Exercise Tolerance, Exercise Hyperpnea and Central Chemosensitivity to Carbon Dioxide in Sleep Apnea Syndrome in Heart Failure Patients

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Background Sleep apnea syndrome (SAS) and exercise hyperpnea are common in patients with chronic heart failure (CHF), and although it is not known whether they are both regulated by the same mechanisms, the hypothesis of the present study was that they are related to augmented central chemosensitivity.

Methods and Results The oxygen desaturation index (ODI) was evaluated in 29 patients and those with ODI >5 times/h underwent polysomnography. Patients with an apnea–hypopnea index (AHI) >15/h without evidence of obstructive apnea were defined as central SAS (CSAS). Cardiopulmonary exercise testing was performed to determine peak oxygen uptake and the VE–VCO2 slope. A hypercapnic gas mixture (7% CO2/93% O2) was used to activate the central chemoreflex. Nine patients had central SAS (CHF-CSAS) and 20 did not have apnea (CHF-nonSAS). Patients with CHF-CSAS had a lower peak oxygen uptake than the CHF-nonSAS group (13.0±2.4 vs 16.9±4.3 ml·kg−1·min−1, p<0.05). There was a significant correlation between central chemosensitivity and the AHI (r=0.63, p<0.05), between central chemosensitivity and the VE–VCO2 slope (r=0.50, p<0.01), whereas the VE–VCO2 slope showed an insignificant tendency to correlate with AHI (r=0.44, p=0.07).

Conclusion CHF-CSAS is associated with impaired exercise tolerance and elevated central chemosensitivity is the responsible mechanism for CSAS and exercise hyperpnea. (Circ J 2005; 69: 695–699)

Key Words: Carbon dioxide; Chemosensitivity; Chronic heart failure; Exercise testing; Sleep apnea syndrome

Sleep apnea syndrome (SAS) is one of the most common complications in chronic heart failure (CHF) patients and its prevalence is estimated to be about 50% in such patients.1–3 Patients with SAS have a poor prognosis compared with those without it4–5 because the development of SAS reflects greater cardiac impairment and/or SAS itself accelerates the deterioration in cardiac function. Therefore, SAS itself has become a target for therapy, using continuous positive airway pressure devices, which can improve cardiac function in patients with both CHF and SAS.6–9

Two forms of SAS are seen in CHF patients. One is central SAS (CHF-CSAS), which often shows a Cheyne-Stokes respiration pattern and the other is obstructive SAS (CHF-OSAS), but central SAS is more common! It is associated with hyperventilation and hypocapnea during sleep, when ventilation is under negative feedback metabolic control10 and the oscillating hypocapnea induced by hyperventilation during sleep is the primary abnormality underlying CHF-CSAS. Once hyperpnea begins and the partial pressure of carbon dioxide (PaCO2) decreases below the apneic threshold, breathing stops. On the other hand, when the PaCO2 increases above the apneic threshold for the chemoreceptors, hyperpnea begins and drives the PaCO2 below the apnea threshold. In addition to the augmented ventilatory response to CO2, the set point for the PaCO2 of the chemoreceptors is abnormal. It has been reported that patients with CHF-CSAS have a lower PaCO2 during both waking and sleeping than those without SAS11 and the threshold for CO2 is changed according to the sleep state.12 The main mechanism for the initiation of CHF-CSAS may be the lowered PaCO2 during waking and the change in the threshold level for PaCO2 according to the sleep stage.

Exercise hyperpnea is also common in CHF patients13 and augmented central carbon dioxide chemosensitivity may also be correlated with excessive ventilatory response to the exercise14 although the primary mechanism responsible for exercise hyperpnea is thought to be augmented ventilation-perfusion mismatching.15

Although the frequency of CHF-CSAS is reportedly correlated with central16 and peripheral CO2 chemosensitivity, the clinical characteristics of sleep apnea in patients with CHF have not been fully clarified. We hypothesized that CHF-CSAS is associated with impaired exercise tolerance and that the nocturnal sleep disturbance and abnormal ventilatory response during exercise are related to augmented central chemosensitivity. The purpose of this study was to evaluate exercise tolerance and the relationships between central chemosensitivity to CO2, exercise hyperpnea, and CHF-CSAS in patients with CHF.

