathing and increasing lung volumes[34]. Continuous positive airway pressure has been reported to improve patient symptoms in Cheyne–Stokes respiration[35], although the physical nature of the treatment makes the design of a placebo-controlled study impossible. The use of continuous positive airway pressure requires specialist supervision since it may be harmful in patients with a low pre-load, and needs careful up-titration to maintain good compliance.

Conclusion

We have shown that oxygen reduces Cheyne–Stokes respiration in heart failure. Symptoms and cognitive function were not improved, possibly because sleep quality remained unchanged. The beneficial effect of oxygen on sympathetic activity in heart failure with Cheyne–Stokes respiration may be of prognostic significance and requires further investigation.

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