Treatment of Cheyne-Stokes respiration with nasal oxygen and carbon dioxide

S. Andreas, K. Weidel. G. Hagenah, S. Heindl

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Abstract: Cheyne-Stokes respiration (CSR) is common in patients with congestive heart failure (CHF) and is associated with significant nocturnal O_2 desaturation, arousals and sympathetic activation. Nocturnal O_2 reduces CSR by only about 50%. More complete suppression of CSR may be achieved by adding CO_2 to O_2. This study therefore aimed to evaluate the effects of nocturnal O_2 plus CO_2 on CSR, sleep and sympathetic activation.

Nine patients with CHF (age 59±5 yrs; left ventricular ejection fraction 17.8±1.2% (mean±SEM) were studied in a cross-over, single-blind, placebo-controlled trial. After an accommodation night the patients were randomly assigned to one night each of O_2 plus CO_2 as well as air applied by nasal prongs.

Nocturnal O_2 plus CO_2 reduced the duration of CSR as percentage of total sleep time (48.0±10 *versus* 7.4±2.0%; p=0.008) and increased arterial oxygen saturation (Sa,O_2) as well as mean transcutaneous carbon dioxide tension (Ptc,CO_2) (5.2±0.3 kPa (39±2 mmHg) *versus* 5.7±03 kPa (43±2 mmHg) p=0.011). Sleep did not improve and arousals were not reduced. Plasma noradrenaline was higher on the treatment night (486±116 *versus* 669±163 ng·L^{-1}; p=0.035).

In conclusion, nocturnal O_2 plus CO_2 improves Cheyne-Stokes respiration in patients with congestive heart failure but has adverse effects on the sequel of Cheyne-Stokes respiration, namely sympathetic activation.
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Dept of Cardiology and Pneumology, Georg-August University, Göttingen, Germany.

Correspondence: S. Andreas
Dept of Cardiology and Pneumology
Georg-August University
Robert-Koch-Str. 40
37075 Göttingen
Germany
Fax: 49 551398918

Cheyne-Stokes respiration (CSR) during sleep is common in patients with severe congestive heart failure (CHF). It induces repetitive oxygen desaturations and impairs sleep [1, 2]. Disturbed sleep is likely to cause daytime symptoms and the repetitive oxygen desaturations and arousals increase sympathetic activity as well as right and left ventricular afterload [3] and may thus further impede left ventricular function and exercise tolerance [4–6]. Effective treatment for CSR is therefore needed. Nocturnal oxygen by nasal prongs reduces CSR by about 50% and consolidates sleep [1, 6–8]. Application of 3% CO_2 prevented CSR by increasing the arterial carbon dioxide tension (Pa,CO_2) above the apnoeic threshold [9] but sleep was adversely affected, this being attributed to the tight-fitting face mask used [10]. The hypothesis was tested that CO_2 in conjunction with O_2 given by nasal prongs is efficacious in the treatment of CSR. Plasma catecholamines were measured, to evaluate possible effects on sympathetic activity.

Methods

Subjects and protocol

All patients with severe heart failure admitted to the department of cardiology were candidates for the study.

Patients under the age of 75 yrs were eligible if they met the following criteria: at least one episode of cardiac decompensation, ejection fraction ð35%, stable condition on cardiac medication and evidence of CSR by nocturnal polysomnography. Exclusion criteria were myocardial infarction within 1 yr of entry, significant obstructive lung disease as defined by a forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <70%, primary valvular heart disease, tibial oedema or evidence of obstructive sleep apnoea (more than five obstructive apnoeas·h^{-1}). Plasma catecholamines were evaluated in 15 healthy subjects (age 53.2±5.3 yrs) without significant sleep-disordered breathing. The study was approved by the local ethics committee. Informed written consent was obtained from all subjects.

The study was designed as a single-blind, placebo-controlled trial. After an accommodation night where no treatment was applied the patients received air as well as O_2 plus CO_2 in a randomized, cross-over fashion on two consecutive nights. Polysomnography was performed during all three nights. Oxygen was given with a flow rate of 2 L·min^{-1} by nasal prongs and CO_2 was admixed simultaneously with a flow rate of 0.2–1 L·min^{-1}. Accordingly, the flow rate of the mixture was 2.2–3 L·min^{-1}. CO_2 flow rate was regulated depending on the transcutaneous carbon dioxide tension (Ptc,CO_2), which was not allowed to increase >7.3 kPa (55 mmHg) and on the occurrence of

CSR. When CSR with apnoea was noted CO$_2$ flow rate was slowly increased from 0.2 to maximally 1 L·min^{-1}. Air was also administered *via* nasal prongs with a flow rate of 2.5 L·min^{-1}.

