

Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy?

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Aims The 6-min walk test may serve as a more simple clinical tool to assess functional capacity in congestive heart failure than determination of peak oxygen uptake by cardiopulmonary exercise testing. The purpose of the study was to prospectively examine whether the distance ambulated during a 6-min walk test (i) correlates with peak oxygen uptake, (ii) allows peak oxygen uptake to be predicted, and (iii) provides prognostic information similar to peak oxygen uptake in patients with dilated cardiomyopathy and left ventricular ejection fraction $\leq 35\%$.

Methods and Results In 113 patients (age: 54 ± 12 years, NYHA: 2.2 ± 0.8) with dilated cardiomyopathy (left ventricular ejection fraction $19 \pm 7\%$) a 6-min walk test and cardiopulmonary exercise testing were performed. The 6-min walk test and peak oxygen uptake were closely correlated at the initial visit ($r=0.68$, $n=113$), as well as after 263 ± 114 ($r=0.71$, $n=28$) and 381 ± 170 days ($r=0.74$, $n=14$). During serial exercise testing the 6-min walk test allowed peak oxygen uptake to be reliably predicted ($r=0.76$ between calculated and real peak oxygen uptake). After 528 ± 234 days, 42 patients were hospitalized due to worsening heart failure and/or died from cardiovascular causes. Compared to clinically stable patients, these

42 patients walked a shorter distance (423 ± 104 vs 501 ± 95 m, $P<0.001$) and had a lower peak oxygen uptake (12.7 ± 4.0 vs 17.4 ± 5.6 ml \cdot min $^{-1}$ \cdot kg $^{-1}$, $P<0.001$). By univariate analysis the 6-min walk test outperformed other prognostic parameters such as left ventricular ejection fraction, cardiac index and plasma norepinephrine concentration and conferred a prognostic power similar to peak oxygen uptake. This predictive value could be further improved in a multivariate model, by combining the 6-min walk test with independent variables, such as left ventricular ejection fraction or cardiac index.

Conclusion The 6-min walk test correlated with peak oxygen uptake when tested serially over the course of the disease. Although both tests define two distinct domains of functional capacity, the 6-min walk test provides prognostic information very similar to peak oxygen uptake in congestive heart failure patients with dilated cardiomyopathy.

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Introduction

The severity of congestive heart failure is usually graded according to patients' symptoms, in particular to the physical activity that induces dyspnoea or fatigue. An ideal instrument for risk stratification and optimal clinical management of congestive heart failure patients should be objective, as well as simple, inexpensive and safe. The NYHA functional heart failure classification

fulfils only some of these criteria. As the NYHA classification is based on the patient's self-assessment, its reliability has been a matter of debate since its introduction in 1948^[1]. A more objective parameter is the peak oxygen uptake, measured during cardiopulmonary exercise testing^[2]. This method has been widely used during the last decade to assess functional capacity and to predict survival in a variety of patient populations with advanced heart failure^[3–7]. Since the measurement of peak oxygen uptake requires sophisticated equipment and specially trained personnel, it is limited to specialized centres.

An alternative is the 6-min walk test, a submaximal exercise test, that simply measures the distance

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ambulated on a level hallway surface during 6-min^[8]. Since the 6-min walk test is a simple and less expensive clinical tool to assess functional capacity in patients with congestive heart failure than determination of peak oxygen uptake by cardiopulmonary exercise testing, the purpose of the present study was to examine prospectively the utility of the 6-min walk test in a well-defined group of 113 patients with dilated cardiomyopathy and a left ventricular ejection fraction $\leq 35\%$. Specifically, the study was designed to examine (i) whether the distance ambulated during the 6-min walk test correlates with peak oxygen uptake, (ii) whether the 6-min walk test allows peak oxygen uptake to be predicted in individual patients, when tested serially over the course of the disease, and (iii) whether the 6-min walk test provides prognostic information similar to peak oxygen uptake, with additional information to other prognostic variables, such as left ventricular ejection fraction, haemodynamic status or plasma norepinephrine concentration.

Methods

Study population

The study group included 113 patients with stable congestive heart failure (NYHA I–III), referred to the Department of Cardiology at the Medical Clinic of the University of Heidelberg between 7 December 1995 and 1 April 1998. All patients had left ventricular dysfunction caused by dilated cardiomyopathy (left ventricular ejection fraction $\leq 35\%$, determined by radionuclide ventriculography). The diagnosis had been confirmed by cardiac catheterization prior to inclusion into the study. Patients with a coronary stenosis, demonstrated angiographically as equal or more than 50% and those with neurological, orthopaedic, peripheral vascular or severe pulmonary diseases, that may have impaired successful completion of submaximal or maximal exercise testing, were excluded from the study. The study was approved by the institutional Ethics Committee and all patients gave their written informed consent. Standard medical therapy with e.g. ACE-inhibitors, digoxin and diuretics was individually optimized based on symptoms and renal function at least 6 weeks prior to exercise testing. All patients continued to take their routine medication, when the cardiopulmonary exercise testing and 6-min walk test were performed.

