Effects of captopril and oxygen on sleep apnoea in patients with mild to moderate congestive cardiac failure

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Abstract

***Objectives*—To determine the effects of captopril and oxygen on sleep quality in patients with mild to moderate cardiac failure.**

***Design*—An open observational study.**

***Patients*—12 patients with New York Heart Association class II-III heart failure were studied at baseline. 9 of these patients were then examined at the end of 1 month of treatment with captopril; 9 of the patients were separately assessed during a single night of supplementary oxygen.**

***Main outcome measures*—Sleep patterns by polysomnography, overnight oximetry, and subjective sleep assessment using visual analogue scores.**

***Results*—Abnormal sleep was present in all baseline studies. Complete polysomnograms after treatment with captopril were obtained in 8 patients. Light sleep (stages 1 and 2) was reduced (mean (SEM) 61%(8)% to 48%(6)% actual sleep time, $P < 0.05$) but slow wave (stages 3 and 4) and REM (rapid eye movement) sleep increased (25%(6)% to 31%(5)%, 14%(2)% to 21%(5)% actual sleep time, $P < 0.05$). Apnoeic episodes (242(59) to 118(30), $P < 0.05$), desaturation events (171(60) to 73(37), $P < 0.05$), and arousals (33(5) to 18(3) $P < 0.01$) were reduced. Visual analogue scores of sleep quality increased 49(5) to 69(5), $P < 0.01$). Complete polysomnograms were obtained in 7 patients treated with oxygen. Light sleep duration was reduced (55% (7)% to 42%(5)% actual sleep time, $P < 0.05$) and slow wave sleep increased (30%(5)% to 38%(6)% actual sleep time, $P < 0.05$). REM sleep duration was not significantly different. Total arousals (33(6)% to 20(2) $P < 0.05$), desaturation events (140(33) to 38(10), $P < 0.01$), and apnoeic episodes (212(53) to 157(33), $P < 0.05$) were reduced. Visual analogue scores of sleep quality were unchanged.**

***Conclusions*—Captopril and oxygen may improve sleep quality and reduce nocturnal desaturation in patients with mild to moderate cardiac failure. Improved sleep quality could explain the reduction in daytime symptoms seen after treatment in patients with chronic heart failure.**

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Paroxysmal nocturnal dyspnoea commonly occurs in patients with congestive cardiac failure. With the introduction of polysomnography, it is now recognised that even in the absence of this classic symptom abnormal breathing patterns during sleep are present in patients with severe disease.[1 2] Periodic breathing, and hypopnoeic and apnoeic episodes in these patients may be associated with hypoxia and can lead to arousal from sleep. Disruption of normal sleep architecture may explain some of the symptoms of heart failure, such as lethargy, traditionally ascribed to poor cardiac output.

Previous studies have examined the effects of oxygen, vasodilators, and sedation on sleep in end stage cardiac failure but there is little information concerning those less severely affected.[2-5] Angiotensin converting enzyme (ACE) inhibitors improve symptoms and prognosis in all grades of heart failure, but whether they also improve the quality of sleep is unknown. We therefore studied sleep in patients with mild to moderate heart failure before and after treatment with captopril. Patients were also assessed during a single night of supplementary oxygen. As there are few data in the literature regarding sleep abnormalities in patients with milder degrees of heart failure an open observational assessment was considered a prerequisite to further detailed study.

Patients and methods

Twelve patients (11 male and one female of mean (SD) age 63(7) years) were recruited from the outpatient department over a 12 month period. All patients had mild to moderate cardiac failure (New York Heart Association class II-III) and were symptomatic despite medication with frusemide (at least 40 mg) or equivalent daily. All had impaired left ventricular function on echocardiography as defined by an increase in left ventricular end diastolic volume greater than 5·5 cm and reduced fractional shortening to < 30%. Cardiomegaly greater than 50% was present in all patients but none had clinical or radiological evidence of pulmonary oedema. Ischaemic heart disease was the cause of symptoms in eight patients, alcoholic cardiomyopathy in two and in the remaining two the cause was unknown.

