Ther Adv Cardiovasc Dis

2019, Vol. 13: 1–10

DOI: 10.1177/1753944719870084

6-minute walking test: a useful tool in the management of heart failure patients

Sophia Giannitsi, Mara Bougiakli, Aris Bechlioulis, Anna Kotsia, Lampros K. Michalis and Katerina K. Naka

***Abstract*:** Reduced functional ability and exercise tolerance in patients with heart failure (HF) are associated with poor quality of life and a worse prognosis. The 6-minute walking test (6MWT) is a widely available and well-tolerated test for the assessment of the functional capacity of patients with HF. Although the cardiopulmonary exercise test (a maximal exercise test) remains the gold standard for the evaluation of exercise capacity in patients with HF, the 6MWT (submaximal exercise test) may provide reliable information about the patient's daily activity. The current review summarizes the value of 6MWT in patients with HF and identifies its usefulness and limitations in everyday clinical practice in populations of HF. We aimed to investigate potential associations of 6MWD with other measures of functional status and determinants of 6MWD in patients with HF as well as to review its prognostic role and changes to various interventions in these patients.

Keywords: functional capacity, heart failure, heart failure with reduced ejection fraction, 6-minute walking test

Received: 21 January 2019; revised manuscript accepted: 22 July 2019.

Correspondence to:
Aris Bechlioulis
Second Department of Cardiology, University of Ioannina Medical School, University Campus, Stavros Niarchos Avenue, Ioannina, 45 500, Greece
md02798@yahoo.gr

Sophia Giannitsi
Mara Bougiakli
Anna Kotsia
Lampros K. Michalis
Katerina K. Naka
Second Department of Cardiology and Michaelidion Cardiac Center, Medical School University of Ioannina, Ioannina, Greece

Introduction

Heart failure (HF) is a worldwide modern epidemic as it is estimated that about 2% of the population suffers from this clinical syndrome while aging of the population is increasing. HF is associated with a high economic burden on health systems; this is mainly dependent on frequent and repeated hospital admissions and long-duration in-hospital stays.[1] Patients with HF commonly report symptoms of reduced functional ability, poor exercise tolerance and shortness of breath on exertion resulting in poor quality of life.[1] Reduced functional capacity in patients with HF has been associated with a worse prognosis and an increased socioeconomic burden and has been the target of various medical and interventional treatment modalities.[1]

Current methods for assessment of functional capacity and exercise tolerance in patients with HF are classified in three categories. First, the self-assessed or physician-reported categorization of patients' physical status that is mainly dependent on what the patient perceives as the limits of his/her daily activities. New York Heart Association (NYHA) classification of functional status is well embraced by several medical societies worldwide and has been used in clinical studies that proved the beneficial effects of various medications on mortality and morbidity in patients with HF.[1] Second, the gold standard measure of exercise capacity is the direct cardiorespiratory assessment of peak oxygen consumption (peak VO_2) in a maximal symptom-limited exercise test (cardiopulmonary exercise test; CPET). This modality offers the opportunity to explain the actual reason of dyspnea and fatigue based on the assessment of all systems involved in physical activity (i.e. heart, circulation, lungs and musculoskeletal system). On the other hand, it is an expensive method that demands special equipment and trained personnel, while its availability in many hospital settings is limited. In addition, patients often find it difficult to cooperate with the test either due to the complexity of the test or the severe impairment of their functional status. Third, the assessment of daily activities performance through submaximal exercise tests including the

6-minute walking test (6MWT) which is a simple and inexpensive test that is well-tolerated by the patient. 6MWT is considered as an alternative to CPET for risk stratification in patients with HF.[2–4]

The purpose of this article was to review the use of 6MWT in patients with HF and identify its usefulness and limitations in everyday clinical practice in populations of HF. Besides a brief review of the methodological issues regarding 6MWT, we aimed to investigate potential associations of 6MWT with other measures of functional status and determinants of 6MWT in patients with HF as well as to review its prognostic role and changes to various interventions in HF.