Cardiopulmonary exercise testing

All patients underwent a symptom-limited bicycle cardiopulmonary exercise test. The testing protocol consisted of a 5 min rest period and 2 min of free pedalling followed by 15W increments every 2 min at a constant pedal speed of 55 to 60 rpm. Blood pressure was measured automatically at 2 min intervals in the

right arm (blood pressure cuff for adults, ERKA, Bad Tölz, Germany). A 12-lead ECG (Servomed, Hellige, Freiburg, Germany) was continuously monitored and recorded every min for determination of heart rate and ST segment changes. Cardiopulmonary exercise testing equipment included a metabolic cart (Oxycon alpha, Jaeger, Würzburg, Germany) with an interfaced supine-positioned (30°) bicycle ergometer (Ergoline, Jaeger, Würzburg, Germany). Metabolic cart breath-by-breath analysis allowed on-line measurements of ventilation, tidal volume, respiratory rate, oxygen consumption and carbon dioxide production. Peak oxygen uptake (pVO_2) was defined as the highest oxygen consumption measured during the last 30 s of symptom-limited exercise. Exercise values were assessed breath by breath and were reported as mean values calculated over 10 s intervals. The predicted peak oxygen uptake (predicted peak oxygen uptake, $\% \text{pVO}_2$) was calculated according to Jones^[9].

6-min walk test

Within 24 h and at least 4 h before cardiopulmonary exercise testing a 6-min walk test was performed on a level hallway surface 132 m long; the test was administered by a registered nurse blinded to the results of cardiopulmonary exercise testing and radionuclide ventriculography. According to the method of Gyatt *et al.*^[8,10] all patients were informed of the purpose, methods and use of the 6-min walk test results. Allowing the patients to set the pace of ambulation with rest and stops as needed, they were asked to walk as far as possible within 6-min. In order to guarantee a standardized and reproducible procedure, the time was called out after 3 and 5 min without offering additional encouragement during the test. The total distance walked in meters (6-WT) during the 6-min walk test was recorded. In none of the patients did the 6-min walk test or cardiopulmonary exercise testing have to be terminated prematurely by the test administrator and no complications occurred during either test.

In order to assess the reproducibility of the test, 10 patients repeated the 6-min walk test on 3 consecutive days. The intra-class-correlation (ICC), a generalization of the Pearson-product-measurement correlation coefficient for bivariate data^[11], served as the measure of reliability. The ICC value of 0.96 obtained in the present study closely corresponds to data reported by others^[8,12,13].

Other parameters

Plasma norepinephrine

In order to determine the plasma concentrations of norepinephrine at rest (after the insertion of an intravenous canula and 30 min in the supine position), 2 ml

of venous blood was drawn (EDTA containing tubes, Sarstedt, Nümbrecht, Germany) and analysed by radioenzymatic assay^[14].

Pulmonary function

Pulmonary function tests were routinely obtained in all patients to exclude significant pulmonary disease as an additional cause of exercise limitation.

Right heart catheterization

Right heart catheterization with measurement of right atrial, pulmonary artery, and pulmonary capillary wedge pressures, and estimation of cardiac output by oxymetry was performed in 84 patients at rest.

Radionuclide ventriculography

Equilibrium radionuclide ventriculography at rest was performed with a multicrystal gamma camera (Orbiter, Siemens, Mannheim, Germany) in the left anterior-oblique view. Twenty min after pre-treatment of red blood cells with 2 ml of stannous pyrophosphate, 30 mCi of ⁹⁹Tc (Dupont, Bad Homburg, Germany) were rapidly injected, followed by data acquisition and analysis (RNV-Version 2.1, Elscint medical technology, Vienna, Austria). The right and left ventricular ejection fraction were derived from time-activity curves as (end-diastolic – end-systolic counts)/end-diastolic counts. While left ventricular ejection fraction was determined in all patients, a reliable right ventricular ejection fraction could be obtained only in 53 patients.

Clinical follow-up

Patients were routinely seen in the outpatient clinic at the Department of Cardiology at the University of Heidelberg. Medical therapy was adjusted to maintain an oedema-free state. Within the follow-up period serial exercise testings (cardiopulmonary exercise testing and 6-min walk test) were performed twice in 28 patients and three times in 14 patients. Follow-up information was available for all surviving patients at the time of analysis (1 May 1998). All cardiac transplantations (n=6 within 251 ± 241 days) were considered censored observations and thus excluded from further analysis. Records of hospitalizations and information about circumstances of death were obtained from hospital medical records or referring physicians. The combined prospective study end-point was defined as progressive heart failure requiring hospital admission for continuous inotropic, diuretic or mechanical support and/or sudden or progressive heart failure death.

Statistical analysis

The data are presented as mean ± SD except where otherwise specified. Spearman rank correlation coefficients were used as a measure of association. To test for

Table 1 *Patients' profile at first visit*

Number of patients (n)	113
Age (years)	54 ± 12
Gender (% male)	80
NYHA functional class	2.2 ± 0.8
NYHA I (n)	22
NYHA II (n)	43
NYHA III (n)	48
Rhythm	
Sinus rhythm (n)	86
Atrial fibrillation (n)	27
Medication	
ACE-inhibitor (n)	113
Digitalis glycoside (n)	76
Diuretic (n)	91
Beta-blocker (n)	17
Warfarin (n)	73
Amiodarone (n)	11
Intracardiac defibrillator (n)	18

significant differences between means, a two-sample Wilcoxon test was used and a value of $P < 0.05$ was considered indicative of a statistically significant difference. Initial univariable descriptive analysis were performed by use of the Kaplan–Meier method and log rank test^[15,16]. To identify the most important predictors of overall and event-free survival, multivariate Cox proportional hazards analysis and a subsequent best-subset selection process was used to determine the highest statistic score for up to 10 variables^[17,18]. Differences in event-free survival were detected by the Kaplan–Meier product limit method and compared by the Petro–Prentice generalized log-rank test.

