The Relation of Respiratory Muscle Strength to Disease Severity and Abnormal Ventilation During Exercise in Chronic Heart Failure Patients

Yusuke Kasahara, Kazuhiro P. Izawa, Satoshi Watanabe, Naohiko Osada, and Kazuto Omiya

1. Background

Breathlessness is a common problem in chronic heart failure (CHF) patients, and respiratory muscle strength has been proposed to play an important role in causing breathlessness in these patients.

Objectives: The aim of this study was to investigate the relation between respiratory muscle strength and the severity of CHF, and the influence of respiratory muscle strength on abnormal ventilation during exercise in CHF patients.

Patients and Methods: In this case series study, we assessed clinically stable CHF outpatients (N = 66, age: 57.7 ± 14.6 years). The peak oxygen consumption (peak VO\textsubscript{2}), the slope relating minute ventilation to carbon dioxide production (VE/VCO\textsubscript{2} slope), and the slope relating tidal volume to respiratory rate (TV/RR slope) were measured during cardiopulmonary exercise testing. Respiratory muscle strength was assessed by measuring the maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP).

Results: The MIP and MEP decreased significantly as the New York Heart Association functional class increased (MIP, P = 0.021; MEP, P < 0.01). The MIP correlated with the TV/RR slope (r = 0.57, P < 0.001) and the VE/VCO\textsubscript{2} slope (r = 0.44, P < 0.001), and the MEP also correlated with the TV/RR slope (r = 0.53, P < 0.001) and the VE/VCO\textsubscript{2} slope (r = 0.25, P < 0.04). Stepwise multiple regression analysis revealed that age and MIP were statistically significant predictors of the TV/RR and VE/VCO\textsubscript{2} slopes (both P < 0.05).

Conclusions: Respiratory muscle strength is related to the severity of CHF, and associated with rapid and shallow ventilation or excessive ventilation during exercise.

Keywords: Heart Failure; Respiratory Muscle; Exercise Test
2. Objectives

The objective of the present study was to clarify both the relation between respiratory muscle strength and the disease severity in CHF, and the association of respiratory muscle strength with abnormal ventilation during exercise in CHF patients in relation to clinical characteristics.

3. Patients and Methods

3.1. Study Design and Subjects

This was a case series study in which the subjects were selected from 84 outpatients who visited St. Marianna university school of medicine hospital for the evaluation of CHF. The inclusion criteria was a left ventricular ejection fraction (LVEF) of < 45% on echocardiography. The exclusion criteria included New York heart association (NYHA) functional class IV or the presence of central neurologic, peripheral vascular, orthopedic, or pulmonary disease. Of the 84 outpatients, 66 met the study criteria and were included in this study (57 men, 9 women; mean age 57.7 ± 14.6 years). None of the patients had been hospitalized within the month preceding the start of the study. All patients were clinically stable and were studied while on stable doses of medications. The present study was approved by the university school of medicine institutional committee on human research. Informed consent was obtained from each subject before study entry.

3.2. Clinical Characteristics

Age, sex, etiology of CHF (dilated cardiomyopathy, ischemic heart disease, and others), and medications were assessed from medical records. The LVEF was calculated by using M-mode echocardiography and served as the index of left ventricular systolic function; and patients were classified into three groups: those with mild (40 ≤ LVEF < 45), moderate (35 ≤ LVEF < 40), and severe (LVEF < 35) left ventricular dysfunction. The NYHA functional class and BNP level were evaluated as indices of the severity of CHF. The NYHA functional class was determined in all patients by an independent investigator, and the BNP level was measured by means of blood sampling at rest before CPX. The NYHA functional class was determined in all patients by an independent investigator, and the BNP level was measured by means of blood sampling at rest before CPX. After centrifugation at 3000 rpm at 4°C for 10 min, the separated plasma was stored at -70°C until analyzed.

3.3. CPX

All 66 patients underwent symptom-limited CPX on a cycle ergometer (CORIVAL 400; Lode Co., Groningen, the Netherlands) with a ramp protocol. After patients had rested on the ergometer for 3 min, exercise was performed with the load increased linearly by 10 or 20 W/min following a 3-min warm-up period at 0-W load. A 12-lead electrocardiogram and the heart rate were continuously monitored on an ML-500 stress test system (Fukuda Denso Co., Tokyo, Japan). Expired gas was sampled by using a breath-by-breath method, and the peak oxygen uptake (VO\(_2\)), carbon dioxide output, minute ventilation, respiratory rate, and tidal volume were measured simultaneously with a respirometer (AE-300S aero monitor; Minato Ikagaku Co., Tokyo, Japan) and a gas analyzer (MG-360; Minato Ikagaku Co., Tokyo, Japan). The respiratory exchange ratio was also calculated.

