

Prognostic value of 6-minute walk corridor testing in women with mild to moderate heart failure

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Background. The prognostic usefulness of 6-min walk testing (6MWT) was reported both in patients with severe as well as in those with moderate systolic heart failure. However, more than 80% of the patients investigated were males and the value of the test had never been separately evaluated in women. The aim of the present study was to prospectively assess the prognostic value of 6MWT in women with mild to moderate congestive heart failure.

Methods. Ninety-five women with congestive heart failure (mean age 63.9 years) were enrolled in the study. All patients were followed for a mean period of 38 months in order to assess the event-free survival (death, heart transplantation). The prognostic value of the distance walked during 6MWT was compared to the NYHA functional classification and to the echocardiographically-derived indexes of heart function. The results were then compared with those of a group of 129 male patients with similar clinical characteristics.

Results. Thirty-four female patients (36%) died of cardiovascular causes and 2 underwent heart transplantation. In the same period, the overall survival in male patients was 74% and 3 patients were successfully transplanted. Regardless of gender, the 3-year event-free survival was significantly lower in patients who walked < 300 m during 6MWT compared to that observed in those with an intermediate (300-400 m) or high level (> 400 m) of performance. At univariate and multivariate analyses, the NYHA class and the distance covered during 6MWT were significantly related to survival in both genders while with regard to the left ventricular ejection fraction, this relationship was observed only in women. The patient's age was not related to the mortality.

Conclusions. A distance < 300 m during 6MWT identifies a subgroup at high risk of death even in female patients with mild to moderate heart failure.

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Introduction

Impaired functional capacity is significantly related to a poor outcome in patients with heart failure^{1,2}. Six-min walk testing (6MWT) was suggested as a simple, safe and inexpensive alternative to the cardiopulmonary exercise test³. The prognostic usefulness of 6MWT was first reported by Bittner et al.⁴ in patients included in the SOLVD study and thereafter confirmed by other authors both in patients with severe heart failure undergoing evaluation for heart transplantation^{5,6} and in patients with moderate (NYHA functional class II-III) systolic heart failure⁷. Women however comprised only 0 to 27% of the populations investigated in these studies. Moreover, the prognostic value of 6MWT had never been separately evaluated in women. The aim of the present study was to prospectively assess the prognostic value of 6MWT in women with mild to moderate congestive

heart failure and to evaluate whether gender-related differences do exist in the prognostic value of 6MWT and other indexes of cardiovascular function.

Methods

The study included 95 women with congestive heart failure who were consecutively admitted to our Institution from January 1, 1994 to June 30, 1995. Their age ranged from 29 to 70 years (mean age 63.9 years). The etiology of heart failure was coronary heart disease in 36%, idiopathic dilated cardiomyopathy in 31%, while 33% suffered from heart failure due to other causes (valvular, hypertensive, restrictive). A diagnosis of diastolic heart failure was made in patients with a left ventricular ejection fraction > 50%, symptoms and chest X-ray evidence of heart failure and/or Doppler evidence of diastolic dysfunction.

This group was compared to 129 males with similar age and severity of heart failure admitted in the same period to our hospital. In this group of males, the etiology of heart failure was ischemic in 50%, due to primary dilated cardiomyopathy in 26% and to other causes in 24%. Patients with recent myocardial infarction (< 3 months), unstable angina or primary lung disease were excluded from the study. Treatment with digoxin (62% in women and 59% in men) and ACE-inhibitors (84% in both groups) was not withdrawn during the study, while the dosage of diuretics was not changed in the 48 hours preceding functional evaluation. The baseline characteristics of the two groups are reported in table I. The clinical characteristics of female patients subdivided according to the NYHA classification are reported in table II.

The walk test was performed according to the suggestions of Guyatt et al.³ in an indoor corridor 25 m long. Patients were instructed to walk the corridor from one end to the other, as fast and as many times as possible, in the established time. The test was performed under the control of a physician who encouraged the patients with phrases such as: "You are doing well" or "You are doing a good job". At the end of the 6 min the physician measured the distance walked by the patient. On the basis of the distance walked, the performance was classified into three different levels (level I > 400 m,

level II 300-400 m, level III < 300 m). The repeatability of the test had been previously assessed in 50 patients of both sexes by performing the test twice in the same day.

Echocardiographic evaluation was performed in the left recumbent position using a SIM 5000 echocardiograph (Esaote Biomedica, Florence, Italy) with mono-plane probes (2.50 and 3.75 MHz). Measurements were made according to the recommendations of the American Society of Echocardiography⁸. The ejection fraction was measured by the area-length method while the mean pulmonary artery pressure was estimated by the acceleration time method.