Polysomnography

Electrodes for an electroencephalogram (C3A2 and C4A1 of the international 10–20 system), electro-oculo-gram, electrocardiogram and submental as well as anterior tibialis electromyogram were set in place. Airflow over the nose and mouth was recorded by thermistors and tho-rax and abdominal wall motion was monitored by strain gauges. Arterial oxygen saturation (Sa,O$_2$) was measured transcutaneously on the tip of the index finger by pulse oximetry (Micro span 3040 G, Biochem Int., Wanheshea, WI, USA). Prior to recording, signals of thorax and ab-dominal wall motion had to be adequate in different sleep positions. During the entire night, the recording was ob-served on a monitor and amplification of signals was cor-rected when necessary. The data were stored on an optical disk by a commercially available computer system (CNS sleep lab, 1000/AMPs, Jäger, Würzburg, Germany). The polysomnogram was visually analysed in 30 s epochs for sleep stages according to RECHTSCHAFFEN and KALES [11].

Arousals [12] and periodic leg movements were scored according to standard criteria. CSR was considered to be present when there were at least three regular cycles of increasing and decreasing airflow as well as increasing and decreasing thoracic and abdominal efforts. A hypop-noea was defined as a fall in oronasal airflow over 50% of baseline for more than 10 s. An apnoea was defined as the absence of oronasal airflow for the same period. Accord-ingly, CSR was classified as CSR with hypopnoea and CSR with apnoea. The apnoea-hypopnoea index was de-fined as the total number of sleeping apnoeas and hypo-pnoeas divided by the total sleep time (TST) in hours. Obstructive apnoeas were scored if present. The average cycle period and the transit time between the increase in ventilation and the nadir in Sa,O$_2$ during CSR were aver-aged over at least 10 consecutive cycles in sleep stage 2. The respiratory rate was averaged over 10 min of undis-turbed sleep and ventilation in stage 2. The amount of time for which Sa,O$_2$ was <90%, corrected for TST and the average cardiac frequency (fC) over the night was com-puted by the CNS System.

Capnography

The transcutaneous O$_2$ and CO$_2$-monitoring system (TINA; Radiometer, Copenhagen, Denmark) was calibra-ted with a 5% CO$_2$ and 20.9% O$_2$ standard calibration gas at the beginning of each study. Fresh bicarbonate solution was inserted around the electrode and a new O$_2$ and CO$_2$-permeable membrane was used for each study. The sensor was placed on the anterior chest and heated to 44°C. Arte-rial oxygen tension (Pa,O$_2$) and Pa,CO$_2$ values were stored at 30 s intervals on a computer and recorded continuously with a paper speed of 20 cm·h^{-1}. Since the accuracy and response characteristics of Pa,O$_2$ recordings falls behind the transcutaneous Sa,O$_2$ system [13], Pa,O$_2$ recordings were not analysed in this study. Recording began after waiting for at least 15 min, until the recording was stable and arterial blood samples could be analysed (ABL 3; Radiometer, Copenhagen, Denmark) for *in vivo* calibra-tion. The capnograph was recalibrated at the end of the study and was always within 3 mmHg of the measured control gases. In four patients a second arterial blood sam-ple was taken at the end of the registration to evaluate the validity of capnography over the night. The capnograph used here has been validated before, with the transcuta-neous measurement closely reflecting Pa,CO$_2$, an insigni-ficant signal drift, a lag time of about 20 s and a 90% response time of about 1 min [13].

Plasma catecholamines and cardiac function

Venous blood samples were obtained from the patients as well as the healthy subjects without applying a tourni-quet from an antecubital vein in the morning, after awak-ening but before rising in the supine position. The samples were collected in pre-shilled heparinized tubes and imme-diately placed on ice, then centrifuged at 4°C. Adrenaline and noradrenaline levels were assayed using the high-per-formance liquid chromatographic (HPLC) technique with fluorescence detection after derivatization with 1,2-diphe-nylethylendiamine [14]. Left ventricular end-diastolic and left atrial diameter were evaluated by echocardiography from a left parasternal view. Left ventricular ejection frac-tion at rest was determined by technetium-99m (^{99m}Tc) gated blood pool scintigraphy.

