

## Prognostic value of the six-minute walk test in heart failure

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## ABSTRACT

**Background:** The 6-minute walk test (6MWT) is a simple and low-cost method that allows assessment of functional capacity in patients with heart failure (HF). However, the prognostic role of 6MWT in HF remains uncertain.

**Objectives:** We aimed to evaluate the 6MWT as a predictor of mid-term adverse outcomes in patients with HF with mid-range and reduced ejection fraction.

**Methods:** Prospective single-center cohort study that included patients with HF with an ejection fraction under 50% at a specialized outpatient HF service. Patients underwent the 6MWT on admission and were compared according to the distance walked: Group I walked  $\geq 350$  meters and group II  $< 350$  meters. The primary outcome was a composite of death from any cause or hospitalization for HF decompensation in one-year follow-up. Secondary outcomes were the components of the primary outcome in an isolated analysis.

**Results:** Sixty patients were included, 43.3% male, with a mean age of  $61.1 \pm 12.9$  years and ejection fraction  $34.3 \pm 10.1\%$ . 52 patients (86.7%) were on guideline-directed triple therapy for HF. The average distance walked in the 6MWT was  $395.1 \pm 98.8$  meters, with 40 patients (66.7%) in group I and 20 (33.3%) in group II. The primary outcome in groups I and II were, respectively, 15.0% and 35.0% ( $p=0.05$ ). One-year mortality was 5.0% vs 15.0% ( $p=0.18$ ) and the hospitalization rate was 10.0% vs 20.0% ( $p=0.28$ ).

**Conclusions:** There was no association of distance  $< 350$  meters in the 6MWT with the primary outcome in patients with HF. Despite the higher occurrence of outcomes in group II, the difference was not statistically significant in this analysis. On a selective basis, the 6MWT may be a useful tool for prognostic stratification in HF, if combined with other methods.

**Keywords:** Heart failure. 6-minute walk test. Prognosis.

## INTRODUCTION

Despite therapeutic advances in recent years, HF is still the leading cardiovascular cause of hospitalizations and its in-hospital mortality is increasing in Brazil [1]. Measuring functional capacity in outpatient follow-up of HF patients is an important method for risk stratification [2]. The 6-minute walk test (6MWT) assesses the total distance walked over the predetermined time of six minutes, and it is a simple, easy and reproducible method of objectively identifying functional capacity with low cost [3].

The 6MWT has shown to be a good predictor of mortality and hospitalization for HF in long-term studies [4,5] despite that there is still great inconsistency in several studies associations, probably due to the lack of standardized analysis in the performance and interpretation of this test, associated to the population heterogeneity [6]. The present study aimed to assess the impact of the 6MWT as a prognostic marker in patients with HF within one year.

## METHODS

### Study Design

Prospective single-center cohort study that evaluated outpatients with HF with mid-range and reduced ejection fraction in a specialized HF clinic of the public health system in Brazil.

### Sample Selection

Eligibility criteria for inclusion in the study were age over 18 years, left ventricular ejection fraction (LVEF) under 50% measured by the Simpson method on transthoracic echocardiogram, and previous follow-up in the HF clinic. The echocardiography equipment used was LOGIQ E9, General Electric (New York City, USA). Patients with acute HF, NYHA IV functional class, neurological or degenerative diseases that alter walking capacity, psychiatric illness preventing the comprehension of the test or any feverish state or acute infectious disease were excluded. Patients were included from August to December 2018 and underwent the 6MWT at the time of inclusion. Regular follow-up at the HF clinic was maintained, and one-year clinical follow-up assessed hard endpoints.

### Analyzed Variables and Outcomes

The analyzed variables were sex, age, body mass index, current smoking, hypertension, diabetes, dyslipidemia and atrial fibrillation. Regarding HF, LVEF, current *New York Heart Association* (NYHA) functional classification, ischemic etiology of the HF, the use of mortality-reducing medications on their respective target doses, and the use of digoxin, furosemide, statins and aspirin.

