Mechanism of Periodic Breathing in Patients With Cardiovascular Disease*

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Although periodic breathing consisting of alternating hyperpnea and hypopnea has been recognized in heart failure patients, its mechanism has not been clarified. We hypothesized that heart failure patients who have oscillations in ventilation will also be found to have oscillations in pulmonary blood flow, as reflected in left ventricular ejection fraction. To test this hypothesis, we analyzed continuously gas exchange and left ventricular ejection fraction during exercise in cardiac patients who exhibited periodic breathing. Of 48 consecutive patients with reduced left ventricular function who performed a symptom-limited incremental exercise test using an upright cycle ergometer, we selected 5 patients who exhibited clear ventilatory oscillations during exercise. These patients repeated the same exercise test on another day for measuring gas exchange and left ventricular ejection fraction continuously. Oscillatory changes were noted both in left ventricular ejection fraction and in ventilation in these patients. These observations offer support for the hypothesis that fluctuations in pulmonary blood flow are primarily responsible for the periodic breathing seen in heart failure patients.

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Periodic breathing consisting of alternating hyperpnea and hypopnea has been recognized in heart failure patients for more than a half a century. In 1987, Kremser et al. reported that 6 of 31 patients with dilated cardiomyopathy showed marked periodic breathing at rest and during moderate exercise and that the magnitude of the changes correlated with the severity of congestive heart failure. They postulated that periodic breathing may compound the effects of the inadequate delivery of oxygen by the failing heart. Ribeiro et al. observed periodic breathing during exercise in 5 of 32 patients with heart failure classified as New York Heart Association functional class 3 or 4. The periodic breathing disappeared after administration of milrinone, a positive inotropic vasodilator agent.

Although this abnormal response is not rare, its mechanism has not been clarified. Ben-Dov et al. recently analyzed oxygen uptake, ventilation, and end-expiratory lung volume during exercise in patients with oscillatory ventilation. They found a greater amplitude of oscillations in oxygen uptake than in ventilation, although no oscillation in heart rate was observed. Oxygen uptake can be determined by the Fick equation based on pulmonary blood flow and arterial and mixed venous oxygen content. Therefore, Ben-Dov et al. suggested that oscillations in pulmonary blood flow may contribute to oxygen uptake and ventilatory oscillations.

It has been suggested by several investigators that hyperpnea at the onset of exercise is caused by the abrupt increase in pulmonary blood flow. If oscillations in pulmonary blood flow exist, causing periodic breathing there should be similar oscillations in systemic vascular tone. Oscillations in left ventricular stroke volume or in ejection fraction would also be noted if cyclic changes exist in preload or afterload resulting from the oscillations in systemic vascular tone. A few investigators, however, have evaluated the hemodynamic changes during periodic breathing, and the mechanism of this breathing still remains obscure.

We hypothesized that heart failure patients who have oscillations in ventilation will also be found to have oscillations in pulmonary blood flow, as reflected in left ventricular ejection fraction, whereas patients without ventilatory oscillations will not have evidence for oscillation in pulmonary blood flow. To test this hypothesis, we analyzed continuously gas exchange and left ventricular ejection fraction in patients with cardiovascular disease who exhibited periodic breathing.

METHODS

Subjects and Exercise Protocol

We studied 48 consecutive patients with reduced left ventricular function, ranging in age from 22 to 77 years. All patients were stable clinically, classified as New York Heart Association functional class 2 and in sinus rhythm. All medications were withheld for 24 hours before exercise testing. Subjects performed a symptom-limited exercise test using an upright, electromagnetically braked cycle ergometer (Siemens-Elema 930B, Siemens Elema AB, Solna, Sweden). After 4 min of rest on the ergometer, subjects began exercising, starting with a 3-min warm-up at 20 W, 60 rpm,
followed by a 1 W increase in the work rate every 6 s.

Oxygen uptake, carbon dioxide output and ventilation were measured, breath-by-breath, when patients were seated on the ergometer at rest and throughout the exercise period using a Respironicon RRM-300 (Minato Medical Science, Tokyo, Japan). The Respironicon RRM-300 consists of a hot-wire flowmeter and gas analyzer (MG-360, Minato Medical Science) that contains a sampling tube, a filter, a suction pump, an oxygen analyzer made with a zirconium element and an infrared carbon dioxide analyzer. Gas exchange and flow measurements were corrected for ambient temperature, barometric pressure, and water vapor. After the test, oxygen uptake, carbon dioxide output, and ventilation were expressed using five-breath moving average.

Based on the results of this test, we selected five patients who exhibited clear ventilatory oscillations at rest and during upright bicycle exercise (Table 1). These patients repeated the exercise test on another day, and gas exchange and left ventricular ejection fraction were measured continuously.

We also recruited five control patients with reduced left ventricular function who did not exhibit ventilatory oscillations at rest (Table 1). These patients were selected to be age-matched and to have similar degrees of heart failure as compared with the patients with spontaneous ventilatory oscillations. They were guided to simulate volitionally periodic breathing at rest,3 in order to evaluate physiologic effects of the breathing pattern on the measurements of ejection fraction. These patients were instructed to oscillate their tidal volume with 1 min cycle, while respiratory rate was maintained constant.

