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Six-minute walking performance in patients with moderate-to-severe heart failure

Is it a useful indicator in clinical practice?

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Aims The 6-min walk test has been incorporated into studies on the efficacy of new therapies and into prognostic stratification for chronic heart failure patients. Firm conclusions on the usefulness of the test in clinical practice are still lacking. The aim of this study was to investigate (1) the correlation between walk test performance and standard indices of cardiac function and exercise capacity, and (2) the prognostic value of the walk test with respect to peak $\dot{V}O_2$ and NYHA class.

Methods and Results Three hundred and fifteen chronic heart failure patients (age: 53 ± 9 years, NYHA class: II (182), III (133)) underwent a functional evaluation and a 6-min walk test. Of these, 270 were followed-up for a minimum of 6 months (mean 387 ± 177 days). Walked distance was 396 ± 92 m. There was no significant correlation between distance walked and central haemodynamic data. Functional capacity, as measured by ergometry, correlated moderately with distance walked (duration: r=0·48, peak $\dot{V}O_2$: r=0·59, anaerobic threshold: r=0·54; all $P<0·001$). During follow-up, 46 patients died from cardiovascular causes and 12 were urgently transplanted. Either of these events were considered end points of the study. Survival analysis was performed from a continuous walk test and peak $\dot{V}O_2$ measurements or after categorization of (a) quartile segmentation, (b) cut-off points from the literature and (c) thresholds from receiver operating characteristic curves. At univariate survival analysis (Cox regression), the association of the walk test with survival was of significance ($P=0·03$, continuous variable), or borderline significance ($0·05 \leq P \leq 0·1$, after categorization). Peak $\dot{V}O_2$ was always significant, indepedent of the scale used ($0·005 \leq P \leq 0·03$). The strongest association was found for NYHA class ($P<0·001$), which showed the highest sensitivity and specificity for the prediction of the event (0·64 and 0·65, respectively). When walk test performance, continuous or categorized, was entered into a multivariate model with NYHA class or peak $\dot{V}O_2$, it lost any significant association with survival ($P>0·76$ in all models with NYHA class and $P>0·27$ in all models with peak $\dot{V}O_2$).

Conclusion In moderate-to-severe chronic heart failure patients, the 6-min walk test is not related to cardiac function and only moderately related to exercise capacity. Walking performance does not provide prognostic information which can complement or substitute for that provided by peak $\dot{V}O_2$ or NYHA class. Hence the test is of limited usefulness as a decisional indicator in clinical practice.
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Key Words: Heart failure, prognosis, exercise, walk test, risk factors.

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Introduction

In patients with chronic heart failure, the 6-min walk test is considered to be realistically related to daily physical activity. Consequently, it has been incorporated into studies of assessment of exercise capacity[1,2], of quality of life[3], of efficacy of new therapeutic agents[4–6] including beta-blockers[7–11] of physical training programmes[12] and of prognostic stratification[13–18]. However, most studies have been performed in small groups of patients, the relationship of the test to standard clinical and functional indicators has not been completely clarified and its prognostic value is still controversial[19–21]. In particular, clarification is required on whether the walk test provides prognostic information that can complement or, perhaps, substitute for that contained in two well-recognized prognostic indicators which describe clinical and functional aspects 'close' to the walk test: peak oxygen consumption ($\dot{V}O_2$), which is the standard measurement for assessment of exercise capacity, and NYHA class, which is the standard grading system of functional status in the clinical setting. The mutual relationship between distance walked during the 6-min test, peak $\dot{V}O_2$ and prognosis has been addressed by a few authors and results appear to be dependent on whether the two variables are used in their original continuous scale or after categorization[14,15,18]. Much less attention has been devoted to the joint prognostic value of the walk test and NYHA class, and a multivariate survival analysis addressing this issue is still lacking. For all these reasons, firm conclusions on the usefulness of the walk test as a decisional and prognostic indicator in clinical practice are difficult to reach.

Starting from these premises, we planned this study with the aim of assessing, in a large population of chronic heart failure patients, (1) the correlation between walk test performance and standard indices of cardiac function and exercise capacity, and (2) the independent prognostic value of the walk test with respect to peak $\dot{V}O_2$ and NYHA class, using both original continuous and categorized variables. This assessment is a pre-requisite to a global (and costly) study on the prognostic value of the 6-min test against all other measurements which have been shown to contain prognostic information on heart failure.

