



## **6MWT Predicts Survival Better Than CPET in Patients with Stable Cardiomyopathy**

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### **Authors' contributions**

*Author A designed the study, wrote the protocol, and wrote the first draft of the manuscript. 'Author B' performed the statistical analysis, and 'Author C' managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Aims:** The prognostic value of different clinical, echocardiographic and functional parameters was evaluated in clinically stable outpatients with heart failure due to idiopathic dilated cardiomyopathy (DCM).

**Study Design:** Observational prospective study.

**Methodology:** 56 patients suffering from idiopathic dilated cardiomyopathy in waiting list for heart transplantation (33 men and 23 women, mean age 56.4 years) and in clinical stable conditions for a minimum of 3 months underwent baseline clinical evaluation, echocardiogram, 6 minute walk test (6 MWT) and cardiopulmonary exercise test (CPET). They were followed for an average period of 26.5 months to assess event-free survival (death, heart transplantation).

**Results:** During follow-up period 23 patients died, 21 for cardiovascular causes. 4 patients underwent heart transplantation. Age and sex were not related to survival. We found a significant predictive value for 6MWT (at 1 year event-free survival was 53% for a distance <300 m), but not for VO<sub>2</sub> peak or respectively anaerobic threshold (AT). At multivariate analysis using Cox-stepwise regression model NYHA class, 6MWT, left ventricular ejection fraction and left ventricular end diastolic diameter were independent prognostic markers of survival.

**Conclusion:** An advanced NYHA class, a higher LVEDD and a distance of < 300m at 6MWT are useful prognostic markers of event free survival in outpatients with stable DCM while CPET was not.

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## 1. INTRODUCTION

Several studies have supported the value of cardiopulmonary exercise test (CPET) in functional evaluation of patients with heart failure and peak oxygen consumption ( $VO_2$  peak) has been reported as the most sensitive independent prognostic index of survival (Cohn and Rector, 1988; Pilote et al., 1989). Heart transplantation is indicated when  $VO_2$  peak falls under 10-12 ml/kg/min (Szlachcic et al., 1985; Mancini et al., 1991). Six minutes walk test (6MWT) has been proposed as a simple, safe and inexpensive alternative to cardiopulmonary exercise test (Guyatt et al., 1985). The prognostic usefulness of 6MWT was first reported by Bittner et al. (1993) in patients included in the Studies of Left Ventricular Dysfunction (SOLVD) Trial and subsequently confirmed by other authors both in patients with moderate (NYHA II-III class) or severe heart failure of different etiologies (mainly coronary artery disease) undergoing evaluation for heart transplantation (Lipkin et al., 1986; Lucas et al., 1999; Rostagno et al., 2003), although accuracy of 6MWT to predict mortality in advanced heart failure was not confirmed by other authors (Aaronson, 1999).

However most of the studies evaluating the usefulness of the different methods of cardiovascular functional evaluation were performed before widespread introduction of beta-blockers, ACE-inhibitors (or AT1 inhibitors) or aldosterone inhibitors, thus that rarely a population of clinically stable outpatients with heart failure in waiting list for heart transplant may be examined.

Aim of present study was to prospectively evaluate the role of 6-minute walk test as prognostic factor both for mortality and overall event free survival (death plus heart transplant) in patients with clinically stable heart failure (CHF) due to idiopathic dilated cardiomyopathy (DCM) and to compare it to other indexes of cardiovascular function, in particular to  $VO_2$  peak.

## 2. MATERIALS AND METHODS

In the study were included 56 consecutive patients with clinically stable idiopathic dilated cardiomyopathy consecutively referred to our institution for clinical and functional evaluation from 01.01.04 to 06.30.04. Thirty-three patients were males and 23 females. Age ranged from 29 to 68 years (mean age 56.3 years). Clinical characteristics of patients are reported in Table 1.

Ten patients were in NYHA class I, 26 in class II and 20 in class III-IV. Diagnosis of primary dilated cardiomyopathy was made according to the criteria proposed by the working group of the European Society of Cardiology and absence of significant coronary disease (stenosis >50% of one of the main coronary artery) had been confirmed by coronary angiography. None of these patients has history of alcohol abuse or uncontrolled arterial hypertension. Patients were in treatment with diuretics (73%), ACE-inhibitors or AT1 –inhibitors (88%), beta-blockers (92%). The dosage of diuretics was not changed in the 48 hours preceding functional evaluation.

