A Characteristic Change in Ventilation Mode During Exertional Dyspnea in Patients With Chronic Heart Failure*

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Although exertional dyspnea is an important symptom limiting daily lives in patients with chronic heart failure, there is no objective assessment of this symptom. To characterize the exertional dyspnea, ventilatory responses to exercise were studied in relation to exertional dyspnea. Gas exchange data were obtained during a maximal bicycle exercise in 43 patients with chronic heart failure and 20 normal subjects. In addition to standard ventilatory variables, the ventilation mode was assessed from the tidal volume-ventilation rate (VT-f) relationship. The exercise was performed again after sublingual administration of 5 mg of isosorbide dinitrate. In normal subjects, the VT and f increased almost proportionally with exercise intensity. In 17 (85 percent) of 20 patients with exertional dyspnea, the VT-f relationship abruptly lost linearity at the onset of exertional dyspnea. This change resulted from an inadequate increase in VT and a further increase in f. In 8 of these 17 patients, isosorbide dinitrate improved exertional dyspnea with normalization of the VT-f relationship; however, in 9 patients whose dyspnea was not improved, the abnormal VT-f relationship was unaltered. Only 2 (9 percent) of 23 patients without exertional dyspnea showed the abnormal VT-f relationship. Other ventilatory variables were not different between patients with and without dyspnea. Thus, exertional dyspnea is characterized by simultaneous appearance of rapid and shallow ventilation. The VT-f relationship appears to be a simple and useful objective assessment of exertional dyspnea in patients with chronic heart failure.

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Exertional dyspnea and working muscle fatigue are two major symptoms limiting daily activities in patients with chronic heart failure. Although working muscle fatigue due to an inappropriate blood supply and/or intrinsic abnormalities in skeletal muscle metabolism can be assessed by measurements of the maximal aerobic power, peak oxygen uptake and anaerobic threshold, there is no objective assessment of exertional dyspnea. A number of studies have consistently demonstrated a hyperventilatory response, i.e., an increased ventilatory equivalent for carbon dioxide, in exercise in patients with chronic heart failure and it has been speculated that this ventilatory abnormality is associated with exertional dyspnea. Sullivan et al., however, failed to show a direct relation between the increase in ventilatory equivalent for carbon dioxide and exertional dyspnea in patients with chronic heart failure.

In acute heart failure with pulmonary congestion, patients complain of dyspnea even at rest, and ventilatory is often rapid and shallow. Although this ventilation mode may be derived from a decreased compliance of the lung to save the energy consumption of the respiratory muscles, the limit of an increase in tidal volume (VT) in response to the central respiratory command may cause the feeling of dyspnea. Thus, exertional dyspnea in chronic heart failure may also be followed by concomitant changes in the ventilation mode. However, serial changes in the ventilation mode during exercise have not been studied in view of characterization of exertional dyspnea.

The present study was designed to test the hypothesis that exertional dyspnea in patients with chronic heart failure can be characterized by a simultaneous change in the ventilation mode. Furthermore, since we have noted that nitrates often improve the exertional dyspnea, the effects of isosorbide dinitrate on exertional dyspnea and ventilatory responses to exercise were also studied.

METHODS

Subjects

We studied 43 ambulatory patients with left ventricular dysfunction and symptoms of mild-to-moderate heart failure, i.e., fatigue or dyspnea on effort, as a heart failure group (Table 1). There were 37 men and 6 women, ranging in age from 22 to 79 years.
Table 1—Characteristics of Subjects*

<table>
<thead>
<tr>
<th></th>
<th>Normal Group</th>
<th>Heart Failure Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>55±1</td>
<td>53±2</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male/</td>
<td>16/4</td>
<td>37/6</td>
<td>NS</td>
</tr>
<tr>
<td>female</td>
<td>FS, %</td>
<td>43±1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>EDD, mm</td>
<td>46±1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Values are mean±SEM. NS=not significant; FS=left ventricular fractional shortening; EDD=left ventricular end-diastolic dimension.

years (53±2 years, mean±SEM). Thirty patients were classified in New York Heart Association functional class II and 13 were in class III. The cause of heart failure was dilated cardiomyopathy in 27 patients, ischemic cardiomyopathy without angina pectoris in 10, and aortic regurgitation in the remaining 6 patients. Left ventricular fractional shortening assessed by M-mode echocardiograms under the guidance of two-dimensional images ranged from 5 to 25 percent (15±1 percent) and end-diastolic dimension ranged from 50 to 88 mm (63±1 mm). All of the patients had been treated with digitals, diuretics, and/or vasodilators for more than 2 months without alteration of dose. β-Adrenergic receptor agonists or antagonists that may influence the ventilation mode were not administered in any patient.