Methods

Subjects

In this study we considered all patients with chronic heart failure and left ventricular ejection fraction <40% who were referred to the Heart Failure Unit of the Montescano Medical Centre for evaluation and therapy for heart failure, usually in conjunction with evaluation for heart transplantation, from January 1995 to December 1996. Patients were given individualized therapy which included ACE inhibitors (89%), vasodilators (46%), digoxin (81%), diuretic drugs (100%), amiodarone (24%) and, in the absence of contraindications, anticoagulants (INR 2-3) or antiplatelet agents (99%). At the time of recruitment, beta-blockers were not considered routine therapy.

Patients with clinical signs of peripheral or cerebral vascular disease or any other non-cardiac conditions limiting physical activity were excluded from this study, as were those patients with cardiac contraindications to the exercise test (symptomatic at rest notwithstanding optimized oral therapy).

Study protocol

Provided clinical stability was fulfilled, a functional evaluation was performed, which in our programme included: two-dimensional Doppler echocardiography; right heart catheterization with a Swan-Ganz catheter for thermodilution introduced via the internal jugular vein (Seldinger techinque) (once a year, in the absence of different indications); a symptom-limited cardiopulmonary exercise test, carried out on a bicycle ergometer (incremental protocol, 10 watts every minute) with simultaneous monitoring of respiratory gases by a CAD/NET System 2001 Medical Graphics analyser. The anaerobic threshold, determined in 257 patients, was defined as (1) the point at which the ventilatory equivalent for O_2 was minimal, followed by a progressive increase; and/or (2) the point after which the respiratory gas exchange ratio exceeded the resting respiratory gas exchange ratio; and/or (3) the point after which a non-linear increase in minute ventilation occurred relative to $\dot{V}CO_2$; 6-min walking tests, which took place in the same, 34 m long, hospital corridor. A standardized procedure was followed throughout. Before the first test the patient was familiarized with the test and the environment by letting him/her go once along the corridor (forwards and backwards) in a totally natural way. Then, after a 15 min rest, he/she was instructed to walk from end to end of the corridor for 6 min and to cover as much distance as possible until the point of exhaustion. Patients were allowed to rest whenever necessary. No encouragement was given during the test. The test was stopped if signs and symptoms of significant distress (dizziness, angina, severe dyspnoea or musculoskeletal pain) occurred. The test was repeated at least 30 min later, and the average of the two measurements was taken as an estimate of the walking performance of each subject[22].

All examinations were performed within one week. For the purpose of prognostic evaluation all the patients were closely followed-up by means of periodic clinical examinations, telephone contacts and questionnaires at home. To be included in the analysis all surviving patients had to have had a minimum of 6 months of follow-up.

Statistical analysis

The correlation between walk test performance and indices of cardiac function and exercise capacity was

assessed by the Pearson correlation coefficient between the former and (a) left ventricular ejection fraction (modified Simpson's rule), (b) deceleration time of transmitral flow, (c) right atrial pressure, (d) pulmonary capillary wedge pressure, (e) cardiac index, (f) duration of bicycle exercise, (g) peak $\dot{V}O_2$ and (h) anaerobic threshold. The association between walk test and NYHA class was assessed by analysis of variance.

The end-point of survival analysis was death or urgent transplantation. Urgent transplantation is actually equivalent to a virtual death and the concept of associating it to true death has gained large consensus among clinicians and researchers. Receiver operating characteristic curves were used to assess the ability of the walk test and peak $\dot{V}O_2$ to predict the outcome in each subject. The area under the curve, which is a measure of the discriminatory power of the predictor, ranging from 0·5 to 1, was measured for the two variables and the two areas were compared statistically[23].

The univariate and multivariate association of walk test performance, peak $\dot{V}O_2$ and NYHA class with survival was assessed by fitting the Cox proportional hazards model to follow-up data. Patients who died of non-cardiovascular causes and those who underwent an elective heart transplantation were considered censored observations. Analysis was carried out using walk test and peak $\dot{V}O_2$ measurements in their original scales (i.e. as continuous variables) and after categorization. For the latter we used three different criteria: (1) quartiles, (2) cut-off points proposed in the literature and (3) values derived from receiver operating characteristic curves.

The first criterion was based on an a priori segmentation of the range of variation of the measurement into three regions: from the minimum to the first quartile, from the first quartile to the median and from the median to the maximum. The first region would comprise those patients with a markedly reduced walking performance or exercise capacity, which, as known from previous studies, are likely to have a high risk. The third region would comprise those patients with preserved walking performance and exercise capacity, which are likely to be associated with a low risk. Finally, the intermediate region would identify a 'grey' or transition region.

