Enhanced Ventilatory Response to Exercise in Patients With Chronic Heart Failure and Central Sleep Apnea

Michael Arzt, MD; Martina Harth, MD; Andreas Luchner, MD; Frank Muders, MD; Stephan R. Holmer, MD; Friedrich C. Blumberg, MD; Günter A.J. Riegger, MD; Michael Pfeifer, MD

Background—In patients with chronic heart failure (CHF), central sleep apnea (CSA) and enhanced ventilatory response (VE/VCO₂ slope) to exercise are common. Both breathing disorders alone indicate poor prognosis in CHF. Although augmented chemosensitivity to CO₂ is thought to be one important underlying mechanism for both breathing disorders, it is unclear whether both breathing disorders are related closely in patients with CHF.

Methods and Results—We investigated 20 CHF patients with clinically important CSA (apnea-hypopnea-index (AHI), number of episodes per hour ≥15) and 10 CHF patients without CSA. Patients with and without CSA did not differ with respect to exercise capacity (peak VO₂, 63.4±3.4% versus 60.8±4.4% of predicted value; P=0.746) and left ventricular ejection fraction (LVEF, 31±2% versus 31±3%; P=0.948). The AHI was not correlated with exercise capacity (peak VO₂, percent of predicted value; P=0.260) and LVEF (percent, P=0.886). In contrast, the positive correlation of the VE/VCO₂ slope, determined by cardiopulmonary exercise testing, with the AHI was highly significant (P<0.001). The VE/VCO₂ slope was significantly increased in patients with CSA compared with those without CSA (29.7 versus 24.9; P<0.001).

Conclusions—The ventilatory response to exercise is significantly augmented in CHF patients with CSA compared with those without. In contrast to peak VO₂ and LVEF, the VE/VCO₂ slope is strongly related to the severity of CSA in patients with CHF, which underscores an augmented chemosensitivity to CO₂ as a common underlying pathophysiological mechanism. (Circulation. 2003;107:1998-2003.)

Key Words: heart failure ■ sleep ■ exercise ■ ventilation

Cheyne-Stokes respiration is a common,1,2 still underestimated breathing disorder in patients with chronic heart failure (CHF). It is characterized by periodic breathing with recurrent episodes of apnea or hypopnea alternating with hyperpnea and occurs in awake conditions as well as during sleep.3,4 The resulting oxyhemoglobin desaturations and excessive arousals lead to severe disturbances in autonomic and cardiac function, including atrial fibrillation, ventricular arrhythmias, and sudden cardiac death.4–7 Interestingly, CHF patients with nocturnal CSA have an increased mortality rate compared with CHF patients without CSA with a similar degree of ventricular dysfunction.6 Identification of heart failure patients with CSA is impeded by several factors. CHF patients with CSA often lack typical clinical symptoms of sleep apnea, because frequency of daytime sleepiness and snoring does not differ between CHF patients with and without CSA.2 A high prevalence of CHF contrasts the limited resources of available laboratories for sleep studies. Nevertheless, diagnosing CSA in CHF patients may be highly important because of growing evidence for beneficial effects of an additional treatment with continuous positive airway pressure on cardiac function and the combined mortality-cardiac transplantation rate.8

A key mechanism for Cheyne-Stokes respiration in patients with CHF is the hypersensitivity to the partial pressure of carbon dioxide (PCO₂).9–12 In these patients, a rise in PCO₂, within the scope of physiological fluctuations, leads to a reflexory excessive hyperventilation driving the PCO₂ under the apneic threshold. In this way, cycles of central apnea and hyperventilation recur alternatingly.10 Controlled by the same feedback mechanism between PCO₂ and ventilatory drive, the chemoreceptor gain for the PCO₂ in CHF patients also leads to an augmented ventilatory response to exercise as a reaction to the rising PCO₂ levels.13,14 The ventilatory response can be measured best as a steep slope of the increase in ventilation with respect to CO₂ output (VE/VCO₂ slope).15,16

Both CSA and augmented VE/VCO₂ slope to exercise are predictors of poor prognosis.6,7,15,17 However, no study has shown association between the VE/VCO₂ slope and the severity of CSA. Therefore, we tested the hypothesis of whether CHF patients with CSA have an augmented VE/VCO₂ slope to exercise compared with those without CSA. Furthermore, we...
compared the association of the Ve/VCO₂ slope, peak VO₂, and left ventricular ejection fraction (LVEF) with the severity of CSA in CHF patients to elucidate the influence of chemosensitivity to CO₂, exercise capacity, and cardiac function on CSA.