Twenty healthy volunteers, 16 men and 4 women, ranging in age from 52 to 69 years (55±2 years) served as a normal group. None had a history, symptom, or sign of cardiovascular diseases. All had normal 12-lead electrocardiograms at rest and during exercise and normal echocardiograms at rest. The mean age was comparable between the heart failure group and the normal group.

A written informed consent was obtained from each subject before entering the study.

Exercise Testing

A ramp upright bicycle exercise test was performed in the postabsorptive state. After a 5-min rest on the upright ergometer, the exercise test was conducted with 1-min unloading pedaling, followed by 15 W incremental loading every 1 min until subjects were nearly exhausted. The initial workload was selected according to the severity of heart failure to avoid too long an exercise duration (10 min or more), ie, 30 W for normal subjects, 15 W for class II patients, and 0 W for class III patients. Gas exchange data were collected throughout exercise using a breath-by-breath respiro-monitor system (model RM-200, Minato Co, Tokyo, Japan) that was calibrated immediately before each study using a 2-L calibration syringe and a gas mixture of 14.93 percent oxygen, 5.00 percent carbon dioxide, and 80.07 percent nitrogen. Oxygen uptake, carbon dioxide output, minute ventilation, respiratory gas exchange ratio, ventilatory equivalent for carbon dioxide, ventilation rate (f), and VT were recorded as mean values every 30 s. These data were represented as a function of exercise workload. The anaerobic threshold was determined as the point at which the ratio of minute ventilation to oxygen uptake begins to rapidly increase. To assess the ventilation mode, the values for f and VT were fed into a personal computer (model PC-9801, NEC Co, Tokyo, Japan), and the relation of VT to f was depicted on the display. Systolic blood pressure and heart rate were measured at 1-min intervals throughout the study using sphygmomanometer and electrocardiograms, respectively. Subjective symptoms were monitored with careful interview every 30 s during exercise. In this study, exertional dyspnea was defined as an uncomfortable feeling of effort on respiration, which began to develop during exercise. The intensity of exertional dyspnea was assessed using Borg's new rating scale from 0 to 10, in which 0 denotes no appreciable dyspnea and 10 denotes maximal dyspnea. The time when patients felt 5 or more intensity of dyspnea was defined as the time of exertional dyspnea onset. The average VT-f relationship for each group was calculated with the data at four reference time points, ie, at rest, at 50 percent of oxygen uptake at the anaerobic threshold, at anaerobic threshold, and at peak exercise. When patients complained of exertional dyspnea, additional data at the onset of exertional dyspnea were also included.

### Isosorbide Dinitrate Study

When patients complained of exertional dyspnea during the exercise test, a second challenge was performed after the sublingual administration of 5 mg of isosorbide dinitrate following 2 h rest for recovery from the fatigue induced by the initial exercise test. Ten minutes after isosorbide dinitrate administration, the second exercise test was performed with the same protocol and measurements as in the first exercise test.

### Reproducibility of VT-f Relationship

To examine the reproducibility of the VT-f relationship, a second exercise test without administration of isosorbide dinitrate was performed 2 h after the completion of the first exercise test in another set of three normal subjects and three patients with heart failure with exertional dyspnea.

### Statistical Analysis

Values were expressed as mean±SEM. Comparisons were performed with analysis of variance for continuous variables and χ² analysis for categorical variables. A p value of less than 0.05 was considered as significant.

### RESULTS

### Subjective Complaint of Exertional Dyspnea

Among 43 patients in the heart failure group, 20 patients complained of exertional dyspnea at a submaximal exercise level, although they could continue exercise until exhaustion. Exertional dyspnea devel-

Table 2—Characteristics of Subgroups of the Heart Failure Group*

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
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<td>n</td>
<td>20</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>51±3</td>
<td>55±3</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male/</td>
<td>19/1</td>
<td>18/5</td>
<td>NS</td>
</tr>
<tr>
<td>female</td>
<td>FS, %</td>
<td>15±1</td>
<td>16±2</td>
</tr>
<tr>
<td></td>
<td>EDD, mm</td>
<td>65±2</td>
<td>62±2</td>
</tr>
<tr>
<td></td>
<td>Etiology</td>
<td>DCM</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICM</td>
<td>4</td>
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<tr>
<td></td>
<td></td>
<td>AR</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>NYHA class II</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>NYHA class III</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

*Values are mean±SEM. NS=not significant; FS=left ventricular fractional shortening; EDD=left ventricular end-diastolic dimension; DCM=dilated cardiomyopathy; ICM=ischemic cardiomyopathy; AR=aortic regurgitation; NYHA=New York Heart Association.