The second criterion aimed at comparing the results of our study with those already published. For peak $\dot{V}O_2$ we used the cut-off points <10, 10–14, >14 ml . kg^{-1} min^{-1}, which are the same or very similar to those used in previous investigations[14,15,17,18]. For the walked distance we used the cut-off points <300, 300–450, >450 m which are basically the ones used by Zugck *et al.*[17] and Lucas *et al.*[18]. In a simplified version (<300, ≥300 m) these cut-off points have also been used by Cahalin *et al.*[14] and Roul *et al.*[15].

The third criterion is based on the computation of receiver operating characteristic curves for both peak $\dot{V}O_2$ and walk test data and on the identification of the cut-off point which optimizes sensitivity and specificity. This point was defined as the value which minimizes the expression (1-sensitivity)^2+(1-specificity)^2. Contrary to the previous two criteria, the receiver operating characteristic criterion is an a posteriori criterion and the results obtained should be interpreted as optimistic.

When the Cox model was fitted to categorized peak $\dot{V}O_2$ and walk test measurements, dummy variables were used to represent the original three-level variable[24], and the corresponding regression coefficients were compared statistically to test for the presence of incremental risk between adjacent risk groups. In case of a non significant result, categorization was reduced to two levels, merging subjects pertaining to equal-risk groups. The survival function in the different risk classes was estimated using the Kaplan–Meier method.

Data are expressed as mean ± standard deviation. A P value <0·05 was considered significant. Statistical analysis was performed with the SAS/STAT statistical package, release 6.12 (SAS Institute Inv., Cary, NC, U.S.A.).

Table 1 Clinical characteristics of the patients enrolled in the study

n	315
Age, years, (mean ± SD)	53 ± 9
Sex, %, M/F	87/13
NYHA class (N (%))	
II	182 (58%)
III	133 (42%)
Disease duration, months, (mean ± SD)	45 ± 9
Left ventricular ejection fraction, %, (mean ± SD)	26 ± 8
Pulmonary wedge pressure, mmHg, (mean ± HD)	18·1 ± 10
Right atrial pressure, mmHg, (mean ± SD)	4·9 ± 4
Cardiac index, l . min^{-1} . m^{-2}, (mean ± SD)	2·1 ± 0·5
Deceleration time, ms, (mean ± SD)	150 ± 70
Exercise duration, min, (mean ± SD)	10·6 ± 5·4
Peak $\dot{V}O_2$, ml . kg^{-1} min^{-1}, (mean ± SD))	14·6 ± 4·4
Anaerobic threshold, ml O_2 . kg^{-1} min^{-1}, (mean ± SD)	13·4 ± 8·6

The haemodynamic pattern was measured in 222 subjects. Exercise testing was performed on 311 subjects. Anaerobic threshold was detected in 257 subjects.

Results

The clinical characteristics of the 315 patients enrolled in the study are shown in Table 1. All patients were aged less than 70 years. Coronary artery disease was responsible for the heart failure in 41% of the cases, and idiopathic dilated cardiomyopathy in 40%. The haemodynamic pattern was measured in 222 patients. Anaerobic threshold was detected in 257 subjects.

The distance walked at the second test was greater than that at the first test (407·6 ± 91 versus 389·9 ± 88 m; P<0·001), confirming the results obtained in a previous study[22]. Walk test performance, measured as the average distance walked in the two repeated tests, was 396 ± 92 m (range: 134 m–686 m), which is close to that found by other investigators in a similar population of subjects using encouragement during the test[15,18].

Table 2 Correlation coefficients between walk test performance and cardiac function and functional capacity in the overall group and after grouping patients according to NYHA class

	All patients	NYHA class II	NYHA class III
Pulmonary wedge pressure	−0·19	−0·17	−0·04
Right atrial pressure	−0·25	−0·17	−0·11
LVEF	0·12	0·17	−0·09
Cardiac index	0·16	0·24	−0·06
Deceleration time	0·17	0·01	−0·09
Exercise duration	0·48*	0·47*	0·42*
Peak $\dot{V}O_2$	0·59*	0·46*	0·38*
Anaerobic threshold	0·54*	0·41*	0·40*

LVEF=left ventricular ejection fraction.
*$P<0·001$.

The 6-min distance walked was significantly shorter in NYHA class III patients than in NYHA class II patients (348 ± 86 vs 436 ± 66 m; $P<0·001$).

Relationship between walk test performance and cardiac function and exercise capacity

As shown in Table 2, there was no significant correlation between the distance walked and central haemodynamic function expressed as left ventricular ejection fraction, pulmonary wedge pressure, right atrial pressure, cardiac index and deceleration time. Functional capacity at the maximal symptom-limited bicycle ergometer test, as expressed by the duration of the test, peak $\dot{V}O_2$ and anaerobic threshold, correlated moderately with walk test performance, the Pearson's coefficients being between 0·48 (exercise duration) and 0·59 (peak $\dot{V}O_2$, Fig. 1). Correlation values slightly decreased when patients were grouped according to NYHA class (Table 2).