Methods

Patients

A total of 104 consecutive ambulatory patients with CHF (file information) were screened for CSA. Thirty-two CHF patients had CSA (apnea-hypopnea-index [AHI], number of episodes per hour ≥15), and 72 did not have CSA. The first 25 of the CHF patients with CSA were evaluated with the present study protocol. Because of the study protocol, 4 patients had to be excluded because of restrictive or obstructive ventilatory disorders and 2 patients were excluded because they had LVEF >45%. All 72 patients without CSA were asked to repeat the sleep study and to perform the rest of the study protocol. Sixteen patients gave written informed consent to perform the study. One had CSA and was assigned to the group of CHF with CSA. Of the remainder, 2 had LVEF >45% in the study echocardiography and 3 had obstructive ventilatory disorder and were excluded from additional analysis.

The study protocol included cardiopulmonary exercise test, ambulatory sleep apnea screening, polysomnographic studies, lung function test, and echocardiography. Cardiopulmonary exercise test and the sleep studies were done by 2 different investigators blinded to the clinical data. All patients gave written informed consent to perform the study protocol, which had been approved by the ethics committee of our institution.

Inclusion criteria were CHF attributable to ischemic, hypertensive, or idiopathic dilated cardiomyopathy with a LVEF <45%, as determined by resting echocardiography according to the guidelines of the American Society of Echocardiography by a single cardiologist who was blinded to the clinical data. Patients (NYHA functional class II and III) were stable over the last 3 months, documented by stable cardiac medication and no hospital admissions. Exclusion criteria were a history of unstable angina, cardiac surgery, or documented myocardial infarction within 90 days of entry into study. Restrictive and obstructive ventilatory disorders (vital capacity and total lung capacity <80% of predicted value, FEV₁ <80% of predicted value, and FEV₁/VC <70% of predicted value) were exclusion criteria.

Exercise Testing

To assess exercise capacity and ventilatory efficiency, patients underwent exercise testing with respiratory gas exchange analysis (Oxycon Champion; Jaeger-Toennies). Special effort was taken to perform symptom-limited exercise testing. Peak VO₂ was measured and expressed as absolute value and as percent predicted from the individual age, sex, and body weight–corrected mean normal values. The Ve/VCO₂ slope was calculated in every subject as the slope of the regression line relating ventilation (Ve) to CO₂ output (VCO₂) during exercise testing and was used as an index of the ventilatory response to exercise. The ratio of Ve and VCO₂ reveals a linear relationship over a wide range; the nonlinear part of this relationship after onset of acidotic drive to ventilation was excluded.

Sleep Apnea Screening

Ambulatory sleep apnea screening was performed using a portable computerized sleep apnea diagnosis set (SOMNOcheck effort; Weimann). Thoracoabdominal excursions were measured qualitatively by an effort sensor (Piezo sensor; value range, 8 Bit) placed over the rib cage and abdomen. The SOMNOcheck system also includes 3 thermistors (value range, 8 Bit) to monitor oronasal airflow, a microphone for recording snoring sounds, and a sensor for detecting the position of the patient. Arterial-blood oxyhemoglobin saturation was recorded by a pulse oximeter. These data were recorded and analyzed using a computer-assisted procedure followed by blinded manual review of the collected data (Weimann).

Standard definitions were used to describe and score the sleep-related breathing disorders. An episode of apnea was defined as a cessation of inspiratory airflow for ≥10 seconds. In case of CSA also, the excursions of the rib cage and abdomen cease, whereas in obstructive apnea, despite breathing excursions of rib cage and abdomen, oronasal airflow is absent. Hypopnea was defined as a >50% reduction of airflow or thoracoabdominal excursions lasting at least 10 seconds, resulting in a ≥4% drop in arterial oxyhemoglobin saturation. The AHI describes the number of episodes of apnea and hypopnea per hour. Clinically important CSA was defined as an AHI of ≥15 episodes per hour with ≥25% obstructive sleep apnea events <25% of total AHI.

Although previous studies showed excellent agreement in determination of the AHI using portable computerized polysomnography compared with laboratory-based polysomnography, the patients diagnosed with clinically important CSA with the portable system also underwent laboratory-based polysomnography (Brainlap, Schwarzer), where the diagnosis of an AHI ≥15 and obstructive sleep apnea events <25% of total AHI were confirmed.