Ventilator Mode Change During Dyspnea in CHF Patients (Yokoyama et al)
opened rather abruptly and hence, its onset could be identified in these patients. According to the presence or absence of exertional dyspnea, the heart failure group was divided into two subgroups: group A consisted of 20 patients with exertional dyspnea, and group B included the remaining 23 patients without exertional dyspnea. In 18 group A patients, whose anaerobic threshold could be determined, the onset of exertional dyspnea preceded the anaerobic threshold by 86 ± 11 s on average, with a range of 30 to 180 s. Group B patients did not complain of exertional dyspnea, but they experienced breathlessness that developed gradually with leg fatigue at a higher exercise level than the anaerobic threshold. The clinical data of each subgroup are shown in Table 2. There were no significant differences in age, sex, cause of heart failure, left ventricular fractional shortening, and the severity of heart failure between the two subgroups. In the normal group, no subject complained of exertional dyspnea, although all subjects as well as patients in group B experienced breathlessness at high exercise levels.

**Gas Analysis Data**

The oxygen uptake, carbon dioxide output, and minute ventilation increased with an increase in exercise intensity in each group. However, in groups A and B, oxygen uptake reached a plateau at a lower exercise level than in the normal group. The minute ventilation was significantly greater in both heart failure groups than in the normal group at a given exercise level (Fig 1), although carbon dioxide output was not significantly different among the three groups. Hence, the ventilatory equivalent for carbon dioxide was significantly higher in groups A and B than in the normal group throughout exercise (Fig 1). Because the anaerobic threshold could not be determined in two patients in group A and four patients in group B, these patients were excluded from the analysis of anaerobic threshold. Oxygen uptake at the anaerobic threshold was significantly less in groups A and B than in the normal group (Table 3). Because a comparable level of near maximal exercise was achieved in each group as shown by the peak respiratory gas exchange ratio, comparing the peak oxygen uptake among groups was justified. The peak oxygen uptake as well as anaerobic threshold was significantly less in groups A and B than in the normal group (Table 3). However, the oxygen uptake at anaerobic threshold and peak oxygen uptake were comparable between groups A and B. Thus, neither ventilatory equivalent for carbon dioxide nor other standard gas exchange data could distinguish patients with exertional dyspnea (group A) from patients without exertional dyspnea (group B).

**Ventilation Mode During Exercise**

In the normal group, the f and VT increased almost proportionally with the exercise intensity, and as a result, the VT-f relationship was nearly linear over a wide range (Fig 2). However, at higher exercise levels than the anaerobic threshold, the increase in VT appeared to saturate gradually. A similar VT-f relationship was observed in group B. In contrast, the VT-f relationship in group A was quite different from the normal group and group B; it shifted downward even in the initial phase of exercise and, then, abruptly lost its linearity at the onset of exertional dyspnea. The break in the VT-f relationship developed from an inadequate increase in VT and a disproportionate increase in f. Thus, rapid and shallow ventilation appeared during exertional dyspnea in group A. When individual responses were examined, 17 of 20 patients in group A showed this abnormal response of the VT-f relationship during

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**Table 3—Gas Analysis Data**

<table>
<thead>
<tr>
<th></th>
<th>Normal Group</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Peak R</td>
<td>1.16 ± 0.01</td>
<td>1.17 ± 0.01</td>
<td>1.20 ± 0.02</td>
</tr>
<tr>
<td>Peak VO₂</td>
<td>29.3 ± 0.5</td>
<td>19.5 ± 0.9†</td>
<td>19.0 ± 0.5†</td>
</tr>
<tr>
<td>ml/min/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT, ml/min/kg</td>
<td>22.2 ± 0.8</td>
<td>16.4 ± 0.7†</td>
<td>15.5 ± 0.5†</td>
</tr>
</tbody>
</table>

*Values are mean ± SEM. R = respiratory gas exchange ratio; VO₂ = oxygen uptake; AT = anaerobic threshold. †p<0.01 vs normal group.
exercise, although the remaining three patients did not show the abrupt change in the VT-f relationship despite significant exertional dyspnea in group B, only two patients showed the abnormal response of the VT-f relationship during exercise. Therefore, the sensitivity and specificity of the VT-f relationship in detecting exertional dyspnea were 85 percent and 89 percent, respectively. Thus, exertional dyspnea in patients with chronic heart failure was characterized by a simultaneous, dynamic change in the ventilation mode indicating an appearance of rapid and shallow ventilation.

