Relation Between Oscillatory Breathing and Cardiopulmonary Function During Exercise in Cardiac Patients

Jo Kato, MD; Akira Koike, MD; Masayo Hoshimoto-Iwamoto, PhD; Osamu Nagayama, BSc; Koji Sakurada; Akira Sato, MD; Takeshi Yamashita, MD; Karlman Wasserman, MD, PhD; Kazutaka Aonuma, MD

Background: Oscillatory breathing, alternating between hyperpnea and hypopnea, has been recognized in cardiac patients, especially in those with heart failure. We evaluated whether the cycle length and amplitude of oscillatory breathing correlate with impaired cardiopulmonary function during exercise.

Methods and Results: We analyzed respiratory gas data during cardiopulmonary exercise testing (CPX) in 17 cardiac patients (68±12 years) who showed clear oscillatory ventilation during CPX. The cycle length (time from peak to peak) and the amplitude (difference between peak and nadir) for both oscillating ventilation (VE) and oscillating O₂ uptake (VO₂) were calculated from several consecutive oscillations noted at rest, and compared with indices of CPX. Oscillating VO₂ preceded oscillating VE in 16 of the 17 patients. Peak VO₂ (10.3±3.1 ml·min⁻¹·kg⁻¹) correlated significantly negatively with the cycle length of the VE oscillation (r=–0.60, P=0.010), and of the VO₂ oscillation (r=–0.61, P=0.008), and the difference in time between the peak of oscillating VE and the corresponding peak of VO₂ (r=–0.58, P=0.012). Similarly, the slope of the increase in VE to the increase in CO₂ output (45.6±11.5) correlated significantly positively with the cycle length of the VE and VO₂ oscillations (r=0.68, P=0.002; r=0.67, P=0.003, respectively).

Conclusions: The cycle length of oscillatory breathing is closely related to impaired cardiac reserve during exercise in cardiac patients. (Circ J 2013; 77: 661–666)

Key Words: Cardiopulmonary function; Exercise testing; Oscillatory ventilation

Oscillatory breathing, alternating between hyperpnea and hypopnea during sleep and commonly referred to as central sleep apnea or Cheyne-Stokes respiration, has long been recognized in cardiac patients. An instability of the ventilatory control system, long circulation time, high sensitivity of ventilation to changes in CO₂, a decrease in the PaCO₂ regulatory set point, or fluctuations in the pulmonary blood flow have been proposed as possible mechanisms underlying this abnormal breathing. A similar breathing pattern has also been recognized during waking hours in cardiac patients, especially those with heart failure. The mechanisms underlying oscillatory breathing while awake are assumed to overlap, at least in part, with those of central sleep apnea. However, reports on the mechanisms of oscillatory breathing while awake are limited. The relation between the magnitude of oscillatory breathing while awake and the severity of heart failure has not been fully investigated.

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Cardiopulmonary exercise testing (CPX) is a useful clinical tool for evaluating the severity of disease and the limitations of activities of daily life in cardiac patients. As described by the Fick’s equation, O₂ uptake (VO₂) is the product of cardiac output and the arteriovenous O₂ difference. Among the parameters obtained from CPX, the peak VO₂ is traditionally considered as the gold standard for identifying patients with a poor prognosis and selecting candidates for cardiac transplantation. The slope of the increase in ventilation (VE) to the increase in CO₂ output (VE–VCO₂ slope) is also an established index reflecting cardiopulmonary dysfunction during exercise.

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The Cardiovascular Institute, Tokyo (J.K., A.K., O.N., K.S., T.Y.); Cardiovascular Division, Institute of Clinical Medicine, Graduate School of Comprehensive Human Science, University of Tsukuba, Tsukuba (J.K., A.S., K.A.); School of Health and Sports Science, Juntendo University, Chiba (M.H.-I.), Japan; and Harbor-UCLA Medical Center, Torrance, CA (K.W.), USA

Mailing address: Akira Koike, MD, The Cardiovascular Institute, 3-2-19 Nishiazabu, Minato-ku, Tokyo 106-0031, Japan. E-mail: koike@cvi.or.jp


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In the present study, we hypothesized that the magnitude of oscillatory breathing while awake becomes large in cardiac patients with increased severity of cardiopulmonary dysfunction. In order to clarify this hypothesis, we evaluated the relationship between the degree of oscillatory breathing and the indices of CPX, especially focusing on the cycle length and amplitude of oscillating VE in cardiac patients with clear oscillatory ventilation. We also sought to clarify the relation between oscillating VE and the corresponding change of VO$_2$ in these patients, firstly by evaluating the presence of VO$_2$ oscillation, and secondly by comparing the cycle length, amplitude, and the phase difference between the VE and VO$_2$ oscillations. Additionally, we compared the characteristics of oscillatory breathing and cardiopulmonary indices between patients whose oscillatory breathing disappeared during exercise and those whose oscillatory breathing was identified from rest until the end of exercise.