6MWT: methodological issues

Guidelines about 6MWT have been published in 2002 from the American Thoracic Society and describe the methodology, indications and contraindications of the test as well as practical recommendations to ensure the quality and reproducibility of the test.[5] Most recently, this methodology has been updated in a new report from both American Thoracic Society and European Respiratory Society.[6] Although a standard methodology has been proposed, there are many versions of the protocol used in various centers; nevertheless, it is important to use the same, strictly standardized protocol when comparing patients or following the same patient before and after intervention in the same center. The 6MWT is a simple test that requires no specialized equipment or advanced training for physicians and assesses the submaximal level of functional capacity of an individual while walking on a flat, hard surface in a period of 6 min (6-minute walk distance; 6MWD). It evaluates the responses of all systems involved during exercise but does not provide specific information on the function of each system as in the case of CPET. Despite a significant correlation of 6MWD with peak VO_2, changes in the 6MWD are not a reliable predictor of changes in peak VO_2 within individual patients and cannot be considered as a substitute of CPET in the assessment of patients with HF.[7]

The 6MWT may be used as a tool for the measurement of functional status of a patient especially in the case of advanced diseases with multiple comorbidities who cannot perform more complex exercise tests, such as patients with HF, chronic obstructive pulmonary disease or cystic fibrosis.[8–10] The prognostic role of 6MWT in terms of morbidity and mortality has been evaluated especially in patients with pulmonary arterial hypertension[11] and in HF populations[12,13] as will be discussed further below. Furthermore, the test has been indicated before and after treatment to assess the response to various medical interventions in many patient populations[14] including HF[15] but also to guide cardiac rehabilitation.

The 6MWT should be performed preferably indoors, on a flat, straight, hard-surfaced corridor usually at least 30 m long. The patient is told to be calm, to have taken his/her medications and to wear comfortable clothing and shoes. The supervisor records baseline oxygen saturation, heart rate and brachial arterial blood pressure and the Borg scale rating for dyspnea and fatigue. Once the patient has understood the instructions, he/she is ready to begin the test. The walking course must be marked every 3 m and it is advisable to place cones in the turnarounds . During the test the participants have to walk at a rate suitable to their condition and they are allowed to stop or slow down if they feel like doing so and resume walking as soon as possible. The supervisor is always present giving encouragement to the patient with standard phrases such as 'You are doing well', 'Keep up the good work'. Encouragement has been shown to affect the distance covered, especially in pediatric populations.[16] At the end of the test the supervisor again records the Borg scale for dyspnea and fatigue and then optionally measures arterial blood pressure, heart rate and oxygen saturation. The number of laps and the additional distance covered are recorded and the 6MWD is calculated.[5,6] A learning effect has been suggested and two measurements have been proposed at the initial assessment to ensure accuracy;[17] this effect may be less important in older patients with severe respiratory impairment and severe HF.[18]

As for safety, absolute contraindications for the 6MWT include acute myocardial infarction or unstable angina (acute phase), uncontrolled arrhythmias causing symptoms or hemodynamic compromise, acute myocarditis or pericarditis, uncontrolled acutely decompensated HF (acute pulmonary edema), acute pulmonary embolism, suspected dissecting aneurysm, severe hypoxemia at rest or acute respiratory failure, acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (such as infection, renal failure, thyrotoxicosis) or mental impairment leading to inability to cooperate. Relative contraindications are resting heart rate >120 beats/min, systolic blood pressure >180 mm Hg or diastolic pressure >100 mmHg. On the other hand, a test should be immediately stopped in case of chest pain, intolerable dyspnea, leg cramps, diaphoresis or any report of not feeling well.[5,6]

The reproducibility of the 6MWT is very good in the hands of physicians or nurses or any other operator that perform it regularly based on an established protocol.[19] It is not known whether the changes in 6MWD should be reported as an absolute value, a percentage change, or a change in the percentage of predicted values.[20] The 6MWD in healthy adults has been reported to range from 400 to 700 m.[21] There are several nonstandardized reference equations for 6MWD from healthy adult populations; their value has not been established due to high variation mainly attributed to the fact that different methodologies were used in various studies (Table 1).[22–38] Age, height, weight, sex, corridor distance, impaired cognition and need for continuous oxygen supplementation may independently affect the 6MWD in patients and therefore these factors should be taken into consideration when interpreting the results of 6MWT.[5,6]

Table 1. Studies in healthy adult populations that produced equations for reference values of six-minute walking distance.