## 2.1 Study Design

The severity of symptoms was assessed using the New York Heart Association functional classification (AHA Medical/Scientific Statement, 1994). Within 3 days from hospital admission all the patients underwent chest X-ray and echocardiographic evaluation. Cardiopulmonary stress testing and 6-minute-walk corridor test were performed during two subsequent days at the same hour in the morning in a randomly assigned sequence.

**Table 1. Clinical characteristics of patients according to NYHA classes**

Clinical characteristics	Class I (10)	Class II (26)	Class III-IV(20)	ANOVA
Age (years)	57.9± 9.8	65.4±10.0	65.2 ±10.4	<0.0001
Follow-up (months)	39.6±15.1	37.8±16.2	26.3±16.4	<0.0001
6MWD (m)	427±71	367±90	242±100	<0.0001
LVEDD (mm)	54.7±9.7	60.0±11.4	63.2±8.9	0.0002
LVEF %	52.5±12.8	42.7±15.1	33.1±14.2	<0.0001
E/A ratio	0.93±0.37	1.27±+0.8	1.55±1.16	0.05
PAP (mmHg)	22.7±8.3	29.0±9.0	32.2±+10.2	<0.0001
pVO <sub>2</sub> (ml/kg/min)	21.6±5.3	18.2±3.7	17.4±4.0	0.012
AT (ml/kg/min)	18.7±3.9	15.5±2.8	14.9±3.1	0.0036

*LVEDD = left ventricular end diastolic diameter, LVEF= left ventricular ejection fraction, PAP= systolic pulmonary artery pressure, pVO<sub>2</sub>=peak oxygen consumption, AT= anaerobic threshold*

## 2.2 Cardiopulmonary Exercise Test

Cardiopulmonary exercise test was conducted at treadmill according to previously described methods (Stevenson, 1996; Rostagno et al., 2003). Cardiopulmonary functional capacity was assessed by determining the anaerobic threshold (AT) and the peak of oxygen consumption by expired gas analysis (OXYCON ALFA -JAEGER, Wuertzburg, Germany). According to VO<sub>2</sub> peak patients were subdivided into three groups (group I >20 ml/kg/min, group II between 15 and 20 ml/kg /min and group III between 10 and 15 ml/kg /min).

## 2.3 6 Minute Walk Corridor Test

The walk test was performed, as previously reported (Rostagno et al., 2003), in an indoor corridor 25 m long according to the suggestions of Guyatt et al. (1985). At the end of the six minutes the physician measured the distance walked by the patient. On the basis of the distance walked, performance was grouped into 3 different levels (level I >450 m, level II 300-450 m, level III < 300 m). The repeatability of the test was assessed in 50 patients by performing the test twice in the same day.

## 2.4 Other Measurements

Echocardiographic examination was performed in the left side recumbent position using a SIM 5000 echocardiograph (Esaote Biomedica, Florence Italy) with monoplane probes (2.50 and 3.75 Mhz). Measurements were made according to the recommendations of the American Society of Echocardiography (Henry et al., 1980). Patients were subdivided in 3 groups according to LVEF: group I > 40%, group II 30-40% group III < 30%.

Systolic pulmonary pressure was calculated adding right ventricle/right atrium pressure gradient to estimated right atrium pressure.

The study has been approved by ethical committee of AOU-Careggi. Informed consent was given by all patients.

## 2.5 Statistical Analysis

Results were expressed as the mean  $\pm$  standard deviation. Differences among groups were evaluated using the Student's t test. Correlation among different variables was evaluated with the standard regression coefficient analysis. Univariate analysis was performed by chi-square test with Yates' correction when necessary. Survival was analysed by the Kaplan Meier method and survival curves were compared by the log-rank test. Cox proportional hazards model was used for multivariate survival analysis. A value of  $p < 0.05$  was considered statistically significant.

## 3. RESULTS AND DISCUSSION

Patients were followed as outpatients with periodical control every 6 months. During an average follow-up period of  $26.5 \pm 17$  months 23 patients died (41%), 21 of cardiovascular causes (17 refractory heart failure, 4 sudden death), 1 for lung cancer and 1 for the consequences of stroke. 4 patients underwent heart transplantation.

