Clinical Significance of the Presence of Oscillatory Breathing Both at Rest and During Exercise in Cardiac Patients

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Summary

Cardiac patients often experience nocturnal and daytime oscillatory breathing (OB). OB noted at rest sometimes becomes unclear or even disappears during exercise. We evaluated the physiological significance of OB by comparing the clinical characteristics of cardiac patients who manifested OB only at rest (group A), only during exercise (group B), and both at rest and during exercise (group C).

Among 3,432 cardiac patients who underwent cardiopulmonary exercise testing (CPX), 114, 94, and 65 patients were identified as group A, B, and C, respectively. Left ventricular ejection function was 57 ± 17% in group A, 49 ± 20% in group B, and 41 ± 21% in group C (P < 0.05 for all comparisons among the 3 groups). The level of brain natriuretic peptide (BNP) was significantly higher in group C than in groups A and B. The peak VO2 was lower and the VE-VCO2 slope was higher in groups B and C than in group A.

The present findings suggest that cardiac function is more impaired in cardiac patients who manifest OB both at rest and during exercise than in cardiac patients who manifest OB only at rest or only during exercise. (Int Heart J Advance Publication)

Key words: Cardiopulmonary function, Exercise testing

Cardiac patients often experience nocturnal and daytime oscillatory breathing (OB). OB, a characteristic breathing pattern alternating between hyperpnea and hypopnea, can be evaluated in detail by cardiopulmonary exercise testing (CPX). An unstable ventilatory control system, long circulation time, high sensitivity of ventilation to changes in CO2, decrease in the PaCO2 regulatory set point, and fluctuations in the pulmonary blood flow have all been proposed as possible mechanisms underlying this abnormal breathing. A number of studies have focused on OB during exercise. In some cases with clearly observable OB at rest, however, the OB becomes harder to discern or even disappears during exercise. This change in OB during exercise can probably be explained by the shortened circulation time resulting from the increased cardiac output with increased exercise intensity. If a shortened circulation time is the explanation, the disappearance of OB during exercise may indicate preserved cardiac function. On the other hand, a continuation of OB from rest until the end of exercise may suggest an insufficient increase in cardiac output during exercise. Thus, cardiac function may differ between the patients who manifest OB only at rest and those who manifest OB both at rest and during exercise.

In the present study, we hypothesized that cardiac function in patients who manifest OB both at rest and during exercise may be worse than those who manifest OB only at rest. We sought to prove this hypothesis by comparing the characteristics of oscillatory breathing and cardiopulmonary indices among patients who showed OB only at rest, only during exercise, and both at rest and during exercise.

Methods

Study patients: A total of 3,432 consecutive patients with various cardiac diseases who underwent CPX at the Cardiovascular Institute between January 2010 and December 2015 were enrolled in this study. CPX was performed to evaluate the severity of cardiac disease and heart failure in addition to the exercise capacity. First, we visually identified 294 patients who manifested at least 3 consecutive cycles of clear ventilatory oscillations during an initial period of 4 minutes of rest before exercise, an exercise period, and a final period of 6 minutes of rest (recovery) after exercise. In the present study, we hypothesized that cardiac function in patients who manifest OB both at rest and during exercise may be worse than those who manifest OB only at rest. We sought to prove this hypothesis by comparing the characteristics of oscillatory breathing and cardiopulmonary indices among patients who showed OB only at rest, only during exercise, and both at rest and during exercise.

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Cardiac patients manifesting OB were stratified into 3 groups according to the pattern of OB observed during CPX. As shown in Table I, group A consisted of patients who presented OB at rest before exercise and/or at rest (recovery) after exercise but not during exercise, group B consisted of those who presented OB only during exercise, and group C consisted of those who presented OB both at rest and during exercise. The OB pattern of a representative subject in each group is shown in Figure 1.

The research protocol was approved by the human subjects committee of the Cardiovascular Institute. The patients were apprised of the purposes and risks of the study, and all of them gave their informed consent.

