Prognostic value of changes over time in exercise capacity and echocardiographic measurements in patients with chronic heart failure

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Aims This study sought to examine the predictive values of changes over time in exercise capacity and echocardiographic measurements of ventricular dimensions or function in predicting mortality in patients with chronic heart failure.

Methods and Results Sixty-two patients with chronic heart failure (58 men, mean [± SD] age 60 ± 10 years, mean peak oxygen consumption (VO2) 18.2 ± 5.9 ml kg⁻¹ min⁻¹, mean left ventricular ejection fraction 38.9 ± 15.8%) who underwent both treadmill exercise testing and echocardiographic examination on two occasions, separated by 19 ± 11 months were followed-up for a mean of 17 months (interquartile range 9–30 months). During the follow-up period, 19 patients (30%) died and three (4.8%) underwent heart transplantation. Of measurements taken at a single time-point (visit 2) exercise duration, peak VO2, ventilatory response to exercise (VE/VCO2), left atrial diameter and left ventricular ejection fraction were found, by Cox proportional-hazard analysis, to predict the outcome in these patients (all P<0.05). Of the changes in parameters between visit 1 to visit 2, only changes in peak VO2 per year (P=0.026) predicted non-transplanted survival (independent of changes in left ventricular ejection fraction and VE/VCO2). In Kaplan–Meier survival analysis patients with increased peak VO2 over time (n=28) showed a better prognosis at 2 years (cumulative survival 75% [95% confidence interval: 56–95%]) than those with a decrease in peak VO2 (n=34, cumulative survival 50% [95% confidence interval: 31–68%]).

Conclusions Although single estimates of peak VO2, VE/VCO2 and left ventricular ejection fraction have significant prognostic importance in patients with chronic heart failure, when monitoring changes over time only peak VO2 remains a significant predictor of outcome.

Key Words: chronic heart failure, prognosis, exercise capacity, haemodynamics.

See page 98 for the Editorial comment on this article

Introduction

Chronic heart failure is a common clinical problem with a poor prognosis[1–2]. Analysis of factors that further determine prognosis within this population have identified peak oxygen consumption (VO2)[3–6] and left ventricular ejection fraction[3,7,8] as the most important independent predictors of mortality.

A single measurement of peak VO2 or left ventricular ejection fraction provides important prognostic information; however, these parameters may vary throughout the course of the disease or as a result of the therapeutic interventions. Few data exist as to how these variables change over time, or how changes from a given baseline may be used to assess the subsequent clinical course or predict survival. Even within the limited data available, there are varying results. Stevenson et al[9] reported that among patients with peak VO2 values less than 14 ml kg⁻¹ min⁻¹, listed for transplantation, those whose values improved by more than 2 ml kg⁻¹ min⁻¹ during follow-up showed a 100%...
2-year survival rate and could be safely removed from
the transplant list. Recently, Gullestad et al. [10] reported
that changes in peak VO$_2$, left ventricular dimensions
and ejection fraction did not add any prognostic infor-
mation in patients considered for cardiac transplanta-
tion. The present study aims to address this issue and
was undertaken to investigate the value of changes over
time in exercise capacity and echocardiographic
measurements of cardiac size or function in predicting
outcome in patients with chronic heart failure.

**Methods**

**Patients**

We studied 62 patients (58 men and four women) with
chronic heart failure, caused by ischaemic heart disease
in 35 patients and dilated cardiomyopathy in 27
patients. They ranged in age from 38 to 89 years (mean
age 60±10 years). Initially, 19 patients were in New
York Heart Association functional (NYHA) class I, 18
in class II, 17 in class III and the remaining 6 were in
class IV. The presence of ischaemic heart disease was
shown by coronary arteriography or documentation of a
myocardial infarction. Patients were classified as having
dilated cardiomyopathy if normal coronary arteries were
demonstrated on coronary angiography. The medical
regimens of all the enrolled patients were optimized and
they were all symptomatically stable. Standardized
medical treatment between the
first and second exami-
nations included angiotensin converting enzyme inhibi-
tors, diuretics, nitrates, digitalis and warfarin in varying
combinations.