Statistical analysis

All variables are given as mean±SEM. The results for air and treatment were compared with the two-tailed pair-ed Wilcoxon's test. Two-way repeated measures analysis of variance (ANOVA) was used to compare the within- and between-treatment differences in Ptc,CO$_2$ for different sleep stages; where appropriate this was followed by *post-hoc* analysis using Fisher's protected least significant dif-ference. The patients and the controls were compared using the Mann-Whitney U-test. Statistical analyses were performed on a personal computer using StatView (Aba-cus, Berkely, CA, USA). A p-value <0.05 was considered statistically significant.

Results

Subject characteristics

One patient withdrew from the study after the first treatment night when receiving air. The data of the remain- ing nine patients are given in table 1. Three patients had coronary artery disease and six had idiopathic dilated cardiomyopathy. Five patients were in New York Heart Ass-ociation (NYHA) class II, three patients in class III and one patient in class IV. Five patients exhibited atrial fibrillation, two patients had a pacemaker and two had a cardioverter-defibrilator with antibradycardiac func-tion implanted. Medication consisted of a diuretic and β-acetyl-digoxin in all patients, and an angiotensin-convert-ing enzyme inhi-bitor in eight patients. Three patients

Table 1. – Characteristics of the nine patients

Parameter	Mean±SEM
Age yrs	59.4±4.8
Body mass index kg·m⁻²	25.2±1.1
Left atrial diameter mm	52.6±1.3
Left ventricular end-diastolic diameter mm	77.6±2.0
Left ventricular ejection fraction %	17.8±1.2
Vital capacity % pred	77.2±5.5
Forced expiratory volume in one second % pred	78.8±12.4
Total lung capacity % pred	87.3±7.8
Arterial pH	7.50±0.01
Arterial partial pressure of CO_2 mmHg	37.4±1.9
Arterial partial pressure of O_2 mmHg	88.9±3.5
HCO_3^- mmol·L⁻¹	28.1±1.8
Base excess mmol·L⁻¹	4.3±1.7

1 mmHg=0.133 kPa.

(including the patient not receiving an angiotensin converting enzyme inhibitor) received a vasodilator. No changes in any of these medications were made for the duration of the study. The patients showed slight restrictive lung function tests as well as hypocapnia (table 1). During the second night four pati-ents received air and five patients CO_2 plus O_2. The flow rate of nasal CO_2 was 0.7±0.1 L·min⁻¹, with no significant change during different sleep stages.

Polysomnography

All patients suffered from CSR during sleep (254±42, range 119–470 min). Nocturnal O_2 plus CO_2 clearly reduced the duration of CSR in all patients (table 2, fig. 1). Eight patients exhibited CSR with apnoea while receiving air, this was the case in only two patients in the treatment night. There were 1.1±0.75 obstructive apnoeas·h⁻¹ TST on air and 0.4±0.2·h⁻¹ on treatment (p=0.091). Sa,O_2 during the night increased (table 2). There was an increase in waking and arousals and a decrease in rapid eye movement (REM) sleep, although these differences did not reach significance (table 2). Arousals related to periodic leg movement were 0.3±0.1 on air and 1.5±1.0·h⁻¹ TST on treatment (p=0.34). Arousals not associated with respiratory events increased from 2.6±0.7 on air to 7.8±2.0·h⁻¹

Table 2. – Effects of treatment on Cheyne-Stokes respiration (CSR) and sleep

	Air	O_2+CO_2	p-value
Duration of CSR % TST	48.0±9.6	7.4±2.0	<0.008
Duration of CSR with apnoea % TST	22.2±8.6	0.4±0.3	<0.012
Apnoea-hypopnoea index n·h⁻¹	36.7±7.3	5.4±1.2	<0.008
% of time in bed with Sa,O_2 <90%	14.1±4.8	1.4±0.8	<0.021
Duration of a cycle period s	61±5	78±2	<0.025
Time in bed min	460±10	478±9	<0.29
Total sleep time min	334±23	3131±20	<0.68
Wake % time in bed	27.4±4.4	34.4±4.1	<0.21
Stage 1 % TST	28.4±7.3	30.1±7.1	<0.59
Stage 2 % TST	51.0±6.5	51±5.3	<0.95
Slow-wave sleep % TST	7.6±2.9	8.5±3.4	<0.99
REM sleep % TST	13.0±2.9	9.6±2.3	<0.10
Arousals n·h⁻¹	13.4±1.6	13.7±1.5	<0.68