Study	Reference equations	Age range (years)	Number of patients	R^2
Enright and colleagues[21]	M: 7.57 × Height(cm)–5.02 × Age–1.76 × Weight(kg)– 309 F: 2.11 × Height(cm)– 2.29 × Weight(kg)–5.78 × Age + 667	>40	290	M: 0.42 F: 0.38
Troosters and colleagues[22]	218 + [5.14×Height(cm)–5.32 × Age]–1.8 × Weight(kg) + 51.31 × Sex, Sex: F = 0, M = 1	50–85	53	0.66
Gibbons and colleagues[23]	794.1–2.99 × Age + 74.7 × Sex, Sex: F = 0, M = 1	20–80	79	0.41
Enright and colleagues[24]	M: 539 + 6.1 × Height(cm)–0.46 × Weight(kg)–5.8 × Age F: 493 + 2.2 × Height(cm)–0.93 × Weight(kg)–5.3 × Age	⩾68	752	M: 0.20 F: 0.20
Chetta and colleagues[25]	479.78 + 1.25 × Height(cm)–2.82 × Age + 39.07 × Sex, Sex: F = 0, M = 1	20–50	102	0.42
Camarri and colleagues[26]	182.86 + 4.12 × Height(cm)–1.75 × Age–1.15 × Weight(kg) + 34.04 × Gender, Sex: F = 0, M = 1	55–75	70	0.36
Poh and colleagues[27]	5.50 × (HRmax/HRmax Predicted) + 6.94 × Height(cm)–4.49 × Age–3.51 × Weight(kg)–473.27	45–85	35	0.78
Masmoudi and colleagues[28]	299.8–4.34 × Age + 3.43 × Height(cm)–1.46 × Weight(kg) + 62.5 × Sex, Sex: F = 0, M = 1	40–80	155	0.60
Alameri and colleagues[29]	2.81 × Height(cm) + 0.79 × Age–28.5	16–50	298	0.25
Ben Saad and colleagues[30]	560.50–5.14 × Age–2.23 × Weight(kg) + 2.72 × Height(cm) + 160 × Sex, Sex: F = 0, M = 1	⩾40	229	0.77
Iwama and colleagues[31]	622.46–1.85 × Age + 61.50 × Sex, Sex: F = 0, M = 1	13–84	134	0.30
Casanova and colleagues[32]	361– 4 × Age + 2× Height(cm)–1.5 × Weight(kg) + 3 × (HRmax/HRmax predicted)–30(if Female)	40–80	440	0.38

(Continued)

Table 1. (Continued)

Study	Reference equations	Age range (years)	Number of patients	R^2
Dourado and colleagues[33]	299.30−2.73 × Age−2.16 × Weight(kg) + 361.73 × Height + 56.39 × Sex, Sex: F = 0, M = 1	⩾40	90	0.55
Soaresa and colleagues[34]	511 + [0.0066 × Height(cm)^2]−0.068 × (Age^2 × 0.03−BMI^2)	20–80	132	0.55
Britto and colleagues[35]	890.46−6.11 × Age + 0.035 × Age^2 + 48.87 × Sex −4.87 × BMI, Sex: F = 0, M = 1	⩾18	617	0.46
Duncan and colleagues[36]	M: 290.6 × [Height (cm) × 0.525] × [Weight(kg)−0.317] × $e^{-0.009 \times Age}$ F: 260.3 × [Height (cm) × 0.525] × [Weight(kg)−0.317] × $e^{-0.009 \times Age}$	50–85	246	0.53
Oliveira and colleagues[37]	787.2−2.0 × Age−4.4 × BMI + 58.4 × Sex, Sex: F = 0, M = 1	18–70	158	0.38

BMI, body mass index; F, female; HR, heart rate; M, male; R^2, a measure of the variance explained by the model/equation.