Statistical Analysis

All data were analyzed by a computer program (SPSS, version 10.0). To assess differences between patients with and without CSA, the Mann-Whitney U test was used. A χ² analysis was used to analyze proportions. All values are reported as mean±SEM. A 2-sided P<0.05 was considered to indicate statistical significance. To calculate the relationship between the apnea indices, the Ve/VCO₂ slope, the peak VO₂, the peak oxygen pulse, and the Epworth sleepiness scale, the Spearman rank correlation was used. Receiver operator characteristic analysis was carried out to determine sensitivity, specificity, positive predictive value, and negative predictive value to several cutoff values of the Ve/VCO₂ slope and parameters of exercise capacity and cardiac function for detecting clinically important CSA (AHI ≥15).

Results

Characteristics of Patients

The AHI, the apnea index, and the hypopnea index were significantly elevated in the patients who did meet the criteria of CSA compared with those without CSA (Table 1). In contrast, the Epworth sleepiness scale indicated no statistically significant difference between groups (Table 1) and did not correlate with the AHI (Figure 1).

The patients in the CSA group were significantly older than those without CSA (Table 1). Patients in the 2 groups were similar with respect to their medications (Table 1). Both groups, 60% had an implanted cardioverter defibrillator. The patients without CSA all had sinus rhythm, whereas in the group with CSA, 20% of the patients had atrial fibrillation (Table 1) and 25% had nocturnal pacing.

Exercise Capacity

Mean LVEF was similar in CHF patients with CSA and without CSA (Table 1). In addition, the clinical performance expressed by the NYHA functional class showed no significant differences (Table 1).

The parameters of the cardiopulmonary exercise test, which are related to exercise capacity and cardiac stroke volume, were not statistically different between the 2 groups and included mean peak VO₂, the peak VO₂ expressed as percent of predicted value, the mean oxygen pulse, and the mean oxygen pulse expressed as percent of predicted value (Table 1).
Linear regression analysis revealed that LVEF, the peak \( \dot{V}O_2 \) (percent of predicted values), and the oxygen pulse (percent of predicted values) were not correlated with the AHI (Figure 1).

**Ventilatory Response to Exercise**

In CHF patients with CSA, the ventilatory response to exercise, determined by the slope of the relationship between ventilation and CO\(_2\) output (\( \dot{V}e/\dot{V}CO_2 \) slope), was highly significantly increased compared with CHF patients without CSA (29.7±0.9 versus 24.9±0.6; \( P<0.001 \); Figure 2). This difference remained highly significant when the \( \dot{V}e/\dot{V}CO_2 \) slope was adjusted for sex and age (percent of predicted values, 104.9±3.2% with CSA versus 91.4±3.1% without; \( P=0.004 \)).

A highly significant correlation between ventilatory response to exercise (\( \dot{V}e/\dot{V}CO_2 \) slope) and the AHI for CHF patients with and without CSA (\( r=0.613; P<0.001 \)) was observed (Figure 3). Most importantly, these results remain highly significant after adjustment for gender and age (\( r=0.531; P=0.003 \); Figure 3).

**Predictive Values of the \( \dot{V}e/\dot{V}CO_2 \) Slope to Detect Central Sleep Apnea in CHF Patients**

There is only little overlap between individual values of the \( \dot{V}e/\dot{V}CO_2 \) slope of CHF patients with and without CSA (Figure 2). In addition, after adjusting for sex and age, the \( \dot{V}e/\dot{V}CO_2 \) slope has high predictive values for detection of AHI ≥15 in the present study population (Table 2).

Compared with parameters related to exercise capacity and functional classification of patients with CHF (peak \( \dot{V}O_2 \), peak oxygen pulse, and LVEF), the \( \dot{V}e/\dot{V}CO_2 \) slope reaches a high area under the receiver operator characteristic curve for detection of clinically important CSA in CHF patients (Table 2). Neither the history of daytime sleepiness (Epworth sleepiness scale) nor resting arterio-capillary and end-tidal carbon dioxide were suitable for detecting CSA in CHF patients (Table 2). Resting arterio-capillary and end-tidal partial pressures for CO\(_2\) did not significantly differ in CHF patients with and without CSA (Table 1).