### 3.1 6 Minute Walk Test

Patients who walked less than 300 m had a significantly higher risk of death or need for urgent heart transplant in comparison to groups who had an intermediate (300-450 m) or respectively an high level of performance ( $>450$  m). Although the difference among groups was already significant at 12 months, at 36 months event free survival was 53% in patients with 6MWD  $< 300$  m, in comparison to 72% and respectively 92% in the other two groups.

Survival curve in patients who walked less than 300 m was significantly worse than those obtained in the other two groups – log rank test  $\chi^2 = 6.26$ ,  $p = 0.044$  (Fig. 1).

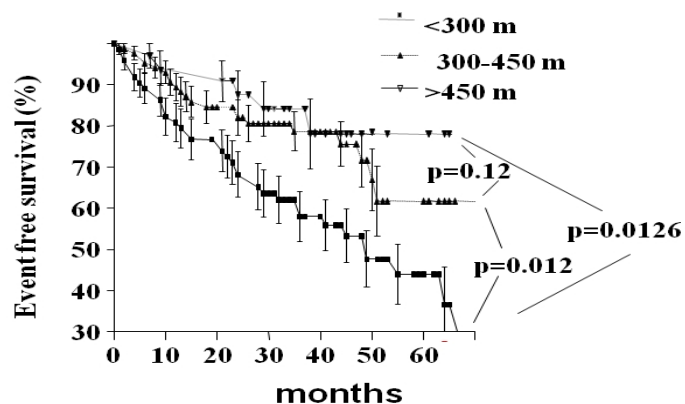


Fig. 1. Kaplan-Meier curves for 6 minute walk test according to the distance walked

### 3.2 Cardiopulmonary Exercise Test

A VO<sub>2</sub> peak above 20 ml/kg/min was associated with a good prognosis (event-free survival 87% at 36 months). Actuarial survival curves did not show any significant difference in event-free survival in patients with VO<sub>2</sub> peak comprised between 15 and 20 ml/kg/min and respectively VO<sub>2</sub> peak comprised 10 and 15 ml/kg /min, At 36 month's event free- survival were respectively 35 % and 42% (Fig. 2).

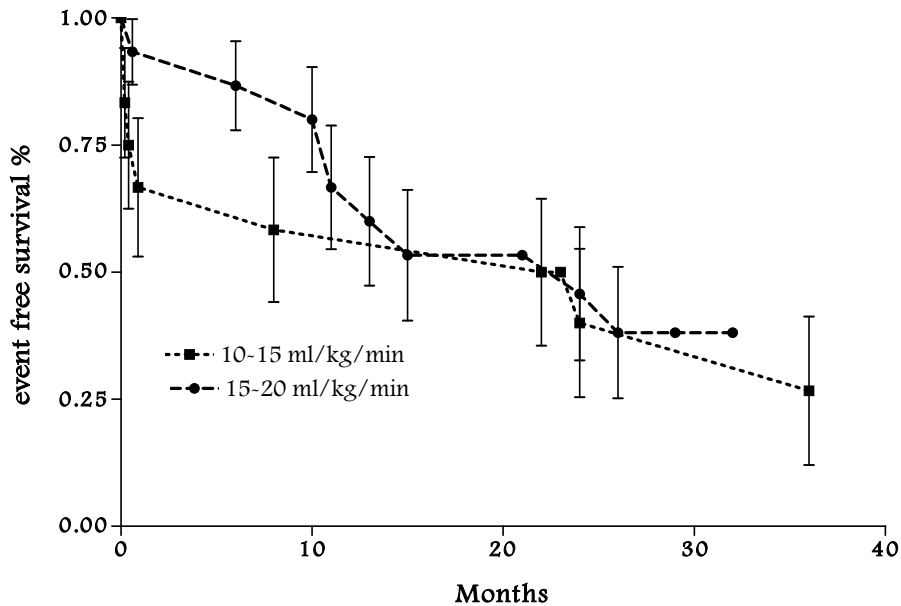


Fig. 2. Kaplan – Meier curves for peak oxygen consumption

To limit age and weight related variability of VO<sub>2</sub> peak measurement, percent of predicted oxygen consumption reached during cardiopulmonary test was calculated for each patient. No significant differences were found among groups stratified according to percent of predicted oxygen consumption.