**Echocardiography**

Standard left ventricular minor axis recordings were
obtained from the left parasternal long axis view with the
cursor by the tips of mitral valve leaflets and in the
semi-lateral position, during quiet expiration. Left ven-
tricular dimensions were taken at end-diastole (onset of
the Q wave of the ECG) and end-systole (first high
frequency component of the second heart sound on a
superimposed phonocardiogram). Fractional shortening
was calculated as the percentage systolic fall in left
ventricular dimension with respect to end-diastolic.
Ejection fraction was also calculated in the same way
using the standard dimensions cubed formula:

$$Ejection\ fraction = \frac{EDD^3 - ESD^3}{EDD^3}$$

where EDD is end-diastolic diameter and ESD is
der-end-systolic diameter.

Left ventricular diastolic measurements included
M-mode isovolumic relaxation time, transmitral peak E
to peak A (E/A) ratio and mitral E-wave deceleration
time. Isovolumic relaxation time was taken as the time
interval between the onset of A$_2$, the second heart sound
at the phonocardiogram and mitral cusp separating
point. The E/A ratio was obtained from the pulsed
Doppler recordings of early and late transmitral flow
velocities taken from the four-chamber view with the
sample volume adjacent to the tips of mitral valve

![Figure 1](image-url) **Study flow chart. C=clinical examination; CPX=cardiopulmonary exer-
cise testing; Echo=echocardiography.**

**Exercise protocol**

A standard Bruce protocol was used with the addition of a
‘stage 0’ consisting of 3 min at a speed of 1 mile per hour
with a 5% gradient. Minute ventilation, oxygen
consumption and carbon dioxide production were cal-
culated on-line every 10 s using a standard inert gas
dilution technique (Amis 2000, Odense, Denmark). Patients
were encouraged to exercise to exhaustion. All
exercise tests were performed on the patients while on a
stable medical regimen. Patients who were limited by
angina or claudication symptoms were not included in
the study.
Table 1  Summary of exercise and echocardiographic data for all groups (means ± SD)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Non-transplanted survivors</th>
<th>Dead or transplanted</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>62</td>
<td>40</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age, months</td>
<td>60.1 ± 9.9</td>
<td>58.6 ± 9.2</td>
<td>62.6 ± 10.8</td>
<td>ns</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>18.9 ± 12.6</td>
<td>22.1 ± 13.4</td>
<td>13.1 ± 8.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, min</td>
<td>Visit 1: 7.8 ± 2.9</td>
<td>8.0 ± 2.6</td>
<td>7.5 ± 3.5</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Visit 2: 7.6 ± 3.8</td>
<td>8.7 ± 3.7</td>
<td>5.5 ± 3.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak VO₂, ml . kg⁻¹ . min⁻¹</td>
<td>Visit 1: 18.2 ± 5.9</td>
<td>18.1 ± 5.1</td>
<td>18.3 ± 7.4</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Visit 2: 18.3 ± 8.1</td>
<td>20.8 ± 8.6*</td>
<td>13.9 ± 4.4*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AT, ml . kg⁻¹ . min⁻¹</td>
<td>Visit 1: 11.6 ± 3.4</td>
<td>11.5 ± 3.4</td>
<td>11.7 ± 3.6</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Visit 2: 11.7 ± 4.9</td>
<td>11.7 ± 3.8</td>
<td>11.6 ± 7.5</td>
<td>ns</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>Visit 1: 37.9 ± 11.1</td>
<td>34.3 ± 8.4</td>
<td>44.4 ± 12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Visit 2: 40.9 ± 14.5</td>
<td>35.9 ± 12.6</td>
<td>50.0 ± 13.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Echocardiography slope</td>
<td>LAD, mm</td>
<td>Visit 1: 45.8 ± 9.0</td>
<td>44.6 ± 9.0</td>
<td>48.5 ± 8.7</td>
</tr>
<tr>
<td></td>
<td>LVEDD, mm</td>
<td>Visit 2: 46.6 ± 9.3</td>
<td>44.5 ± 8.6</td>
<td>51.1 ± 9.3*</td>
</tr>
<tr>
<td></td>
<td>LVEDS, mm</td>
<td>Visit 1: 68.9 ± 10.0</td>
<td>68.8 ± 10.2</td>
<td>69.3 ± 9.7</td>
</tr>
<tr>
<td></td>
<td>LVEF, %</td>
<td>Visit 2: 65.0 ± 12.0</td>
<td>65.5 ± 12.5</td>
<td>71.0 ± 10.7</td>
</tr>
<tr>
<td></td>
<td>IVRT, ms</td>
<td>Visit 1: 58.4 ± 11.7</td>
<td>57.4 ± 12.7</td>
<td>60.0 ± 9.9</td>
</tr>
<tr>
<td></td>
<td>E/A ratio</td>
<td>Visit 2: 56.3 ± 14.2</td>
<td>54.9 ± 14.9*</td>
<td>60.8 ± 11.9</td>
</tr>
<tr>
<td></td>
<td>E-DT, ms</td>
<td>Visit 1: 38.9 ± 15.8</td>
<td>41.1 ± 17.7</td>
<td>34.9 ± 10.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visit 2: 43.6 ± 16.2*</td>
<td>47.1 ± 16.8*</td>
<td>37.1 ± 12.8</td>
</tr>
</tbody>
</table>