### Methods

**Study Patients**

Among the 5,634 cardiac patients who performed CPX between January 2005 and December 2009 at the Cardiovascular Institute for the evaluation of exercise capacity and/or severity of heart failure, we identified those in whom at least 3 consecutive cycles of clear ventilatory oscillations were noted from the beginning of rest until the end of the 4-min warm-up exercise. Thereafter, we calculated the mean of the differences (amplitudes) between the peak and nadir of oscillating VE during the 4 min at rest and the mean resting VE in these subjects. We then selected 17 subjects whose amplitude was $>40\%$ of the mean VE. Although these criteria of ventilatory oscillation were based on previous reports, we used more strict criteria in the present study. In the previous reports, the definitions were at least 2 consecutive cycles and the amplitude $>25\%$ or $>30\%$. No patients with documented lung disease were included in the study population.

**Exercise Protocol and Respiratory Gas Analysis**

An incremental exercise test was performed using an upright, electromagnetically braked cycle ergometer (Corival 400, Lode, Holland). The exercise test began with a 4-min rest on the ergometer followed by a 4-min warm-up at 0 or 20 W at 60 rpm. The load was then increased incrementally by 1 W every 6 s (10 W/min). The work rate of the warm-up exercise (0 or 20 W) was set according to the subject’s daily activity.

VO$_2$, VCO$_2$, and VE were measured from the 4 min prior to starting the exercise until the end of exercise using an Aeromonitor AE-300s (Minato Medical Science, Osaka, Japan). The Aeromonitor AE-300s consists of a microcomputer, a hot-wire flow meter, and a gas analyzer, which contains a sampling tube, filter, suction pump, O$_2$ analyzer made by a paramagnetic oxygen cell, and an infrared CO$_2$ analyzer. The Aeromonitor AE-300s calculated VO$_2$ and VCO$_2$, breath-by-breath, on the basis of the mathematical analysis described by Beaver et al. Time alignment of concentration and flow is provided by the time delays. Time delays of O$_2$ and CO$_2$ analyzers (flow delay from sampling site to analyzer plus response time of analyzer) were determined with respect to the flow signal.

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-s averages, and these averages were translated into a 5-point moving average. Peak VO$_2$ was defined as the average value obtained during the last 15 s of incremental exercise. The percentage of peak VO$_2$: was calculated by dividing the measured peak VO$_2$ by the predicted peak VO$_2$. The predicted peak VO$_2$: was determined based on a normal Japanese population. The VE-VCO$_2$: slope was calculated, as reported previously.

### Table. Clinical Characteristics, Diagnosis and Cardiopulmonary Indices in Each Patient

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Cardiac diagnosis</th>
<th>LVEF (%)</th>
<th>Peak VO$_2$ (ml·min$^{-1}$·kg$^{-1}$)</th>
<th>Peak VO$_2$ (%)</th>
<th>VE-VCO$_2$: slope</th>
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<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>M</td>
<td>162.0</td>
<td>64.0</td>
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<td>2</td>
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<td>3</td>
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<td>M</td>
<td>171.6</td>
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<td>Dilated phase of HCM</td>
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<td>7.9</td>
<td>31.0</td>
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<td>4</td>
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<td>57.0</td>
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<td>6</td>
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<td>M</td>
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<td>60.5</td>
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<td>59.7</td>
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<td>153.8</td>
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<td>10.9</td>
<td>45.0</td>
<td>34.8</td>
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<tr>
<td>10</td>
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<td>62.0</td>
<td>CAD</td>
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<tr>
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<tr>
<td>14</td>
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<td>Dilated phase of HCM</td>
<td>16.0</td>
<td>6.3</td>
<td>26.0</td>
<td>50.5</td>
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<tr>
<td>15</td>
<td>58</td>
<td>M</td>
<td>162.0</td>
<td>68.0</td>
<td>CAD</td>
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<tr>
<td>16</td>
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<td>18.0</td>
<td>13.8</td>
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<tr>
<td>17</td>
<td>74</td>
<td>F</td>
<td>149.8</td>
<td>39.7</td>
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<tr>
<td>Mean</td>
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<td>16.1</td>
<td>3.1</td>
<td>12.2</td>
<td>11.5</td>
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</tbody>
</table>