Prognostic value of the walk test

For the purpose of prognostic evaluation, 270 patients (patients with events and patients without events who survived at least 6 months) were considered. The clinical characteristics of these patients were superimposable on those of the entire sample. During the follow-up, lasting 387 ± 177 days (median 374 days), 46 patients died of cardiac death and 12 were urgently transplanted (out of 28 transplanted patients).

Receiver operating characteristic curves for the prediction of the event using the walk test and peak $\dot{V}O_2$ measurements are shown in Fig. 2. The area under the curve was, respectively, 0·59 and 0·63 ($P=0·1$), indicating a similar predictive accuracy of the two prognostic variables. The optimal value for the threshold was found at 405 m for the walk test and at 13 ml . kg^{-1} min^{-1} for peak $\dot{V}O_2$. The corresponding sensitivity and specificity were: 0·6 and 0·52 for the walk test and 0·58 and 0·65 for peak $\dot{V}O_2$.

Results from univariate and multivariate Cox regression analysis, using as predictors the continuous walk

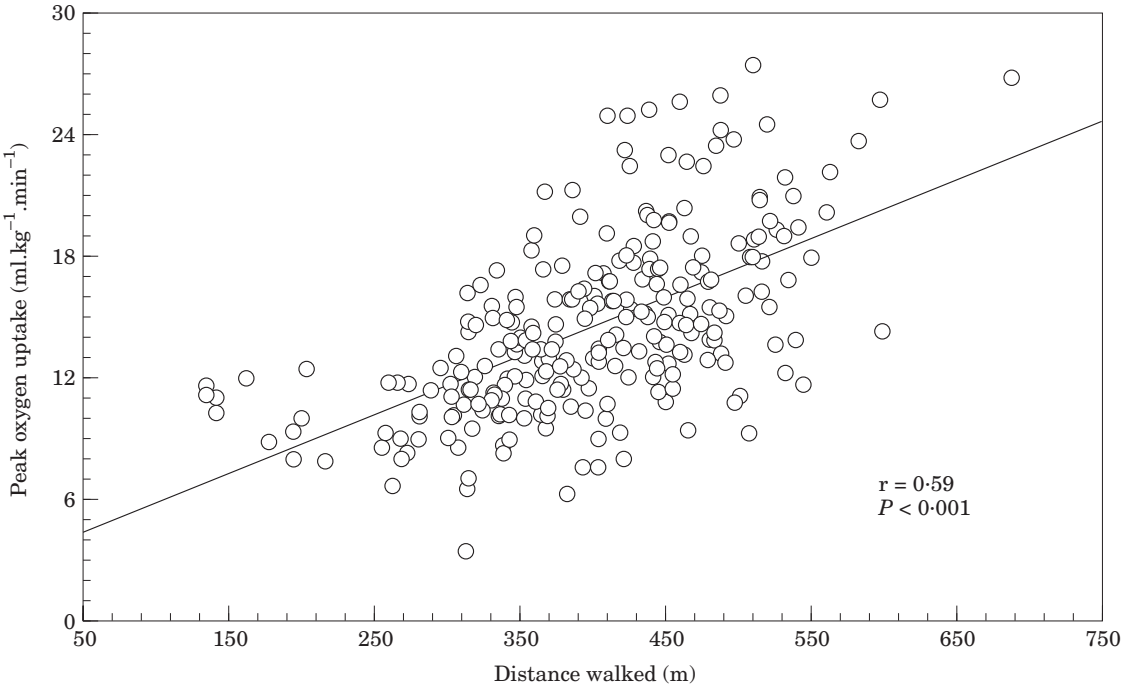

Figure 1 **Scatterplot of the relationship between peak $\dot{V}O_2$ at the maximal symptom-limited ergometer test and distance walked during the 6-min walk test.**