Methods

Subjects
From April 2001 to April 2003 consecutive patients with

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CHF caused by ischemic cardiomyopathy (ICM) or idiopathic dilated cardiomyopathy (DCM) who could undergo cardiopulmonary testing were enrolled in this study. All patients had undergone previous coronary angiography and the diagnosis of ICM or DCM had been confirmed. The entry criteria were (1) at least 1 previous episode of clinical heart failure, (2) echocardiographic left ventricular ejection fraction (LVEF) ≤45%, and (3) stable clinical condition defined as no medication change within 2 weeks. We excluded patients who had the following conditions: unstable angina pectoris, acute myocardial infarction, cardiac surgery within in 6 months prior to study entry, and chronic obstructive lung disease. Thirty-two patients met the criteria and 3 who refused to have SAS. If a patient had ODI <5 times per hour, were considered not to have SAS. If a patient had ODI ≥5 times per hour, we excluded them from the study. CHF-CSA and CHF-nonSAS group refused to participate in this protocol. Patients with the high O2 concentration the peripheral hypercapnic response is known to be very small or negligible.20 Breath-by-breath tidal volume and P ETCO2 were measured continuously using a gas analyzer. The linear slope between ventilation and PTrCO2 was calculated by linear regression analysis.

Central Chemosensitivity to CO2

Central hypercapnic chemosensitivity was assessed during rebreathing of CO214,19 One patient in the CHF-nonSAS group refused to participate in this protocol. Patients rebreathed through a 6-l bag containing a mixture of 7% CO2 and 93% O2 for 4 min. The test was stopped as soon as they were too breathless to continue or if PetCO2 exceeded 10%. This test can estimate the sensitivity of central chemoreceptors, because with the high O2 concentration the peripheral hypercapnic response is known to be very small or negligible.20 Breath-by-breath tidal volume and PetCO2 were measured continuously using a gas analyzer. The linear slope between ventilation and PetCO2 was calculated by linear regression analysis and expressed in terms of liters per minute per millimeter of mercury (L•min⁻¹•mmHg⁻¹).

Sleep Study

All patients underwent nightly pulse oxymetry (Pulsox-M24, TEIJIN, Tokyo, Japan). The oxygen desaturation index (ODI), which is defined as the frequency of a decrease in desaturation ≥4% in the arterial oxyhemoglobin saturation per hour, was used to evaluate the presence of sleep apnea.21 Patients with ODI ≤5 times per hour, were considered not to have SAS. If a patient had ODI ≥5 times per hour, the patient underwent further evaluation with polysomnography (PS2 plus, Compumedics Sleep, Victoria, Australia). The electroencephalogram, body position, eye and leg movements, electrocardiogram, nasobuccal air flow, chest and abdominal effort, and O2 saturation were continuously measured using a breath-by-breath gas analyzer (Minato AE300S, Minato Ikagaku, Osaka, Japan). The V•CO2, V•O2, and ventilatory equivalent (VE) were continuously measured using a breath-by-breath gas analyzer (Minato AE300S, Minato Ikagaku, Osaka, Japan). The VE–VCO2 slope was calculated by linear regression analysis.

Measurement of LVEF

All patients underwent echocardiographic evaluation (SONOS 5500 or 2000, Philips Medical Systems, MA) and LVEF was calculated by the Simpson method.

Exercise Testing and Exercise Hyperpnea

Symptom-limited cardiopulmonary exercise testing was performed using a stationary cycle ergometer (Recor 500P, Load, Delft, The Netherlands). After a 3-min rest period, exercise began with a 3-min warm-up at a workload of 10 W and a pedal rate of 60 rounds/min. Exercise intensity was increased incrementally by 1 W every 6 s. All patients were encouraged to exercise to exhaustion, and none experienced angina pectoris, syncope or showed ischemic ST changes or severe arrhythmia during the exercise test. Oxygen consumption (V•O2), CO2 production (V•CO2), and

Table 1 Demographics and Clinical Characteristics of CHF Patients With and Without Central Sleep Apnea