Values are shown as mean±SEM. TST: total sleep time; Sa,O_2: arterial oxygen saturation; REM: rapid eye movement.
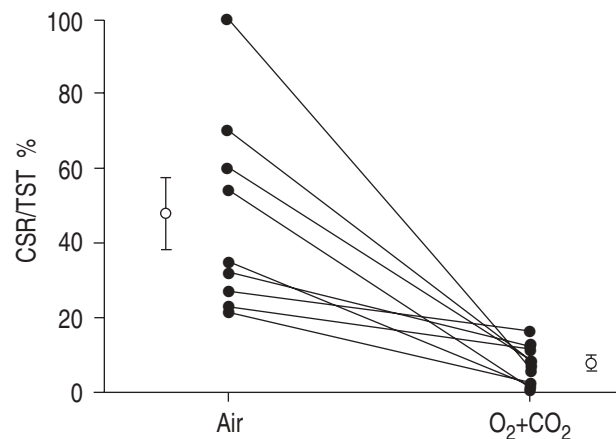

Fig. 1. – Effects of nocturnal nasal O_2 plus CO_2 compared with air on the duration of Cheyne-Stokes respiration (CSR) corrected for total sleep time (TST). Individual data for all nine patients as well as mean and SEM are given. Significant difference between groups: p=0.008.

TST while on treatment (p=0.008). Transit time was 81.5±5.7 s on air and 82.6±5.9 s while on treatment (p=0.94). The average fc during the night was 77.4±2.8 min⁻¹ on air and 80.8±4.4 min⁻¹ while on treatment (p=0.21). The respiratory frequency (fR) in sleep stage 2 was 19.0±1.7 min⁻¹ on air and 19.4±1.5 min⁻¹ while on treatment (p=0.11). One patient woke up while on O_2 plus CO_2 and reported shortness of breath. Orthopnoea and wheezing, slowly improving with sublingual nitrate and nasal O_2, was observed. No such episode was noticed in any patient in the accommodation night or while receiving air.

Capnography

The Ptc,CO_2 during different sleep stages was higher in the treatment night than with air (table 3). The mean Ptc,CO_2 averaged over the whole night and the minimal Ptc,CO_2 increased from 5.2±2.7 to 5.7±0.3 kPa (39.1±2.0 to 43.2±2.4 mmHg) (p=0.011) and from 4.2±0.1 to 4.7±0.2 kPa (31.5±1.1 to 35.4±1.8 mmHg) (p=0.011), respectively. Sleep stages showed a significant impact on Ptc,CO_2 under air as well as under treatment, with the lowest Ptc,CO_2 values during wake and the highest during REM sleep (table 3). Since only six and five patients show-

Table 3. – Effects of treatment on the transcutaneous partial pressure of CO_2 (Ptc,CO_2)

Ptc,CO_2 mmHg	Air	O_2+CO_2
Wake	36.0±1.7	41.2±2.2
Stage 1	37.6±2.1	42.6±2.5
Stage 2	38.4±2.3	43.2±2.5
REM sleep	38.4±2.9	47.3±2.8

Values are shown as mean±SEM. p=0.003 for between-treat-ment effects and p<0.001 for effects of sleep stages (two-way repeated measures analysis of variance). The differences in Ptc,CO_2 (using the data for air as well as O_2 plus CO_2) between sleep stages, except between stage 1 and 2, were significant at p<0.05. Since only five patients showed slow-wave sleep this stage was excluded from the analysis. REM: rapid eye movement. 1 mmHg=0.133 kPa.