Results

Patient's baseline characteristics

Baseline characteristics of all patients (n=113) are shown in Tables 1 and 2. The mean functional NYHA class was 2.2 ± 0.8 , with 42% of the patients being in NYHA functional class III. In 56 patients, the left ventricular ejection fraction was $\leq 20\%$ and in 43 patients the right ventricular ejection fraction was $\leq 35\%$.

Mean cardiac filling pressures were mildly elevated and cardiac index (CI, $2.1 \pm 0.6 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) was markedly decreased. Seventy six percent of the patients were in sinus rhythm. Mean plasma norepinephrine concentrations at rest were elevated ($2.8 \pm 2.3 \text{ nmol} \cdot \text{l}^{-1}$), with 16 patients having a plasma norepinephrine concentration of more than $4 \text{ nmol} \cdot \text{l}^{-1}$ (Table 2).

The cardiopulmonary responses during cardiopulmonary exercise testing are summarized in Table 3. No complications occurred during maximal exercise testing and all tests were terminated because of dyspnoea (38%) or fatigue (62%). Most of the patients

Table 2 NYHA functional class, haemodynamic data, left and right ventricular ejection fraction and plasma norepinephrine at baseline and their relationship to peak oxygen uptake (pVO_2) and the 6-min walk test (6'WT)

		pVO_2	6'WT
NYHA functional class	2.2 ± 0.8	$r = -0.59^*$	$r = -0.58^*$
Resting haemodynamics			
Heart rate (beats \cdot min $^{-1}$)	85 ± 18	$r = 0.08$	$r = 0.03$
Systolic blood pressure (mmHg)	116 ± 21	$r = 0.10$	$r = 0.10$
Diastolic blood pressure (mmHg)	79 ± 17	$r = 0.14$	$r = 0.18$
Mean right atrial pressure (mmHg)	6 ± 4	$r = -0.19$	$r = -0.13$
Mean pulmonary arterial pressure (mmHg)	25 ± 11	$r = -0.37^*$	$r = -0.15$
Mean pulmonary capillary wedge pressure (mmHg)	16 ± 9	$r = -0.25^*$	$r = -0.13$
Cardiac index (l \cdot min $^{-1}$ \cdot m $^{-2}$)	2.1 ± 0.6	$r = 0.02$	$r = -0.08$
Radionuclide ventriculography			
Left ventricular ejection fraction (%)	19 ± 7	$r = 0.34^*$	$r = 0.15$
Right ventricular ejection fraction (%)	25 ± 10	$r = 0.25$	$r = 0.32^*$
Plasma norepinephrine concentration at rest			
Norepinephrine (nmol \cdot l $^{-1}$)	2.8 ± 2.3	$r = -0.18$	$r = -0.14$

Data are presented as means \pm SD, * $P < 0.01$.

Table 3 Exercise performance and relationship between peak oxygen uptake (pVO_2) and the 6-min walk test (6'WT) at the initial visit

		pVO_2	6'WT
Cardiopulmonary exercise testing			
pVO_2 (ml \cdot min $^{-1}$ \cdot kg $^{-1}$)	15.4 ± 5.4	—	$r = 0.68^*$
pVO_2 (%)	50 ± 16	$r = 0.68^*$	$r = 0.61^*$
Exercise duration (min)	12.5 ± 5.2	$r = 0.87^*$	$r = 0.70^*$
Maximal work load (W)	85 ± 39	$r = 0.82^*$	$r = 0.68^*$
Maximal heart rate (beats \cdot min $^{-1}$)	140 ± 29	$r = 0.47^*$	$r = 0.51^*$
Maximal systolic blood pressure (mmHg)	154 ± 31	$r = 0.50^*$	$r = 0.42^*$
Maximal diastolic blood pressure (mmHg)	87 ± 21	$r = 0.09$	$r = 0.16$
6-min walk test			
Ambulated distance (m)	466 ± 107	$r = 0.68^*$	—
Maximal heart rate (beats \cdot min $^{-1}$)	98 ± 21	$r = -0.04$	$r = 0.17$
Maximal systolic blood pressure (mmHg)	132 ± 26	$r = 0.14$	$r = 0.12$
Maximal diastolic blood pressure (mmHg)	76 ± 13	$r = 0.06$	$r = -0.07$

Data are presented as means \pm SD, * $P < 0.01$.

had a markedly reduced peak oxygen uptake, (mean 15.4 ± 5.4 ml \cdot min $^{-1}$ \cdot kg $^{-1}$, range from 5.2 – 39.7 ml \cdot min $^{-1}$ \cdot kg $^{-1}$), with 12 and 52 patients achieving less than 10 and 14 ml \cdot min $^{-1}$ \cdot kg $^{-1}$, respectively.

The mean distance ambulated during the 6-min walk test was 466 ± 107 m (range from 182–692 m). Ten patients reached less than 300 m and 47 patients less than 450 m, with no patient requiring a rest stop.

The study population was subdivided into respective groups according to their NYHA functional class. NYHA III patients walked a significantly shorter distance and had significantly lower peak oxygen uptake as compared to NYHA I patients, although all patients had a similar left ventricular ejection fraction (Fig. 1). NYHA III patients were additionally characterized by significantly elevated plasma norepinephrine concentrations at rest (3.4 ± 1.7 nmol \cdot l $^{-1}$).