<table>
<thead>
<tr>
<th></th>
<th>CHF-CSA</th>
<th>CHF-nonSAS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (women)</td>
<td>9 (1)</td>
<td>20 (5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (years)</td>
<td>73±6</td>
<td>61±12</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61±11</td>
<td>62±14</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161±9</td>
<td>162±9</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23±3</td>
<td>23±4</td>
<td>NS</td>
</tr>
<tr>
<td>DCM/ICM</td>
<td>6/3</td>
<td>1/6</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class II/III</td>
<td>6/3</td>
<td>18/2</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>22±12</td>
<td>29±9</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODI (times/h)</td>
<td>20±7</td>
<td>4±5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AHI (times/h)</td>
<td>24±8 (n=9)</td>
<td>7±3 (n=4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>OSA (times/h)</td>
<td>16±8 (n=9)</td>
<td>1±1 (n=4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CSA (times/h)</td>
<td>14±8 (n=9)</td>
<td>1±1 (n=4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Medications</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>6</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>5</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>9</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5</td>
<td>8</td>
<td>NS</td>
</tr>
</tbody>
</table>

CHF, chronic heart failure; CSA, central sleep apnea; SAS, sleep apnea syndrome; BMI, body mass index (BMI = weight in kilograms divided by the square of the height in meters); DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ODI, oxygen desaturation index; AHI, apnea hypopnea index; AI, apnea index; OSA, obstructive sleep apnea; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

Fig 1. Classification of patients.
recorded. An episode of apnea was defined as cessation of airflow for at least 10 s; an episode of obstructive apnea was defined as the absence of airflow in the presence of rib-cage and abdominal excursion; an episode of central apnea was defined as the absence of airflow, and the absence of both rib-cage and abdominal excursion; and hypopnea was defined as a reduction in airflow lasting at least 10 s accompanied by at least a 3% decrease in arterial oxyhemoglobin saturation. The number of episodes of apnea and hypopnea per hour was defined as the apnea–hypopnea index (AHI). Patients with \( \geq 5 \) episodes per hour of obstructive apnea were excluded from the present study. Patients with AHI \( \geq 15 \) per hour were classified as the CHF-CSAS group and the others were classified as the CHF-nonSAS group. 1 The patients were divided into 3 groups (CHF-nonSAS, CHF-CSAS and obstructive apnea) as shown in Fig 1.

**Statistical Analysis**

All descriptive data are expressed as the mean ± SD. The Mann-Whitney test was used to assess differences between patients with and without CSAS. The chi-square test was used to compare dichotomous variables. The correlations between central chemosensitivity to CO\(_2\) and VE–VCO\(_2\) slope and AHI, the correlation between central chemosensitivity to CO\(_2\) and peak VO\(_2\) were assessed by the Pearson least-squares correlation test. A value of \( p<0.05 \) was considered statistically significant. All calculations were done using StatView software, version 5.0 (SAS Institute Inc, Cary, NC, USA).

**Results**

Nine patients had CHF-CSAS and 20 did not have apnea (CHF-nonSAS); the 3 patients with obstructive apnea were excluded. The clinical characteristics of the patients are summarized in Table 1. The mean age of the patients with CSAS was significantly higher than that of the patients without SAS. In the sleep study, the ODI, AHI, apnea index and central sleep apnea in patients with CSAS were all significantly higher than in those without SAS. There were no significant differences except for age and sleep...
study results, between the 2 groups with respect to underlying diseases, anthropometric data, severity of CHF, or medical therapy.

As is shown in Fig 2, patients in the CHF-CSAS group had a lower peak O2 uptake than those in the CHF-nonSAS group (13.0±2.4 vs 16.9±4.3 ml·kg⁻¹·min⁻¹, p<0.01). Fig 3 shows a significantly higher central chemosensitivity in patients with CHF-CSAS (10.1±6.7 L·min⁻¹·mmHg⁻¹) than in patients without SAS (3.8±2.5 L·min⁻¹·mmHg⁻¹). Patients in the CHF-CSAS group had a significantly steeper VE–VCO₂ slope (46±13 vs 33±8, p<0.01) than the CHF-nonSAS group (Fig 4).

There was a highly significant correlation between central chemosensitivity to CO₂ and AHI (n=12, r=0.63; p<0.05). A significant correlation (r=0.50, p<0.01) was observed between exercise hyperpnea and hypersensitivity to CO₂ (n=13; Fig 6). The VE–VCO₂ slope was insignificantly correlated with AHI (r=0.44, p=0.07) (Fig 7).