Table 4. – Effects of treatment on plasma catecholamines

	Air	$O_2 + CO_2$	p-value
Adrenaline ng·L⁻¹	28.0±7.1	35.0±3.9	0.72
Noradrenaline ng·L⁻¹	486±116	669±163	0.035

Values are shown as mean±SEM.

ed slow-wave sleep in their air and treatment night respectively, this sleep stage was excluded from ANOVA. However, when results were recalculated including slow-wave sleep, Ptc,CO₂ for slow-wave sleep was as high as for stages 1 and 2 and lower than in REM sleep. The mean increase in Ptc,CO₂ with treatment was 5.1±1.0 in wake, 4.9±1.1 in stage 1, 5.4±1.2 in stage 2 and 8.4±2.2 mmHg in REM (p=0.023 by ANOVA with the highest increase in REM). In four patients a second arterial blood-gas analysis was performed at the end of the night (8.6+0.4 h after calibration) to evaluate the reliability of the transcutaneous measurement over a longer period. The transcutaneous values were -0.2, 0.3, 0.5 and 0.8 kPa (-1.4, 1.9, 4.1 and 6.0 mmHg) higher than the blood-gas analysis values.

Plasma catecholamines

Plasma noradrenaline was 247±23 ng·L⁻¹ in the healthy subjects and lower than in the patients while on air (p=0.042). Plasma adrenaline was 21.5±10.3 ng·L⁻¹ in the healthy subjects and not different from the patients while on air (p=0.27). Plasma noradrenaline was higher in the treatment night than on the air night in seven patients, this difference being statistically significant (table 4). Plasma adrenaline did not change significantly.

Discussion

This study has given rise to a novel, seemingly paradoxical observation. In patients with CHF nasal O₂ plus CO₂ clearly reduced nocturnal CSR and O₂ desaturations, but sleep did not improve and there was evidence of increased sympathetic activity.

CSR during sleep is common in patients with severe CHF, induces repetitive oxygen desaturation and impairs sleep [2, 15]. The 80% reduction in CSR in the present study compares favourably to the ~50% reduction reported with nasal O₂ [1, 6–8]. However, despite the clear reduction in CSR with nasal O₂ plus CO₂ there was no improvement in sleep quality. These findings corroborate the study of STEENS *et al.* [10], who administered 3% CO₂ *via* a nasal mask in 6 patients with CSR. In this study CSR was virtually abolished but sleep did not improve. The authors attributed this to the tight-fitting mask impairing sleep. They did not report on Pa,CO₂, minute ventilation or nocturnal dyspnoea, but evaluated end-tidal carbon dioxide tension (PET,CO₂) in two patients over a short period and found it to increase by 0.5–0.7 kPa (4–5 mmHg). Similar results were reported in a recent study on six patients with idiopathic central sleep apnoea [16]. The results of the present study suggest that the increase in Pa,CO₂ *per se* impairs sleep, since a reduction in CSR should be followed by improved sleep and O₂ has already been shown to improve sleep in patients with CSR and heart failure [1,

6–8]. The method by which CO₂ was applied cannot explain the adverse effects on sleep, since nasal prongs were administered on both nights. In a case report, VILLIGER *et al.* [17] described a patient with CSR and heart failure breathing 3% CO₂ in a tent [17]. This led to complete cessation of CSR. Data on sleep or cardiac function were, however, not reported. BADR *et al.* [18] described the effects of inhaled 2% CO₂ in a patient with persistent central sleep apnoea after being treated with tracheostomy for obstructive sleep apnoea. Similarly to a recent case report [19], central apnoeas were suspended and sleep architecture was improved. However, unlike in the present study, these patients did not have heart failure.

Patients with CHF, as with normal subjects, increase their ventilation following an increase in inspired Pa,CO₂. During the day minute ventilation will increase by about 1.5–3 L·min⁻¹ and fR by <0.5 min⁻¹ when PET,CO₂, which closely resembles Pa,CO₂, is increased by 0.1 kPa (1 mmHg) [20, 21]. However, the hypercapnic ventilatory response diminishes during sleep, depending on the sleep stage, by >50% [22] and with supplemental O₂ [23]. Subjects with nocturnal periodic breathing or CSR and heart failure are more likely to show an increased ventilatory response [24, 25]. Since Pa,CO₂ averaged over the night increased by ~0.5 kPa (4 mmHg) in the patients while on treatment, minute ventilation can be expected to increase by at least 2 L·min⁻¹. Given a resting ventilation of about 8 L·min⁻¹, this means a 25% increase in minute ventilation. Minute ventilation could not be measured reliably, but fR in undisturbed sleep stage 2 was higher on the treatment night, although this difference did not reach statistical significance. In the light of increased work of breathing, especially in the supine posture, and respiratory muscle weakness in patients with heart failure [26] this increase in minute ventilation may well promote arousals due to mechanoreceptor stimulation [27]. Furthermore, an increase in Pa,CO₂ will directly cause arousals by brainstem afferents from chemoreceptors.