To assess exercise tolerance, peak VO\(_2\) was calculated from the average of the VO\(_2\) values measured during the 30 seconds before peak exercise was reached, and VO\(_2\) at the anaerobic threshold (AT) was determined by using the V-slope method (14). The VE/VO\(_2\) slope was calculated with linear regression analysis by using the minute ventilation and carbon dioxide production values obtained during exercise (15). The TV/RR slope was also calculated with linear regression analysis by using the tidal volume and respiratory rate values obtained during exercise (16). Each value was determined as an index of the ventilatory response to graded exercise below the respiratory compensation point, to avoid the influence of the end point of CPX. Ratings of perceived exertion as measured by using the Borg scale were obtained at the end point of CPX (17).

3.4. Respiratory Muscle Strength

Measurements of maximal respiratory muscle strength were performed with Vitalopower KH-101 (Chest M. I. Inc., Tokyo, Japan), and followed a method similar to that described by Black and Hyatt (18). By using a nose clip and mouthpiece, the patients maintained maximal inspiratory and expiratory effort against a closed valve for at least 1 s to measure the maximal inspiratory pressure (MIP) at residual volume or the maximal expiratory pressure (MEP) at total lung capacity, respectively. Each measurement was repeated three times, and the highest values of the MIP and MEP were used as the indices of maximal inspiratory and expiratory muscle strength, respectively. Because the MIP and MEP negatively correlate with age, the percent (%) predicted MIP and MEP were calculated by using the linear regression models reported by Black and Hyatt (18):

\[
%\text{Predicted MIP or MEP} = \left[ \frac{\text{measured MIP or MEP}}{\text{predicted MIP or MEP}} \right] \times 100
\]

According to the Equations 2

\[
\text{Predicted MIP} = 143 - 0.55 \times \text{age (male)} + 104 - 0.51 \times \text{age (female)}
\]

\[
\text{Predicted MEP} = 268 - 1.03 \times \text{age (male)} + 170 - 0.53 \times \text{age (female)}
\]
3.5. Statistical Analysis

Results are expressed as means ± SE. The Kolmogorov-Smirnov test was performed to assess normality, and logarithmic transformation of the variables was performed as needed to improve normality. One-way analysis of variance (ANOVA) and the χ² test were used to analyze the differences in clinical characteristics. ANOVA or analysis of covariance (ANCOVA) was performed to determine the differences among the NYHA class groups and among the left ventricular dysfunction groups in the results from CPX and respiratory muscle strength testing. ANCOVA was used if age was determined as the covariate with the results of CPX and respiratory muscle strength. If the F ratio was significant in ANOVA or ANCOVA, Tukey’s multiple range test was applied to determine the significant differences between the two NYHA class groups. Pearson’s correlation coefficient was used in a regression analysis to determine the correlations between the respiratory muscle strength parameters and CPX or BNP. Spearman rank correlation coefficient was used to evaluate the relations between Borg scale values and muscle strength parameters, CPX, or BNP. Age, sex, body mass index, LVEF, BNP, MIP, and MEP were entered stepwise in the multiple regression analysis for the prediction of the VE/VCO₂ and TV/RR slopes. A P value of <0.05 was considered statistically significant. The statistical analyses were performed with SPSS 12.0J statistical software program (SPSS Japan, Tokyo, Japan), and statistical power analysis was performed for multiple regression analysis with the G’Power 3 program (Heinrich-Heine-Universität, Düsseldorf, Germany) in the post hoc test.

4. Results

The patients’ clinical characteristics, including age, sex, body mass index, BNP level, LVEF, etiology of CHF, and medications, are shown in Table 1. There were no significant differences between the NYHA class groups in sex, body mass index, LVEF, etiology of CHF, and medications. Carvedilol was prescribed as the β-blocker in 57 patients. Age was significantly higher in NYHA class III patients than in NYHA class I/II patients (P = 0.003 and P = 0.014, respectively). The log BNP level was significantly higher in NYHA class II/III patients than in NYHA class I patients (P = 0.040 and P = 0.005, respectively).

The results obtained from CPX and respiratory muscle strength testing are shown in Table 2. No patient showed ischemic ST change, or experienced chest pain or serious arrhythmia during CPX. ANCOVA revealed that age was the only covariate in the MIP (F = 5.61, P = 0.021), whereas age was not determined to be a significant covariate in CPX and the MEP.