6MWT in populations with HF

Correlation with other established markers of functional capacity

It has been reported that 6MWD is associated with the functional status of patients with HF and relates to established CPET measures, while it adds prognostic information over and beyond these measures. Previous studies have shown only a mild-to-moderate inverse correlation between the functional status assessed by NYHA classification and 6MWD.[3,10,18,39] In a recent systematic review, an inverse correlation between NYHA class II–IV and 6MWD (mean values ~400 m, 320 m and 225 m, respectively for NYHA class II, III and IV) was observed while an overlap in 6MWD between NYHA class I and II patients with HF (mean value ~400 m) was shown.[40]

It has been previously shown that CPET parameters such as VO_2 peak, VO_2 max and anaerobic threshold are the best indicators of functional capacity in patients with HF.[4,41] Several studies have shown moderate-to-strong correlations of 6MWD with peak aerobic capacity (peak VO_2) in CPET in HF populations (Table 2);[2,4,7,10,13,18,42–51] in patients with HF being evaluated for transplantation, a 6MWD < 350 m has a sensitivity of 71% and specificity of 60% for predicting VO_2 max <14 ml/kg/min.[5,52] Maximal power output during the CPET was found to be also independently associated with 6MWD.[18] A high VE/VCO_2 slope, an important prognostic marker in patients with HF, derived from CPET,[4,41] has

Table 2. Studies providing a correlation between 6-minute walking distance and peak VO_2 in patients with heart failure.

Study	Peak VO_2
Guyatt and colleagues[2]	$r = 0.42$, $p < 0.001$
Cahalin and colleagues[12]	$r = 0.64$, $p < 0.001$
Roul and colleagues[41]	$r = 0.65$, $p = 0.011$*
Lucas and colleagues[42]	$r = 0.28$, p = NS
Rostagno and colleagues[43]	$r = 0.56$, $p < 0.05$
Zugck and colleagues[9]	$r = 0.68$, $p < 0.01$
Opasich and colleagues[44]	$r = 0.59$, $p < 0.001$
Cheetham and colleagues[6]	$r = 0.81$, $p < 0.001$
Guazzi and colleagues[4]	$r = 0.68$, $p < 0.001$
Jehn and colleagues[45]	$r = 0.72$, $p < 0.001$
Carvalho and colleagues[46]	$r = 0.70$, $p = 0.0002$
Forman and colleagues[50]	$r = 0.54$, $p < 0.001$
Deboeck and colleagues[47]	$r = 0.52$, $p < 0.05$
Omar and colleagues[48]	$r = 0.40$, $p < 0.001$
Uszko-Lecer and colleagues[17]	$r = 0.58$, $p < 0.001$
Yoshimura and colleagues[49]	$r = 0.62$, $p < 0.001$

*Only in patients with low activity status.

been inversely associated with 6MWD.[4,50] On the other hand, in a randomized trial, in older patients with HF with preserved ejection fraction, 6MWD did not correlate with measures obtained from CPET and thus its usefulness as a test of functional capacity in this population has been challenged.[53]

Although both 6MWT and CPET define two distinct domains of functional capacity, it has been suggested that the 6MWT provides prognostic information very similar to peak oxygen uptake in patients with HF and reduced ejection fraction.[51] This predictive value has been shown to be further improved by combining the 6MWT with other variables, such as left ventricular ejection fraction or cardiac index.[10] 6MWT, as a submaximal test, may provide prognostic information that can complement or substitute the information given by peak VO_2 in the case when CPET is unavailable. On the other hand, in severely impaired patients with advanced HF, in whom a maximal exercise test cannot be obtained, 6MWT may serve as an indicator of maximal exercise.

Determinants of the 6MWD in patients with HF

It has been previously shown that various clinical, biochemical and echocardiographic parameters may affect and predict the results of the 6MWT. Several studies have identified clinical parameters, serum biomarkers or echocardiographic markers that were related to the distance walked in 6MWT in patients with HF. Older age, female sex, low body mass index, anemia, increased heart rate at rest and diabetes have been shown to relate to decreased 6MWD in patients with HF in various studies;[3,51,54,55] similar findings were reported in patients without HF.[55] Depression in patients with HF not only determines symptoms such as fatigue and the sense of physical wellbeing but also contributes to functional performance, as assessed by a decreased 6MWD independently of the presence of other confounders.[49,55] Estimated glomerular filtration rate was identified as an important determinant of the distance covered during the 6MWT.[18] Renal insufficiency has been suggested as a limiting factor to exercise capacity in patients with HF[56] and a reduction in estimated glomerular filtration rate may be used as an early marker to identify declining functional capacity in these patients.[57] Furthermore, in patients with chronic HF, N-terminal prohormone of brain natriuretic peptide, a biomarker of HF severity, was found to be a significant predictor of 6MWD, but this relationship was substantially less strong than that seen for peak VO_2.[58]