Discussion

There are 3 major findings of this study. First, patients with CHF-CSAS had impaired exercise tolerance compared with the CHF-nonSAS group. Second, central chemosensitivity was significantly augmented in CHF-CSAS patients and correlated with AHI. Third, exercise hyperpnea was associated with CHF-CSAS. This is the first study to show that chemosensitivity to CO₂ is an underlying pathophysiological mechanism responsible for CSAS and exercise hyperpnea in CHF patients.

In the present study, patients with CHF-CSAS had a lower peak O₂ uptake than those without SAS, contrary to a previous report. This discrepancy could be explained by differences in patient selection. In our study, pulse oximetry was performed as a screening test. However, ODI <5 should be enough to deny the presence of AHI over 15/h because of its sensitivity. In the other report, electroencephalography was not performed in cases of AHI <15 on portable polysomnography. Portable polysomnography may underestimate the AHI and some patients who have CSAS may have been misclassified as not having CSAS. Besides, in that study, only 10 of 72 patients who did not have SAS underwent exercise testing. Therefore, no difference in the peak O₂ uptake may have been seen between patients with and without CSAS. Furthermore, it is reported that augmented sympathetic nerve activity is associated with the severity of SAS. Sympathetic nerve activity is related to peak O₂ uptake. Augmented sympathetic nervous activity is known to lead to chronotropic incompetence and impaired cardiac muscle contractility, leading to diminished peak O₂ uptake. Peak O₂ uptake is a strong predictor of mortality in patients with heart failure. Patients with SAS have a poor prognosis compared with those without SAS. Those reports suggest that patients with CHF-CSAS might have decreased peak O₂ uptake, which supports the present findings.

There is controversy whether the severity of SAS is related to cardiac function. In the present study, there were no differences in LVEF between the 2 groups and other studies have also not shown a relationship between LVEF and SAS. However, this is not concrete evidence that cardiac function and SAS have no correlation, because LVEF is not necessarily a parameter of cardiac function. That is, resting parameters such as LVEF do not reflect functional reserve. From our study, cardiac function seems deteriorated in patients with SAS, as has been reported, because O₂ uptake is a marker of cardiac function at peak exercise.

In the present study, patients with CHF-CSAS had a significantly steeper VE–VCO₂ slope than those without SAS, as previously described. In other words, patients with CHF-CSAS have more severe exercise hyperpnea than patients without SAS. In the present study, exercise hyperpnea was correlated with central chemosensitivity to CO₂ as was previously reported. Augmented chemosensitivity has been proposed as a cause of exercise hyperpnea.

In the present study, the VE–VCO₂ slope was insignificantly correlated with AHI. Patients with CHF-CSAS have hyperpnea not only at rest and during sleep, but also during exercise, as previously reported. However, the correlation...
coefficient between the VE–\(\text{VCO}_2\) slope and AHI was less than between chemosensitivity and the AHI. In the study by Artz et al.,\(^2\) chemosensitivity was not observed and it was presumed that the steeper VE–\(\text{VCO}_2\) slope was caused by augmented chemosensitivity. In the present study, we observed a relationship among VE–\(\text{VCO}_2\) slope, chemosensitivity and AHI, which suggests that AHI was correlated with abnormal ventilatory responses during exercise through augmented central chemosensitivity. Other mechanisms for the steeper VE–\(\text{VCO}_2\) slope in CHF-CSAS patients were also considered. Exercise hyperpnea correlates with ventilatory perfusion abnormalities and increasing physiological pulmonary dead space.\(^29\) Because of left ventricular end-diastolic volume and pulmonary capillary wedge pressure are associated with CHF-CSAS,\(^26,27\) and because of the presence of increased ventilatory perfusion abnormalities and physiological pulmonary dead space, the VE–\(\text{VCO}_2\) slope in patients with CHF-CSAS is increased.

**Study Limitation**

These results are not definitive because of the small sample size. For a definitive study, polysomnography would need to be performed in a larger sample size.

**Conclusion**

CHF-CSAS is associated with impaired exercise tolerance, which partially explains the poor prognosis associated with CSAS. Exercise hyperpnea was also observed in CHF-CSAS patients and augmented central chemosensitivity, which was significantly correlated with the VE–\(\text{VCO}_2\) slope in the present study, is one of the mechanisms responsible for both SAS and exercise hyperpnea.

**References**


