VENTILATORY VARIABLES ARE STRONG PROGNOSTIC MARKERS IN ELDERLY PATIENTS WITH HEART FAILURE

M Mejhert, E Linder-Klingsell, M Edner, T Kahan, H Persson

Objective: To evaluate the safety and prognostic capacity of cardiopulmonary exercise testing in patients ≥ 60 years old who are hospitalised with heart failure caused by left ventricular dysfunction.

Design: Prospective study.

Setting: University hospital.

Patients: Study participants were 67 patients (66% men) with clinical heart failure stabilised on medical treatment. The study is a part of a nursing intervention study. Mean (SD) age was 74 (6) years, New York Heart Association functional class II–III, and ejection fraction 0.36 (0.11).

Interventions: Cardiopulmonary exercise testing and echocardiography.

Main outcome measures: Peak oxygen consumption (V˙O2), peak ventilatory equivalents for carbon dioxide (VE/V˙CO2) and oxygen (VE/V˙O2), left ventricular volumes, and mortality.

Results: Mean (SD) age was 74 (6) years, New York Heart Association functional class II–III, and ejection fraction 0.36 (0.11). During 12–59 months of follow up, 14 patients died. In univariate analyses peak V˙O2, VE/V˙CO2, and VE/V˙O2 were all strongly related (p < 0.01) to mortality. In a multivariate Cox regression analysis, peak VE/V˙CO2 was the strongest predictor of mortality (p < 0.001), followed by left ventricular end systolic volume (p < 0.001). A cut off of peak VE/V˙CO2 at ≥ 45 gave a univariate hazard ratio of 6.7 for death during follow up. No adverse events occurred during the exercise test.

Conclusion: These findings extend results found in selected middle aged patients to elderly patients with heart failure and show that ventilatory parameters from a cardiopulmonary exercise test, such as peak V˙O2, VE/V˙O2, and VE/V˙CO2, are powerful predictors of mortality.
Evaluation of cardiac function, morbidity, and mortality are secondary end points.

After stabilisation of their heart failure, all patients were asked to perform a cardiopulmonary exercise test with metabolic monitoring before discharge. We here report on the 67 subjects in this elderly population who underwent the test. The main reasons not to perform the exercise test (n = 141) were unwillingness to participate in the test (n = 46), other conditions such as asthma, blindness, and temporary confusion (n = 42), other diseases of the cardiovascular system such as arrhythmias, angina, and stroke (n = 21), non-availability of exercise equipment (n = 21), and joint diseases (n = 11).

Outcome on all cause mortality was determined from death certificates when all patients had a follow up of at least one year. Each patient gave informed consent to participate in the study, which was approved by the local ethics committee and conforms to the principles outlined in the Declaration of Helsinki.

Exercise test and protocol

The exercise test was performed on an electrically braked bicycle. The equipment used was a cardiopulmonary exercise system (Medical Graphics, St Paul, Minnesota, USA) for breath by breath measurements of VE, VO2, and VCO2. Derived entities such as VE for O2 and CO2 (VE/O2, VE/CO2), the respiratory quotient VCO2/VO2, and respiratory rate per minute were presented on line. The equipment was calibrated before every test. A 12 lead ECG was monitored for possible arrhythmia and ST segment changes. The test began with two minutes of sampling at rest and was followed by two minutes of freewheeling exercise. A ramp test with a continuous increase of workload by 10 W/min was chosen. The exercise test was symptom limited, using a Borg scale from 0 to 10 for dyspnoea, fatigue, and chest pain. The patients were encouraged to exercise until they were exhausted. The physician interfered according to standard criteria. Blood pressure and heart rate were measured every other minute. All respiratory parameters were measured from plots over time, giving moving average values. Peak VO2, VE/VO2, and VE/VCO2 were calculated as the last value of three during the last 30 seconds of exercise. If this last value was not the highest, the mean of the last three values was calculated. Slopes of VE/VO2 and VE/VCO2 were calculated by linear regression analysis. The anaerobic threshold was calculated by the V slope method.25