**Effect of Isosorbide Dinitrate**

The effect of isosorbide dinitrate was examined in 17 patients in group A who showed the abnormal VT-f relationship during exertional dyspnea. Exertional dyspnea disappeared with isosorbide dinitrate in five patients, and the onset delayed for 1 min or more compared with the first exercise test in three other patients. In these eight patients, isosorbide dinitrate also improved the abnormal response of the VT-f relationship (Fig 3) without significant changes in the peak exercise heart rate (149±5 vs 152±5 beats/min), peak exercise systolic blood pressure (185±10 vs 179±10 mm Hg), oxygen uptake at the anaerobic threshold (15.9±1.1 vs 16.8±1.1 ml/min/kg), or the peak oxygen uptake (18.5±1.3 vs 20.0±1.3 ml/min/kg). In the remaining nine patients whose exertional dyspnea was not improved, the abnormal VT-f relationship remained unchanged even after the administration of isosorbide dinitrate.

**Reproducibility of the VT-f Relationship**

The first and second VT-f relationships obtained with a 2-hour interval were almost identical in all six subjects despite the presence or absence of heart failure, suggesting good reproducibility. There were also no significant differences in peak exercise heart rate (152±5 vs 154±7 beats/min), peak exercise systolic blood pressure (193±14 vs 195±14 mm Hg), oxygen uptake at the anaerobic threshold (17.2±1.8 vs 16.9±2.2 ml/min/kg), or the peak oxygen uptake (23.1±3.8 vs 24.3±2.9 ml/min/kg). Furthermore, the time of onset of exertional dyspnea and its intensity were not different in the two exercise tests.

**FIGURE 2**. Average VT-f relationships in the normal group and heart failure group divided into two subgroups according to the presence (group A) or the absence (group B) of exertional dyspnea (ED). Each relationship is constructed with coordinates from four reference time points: the time at rest, at 50 percent of the anaerobic threshold (AT), at AT, and at the peak exercise. In group A, the additional point is the time of ED onset. Data are expressed as mean ± SEM.

**FIGURE 3**. Average VT-f relationships before (solid line) and after (dashed line) isosorbide dinitrate (ISDN) administration in eight patients with heart failure in whom ISDN was effective in decreasing exertional dyspnea (ED) (left panel) and in nine patients in whom ISDN was ineffective (right panel). AT = anaerobic threshold. Data are expressed as mean ± SEM.
of the three patients with heart failure.

**DISCUSSION**

The present study demonstrates that exertional dyspnea in patients with chronic heart failure is characterized by a simultaneous change in the ventilation mode as reflected by an abrupt change in the Vt-f relationship indicating the appearance of rapid and shallow ventilation. Standard gas exchange measurements, including ventilatory equivalent for carbon dioxide, were unable to provide an objective measure of exertional dyspnea. Several investigators have already demonstrated rapid and shallow ventilation during exercise in patients with chronic heart failure. However, serial changes in the ventilation mode have not been studied in order to characterize exertional dyspnea. In this study, we disclosed that the ventilation mode undergoes a dynamic change during exertional dyspnea in patients with chronic heart failure. The direct relationship between exertional dyspnea and the change in ventilation mode was also suggested from the effects of isosorbide dinitrate; an improvement in exertional dyspnea was followed by the normalization of the ventilation mode (Fig 3).

The appearance of rapid and shallow ventilation indicates that the central respiratory command that regulates the ventilation mode is altered in conjunction with exertional dyspnea. Afferent signals arising from peripheral organs, which are perceived as exertional dyspnea at the high sensory center, might simultaneously affect the respiratory center to change the ventilation mode. Although it is unclear in this study what signals are sensed, there are two possible mechanisms: (1) an excessive carbon dioxide production in skeletal muscles or blood gas abnormalities that may stimulate peripheral or central chemoreceptors, or (2) pulmonary congestion or a consequent alteration in mechanical properties of the lung that may stimulate mechanoreceptors in the lung.