**TABLE 1. Characteristics of CHF Patients With and Without Central Sleep Apnea**

<table>
<thead>
<tr>
<th></th>
<th>Central Sleep Apnea (n=20)</th>
<th>No Central Sleep Apnea (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±2</td>
<td>54±1</td>
<td>0.008</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>100</td>
<td>90</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28±1</td>
<td>29±1</td>
<td>0.681</td>
</tr>
<tr>
<td>Cause of heart failure, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>17 (85)</td>
<td>6 (60)</td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>3 (15)</td>
<td>4 (40)</td>
<td></td>
</tr>
<tr>
<td>ICD, n (%)</td>
<td>12 (60)</td>
<td>6 (60)</td>
<td>NS</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>16 (80)</td>
<td>10 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (20)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>18 (90)</td>
<td>10 (100)</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>16 (80)</td>
<td>8 (80)</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>11 (55)</td>
<td>6 (60)</td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>18 (90)</td>
<td>8 (80)</td>
<td></td>
</tr>
<tr>
<td>Sleep characteristics, No. of episodes/h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
<td>29.1±2.6</td>
<td>7.2±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apnea index</td>
<td>11.6±2.2</td>
<td>1.3±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypopnea index</td>
<td>17.4±2.7</td>
<td>5.9±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epworth sleepiness scale</td>
<td>7.2±0.7</td>
<td>6.9±1.7</td>
<td>0.804</td>
</tr>
<tr>
<td>Exercise capacity and cardiac function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2.2±0.1</td>
<td>2.1±0.1</td>
<td>0.681</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>31±2</td>
<td>31±3</td>
<td>0.948</td>
</tr>
<tr>
<td>Peak ( \dot{V}O_2 ), mL·kg(^{-1})·min(^{-1})</td>
<td>15.9±1.1</td>
<td>16.3±1.3</td>
<td>0.914</td>
</tr>
<tr>
<td>Peak ( \dot{V}O_2 ), % of predicted value</td>
<td>63.4±3.4</td>
<td>60.8±4.4</td>
<td>0.746</td>
</tr>
<tr>
<td>Peak oxygen pulse, mL</td>
<td>12.8±8</td>
<td>13.9±1.1</td>
<td>0.500</td>
</tr>
<tr>
<td>Peak oxygen pulse, % of predicted value</td>
<td>90.3±5.4</td>
<td>83.1±5.4</td>
<td>0.533</td>
</tr>
<tr>
<td>Partial pressure for CO(_2) at rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriocapillary ( \dot{C}O_2 ), mm Hg</td>
<td>38.2±0.7</td>
<td>38.1±0.9</td>
<td>0.745</td>
</tr>
<tr>
<td>End-tidal ( \dot{C}O_2 ), kPa</td>
<td>4.5±0.1</td>
<td>4.8±0.1</td>
<td>0.075</td>
</tr>
</tbody>
</table>

Data are mean±SEM or No. (%) of patients. NS indicates not significant.
Discussion

The major finding of this study is the highly augmented $\dot{V}_E/\dot{V}_{CO_2}$ slope in CHF patients with CSA compared with those without and the close correlation of the $\dot{V}_E/\dot{V}_{CO_2}$ slope with the AHI, indicating CSA. In contrast to the $\dot{V}_E/\dot{V}_{CO_2}$ slope, parameters of exercise capacity and cardiac function (peak $\dot{V}O_2$, oxygen pulse, and LVEF) were not related to central sleep apnea.

Thus, these results support the pathophysiological concept that it is common in CHF patients to have an augmented peripheral and central chemosensitivity to carbon dioxide. It is known that CHF patients with CSA have an increased ventilatory response to carbon dioxide and that the degree of carbon dioxide hypersensitivity correlates with the AHI. The elevated chemoreceptor responsiveness destabilizes the respiratory control system by increasing the tendency to hyperventilate, thus precipitating ventilatory overshoot, and leads to oscillatory breathing patterns in CHF patients even during wakefulness.

Exercise in healthy individuals also leads to an augmentation of chemosensitivity, which could be explained by rising catecholamine levels during exercise. Interestingly, chemosensitivity to hypercapnia and hypoxia during exercise were shown to be augmented in patients with CHF compared with
healthy control subjects. Hypercapnic chemosensitivity assessed by the Read's rebreathing method was significantly correlated to ventilatory response to exercise (VE/VCO2-slope) in healthy subjects and patients with CHF.

In addition to the pathophysiological link, severity of CSA and the VE/VCO2 slope share the attribute to be predictors of poor prognosis in patients with CHF. Lanfranchi et al determined the AHI to be a powerful predictor of cardiac mortality, independently of clinical and echocardiographic data. In addition, CHF patients with preserved exercise capacity (peak V̇O2 ≥18 mL · kg⁻¹·min⁻¹) can have a remarkably enhanced ventilatory response to exercise associated with poor prognosis. Ponikowsky et al and Kleber et al even concluded that the VE/VCO2 slope is a better prognostic parameter for CHF patients than the peak oxygen consumption, which is presently accepted as the best single measure of prognosis in ambulatory patients with severe heart failure.

