Ventilation/carbon dioxide production ratio in early exercise predicts poor functional capacity in congestive heart failure

R V Milani, M R Mehra, T K Reddy, C J Lavie, H O Ventura

Abstract
Objectives—To evaluate whether changes in the ventilation/carbon dioxide production ratio during early exercise could reliably serve as a surrogate marker for maximal oxygen consumption in heart failure patients. Maximal oxygen consumption is an important determinant of the severity of congestive heart failure, with values > 14 ml/kg/min conferring a good 2-year survival. However, many patients undergoing cardiopulmonary exercise testing cannot exercise maximally because of other functional limitations.

Methods—Ventilation/carbon dioxide production ratio was assessed at rest, anaerobic threshold, and peak exercise in 75 patients with chronic heart failure and in 12 healthy controls. Patients were divided into two groups on the basis of heart failure severity as judged by maximal oxygen consumption.

Results—Patients with mild-moderate heart failure had a 20% reduction in the ventilation/carbon dioxide production ratio at anaerobic threshold similar to that in healthy controls. Patients with severe heart failure failed to reduce this ratio at anaerobic threshold. Furthermore, a reduction in the ventilation/carbon dioxide production ratio in early exercise of less than 10% predicted a maximal oxygen consumption of < 14 ml/kg/min with a positive predictive value of 96% and a negative predictive value of 88%.

Conclusions—A reduction of the ventilation/carbon dioxide production ratio of less than 10% with early exercise reliably predicts poor functional capacity in congestive heart failure. Changes in this ratio during early exercise may be used as a surrogate for maximal oxygen consumption in patients who cannot exercise maximally.

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Keywords: heart failure; oxygen uptake; exercise tolerance; carbon dioxide output

Cardiopulmonary exercise testing is a useful clinical tool in assessing the severity of functional impairment in patients with congestive heart failure.1 Maximal oxygen uptake during exercise (VO₂max) not only allows accurate evaluation of exercise capacity, but has also been shown to be a strong predictor of clinical outcome in patients with heart failure.2 Thus a VO₂max ≤ 14 ml/kg/min is associated with a decreased one year survival of 47% and a two year survival of 32%.3 This important clinical observation has been widely applied in risk stratification of patients with moderate to severe heart failure and is currently used to assess the urgency of considering cardiac transplantation in those patients in whom clinical variables alone are insufficient in predicting prognosis. However, many patients are unable to achieve VO₂max because of severe peripheral muscular deconditioning, low threshold angina, or peripheral vascular disease. Likewise, maximal exercise testing in some patients may lead to severe myocardial ischaemia or malignant dysrhythmias. In such patients a surrogate marker of VO₂max that can be analysed at low thresholds of exercise would be desirable. Carbon dioxide output is closely linked to the regulation of ventilatory function of the lungs during exercise. Minute ventilation and carbon dioxide output are predictably related by the alveolar gas equation, and this relation remains coupled throughout exercise in normal individuals.4 Conversely, although this relation has been reported to become uncoupled in patients with advanced heart failure,5 little is known about the clinical utility of changes in the ventilation/carbon dioxide production ratio in early exercise as it relates to the severity of advanced heart failure. The purpose of our investigation was twofold: first, to establish the clinical utility of measuring the ventilation/carbon dioxide production ratio in early exercise to see whether this variable could serve as a surrogate marker for VO₂max. Second, to stratify patients with heart failure into high and low risk groups based on the ability of the ventilation/carbon dioxide production ratio to predict maximal aerobic capacity.

Patients and methods
PATIENTS
Seventy five consecutive patients with New York Heart Association (NYHA) class II-III heart failure, who were referred for cardiopulmonary exercise testing as part of a heart transplantation evaluation, were prospectively enrolled in the study. The study was approved by the hospital’s institutional review committee and all patients gave informed consent. The cause of heart failure was ischaemic heart disease in 49 patients and dilated cardiomy-
opathy in 26, and all patients had been in heart failure for more than six months. All patients were on stable doses of their medications and had no exacerbation of symptoms or need for intravenous inotropic support for at least four weeks before assessment. Patients were excluded if they exhibited severe peripheral vascular disease, significant muscular deconditioning, low threshold angina, or had orthopaedic limitations preventing them from maximal exercise testing. The average age of the 16 females and 59 males was 51 (11) years (range 22–70 years). A control group of 12 healthy non-smoking, age matched subjects also underwent cardiopulmonary exercise testing. The average age of the 11 males and 1 female was 51 (15) years (range 33–73). These subjects were free of any known cardiopulmonary disease. A third group of eleven patients with NYHA class III–IV heart failure who showed exercise limitations because of significant muscular deconditioning or peripheral vascular disease completed cardiopulmonary exercise testing. These patients were also on stable doses of their medications and had no exacerbation of symptoms or need for intravenous inotropic support for at least four weeks before assessment. The average age of the nine males and two females was 54 (12) years (range 37–71).