There was a strong univariate association between distance ambulated during the 6-min walk test and peak oxygen uptake (in men: $r = 0.69$, $P < 0.001$, in women: $r = 0.59$, $P < 0.001$) (Fig. 2), maximal workload ($r = 0.68$, $P < 0.001$) and exercise duration ($r = 0.70$, $P < 0.001$) (Table 3). However, there was no significant relationship between the 6-min walk test and either left ventricular ejection fraction, CI or resting plasma norepinephrine concentrations (Table 2).

Serial assessment of cardiopulmonary exercise testing and 6-min walk test during follow-up

After the initial examination, 28 patients performed a second (V_2), and 14 a third (V_3) cardiopulmonary

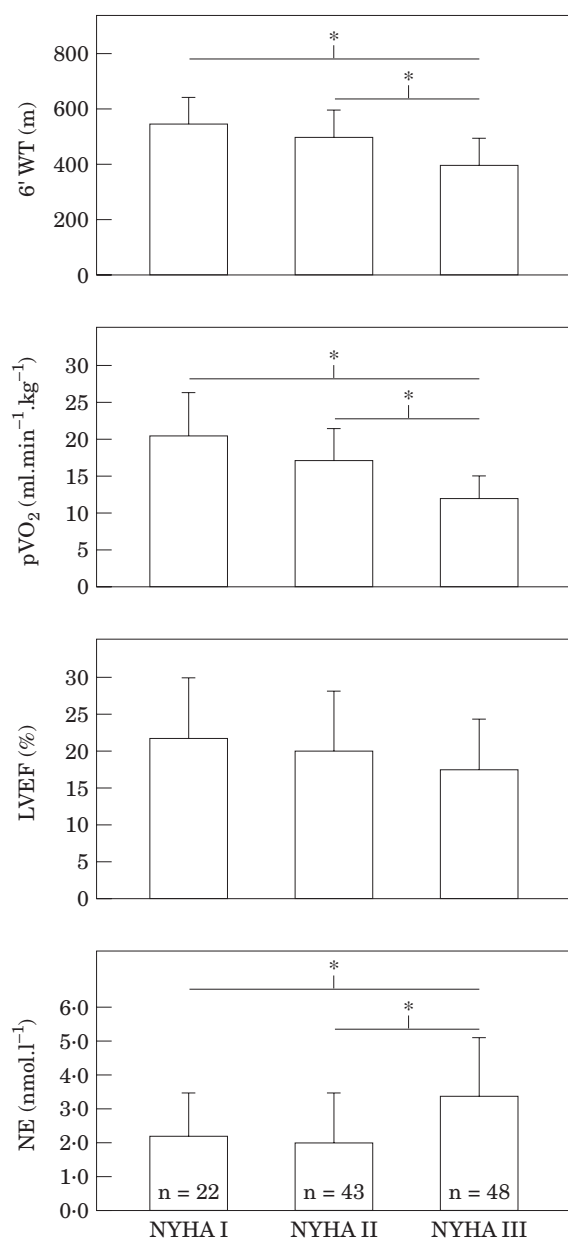


Figure 1 NYHA functional class at the initial visit in relation to the ambulated distance (6'WT), to the peak oxygen uptake (pVO₂), to the left ventricular ejection fraction (LVEF) and to the plasma norepinephrine concentration (NE). Data are presented as means \pm SD, * $P < 0.05$.

exercise testing and 6-min walk test. At follow-up visits 2 and 3, three patients covered a smaller distance, whereas 13 remained almost unchanged (difference ≤ 50 m vs V_1) and 12 improved their ambulated distance as compared to the baseline value at visit 1 (data not shown). The strong univariate association found between distance ambulated during the 6-min walk test and peak oxygen uptake was also found at V_2 ($r=0.71$, $P < 0.001$) and V_3 ($r=0.74$, $P < 0.001$) (Fig. 2). Additionally, the peak oxygen uptake at subsequent visits could

be reliably estimated based on the results of the repeated 6-min walk tests by calculating (Fig. 3): peak oxygen uptake (V_2 or V_3) = peak oxygen uptake (V_1) \times 6-min walk test (V_2 or V_3) / 6-min walk test (V_1).

Survival analysis

After a mean follow-up of 528 ± 234 days six patients received a cardiac transplant and were not included in the survival analysis (censored observations). Of the remaining 107 patients, 22 (21%) died of cardiovascular causes (annual mortality rate 15%) and 31 patients (29%) were hospitalized due to worsening heart failure. No non-cardiac death was registered. A subgroup analysis of the 18 patients with an intracardiac defibrillator revealed that three patients (17%) died and three (17%) were hospitalized due to worsening heart failure. Eleven (35%) of the 31 hospitalized patients died during consecutive follow-up (Table 4).

Event-free survivors had a significantly longer exercise duration, higher maximal workload, maximal systolic blood pressure, maximal heart rate, left ventricular ejection fraction and right ventricular ejection fraction, but lower norepinephrine plasma concentrations, pulmonary capillary wedge and pulmonary arterial pressures and a lower NYHA functional class compared to non-survivors ($n=22$). Table 4 summarizes the significant differences between event-free survivors ($n=65$), hospitalized patients ($n=20$) and non-survivors ($n=22$).