Identification of high-risk CHF patients with central sleep apnea and cardiopulmonary reflex instability is important, because these patients could benefit from various forms of positive airway pressure, including continuous positive airway pressure (CPAP), bilevel, and adaptive pressure support servo-ventilation therapy. CPAP is the therapy that was tested most extensively. This respiratory support therapy is able to improve cardiac function and quality of life and can reduce hospital admissions. The findings of Sin et al indicate that CPAP therapy may improve mortality and transplant-free survival in patients with central sleep apnea but not in patients without.

For diagnosing CSA in CHF patients, polysomnography screening is necessary. But because of the high prevalence of CHF, resources of sleep laboratories do not meet the need for large-scale screening. Although the prevalence of CSA is higher in CHF patients with low exercise capacity and higher NYHA functional class, these parameters are not valid as prescreening criteria. We found, similar to other investigators, that exercise capacity and cardiac function are not compellingly associated with the severity of CSA in CHF patients. Alternatively, predicting for CSA could be the VE/VCO2 slope, which is easy to obtain in a cardiopulmonary exercise test as a part of the routine workup of patients with CHF, even under submaximal exercise, when maximal exercise is contraindicated or not achievable. As a consequence of the close correlation of the VE/VCO2 slope with the AHI in our study, one can conclude that a high VE/VCO2 slope in patients with CHF should lead to complete laboratory sleep analysis.

A limitation of the present study is that correlations and predictive values were calculated in a study population of 30

TABLE 2. Predictive Values of VE/VCO2 Slope, Left Ventricular Ejection Fraction, Peak VO2, Peak Oxygen Pulse, Epworth Sleepiness Scale, and Resting Partial Pressure for CO2 for Detection of Central Sleep Apnea

<table>
<thead>
<tr>
<th>Area Under ROC Curve (±SE)</th>
<th>Cutoff Value</th>
<th>Sensitivity/Specificity, %</th>
<th>Positive/Negative Predictive Value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilatory response to exercise</td>
<td>VE/VCO2 slope, % predicted</td>
<td>0.770±0.10</td>
<td>91.9</td>
</tr>
<tr>
<td>Exercise capacity and cardiac function</td>
<td>LVEF, %</td>
<td>0.500±0.12</td>
<td>31.5</td>
</tr>
<tr>
<td>Peak VO2, % predicted</td>
<td>0.536±0.11</td>
<td>54.0</td>
<td>70/50</td>
</tr>
<tr>
<td>Peak oxygen pulse, % predicted</td>
<td>0.572±0.11</td>
<td>89.5</td>
<td>55/50</td>
</tr>
<tr>
<td>Epworth sleepiness scale</td>
<td>0.520±0.15</td>
<td>6.5</td>
<td>55/50</td>
</tr>
<tr>
<td>Partial pressure for CO2 at rest</td>
<td>Arteriovenous CO2, mm Hg</td>
<td>0.544±0.12</td>
<td>37.7</td>
</tr>
<tr>
<td>End-tidal CO2, kPa</td>
<td>0.278±0.12</td>
<td>4.28</td>
<td>53/86</td>
</tr>
</tbody>
</table>

ROC indicates receiver operator characteristic.
CHF patients, excluding all patients with concomitant diseases that could influence the prevalence of CSA and ventilatory response to exercise. Thus, care must be taken to extrapolate our findings to a broader spectrum of patients, and the data should be confirmed in a larger study on unselected CHF patients. After exclusion of patients with ventilatory disorders, the study population was well matched according to sex, body mass index, pulmonary function, arteriocapillary partial pressure of carbon dioxide,5,10 and presence of implanted cardioverter defibrillator.34 Similar to former studies related to peak exercise capacity and cardiac function. Second, ventilatory response to exercise in CHF patients are not age-regulated, analyses of this study were performed on age-adjusted variables, which showed similar results as the results from unadjusted variables.

Three conclusions may be drawn from this study. First, the present data emphasize that the severity of central sleep apnea and ventilatory response to exercise in CHF patients are not related to peak exercise capacity and cardiac function. Second, the V̇E/˙VCO₂ slope, as an indicator of ventilatory response to exercise, is highly augmented in CHF patients with CSA compared with those without. Third, because of their close positive correlation, the V̇E/˙VCO₂ slope could be helpful for the decision of whether CHF patients should receive full laboratory sleep analysis.

References
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