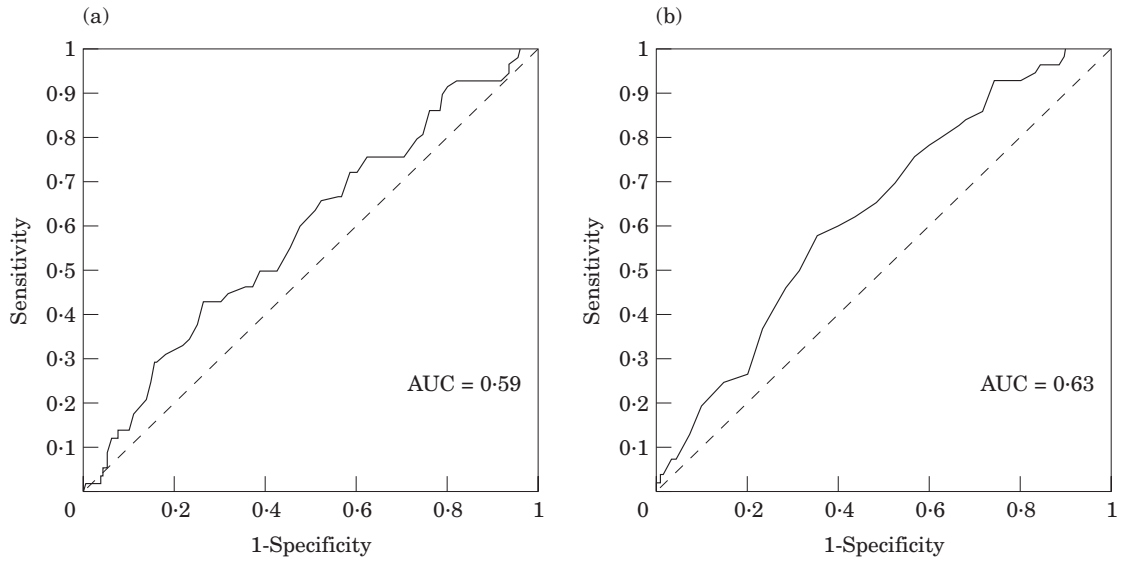

Figure 2 **Receiver operating characteristic curves for the prediction of the event (death or urgent transplantation) using (a) the 6-min walk test and (b) peak $\dot{V}O_2$ data. AUC=area under the curve.**

test and peak $\dot{V}O_2$ measurements and NYHA class, are given in Table 3. All three variables were significantly associated with survival, the strongest statistical significance being found for the NYHA class. However, when the 6-min walk distance was entered into a multivariate model with either peak $\dot{V}O_2$ or NYHA class, it dramatically lost statistical significance, which was instead preserved by the other two covariates. This indicates that either peak $\dot{V}O_2$ or NYHA class have a stronger association with the survival experience of the patients and, in a sense, 'contain' the prognostic information of the walk test.

Classifying walk test performance according to quartile values, the first group of patients had values comprised between 134 m (minimum) and 343 m (25th percentile), the second group between 343 m and 404 m (median), and the third group between 404 m and 686 m (maximum). Corresponding ranges for peak $\dot{V}O_2$ were: 3·5–11·4 ml . kg^{-1} min^{-1} (first group), 11·4–13·9 ml . kg^{-1} min^{-1} (second group) and 13·9 ml . kg^{-1} min^{-1}–27 ml . kg^{-1} min^{-1} (third group). When the Cox model was separately fitted to these categorized measurements, a non-significant incremental risk was found both in the walk test and peak $\dot{V}O_2$ between subjects in the first and those in the second group (P=0·47 for walk test and P=0·87 for peak $\dot{V}O_2$). Hence, patients in the two lowest categories were merged together giving rise to a binary representation of the two variables: ≤median versus >median. It is worth noting that the median value of peak $\dot{V}O_2$ is very close to the cut-off point of 14 ml . kg^{-1} min^{-1}, which has been recommended for chronic heart failure to be listed for cardiac transplantation[25].

Table 3 ***Results from univariate and multivariate Cox regression analysis using the walk test and peak $\dot{V}O_2$ measurements as continuous variables***

Model		Wald χ^2	P	Risk ratio	95% CI
U	WT	4·7	0·03	0·997	0·994–1·00
U	Peak $\dot{V}O_2$	7·8	0·005	0·91	0·86–0·97
U	NYHA<3	12·8	<0·001	2·7	1·6–4·5
M1	WT<3	0·31	0·58	0·999	0·996–1·002
M1	Peak $\dot{V}O_2$	4·2	0·04	0·92	0·85–0·99
M2	WT	0·09	0·76	1	0·996–1·003
M2	NYHA<3	9·1	0·002	2·5	1·4–4·7

U=univariate model; M1=first multivariate model: Walk test+peak $\dot{V}O_2$; M2=second multivariate model: Walk test+NYHA class; CI=confidence interval for the risk ratio.