### Table 1. Clinical Characteristics Stratified by NYHA Functional Class

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N = 66)</th>
<th>NYHA I (n = 23)</th>
<th>NYHA II (n = 32)</th>
<th>NYHA III (n = 11)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.7 ± 1.8</td>
<td>53.1 ± 3.0</td>
<td>56.6 ± 2.4</td>
<td>70.5 ± 3.3 d,e</td>
<td>0.003</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>57/9</td>
<td>21/2</td>
<td>27/5</td>
<td>9/2</td>
<td>0.678</td>
</tr>
<tr>
<td>BMI, kg/m²²</td>
<td>23.4 ± 0.5</td>
<td>24.3 ± 0.9</td>
<td>22.7 ± 0.8</td>
<td>23.4 ± 0.6</td>
<td>0.387</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>253.2 ± 29.4</td>
<td>124.4 ± 16.2</td>
<td>279.5 ± 47.8 d</td>
<td>399.3 ± 70.3 d</td>
<td>0.005</td>
</tr>
<tr>
<td>Log BNP</td>
<td>5.12 ± 0.12</td>
<td>4.57 ± 0.17</td>
<td>5.21 ± 0.17</td>
<td>5.83 ± 0.18 d</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>28.1 ± 1.1</td>
<td>27.9 ± 1.8</td>
<td>28.9 ± 1.8</td>
<td>26.0 ± 2.2</td>
<td>0.673</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.418</td>
</tr>
<tr>
<td>DCM</td>
<td>31 (47.0)</td>
<td>8 (34.8)</td>
<td>17 (53.1)</td>
<td>6 (54.5)</td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>16 (24.2)</td>
<td>5 (19.4)</td>
<td>8 (25.0)</td>
<td>3 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Others (HHD, AF, HCM)</td>
<td>19 (28.8)</td>
<td>10 (43.5)</td>
<td>7 (21.9)</td>
<td>2 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>57 (86.4)</td>
<td>22 (95.7)</td>
<td>27 (84.4)</td>
<td>8 (72.7)</td>
<td>0.171</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>61 (92.4)</td>
<td>19 (73.9)</td>
<td>31 (93.8)</td>
<td>11 (100)</td>
<td>0.192</td>
</tr>
<tr>
<td>Digoxin</td>
<td>14 (21.2)</td>
<td>7 (30.4)</td>
<td>4 (12.5)</td>
<td>3 (27.2)</td>
<td>0.239</td>
</tr>
<tr>
<td>Diuretics</td>
<td>63 (95.5)</td>
<td>20 (87.0)</td>
<td>32 (100)</td>
<td>11 (100)</td>
<td>0.053</td>
</tr>
</tbody>
</table>

*Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; HCM, hypertrophied cardiomyopathy; HHD, hypertensive heart disease; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; NS, not significant; NYHA, New York Heart Association functional class.

*Data are presented as No. (%) or mean ± SE.

*P values in the analysis of variance or χ² test.

*P < 0.05 vs. NYHA I in the post hoc test.

*P < 0.05 vs. NYHA II in the post hoc test.
The VO\textsubscript{2} at AT was significantly lower in NYHA class III patients than in NYHA class I/II patients (P < 0.001 and P < 0.001, respectively). Although there was no significant difference in the peak respiratory exchange ratios between the NYHA class groups, the peak VO\textsubscript{2} was significantly lower in NYHA class III patients than in NYHA class I/II patients (P < 0.001 and P < 0.001, respectively), and was significantly lower in NYHA class II patients than in NYHA class I patients (P < 0.004). The VE/VCO\textsubscript{2} slope was significantly higher in NYHA class III patients than in NYHA class I/II patients (P < 0.001 and P = 0.004, respectively). The TV/RR slope was significantly lower in NYHA class III patients than in NYHA class I patients (P = 0.004); however, there was no significant difference in the TV/RR slope between the NYHA class II and III patients.

The MIP was significantly lower in NYHA class II and III patients than in NYHA class I patients (P = 0.029 and P = 0.014, respectively), and the % predicted MIP was significantly lower in NYHA class III patients than in NYHA class I patients (P = 0.009). The MEP was significantly lower in NYHA class III patients than in NYHA class I patients (P = 0.012), whereas there was no significant difference among NYHA class patients in % predicted MEP.

There was no significant difference between the mild, moderate, and severe left ventricular dysfunction groups in respiratory muscle strength and the results in CPX.