Patients were excluded if they had any of the following: (1) morbid obesity (> 115% of ideal body weight); (2) a history of significant respiratory disease confirmed with abnormal pulmonary function tests; (3) daytime hypoxia (arterial oxygen pressure < 12 kPa); (4) significant neurological disease or primary sleep disorder; (5) contraindications to ACE inhibitor therapy; or (6) concurrent administration of β blockers, cardiac glycosides, vasodilators, or other medication known to alter sleep architecture, including sedatives and antidepressants.

Patients were initially studied over a period of three consecutive nights. All were admitted for an adaptation night followed by a baseline night of full polysomnography. During the third night of assessment patients received supplemental oxygen delivered by nasal cannulas at a rate of 2 l/min. Captopril 75 mg daily was then prescribed over a one month period after which patients were studied for a fourth night.

SLEEP ASSESSMENT

All patients retired to bed at their usual times and the study was terminated at their normal time of rising. The MEDILOG Multiparameter Analysis System (Oxford Medical, Oxford) was used to record the polysomnographs. Surface electrodes were used to record the electroencephalogram, electro-oculogram, and mental electromyogram. Two further electrodes were placed over the anterior chest wall and respiratory movements were measured by impedance. Heart rate and rhythm were monitored with standard limb leads. Arterial oxygen concentration was measured throughout the night with a pulse oximeter (Biox 3700; Ohmeda, Boulder, Colorado) attached to the right index finger. Oral and nasal airflow were detected with small thermistors held in place by an adjustable head band and connected to the multichannel recorder. The data were analysed using the MEDILOG 9000-III Replay and Display System and a SS90-III Sleep Stager (Oxford Medicals, Oxford). Standard criteria were used to define abnormal sleep patterns and sleep stage.[6] Actual sleep time was defined as the time spent in bed minus total wake time (as recorded from α activity and increased frequency of the eletroencephalogram). The following definitions were used by the computer to classify abnormal breathing patterns and arousal. Apnoea was defined as the absence of airflow for more than 10 s. 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 periodic breathing cycle. The apnoea-hypopnoea index was calculated by the computer system from the stored data.

Arousal was defined as awakening from sleep for greater than 5 s, as evidenced by the simultaneous occurrence of α activity on the electroencephalogram, electromyogram activation, and eye movements. Desaturation events were defined as a reduction in oxygen concentration of 4% or greater.

Sleep stage, arousal, and apnoea classification by the computer were subsequently checked in all patients from inspection of the raw data traces by an independent trained technician (RS).

CARDIAC OUTPUT AND RESPIRATORY GAS MEASUREMENTS

Cardiac output and respiratory gas exchange were measured before the first and third night of polysomnography. All patients fasted for a minimum of 6 h before assessment. Respiratory gases were measured with a mass spectrometer (VG Medicals, Cheshire) and cardiac output using the indirect Fick principle with carbon dioxide as the indicator. Carbon dioxide production was calculated from the minute ventilation and mixed expired carbon dioxide concentration. The partial pressure of carbon dioxide in pulmonary venous blood was derived from end tidal carbon dioxide concentration and the partial pressure in mixed venous blood was measured after a rebreathing manoeuvre. These three variables were then used to solve the Fick equation. This method is non-invasive and correlates with thermodilution.[7] All measurements were made with the patient standing at rest.

SLEEP QUALITY AND SYMPTOM ASSESSMENT

Patients were asked to assess their daytime symptoms, including energy scores and subjective sleep quality, using a visual analogue scale after each night in hospital. Forms were completed in the absence of the investigators. All patients gave informed consent and the study was approved by the hospital ethics committee.

STATISTICAL ANALYSIS

Data obtained from the sleep studies during oxygen treatment and after 1 month of captopril were separately compared with those from baseline. All variables are expressed as means (SEM) and were compared using a Wilcoxon signed rank test. Observed differences were considered significant at $P < 0{\cdot}05$.