Using literature cut-off points, a non-significant incremental risk was found between patients walking a distance between 300 m and 450 m and patients walking a distance >450 m (P=0·46). Conversely, patients with a peak $\dot{V}O_2$ <10 ml . kg^{-1} min^{-1} had a risk not significantly different from that of patients with a peak $\dot{V}O_2$ between 10 ml . kg^{-1} min^{-1} and 14 ml . kg^{-1} min^{-1} (P=0·80), a result in agreement with that found by Zugck *et al.*[17]. Hence, as done before, homogeneous risk groups were merged together.

It appears from results obtained so far, including receiver operating characteristic analysis, that categorization of walk test performance and peak $\dot{V}O_2$ led to binary representations of the two variables which were often very close to each other. We thus identified a representative subset of these representations which could be meaningful from a clinical point of view. This subset included cut-off points 300 m and 404 m for walk test performance and 14 ml . kg^{-1} min^{-1} for peak $\dot{V}O_2$. Corresponding results for univariate and multivariate survival analysis are given in Table 4. The risk ratio for a 6-min walk distance <300 m vs a distance ≥300 m was marginally non-significant, whereas it was of borderline significance for a threshold of 404 m. Failure to detect a

Table 4 Results from univariate and multivariate Cox regression analysis using walk test and peak $\dot{V}O_2$ measurements dichotomised according to most representative cut-off points

Model		Wald χ^2	*P*	Risk ratio	95% CI
U	WT <300 m	2·7	0·1	1·9	0·9–4·0
U	WT ≤404 m	3·9	0·05	1·7	1·0–2·9
U	Peak $\dot{V}O_2$ ≤14 ml . kg^{-1} min^{-1}	4·6	0·03	1·8	1·1–3·1
M1	WT <300 m	1·0	0·32	1·5	0·7–3·2
M1	Peak $\dot{V}O_2$ ≤14 ml . kg^{-1} min^{-1}	3·1	0·08	1·7	0 9–2·9
M2	wt <300 m	0·1	0·77	1·1	0·5–2·5
M2	NYHA <3	9·2	0·002	2·6	1·4–4·7
M3	WT ≤404 m	1·2	0·27	1·4	0·7–2·6
M3	Peak $\dot{V}O_2$ ≤14 ml . kg^{-1} min^{-1}	1·7	0·19	1·5	0·8–2·8
M4	WT ≤404 m	0·1	0·78	1·1	0·6–2·0
M4	NYHA <3	9·2	0·002	2·6	1·4–4·7

U=univariate model; M1–M4=bivariate models; CI=confidence interval for the risk ratio. Univariate results for the NYHA class are given in Table 3.

definite significant increase in the risk in patients walking a distance <300 m was probably due to the small number of patients in this group (9% of the overall cohort). Patients with a peak $\dot{V}O_2$ ≤14 ml . kg^{-1} min^{-1} had a risk significantly higher than patients with a maximal oxygen consumption >14 ml . kg^{-1} min^{-1}. When categorized, the walk test was entered into the proportional hazards regression model together with peak $\dot{V}O_2$; each of them, adjusted for the other, showed a non-significant association with survival, indicating that in this binary representation they contained similar prognostic information of their binary representation. Conversely, when we analysed the bivariate models with the categorized walk test and NYHA class, a definite non-significant result ($P \geq 0{\cdot}77$) was found for the former, whereas the latter preserved high statistical significance ($P=0{\cdot}002$).

Kaplan–Meier estimates of survival functions for patients grouped according to the representative cut-off points are given in Figs 3 and 4, respectively. These curves can be compared to the survival functions of the patients classified according to NYHA class. Values of sensitivity and specificity for the prediction of the event using these categorizations are given in Table 5. As expected from previous results, the predictor with the worst performance is the 6-min walk distance, whereas best accuracy is achieved by NYHA class.

Discussion

In this study on a large population of moderate-to-severe chronic heart failure patients who did not complain of resting symptoms at the time of the evaluation we found no significant correlation between the distance walked during the 6-min test and haemodynamic indices, and found only a moderate correlation with functional capacity indicators. Moreover, we found that walk test performance, either expressed in the original scale of measurement or after categorization, although significant, or of borderline significance, when associated with survival, or when considered as a single predictor of death or urgent transplantation, lost statistical significance when adjusted for peak $\dot{V}O_2$ or NYHA class. This result was consistent across different choices of cut-off points for the categorization of both distance walked and peak $\dot{V}O_2$.

