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 confering 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 then 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.**

(*Heart* 1996;**76**:393–396)

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

Department of Internal Medicine, Section on Cardiology, Cardiovascular Health Center, Ochsner Heart and Vascular Institute, Ochsner Medical Institutions, New Orleans, Louisiana, USA
R V Milani
M R Mehra
T K Reddy
C J Lavie
H O Ventura

Correspondence to:
Dr R V Milani, Section on Cardiology, Ochsner Medical Institutions, 1514 Jefferson Highway, New Orleans, LA 70121, USA.

Accepted for publication 3 May 1996

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 (VO_{2max}) 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 $VO_{2max} \leqslant 14$ 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 VO_{2max} 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 VO_{2max} 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 VO_{2max}. 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 cardiomyopathy 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 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 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.[6] 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.[7] VO_{2max} 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 in to two groups, based on VO_{2max} attained, with group 1 (mild to moderate) having a $VO_{2max} > 14$ ml/kg/min and group 2 (severe) achieving a $VO_{2max} \leqslant 14$ 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.[8 9] 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. P values $\leqslant 0.05$ 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 $VO_{2max} > 14$ 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 a $VO_{2max} \leqslant 14$ 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) v 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 (VO_{2max} > 14 ml/kg/min) and group 2 ($VO_{2max} \leqslant$ 14 ml/kg/min) and in healthy control subjects (mean (SD))

Characteristic	Controls (n = 12)	Group 1 (n = 43)	Group 2 (n = 32)
Age (y)	51 (15)	51 (11)	51 (11)
M/F	11/1	36/7	23/9
Weight (kg)	88·9 (18·0)	83·5 (19·7)	89·3 (22·4)
Body mass index (kg/m²)	30·3 (5·8)	27·6 (5·7)	30·0 (5·3)
NYHA class	—	2·7 (0·5)	2·8 (0·4)
Ejection fraction	0·60 (0·06)	0·20 (0·07)	0·21 (0·07)

VO_{2max}, maximal oxygen uptake; NYHA, New York Heart Association.

Table 2 Metabolic variables during exercise in heart failure patients in group 1 (VO_{2max} > 14 ml/kg/min) and group 2 ($VO_{2max} \leqslant$ 14 ml/kg/min) and in healthy control subjects (mean (SD))

Variable	Controls (n = 12)	Group 1 (n = 43)	Group 2 (n = 32)
V_E/VCO_2 rest	36·4 (4·0)	42·2 (7·0)	42·1 (7·9)
V_E/VCO_2 AT	29·1 (2·6)	33·7 (5·1)	40·1 (7·3)
V_E/VCO_2 peak	31·2 (4·8)	35·1 (5·3)	40·8 (8·2)
$\Delta V_E/VCO_2$ rest to AT (%)	−20*	−20*	−5
VO_2 AT (ml/kg/min)	19·6 (6·3)	13·1 (2·3)	9·1 (2·1)
AT time/total exercise time (%)	51	58	58
VO_{2max} (ml/kg/min)	29·7 (7·9)	18·5 (2·7)	11·7 (1·8)

V_E/VCO_2, ventilation/carbon dioxide production ratio; AT, anaerobic threshold; VO_2 AT, oxygen uptake at anaerobic threshold; VO_{2max}, maximal oxygen uptake; *P < 0·0001.

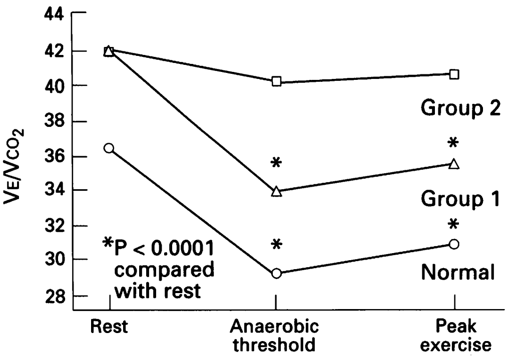

Figure 1 Changes in ventilation/carbon dioxide production ratio (V_E/VCO_2) at baseline, anaerobic threshold, and peak exercise in healthy controls (n = 12), patients with mild–moderate heart failure (group 1 (n = 43): VO_{2max} > 14 ml/kg/min), and in patients with severe heart failure (group 2 (n = 32): $VO_{2max} \leqslant 14$ 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) *v* 40·1 (7·3), P < 0·0001) and at VO_{2max} (35·1 (5·3) *v* 40·8 (8·2), P < 0·001) in groups 1 and 2 respectively (fig 1).

VENTILATION/CARBON DIOXIDE PRODUCTION RATIO AND PREDICTION OF VO_{2max}

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%.

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%)).