Furthermore, in patients with HF with reduced left ventricular systolic function, decreased 6MWD was associated with lower ejection fraction, longer total isovolumic time, higher Tei index, increased left atrial dimensions and left ventricle mass, mitral inflow E/A ratio and higher E/E′ ratio.[46,59,60] However, in multivariate analysis, only the E/E′ ratio and total isovolumic time independently predicted poor exercise performance suggesting that higher left ventricle filling pressures and more asynchronous left ventricle, were associated with decreased 6MWD[60] although not consistently.[59] In asymptomatic patients with hypertensive cardiomyopathy and preserved systolic heart function, 6MWD was also associated with the degree of diastolic dysfunction; independent predictors for abnormal 6MWT were increased E/E′ and decreased deceleration time of E-wave.[61] Finally, not only cardiac function, but also peripheral vascular function may affect exercise capacity in patients with HF. Improvement in ventricular-arterial coupling and aortic elastic properties in patients with HF, as assessed by a greater decrease in aortic pulsatile load using vasodilator therapy, has been related to improved submaximal exercise capacity assessed by 6MWT.[62]

Prognostic role of 6MWT test in patients with HF

The prognostic role of the 6MWT in patients with HF has been thoroughly investigated both in the chronic stable state and following a decompensation of acute HF, and specific cut-off 6MWD values as well its changes through time, have been associated with impaired prognosis.

A great number of studies have assessed the prognostic role of 6MWT mainly in stable patients with chronic HF; there are several inconsistencies in the associations observed in these studies and these may be attributed to differences in study design, cut-off values for 6MWD, population differences etc. In patients with HF with reduced ejection fraction, decreased performance in 6MWT has been related to increased mortality, nonfatal cardiovascular events and HF hospitalizations[12,39,44,51,54,63–65] mainly in populations with mild-to-moderate HF (NYHA class II–III) with a similar prognostic accuracy to VO_2 peak.[51] On the contrary, only few older studies reported a lack of prognostic role of 6MWD in patients with HF.[43,66] Most of the studies showing a prognostic role agree that a 6MWD $\leqslant$ 300 m is indicative of poor prognosis[13,42,44,63] while an even lower 6MWD < 200 m could identify patients with stable HF who are at markedly increased risk of death.[54] Accordingly, in a pediatric population diagnosed with dilated cardiomyopathy, a 6MWD < 63% of the predicted value was independently associated with increased mortality and heart transplantation.[67]

Changes in 6MWT performance and their prognostic role are less well studied. A stable 6MWD over 1 year in patients with HF and reduced ejection fraction was suggestive of increased survival rates.[68] On the other hand, a recent meta-analysis of trials in patients with HF using 6MWT showed a low level of association between improvements in 6MWD and mortality/hospitalizations and moderate levels of correlation between 6MWD with quality of life.[69] The magnitude of 6MWD improvement to show a benefit in quality of life is ~80 m which is higher than a 30–50 m increase in 6MWD observed in HF trials showing a favorable treatment effect on morbidity and mortality.[69,70]

The implementation of 6MWT in the setting of acutely decompensated HF is less studied. During decompensation it is difficult to accurately and safely estimate the functional status of the patient while the prognostic role of such an assessment does not have an established value. In this setting, the 6MWT was performed close to the discharge date after the initial stabilization of the HF patient. Decreased 6MWD has been shown to be one of the strongest independent predictors of long-term mortality and HF hospitalizations[3,71] in patients hospitalized for acute HF, although this was not a consistent finding in all studies.[72]

The role of 6MWT in the assessment of interventions in patients with HF

The 6MWT has been extensively used in various clinical studies in the assessment of response to interventions in patients with HF as a measure to evaluate the effect of the treatment on a patient's functional status. It is considered to be an easy, widely available and well-tolerated tool, yet with a questionable role in patients with HF, in contrast to populations of pulmonary arterial hypertension in whom 6MWT has been established as an important endpoint in clinical studies that led to therapy approval.[11] In general, variation of 6MWD in stable patients with HF over 6–12 months periods has been shown to be as low as ~36 m;[73] this finding may be relevant for the follow up of patients with HF as well as the investigation of clinically important changes in 6MWD following various interventions.