CAD, coronary artery disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; VE, ventilation; VCO$_2$, CO$_2$ output; VO$_2$, O$_2$ uptake.
Analysis of Oscillatory Breathing

Oscillatory breathing in a representative subject (no. 1 in Table) is shown in Figure 1. The cycle length of oscillating VE was calculated as the interval from the peak to the following peak of oscillating VE for each of the cycles noted at rest, and then expressed as the mean value. The amplitude of oscillating VE was calculated as the difference between the peak and nadir of oscillating VE for each of the cycles noted at rest, and then expressed as the mean value. The amplitude of oscillating VE was also expressed as a percentage of the mean of resting VE. The cycle length and amplitude of oscillating VO₂ were calculated, similarly. From our experience, the oscillatory pattern of VO₂ usually precedes VE (Figure 1). Thus, the time difference between the peak of oscillating VO₂ and the corresponding peak of oscillating VE (the time from the peak of oscillating VE – the time of the corresponding peak of oscillating VO₂) was calculated for each of the cycles noted at rest. The cardiopulmonary indices and characteristics of oscillatory breathing were compared between patients whose oscillatory breathing was identified until the end of exercise (n=8) and those whose oscillatory breathing disappeared before 2 min to the end of exercise (n=9).

Statistical Analysis

Data are presented as the mean±SD. Linear regression analysis was used to correlate the measured variables. Intergroup differences for variables were compared using the unpaired t-test or Fisher’s exact test, where appropriate. For all comparisons, P<0.05 was considered statistically significant.

Results

Patient characteristics are presented in Table 1. On average, the left ventricular ejection fraction (LVEF) measured by echocardiography was 29.6±16.1%. Peak VO₂ was 10.3±3.1 ml/min⁻¹·kg⁻¹ and the percentage of predicted peak VO₂ was 42.8±12.2%. The VE-VCO₂ slope was 45.6±11.5. The brain natriuretic peptide (BNP) concentration, which was measured within 14 days from the date of CPX (3.8±4.2 days, n=13) was 1,347.2±1,050.9 pg/ml. For the oscillating VE, the cycle length was 90.9±25.0 s, and amplitude was 12.3±5.6 L/min. This amplitude corresponded to 96.3±37.5% of the mean VE measured at rest. In all the subjects, a clear oscillatory change of VO₂ was noted, similar to oscillating VE. For the oscillating VO₂, the cycle length was 90.1±23.0 s and amplitude was 275.3±103.1 ml/min. This amplitude corresponded to 113.4±41.5% of the mean VO₂ measured at rest, and significantly higher than that of VE (P<0.0001). Oscillating VO₂ was found to precede oscillating VE in 16 of the 17 subjects. In the remaining patient, there was no phase difference between oscillating VO₂ and VE. The phase difference between oscillating VO₂ and VE was, on average, 11.1±6.7 s in all the subjects.

The cycle length of the VE oscillation and that of the VO₂ oscillation both had a significant negative correlation with resting LVEF (r=−0.65, P=0.004; r=−0.66, P=0.003, respectively), but neither had a significant correlation with BNP. The phase difference between the VO₂ and VE oscillations had a negative correlation with LVEF (r=−0.63, P=0.005) and a positive correlation with BNP (r=0.70, P=0.007).

Figure 2A shows the relationship between the cycle length of the VE oscillation and peak VO₂. The cycle length of the VE oscillation showed a significant negative correlation with peak VO₂ (r=−0.60, P=0.010), indicating a longer cycle length of the VE oscillation in patients with lower peak VO₂. Similarly, the cycle length of the VO₂ oscillation had a significant negative correlation with peak VO₂ (r=−0.61, P=0.008) (Figure 2B). As shown in Figure 2C, there was a significant negative correlation between the phase difference between the VO₂ and VE oscillations and peak VO₂ (r=−0.58, P=0.012), indicating a longer phase difference between the VO₂ and VE oscillations in a patient with a lower peak VO₂.