Results

Abnormal sleep architecture and breathing patterns were identified in all twelve baseline studies according to standard criteria.[8] All patients experienced frequent arousal in association with episodes of apnoea, hypopnoea, and desaturation. These were predominantly found during light (stages 1 and 2) sleep. There was no evidence of obstructive sleep apnoea in any sleep recording. All patients were treated with captopril but equipment failure and poor quality polysomnograms reduced the final data available for analysis. Nine patients were studied after treatment with captopril and satisfactory polysomnograms were obtained in eight. Before treatment with captopril six of these patients and three others were also assessed during a

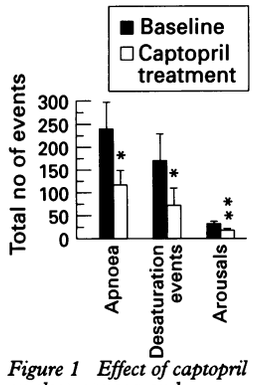

*Figure 1 Effect of captopril on sleep apnoea and desaturation. *P < 0·05; **P < 0·01 v baseline. Bars are means (SEM).*

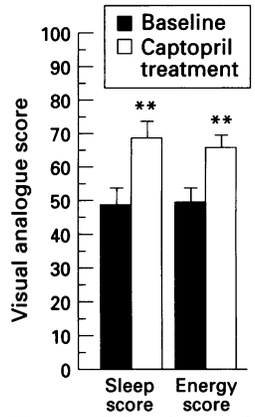

*Figure 2 Effect of captopril on sleep quality and energy score. **P < 0·01 v baseline. Bars are means (SEM).*

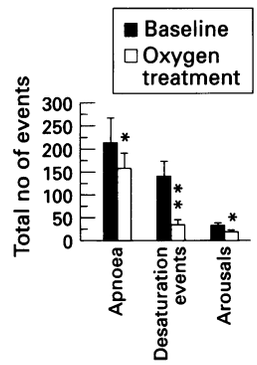

*Figure 3 Effect of oxygen treatment on sleep apnoea and desaturation. *P < 0·05; **P < 0·01 v baseline. Bars are means (SEM).*

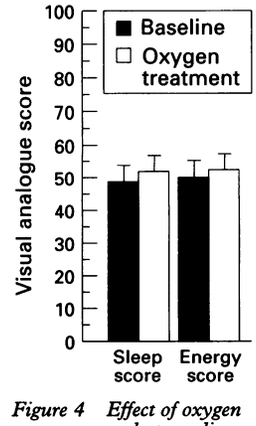

Figure 4 Effect of oxygen treatment on sleep quality and energy score. Bars are means (SEM).

Table 1 Effect of captopril on sleep architecture and oxygen saturation

Variable	Baseline (n = 8)	Captopril (75 mg daily for 1 month) (n = 8)
Actual sleep time (min)	412 (29)	342 (22)
Stages 1 and 2 (% actual sleep)	61 (8)	48 (6)*
Stages 3 and 4 (% actual sleep)	25 (6)	31 (5)*
REM sleep (% actual sleep)	14 (2)	21 (5)*
No of arousals	33 (5)	18 (3)**
Desaturation events	171 (60)	73 (37)*
Apnoea/hypopnoea	242 (59)	118 (30)*
Apnoea/hypopnoea/h	35 (7)	20 (5)*
Minimum oxygen saturation (%)	83 (3)	85 (4)

Values are means (SEM). *P < 0·05; **P < 0·01 *v* baseline. REM, rapid eye movement.

night of supplemental oxygen. Satisfactory polysomnograms were obtained in seven of the nine patients who received supplemental oxygen.

EFFECT OF CAPTOPRIL ON SLEEP

Table 1 gives baseline values and the effect of captopril on sleep architecture in eight patients. Actual sleep time did not significantly change but light sleep (stages 1 and 2) was significantly reduced. Slow wave sleep (stages 3 and 4) and the duration of rapid eye movement associated with sleep increased after treatment. Apnoeic episodes, desaturation events, and arousal were all reduced (fig 1). Subjective sleep quality and daytime energy improved (fig 2).

EFFECT OF CAPTOPRIL ON CENTRAL HAEMODYNAMICS AND RESPIRATORY GAS EXCHANGE

There were no significant changes in cardiac output and oxygen uptake after treatment. End tidal carbon dioxide concentrations were significantly increased and daytime minute ventilation reduced (table 2).