As compared to clinically stable patients ($n=65$), hospitalized and/or non-surviving patients ($n=42$, combined end-point) ambulated during the 6-min walk test a markedly reduced distance (501 ± 95 vs 423 ± 104 m, $P < 0.001$) was demonstrated with seven and 14 patients achieving less than 300 and 450 m, respectively. Similarly, the peak oxygen uptake was diminished (17.4 ± 5.6 vs 12.7 ± 4.0 ml \cdot min⁻¹ \cdot kg⁻¹, $P < 0.001$), as six and 16 patients achieved less than 10 and 14 ml \cdot min⁻¹ \cdot kg⁻¹, respectively. Likewise, a peak oxygen uptake of less than 50% of the predicted peak oxygen uptake value indicated a higher mortality rate, since only four out of 48 patients with predicted peak oxygen uptake $> 50\%$, but 19 out of 59 patients with predicted peak oxygen uptake $< 50\%$ died. Clinically stable patients had only a slightly higher left ventricular ejection fraction (20 ± 7 vs $17 \pm 7\%$, $P=0.033$). The walking distance of the six transplanted patients was similar to those patients who died during follow-up (384 m vs 399 ± 114 m) and significantly reduced compared to event-free survivors (501 ± 95 m).

Predictors of event-free survival

By univariate analysis ten variables out of the clinical, exercise capacity, neurohumoral and haemodynamic data were tested. NYHA class ($P=0.009$), predicted peak oxygen uptake ($P=0.006$), peak oxygen uptake, ($P=0.003$) and the 6-min walk test ($P=0.001$) were significant predictors of event-free survival. However, event-free survival was independent from CI ($P=0.11$),

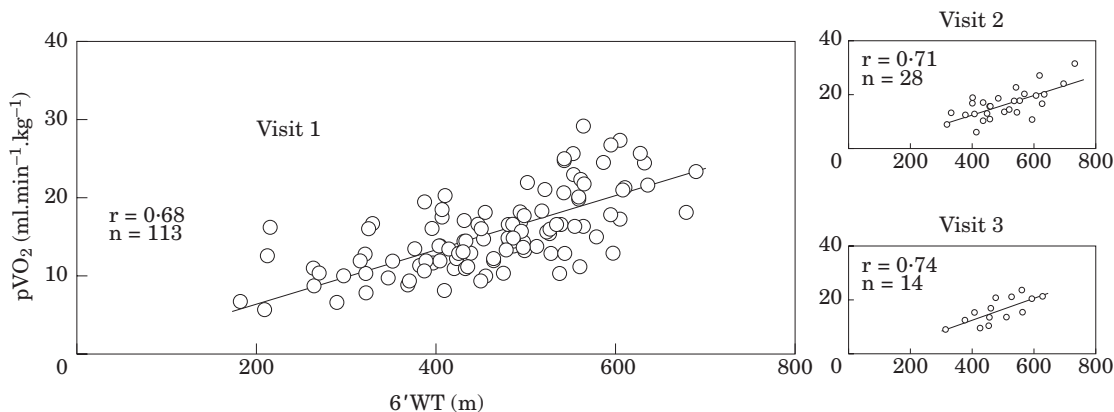


Figure 2 Relationship between the ambulated distance (6'WT) and peak oxygen uptake (pVO_2) at the initial visit (visit 1) as well as the first (visit 2, after 263 ± 144 days) and second (visit 3, after 263 ± 144 days) follow-up visit.

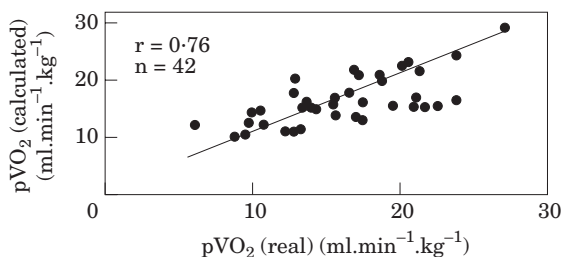


Figure 3 Relationship between real and calculated peak oxygen uptake (pVO_2) at follow-up visits. For further details see Methods.

age ($P=0.12$), left ventricular ejection fraction ($P=0.13$), heart rate ($P=0.35$), plasma norepinephrine concentration ($P=0.54$) or sex ($P=0.93$). A subsequent best-subset selection process revealed that the predictive value of the 6-min walk test alone (score: 10.5) could be further enhanced by combining with either left ventricular ejection fraction (14.9) or cardiac index (16.3). Adding other variables to this two-variable model failed to increase the predictive value.

Kaplan–Meier analysis

The patients were stratified into three groups on the basis of proposed cut-off values^[3,19]. Differences in event-free survival were constructed according to the Kaplan–Meier method. Event-free survival time was significantly lower in patients with a reduced ambulated distance during the 6-min walk test (stratified by <300 and 300–450 m), compared to patients reaching more than 450 m. Similarly, a peak oxygen uptake <10 and a peak oxygen uptake between 10 and 14 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively, predicted a worse outcome compared to patients with peak oxygen uptake >14 $ml \cdot min^{-1} \cdot kg^{-1}$ (each $P<0.001$, Fig. 4).

Discussion

The 6-min walk test has been proposed as an objective measure of submaximal exercise capacity of congestive

heart failure patients^[8]. It is thought to reflect a patient's level of impairment and functional status during daily activities better than maximal exercise testing, including assessment of peak oxygen uptake by cardiopulmonary exercise testing^[20]. The present study was designed to prospectively evaluate whether the 6-min walk test may be used as a reliable substitute for peak oxygen uptake in a well-defined group of 113 patients with congestive heart failure (left ventricular ejection fraction $\leq 35\%$) due to dilated cardiomyopathy.