The 17 s prolongation of the cycle period with CO₂ plus O₂ (table 2) lies between the insignificant change observed with 3% CO₂ [10] and a 23 s increase observed with nasal oxygen [6] and might be explained by the delayed and dampened response of the respiratory control system with higher Sa,O₂ [23].

As in previous studies on patients with CHF and CSR, the present patients were mildly hypocapnic [9, 28]. Hyperventilation due to a non-CO₂-dependent central neural drive, probably mediated by a reduced blood flow to chemoreceptors, an altered input from pulmonary J-receptors and muscle metaboreceptors, as well as humoral factors such as catecholamines, are the main causes of hypocapnia in these patients [20, 29]. In this study Ptc,CO₂ rose from wake, to stage 1 and 2 to REM sleep. This corroborates previous studies on patients with CSR [9, 28] and normal subjects [22].

Not surprisingly, Ptc,CO₂ and Sa,O₂ increased on the treatment night. This is probably the cause of the reduction of CSR that is mediated by a combination of the following mechanisms. It increases O₂ and CO₂ stores mainly in the lung, thereby dampening the respiratory control system [25]. The increase in Pa,CO₂ near to, or above, the apnoeic threshold will also reduce apnoea [24, 28].

The results demonstrate that CSR was not prevented in all patients, although the minimal Ptc,CO₂ was elevated by

at least 0.3 kPa (2 mmHg) in all patients with O_2 plus CO_2. This is probably due to the Pa,CO_2 oscillations that were still present. These oscillations are not unexpected, since the flow over the nasal prongs is constant and therefore any change in tidal volume will cause an opposite change in the inspired and, consequently, the arterial CO_2 concentration, thereby destabilizing the ventilatory feedback system. Furthermore, variable inspiratory gas concentrations may arise because of associated mouth breathing. Nasal prongs were used instead of a face mask, since the compliance with nasal prongs is higher than with a mask [30] and any treatment of CSR should reveal a good long-term compliance. Other than this, only an inconveniently tight-fitting face mask with an attached reservoir would avoid the above-mentioned variable insp-iratory gas concentrations.

The overestimation of the Ptc,CO_2 measurement compared with the blood-gas analysis in the patients in whom a second arterial blood-gas analysis was performed at the end of the night suggests that the transcutaneous measurement is less reliable over a longer period. NAUGHTON *et al.* [28] reported that their transcutaneous measurement closely reflected Pa,CO_2 over a period of 6 h in a similar subset of patients.

Increased sympathetic nerve activity and other markers of sympathetic system activation are present in CHF and are related to impaired exercise tolerance and mortality in these patients [4, 5]. Furthermore, the reduction in mortality following the treatment of heart failure with, for example, angiotensin-converting enzyme inhibitors [5] or the β-blocking agent carvedilol, is paralleled by a decrease in plasma noradrenaline. These findings are accounted for by the unfavourable effects of noradrenaline *via* its toxicity on cardiac muscle cells [31]. The observed increase in plasma noradrenaline with O_2 plus CO_2 in patients with CHF is therefore clearly disadvantageous. A number of reasons may explain the observed increase in plasma noradrenaline. As discussed above, hypercapnia increases minute ventilation. This will lead to an increased work of breathing and therefore increased metabolic demand and cardiac output [26, 32] especially in heart failure patients showing poor lung compliance and some degree of hyperventilation. In healthy persons increased systemic vascular resistance and in dogs increased capacitance vessel tone was observed with hypercapnia [33]. Furthermore, hyperoxia may also increase systemic vascular resistance in heart failure in a dose-dependent way [34]. Hypercapnia increased mean pulmonary artery pressure and pulmonary vascular resistance in a recent study on healthy subjects using Doppler echocardiography [35]. Similar findings were reported in an older study using right heart catheterization [33]. In aggregate hypercapnia increased ventricular workload by increasing cardiac output as well as right and left ventricular afterload and thereby is likely to elevate sympathetic activity. In addition, hypercapnia acutely increased sympathetic activity by chemoreceptor excitation, as recorded by microneurography [36]. Corresponding findings were reported in subjects exposed to an inspiratory CO_2 content of 3.8%, which was followed by an increase in urinary catecholamines and cardiac frequency [37]. Taken together, hypercapnia elevates sympathetic activity and right as well as left ventricular afterload. All of these changes are disadvantageous in patients with heart failure and seem to outweigh the observed positive effects of O_2

plus CO_2, specifically the reduction in CSR and O_2 desaturation.