EFFECT OF OXYGEN ON SLEEP

Table 3 gives baseline values and the effect of oxygen treatment on sleep architecture in seven patients. Actual sleep time was unchanged but light sleep (stages 1 and 2) was significantly reduced. Slow wave (stages 3 and 4) sleep increased but the duration of rapid eye movement associated with sleep was similar to that of baseline values. As with captopril apnoeic episodes and desaturation events were also reduced and there was a significant decrease in the number of arousals (fig 3). This improvement was not reflected in the patients' subjective assessment of sleep quality (fig 4).

Table 2 Effect of captopril on cardiac output and respiratory gas exchange

Variable	Baseline (n = 8)	Captopril (n = 8)
Cardiac output (l/min)	4·8 (0·4)	5·2 (0·4)
Oxygen uptake (ml/kg/min)	4·5 (0·3)	4·4 (0·4)
End tidal carbon dioxide (kPa)	4·36 (0·4)	4·66 (0·36)*
Minute ventilation	16·2 (1·5)	13 (1·4)*

Values are means (SEM). *P < 0·05 *v* baseline.

Table 3 Effect of oxygen on sleep architecture and oxygen saturation

Variable	Baseline (n = 7)	Oxygen (1 night only) (n = 7)
Actual sleep time (min)	394 (30)	399 (22)
Stages 1 and 2 (% actual sleep)	55 (7)	42 (5)*
Stages 3 and 4 (% actual sleep)	30 (5)	38 (6)*
REM sleep (% actual sleep)	15 (3)	20 (2)
No of arousals	33 (6)	20 (2)*
Desaturation events	140 (33)	38 (10)**
Apnoea/hypopnoea	212 (53)	157 (33)*
Apnoea/hypopnoea/h	32 (7)	23 (4)*
Minimum oxygen saturation (%)	79 (5)	87 (1)*

Values are means (SEM). *P < 0·05; **P < 0·01 *v* baseline. REM, rapid eye movement.

Discussion

Our observations suggest that captopril improves abnormalities of breathing during sleep in patients with mild to moderate cardiac failure. Patients have fewer arousals and spend more time in sleep stages 3 and 4. They enjoy a better night's sleep and feel less lethargic throughout the day. Supplemental oxygen had a similar effect on sleep stage and breathing abnormalities, although there was no statistically significant improvement in sleep quality scores assessed by the patients. It is unlikely that these changes are explained by adaptation to the sleep laboratory as patients reassessed after 1 month of taking captopril were admitted only for a single night. Furthermore, although the proportion of light sleep can change with adaptation, there is considerable evidence demonstrating that abnormalities of breathing are less subject to nightly variation.[9–12]

Although patients had been told that their symptoms might improve no comments were made regarding sleep quality and so we believe their subjective response to be real. The use of visual analogue scales to assess daytime symptoms and sleep quality is previously described,[13] although more formal measures of the quality of life and sleep latency testing are perhaps more reliable.[14–16] A placebo response seems unlikely given the objective evidence of improved sleep quality but firm conclusions from these data are limited by the study design. A controlled double blind randomised trial is needed to confirm our findings.

Most previous studies in heart failure have focused on patients with severe symptoms.[1 4 17] Periodic breathing with Cheyne-Stokes respiration during sleep is well described.[2] Explanations for these abnormalities are probably multifactorial and various mechanisms have been proposed,[3] including a reduction in oxygen stores, increased hypoxic sensitivity, and delayed circulation time between the carotid body and lung. Abnormal respiratory patterns are also associated with increased oscillation in arterial carbon dioxide pressure ($PaCO_2$) around the apnoeic threshold.[18 19] This represents a critical level of arterial carbon dioxide (CO_2) below which apnoea occurs during sleep.

Cheyne-Stokes respiration is more common in early sleep in patients with heart failure and an increase in the duration of stages 1 and 2 correlates closely with sleep disruption. The ventilatory response to hypoxia and hypercapnia is greater during this period and

respiratory control unstable.[1] Deeper sleep occurs during the later stages (3 and 4) and Cheyne-Stokes respiration often disappears. Cheyne-Stokes respiration is characterised by hyperpnoeic and apnoeic stages. Apnoea occurs after an increase in ventilation which lowers the $PaCO_2$ below the apnoeic threshold. A subsequent increase in CO_2 concentration restores ventilation and the cycle then continues. Arousal in patients with heart failure coincides with the hyperpnoeic stage, in contrast to these with obstructive sleep apnoea in whom arousal coincides with apnoea causing breathing to resume.[1] The significance of this difference is unclear.