The 6MWT was performed by the medical staff after clinical evaluation, following a standardized protocol for the test execution. Patients were previously instructed to stop the exercise test if they had severe dyspnea, chest pain, syncope or presyncope, and to pause to rest or slow down if they had fatigue or mild dyspnea. To perform the test, the command given was to walk in the greatest possible effort on a 15-meter linear track, marked at every three meters, in order to walk as far as possible for six minutes. After four minutes, they received verbal stimuli to continue the walk test. Heart rate and oxygen saturation were continuously monitored. The test was interrupted by staff if patients presented chest pain, severe respiratory discomfort, syncope or presyncope, or if oxygen saturation dropped below 90%. Patients were divided in two groups according to the distance walked in the 6MWT: group I was composed of patients who walked a distance greater than or equal to 350 meters and group II walked less than 350 meters. The number of tests that needed to be interrupted before the end due to medical reasons of six minutes was also accounted in each group. In the 12-month clinical follow-up, a primary

composite outcome of death or hospitalization for decompensated HF was considered. Secondary outcomes were the primary outcome individual components (death and hospitalization for HF). In addition, the total number of hospitalizations in each group was analyzed as number of HF hospitalizations per 100 patients/year. Contact with patients for clinical follow-up was carried out through regular medical appointments at the HF clinic.

### Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) software version 23.0, using the Person's chi-square test, Fisher's exact test and t student test. Values of  $p < 0.05$  were considered statistically significant.

### Ethical aspects

The study was approved by the Research Ethics Committee number 663779. The study followed the rules of Ethics in Research, in terms of the Declaration of Helsinki and Resolution 466/2012 of the National Health Council, thus respecting human dignity, fulfilling the requirement with free and informed consent from participants, individuals or groups, which expresses their consent to participate in the research.

## RESULTS

Amongst 134 patients analyzed throughout five months, 60 patients were included, 40 (66.7%) in group I and 20 (33.3%) in group II as classified after the 6MWT, 26 (43.3%) were male, mean age  $61.1 \pm 12.9$  years and LVEF  $34.3 \pm 10.1\%$ . As per NYHA functional class, 31 (51.7%) were in functional class I, 25 (41.7%) in functional class II and four (6.7%) in functional class III. The clinical characteristics of the two groups were described in table 1.

**Table 1.** Baseline clinical characteristics according to the distance walked in the six-minute walk test.

Clinical features	Group I ( $\geq 350m$ )	Group II ( $< 350m$ )	P-value
Age, mean $\pm$ SD	$59,9 \pm 11$	$63,4 \pm 14$	0,34
Male, n (%)	15 (37,5)	11 (55)	0,19
Female, n (%)	25 (62,5)	9 (45)	0,19
Body mass index, mean $\pm$ SD	$28,1 \pm 6$	$28,2 \pm 10$	0,96
Hypertension, n (%)	25 (62,5)	15 (75)	0,33
Diabetes, n (%)	19 (47,5)	11 (55)	0,58
Dyslipidemia, n (%)	28 (70)	16 (80)	0,4
Atrial fibrillation, n (%)	6 (15)	3 (15)	1
Ejection fraction, mean $\pm$ SD	$36,6 \pm 10,1$	$29,5 \pm 6,6$	0,001
Ischemic etiology, n (%)	10 (25)	5 (25)	1
Functional class I	25 (62,5)	6 (30)	0,01
Beta-blocker use, n (%)	40 (100)	18 (90)	0,02
Betablocker use on target dose, n (%)	25 (62,5)	11 (55)	0,57
ACEI*/ARB** use, n (%)	17 (42,5)	7 (35)	0,57
ACEI*/ARB** use on target dose, n (%)	13 (32,5)	6 (30)	0,84
Sacubitril/valsartan use, n (%)	20 (50)	13 (65)	0,27

Sacubitril/valsartan use on target dose, n (%)	14 (35)	8 (40)	0,7
Spiromolactone use, n (%)	37 (92,5)	20 (100)	0,1
Furosemide use, n (%)	14 (35)	9 (45)	0,45
Digoxine use, n (%)	2 (5)	0 (0)	0,19
Test interruptions before end by medical staff, n (%)	1 (2,5)	13 (65)	0,0001

\*ACEI: angiotensin-converting enzyme inhibitor; \*\*ARB: angiotensin II receptor blocker.

As per mortality-reducing medications, the overall rate of beta-blockers use (carvedilol, metoprolol succinate and bisoprolol) was 96.7%, with a target dose use of 63.7%; angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) use was 40%, with a target dose use of 79.1%; sacubitril/valsartan use was 55%, with a target dose use of 66.6%; spironolactone use was 95%. In addition, 38.3% were on furosemide, 71.7% were on statin therapy and 45% were on use of aspirin. The average distance walked in the 6MWT was  $395.1 \pm 98.8$  meters. In one-year clinical follow-up there were five (8.3%) deaths, eight patients (13.3%) were hospitalized due to HF decompensation, and two (25%) of these needed to be hospitalized more than once during the study period. Comparisons of outcomes in the two groups are shown in Table 2.

