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

Authors:

| # | First name | Middle name | Last name     | Affiliation | ORCID               | E-mail address         |
|---|------------|-------------|---------------|-------------|---------------------|------------------------|
| 1 | Vinicius   | Angelo      | Astolpho     | 1           | 0000-0002-9325-483X | v.astolpho@gmail.com   |
| 2 | Roberto    | Ramos       | Barbosa      | 1, 2        | 0000-0002-6359-2678 | roberto.cardio@gmail.com |
| 3 | Gabriela   | Lira        | Devens       | 2           | 0000–0002-9468-9616 | gabrieladevens@hotmail.com |
| 4 | Leticia    | Admiral     | Louzada      | 2           | 0000-0003-4303-1010 | leticiadmiral@hotmail.com |
| 5 | Pietro     | Dall’Orto   | Lima         | 1           | 0000-0002-2692-9753 | pietrolima@gmail.com   |
| 6 | Rodolfo    | Costa       | Sylvestre    | 1           | 0000-0002-1909-4599 | rodolfosylvestre_1993@hotmail.com |
| 7 | Renato     | Giestas     | Serpa        | 1, 2        | 0000-0001-7219-405X | jrserpa@terra.com.br   |
| 8 | Osmar      | Araujo      | Calil        | 1, 2        | 0000-0002-0795-7740 | osmarcalil@uol.com.br  |
| 9 | Luiz       | Fernando    | Machado      | 1, 2        | 0000-0002-1092-8190 | uip@terra.com.br       |

1. Hospital da Santa Casa de Misericórdia de Vitória, Serviço de Cardiologia. Vitória, ES – Brasil.
2. Escola de Medicina da Santa Casa de Misericórdia de Vitória, Departamento de Cardiologia. Vitória, ES – Brasil.

**Corresponding author:** Vinicius Angelo Astolpho  
E-mail: v.astolpho@gmail.com  
Address: Av. Nossa Sra. da Penha, 2190, Bela Vista, 29027-502. Vitória, ES – Brasil  
Tel: +55 27 3334-3500
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 ≥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 ± 12.9 years and ejection fraction 34.3 ± 10.1%. 52 patients (86.7%) were on guideline-directed triple therapy for HF. The average distance walked in the 6MWT was 395.1 ± 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 at 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 ± 12.9 years and LVEF 34.3 ± 10.1%. As per NYHA functional class, 31 (51.7%) were in functional class I, 25 (41.7%) infunctional 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 (≥350m) | Group II (<350m) | P-value |
|-----------------------------------|----------------|-----------------|---------|
| Age, mean ± SD                    | 59,9 ±11       | 63,4 ±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 ± SD        | 28,1 ±6        | 28,2 ±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 ±SD       | 36,6 ±10,1     | 29,5 ± 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    |
| Beta-blocker 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    |
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 ± 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.

**DISCUSSION**

In this single-center analysis, there was a marginal difference for the primary outcome between the groups <350 meters and ≥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]. Nevertheless, its use can be useful in specialized services in clinical practice, as it is an objective and low-cost tool.

| Outcomes                              | **Group I (≥ 350m)** | **Group II (< 350m)** | **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        |
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 (VO2) <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 VO2 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 Astolpho on reasonable request.
CONFLICTS OF INTEREST
The authors declare that there is no conflict of interest regarding the publication of this article.

ACKNOWLEDGEMENTS
None to be declared.

FUNDING SOURCE
None.

REFERENCES
1. Fernandes ADF, Fernandes GC, Mazza MR, Knijnik LM, Fernandes GS, Vilela AT, Badiye A, et al. A 10-year trend analysis of heart failure in the less developed Brazil. Arq Bras Cardiol; 2020 Feb;114(2):222-231.
2. Schalcher C, Brehm H, Rickli M. Prolonged oxygen uptake kinetics during low-intensity exercise are related to poor prognosis in patients with mild-to-moderate congestive heart failure, Chest, 2003;124(2):580-6.
3. Ingle L, Rigby AS, Carroll S, Butterly R, King RF, Cooke CB, et al. Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. Eur Heart J. 2007;28(5):560-8.
4. Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD Investigators. JAMA. 1993;270(14):1702-7.
5. Ferreira JP, Metra M, Anker SD, Dickstein K, Lang CC, Ng L, et al. Clinical correlates and outcome associated with changes in 6-minute walking distance in patients with heart failure: findings from the BIOSTAT-CHF study. Eur J Heart Fail. 2019;21(2):218-226.
6. Giannitsi S, Bougiakli M, Bechlioulis A, Kotsia A, Michalis LK, Naka KK. 6-minute walking test: a useful tool in the management of heart failure patients. Ther Adv Cardiovasc Di. 2019 Aug;13:1-10.
7. Zugck C, Kruger C, Durr S, Gerber SH, Haunstetter A, Hornig K, et al. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? Eur Heart J. 2000;21(7):540-9.
8. Piepoli MF, Spoletini I, Rosano G. Monitoring functional capacity in heart failure. Eur Heart J Suppl. 2019;21(Suppl M):M-M12.
9. Arslan S, Erol MK, Gundogdu F, Sevimli S, Aksakal E, Senocak H, et al. Prognostic value of 6-Minute walk test in stable outpatients with heart failure. Tex Heart Inst J 2007;34:166-9.
10. Ingle L, Cleland JG, Clark AL. The relation between repeated 6-minute walk test performance and outcome in patients with chronic heart failure. Ann Phys Rehabil Med. 2014; 57 (4): 244-53.
11. Ingle L, Cleland JG, Clark AL. The long-term prognostic significance of 6-minute walk test distance in patients with chronic heart failure. Biomed Res Int. 2014;2014:505969.
12. Brenyo A, Goldenberg I, Moss AJ, Rao M, McNitt S, Huang DT, et al. Baseline functional capacity and the benefit of cardiac resynchronization therapy in patients with mildly symptomatic heart failure enrolled in MADIT-CRT. Heart Rhythm. 2012;9(9):1454-9.
13. Hinder M, Yi BA, Langenickel TH. Developing drugs for heart failure with reduced ejection fraction: what have we learned from clinical trials? Clin Pharmacol Ther. 2018;103(5):802-814.
14. Uszko-Lencer NHMK, Mesquita R, Janssen E, Brunner-La Rocca HP, Pitta F, Wouters EFM, Spruit MA. Reliability, construct validity and determinants of 6-minute walk test performance in patients with chronic heart failure. Int J Cardiol 2017; 240:285–290.
15. Chin KL, Skiba M, Tonkin A, Reid CM, Liew D, Krum H, et al. The treatment gap in patients with chronic systolic heart failure: a systematic review of evidence-based prescribing in practice. Heart Fail Rev. 2016; 21(6):675-97.
16. Teng TK, Tromp J, Tay WT, Anand I, Ouwerkerk W, Chopra V, et al. Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: a cohort study. Lancet Glob Health. 2018;6(9):1008-18.
17. Zielinska D, Bellwon J, Rynkiewicz A, Elkady MA. Prognostic value of the six-minute walk test in heart failure patients undergoing cardiac surgery: A Literature Review.
18. Yancy CW, Jessup CM, Bozkurt VCB, Butler J, Casey DE, et. Al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. 2017; 117 – 161