Echocardiography

All examinations were performed with an Acuson 128 XP/10 (Mountain View, California, USA) with a 2.5–4.0 MHz (V4c) probe and the patient in the left semilateral position. Recordings were stored on videotape and analysed at the end of the study. Left ventricular dimensions in diastole and systole were measured by M mode technique. The EF was calculated according to the recommendations of the American Society of Echocardiography.26 Biplane volumes were calculated from area tracings using the disc summation method (modified Simpson’s rule). Left ventricular systolic function was also evaluated with the AVPD method.27 The displacement was measured by M mode from an apical window. Mean values from four sites and three beats or more were used and the overall mean was calculated. Patients were enrolled into the study if a screening echocardiographic examination after medical stabilisation showed systolic dysfunction, defined as EF < 0.45 or AVPD < 10 mm. These measurements were not used further in the study. All echocardiographic findings presented in this paper are from an extensive baseline investigation, sometimes performed a few days after screening.

Statistical procedures

Data are presented as frequencies, median or mean (SD), as appropriate. The χ2 test was used for comparison of proportions. For correlations, Pearson’s product–moment method was used. Survival curves were generated by the Kaplan–Meier method and the log rank test was used to assess differences in outcome between groups. The prognostic power of the variables for mortality was evaluated by Cox proportional hazard survival analysis, performed with Statistics 5.5 software (StatSoft, Tulsa, Oklahoma, USA) by a stepwise procedure. Hazard ratios and 95% confidence intervals were calculated, when appropriate. The final model was adjusted for age, sex, and NYHA functional class. A probability value of p < 0.05 was considered significant.

RESULTS

Table 1 gives demographic characteristics and medication of the patients who underwent exercise testing. The mean daily doses at baseline of angiotensin converting enzyme inhibitors were 55 mg of captopril, 4 mg of ramipril, and 14 mg of enalapril. The mean daily furosemide dose was 128 mg. When the study group was compared with the remaining patients in the entire OPTIMAL study who did not perform a cardiopulmonary exercise test, the latter group were somewhat older but the groups were otherwise comparable.

Cardiopulmonary exercise test

Table 2 and fig 1 show the results of the exercise test of 67 patients. No adverse events occurred during the tests. The anaerobic threshold was not always reached or possible to detect but was determined in 49 patients (73%). The peak respiratory quotient was > 1 in 53 patients (79%). While VE/VO2 increased between the anaerobic threshold and the maximal effort, the corresponding VE/VCO2 was relatively unchanged throughout the test. Table 2 shows that the anaerobic threshold was reached at approximately 30% of peak work rate. The threshold probably is low because some patients (n = 13) reached the anaerobic threshold very early, during the two minutes of rest on the bicycle or the following two minutes working without load. All of these 13 patients continued to exercise, though, reaching a mean peak work load of 51 W. Forty eight patients chose to stop the test because of exhaustion (n = 21), dyspnoea (n = 14), or both in combination (n = 13). The physician discontinued the test because of a fall in blood pressure (n = 12), angina pectoris or arrhythmia in one patient each, and pronounced ST segment depression in the remaining five subjects. The physician did not stop any test because of conductance disorders or depressed heart rate responses.

Table 1 Demographic data at baseline (n=67)

<table>
<thead>
<tr>
<th>Mean (range) (age years)</th>
<th>74 (60–86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>44 (66%)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.36 (0.11)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>I–IV</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>86 (21)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>134 (28)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>81 (14)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>44 (67%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>32 (48%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (30%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Valve disease</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>63 (94%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>55 (82%)</td>
</tr>
<tr>
<td>β Blockers</td>
<td>40 (60%)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>34 (51%)</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise indicated. ACE, angiotensin converting enzyme; NYHA, New York Heart Association functional class. There were 49 patients in NYHA II, 17 in NYHA III, and 1 in NYHA IV
Echocardiography

The baseline ejection fraction was 0.36 (0.11) and atrioventricular plane displacement 6.9 (2.0) mm. The baseline left ventricular end systolic diameter was 47 (13) mm, left ventricular end diastolic diameter 57 (10) mm, end systolic volume 89 (51) ml, and end diastolic volume 132 (61) ml. Table 3 shows echocardiographic characteristics in relation to mortality. Table 4 shows the correlations between ventilatory and echocardiographic data. The strongest correlation was between peak VO\textsubscript{2} and atrioventricular plane displacement.