Traditionally, the 6MWT has been used to evaluate the effect of various exercise and rehabilitation programs in patients with HF with quite promising results.[74,75] In an early review,[76] clinical trials that were conducted to assess the effectiveness of treatments using 6MWT found contradictory results for various established life-saving treatments in HF. No significant improvement in 6MWD was observed in most of the studies using angiotensin-converting-enzyme inhibitors and beta blockers. On the other hand, the 6MWD was improved in the majority of studies using cardiac resynchronization therapy. In fact, decreased 6MWD (<350 m) could identify a group of patients that derived the most pronounced benefit from cardiac resynchronization therapy as manifested by a significant reduction in mortality.[77] Modern medical therapies in patients with HF, such as intravenous iron supplementation and sacubitril/valsartan treatment have been associated with an improvement in 6MWD (by ~35–40 m) although this improvement has not been directly related to prognosis in these patients.[78,79] Furthermore, novel treatments with transcatheter mitral or aortic valve interventions have been shown to improve 6MWT performance in patients with HF indicating a significant beneficial effect on the functional status of these patients.[80,81] In a recent meta-analysis of percutaneous mitral intervention using Mitra Clip in patients with HF and functional mitral regurgitation a mean increase of ~100 m in 6MWD was reported.[81]

Summary

The 6MWT is an easily performed, widely available and well-tolerated test for assessing the functional capacity of patients with HF in everyday clinical practice. Although maximal exercise tests, such as CPET, are the gold standard for assessing functional capacity, the 6MWT may provide reliable information about the patient's daily activity and the short-term prognosis especially in patients with HF and reduced ejection fraction, either in a chronic stable state or after an acute decompensation. Future studies are needed to standardize the methodology of 6MWT and establish the prognostic role of 6MWD in patients with HF with either reduced or preserved ejection fraction as well as the importance of changes in 6MWD in these patients.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Aris Bechlioulis https://orcid.org/0000-0003-1721-2539

References

1. Ponikowski P, Voors AA, Anker SD, *et al*. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129–2200.
2. Guyatt GH, Sullivan MJ, Thompson PJ, *et al.* The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985; 132: 919–923.
3. Alahdab MT, Mansour IN, Napan S, *et al.* Six minute walk test predicts long-term all-cause mortality and heart failure rehospitalization in African-American patients hospitalized with acute decompensated heart failure. *J Card Fail* 2009; 15: 130–135.
4. Guazzi M, Dickstein K, Vicenzi M, *et al.* Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. *Circ Heart Fail* 2009; 2: 549–555.
5. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
6. Holland AE, Spruit MA, Troosters T, *et al.* An official European respiratory society/American thoracic society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014; 44: 1428–1446.
7. Cheetham C, Taylor R, Burke V, *et al.* The 6-minute walk test does not reliably detect changes in functional capacity of patients awaiting cardiac transplantation. *J Heart Lung Transplant* 2005; 24: 848–853.
8. Nixon PA, Joswiak ML and Fricker FJ. A six-minute walk test for assessing exercise tolerance in severely ill children. *J Pediatr* 1996; 129: 362–366.
9. Hajiro T, Nishimura K, Tsukino M, *et al.* Analysis of clinical methods used to evaluate dyspnea in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158: 1185–1189.
10. Zugck C, Kruger C, Durr S, *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: 540–549.
11. Galie N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; 37: 67–119.
12. Bittner V, Weiner DH, Yusuf S, *et al.* Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD investigators. *JAMA* 1993; 270: 1702–1707.
13. Cahalin LP, Mathier MA, Semigran MJ, *et al.* The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest* 1996; 110: 325–332.
14. Vitale G, Sarullo S, Vassallo L, *et al.* Prognostic value of the 6-min walk test after open-heart valve surgery: experience of a cardiovascular rehabilitation program. *J Cardiopulm Rehabil Prev* 2018; 38: 304–308.
15. O'Keeffe ST, Lye M, Donnellan C, *et al.* Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. *Heart* 1998; 80: 377–382.
16. Morales MN, Audag N, Caty G, *et al.* Learning and encouragement effects on six-minute walking test in children. *J Pediatr* 2018; 198: 98–103.

17. Spencer L, Zafiropoulos B, Denniss W, *et al.* Is there a learning effect when the 6-minute walk test is repeated in people with suspected pulmonary hypertension? *Chron Respir Dis* 2018; 1479972317752762.