Figure 3A shows the relationship between the cycle length of the VE oscillation and the VE-VCO₂ slope. The cycle length of the VE oscillation showed a significant positive correlation with the VE-VCO₂ slope (r=0.68, P=0.002). The cycle length of the VO₂ oscillation also had a significant positive correlation with the VE-VCO₂ slope (r=0.67, P=0.003) (Figure 3B). Figure 3C shows the correlation between the phase difference...
between the VO₂ and VE oscillations and the VE-VCO₂ slope. The correlation between these 2 variables was not significant, contrary to the significant correlation between the phase difference and peak VO₂.

In the analysis of the amplitude of the VE and VO₂ oscillations, neither had a significant correlation with resting LVEF or BNP. Also, the amplitude of the VE and VO₂ oscillations did not have significant correlations with peak VO₂ or the VE-VCO₂ slope.

In the comparisons between patients whose oscillatory breathing disappeared during exercise (n=9) and those whose oscillatory breathing was identified until the end of exercise (n=8), the former had a significantly higher peak VO₂: (12.0±2.6 vs. 8.4±2.5 ml·min⁻¹·kg⁻¹, P=0.011). There was no significant difference between the 2 groups in the other cardiopulmonary indices or the characteristics of oscillatory breathing, including the cycle length and amplitude for both VE and VO₂. In all the subjects, the oscillatory change was noted also in VCO₂. The oscillating VCO₂ followed the oscillating VO₂ in 13 subjects. For the remaining subjects, the phase difference between oscillating VO₂ and VCO₂ was negligible.

**Discussion**

We found that the cycle length of oscillating VE significantly correlates negatively with peak VO₂ and positively with the VE-VCO₂ slope. The oscillatory change in VO₂ was also noted, with similar pattern and cycle length to those of oscillating VE. The cycle length of oscillating VO₂ also significantly correlated with peak VO₂ and the VE-VCO₂ slope. Interestingly, oscillating VO₂ preceded oscillating VE in 16 of the 17 subjects in the present study. The phase difference between VO₂ and VE correlated negatively with peak VO₂ and LVEF, and positively with BNP, showing a longer phase difference in patients with a lower peak VO₂, lower LVEF and higher BNP.

**Parameters Obtained From CPX**

Parameters obtained from CPX are known to reflect the severity of heart failure in cardiac patients. A strong relationship between peak VO₂ and peak exercise cardiac output has been found in patients with heart failure. The VE-VCO₂ slope, which ranges from approximately 24 to 34 in healthy subjects, becomes steeper in cardiac patients according to the severity of the heart failure. A steep VE-VCO₂ slope during exercise is assumed to relate mainly to a ventilation-perfusion mismatch, such as an increased ratio of pulmonary dead space to tidal volume. A steep VE-VCO₂ slope implies the presence of heart failure resulting from either systolic or diastolic dysfunction, regardless of the etiology of cardiac disease. Concomitant lung disease may also steepen this slope. In the present study, it was found that cardiac patients with more advanced heart failure, as reflected by a lower peak VO₂ and higher VE-VCO₂ slope, have a longer cycle length of oscillatory breathing and a longer phase difference between oscillating VO₂ and VE.

**Mechanisms of Oscillatory Breathing**

Similar to the mechanisms underlying central sleep apnea, the instability of the respiratory control system is considered
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supported by our finding that the patients whose oscillatory breathing disappeared during exercise had a higher peak \( \dot{V}O_2 \) than those whose oscillatory breathing persisted until the end of exercise.

Although a patient with a longer cycle length of oscillatory breathing can be expected to have a higher amplitude, there was no significant correlation between the amplitude of oscillatory breathing and cardiopulmonary indices in the present study. The cycle length of oscillatory breathing must be strongly related to circulation time, which is closely linked to the severity of heart failure. However, the amplitude of oscillatory breathing must be determined not only by the circulation time, but also by other contaminating factors, including the degree of chemosensitivity and intensity of the baroreflex of each subject, which would explain the non-significant correlation between the amplitude of oscillatory breathing and cardiopulmonary indices.

Fluctuations in pulmonary blood flow have been proposed as another possible mechanism underlying oscillatory breathing.