Plasma noradrenaline concentrations are not optimal as a measure of sympathetic activation. Only a fraction of neurally released noradrenaline appears in the plasma and this reflects not neurotransmitter release, but rather the balance between spillover and clearance [4]. It may well be that the evaluation of sympathetic activity with more reliable (and more invasive) methods, such as microneurography or the determination of cardiac noradrenaline spillover, would have shown a more striking increase in sympathetic activity.

The influence of the treatment of CSR on sympathetic activity has been addressed in a recent study using nocturnal O_2 over 1 month in patients with CHF. With this treatment a reduction in plasma norepinephrine concentrations was observed, suggesting reduced sympathetic activity [38]. This may account for the increase in exercise capacity following nocturnal O_2 [6].

The present study reveals that nocturnal O_2 plus CO_2 reduces Cheyne-Stokes respiration but does not improve quality of sleep. Furthermore, there was evidence of increased sympathetic activation and therefore this approach is inopportune in the treatment of patients with congestive heart failure. The simple reduction of nocturnal Cheyne-Stokes respiration cannot be the only objective in the management of patients with heart failure. The impact on the sequelae of Cheyne-Stokes respiration, namely quality of sleep and sympathetic system activation, should also be beneficial.

References

1. Hanly PJ, Milar TW, Steljes DG, Baert R, Frais MA, Kryger MH. The effect of oxygen on respiration and sleep in patients with congestive heart failure. *Ann Intern Med* 1989; 111: 777–782.
2. Javaheri S, Parker TJ, Wexler L, *et al.* Occult sleep-disordered breathing in stable congestive heart failure. *Ann Intern Med* 1995; 122: 487–492.
3. Naughton MT, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med* 1995; 152: 473–479.
4. Floras JS. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. *J Am Coll Cardiol* 1993; 22: 72a–84a.
5. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. *Circulation* 1990; 82: 1730–1736.
6. Andreas S, Clemens C, Sandholzer H, Figulla HR, Kreuzer H. Improvement of exercise capacity with treatment of Cheyne-Stokes respiration in patients with congestive heart failure. *J Am Coll Cardiol* 1996; 27: 1486–1490.
7. Walsh JT, Andrews R, Starling R, Cowley AJ, Johnston ID, Kinnear WJ. Effects of captopril and oxygen on sleep apnoea in patients with mild to moderate congestive cardiac failure. *Br Heart J* 1995; 73: 237–241.
8. Franklin KA, Erikson P, Sahlin C, Lundgren R. Reversal

of central sleep apnea with oxygen. *Chest* 1997; 111: 163–169

9. Hanly P, Zuberi N, Gray G. Pathogenesis of Cheyne-Stokes respiration in patients with congestive heart failure. Relationship to arterial P_{CO_2}. *Chest* 1993; 104: 1079–1084.

10. Steens RD, Millar TW, Su X, *et al.* Effect of inhaled 3% CO_2 on Cheyne-Stokes respiration in congestive heart failure. *Sleep* 1994; 17: 61–68.

11. Rechtschaffen A, Kales A. Manual of standardized terminology techniques and scoring system for sleep stages of human subjects. *Natl Inst Health Publ* 1986; 68: 0204.

12. American Sleep Disorders Associating. EEG Arousals: scoring rules and examples. A preliminary report from the sleep disorders atlas task force of the American Sleep Disorders Association. *Sleep* 1992; 15: 173–184

13. Kesten S, Chapman KR, Rebuck AS. Response characteristics of a dual transcutaneous oxygen/carbon dioxide monitoring system. *Chest* 1991; 99: 1211–1215.

14. Van der Hoorn FAJ, Boosma F, Mann AJ, Schalekamp MADH. Determination of catecholamines in human plasma by high-performance liquid chromatography: comparison between a new method with fluorescence detection and an established method with electrochemical detection. *J Chromatogr* 1989; 487: 17–28

15. Hanly P, Zuberi-Khokhar N. Daytime sleepiness in patients with congestive heart failure and Cheyne-Stokes respiration. *Chest* 1995; 107: 952–958.