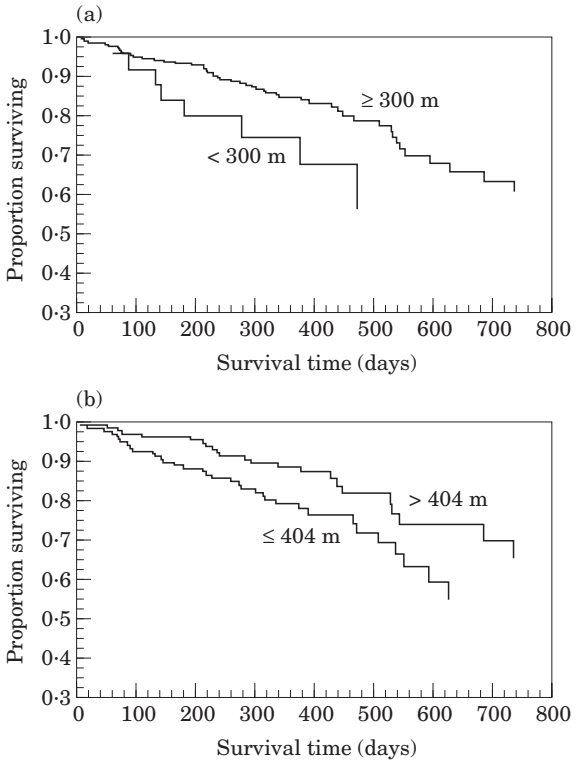

***Figure 3* Kaplan–Meier estimates of survival curves of patients grouped according to walk test performance (a) <300 m vs ≥300 m and (b) ≤404 m vs >404 m.**

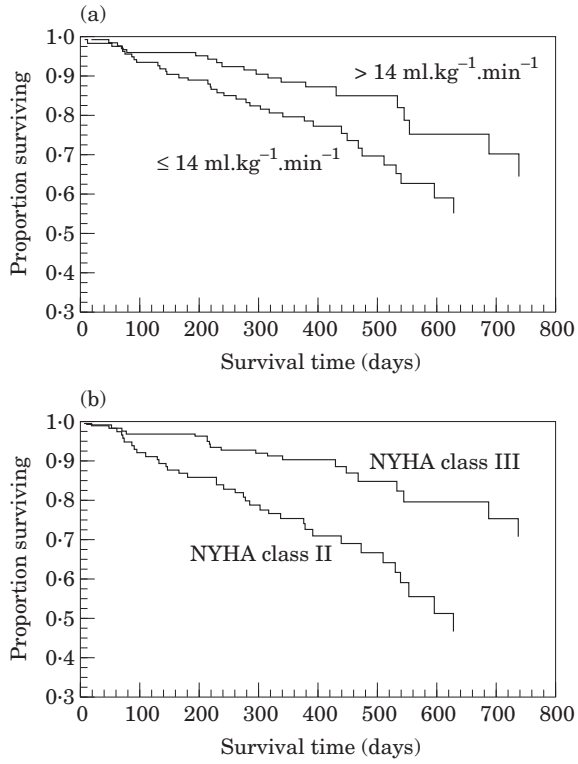

Figure 4 **Kaplan–Meier estimates of survival curves of patients grouped according to peak $\dot{V}O_2$ (a) ≤ 14 ml . kg^{-1} min^{-1} vs >14 ml . kg^{-1} min^{-1}, and (b) NYHA class II vs NYHA class III.**

Table 5 Sensitivity and specificity of the walk test, peak $\dot{V}O_2$ and NYHA class for the identification of patients who experienced an event (death or urgent transplantation) according to most representative categorizations of continuous variables

	Sensitivity (%)	Specificity (%)
WT <300 m	14	92
WT ≤404 m	60	52
Peak $\dot{V}O_2$ ≤14 ml . kg . $^{-1}$ min^{-1}	65	52
NYHA <3	64	65

WT=walk test.

Six-minute walking performance as a descriptive indicator

Walk test performance did not significantly correlate with any systolic (left ventricular ejection fraction and cardiac index) or diastolic (deceleration time and right and left filling pressures) cardiac function indicators. This is not surprising, as in chronic heart failure patients we are used to seeing a dissociation between cardiac and peripheral function. Similar findings have been well reported regarding peak $\dot{V}O_2$ and are explained by the development of peripheral and metabolic factors occurring as the disease progresses[26,27]. On average, our patients had had symptoms for about 4 years. Thus peripheral deconditioning could also explain the lack of correlation between cardiac dysfunction and capacity to perform a daily task such as walking.