CARDIOPULMONARY EXERCISE TESTING

All patients and healthy controls were exercised maximally on a treadmill using an individually tailored ramping treadmill protocol, designed to give a test lasting 8–12 minutes. Patients were encouraged to exercise until symptoms were intolerable. Breath to breath gas analysis was performed on-line using a MedGraphics CPX/D metabolic cart. Incremental data including minute ventilation, oxygen consumption, and carbon dioxide production were collected every 15 seconds. From these data, maximal oxygen consumption, anaerobic threshold, and respiratory exchange ratio were calculated as previously described. VO2max was determined after failure to increase oxygen uptake despite increasing workload. The ventilation/carbon dioxide production ratio was averaged and plotted against time at baseline, anaerobic threshold, and at maximal oxygen consumption. Heart failure patients were divided into two groups, based on VO2max attained, with group 1 (mild to moderate) having a VO2max > 14 ml/kg/min and group 2 (severe) achieving a VO2max ≤ 14 ml/kg/min.

ECHOCARDIOGRAPHY

All subjects underwent standard cross sectional echocardiography within three months of evaluation. Ejection fraction was visually estimated by two experienced echocardiographers in our non-invasive laboratories and reported as the average of the two. Both observers were independently blinded to the review of all data.

STATISTICAL ANALYSIS

Between group analysis was performed with Student’s t test and by chi square analysis. Linear regression using the least squares method was used. F values ≤ 0.05 were taken to be significant. Data are expressed as mean (SD).

Results

PATIENT CHARACTERISTICS

Baseline demographic and clinical characteristics of heart failure patients and healthy controls are outlined in Table 1. Of the cohort of 75 heart failure patients, 43 (57%) were classified as having mild to moderate heart failure (group 1), achieving a VO2max > 14 ml/kg/min (mean 18.5 (2.7), range 14-1 to 27-9 ml/kg/min), and 32 (43%) were classified as having severe heart failure (group 2) with VO2max ≤ 14 ml/kg/min (mean = 11.7 (1.8), range 7.6 to 14.0 ml/kg/min). There were no differences in age, gender, New York Heart Association classification, ejection fraction, or cardiac medications between groups 1 and 2.

VENTILATION/CARBON DIOXIDE PRODUCTION RATIO

Table 2 shows the calculated ventilation/carbon dioxide production ratio at each of the three exercise time points. At rest, there was no difference in the mean ratio for patients in groups 1 and 2 (42.2 (7.0) vs 42.1 (7.9); P = NS), although these were significantly higher than the ratio of 36.4 (4.0) in healthy controls (P < 0.05 compared with both groups 1 and 2). Anaerobic threshold was achieved at 51% of the total exercise time, and the mean ventilation/carbon dioxide production ratio dropped 20% to 29.1 (2.6) (P < 0.0001) in the healthy controls. In group 1, anaerobic threshold occurred at 58% of the total exercise time, and the ratio dropped 20% to 33.7 (5.10) (P < 0.0001). However, in group 2, the ratio fell insignificantly by 5% to 40.1 (7.3); (P = NS) despite the anaerobic threshold occurring.

