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

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Cheyne-Stokes respiration (CSR) during sleep is common in patients with 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 O2 by nasal prongs reduces CSR by about 50% and consolidates sleep [1, 6–8]. Application of 3% CO2 prevented CSR by increasing the arterial carbon dioxide tension (P\text{a,CO2}) 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 CO2 in conjunction with O2 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 \(<35\%\), 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-disorder-related 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 were randomly assigned to one night each of O2 plus CO2 as well as air applied by nasal prongs.

Nocturnal O2 plus CO2 reduced the duration of CSR as percentage of total sleep time (48.0±10 \(\text{versus}\) 7.4±2.0%; \(p=0.008\)) and increased arterial oxygen saturation \((\text{Sao2})\) as well as mean transcutaneous carbon dioxide tension \((P_{tc,CO2})\) (5.2±0.3 kPa (39±2 mmHg) \(\text{versus}\) 5.7±0.3 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 \(\text{versus}\) 669±163 ng·L\(^{-1}\); \(p=0.035\)).

In conclusion, nocturnal O2 plus CO2 improves Cheyne-Stokes respiration in patients with congestive heart failure but has adverse effects on the sequel of Cheyne-Stokes respiration, namely sympathetic activation.

CSR. When CSR with apnoea was noted CO₂ 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-oculogram, electrocardiogram and submental as well as anterior tibialis electromyogram were set in place. Airflow over the nose and mouth was recorded by thermistors and thorax and abdominal wall motion was monitored by strain gauges. Arterial oxygen saturation (\(S_a,O_2\)) and abdominal wall motion was monitored by strain gauges. Arterial oxygen saturation (\(S_a,O_2\)) 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 abdominal wall motion had to be adequate in different sleep positions. During the entire night, the recording was observed on a monitor and amplification of signals was corrected 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 hypopnoea 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. Accordingly, CSR was classified as CSR with hypopnoea and CSR with apnoea. The apnoea-hypopnoea index was defined as the total number of sleeping apnoeas and hypopnoeas 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 \(S_a,O_2\) during CSR were averaged over at least 10 consecutive cycles in sleep stage 2. The respiratory rate was averaged over 10 min of undisturbed sleep and ventilation in stage 2. The amount of time for which \(S_a,O_2\) was <90%, corrected for TST and the average cardiac frequency (\(f_C\)) over the night was computed by the CNS System.

**Capnography**

The transcutaneous O₂ and CO₂-monitoring system (TINA; Radiometer, Copenhagen, Denmark) was calibrated with a 5% CO₂ and 20.9% O₂ standard calibration gas at the beginning of each study. Fresh bicarbonate solution was inserted around the electrode and a new O₂ and CO₂-permeable membrane was used for each study. The sensor was placed on the anterior chest and heated to 44°C. Arterial oxygen tension (\(P_a,O_2\)) and \(P_a,CO_2\) 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 \(P_a,O_2\) recordings falls behind the transcutaneous \(S_a,O_2\) system [13], \(P_a,O_2\) 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 calibration. 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 sample 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 transcutaneous measurement closely reflecting \(P_a,CO_2\), an insignificant 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 tourniquet from an antecubital vein in the morning, after awakening but before rising in the supine position. The samples were collected in pre-shilled heparinized tubes and immediately placed on ice, then centrifuged at 4°C. Adrenaline and noradrenaline levels were assayed using the high-performance liquid chromatographic (HPLC) technique with fluorescence detection after derivatization with 1,2-diphenylethlylendiamine [14]. Left ventricular end-diastolic and left atrial diameter were evaluated by echocardiography from a left parasternal view. Left ventricular ejection fraction at rest was determined by technetium-99m (⁹⁹mTc) gated blood pool scintigraphy.

**Statistical analysis**

All variables are given as mean±SD. 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 \(P_a,CO_2\) for different sleep stages; where appropriate this was followed by post-hoc analysis using Fisher’s protected least significant difference. The patients and the controls were compared using the Mann-Whitney U-test. Statistical analyses were performed on a personal computer using StatView (Abacus, 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 remaining 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 Association (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-defibrillator with anti-bradycardiac function implanted. Medication consisted of a diuretic and β-acetyl-digoxin in all patients, and an angiotensin-converting enzyme inhi-bitor in eight patients. Three patients...
Mean±SEM