The MIP and MEP positively correlated with the peak VO\textsubscript{2} (r = 0.35, P = 0.004 and r = 0.31, P = 0.011, respectively). There was a positive but poor correlation between the MIP and VO\textsubscript{2} at AT (r = 0.26, P = 0.038), whereas there was no statistical significance in the relation between the MEP and VO\textsubscript{2} at AT (r = 0.24, P = 0.054).

The correlations between the MIP or MEP and the log BNP level are shown in Figure 1. There were negative correlations between the MIP or MEP and the log BNP level (r = -0.40, P = 0.001 and r = -0.28, P = 0.022, respectively). The correlations between the MIP or MEP and the TV/RR slope, and between the MIP or MEP and the VE/VCO\textsubscript{2} slope in all 66 patients are shown in Figure 1. There were positive correlations between the MIP or MEP and the TV/RR slope (r = 0.57, P < 0.001 and r = 0.53, P < 0.001, respectively), and negative correlations between the MIP or MEP and the VE/VCO\textsubscript{2} slope (r = -0.44, P < 0.001 and r = -0.25, P = 0.040, respectively). In addition, there was a negative correlation between the TV/RR slope and the VE/VCO\textsubscript{2} slope (r = -0.54, P < 0.001).

The results of multiple regression analysis are shown in Table 3. Stepwise multiple regression analysis revealed that age and the MIP were statistically significant predictors of the TV/RR and VE/VCO\textsubscript{2} slopes (both P < 0.05). The estimated r\textsuperscript{2} values were 0.25 for the VE/VCO\textsubscript{2} slope and 0.37 for the TV/RR slope. The statistical power was calculated to be 0.99 in the regression model for the VE/VCO\textsubscript{2} slope (effect size = 0.33, sample size = 66, tested predictors = 2, total predictor = 7), and to be 1.0 in the regression model for TV/RR (effect size = 0.59, sample size = 66, tested predictors = 2, total predictor = 7).
Figure 1. Correlation between Respiratory Muscle Strength and the BNP Level, TV/RR Slope, or VE/VCO₂ Slope

- MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; BNP, brain natriuretic peptide; TV/RR slope, slope relating tidal volume to respiratory rate; VE/VCO₂ slope, slope relating minute ventilation to carbon dioxide production.
The correlations between the Borg scale and physiological parameters are shown in Table 4. There were negative correlations between the Borg scale values and the MIP or the TV/RR slope, and there was a positive correlation between the Borg scale values and the VE/VCO₂ slope in all 66 patients.

5. Discussion

5.1. Respiratory Muscle Dysfunction and CHF Severity

It is well known that respiratory muscle strength is decreased in CHF patients compared with normal persons (19). However, there are few reports on the relation between respiratory muscle strength and the severity of CHF. One previous study reported that inspiratory muscle strength is significantly decreased in NYHA class III patients compared with that in NYHA class I and II patients (19). Although there are significant correlations between inspiratory muscle strength and age, no study, to our knowledge, has investigated the difference among NYHA classes in relation to age. In the present study, differences in respiratory muscle strength were assessed with ANCOVA by using age as the covariant.

When age was determined as the covariant, the inspiratory muscle strength appears to reflect the severity of CHF through the symptoms manifested during exercise or the performance of the activities of daily living.

Table 3. Results of Stepwise Multiple Regression Analysis for the Prediction of the VE/VCO₂ and TV/RR Slopes from Age, Sex, BMI, LVEF, BNP, MIP, and MEP

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Dependent Variable: VE/VCO₂ Slope (R² = 0.25, F = 10.54, P &lt; 0.001)</th>
<th>Dependent Variable: TV/RR Slope (R² = 0.37, F = 18.7, P &lt; 0.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression Coefficient B</td>
<td>Standard Error</td>
</tr>
<tr>
<td>MIP, cm H₂O</td>
<td>-0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>Constant</td>
<td>27.10</td>
<td>4.91</td>
</tr>
</tbody>
</table>

Table 4. Correlations between Borg Scale at Peak Exercise and Physiological Measures

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients (N = 66)</th>
<th>Slope</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borg scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIP, cm H₂O</td>
<td>-0.28</td>
<td>-0.23</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>MEP, cm H₂O</td>
<td>-0.23</td>
<td>-0.25</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>VO₂ at AT, mLkg⁻¹min⁻¹</td>
<td>-0.23</td>
<td>-0.25</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Peak VO₂, mLkg⁻¹min⁻¹</td>
<td>0.26</td>
<td>0.26</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>VE/VCO₂ Slope</td>
<td>-0.47</td>
<td>-0.47</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Abbreviations: AT, anaerobic threshold; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; RER, respiratory exchange ratio; RR, respiratory rate; TV, tidal volume; V̇CO₂, carbon dioxide output; VE, minute ventilation.
because of chronically insufficient blood flow to the skeletal muscles and depressed oxidative capacity (1), including the respiratory muscles.