The nature and purpose of the study and the risks involved were explained, and informed consent was obtained from each patient.

**Measurement of Left Ventricular Ejection Fraction**

Left ventricular ejection fraction was measured by a computerized cardiac monitoring system (RRG-607, Aloka Co, Tokyo, Japan). The validity of the measurement techniques used in this study has been reported previously.8-10 Briefly, this system consists of a cadmium telluride detector (A-116, Radiation Monitoring Devices, Boston), a preamplifier unit, a portable data acquisition unit and a personal computer (PC-9801, NEC Corp, Tokyo, Japan). After the patients' red blood cells had been labeled with 30 mCi of technetium 99mTc by the semi-in vitro method, the cadmium telluride detector was positioned over the left ventricular region.

The microcomputer calculated the counts over the left ventricular region of interest during the cardiac cycle at 50-ms intervals throughout the exercise test. Thereafter, the left ventricular ejection fraction was calculated, beat-by-beat, with 70 percent of the end-diastolic counts as background activity.

**Statistical Analysis**

All data are given as mean ± SD. Peak oxygen uptake was compared between patients with periodic breathing and those without periodic breathing using unpaired Student's t test. A difference was considered significant when p value was less than 0.05.

**RESULTS**

Peak oxygen uptake of 5 patients who exhibited periodic breathing was 23.0 ± 2.1 ml/min/kg (Table 1) and was not significantly different from that of the other 43 patients who did not exhibit ventilatory oscillations (22.0 ± 5.0 ml/min/kg).

Figure 1 represents the respiratory gas exchange and heart rates at rest and during exercise in one patient (patient 2 in Table 1). Clear oscillations in oxygen uptake, carbon dioxide output, minute ventilation, and tidal volume were noted at rest and during 20 W pedalling. In addition, there were marked oscillations in ventilatory equivalents for oxygen and carbon dioxide, probably because of the phase difference that existed among these variables. These oscillations, however, were not apparent during moderate to heavy exercise.

Figure 2 shows the relations between ventilation and left ventricular ejection fraction at rest and during exercise in five patients who exhibited ventilatory oscillations. Ventilation increased and decreased cyclically at rest and during light to moderate exercise, resulting in an oscillation that lasted about 1 min. Left ventricular ejection fraction also showed an oscillation, with a similarly cyclic nature. Oscillations in

**Table 1—Patient Characteristics, Left Ventricular Ejection Fraction (EF) at Rest, Peak $O_2$ Uptake ($V_{O_2}$) and cardiac diagnosis**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Ht, cm</th>
<th>Wt, kg</th>
<th>Rest EF, %</th>
<th>Peak $V_{O_2}$, ml/min/kg</th>
<th>Cardiac Diagnosis</th>
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<tr>
<td>1</td>
<td>53</td>
<td>M</td>
<td>158</td>
<td>73</td>
<td>30.8</td>
<td>26.7</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>167</td>
<td>72</td>
<td>28.7</td>
<td>20.7</td>
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<tr>
<td>3</td>
<td>57</td>
<td>M</td>
<td>153</td>
<td>56</td>
<td>34.3</td>
<td>22.8</td>
<td>Old myocardial infarction (ant)</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>M</td>
<td>170</td>
<td>88</td>
<td>23.3</td>
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<td>Old myocardial infarction (inf)</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>M</td>
<td>163</td>
<td>73</td>
<td>36.4</td>
<td>21.5</td>
<td>Old myocardial infarction (inf)</td>
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<tr>
<td>Mean</td>
<td>55</td>
<td>M</td>
<td>162</td>
<td>72</td>
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<td>SD</td>
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<td>Control Patients Without Ventilatory Oscillations*</td>
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<td>54</td>
<td>M</td>
<td>153</td>
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<td>29.7</td>
<td>15.0</td>
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<td>7</td>
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<td>F</td>
<td>148</td>
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<td>25.8</td>
<td>15.0</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>M</td>
<td>162</td>
<td>39</td>
<td>41.3</td>
<td>15.0</td>
<td>Dilated cardiomyopathy</td>
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<tr>
<td>9</td>
<td>63</td>
<td>F</td>
<td>153</td>
<td>64</td>
<td>44.6</td>
<td>15.0</td>
<td>Old myocardial infarction (inf)</td>
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<tr>
<td>10</td>
<td>60</td>
<td>F</td>
<td>162</td>
<td>45</td>
<td>38.6</td>
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<td>Dilated cardiomyopathy</td>
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<td>156</td>
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<td>36.6</td>
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<td>SD</td>
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<td>6</td>
<td>7</td>
<td>6.3</td>
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*Control patients were guided to simulate volitionally periodic breathing.
left ventricular ejection fraction and ventilation became unclear at the similar work rate during exercise. In contrast, there was no oscillatory change in left ventricular ejection fraction for the control patients who simulated volitionally periodic breathing (Fig 3).