Statistical analysis. Results were expressed as means ± SD. Differences among groups were evaluated using the ANOVA or χ^2 analysis when appropriate. Univariate and multivariate analyses of the association of the different variables with survival were performed. Univariate analysis was performed after categorization of data according to cut-off points proposed in the literature. Multivariate analysis was assessed by the stepwise Cox regression method. Survival was analyzed by the Kaplan-Meier method and survival curves were compared by the log-rank test. A value of $p < 0.05$ was considered statistically significant.

Results

Patients had been prospectively followed for an average period of 38 months. At the end of follow-up, 34 female patients had died (36%), all of cardiovascular causes, 5 of sudden death and 1 of the sequelae of embolic stroke while on the waiting list for heart transplantation. Two patients underwent heart transplantation. We lost track of 4 patients at follow-up. The overall survival in male patients was 74%; 4 patients died suddenly and 1 of lung cancer. Three patients underwent heart transplantation. Nine patients were lost to follow-up.

The average distance walked during 6MWT was 309 ± 112 m for the whole female group in comparison to 324 ± 114 m for males ($p < 0.002$). In both genders, patients in NYHA class I walked a distance significantly longer than patients with a higher NYHA functional class.

Table I. Clinical characteristics of patients subdivided according to gender.

	Females (n = 95)	Males (n = 129)
Age (years)	63.9 ± 10.9	62.4 ± 10.5
NYHA class	2.12 ± 0.80	2.14 ± 0.80
6-min walk test (m)	309 ± 112	324 ± 114
LVEDD (mm)	56.3 ± 9.6	59.6 ± 11.2
FS (%)	27.1 ± 8.4	25.3 ± 8.5
LVEF (%)	44.9 ± 15	39.8 ± 16
PAP (mmHg)	29.7 ± 9.6	29 ± 9.8
E/A ratio	1.2 ± 0.6	1.3 ± 0.6

FS = fractional shortening; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; PAP = mean pulmonary artery pressure.

Table II. Clinical characteristics of female patients subdivided according to NYHA class.

	NYHA class			ANOVA
	I	II	III-IV	
Age (years)	59.2 ± 10.1	64.8 ± 10.6	66.1 ± 11.2	0.06
6-min walk test (m)	401 ± 69	327 ± 100	217 ± 87	< 0.0001
LVEDD (mm)	52.9 ± 7.9	54.6 ± 9.4	60.5 ± 9.5	0.0065
FS (%)	31.4 ± 6.2	30.1 ± 7.4	20.7 ± 8	< 0.0001
LVEF (%)	55.5 ± 10.4	49.7 ± 14.6	33.5 ± 16	< 0.001
PAP (mmHg)	22.5 ± 8.9	31.7 ± 9.3	34.2 ± 11	< 0.0062

Abbreviations as in table I.

Age did not influence the prognosis neither in female nor in male patients.

In women, the 3-year event-free survival was significantly lower in the group of patients who walked < 300 m (44%) than in those who had an intermediate (300-400 m) or high level (> 400 m) of performance in whom the event-free survivals were respectively 82 and 100%. The event-free survivals in male patients at 3 years were respectively 49% for the lower performance group, 73% for the intermediate, and 80% for patients who walked > 400 m. The actuarial survival curve in patients who walked < 300 m was significantly different from those obtained in the other two groups (Fig. 1) while the difference observed between the other two groups did not reach statistical significance.

Survival did not differ between patients in NYHA functional classes I and II in both gender groups and was significantly higher than in patients in NYHA classes III-IV. The survival curves are shown in figure 2.

The left ventricular ejection fraction was not a significant predictor of event-free survival in male patients while females with a left ventricular ejection fraction < 35% showed a higher mortality in comparison to the other groups (Table III). In both sexes, patients with diastolic dysfunction showed the best survival.

The event-free survival was related to the degree of pulmonary hypertension in both groups. An elevated

mean pulmonary artery pressure (> 30 mmHg) was associated with a 3-year survival of 40% in women and 60% in men, in comparison to 62% in women and 73% in male patients with a mildly elevated pulmonary artery pressure, and 82% in women and 78% in men with a normal pulmonary artery pressure.

In table III the prognostic significance of the different clinical variables at univariate analysis is reported. At stepwise regression analysis, the NYHA functional class and the distance covered at the 6MWT were independently related to the event-free survival.