On the other hand, there is no significant difference between the left ventricular dysfunction groups in respiratory muscle strength and the results in CPX in the present study. These results support previous studies in which there was no significant correlation between LVEF and respiratory muscle strength, and there was a poor relation between LVEF and exercise capacity (26, 27).

5.2. Relations between Respiratory Muscles and Excessive Ventilation during Exercise

Respiratory muscle weakness has also been proposed to cause symptoms of breathlessness in CHF patients (4), and rapid and shallow ventilation and excessive ventilation are often observed in CHF patients during incremental exercise testing (5, 20). The present study demonstrated a relation between the ratings of perceived exertion and respiratory muscle strength or parameters of abnormal ventilation. The Borg scale value at the end point of CPX correlated significantly with the MIP. The results of the present study seem to support those of a previous study reporting a correlation between inspiratory muscle strength and ratings of perceived exertion during the performance of daily activities (4). Furthermore, there were significant correlations between Borg scale values and the TV/RR slope or the VE/VCO₂ slope, and thus it seems that objective parameters of abnormal ventilation assessed during CPX may reflect the subjective parameter of dyspnea during exercise.

Anatomical dead space ventilation was reported to be higher in CHF patients than in control subjects during exercise, and the ratio of anatomical dead space ventilation for VE is higher in CHF patients than in control subjects at peak exercise (28). The results of the present study indicated that respiratory muscle weakness and rapid and shallow ventilation occurred in patients with severe CHF, and such ventilation may result from inspiratory muscle weakness because the MIP was significant in predicting the TV/RR slope in multiple regression analysis. The results of the present study imply that inspiratory muscle strength weakness leads to rapid and shallow ventilation, which may result in an increase of anatomical dead space during exercise.

The present study also showed that the TV/RR slope correlated with the VE/VCO₂ slope. This result seems to be related to an increase of anatomical dead space, and indicates that rapid and shallow ventilation may be an important cause of excessive ventilation as shown by the VE/VCO₂ slope (20, 28). Several factors result in excessive ventilation, such as overactivity of the ergoreflex (10), hyperventilation of peripheral and/or central chemoreceptors (29), and reduced lung compliance (9). However, it is not clear whether respiratory muscle strength affects excessive ventilation during exercise. The present study showed that MIP was significant in predicting the VE/VCO₂ slope in multiple regression analysis. Thus, it appears that inspiratory muscle weakness, rather than clinical characteristics such as age, sex, body mass index, BNP, or LVEF, may cause an increase in the VE/VCO₂ slope through the influence of an inefficient ventilation pattern.

5.3. Limitations

The present study has several limitations. First, we enrolled CHF patients who were predominantly men. Therefore, a future study should validate the possible effects of sex differences. Second, although several studies have reported on the effect of respiratory muscle training (30), we did not examine the effect of improvement in respiratory muscle strength on excessive ventilation during exercise in this study. Therefore, the influence of respiratory muscle strength training on breathlessness or excessive ventilation during exercise should be investigated in the future.

5.4. Conclusions

In the present study, we found decreased respiratory muscle strength in patients with severe CHF and showed that the decrease in respiratory muscle strength correlates with the decreased exercise tolerance of patients with CHF.

5.5. Clinical Implication

Inspiratory muscle strength relates to rapid and shallow ventilation or excessive ventilation during exercise. Therefore, it may be useful to assess the respiratory muscle strength of CHF patients with symptoms of breathlessness, to predict patients who may experience abnormal ventilation during exercise.

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Authors’ Contributions

Study concept and design: Yusuke Kasahara and Kazuhiro P. Izawa. Analysis and interpretation of data: Yusuke Kasahara and Kazuhiro P. Izawa. Drafting of the manuscript: Yusuke Kasahara. Critical revision of the manuscript for important intellectual content: Kazuhiro P. Izawa, Satoshi Watanabe, Naohiko Osada and Kazuto Omiya. Statistical analysis: Yusuke Kasahara and Kazuhiro P. Izawa.

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