Predictors of survival

Table 3, fig 1, and fig 2 show patient characteristics, and exercise and echocardiographic results in relation to mortality in December 2000, when all patients had been followed up for at least one year. During follow up 14 patients died (median survival 11.8 months). Median follow up time for the survivors was 30.8 months. In univariate analyses, mortality was positively related, in declining order of significance, to peak VO\textsubscript{2} (50.8 vs 40.9, p < 0.001), peak VE/VO\textsubscript{2} (54.9 vs 43.3, p < 0.001), slope VE/VO\textsubscript{2} (46.8 vs 39.7, p = 0.006), and slope VE/CO\textsubscript{2} (49.7 vs 43.8, p = 0.02), and inversely related to peak VO\textsubscript{2} (9.3 vs 12.4 ml/kg/min, p = 0.004). As expected, peak and slope VE/VO\textsubscript{2} (r = 0.8) and VE/CO\textsubscript{2} (r = 0.9) were highly correlated. Thus, in univariate analysis, peak VE/CO\textsubscript{2} and VE/CO\textsubscript{2} were stronger prognostic predictors than slope. Furthermore, a low ejection fraction (p < 0.05) and large left end systolic (p < 0.001) and end diastolic (p < 0.05) volumes predicted mortality. The strongest univariate predictor of mortality in Cox regression analysis was peak VE/CO\textsubscript{2}, (Wald \chi\textsuperscript{2} = 15.3, p < 0.001), followed by peak VE/VO\textsubscript{2} (Wald \chi\textsuperscript{2} = 11.7, p < 0.001) and left ventricular end systolic volume (Wald \chi\textsuperscript{2} = 11.0, p < 0.001). In the final multivariate model, peak VE/CO\textsubscript{2} was the strongest independent prognostic predictor (Wald \chi\textsuperscript{2} = 11.3, p < 0.001) when adjusted for age, sex, and NYHA class (global \chi\textsuperscript{2} = 30.3, p < 0.001). Peak VO\textsubscript{2} had no independent prognostic value in addition to either peak VE/CO\textsubscript{2} or left ventricular end systolic volume.
With a cut off for peak $V_{\dot{E}}/V_{\dot{CO}_2}$ of $\geq 45$, the univariate hazard ratio of survival was $6.7$ (95% confidence interval 1.9 to 24.2). Adjusted for age, sex, left ventricular end systolic volume, and NYHA class, the hazard ratio of survival was $4.3$ ($p < 0.05$). Sensitivity was $79\%$ for mortality, specificity was $70\%$, the positive predictive value was $44\%$, the negative predictive value was $92\%$, and the positive likelihood ratio was $2.6$. We did not find age, sex, aetiology of heart failure, presence of atrial fibrillation, or medication to have an impact on mortality.

**DISCUSSION**

The present prospective study is the first to assess the usefulness of a cardiopulmonary exercise test in elderly patients hospitalised with heart failure. We found peak $V_{\dot{O}_2}$ to be severely impaired among these patients, reaching only $62\%$ of the predicted value. The peak $V_{E}/V_{CO_2}$ reached high values and was the strongest predictor of mortality in univariate and in multivariate analyses. Our finding support and extend recent observations by Davies et al from exercise testing in ambulatory elderly patients with heart failure. They included patients with a mean age of 75.9 years and found a mean peak $V_{O_2}$ of 15.2 ml/kg/min, a mean slope $V_{E}/V_{CO_2}$ of 38.7, and both to predict the prognosis. The slightly better performance in their patients probably is a result of the difference between ambulatory and hospitalised patients with heart failure. Indeed, peak $V_{\dot{E}}/V_{\dot{CO}_2}$ and other measurements, particularly $V_{E}/V_{CO_2}$ have been shown to predict mortality in patients with heart failure. In a study of 60 male patients with heart failure in NYHA class II and III, Bol et al found that the slope of $V_{E}/V_{O_2}$ was the strongest prognostic predictor of all cause mortality. Both peak and slope $V_{E}/V_{O_2}$ and $V_{E}/V_{CO_2}$ have been used. It may be argued that slope is less effort dependent, as the peak depends on the level of exercise. In our study, however, the predictive power of the peak value was stronger.