Very recently, Murphy et al investigated the relationship between the presence of oscillatory breathing during exercise and cardiac function in patients with left ventricular dysfunction. They found that oscillatory breathing is closely related to a reduced cardiac index during exercise. They also noted that the increase in cardiac index during exercise was inversely related to the cycle length and amplitude of oscillating VE. The cycle length of oscillating VE possibly corresponds to circulation time. In the present study, we found that cardiac patients with more impaired cardiopulmonary dysfunction during exercise, as reflected in the CPX indices, had a longer cycle length of oscillating VE. This finding supports the hypothesis by Murphy et al that oscillatory breathing is an important surrogate for hemodynamic impairment in patients with heart failure. It is known that the oscillatory breathing noted at rest sometimes becomes unclear or even disappears during high-intensity exercise. This would also support the hypothesis that the circulation delay is an important factor determining oscillatory breathing, because the circulation time becomes shorter with the increased intensity of exercise as a result of the increase in cardiac output. This hypothesis is also supported by our finding that the patients whose oscillatory breathing disappeared during exercise had a higher peak \( \dot{V}O_2 \) than those whose oscillatory breathing persisted until the end of exercise.

Although a patient with a longer cycle length of oscillatory breathing can be expected to have a higher amplitude, there was no significant correlation between the amplitude of oscillatory breathing and cardiopulmonary indices in the present study. The cycle length of oscillatory breathing must be strongly related to circulation time, which is closely linked to the severity of heart failure. However, the amplitude of oscillatory breathing must be determined not only by the circulation time, but also by other contaminating factors, including the degree of chemosensitivity and intensity of the baroreflex of each subject, which would explain the non-significant correlation between the amplitude of oscillatory breathing and cardiopulmonary indices.

Fluctuations in pulmonary blood flow have been proposed as another possible mechanism underlying oscillatory breathing.

Previous investigations have tried to uncover the mechanisms of oscillatory breathing by mainly focusing on the change in VE. We found that patients with oscillating VE have a similar \( \dot{V}O_2 \) oscillation with an almost identical cycle length. We also noted that the \( \dot{V}O_2 \) oscillation preceded oscillating VE and that the amplitude of oscillating \( \dot{V}O_2 \) was higher than that of oscillating VE. If VE changes primarily because of a stimulus of the central nervous system to respiratory muscles, the change in VE has to precede the change in \( \dot{V}O_2 \). Thus, our present findings may support the central hypothesis that oscillatory ventilation develops by central vasomotor rhythm (ie,
fluctuations in pulmonary blood flow). In the present study, the phase difference between VO$_2$ and VE was longer in patients with a lower peak VO$_2$. The phase difference between VO$_2$ and VE might be determined by a delay in the ventilatory response to the fluctuations of pulmonary blood flow. This delayed ventilatory response can be accounted for by the longer circulation time in patients with more advanced heart failure.

Clinical Implications

The presence of oscillatory breathing is considered to be a strong indicator of poor prognosis in patients with heart failure. An analysis of the cycle length of oscillatory breathing might further enhance the prognostic power of oscillatory breathing in these patients. A therapeutic approach to shortening the cycle length of oscillatory breathing or diminish the oscillatory breathing itself may be effective in improving the prognosis of patients with heart failure.

Study Limitations

In our previous report, we defined oscillatory breathing as at least 2 consecutive cycles and amplitude >30%. However, in the present study, we used more strict criteria (at least 3 consecutive cycles and amplitude >40%), in order to reduce the influence of physiological noise on the delicate calculation of phase difference between the VO$_2$ and VE oscillations. Accordingly, our present subjects had more impaired cardiopulmonary function than those in our previous report, as reflected in the lower peak VO$_2$: 42.8 ± 12.2% vs. 54.1 ± 10.5%. Thus, some of the results obtained in the present study, such as the cycle length of oscillatory breathing and the phase difference between the VO$_2$ and VE oscillations, may not be applicable to the patients with relatively low amplitude of oscillatory breathing.

Because we focused on oscillatory breathing while subjects were awake, it is not known whether our subjects also have central sleep apnea. We evaluated the cycle length and amplitude of oscillatory breathing only for a resting period of 4 min, in order to calculate the ratio of the amplitudes of oscillating VO$_2$ and VE to the mean of their resting values. If the resting period (analysis interval) had been longer, the correlation between the cycle length and CPX indices might have become stronger and the correlation between the amplitude and CPX indices might have become significant. The varied underlying diagnoses in our study population might also account for some of the observed findings, such as no significant correlation between the amplitude of oscillatory breathing and cardiopulmonary indices. A larger study population would be necessary to further explore the mechanisms and clinical significance of oscillatory breathing in cardiac patients.

Conclusions

The present findings suggest that the cycle length of oscillatory breathing is closely related to impaired cardiac reserve during exercise in cardiac patients.

References