In this patient population, the distance ambulated during the 6-min walk test (i) correlated closely with peak oxygen uptake, (ii) predicted individual peak oxygen uptake when determined serially in the same patient, and (iii) provided similar prognostic information as peak oxygen uptake. In a multivariate survival analysis, the distance ambulated during the 6-min walk test enabled a prognosis to be predicted, independent of established parameters used for risk stratification in congestive heart failure, such as left ventricular ejection fraction, cardiac index and plasma norepinephrine concentration. The results of the present study indicate that in a well-defined patient group the 6-min walk test may serve as a cost effective alternative to peak oxygen uptake.

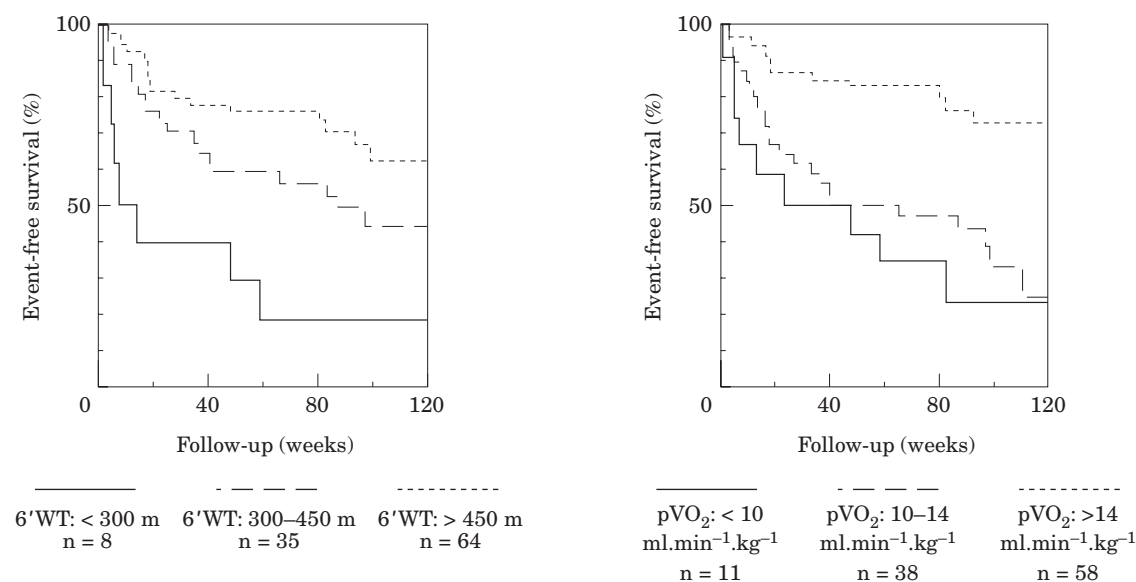
Safety, ease of administration and reliability of the 6-min walk test

The 6-min walk test was well accepted by individuals of both sexes and all age groups. Consistent with previous studies^[8,19–23], the 6-min walk test could be safely conducted even in patients with advanced congestive heart failure. In addition, the high reproducibility of the 6-min walk test in individual patients, with an intra-class correlation of 0.96 in the present as well as in the previous studies^[8,12,13], makes the 6-min walk test a potential candidate for routine assessment of functional capacity in congestive heart failure patients. However, similar to other tests used to determine exercise capacity, such as bicycle or treadmill exercise, its value is

Table 4 Comparison between event-free survivors, hospitalized patients and non-survivors

	Event-free survivors (I)	Hospitalized patients (II)	I vs II	Non-survivors (III)	I vs III
Number of patients (n)	65	20		22	
6-min walk test					
Ambulated distance (m)	501 ± 95	450 ± 86	ns	399 ± 114	<i>P</i> <0.001
Cardiopulmonary exercise testing					
pVO ₂ (ml . min ⁻¹ . kg ⁻¹)	17.4 ± 5.5	13.5 ± 3.7	<i>P</i> =0.005	11.9 ± 4.2	<i>P</i> <0.001
%pVO ₂ (%)	56 ± 15	44 ± 13	<i>P</i> =0.008	42 ± 15	<i>P</i> <0.001
Exercise duration (min)	14.5 ± 5.4	10.2 ± 3.0	<i>P</i> =0.003	9.4 ± 3.9	<i>P</i> <0.001
Maximal work load (W)	101 ± 41	67 ± 23	<i>P</i> =0.001	62 ± 29	<i>P</i> <0.001
Maximal heart rate (beats . min ⁻¹)	148 ± 27	136 ± 31	ns	125 ± 22	<i>P</i> <0.001
Maximal systolic blood pressure (mmHg)	163 ± 30	143 ± 34	<i>P</i> =0.022	143 ± 26	<i>P</i> =0.008
Maximal diastolic blood pressure (mmHg)	89 ± 21	79 ± 31	ns	92 ± 14	ns
Other parameters					
Age (years)	53 ± 12	54 ± 8	ns	58 ± 12	ns
NYHA class	2.0 ± 0.7	2.5 ± 0.7	<i>P</i> =0.005	2.6 ± 0.7	<i>P</i> =0.002
Heart rate (beats . min ⁻¹)	85 ± 15	87 ± 18	ns	86 ± 14	ns
Systolic blood pressure (mmHg)	121 ± 18	112 ± 22	ns	113 ± 13	ns
Diastolic blood pressure (mmHg)	82 ± 10	80 ± 13	ns	78 ± 10	ns
Mean right atrial pressure (mmHg)	5.2 ± 4.0	7.0 ± 5.0	ns	6.5 ± 3.3	ns
Mean pulmonary arterial pressure (mmHg)	22 ± 10	26 ± 13	ns	30 ± 10	<i>P</i> =0.003
Mean pulmonary capillary wedge pressure (mmHg)	14 ± 8	18 ± 9	ns	19 ± 9	<i>P</i> =0.045
Cardiac index (l . min ⁻¹ . m ⁻²)	2.2 ± 0.7	2.1 ± 0.5	ns	1.9 ± 0.5	ns
Left ventricular ejection fraction (%)	20 ± 7	20 ± 7	ns	15 ± 7	<i>P</i> =0.004
Right ventricular ejection fraction (%)	28 ± 10	18 ± 6	<i>P</i> =0.011	18 ± 7	<i>P</i> =0.003
Plasma norepinephrine concentration (nmol . l ⁻¹)	2.2 ± 1.6	2.7 ± 1.4	ns	3.5 ± 2.0	<i>P</i> =0.025