Mancini et al divided middle aged patients with heart failure into four classes according to the cardiopulmonary exercise test results of peak $V_{O_2}$. Not always compatible with the NYHA classes, this classification has been shown to be useful as a prognostic tool for patients on the waiting list for a heart transplant. Thus, a patient with peak $V_{O_2} > 14$ ml/kg/min has a good prognosis and can often be deferred from the transplant waiting list. Interestingly, when we applied this cut off to our subjects representing a different group of patients with heart failure, we found 95% survival in subjects with peak $V_{O_2} > 14$ ml/kg/min. However, our results show that peak $V_{E}/V_{CO_2}$ provides the strongest predictive information. Thus, in a multivariate analysis also including left ventricular end systolic volume, we show $V_{E}/V_{CO_2}$ to be superior. A cut off for $V_{E}/V_{CO_2}$ of $\geq 45$ may be most useful in assessing mortality risk in clinical practice.

The prognostic value of echocardiography in elderly patients with heart failure is unclear. Taffet et al showed that in male patients with heart failure who were 75 years or older, the ejection fraction was not related to one year survival. However, many elderly patients may have heart failure caused by diastolic dysfunction and systolic function is often preserved. In the present study, confined to patients with systolic left ventricular dysfunction, left ventricular end systolic volume was an independent strong prognostic indicator. Furthermore, there was a correlation between ventilatory variables and echocardiographic findings, in particular systolic left ventricular function. Few studies have investigated relations between $V_{O_2}$ and echocardiographic findings. In the study of Bol et al the combination of a high $V_{E}/V_{O_2}$ slope and a relatively high left ventricular ejection fraction was particularly unfavourable for prognosis. Florosa et al described changes in peak $V_{O_2}$ but not ejection fraction over time to predict outcome. In another study in middle aged patients with dilated cardiomyopathy, peak $V_{O_2}$ correlated with left ventricular dimensions, filling patterns, and ejection fraction. Thus, left ventricular size and in particular end systolic volume provide independent prognostic information in elderly patients with heart failure, whereas ejection fraction fails to do so in this context. However, peak $V_{E}/V_{CO_2}$ provides stronger prognostic information.

There are potential limitations to this study. Firstly, only one in three of these elderly hospitalised patients with heart failure eventually performed the cardiopulmonary exercise test. Cardiac patients unable to perform a provocation test probably have a worse prognosis. This would decrease the predictive value of the provocation test in the current study. In our study, the patients who underwent the cardiopulmonary exercise test had a prognosis similar to those of the other patients in OPTIMAL. Secondly, this study included only patients with systolic left ventricular dysfunction. The prognostic information of the cardiopulmonary exercise test in patients with diastolic dysfunction remains to be studied.

The cardiopulmonary exercise test has been used for several years in middle aged patients, often on the transplant waiting list. We show that it can be used safely in elderly hospitalised patients with heart failure and can provide strong and independent prognostic information.

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**REFERENCES**

A 57 year old woman underwent echocardiography following deep vein thrombosis of the left lower limb with consecutive pulmonary embolism. The exam incidentally revealed a giant congenital aneurysm of the non-coronary sinus of Valsalva with protrusion towards both atrial cavities, but without signs of rupture or penetration. There was low perfusion of the aneurysmal sack confined to diastole as its orifice was small and additionally covered by the non-coronary cusp during systole; no thrombus material could be detected inside the aneurysm. Mild aortic regurgitation resulted from slight detachment of the non-coronary commissure. Preoperative cardiac catheterisation confirmed the huge balloon-like aneurysm of the non-coronary sinus of Valsalva. The aneurysm ruptured while the patient was on the waiting list for elective operation and an emergency ligation had to be performed a few weeks after initial diagnosis. The postoperative course was uneventful and the patient is doing well.

Left and centre panels below show right anterior oblique angiographic projection of the left ventricle, the aortic root and the ascending aorta with the balloon-like aneurysm of the non-coronary sinus of Valsalva extending posteriorly and also to the right of the non-coronary sinus. Note the relatively faint filling of the aneurysmal sack with contrast dye as compared to the left ventricle and the aorta.

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Giant congenital aneurysm of the non-coronary sinus of Valsalva

IMAGES IN CARDIOLOGY

Giant congenital aneurysm of the non-coronary sinus of Valsalva

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