### 3.3 Other Variables

We did not find any significant difference in prognosis when patients were stratified according to age: event free survival at 36 months was 20% for the younger group (< 55 years) and 28% in the other two groups (56-65 years, >65 years).

Survival was 91% in patients in NYHA I class, 83% in patients in NYHA II class, a difference not statistically significant. In patients in advanced NYHA classes (III-IV) survival was less than 50%. In these last patients Kaplan Meier survival curve was statistically different (p<0.0001 in comparison to both other groups). Both left ventricular end diastolic diameter and left ventricular ejection fraction were associated with event free survival.

A restrictive pattern of left ventricular filling (characterized by an E/A ratio >2) was associated with a significantly higher event-free survival was significantly lower in comparison to patients with normal pattern of left ventricular filling (64 vs 85%).

Pulmonary hypertension (mean pulmonary artery pressure > 30 mmHg) was related to a significantly lower 3 year survival (62% in comparison to 76% of patients with normal or slightly elevated pulmonary artery pressure).

### 3.4 Comparison with Other Variables

The relation with event free survival of various clinical, echocardiographic and functional parameters, categorized into different groups as described in method section, was examined. An advanced NYHA class (III-IV) was related to a significant lower probability of event free survival. A significant statistical relation with survival was found also for low LV ejection fraction, higher LV end-diastolic diameter and a restrictive pattern of LV diastolic filling (Table 2).

**Table 2. Univariate analysis**

	$\chi^2$	P
<b>Age- years</b>	2.13	0.34
<b>LVEF (%)</b>	23.21	0.0001
<b>LVFS(%)</b>	18.78	0.0005
<b>LVEDD mm</b>	15.75	0.001
<b>NYHA class</b>	41.6	0.0001
<b>AT (ml/kg/min)</b>	0.023	0.877
<b>pVO<sub>2</sub> (ml/kg/min)</b>	0.024	0.877
<b>6 MWD –meters</b>	9.68	0.007
<b>MPAP-mmHg</b>	5.919	0.0518
<b>E/A ratio</b>	17.19	0.0002

*LVFS= fractional shortening, LVEF= left ventricular ejection fraction, LVEDD = left ventricular end diastolic diameter, AT= anaerobic threshold, pVO<sub>2</sub>=peak oxygen consumption, MPAP= mean pulmonary artery pressure.*

Among functional indexes only a distance covered during 6MWT < 300 m was statistically related to a decreased event free survival while we failed to find any statistically significant relation between mortality and VO<sub>2</sub> peak or anaerobic threshold subgroups. The correction for age and weight using percent of predicted VO<sub>2</sub> peak values did not improve the predictive value of CPET. At multivariate analysis using Cox stepwise regression model, LV fractional shortening and the distance covered during 6MW were the strongest prognostic indexes, although LVEF, LVEDD and systolic pulmonary artery pressure were significantly related to event free survival (Table 3). The risk of death increased by 2.58 times for each change in NYHA class and decreased by 5/1000 per every meter walked at 6MWT.

### 3.5 Discussion

The prognostic value of VO<sub>2</sub> peak at CPET in patients with advanced heart failure has been fully established (Mancini et al., 1991) and a value <10 ml/min/kg is universally accepted as indication for heart transplant. However these results have been obtained in highly selected groups and before the widespread introduction of beta-blockers and ACE-inhibitors (or AT1 inhibitors). At present few investigations have been performed to evaluate the prognostic value of different clinical and laboratory parameters in patients with full medical treatment and stable heart failure. Present investigation has been performed in ambulatory patients in waiting list for heart transplant with established diagnosis of idiopathic dilated

cardiomyopathy who has been clinically stable for at least 3 months before investigation. Three year event free survival (death or heart transplant) has been 55%.