18. Uszko-Lencer N, Mesquita R, Janssen E, *et al.* Reliability, construct validity and determinants of 6-minute walk test performance in patients with chronic heart failure. *Int J Cardiol* 2017; 240: 285–290.

19. Beriault K, Carpentier AC, Gagnon C, *et al.* Reproducibility of the 6-minute walk test in obese adults. *Int J Sports Med* 2009; 30: 725–727.

20. Balashov K, Feldman DE, Savard S, *et al.* Percent predicted value for the 6-minute walk test: using norm-referenced equations to characterize severity in persons with CHF. *J Card Fail* 2008; 14: 75–81.

21. Enright PL. The six-minute walk test. *Respir Care* 2003; 48: 783–785.

22. Enright PL and Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998; 158: 1384–1387.

23. Troosters T, Gosselink R and Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; 14: 270–274.

24. Gibbons WJ, Fruchter N, Sloan S, *et al.* Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. *J Cardiopulm Rehabil* 2001; 21: 87–93.

25. Enright PL, McBurnie MA, Bittner V, *et al.* The 6-min walk test: a quick measure of functional status in elderly adults. *Chest* 2003; 123: 387–398.

26. Chetta A, Zanini A, Pisi G, *et al.* Reference values for the 6-min walk test in healthy subjects 20–50 years old. *Respir Med* 2006; 100: 1573–1578.

27. Camarri B, Eastwood PR, Cecins NM, *et al.* Six minute walk distance in healthy subjects aged 55–75 years. *Respir Med* 2006; 100: 658–665.

28. Poh H, Eastwood PR, Cecins NM, *et al.* Six-minute walk distance in healthy Singaporean adults cannot be predicted using reference equations derived from Caucasian populations. *Respirology* 2006; 11: 211–216.

29. Masmoudi K, Aouicha MS, Fki H, *et al.* The six minute walk test: which predictive values to apply for Tunisian subjects aged between 40 and 80 years?. *Tunis Med* 2008; 86: 20–26.

30. Alameri H, Al-Majed S and Al-Howaikan A. Six-min walk test in a healthy adult Arab population. *Respir Med* 2009; 103: 1041–1046.

31. Ben Saad H, Prefaut C, Tabka Z, *et al.* 6-minute walk distance in healthy North Africans older than 40 years: influence of parity. *Respir Med* 2009; 103: 74–84.

32. Iwama AM, Andrade GN, Shima P, *et al.* The six-minute walk test and body weight-walk distance product in healthy Brazilian subjects. *Braz J Med Biol Res* 2009; 42: 1080–1085.

33. Casanova C, Celli BR, Barria P, *et al.* The 6-min walk distance in healthy subjects: reference standards from seven countries. *Eur Respir J* 2011; 37: 150–156.

34. Dourado VZ, Vidotto MC and Guerra RL. Reference equations for the performance of healthy adults on field walking tests. *J Bras Pneumol* 2011; 37: 607–614.

35. Soaresa MR and Pereira CA. Six-minute walk test: reference values for healthy adults in Brazil. *J Bras Pneumol* 2011; 37: 576–583.

36. Britto RR, Probst VS, de Andrade AF, *et al.* Reference equations for the six-minute walk distance based on a Brazilian multicenter study. *Braz J Phys Ther* 2013; 17: 556–563.

37. Duncan MJ, Mota J, Carvalho J, *et al.* An evaluation of prediction equations for the 6 minute walk test in healthy European adults aged 50–85 years. *PLoS One* 2015; 10: e0139629.

38. Oliveira MJ, Marcoa R, Moutinho J, *et al.* Reference equations for the 6-minute walk distance in healthy Portuguese subjects 18–70 years old. *Pulmonology*. Epub ahead of print 3 July 2018. DOI: 10.1016/j.pulmoe.2018.04.003.

39. Wegrzynowska-Teodorczyk K, Rudzinska E, Lazorczyk M, *et al.* Distance covered during a six-minute walk test predicts long-term cardiovascular mortality and hospitalisation rates in men with systolic heart failure: an observational study. *J Physiother* 2013; 59: 177–187.