Discussion

Despite the similar prevalence of heart failure in both genders^{9,10}, large clinical trials were mainly conducted in male populations (70-100%) so that evidence for the benefit derived from different medical treatments has not been provided for both sexes¹¹. Similarly, so far few investigations studied the usefulness of different methods for the prognostic stratification of women with heart failure. In comparison to healthy men, it has been shown that women achieve lower exercise workloads so that the measurement of any objective index of cardiac performance may be misleading in evaluating this parameter if reference values reported in

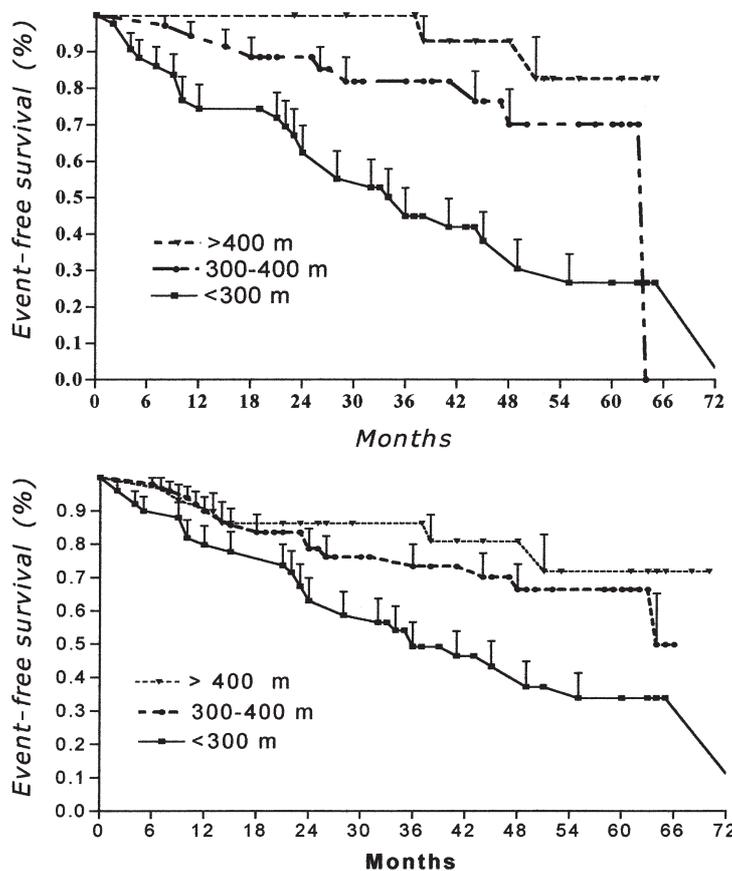


Figure 1. Event-free survival curves according to the distance walked at 6-min walk testing in female (upper panel) and male patients (lower panel).

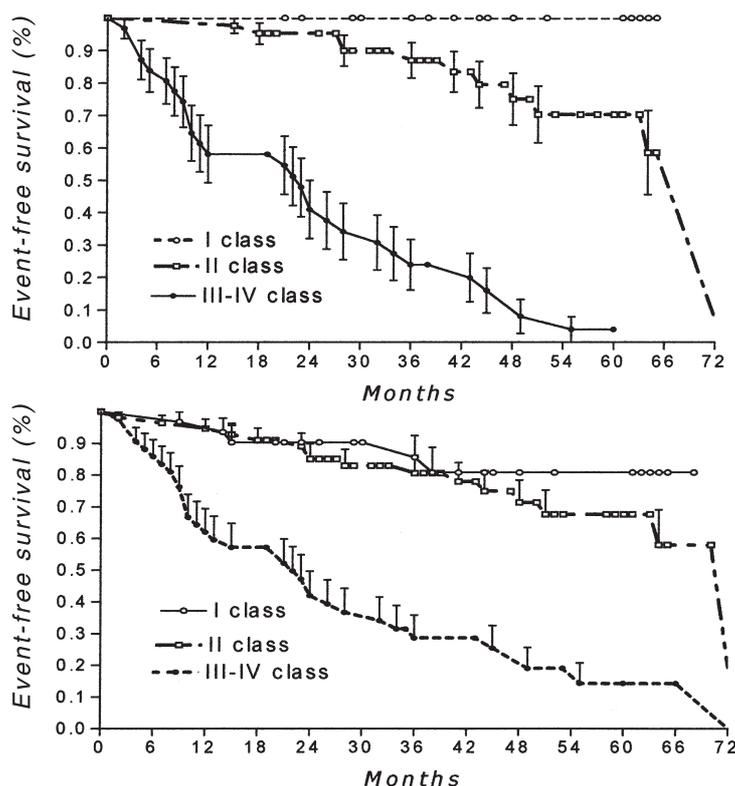


Figure 2. Event-free survival curves according to NYHA functional class in female (upper panel) and male patients (lower panel).

Table III. Prognostic value of different variables at univariate analysis after categorization of data.