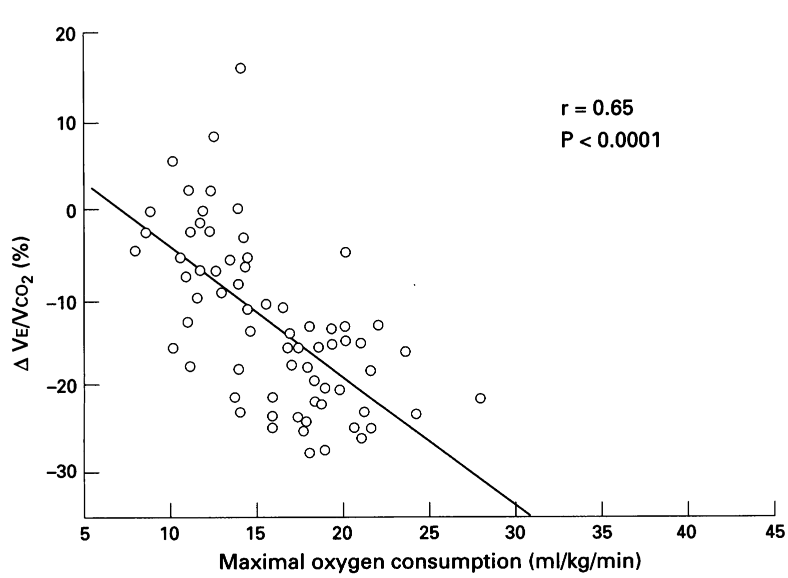

Figure 2 Relation between the reduction in ventilation/carbon dioxide production ratio (V_E/VCO_2) with early exercise and the severity of heart failure as determined by maximal oxygen uptake (VO_{2max}) in 75 heart failure patients.

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 ($VO_{2max} \leqslant 14$ 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.[4] Normal subjects (as in our healthy controls) demonstrate a decrease in the ventilation/carbon dioxide production ratio at the onset of exercise and thereafter a small increase in the ratio towards the end of peak exercise. While the former may reflect an increase in arterial carbon dioxide or a decrease in the dead space fraction, the latter may result from either an increase in the dead space fraction or another drive to ventilation resulting in a decrease in arterial carbon dioxide.[5,10] The response of the ventilation/carbon dioxide production ratio to exercise in patients with heart failure, however, has been found to be highly variable.[11-13] A previous study by Clark *et al* described three distinct patterns of ventilation/carbon dioxide production ratio response to exercise in a group of 29 patients with varying degrees of heart failure.[5] While their study concluded that these patterns correlated with heart failure severity, their measure of severity was exercise time alone, and not maximal oxygen consumption, a more clinically relevant measure of prognosis. Furthermore, the assessment of an adequate ventilation/carbon dioxide production ratio response pattern was based on the prerequisite of completion of maximal exercise. Our findings lend support to these prior observations and further demonstrate that assessment of this ratio not only risk stratifies patients with heart failure based on the clinically meaningful variable of VO_{2max}, but also suggest that this can be reliably achieved even at submaximal exercise. While attainment of VO_{2max} 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.[14] 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.[15] 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 VO_{2max}. 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 VO_{2max}. 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 ($VO_{2max} \leqslant 14$ 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.

We thank Barbara Hand who assisted with data collection for this study.

1 Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. *Am J Cardiol* 1985;**55**:22A–31A.
2 Cohn JN, Archibald DG, Francis GS, *et al.* Veterans administration cooperative study on vasodilator therapy of heart failure: influence of prerandomization variables on the reduction of mortality by treatment with hydralazine and isosorbide dinitrate. *Circulation* 1987;**75**: IV49–54.
3 Manicni DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; **83**:778–86.
4 Whipp BJ, Ward SA, Wasserman K. Ventilatory responses to exercise and their control in man. *Am Rev Resp Dis* 1984;**129**:S17–20.
5 Clark AL, Poole-Wilson PA, Coats AJS. Relation between ventilation and carbon dioxide production in patients with congestive heart failure. *J Am Coll Cardiol* 1992;**20**: 1326–32.
6 Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Hamilton-Wessler M, Froelicher V. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol* 1991;**17**:1334–42.
7 Wasserman K. New concepts in assessing cardiovascular function. *Circulation* 1988;**78**:1060–71.
8 Rich S, Shiekh A, Gallastegui J, Kondos GT, Mason T, Lam W. Determination of left ventricular ejection fraction by visual estimation during real-time two-dimensional echocardiography. *Am Heart J* 1982;**104**:603–6.
9 Amico AF, Lichtenberg GS, Reisner SA, Stone CK, Schwartz RG, Meltzer RS. Superiority of visual versus computerized echocardiographic estimation of radionuclide left ventricular ejection fraction. *Am Heart J* 1989;**118**:1259–65.
10 Rajfer SI, Nemanich JW, Shurman AJ, Rossen JD. Metabolic responses to exercise in patients with heart failure. *Circulation* 1987;**76**:VI46–53.
11 Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation in patients with chronic cardiac failure. *Circulation* 1982;**65**:1213–23.
12 Buller NP, Poole-Wilson PA. Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. *Br Heart J* 1990;**63**:281–3.
13 Sullivan MJ, Higginbotham MB, Cobb FR. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation* 1988;**77**:552–9.
14 Mancini DM, Walter G, Reichek N, *et al.* Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation* 1992;**85**:1364–73.
15 Drexler H, Riede U, Münzel T, König H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. *Circulation* 1992;**85**:1751–9.