**Table 2.** Clinical outcomes of the study population according to the results of the 6MWT.

Outcomes	Group I ( $\geq 350$ m)	Group II ( $< 350$ m)	P-value
Death or hospitalization	6 (15,0%)	7 (35,0%)	0,05
Death	2 (5,0%)	3 (15,0%)	0,18
Hospitalization	4 (10,0%)	4 (20,0%)	0,28
Number of hospitalizations per 100 patients/year	5 (12,5)	6 (30,0)	0,09

## DISCUSSION

In this single-center analysis, there was a marginal difference for the primary outcome between the groups  $<350$  meters and  $\geq 350$  meters walked in the 6MWT. There was a trend toward association between shorter walked distance and adverse composite outcomes (death or hospitalization) in patients with HF, although without statistical significance. A shorter distance also showed a trend towards association with mortality and with hospital readmissions for HF decompensation. In addition, we observed an association of greater distance with more frequent use of beta-blockers and higher LVEF. The 6MWT has been increasingly used due to its wide availability, ease of execution and safety, in addition to having a role in the prognostic evaluation in patients with HF [7,8]. However, there are still no standardized normative values in groups division or cutoff prognostic values for the distance walked in the test, which creates discrepancies in the interpretation of its result [6,9,12]. Besides, there is no formal recommendation to encourage the widespread use of the 6MWT in HF [13].<sup>13</sup> Nevertheless, its use can be useful in specialized services in clinical practice, as it is an objective and low-cost tool.

In our study, division of groups took into account values related to prognostic results according to the cardiopulmonary exercise test (CPET) [14]. Distance <350 meters in the 6MWT has a 71% sensitivity and 60% specificity to predict maximum oxygen consumption (VO<sub>2</sub>) <14 ml/kg/min obtained by CPET in patients with HF [6]. CPET is the gold-standard method for assessing functional capacity in cardiovascular diseases by measuring VO<sub>2</sub> during a maximal stress test [8]. However, performing CPET routinely is expensive and requires specialized and properly trained team.

Considering larger studies that used different patterns of group division, worse prognosis was observed in patients who walked less than 360 meters, which makes the 6MWT an independent predictor of mortality in HF [5,11]. We emphasize that our results show convergence with other studies, despite differences regarding sample size and follow-up period. Besides, this study comprehends a heterogeneous population, which included patients with mild, moderate and severe left ventricular dysfunction. However, previous studies reveal that the 6MWT has limited prognostic value in patients with mild left ventricular dysfunction, while in patients with severe myocardial systolic dysfunction it remains a predictor of mortality [3]. For these reasons, the 6MWT may have a more relevant role in risk stratification for patients with more severe and advanced HF with reduced ejection fraction, in which uncertainty about prognosis or the real functional class persist, allowing HF clinics to improve clinical management and reduce unfavorable outcomes in mid and long term.

Regarding medications that reduce mortality in HF, most of our patients were using guideline-recommended triple therapy. Compared to other studies [15,16], the overall rate of beta-blocker use reached a high percentage, which is an advantage in basic care quality, with a focus on therapeutic adherence, strongly recommended in an outpatient service specialized in HF. Previous studies demonstrate that the 6MWT does not evaluate the effectiveness of pharmacological therapy [17,18], and the association between medical therapy and distance walked in the 6MWT is difficult to assess by our analysis, since it was not designed for this purpose.

Although relevant, our study has important limitations. The sample is not widely representative, mainly because it excludes a portion of patients with neural-motor disorders, recent decompensation and very elderly HF patients. Therefore, our results are not applied to a population of greater HF severity. Even so, it is a study focused on the Brazilian population using public health assistance, which lacks reliable information in studies. Also, care is provided at a local HF reference clinic, which focuses on multiprofessional support and adherence to optimized medical treatment. These reference centers have shown to be capable of improving clinical outcomes [18]. The reduced sample size may have influenced the results regarding statistical significance, despite the proportional difference in the primary outcome between groups. Further studies are still needed to identify the best use of the 6MWT, with an emphasis on seeking to standardize the analysis, increasing the reliability for its use in target populations.

## CONCLUSIONS

The walked distance on the 6MWT, despite showing a trend towards association with the composite outcome of death or hospitalization for HF, could not predict prognosis in the mid-term follow-up. However, the 6MWT can be a useful and low-cost tool for assessing patients with HF, especially when questions rise about prognosis and functional capacity.

## DATA AVAILABILITY STATEMENT

Data can be provided by corresponding author Vinicius Angelo Astolfo on reasonable request.

**CONFLICTS OF INTEREST**

The authors declare that there is no conflict of interest regarding the publication of this article.

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