	Females		Males	
	χ^2	p	χ^2	p
Age (years)	1.73	NS	1.33	NS
NYHA class	50.25	0.0001	35.75	0.0001
6-min walk test	21.60	0.0001	14.66	0.0007
LVEDD (mm)	9.64	0.01	8.94	0.02
LVEF (%)	9.36	0.01	2.56	NS
PAP (mmHg)	11.62	0.003	13.36	0.001

Abbreviations as in table I.

studies mainly performed in male populations are used. For example, most of the information on the prognostic value of the peak oxygen consumption derives from investigations performed in mainly male populations (70-100%) so that reference to absolute values of the peak oxygen consumption may overestimate the severity of cardiovascular impairment in female patients. Richards et al.¹² reported that the percentage of the predicted maximum oxygen consumption describes the degree of functional impairment in women better than the peak oxygen consumption.

Results from the present investigation suggest that the distance covered during 6MWT has a significant predictive value in women with mild to moderate heart

failure similar to, if not higher than in a group of male patients with the same baseline clinical characteristics. We found a closer linear relationship between the distance covered during 6MWT and the peak oxygen consumption at cardiopulmonary exercise testing in women than in men ($r = 0.60$ in women in comparison to 0.50 in male patients) and this suggests that in females the performance at 6MWT more frequently approaches the maximal exercise capacity.

The mortality was significantly higher in patients of both sexes who walked < 300 m during the test in comparison to patients with a better performance. In women, but not in men, an event-free survival of 100% was found in patients who covered > 400 m during the walk test, thus indicating that this subgroup is at very low risk of events within 3 years of follow-up.

A high NYHA class (III-IV) but not age was significantly related to survival. Similar results were found in male patients. A decreased left ventricular ejection fraction was related to higher event rates in women but not in men. The NYHA class and the distance covered at 6MWT were independent predictors of the event-free survival.

Several investigations have clearly shown the prognostic value of the NYHA classification in patients with heart failure of different severity. However, in subgroups with more severe disease objective methods of evaluation of the functional capacity, such as the measurement of the peak oxygen consumption, may allow a

more correct prognostic stratification. Patients enrolled in the present investigation had heart failure of different severity and etiology and may be considered representative of the population admitted to a general hospital. In such patients, NYHA classification could still give a better prognostic stratification by allowing the identification of those subgroups (class I and II patients) at low risk of events. Larger studies are needed to establish if an impaired functional performance (or increased biologic markers such as brain natriuretic peptide levels) may allow a further prognostic stratification in these low risk subgroups.

The prognostic value of 6MWT in patients with heart failure was first reported by Bittner et al.⁴. Among the 898 patients followed for a mean period of 242 days, only 22% were women. The average distance covered by females in that study was similar to that observed in the present one (330 m in comparison to 310 m in our study). The authors did not report the analysis of survival by gender. Other investigations evaluated the prognostic role of 6MWT in patients with mild to moderate⁷ or severe heart failure^{5,6}; however, each study included < 20 female patients and the percentage of women ranged from 0 to 18%. None of these investigations examined the performance of women separately. Ninety-nine women with advanced heart failure (23% of the population investigated) were enrolled in the FIRST trial¹³. In this investigation, the distance covered at the 6MWT was greater in men than in women and gender was a significant independent predictor of the results of 6MWT. The distance covered at 6MWT however was a significant predictor of survival ($r = 0.995$, 95% confidence interval 0.993-0.996, for each meter of increase in 6-min walk distance).

The present investigation has some limitations. First, the functional capacity was assessed by a submaximal test such as the 6MWT. As previously demonstrated, the results of the test are largely dependent on patient motivation and we cannot exclude that even in this group of patients, the evaluation of cardiovascular performance using cardiopulmonary exercise testing with the identification of the anaerobic threshold might have offered a better prognostic stratification.

We did not systematically record the degree of mitral regurgitation so that we cannot establish its relative role in the impairment of exercise capacity and its relation with the left ventricular ejection fraction. Moreover, pulmonary hemodynamic parameters were derived from Doppler echocardiographic examination and not measured directly during right heart catheterization; however, a good correlation between the noninvasive estimation and the invasive measurement has been previously demonstrated and confirmed in our laboratory. Finally, we examined a population with mild to moderate heart failure of different etiologies and we cannot exclude that in some patients myocardial ischemia (coronary artery disease was the cause of heart failure in 50% of male and in 36% of female patients) may have limit-

ed exercise capacity to a larger extent than left ventricular dysfunction *per se*. However, none of the patients complained of angina during the 6MWT.

In summary, our results suggest that at 6MWT, a distance < 300 m identifies a subgroup at high risk of death. This applies for patients of both genders with mild to moderate heart failure. With regard to this disease, the prognostic value may be higher in women than in male patients with similar baseline characteristics because in women the performance at 6MWT more closely approaches the maximal exercise capacity. Conversely, in women, but not in men, a covered distance > 400 m is related, on the whole, to a 3-year survival free of major events (100% event-free survival vs 80%). Referral to tertiary centers for further functional evaluation is recommended for patients with an impaired performance at 6MWT if heart transplantation is a therapeutic option.

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