O2+CO2

Air

O2+CO2

Mean±SEM

O2+CO2

Air

O2+CO2

Table 1. – Characteristics of the nine patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SEM</th>
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<tbody>
<tr>
<td>Age yrs</td>
<td>59.4±4.8</td>
</tr>
<tr>
<td>Body mass index kg·m⁻²</td>
<td>25.2±1.1</td>
</tr>
<tr>
<td>Left atrial diameter mm</td>
<td>52.6±1.3</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter mm</td>
<td>77.6±2.0</td>
</tr>
<tr>
<td>Left ventricular ejection fraction %</td>
<td>17.8±1.2</td>
</tr>
<tr>
<td>Vital capacity % pred</td>
<td>77.2±5.5</td>
</tr>
<tr>
<td>Forced expiratory volume in one second % pred</td>
<td>78.8±12.4</td>
</tr>
<tr>
<td>Total lung capacity % pred</td>
<td>87.3±7.8</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.50±0.01</td>
</tr>
<tr>
<td>Arterial partial pressure of CO₂ mmHg</td>
<td>37.4±1.9</td>
</tr>
<tr>
<td>Arterial partial pressure of O₂ mmHg</td>
<td>88.9±3.5</td>
</tr>
<tr>
<td>HCO₃⁻ mmol·L⁻¹</td>
<td>28.1±1.8</td>
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<tr>
<td>Base excess mmol·L⁻¹</td>
<td>4.3±1.7</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Air</th>
<th>O₂+CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of CSR % TST</td>
<td>48.0±9.6</td>
<td>7.4±2.0</td>
</tr>
<tr>
<td>Duration of CSR with apnoea % TST</td>
<td>22.2±8.6</td>
<td>0.4±0.3</td>
</tr>
<tr>
<td>Apnoea-hypopnoea index n·h⁻¹</td>
<td>36.7±7.3</td>
<td>5.4±1.2</td>
</tr>
<tr>
<td>% of time in bed with SaO₂&lt;90%</td>
<td>14.1±4.8</td>
<td>1.4±0.8</td>
</tr>
<tr>
<td>Duration of a cycle period s</td>
<td>61.5±5</td>
<td>78.2±2</td>
</tr>
<tr>
<td>Time in bed min</td>
<td>460±10</td>
<td>478±9</td>
</tr>
<tr>
<td>Total sleep time min</td>
<td>334±23</td>
<td>3131±20</td>
</tr>
<tr>
<td>Wake % time in bed</td>
<td>27.4±4.4</td>
<td>34.4±4.1</td>
</tr>
<tr>
<td>Stage 1 % TST</td>
<td>28.4±7.3</td>
<td>30.1±7.1</td>
</tr>
<tr>
<td>Stage 2 % TST</td>
<td>51.0±5.6</td>
<td>51.5±5.3</td>
</tr>
<tr>
<td>Slow-wave sleep % TST</td>
<td>7.6±2.9</td>
<td>8.5±2.4</td>
</tr>
<tr>
<td>REM sleep % TST</td>
<td>13.0±2.9</td>
<td>9.6±2.3</td>
</tr>
<tr>
<td>Arousals n·h⁻¹</td>
<td>13.4±1.6</td>
<td>13.7±1.5</td>
</tr>
</tbody>
</table>

Table 3. – Effects of treatment on the transcutaneous partial pressure of CO₂ (P₀₂ₐₗ₃CO₂)

<table>
<thead>
<tr>
<th>P₀₂ₐₗ₃CO₂ mmHg</th>
<th>Air</th>
<th>O₂+CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wake</td>
<td>36.0±1.7</td>
<td>41.2±2.2</td>
</tr>
<tr>
<td>Stage 1</td>
<td>37.6±2.1</td>
<td>42.6±2.5</td>
</tr>
<tr>
<td>Stage 2</td>
<td>38.4±2.3</td>
<td>43.2±2.5</td>
</tr>
<tr>
<td>REM sleep</td>
<td>38.4±2.9</td>
<td>47.3±2.8</td>
</tr>
</tbody>
</table>

Values are shown as mean±SEM. p=0.003 for between-treatment effects and p<0.001 for effects of sleep stages (two-way repeated measures analysis of variance). The differences in P₀₂ₐₗ₃CO₂ (using the data for air as well as O₂ plus CO₂) 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.

Polysomnography

All patients suffered from CSR during sleep (254±42, range 119–470 min). Nocturnal O₂ plus CO₂ 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 on air and 0.4±0.2·h⁻¹ on treatment (p=0.091). Arousals not associated with respiratory events increased from 2.6±0.7 on air to 7.8±2.0·h⁻¹ TST while 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 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 fasting during the night was 77.4±2.8 mm⁻¹ on air and 80.8±4.4 mm⁻¹ while on treatment (p=0.21). The respiratory frequency (f₀) in sleep stage 2 was 19.0±1.7 mm⁻¹ on air and 19.4±1.5 mm⁻¹ while on treatment (p=0.11). One patient woke up while on O₂ plus CO₂ and reported shortness of breath. Orthopnoea and wheezing, slowly improving with sublingual nitrate and nasal O₂, was observed. No such episode was noticed in any patient in the accommodation night or while receiving air.