Data are presented as means ± SD, not significant (ns, *P*≥0.05). The group of the hospitalized patients (II) contains only those patients, who remained alive during consecutive follow-up. The 11 patients, who were first hospitalized and then died due to worsening heart failure, are included into the group of the non-survivors (III).

**Figure 4** Kaplan–Meier analysis of event-free survival with the patients stratified into three groups on the basis of the distance ambulated during the 6 min walk (6'WT) and on the peak oxygen uptake (pVO₂).

hampered in congestive heart failure patients whose exercise performance is limited by concomitant diseases, such as orthopaedic, neurological, peripheral vascular or severe pulmonary disease and/or exercise-induced

angina pectoris. Therefore, in the present study strict exclusion criteria were used and only congestive heart failure patients suffering from dilated cardiomyopathy were included.

Relationship between the 6-min walk test, peak oxygen uptake and other variables

The distance ambulated during the 6-min walk test and peak oxygen uptake were significantly reduced with increasing NYHA functional class. A strong univariate relationship between the 6-min walk test and both peak oxygen uptake ($r=0.68$) and predicted peak oxygen uptake ($r=0.61$) was observed. A similar relationship ($r=0.64$ and $r=0.58$, respectively) has previously been reported in 45 patients with symptomatic congestive heart failure due to a heterogeneous aetiology^[13]. The distance ambulated during the 6-min walk test also correlated significantly ($r=0.68$) with the maximum workload achieved during cardiopulmonary exercise testing. These findings indicate that submaximal exercise performance, as assessed by the 6-min walk test, may be used as a predictor of maximal exercise capacity. In contrast, there was no clinically relevant relationship between the 6-min walk test (or peak oxygen uptake) and left ventricular ejection fraction, right ventricular ejection fraction, cardiac index, cardiac filling pressures, or plasma norepinephrine in the present study. Therefore, it may be concluded that the distance ambulated during the 6-min walk test contains information that is complementary to haemodynamic parameters, such as left ventricular ejection fraction or cardiac index.

The *inter*-individual variability of the relationship between the distance ambulated during the 6-min walk test and peak oxygen uptake prompted us to test the hypothesis that the *intra*-individual variability is smaller than the *inter*-individual variability when serial exercise tests are performed in the same patient.

Prediction of individual peak oxygen uptake by the 6-min walk test during serial exercise testing

Serial exercise testing revealed a stable relationship between the 6-min walk test and peak oxygen uptake over a period of up to 381 ± 170 days. Based on the individual relationship between the 6-min walk test and peak oxygen uptake at the initial visit, peak oxygen uptake was calculated from the distance ambulated at respective follow-up visits. For calculation of peak oxygen uptake the following equation — a simple rule of three — was used:

$$\text{peak oxygen uptake (at follow-up)} = \frac{\text{peak oxygen uptake (at initial visit)} \times \text{6-min walk test (at follow-up)}}{\text{6-min walk test (at initial visit)}}$$

Both the calculated and the actually determined peak oxygen uptake were closely related ($r=0.76$, $P<0.001$). This finding indicates that the 6-min walk test may be used as a reliable predictor of peak oxygen uptake in individual patients. As the assessment of the distance ambulated during the 6-min walk test requires much less sophisticated equipment, fewer personnel and less time

than determination of peak oxygen uptake by cardiopulmonary exercise testing, the 6-min walk test appears to be a cost-effective instrument to follow the individual course of the disease in congestive heart failure patients.

Prognostic value of the 6-min walk test in comparison to peak oxygen uptake

During follow-up, 39% of the patients reached the pre-specified end-point (hospitalization due to worsening heart failure and/or cardiac death). The annual mortality of 15% in the current patient population corresponds to the mortality rates recently reported for congestive heart failure patients with a similar left ventricular ejection fraction^[24,25].