The distance ambulated during the test showed a moderate association with peak $\dot{V}O_2$, with a correlation coefficient of 0·59. This implies that only about 35% of peak $\dot{V}O_2$ variation can be explained by variations in walking performance. From the large spread of the data shown in Fig. 1 it can be seen, for instance, that patients who walked a distance ranging from 350 m to 450 m had a peak $\dot{V}O_2$ comprised between 6 ml . kg^{-1} min^{-1} and 25 ml . kg^{-1} min^{-1}. Hence, the result of the 6-min walk test cannot be used in the individual patient as an alternative to, or as a surrogate of, peak $\dot{V}O_2$. Our findings in a sizeable group of patients are similar to those reported in the literature in smaller groups[2,14,15,17,18,28]. A subjective component plays an important role in both peak $\dot{V}O_2$ and distance walked. However, the detection of an anaerobic threshold during a cardiopulmonary exercise test guarantees almost maximal exercise performance, whereas a similar guarantee is not available during the 6-min walk test. That is to say, subjective attitudes, self-motivation and mood can affect the result of the test.

Although the distance walked during the test is usually considered an index of submaximal exercise capacity, we found that its relationship to anaerobic threshold is poor. Indeed, some authors[28–30] showed that in chronic heart failure patients the peak $\dot{V}O_2$ during the 6-min walk test was similar to that reached during the cardiopulmonary exercise test and a similar anaerobic threshold was also detected[28]. Cahalin *et al.*[31] observed that in some cases the maximal heart rate and blood pressure reached during the 6-min test were near their respective peak values at maximal exercise test. Therefore, instead of being a measure of submaximal capacity, in some cases the 6-min test may reflect maximal exercise tolerance and the energy required may also be provided by anaerobic metabolism.

Six-minute walking performance as a prognostic indicator

Survival analysis in the study was carried out on 270 patients who were followed-up for at least 6 months, up to 24 months. In order to reach robust conclusions, walk test performance was considered either as a continuous variable in the original scale of measurement or as a categorical variable. Categorization was performed using quartile segmentation, cut-off points proposed in the literature and optimal thresholds from receiver operating characteristic curves. The same analysis procedure was applied to peak $\dot{V}O_2$ measurements. Results of survival analysis using the Cox proportional hazards model showed consistently that the distance walked during the 6-min test is significantly or borderline

significantly associated with survival when considered as a univariate predictor. A highly significant univariate association with survival was found for peak $\dot{V}O_2$ and NYHA class, with the lowest *P*-value in the latter. When the joint prognostic value of walk test with peak $\dot{V}O_2$ or NYHA class was assessed, the 6-min walk distance dramatically lost statistical significance, indicating that its prognostic information was already 'contained' in the other predictor. These results were consistent using continuous or categorized variables. It has to be noted, however, that when the categorized walk test and peak $\dot{V}O_2$ were considered, they became simultaneously non-significant in the bivariate model, indicating similar prognostic information. Conversely, when a categorized walk test was entered in the bivariate survival model together with NYHA class, the latter preserved a high statistical significance, indicating a stronger prognostic power.

When the predictive accuracy of the three variables was assessed in terms of sensitivity and specificity, NYHA class clearly showed a better performance than the 6-min walk test, whereas only a slight increase in performance was observed for peak $\dot{V}O_2$. Indeed, the statistical comparison of the overall discriminatory power of peak $\dot{V}O_2$ and the walk test by receiver operating characteristic curves failed to detect a significant difference between the two. As NYHA class is an 'always available' indicator, our results suggest that, although simple and cheap, the administration of a walk test is redundant in the prognostic stratification of chronic heart failure patients. It should be stressed, however, that our population did not include resting symptomatic patients (NYHA class IV), patients with a mild severity of functional impairment (NYHA class I) and elderly people.

Our results concerning the univariate and multivariate association of the walk test and peak $\dot{V}O_2$ with prognosis are in substantial agreement with previous studies on the subject, which considered similar or partly similar populations of patients. Cahalin *et al.*[14], Roul *et al.*[15] and Lucas *et al.*[18] found a significant, or borderline significant univariate association between the categorized walk test and the outcome (death + hospital admission for heart failure or death + urgent transplantation), but in a multivariate model statistical significance was definitely lost. Zugck *et al.*[17] found that the walk test and peak $\dot{V}O_2$ were significant univariate predictors of the outcome (death + hospital admission for heart failure) either used as continuous variables or after stratification, but multivariate analysis to assess their mutual prognostic relationship was not done. Of note, contrary to our study protocol, in all these studies only one walk test was administered to the patients and in two of them[15,18] encouragement of the patients was used during the test

Conclusions

In summary, in moderate-to-severe heart failure patients the distance walked in the 6-min test is not related to cardiac function and only moderately related to exercise capacity. Walking performance does not provide prognostic information which can either complement or substitute that provided by peak $\dot{V}O_2$ or NYHA class. We are thus led to conclude that in this population of chronic heart failure patients the walk test is of limited usefulness as a decisional indicator in clinical practice.

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