**DISCUSSION**

Quite recently, Ben-Dov et al\(^3\) found that the amplitude of oscillations in oxygen uptake were more prominent than concomitant oscillations in ventilation in patients with congestive heart failure who exhibited periodic breathing. They compared oscillations in oxygen uptake in heart failure patients with those induced by volitional periodic breathing in healthy subjects, and they found that oxygen uptake oscillations in patients were greater in its magnitude than those induced by the simulated periodic breathing in healthy subjects. Oscillations in oxygen uptake could not be explained entirely by primary changes in respiratory center output or by changes in lung gas stores.\(^3\) Ben-Dov et al\(^3\) therefore, speculated that fluctuations in pulmonary blood flow might be responsible for the gas exchange oscillations, although they did not measure pulmonary blood flow.
or cardiac output.

In 1974, Wasserman et al reported that hyperpnea can be caused by the decrease in cardiac output, i.e., pulmonary blood flow. Since then, an association of ventilation with pulmonary blood flow (or cardiac output) has been reported by several investigators. It has also been suggested that the ventilatory stimulation occurs by the increase in carbon dioxide delivery to the lung and by the strain of the right ventricle, while the precise mechanisms of the control of ventilation still remains obscure.

In the present study, we hypothesized that patients with periodic breathing have oscillations in pulmonary blood flow, as reflected in left ventricular ejection fraction. We measured continuously left ventricular ejection fraction at rest and during incremental exercise in patients with cardiovascular disease who exhibited periodic breathing. We found clear oscillations in left ventricular ejection fraction, oxygen uptake, carbon dioxide output, and ventilation. We also found that oscillations in ventilation were primarily the result of the oscillations in tidal volume, as shown in Figure 1. There was, however, no clear oscillation in heart rate, which is consistent with previous observations.

In our study, duration of the oscillation (time from peak to peak) was 45 to 60 s for both ventilation and left ventricular ejection fraction, which is similar to duration of ventilatory oscillations noted in previous reports. The magnitude of the oscillation in ventilation, however, was relatively low in our study, possibly because we selected less severely ill patients (NYHA class 2), compared with other specialists, who were able to perform the incremental exercise test adequately.

Although the ventilation was measured breath-by-breath and the left ventricular ejection fraction was calculated beat-by-beat, there was a phase difference of about 30 s between left ventricular ejection fraction and ventilation (Fig 2). This might be from a transit time between the left ventricle and pulmonary artery, in addition to a time required to alter the ventilation by the stimulus which is related to changes in pulmonary blood flow.

There have been no previous studies in which left ventricular function was measured continuously in patients with periodic breathing, in part because of the inability to measure cardiac function continuously during exercise. Although beat-to-beat measurements of the left ventricular dimension during moderate exercise may be possible with echocardiography in normal subjects, these measurements are difficult to obtain in cardiac patients, who may have left ventricular asynchrony. In the present study, we measured left ventricular ejection fraction with a computerized cadmium telluride detector, a portable nonimaging device that allows beat-to-beat assessment of the radionuclide time-activity curve at rest and during exercise. The cadmium telluride detector was positioned over the left ventricular region with a specially designed vest that held it in place, preventing dislocation of the detector during exercise. Several investigators have reported an excellent correlation between left ventricular ejection fraction measured by the cadmium telluride detector and that recorded with a gamma camera or by contrast ventriculography.

If the oscillatory changes in left ventricular ejection fraction were secondary to the oscillations in ventilation, patients without spontaneous ventilatory oscillations should show oscillations in ejection fraction secondary to volitional oscillations in ventilation. To test this hypothesis, age-matched control patients, who did not exhibit ventilatory oscillations, were guided to simulate periodic breathing. While they did not perform exercise testing, they had similar degrees of heart failure and would be similarly preload and afterload sensitive as compared with the patients with spontaneous ventilatory oscillations. However, the results disproved the hypothesis. We found no oscillations in ejection fraction in the control patients (Fig 3).

It is well known that preload plays an important role in determining the response of left ventricular stroke volume through the Starling mechanism. The change in stroke volume must be reflected in the change in ejection fraction. Left ventricular ejection fraction would also reflect peripheral vascular resistance at rest and during mild to moderate exercise in patients with cardiovascular disease. Thus, we believe that oscillations in left ventricular ejection fraction noted in the present study reflects alterations in preload, afterload, or both due to oscillations in systemic vascular tone.

Oscillations in output of neurologic stimuli from the medullary vasomotor center have been previously reported. This phenomenon would explain why oscillations found at rest or at low levels of exercise disappeared during heavy exercise: peripheral vascular resistance would reach its maximum level and be unable to change during heavy exercise because of the increase in circulating catecholamine or other humoral factors.

In our study, oscillatory changes in left ventricular ejection fraction were noted in cardiac patients with periodic breathing. This observation supports the hypothesis that fluctuations in pulmonary blood flow are primarily responsible for the periodic breathing seen in heart failure patients.

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