16. Xie A, Rankin F, Rutherford R, Bradley TD. Effects of inhaled CO_2 and added dead space on idiopathic central sleep apnea. *J Appl Physiol* 1997; 82: 918–926.

17. Villiger PM, Hess CW, Reinhart WH. Beneficial effect of inhaled CO_2 in a patient with nonobstructive sleep apnoea. *J Neurol* 1993; 241: 45–48.

18. Badr MS, Grossman JE, Weber SA. Treatment of refractory sleep apnea with supplemental carbon dioxide. *Am J Respir Crit Care Med* 1994; 150: 561–564.

19. Hommura F, Nishimura M, Oguri M, *et al.* Continuous *versus* bilevel positive airway pressure in a patient with idiopathic central sleep apnea. *Am J Respir Crit Care Med* 1997; 155: 1482–1485.

20. Chua TP, Clark AL. Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1996; 27: 650–657.

21. Andreas S, Morguet AJ, Werner GS, Kreuzer H. Ventilatory response to exercise and to carbon dioxide in patients with heart failure. *Eur Heart J* 1996; 17: 750–755.

22. Douglas NJ, White DP, Weil JV, Pickett CK, Zwillich CW. Hypercapnic ventilatory response in sleeping adults. *Am Rev Respir Dis* 1982; 126: 758–762.

23. Gelfand R, Lambertsen CJ. Dynamic respiratory response to abrupt change of inspired CO_2 at normal and high P_{O_2}. *J Appl Physiol* 1973; 35: 903–913.

24. Xie A, Rutherford R, Rankin F, Wong B, Bradley TD. Hypocapnia and increased ventilatory responsiveness in patients with idiopathic central sleep apnea. *Am J Respir Crit Care Med* 1995; 152: 1950–1955

25. Khoo MC, Gottschalk A, Pack AI. Sleep-induced periodic breathing and apnea: a theoretical study. *J Appl Physiol* 1991; 70: 2014–2024.

26. Mancini DM, Henson D, LaManca J, Levine S. Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. *Circulation* 1992; 86: 909–918.

27. Kimoff RJ, Kozar LF, Yasuma F, Bradley TD, Phillipson EA. Effect of inspiratory muscle unloading on arousal responses to CO_2 and hypoxia in sleeping dogs. *J Appl Physiol* 1993; 74: 1325–1336.

28. Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the submitted pathogenesis of central sleep apneas in patients with congestive heart failure. *Am Rev Respir Dis* 1993; 148: 330–338.

29. Clark AL, Poole-Wilson PA, Coats AJS. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol* 1996; 20: 1092–1102.

30. Costello RW, Liston R, McNicholas WT. Compliance at night with low flow oxygen therapy: a comparison of nasal cannulae and Venturi face masks. *Thorax* 1995; 50: 405–406.

31. Mann DL, Kent RL, Parsons B, Cooper GT. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation* 1992; 85: 790–804.

32. McParland C, Krishnan B, Wang Y, Gallagher C. Inspiratory muscle weakness and dyspnea in chronic heart failure. *Am Rev Respir Dis* 1992; 146: 467–472.

33. Kilburn KH, Asmundsson T, Britt RC, Cardon R. Effects of breathing 10 per cent carbon dioxide on the pulmonary circulation of human subjects. *Circulation* 1969; 39: 639–653.

34. Haque WA, Boehmer J, Clemson BS, Leuenberger UA, Silber DH, Sinoway LI. Hemodynamic effects of supplemental oxygen administration in congestive heart failure. *J Am Coll Cardiol* 1996; 27: 353–357.

35. Kiely DG, Cargill RI, Lipworth BJ. Effects of hypercapnia on hemodynamic, inotropic, lusitropic, and electrophysiologic indices in humans. *Chest* 1996; 109: 1215–1221.

36. Somers VK, Mark AL, Abboud FM. Interaction of baroreceptor and chemoreceptor reflex control of sympathetic nerve activity in normal humans. *J Clin Invest* 1991; 87: 1953–1957.

37. Grover RF, Reeves JT, Maher JT, *et al.* Maintained stroke volume but impaired arterial oxygenation in man at high altitude with supplemental CO_2. *Circ Res* 1976; 38: 391–396.

38. Kinnear RS, Starling R, Staniforth A. Effect of long-term nocturnal oxygen on sleep quality and cognitive function in chronic heart failure with Cheyne-Stokes respiration. *Eur Respir J* 1997; 10: S278(Abstract).