### Table 1 Baseline demographic and clinical characteristics of heart failure patients in group 1 (VO2max > 14 ml/kg/min) and group 2 (VO2max ≤ 14 ml/kg/min) and in healthy control subjects (mean (SD))

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n = 12)</th>
<th>Group 1 (n = 43)</th>
<th>Group 2 (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>51 (15)</td>
<td>51 (11)</td>
<td>51 (11)</td>
</tr>
<tr>
<td>M/F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.9 (18.0)</td>
<td>85.4 (19.7)</td>
<td>89.3 (22.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.3 (5.8)</td>
<td>27.4 (5.7)</td>
<td>30.0 (5.3)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.60 (0.06)</td>
<td>0.20 (0.07)</td>
<td>0.21 (0.07)</td>
</tr>
<tr>
<td>VO2max, maximal oxygen uptake; NYHA, New York Heart Association.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2 Metabolic variables during exercise in heart failure patients in group 1 (VO2max > 14 ml/kg/min) and group 2 (VO2max ≤ 14 ml/kg/min) and in healthy control subjects (mean (SD))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 12)</th>
<th>Group 1 (n = 43)</th>
<th>Group 2 (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇E/V̇CO2 rest</td>
<td>36.4 (4.0)</td>
<td>42.2 (7.0)</td>
<td>42.1 (7.9)</td>
</tr>
<tr>
<td>V̇E/V̇CO2 AT</td>
<td>29.1 (2.6)</td>
<td>35.7 (5.1)</td>
<td>40.1 (7.3)</td>
</tr>
<tr>
<td>V̇E/V̇CO2 peak</td>
<td>31.2 (4.8)</td>
<td>35.1 (5.3)</td>
<td>40.8 (8.2)</td>
</tr>
<tr>
<td>Δ V̇E/V̇CO2 rest to AT (%)</td>
<td>20.0</td>
<td>-20.0</td>
<td>-5</td>
</tr>
<tr>
<td>VO2 AT (ml/kg/min)</td>
<td>19.6 (6.3)</td>
<td>13.1 (2.3)</td>
<td>9.1 (2.1)</td>
</tr>
<tr>
<td>AT time/total exercise time (%)</td>
<td>51</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>VO2max (ml/kg/min)</td>
<td>29.7 (7.9)</td>
<td>18.5 (2.7)</td>
<td>11.7 (1.8)</td>
</tr>
</tbody>
</table>

V̇E/V̇CO2 ventilation/carbon dioxide production ratio; AT, anaerobic threshold; VO2 AT, oxygen uptake at anaerobic threshold; VO2max, maximal oxygen uptake; *P < 0.0001.
Ventilation/carbon dioxide production ratio in early exercise predicts poor functional capacity in congestive heart failure

**Results**

Ventilation/carbon dioxide production ratio during early exercise in heart failure patients with exercise limitations, 11 patients with these limitations were assessed. All patients in this group achieved anaerobic threshold; however, the mean total exercise time was significantly impaired (5-9 (0-7) minutes). The mean ventilation/carbon dioxide production ratio fell by 16 (9)% for the group. Although the mean peak VO$_2$ was 11-1 (2-6) ml/kg/min for the group, seven patients achieved a reduction in the ventilation/carbon dioxide production ratio of greater than 10% (mean = 21 (5%).

**Discussion**

The results of our study demonstrate that changes in the ventilation/carbon dioxide production ratio with early exercise predict severity of congestive heart failure as judged by maximal oxygen consumption. Furthermore, lack of a 10% decrease in the ventilation/carbon dioxide production ratio from rest to anaerobic threshold identifies heart failure patients with severely impaired aerobic capacity (VO$_2$max $\leq$ 14 ml/kg/min) with a sensitivity of 81% and specificity of 98%. Thus, early measurement of ventilation/carbon dioxide production ratio reliably stratifies patients with heart failure by predicting high and low maximum oxygen consumption, a finding of particular importance in patients who fail to achieve peak aerobic capacity. The relation between ventilation and carbon dioxide production during exercise varies with the arterial carbon dioxide and the dead space fraction.

**Results in Patients with Exercise Limitations**

To test the validity of using the ventilation/carbon dioxide production ratio during early exercise in heart failure patients with exercise limitations, 11 patients with these limitations were assessed. All patients in this group achieved anaerobic threshold; however, the mean total exercise time was significantly impaired (5-9 (0-7) minutes). The mean ventilation/carbon dioxide production ratio fell by 16 (9)% for the group. Although the mean peak VO$_2$ was 11-1 (2-6) ml/kg/min for the group, seven patients achieved a reduction in the ventilation/carbon dioxide production ratio of greater than 10% (mean = 21 (5%).