AT=anaerobic threshold; VE/VCO₂ slope=ventilatory response to exercise; LAD=left atrial diameter; LVEDD=left ventricular end-diastolic diameter; LVEDS=left ventricular end-systolic diameter; LVEF=left ventricular ejection fraction; IVRT=isovolumic relaxation time; E/A ratio=ratio between early and late transmitral flow velocities; E-DT=E-wave deceleration time; *P<0.05 between final and initial examination points; ns=not significant.

leaflets. The mitral E-wave deceleration time was measured from the peak of the E wave to its end.

Statistical analysis

ANOVA techniques were used to analyse the relationship of changes in studied parameters with baseline variables. A paired t-test was used to compare the results of the first and second assessments. Differences between group means were compared by unpaired t-test. Survival curves were constructed using the Kaplan–Meier product limit method when the patients were dichotomized by the direction of change in each physiological value (increase vs decrease). Cox’s proportional-hazards regression analysis was used to identify continuous independent variables predictive of survival. For all tests, a P value less than 0.05 was considered statistically significant. Values are expressed as mean ± SD. Statistical analysis was performed using a standard statistical program package (StatView, version 4.5; Abacus Concepts).

Results

During the mean 17 months follow-up (range 4–61 months) after the second evaluation 19 (30.6%) patients died and three (4.8%) underwent cardiac transplantation. A summary of the main exercise and echocardiographic data for all 62 patients and for subgroups of non-transplanted survivors and dead/transplanted patients is presented in Table 1.

At first examination, the group as a whole had mild-to-moderate ventricular dysfunction indicated by the mean left ventricular ejection fraction of 38.9 ± 15.8%. The few patients with only mildly impaired ejection fraction, nevertheless, had symptomatic evidence of heart failure. The mean values of peak VO₂ in the whole group of patients was 18.2 ± 5.9 ml . kg⁻¹ . min⁻¹ indicating moderate impairment of functional capacity. At this examination non-transplanted survivors did not differ significantly from dead/transplanted patients with respect to age, peak VO₂, anaerobic threshold or echocardiographically determined cardiac dimensions or function. However, the ventilatory response to exercise at initial examination was significantly higher in the dead/transplanted patients compared with non-transplanted survivors (44.4 ± 12.5 vs 34.3 ± 8.4, P<0.001).

During the study interval between the first and second examinations in the patient population as a whole, left ventricular dimensions showed no consistent change, although ejection fraction increased slightly from
Changes in peak VO$_2$ and survival in heart failure

Table 2 Results of univariate Cox proportional-hazard regression analysis of exercise and echocardiographic variables using either data from the second examination or rates of change of these variables per year in 62 patients with chronic heart failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values at second examination</th>
<th>Rate of change per year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\chi^2$</td>
<td>P-value</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>11.16</td>
<td>0.01</td>
</tr>
<tr>
<td>Peak VO$_2$</td>
<td>10.46</td>
<td>0.01</td>
</tr>
<tr>
<td>VE/VCO$_2$ slope</td>
<td>26.95</td>
<td>0.01</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>13.30</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEDD</td>
<td>2.90</td>
<td>0.09</td>
</tr>
<tr>
<td>LVESD</td>
<td>3.70</td>
<td>0.05</td>
</tr>
<tr>
<td>LVEF</td>
<td>4.64</td>
<td>0.03</td>
</tr>
<tr>
<td>IVRT</td>
<td>0.83</td>
<td>0.36</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.51</td>
<td>0.22</td>
</tr>
<tr>
<td>E-DT</td>
<td>0.5</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Abbreviations are as in Table 1.