The reason for the initiation of periodic breathing in some individuals with heart failure but not others is unknown. Daytime hyperventilation causing hypocapnia may determine which patients develop abnormal sleep architecture.[18 19] This is more common in patients developing Cheyne-Stokes respiration and nocturnal periodic breathing. The increase in ventilation is thought to be caused by stimulation of pulmonary receptors by interstitial oedema. In the patients treated with captopril in our study there was a small but significant decrease in daytime minute ventilation associated with improved sleep quality and reduction in breathing abnormalities. Daytime hypocapnia was also reduced as evidenced by the increase in $PaCO_2$, estimated from end tidal CO_2 concentration.

Abnormal breathing patterns are well described in those with severe symptoms and it has been suggested that this relates to poor ventricular function.[20 21] Alternatively, this could reflect the patients selected for study as there has been little assessment of patients with less severe ventricular dysfunction. Sleep abnormalities did not relate to resting cardiac output or cardiac index in our patients with mild to moderate heart failure.

Nocturnal hypoxia seen in our patients has previously been described in those with severe symptoms.[1 3 4] Periodic breathing, however, is not the only cause of desaturation during sleep in patients with heart failure. Reduced lung compliance, poor ventricular function, and loss of effective lung volume when supine are additional contributory factors.[1 22] The clinical significance of oxygen saturation abnormalities has yet to be determined, particularly as many patients have normal arterial oxygen concentrations during the day. Myocardial infarction,[23] high grade arrhythmias,[24] and systemic[25] and pulmonary hypertension[26] are all associated with nocturnal hypoxia. Supplemental oxygen significantly improves sleep quality and reduces nocturnal desaturation in patients with severe heart failure.[3] We have demonstrated that breathing abnormalities and desaturation in milder degrees of heart failure also respond to oxygen therapy. A placebo randomised study of the effects of oxygen, however, would be necessary to confirm this finding. For reasons that are unclear there was no significant improvement in the patients' subjective assessment using a visual analogue scale. One possible explanation is that, although oxygen acutely corrects sleep abnormalities, prolonged administration is required before patients themselves appreciate any benefit. The long-term effects of oxygen supplementation in this context are unknown.

There have been few studies of the effects of drugs on sleep in patients with congestive cardiac failure. Improved breathing abnormalities and oxygen saturation were reported in six patients with decompensated severe symptoms administered standard medical treatment.[4] Such management consisted of intravenous diuretics, inotropes, and oxygen making it impossible to assess the individual therapeutic effects. Benzodiazepines have recently been shown to reduce nocturnal arousals and Cheyne-Stokes respiration in severe heart failure, apparently with little effect on arterial oxygen saturation.[5 27] There are several possible mechanisms by which captopril may improve sleep quality in patients with heart failure. Improved cardiac function could reduce circulatory delay and stabilise ventilatory control. The reduction in minute ventilation and increase in $PaCO_2$ seen in the patients we studied could have a similar effect. Alternatively, captopril may attenuate the adverse effects of hypoxia. Hypoxia is associated with increased renin and catecholamine levels but the effects of neurohormonal activation on central ventilatory control are unknown.[20 26] Captopril may similarly improve cardiac function and respiratory gas exchange by reducing hypoxic vasoconstriction of systemic and pulmonary vessels.[26]

The role of nasal continuous positive airway pressure in patients with heart failure has yet to be defined, with conflicting data from several small studies.[28 30] It is unclear why continuous positive airway pressure should be effective in central apnoea, although it has been suggested that by increasing functional residual capacity arterial oxygen and carbon dioxide concentrations increase.[2] This would stabilise the respiratory system to the effects of hypocapnia, reducing both periodic breathing and Cheyne-Stokes respiration. Our data suggest that captopril has similar effects on sleep.

Poor sleep quality is likely to contribute to the overwhelming fatigue seen in patients with all grades of congestive cardiac failure. Captopril appears to improve sleep quality subjectively and objectively in patients with less severe disease. This may in part explain the benefits already described in patients treated with ACE inhibitors in terms of symptoms, quality of life, and prognosis.

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