Capnography

The P₀₂ₐₗ₃CO₂ during different sleep stages was higher in the treatment night than with air (table 3). The mean P₀₂ₐₗ₃CO₂ averaged over the whole night and the minimal P₀₂ₐₗ₃CO₂ increased from 5.2±2.1 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 P₀₂ₐₗ₃CO₂ under air as well as under treatment, with the lowest P₀₂ₐₗ₃CO₂ values during wake and the highest during REM sleep (table 3). Since only six and five patients show-

1 mmHg=0.133 kPa.

During the second night four patients received air and five patients CO₂ plus O₂. The flow rate of nasal CO₂ was 0.7±0.1 L·min⁻¹, with no significant change during different sleep stages.
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, \( P_{a,CO_2} \) for slow-wave sleep was as high as for stages 1 and 2 and lower than in REM sleep. The mean increase in \( P_{a,CO_2} \) 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 \( O_2 \) plus \( CO_2 \) clearly reduced nocturnal CSR and \( O_2 \) 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 \( O_2 \) [1, 6–8]. However, despite the clear reduction in CSR with nasal \( O_2 \) plus \( CO_2 \) there was no improvement in sleep quality. These findings corroborate the study of Steens et al. [10], who administered 3% \( CO_2 \) 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 \( P_{a,CO_2} \), minute ventilation or nocturnal dyspnoea, but evaluated end-tidal carbon dioxide tension (\( PET_{CO_2} \)) 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 \( P_{a,CO_2} \) per se impairs sleep, since a reduction in CSR should be followed by improved sleep and \( O_2 \) has already been shown to improve sleep in patients with CSR and heart failure [1, 6–8]. The method by which \( CO_2 \) was applied cannot explain the adverse effects on sleep, since nasal prongs were administered on both nights. In a case report, Vleen et al. [17] described a patient with CSR and heart failure breathing 3% \( CO_2 \) in a tent [17]. This led to complete cessation of CSR. Data on sleep or cardiac function were, however, not reported. Bar et al. [18] described the effects of inhaled 2% \( CO_2 \) 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 \( P_{a,CO_2} \). During the day minute ventilation will increase by about 1.5–3 L·min\(^{-1} \) and \( fR \) by <0.5 min\(^{-1} \) when \( PET_{CO_2} \), which closely resembles \( P_{a,CO_2} \), 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 \( O_2 \) [23]. Subjects with nocturnal periodic breathing or CSR and heart failure are more likely to show an increased ventilatory response [24, 25]. Since \( P_{a,CO_2} \) 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 \( P_{a,CO_2} \) will directly cause arousals by brainstem afferents from chemoreceptors.

The 17 s prolongation of the cycle period with \( CO_2 \) plus \( O_2 \) (table 2) lies between the insignificant change observed with 3% \( CO_2 \) [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 \( SaO_2 \) [23].

As in previous studies on patients with CHF and CSR, the present patients were mildly hypocapnic [9, 28]. Hyper-ventilation due to a non-\( CO_2 \)-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 \( P_{a,CO_2} \) rose from wake, to stage 1 and 2 to REM sleep. This correlates with previous studies on patients with CSR [9, 28] and normal subjects [22].

Not surprisingly, \( P_{a,CO_2} \) and \( SaO_2 \) 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 \( O_2 \) and \( CO_2 \) stores mainly in the lung, thereby dampening the respiratory control system [25]. The increase in \( P_{a,CO_2} \) 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 \( P_{a,CO_2} \) was elevated by

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<th>Table 4. – Effects of treatment on plasma catecholamines</th>
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<tr>
<td>Adrenaline ng·L(^{-1} )</td>
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<tr>
<td>Noradrenaline ng·L(^{-1} )</td>
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</tbody>
</table>

Values are shown as means.
at least 0.3 kPa (2 mmHg) in all patients with O$_2$ plus CO$_2$. This is probably due to the $P_{ac}$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, consecutively, 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, an inconveniently tight-fitting face mask with an attached reservoir would avoid the above-mentioned variable inspiratory gas concentrations.

The overestimation of the $P_{ac}$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 transtcutaneous measurement is less reliable over a longer period. NAUGHTON et al. [38] reported that their transtcutaneous measurement closely reflected $P_{ac}$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 microencephalography [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 microencephalography 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.

**Acknowledgement:** The authors thank P.D. Niedmann for analysing the plasma catecholamines.

**References**