In normal subjects, an increase in carbon dioxide production and subsequent metabolic acidosis which drive the respiratory center may be perceived as breathlessness by the high sensory center via arterial or central chemoreceptors during severe exercise above the anaerobic threshold. It has also been suggested that the increase in ventilation rate predominates over the increase in tidal volume under such conditions, as was observed in the normal subjects (Fig 2). In chronic heart failure, these physiologic responses may be enhanced through an early and excessive accumulation of carbon dioxide, causing a feeling of exertional dyspnea and the abnormal ventilatory response, because the maximal aerobic power and ventilatory efficiency are decreased in this disease. However, this hypothesis is not consistent with the findings presented herein, as decreases in the anaerobic threshold and exercise ventilatory efficiency, ie, an increased ventilatory equivalent for carbon dioxide, were not different in patients with and without exertional dyspnea. Furthermore, the onset of exertional dyspnea was independent of the time to onset of the anaerobic threshold. Thus, the exertional dyspnea felt by patients with heart failure may be different in the characteristics and mechanisms from physiologic breathlessness during exercise.

The exertional dyspnea and change in the ventilation mode in patients with heart failure may be associated with hypoxemia and/or hypercapnia due to exercise-induced pulmonary congestion. However, this is not plausible because arterial blood gas abnormalities are infrequent during exercise in patients with chronic heart failure.

The most likely afferent signal causing exertional dyspnea and the change in ventilation mode is an alteration in mechanical properties of the lung due to pulmonary congestion perceived by pulmonary mechanoreceptors. It has been demonstrated that the pulmonary capillary wedge pressure elevates abnormally from the early phase of exercise in patients with heart failure. This abnormality could be sensed by pulmonary juxtacapillary receptors (J-receptors). Furthermore, the reduced lung distensibility due to congestion gives rise to a decrease in alveolar distention at a given tension generated by respiratory muscles; this discordance may be recognized by the muscle spindles and pulmonary stretch receptors. Respiratory muscle fatigue due to increased respiratory work and reduced blood flow to the respiratory muscles gives rise to a decrease in muscle tension, which may also be sensed by the muscle spindles.

The effect of isosorbide dinitrate appears to support the mechanoreceptor hypothesis. In the present study, improvements in exertional dyspnea and the ventilation mode were observed after the sublingual administration of 5 mg of isosorbide dinitrate in 8 of 17 patients with heart failure (Fig 3). Since the reproducibility of exertional dyspnea and ventilation mode was adequate, these improvements were attributed to the drug effect rather than a placebo or learning effect in the repetitive exercise. Although the pulmonary wedge pressure was not measured in this study, this dose of isosorbide dinitrate has been demonstrated to selectively decrease the filling pressure during exercise in patients with chronic heart failure. Indeed, peak exercise heart rate and systolic blood pressure were not significantly altered by drug administration. Thus, improvements in exertional dyspnea and the ventilation mode with isosorbide dinitrate could be attributed to a reduction in
exercise-induced pulmonary congestion, supporting the mechanoreceptor-mediated mechanism explanation for the development of exertional dyspnea. Although the reason why isosorbide dinitrate failed to elicit appreciable improvements in the remaining nine patients is unclear; the dose of the drug may have been inadequate to lower the filling pressure in these patients.

Direct measurements of pulmonary wedge pressure, lung distensibility, and the tension generated by respiratory muscles during exercise are required to draw a firm conclusion as to mechanisms of exertional dyspnea and the abnormal response of the ventilation mode. However, these parameters may not correlate well with exertional dyspnea, because it is suggested in this study that the symptom of exertional dyspnea is independent of the severity of heart failure (Tables 2 and 3, and Fig 1). Although exercise-induced pulmonary congestion appears to be a primary mechanism of exertional dyspnea, other factors such as a sensitivity or threshold of pulmonary mechanoreceptors or high sensory center may also play an important role in sensing exertional dyspnea.

The physiologic significance of the characteristic change in the ventilation mode during exertional dyspnea remains unclear. However, it is suggested that when the pulmonary distensibility is decreased, rapid and shallow ventilation helps to achieve a given minute ventilation saving the respiratory muscle oxygen consumption. Thus, the rapid and shallow ventilation may result from physiologic adjustments to reduced pulmonary distensibility. Although a reduction in maximal aerobic power is the most important factor of exercise intolerance in patients with chronic heart failure, there is no doubt that exertional dyspnea is also an unpleasant symptom in daily submaximal activity. Thus, it is important to assess exertional dyspnea and the therapeutic efficacy on this symptom of chronic heart failure treatment. The Vf-f relationship proposed in this study may be a simple and useful clinical index for objective evaluation of exertional dyspnea in patients with chronic heart failure.

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