38.9 ± 15.8% to 43.6 ± 16.2%, P < 0.03. Comparing the subgroups of patients, there was a slight but significant increase in exercise capacity as assessed by peak VO$_2$ among non-transplanted survivors (20.8 ± 8.6 vs 18.1 ± 5.1 mL kg$^{-1}$ min$^{-1}$, P < 0.05). At the same time interval, the subgroup of dead/transplanted patients significantly decreased peak VO$_2$ (13.9 ± 4.4 vs 18.3 ± 7.4 mL kg$^{-1}$ min$^{-1}$, P < 0.03) accompanied by a significant increase in left atrial diameter (51.1 ± 9.3 vs 48.5 ± 8.7 mm, P < 0.05).

There were some significant differences in exercise and echocardiographic parameters between the studied groups at the time of the second examination. Exercise capacity was significantly higher in the non-transplanted survivors as indicated by exercise duration (8.7 ± 3.7 min vs 5.5 ± 3.1 min, P < 0.01), peak VO$_2$ (20.8 ± 8.6 mL kg$^{-1}$ min$^{-1}$ vs 13.8 ± 4.4 mL kg$^{-1}$ min$^{-1}$, P < 0.001) and VE/VCO$_2$ slope (35.9 ± 12.6 vs 50.0 ± 13.3, P < 0.001). This group was also characterized by a significantly higher left ventricular ejection fraction (47.1 ± 16.8% vs 37.1 ± 12.8%, P < 0.03) and a smaller left atrial diameter (44.5 ± 8.6 mm vs 51.1 ± 9.3 mm, P < 0.02).

The results of univariate Cox proportional-hazard regression analysis of exercise and echocardiographic variables at the second examination and time-adjusted changes of these variables per year are presented in Table 2. The absolute values of exercise duration (P = 0.001), peak VO$_2$ (P = 0.001), VE/VCO$_2$ slope (P = 0.0001), left atrial diameter (P = 0.0003) and left ventricular ejection fraction (P = 0.031) at the second examination were found to be predictive of outcome in the patient population, and of the time-adjusted parameters only changes in peak VO$_2$ per year were found to be a statistically significant (P = 0.026) predictor of outcome. In multivariate analysis (Table 3) the value of the VE/VCO$_2$ slope at the time of the second examination was found to be the most important predictor of outcome, independent of peak VO$_2$ and left ventricular ejection fraction. At the same time changes in peak VO$_2$ per year were found to predict outcome independent of changes in the VE/VCO$_2$ slope and left ventricular ejection fraction.

In between the first test and the second, in 28 (45.2%) of the patients peak VO$_2$ had increased whereas in 34 (54.8%) it had decreased.

Figure 2 gives the survival Kaplan–Meier curves of the patients categorized by the direction of changes in peak VO$_2$ over time. Patients with increased peak VO$_2$ over time (n = 28, mean $\pm$ 7.7 ± 8.3 mL kg$^{-1}$ min$^{-1}$) showed a better prognosis at 2 years (cumulative survival 75% [95% confidence interval: 56–95%] than those with a decrease in peak VO$_2$ (n = 34, mean $\pm$ 4.8 ± 5.4 mL kg$^{-1}$ min$^{-1}$ year$^{-1}$; cumulative survival 50% [95% confidence interval: 31–68%]).

**Discussion**

It is currently widely accepted that peak VO$_2$ and left ventricular ejection fraction have significant prognostic importance in patients with heart failure. This is confirmed in our study. However, when the rates of change of exercise and echocardiographic parameters over time were considered, only the rate of change of peak VO$_2$ was a significant outcome predictor. Another finding of this study was that the values of the slope relating ventilation and carbon dioxide production (Ve/VCO$_2$ slope) predicted outcome in these patients better than those of peak VO$_2$ or left ventricular ejection fraction.

Numerous studies have attempted to address the problem of identifying prognostic factors among the
variables collected in patients with chronic heart failure. Although several indicators of functional clinical status, exercise criteria\[^{1,3,5,12-14}\] and haemodynamic function\[^{6,7,15,16}\] have been found to be more or less strongly and independently related to survival in these patients, most of these studies have analysed exercise criteria and left ventricular performance data at a single time point.