**CPX:** A symptom-limited incremental exercise test was performed using an upright, electromagnetically braked cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering Co., Ltd., Tokyo). The exercise test began with a 4-minute rest on the ergometer followed by a 4-minute warm-up at 0 W or 20 W at 60 rpm. The load was then increased incrementally by 1 W every 6 seconds (10 W/minute). The O2 uptake (VO2), CO2 output (VCO2), and VE were measured throughout the test using an Aeromonitor AE-300s (Minato Medical Science, Osaka, Japan), as previously described.11,12 Before the parameters from the respiratory gas analysis were calculated, breath-by-breath data were interpolated to give second-by-second values. These second-by-second values were then calculated as successive 3-second averages and translated into a 5-point moving average. The peak VO2 was calculated as an average of the values obtained during the last 15 seconds of incremental exercise.13 The percentage of peak VO2 was calculated by dividing the measured peak VO2

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**Table 1. Types of Oscillatory Breathing in Cardiac Patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Rest before exercise</th>
<th>Exercise</th>
<th>Rest (recovery) after exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 114)</td>
<td></td>
<td>45 +</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56 -</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13 +</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>B (n = 94)</td>
<td></td>
<td>94</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>C (n = 65)</td>
<td></td>
<td>33</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>C-1</td>
<td></td>
<td>20</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>C-2</td>
<td></td>
<td>12</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Group A: patients who presented OB at rest before exercise and/or at rest (recovery) after exercise. Group B: patients who presented OB only during exercise. Group C: patients who presented OB both at rest before exercise and during exercise. Group C-1: patients who presented OB both at rest before exercise and during exercise. Group C-2: patients who presented OB both at rest (recovery) after exercise and during exercise. Group C-3: patients who presented OB during all periods.

**Figure 1.** Minute ventilation (VE) during cardiopulmonary exercise testing of a representative subject in group A (a patient with old myocardial infarction), group B (a patient with valvular heart disease), and group C (a patient with atrial fibrillation and congestive heart failure).
The VE-VCO2 slope during incremental exercise was calculated during the last 15 seconds of incremental exercise. PCO2 (PETCO2) at rest was calculated as an average of value less than 0.05 was considered statistically significant windows (Microsoft Corporation, Redmond, WA, USA). A version 19.0 software (SPSS Inc., Chicago, Illinois) for Windows (Microsoft Corporation, Redmond, WA, USA). A P value less than 0.05 was considered statistically significant for all comparisons.

Results

Among 273 cardiac patients with oscillatory breathing, 114 (42%) were categorized as group A, 94 (34%) as group B, and 65 (24%) as group C (Table I). There were no significant differences among the 3 groups in gender, height, weight, body mass index, or cardiac disease etiology, though idiopathic dilated cardiomyopathy was slightly more frequent in group C (Table II).

LVEF was 57 ± 17% in group A, 49 ± 20% in group B, and 41±21% in group C (P < 0.05 for all comparisons among the 3 groups) (Table III). The level of BNP was significantly higher in group C than in groups A and B. As shown in Table III, groups B and C both had a significantly lower peak VO2 than group A (group A, 18.2 ± 5.9; group B, 15.4 ± 5.7; group C, 14.0 ± 5.5 mL/minute/kg). The VE-VCO2 slope was significantly higher in groups B and C than in group A (group A, 36 ± 5; group B, 15.4 ± 5.7; group C, 14.0 ± 5.5 mL/minute/kg). For the oscillating VE, the cycle length was longer in group C than in groups A and B (group A, 58 ± 16; group B, 64 ± 18; group C, 72 ± 28 seconds), and oscillatory amplitude was higher in groups B and C than in group A (group A, 36 ± 5; group B, 33 ± 5; group C, 32 ± 6 mmHg). For the oscillating VE, the cycle length was longer in group C than in groups A and B (group A, 58 ± 16; group B, 64 ± 18; group C, 72 ± 28 seconds), and oscillatory amplitude was higher in groups B and C than in group A (group A, 36 ± 5; group B, 33 ± 5; group C, 32 ± 6 mmHg).

The cycle length of the oscillating VE was slightly longer in group C than in groups A and B (group A, 58 ± 16; group B, 64 ± 18; group C, 72 ± 28 seconds), and oscillatory amplitude was higher in groups B and C than in group A (group A, 36 ± 5; group B, 33 ± 5; group C, 32 ± 6 mmHg). For the oscillating VE, the cycle length was longer in group C than in groups A and B (group A, 58 ± 16; group B, 64 ± 18; group C, 72 ± 28 seconds), and oscillatory amplitude was higher in groups B and C than in group A (group A, 36 ± 5; group B, 33 ± 5; group C, 32 ± 6 mmHg).