**Ventilation/Carbon Dioxide Production Ratio and Prediction of VO$_2$max**

The relation between change in the ventilation/carbon dioxide production ratio during early exercise and maximal oxygen consumption was relatively linear in the heart failure patients ($r = 0.65$; $p < 0.0001$) (fig 2). Twenty six (81%) of the 32 group 2 patients demonstrated a reduction of the ventilation/carbon dioxide production ratio of less than 10%, whereas, 42 (98%) of the 43 group 1 patients had a ratio reduction of greater than 10%.

**Limitations**

To test the validity of using the ventilation/carbon dioxide production ratio during early exercise in heart failure patients with exercise limitations, 11 patients with these limitations were assessed. All patients in this group achieved anaerobic threshold; however, the mean total exercise time was significantly impaired (5-9 (0-7) minutes). The mean ventilation/carbon dioxide production ratio fell by 16 (9)% for the group. Although the mean peak VO$_2$ was 11-1 (2-6) ml/kg/min for the group, seven patients achieved a reduction in the ventilation/carbon dioxide production ratio of greater than 10% (mean = 21 (5%).

**Figure 1 Changes** in ventilation/carbon dioxide production ratio (VE/VECO$_2$) at baseline, anaerobic threshold, and peak exercise in healthy controls (n = 12), patients with mild-moderate heart failure (group 1 (n = 43): VO$_2$max > 14 ml/kg/min), and in patients with severe heart failure (group 2 (n = 32): VO$_2$max $\leq$ 14 ml/kg/min).

At 58% of total exercise. Although, there was no difference in the ventilation/carbon dioxide production ratio between heart failure groups at baseline, this relation became widely disparate at both anaerobic threshold (33-7 (5-1) vs 40-1 (7-3), $P < 0.0001$) and at VO$_2$max (35-1 (5-3) vs 40-8 (8-2), $P < 0.001$) in groups 1 and 2 respectively (fig 1).

**Figure 2 Relation between the reduction in ventilation/carbon dioxide production ratio (VE/VECO$_2$) with early exercise and the severity of heart failure as determined by maximal oxygen uptake (VO$_2$max) in 75 heart failure patients.**

$r = 0.65$

$P < 0.0001$
ment of $\text{VO}_{2\max}$ is clearly desirable for assessment of prognosis in heart failure, several limitations are often present that preclude its successful determination. These limitations include low threshold angina, peripheral vascular disease, orthopaedic impairments, and skeletal muscle atrophy. Although, the prevalence of each of these conditions varies in patients with heart failure, skeletal muscle atrophy seems to be relatively common and can significantly impair exercise capacity. Indeed, in a study evaluating the prevalence of skeletal muscle atrophy in heart failure, a significant diminution in muscle mass was found in 68% of 62 patients evaluated, and this directly correlated with peak exercise oxygen consumption. Furthermore, in a study of 57 heart failure patients, Drexler et al found a significant reduction in the mitochondrial density of skeletal muscle, which correlated to the duration of heart failure as well as the maximal oxygen consumption. These data reveal that the reduced density and oxidative capacity of skeletal muscle in heart failure is a prevalent finding, especially in long standing heart failure, and would significantly reduce exercise capacity and the ability to attain $\text{VO}_{2\max}$. Our study enables the clinician to evaluate indirectly peak aerobic capacity by early changes in the ventilation/carbon dioxide production ratio response and might allow prognostic assessment based on peak aerobic capacity in patients who fail to achieve $\text{VO}_{2\max}$. Indeed, this investigation demonstrates that a less than 10% decrease in the ventilation/carbon dioxide production ratio from rest to anaerobic threshold correctly identifies heart failure patients with severely impaired aerobic capacity ($\text{VO}_{2\max} \leq 14 \text{ ml/kg/min}$) with a positive predictive value of 96% and a negative predictive value of 88%. In conclusion, changes in the ventilation/carbon dioxide production ratio with early exercise predict severity of congestive heart failure as judged by maximal oxygen consumption. These findings might be useful to provide prognostic risk stratification of patients with chronic heart failure, a finding of particular relevance in the many patients who cannot achieve maximal aerobic capacity.

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