The present study addressed a group of 62 patients with mild to moderate heart failure (peak VO\(_2\) 18·2 ml kg\(^{-1}\) min\(^{-1}\) and left ventricular ejection fraction 38\%\(^{-}\)). Even in this small sample size, several exercise and haemodynamic variables were significantly related to the prognosis when the end point was either death or transplantation: exercise duration, peak VO\(_2\), VE/VCO\(_2\) slope, left atrial chamber and left ventricular ejection fraction. These results add to the consensus from other studies that peak VO\(_2\)\[^{3-6}\] and left ventricular ejection fraction\[^{3,7,8,17}\] are among the most important predictors of prognosis.

The main aim of this study was to obtain guidance in the clinical interpretation of changes in the medium term in exercise capacity and echocardiographic measurements of cardiac size and function in patients with chronic heart failure. Levine \textit{et al.}\[^{18}\] observed that

Table 3 Results of multivariate Cox proportional-hazard regression analysis of exercise and echocardiographic variables using either data from the second examination point or rates of change of these variables per year in 62 patients with chronic heart failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values at second examination</th>
<th>Rate of change per year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\chi^2)</td>
<td>(P)-value</td>
</tr>
<tr>
<td>Peak VO(_2) and VE/VCO(_2) slope</td>
<td></td>
<td></td>
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<tr>
<td>Peak VO(_2), ml kg(^{-1}) min(^{-1})</td>
<td>0·89</td>
<td>0·34</td>
</tr>
<tr>
<td>VE/VCO(_2) slope</td>
<td>11·65</td>
<td>0·01</td>
</tr>
<tr>
<td>Peak VO(_2) and LVEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO(_2), ml kg(^{-1}) min(^{-1})</td>
<td>8·81</td>
<td>0·01</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>3·06</td>
<td>0·08</td>
</tr>
<tr>
<td>Peak VO(_2) and VE/VCO(_2) and LVEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO(_2), ml kg(^{-1}) min(^{-1})</td>
<td>1·00</td>
<td>0·31</td>
</tr>
<tr>
<td>VE/VCO(_2) slope</td>
<td>7·92</td>
<td>0·01</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0·28</td>
<td>0·59</td>
</tr>
</tbody>
</table>

Abbreviations are as in Table 1.
outcome of patients on a transplant waiting list could not be predicted from the patient’s initial screening examination. Patients with the most favourable outcome showed clinical and haemodynamic improvement over approximately 2 years, in contrast to those who died or needed transplantation[18]. Stevenson et al.[19] recently reported that of 107 patients with a peak VO₂ more than 14 ml kg⁻¹ min⁻¹ who had been listed for transplantation, 31 increased their peak VO₂ by at least 2 ml kg⁻¹ min⁻¹ accompanied by a stable clinical status. These patients were removed from the waiting list and exhibited a short-term survival not different from patients who had received heart transplantation. These findings are in contrast with those of Gulleston et al.[10] in that there were no significant differences in outcome between those who increased vs those who decreased their peak VO₂. The reason for these discrepant results may be the result of patient selection and the specific treatment regimen. The patients enrolled in these studies had severe heart failure and were listed for cardiac transplantation or were under serious consideration for transplantation.

In the present study, the patients had milder heart failure (mean ejection fraction 39%), perhaps more representative of the general outpatient population. Moreover, we determined the change in the studied variables per year, in order to standardize the time evaluation. Our results are consistent with the data of Stevenson et al.[19] in that the increase in peak VO₂ over time is associated with better prognosis in patients with chronic heart failure. These results support the new accepted indications for cardiac transplantation that are focused now on peak oxygen uptake and some specific clinical features, such as severe ischaemia and refractory symptomatic ventricular arrhythmias, rather than the previous more general guidelines that concentrated on ejection fraction and the New York Heart Association classification[19,20].