Evaluation of potential candidates for cardiac transplantation requires reliable risk stratification. Several variables have been proposed to predict prognosis in congestive heart failure, including NYHA functional class, cardiothoracic ratio on chest X-ray, left ventricular ejection fraction and right ventricular ejection fraction, left ventricular volumes, cardiac index, cardiac filling pressures, serum sodium, and plasma concentrations of norepinephrine, natriuretic peptides and endothelins^[26,27]. However, these parameters only weakly correlate or do not correlate at all with each other. During the last decade, peak oxygen uptake has emerged as an independent predictor of prognosis that is generally accepted as the most reliable of all objective parameters used to determine the timing of heart transplantation in congestive heart failure patients^[28]. A peak oxygen uptake $<14 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ has been found in several studies to indicate a significantly reduced prognosis in congestive heart failure patients^[3,29] and is currently recommended as a relative indication for heart transplantation^[30]. In the present study, the 1-year mortality of congestive heart failure patients with a peak oxygen uptake $<10 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ was 50% compared to 26% in those patients with a peak oxygen uptake of $10\text{--}14 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ and 5% in those with a peak oxygen uptake of $>14 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. However, those congestive heart failure patients who died were not only characterized by a markedly reduced peak oxygen uptake but also ambulated a significantly lower distance during the 6-min walk test. Accordingly, the 1-year mortality was closely related to the distance ambulated during the 6-min walk test, with the values being 57%, 24%, and 8% for congestive heart failure patients walking $<300 \text{ m}$, $300\text{--}450 \text{ m}$, and $>450 \text{ m}$, respectively.

In contrast to two recent reports on patients with congestive heart failure of different aetiology in our well-defined group of patients with dilated cardiomyopathy the 6-min walk test was not inferior to peak oxygen uptake in predicting long-term (>6 months) survival^[13], nor limited to predicting the outcome only for a subset of patients ambulating less than 300 m ^[31]. Furthermore, univariate and multivariate analysis

revealed that the distance ambulated during the 6-min walk test outperformed other prognostic parameters, such as left ventricular ejection fraction, cardiac index or plasma norepinephrine, and conferred a prognostic power at least equivalent to peak oxygen uptake, predicted peak oxygen uptake or NYHA functional class. This predictive value of the 6-min walk test could be further enhanced if combined with independent, but in the univariate analysis less powerful variables, such as left ventricular ejection fraction or cardiac index.

Limitations of the study

The present study consisted of a well-defined group of 113 patients with a markedly reduced left ventricular ejection fraction ($\leq 35\%$) due to dilated cardiomyopathy in order to exclude limitations of exercise performance caused by angina pectoris or by concomitant (e.g. peripheral vascular) diseases. Since ischaemic heart disease has been shown to be one of the most common causes of impaired left ventricular function^[32,33], the applicability of our results to patients with congestive heart failure of different aetiologies and/or milder left ventricular dysfunction may be limited. However, an almost similar relationship was obtained in a group of congestive heart failure patients with mixed aetiologies^[13]. Furthermore, Bittner *et al.*^[19] previously reported a similar relationship between distance ambulated during the 6-min walk test and both morbidity and mortality in the SOLVD study group, which mainly comprised patients with an ischaemic aetiology of congestive heart failure and mild to moderate impairment of left ventricular function (left ventricular ejection fraction $<45\%$ or radiological evidence of heart failure).

Randomization was started before beta-blocker treatment became part of routine clinical practice in congestive heart failure patients. Although clinical trials have clearly shown that beta-blocker treatment reduces morbidity and mortality, its effect on functional capacity seems to be marginal^[34]. Therefore one might assume, that beta-blocker treated patients have a better prognosis for a given 6-min walk test or peak oxygen uptake, compared to those without beta-blocker treatment. As only 15% of our patients received a beta-blocker, this issue cannot be answered conclusively in the present study.

The 6-min walk test requires strict standardization in order to yield reproducible results. For maximal exercise testing the speed of the treadmill or the constant pedal speed is set by the operator, whereas the walking speed during the test almost entirely depends on the patient, as it is self-paced. Therefore, thorough instruction of the patient and a standardized mode and intensity of motivation are prerequisites for reproducible results^[10]. In addition, differences in the length of the hallway resulting in less or more frequent turns may also affect the distance ambulated during the 6-min walk test. On the other hand, some patients may have difficulty tolerating the facial mask required for respiratory gas analysis

during cardiopulmonary exercise testing. Furthermore, the results of cardiopulmonary exercise testing may also vary as maximum workload depends on patient motivation^[35], and a stable plateau of oxygen consumption at peak exercise is—in contrast to healthy people—not reached in most of the congestive heart failure patients^[36].

The results of exercise tests may improve with repeated testing due to a 'training effect'. Nevertheless, in the present study the distance ambulated on three consecutive days was very constant (variance $<5\%$) in individual patients. Furthermore, the stable relationship of distance ambulated during the 6-min walk test and peak oxygen uptake during serial testing rules out that one of the exercise tests is more prone to a 'training effect' than the other.

Finally, it has to be mentioned that the 6-min walk test does not provide information on exercise-induced ECG changes (e.g. ST depression). However, this potential disadvantage, in comparison to cardiopulmonary exercise testing, appears to be of minor relevance for patients with a non-ischaemic aetiology of left ventricular dysfunction.

Conclusions

Determination of submaximal exercise capacity by the 6-min walk test provides information similar to peak oxygen uptake and has an independent prognostic value in addition to established parameters such as left ventricular ejection fraction, cardiac index and plasma norepinephrine concentration. Since functional capacity in congestive heart failure patients may vary, even over short periods of time, serial exercise testing by the 6-min walk test may be preferred to cardiopulmonary exercise testing, as it is a simpler clinical tool and characterized by higher cost effectiveness. The ability of the 6-min walk test to predict peak oxygen uptake and its prognostic relevance may also be useful in serial evaluation of the patient's status and/or response to therapeutic interventions.

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