**Table 3. Multivariate analysis**

	Hazard ratio (CI 95%)	P
Age-years	1.007 (0.98-1.03)	0.58
NYHA class	2.58 (1.87-3.57)	0.000
AT(ml/kg/min)	0.99 (0.85-1.15)	0.85
pVO <sub>2</sub> (ml/kg/min)	1.01 (0.91-1.11)	0.84
6 MWD m	0.995 (0.993-0.997)	0.000
MPAP mmHg	1.03 (1.00-1.06)	0.028
E/A ratio	1.23 (0.90-1.69)	0.181

*LVFS= fractional shortening, LVEF= left ventricular ejection fraction, LVEDD = left ventricular end diastolic diameter, AT= anaerobic threshold, pVO<sub>2</sub>=peak oxygen consumption, MPAP= mean pulmonary artery pressure,*

Our results indicate that the distance covered during 6 minute walk test is an independent predictor of survival in this selected group of patients. In particular mortality is significantly higher in the group of patients who covered less than 300 m during the test. The prognostic significance of low LV ejection fraction, high (III-IV) NYHA class, pulmonary hypertension and a restrictive pattern of left ventricular filling are in agreement with previous investigations in patients with heart failure due to different etiologies (Ho et al., 1993; Xie et al., 1994; Pinamonti, 1997; Myers et al., 1998). At variance we were not able to identify any significant predictive value of pVO<sub>2</sub> in the group of patients under investigation. Survival curves did not significantly differ between patients who reached or did not reach a VO<sub>2</sub> peak of 14 ml/kg/min. As reported in the methods section all patients reached anaerobic threshold.

The demonstration that a cheap and simple method of functional evaluation such as 6MWD is provided with an independent prognostic value in patients with clinically stable DCM is of high practical relevance allowing patients to be followed also in peripheral centers. Although even NYHA classification has a relevant discriminator power however is not very clinically useful because it allows an almost binary distribution (event free survival 80-90 in class NYHA I-II, 50% or less in NYHA class III-IV).

Prognostic value of 6MWD in patients with heart failure was first reported by Bittner et al. (1993). They followed 898 patients with left ventricular dysfunction or radiological evidence of pulmonary congestion from the SOLVD investigation for a mean period of 242 days. Mortality was 10.23% in patients who walked less than 350 m in comparison to 2.99% (p<0.01) in patients who walked more than 450 m. Ejection fraction and the distance walked resulted as independent predictors of mortality or hospitalization.

Roul et al. (1998) followed 121 patients with mild to moderate heart failure (II-III NYHA Class) due to systolic dysfunction (average LVEF 29±13%) for a mean period of 18 months. Distance walked during 6MWT was not significantly lower in patients who reached the combined end point of death or hospitalization for heart failure in comparison to event-free group (410±26m vs 448±92m) while VO<sub>2</sub> peak was significantly higher in event free patients (18.5 ± 4 ml/kg/min vs 13.9±4 ml/kg/min, p<0.0001). However patients who walked less than 300m had a higher rate of combined events of death and hospitalization.

The prognostic value of 6MWT has been studied also in patients with severe heart failure (III-IV NYHA classes) referred for heart transplantation. Swedberg et al. (1995) evaluated 359 patients in a multicentric trial of continuous epoprostenol administration. Patients walking a distance below the median, 210m had a 6 month mortality of 50% vs 20% in patients who covered a longer distance. Cahalin et al. (1996) studied 45 patients referred for heart transplantation evaluation. A distance during 6MWT < 300 m predicted an increased likelihood of death or hospitalization for inotropic or mechanical support within 6 months but failed to predict overall or event-free survival at a follow-up of 62 weeks. Two studies performed in stable outpatients with heart failure due to dilated or ischemic cardiomyopathy (NYHA class II-III) outlined that a distance covered at 6 minute walk test < 300 m was associated with a significant worse prognosis with a 2 year mortality 4 to 6 folds higher than in patients with a 6 minute walk test distance > 300m (Urtis et al., 2004; Arlsan, 2007).

The results from present investigation suggest that in a population of clinically stable outpatients with heart failure due to idiopathic cardiomyopathy a distance walked during six minute walk test < 300m identify a high risk subgroup with a 3 year event free survival approaching 60%. In this subset of patients  $pVO_2$  at cardiopulmonary exercise test did not show any predictive value of event-free survival.

#### **4. CONCLUSION**

In our opinion 6MWD, in addition to echocardiography, but not CPET may be useful in clinically stable patients with idiopathic cardiomyopathy to identify subjects at risk of death or urgent heart transplant due to sudden clinical worsening. It must be underlined that the main limit of the investigation is the low number of patients included, that does not allow drawing definite conclusions.

#### **ETHICAL APPROVAL**

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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