It is also unclear whether serial measurements of left ventricular variables of size or function have any impact on later prognosis in patients with heart failure. Changes in left ventricular ejection fraction have been reported by Cintron et al.[17] to affect outcome in patients with congestive heart failure. However, those authors point out that the results may not represent the true progression of the disease because the measurements began after randomization in a trial. Konstam et al.[21] in a subset of the SOLVD study demonstrated that the natural course of heart failure included a progressive increase in left ventricular cavity size and that this could be prevented or reversed by long-term angiotensin converting enzyme inhibition, but whether this was directly associated with altered prognosis was not assessed. The results of the present study are consistent with those of Gulleston et al.[19] in that changes in left ventricular dimensions and ejection fraction do not yield prognostic information in clinically stable patients with chronic heart failure.

The prognostic value of diastolic abnormalities as assessed by Doppler echocardiography has yet to be defined. Several studies have found the mitral deceleration time and the E/A ratio to correlate with long-term survival in patients with left ventricular dysfunction[22–24]. Few data exist as to how changes over time in quantitative impressions of overall left ventricular diastolic function are related to the outcomes in these patients. Traversi et al.[25] found changes in mitral flow patterns after chronic optimized therapy provided independent prognostic information. More recently, Temporelli et al.[26] reported that prolongation of an initially short transmitral deceleration time of early filling predicts a more favourable outcome in clinically stable patients with chronic heart failure. In our study neither changes over time in the deceleration time of early left ventricular filling, isovolumic relaxation time nor changes in the E/A ratio yielded prognostic information.

An additional finding of this study is the predictive value of the slope relating ventilation and carbon dioxide production. This ventilatory response to exercise has received much attention in recent years. A greater minute volume at a given level of carbon dioxide production reflects the severity of the ventilatory abnormality in chronic heart failure and strongly correlates with exercise capacity in these patients[27]. Studying the mechanisms underlying this inefficient ventilation, Sullivan et al.[28] suggested that increased dead space ventilation due to impaired lung perfusion might play a role. This result was supported by Metra et al.[29], who found dead space fraction to be the only independent correlate of the VE/VCO₂ slope. The recent results of our group demonstrated that chemosensitivity is increased in patients with chronic heart failure[30]. This augmented chemosensitivity was correlated with the VE/VCO₂ slope and may serve a potential source of increased ventilation.

Although the mechanisms of exercise hyperpnoea in chronic heart failure are under continuous study, the literature contains little about the predictive value of the VE/VCO₂ slope[27]. The results of our study indicate that the value of the ventilatory response to exercise is a statistically significant predictor of outcome. In multivariate analysis the predictive value of the VE/VCO₂ slope was independent of such important predictive variables as peak VO₂ and left ventricular ejection fraction. These results provide promising information and merit further investigations on larger cohorts of patients.

Conclusions

Peak oxygen consumption, ventilatory response to exercise and left ventricular ejection fraction have significant prognostic importance in patients with chronic heart failure. Serial measurements of exercise capacity also provide important prognostic information. Changes in peak VO₂ over time predict survival in chronic heart failure patients significantly better than changes in
echocardiographic measurements of cardiac size or function.

**Study limitations**

The individual measurements we made, particularly in echocardiographic left ventricular cavity size and function, will have been subject to measurement error, a problem compounded when small differences between those made on two occasions several months apart were derived. This effect was minimized by using identical equipment and techniques on both occasions. The left ventricular ejection fraction was calculated using the standard dimensions cubed formula, which assumes that the ventricle is an ellipsoid. This method could overestimate the size and ejection fraction of the left ventricle, especially in ischaemic cases, and therefore influence the prognostic power of left ventricular ejection fraction.

The relatively small sample size and the non-consecutive enrolment of subjects limit this study. However, serial assessments and time-adjusted standardization of the data were performed. Treatment was individualized and was thus not uniform throughout the group of patients studied, and the majority of observations were made before the introduction of beta-blocking drugs into the treatment of such patients.

**Clinical implications**

Parameters of exercise capacity and echocardiographic measurements of cardiac size or function have significant prognostic importance in patients with chronic heart failure. Serial assessments of exercise capacity may provide further prognostic information. The results of the study indicate that changes in peak VO2 over time enhance risk stratification and may be useful for candidate selection for radical interventions.

The present study suggests that peak VO2 is useful in following the course of disease, and may give valuable information as to whether therapeutic interventions have been effective and a more favourable prognosis achieved. Indeed, an increase in peak oxygen consumption might be viewed as a therapeutic goal in the treatment of heart failure, although of course peak oxygen consumption might be viewed as a therapeutic goal in the treatment of chronic heart failure.

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