For the comparisons among the group C patients, the VE-VCO2 slope was significantly higher in group C-3 than in groups C-1 and C-2 (group C-1, 39 ± 10; group C-2, 39 ± 9; group C-3, 53 ± 21; P < 0.01). PETCO2 at peak exercise was significantly lower in group C-3 than in group C-2 (group C-1, 33 ± 6; group C-2, 34 ± 5; group C-3, 28 ± 7 mmHg; P < 0.05). The cycle length of the

### Table II. Clinical Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 273)</th>
<th>Group A (n = 114)</th>
<th>Group B (n = 94)</th>
<th>Group C (n = 65)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>238/35</td>
<td>99/15</td>
<td>82/12</td>
<td>57/8</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 11</td>
<td>61 ± 12</td>
<td>66 ± 11*</td>
<td>67 ± 11*</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 9</td>
<td>169 ± 8</td>
<td>167 ± 9</td>
<td>166 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 ± 15</td>
<td>69 ± 16</td>
<td>67 ± 12</td>
<td>67 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24 ± 4</td>
<td>24 ± 4</td>
<td>24 ± 3</td>
<td>24 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>87 (31.9%)</td>
<td>33 (29.0%)</td>
<td>36 (38.3%)</td>
<td>18 (27.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Arrhythmia disease</td>
<td>71 (26.0%)</td>
<td>30 (26.3%)</td>
<td>22 (23.4%)</td>
<td>19 (29.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>59 (21.6%)</td>
<td>28 (24.6%)</td>
<td>20 (21.3%)</td>
<td>11 (16.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>32 (11.7%)</td>
<td>7 (6.1%)</td>
<td>10 (10.6%)</td>
<td>15 (23.1%) &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>5 (1.8%)</td>
<td>4 (3.5%)</td>
<td>1 (1.0%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Other cardiac disease</td>
<td>19 (7%)</td>
<td>12 (10.5%)</td>
<td>5 (5%)</td>
<td>2 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>163 (59.7%)</td>
<td>52 (45.6%)</td>
<td>64 (68.1%)</td>
<td>47 (72.3%) &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>143 (52.4%)</td>
<td>57 (50.0%)</td>
<td>54 (57.4%)</td>
<td>32 (49.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>112 (41.0%)</td>
<td>29 (25.4%)</td>
<td>41 (43.6%)</td>
<td>42 (64.6%) &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Ca-channel blockers</td>
<td>74 (27.1%)</td>
<td>31 (27.2%)</td>
<td>28 (29.8%)</td>
<td>15 (23.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nitrates</td>
<td>8 (2.9%)</td>
<td>5 (4.4%)</td>
<td>2 (2.1%)</td>
<td>1 (1.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Digitalis</td>
<td>16 (5.9%)</td>
<td>5 (4.4%)</td>
<td>6 (6.4%)</td>
<td>5 (7.7%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; and NS, not significant.
VE oscillation was longer in group C-3 than in groups C-1 and C-2 (group C-1, 68 ± 22; group C-2, 62 ± 18; group C-3, 100 ± 39 seconds; \( P < 0.001 \)).

The cycle length of the VE oscillation had a significant negative correlation with the resting LVEF (\( r = -0.47, P < 0.001 \)) (Figure 2A) and a positive correlation with the log BNP in all of the patients (\( r = 0.50, P < 0.001 \)) (Figure 2B). The cycle length of the VE oscillation was negatively correlated with the peak VO\(_2\) (\( r = -0.34, P < 0.001 \)) (Figure 2C) and positively correlated with the VE-VCO\(_2\) slope in all of the patients (\( r = 0.52, P < 0.001 \)) (Figure 2D).

Since there was a significant difference in age among groups A, B and C, we extracted subjects whose age \( \geq 65 \) years, and then performed the same analysis after stratifying into 3 groups using the same criteria: group A’ (\( n = 44, 72 \pm 5 \) years), group B’ (\( n = 53, 73 \pm 6 \) years), and group C’ (\( n = 39, 74 \pm 6 \) years). Although the age did not differ among these groups, LVEF was significantly lower and BNP was significantly higher in group C’ than in groups A’ and B’. As compared to group A’, group C’ had a significantly lower peak VO\(_2\) (group A’, 17.0 ± 6.3; group B’, 14.6 ± 4.5; group C’, 12.9 ± 5.3 mL/minute/kg; \( P < 0.01 \)) and higher VE-VCO\(_2\) slope (group A’, 36 ± 8; group B’, 40 ± 8; group C’, 44 ± 14; \( P < 0.01 \)). The cycle length of oscillating VE was longer in group C’ than in group A’ (group A’, 58 ± 14; group B’, 67 ± 18; group C’, 77 ± 31 seconds; \( P = 0.001 \)).

### Discussion

The cycle length of oscillating VE showed a significant negative correlation with LVEF and peak VO\(_2\) and a positive correlation with BNP and the VE-VCO\(_2\) slope in all of the subjects. The cardiac patients who manifested OB both at rest and during exercise (group C) had worse cardiac function than the patients manifesting OB at rest before exercise and/or at rest (recovery) after exercise (group A) and the patients manifesting OB only during exercise (group B). Specifically, group C had significantly lower LVEF, peak VO\(_2\), and PETCO\(_2\) at peak exercise and significantly higher BNP and VE-VCO\(_2\) slope than group A and group B. The cycle length and amplitude of oscillating VE were longer and higher in group C than in groups A and B.

### Parameters obtained from CPX:

The peak VO\(_2\) generally reflects peak exercise cardiac output in cardiac patients. The VE-VCO\(_2\) slope mainly reflects the degree of ventilation/perfusion (V/Q) mismatch and progressively steepens in patients with worsening severity of heart failure resulting from either systolic or diastolic dysfunction.\(^{17,20}\) The hypo-perfusion to the lung caused by reduced pulmonary blood flow in patients with left ventricular dysfunction exacerbates the V/Q mismatch (high V/Q), leading to progressively lower PETCO\(_2\).\(^{17,20,22}\) The lower peak VO\(_2\), higher VE-VCO\(_2\) slope, and lower PETCO\(_2\) observed in the group C patients of the present study suggest that the cardiac dysfunction was more advanced in group C than in groups A and B.

### Mechanisms of oscillatory breathing:

OB observed at rest or at low levels of exercise sometimes disappears during moderate-to-heavy exercise.\(^9\) The prolonged circulation time is assumed to be one of the significant factors of OB. The increased cardiac output with exercise at increased intensity shortens the circulation time. Probably for this reason, the clear OB noted at rest becomes un-
clear or even disappears during high-intensity exercise in some subjects. Yet in patients with insufficient increases in cardiac output during exercise, OB can be expected to persist until the end of exercise because of the prolonged circulation time during exercise. Therefore, the worse cardiac function exhibited by patients manifesting OB both at rest and during exercise versus patients manifesting OB only at rest in our study strongly supports the hypothesis that the circulation time is a significant determinant of OB.

Murphy, et al. noted that the cycle length was inversely related to the increase in cardiac index during exercise. In our study, the cycle length of group C was significantly longer than the cycle lengths of the others groups. The cycle length of VE oscillation showed negative correlations with LVEF and peak VO$_2$, and positive correlations with BNP and VE-VCO$_2$ slope. The present findings thus indicate that the cycle length of oscillatory breathing is related to the circulation time and closely linked to the severity of heart failure.

Approximately one third of the present subjects presented OB only during exercise and not at rest (group B). We speculate that the appearance of OB only during exercise in group B may at least be partly explained by a blunting of the OB that probably existed at rest due to instability of the respiration mode, given that ventilation is more variable at rest than during exercise.

Previous investigations have mainly focused on OB during exercise. However, we also paid attention to the presence of OB at the resting state. While the clinical significance of CPX indices, such as peak VO$_2$ and VE-VCO$_2$ slope, has been established, the present findings suggest that the presence of OB both at rest and during exercise can be used as a simple marker of advanced cardiac dysfunction. The analysis of the cycle length of OB would be helpful to further stratify the severity of cardiac dysfunction.

Study limitations: Our criterion for enrolling subjects with OB was at least 3 consecutive cycles with an amplitude of greater than 25%, which was based on the definition by Murphy, et al. Their definition of exercise OB consisted of 3 criteria: 1) at least 3 consecutive cycles of clear ventilatory oscillations, 2) the amplitudes of VE oscillation ≥ 25% of the mean VE, and 3) OB persisting for ≥ 60% of exercise duration. However, we adopted the first 2 criteria to determine the presence of OB at rest and during exercise. Thus, our subjects who were considered to have OB during exercise (groups B and C) may not necessarily meet the third criterion of Murphy, et al. The frequency of OB depends on the specific definition used for determining oscillatory breathing, as well as the severity and/or etiology of cardiac disease in the study population. The BNP was only determined in 169 patients in the present study. We could not obtain the information on the
severity of heart failure, i.e., the New York Heart Association functional classifications. The proportion of the patients in whom an angiotensin converting enzyme inhibitor and angiotensin receptor blocker were prescribed was relatively low. This was probably because the present study included patients without heart failure. Further investigation will be necessary to clarify the mechanisms of the appearance of OB only during exercise.

Conclusions: The present findings suggest that cardiac function is more impaired in cardiac patients who manifest OB both at rest and during exercise than in cardiac patients who manifest OB only at rest or only during exercise.

Disclosures
Conflicts of interest: None.

References