40. Yap J, Lim FY, Gao F, *et al.* Correlation of the New York heart association classification and the 6-minute walk distance: a systematic review. *Clin Cardiol* 2015; 38: 621–628.

41. Metra M, Ponikowski P, Dickstein K, *et al.* Advanced chronic heart failure: a position statement from the study group on advanced heart failure of the heart failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2007; 9: 684–694.

42. Roul G, Germain P and Bareiss P. Does the 6-minute walk test predict the prognosis in

patients with NYHA class II or III chronic heart failure? *Am Heart J* 1998; 136: 449–457.

43. Lucas C, Stevenson LW, Johnson W*, et al*. The 6-min walk and peak oxygen consumption in advanced heart failure: aerobic capacity and survival. *Am Heart J* 1999; 138: 618–624.

44. Rostagno C, Galanti G, Comeglio M*, et al*. Comparison of different methods of functional evaluation in patients with chronic heart failure. *Eur J Heart Fail* 2000; 2: 273–280.

45. Opasich C, Pinna GD, Mazza A*, et al*. Six-minute walking performance in patients with moderate-to-severe heart failure; is it a useful indicator in clinical practice? *Eur Heart J* 2001; 22: 488–496.

46. Jehn M, Schmidt-Trucksass A, Schuster T*, et al*. Daily walking performance as an independent predictor of advanced heart failure: prediction of exercise capacity in chronic heart failure. *Am Heart J* 2009; 157: 292–298.

47. Carvalho EE, Costa DC, Crescencio JC*, et al*. Heart failure: comparison between six-minute walk test and cardiopulmonary test. *Arq Bras Cardiol* 2011; 97: 59–64.

48. Deboeck G, Van Muylem A, Vachiery JL*, et al*. Physiological response to the 6-minute walk test in chronic heart failure patients versus healthy control subjects. *Eur J Prev Cardiol* 2014; 21: 997–1003.

49. Omar HR and Guglin M. The longitudinal relationship between six-minute walk test and cardiopulmonary exercise testing, and association with symptoms in systolic heart failure: analysis from the ESCAPE trial. *Eur J Intern Med* 2017; 40: e26–e28.

50. Yoshimura K, Urabe Y, Maeda N*, et al*. Dynamics of cardiorespiratory response during and after the six-minute walk test in patients with heart failure. *Physiother Theory Pract* 2018; 1–12.

51. Forman DE, Fleg JL, Kitzman DW*, et al*. 6-min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. *J Am Coll Cardiol* 2012; 60: 2653–2661.

52. Shah MR, Hasselblad V, Gheorghiade M*, et al*. Prognostic usefulness of the six-minute walk in patients with advanced congestive heart failure secondary to ischemic or nonischemic cardiomyopathy. *Am J Cardiol* 2001; 88: 987–993.

53. Maldonado-Martin S, Brubaker PH, Eggebeen J*, et al*. Association between 6-minute walk test distance and objective variables of functional capacity after exercise training in elderly heart failure patients with preserved ejection fraction: a randomized exercise trial. *Arch Phys Med Rehabil* 2017; 98: 600–603.

54. Curtis JP, Rathore SS, Wang Y*, et al*. The association of 6-minute walk performance and outcomes in stable outpatients with heart failure. *J Card Fail* 2004; 10: 9–14.

55. Ingle L, Rigby AS, Nabb S*, et al*. Clinical determinants of poor six-minute walk test performance in patients with left ventricular systolic dysfunction and no major structural heart disease. *Eur J Heart Fail* 2006; 8: 321–325.

56. McCullough PA, Franklin BA, Leifer E*, et al*. Impact of reduced kidney function on cardiopulmonary fitness in patients with systolic heart failure. *Am J Nephrol* 2010; 32: 226–233.

57. Vuckovic KM and Puzantian H. Estimated glomerular filtration rate and 6-minute walk distance in African Americans with mild to moderate heart failure. *Cardiorenal Med* 2017; 7: 227–233.

58. Felker GM, Whellan D, Kraus WE*, et al*. N-terminal pro-brain natriuretic peptide and exercise capacity in chronic heart failure: data from the heart failure and a controlled trial investigating outcomes of exercise training (HF-ACTION) study. *Am Heart J* 2009; 158: S37–44.

59. Gardin JM, Leifer ES, Fleg JL*, et al*. Relationship of Doppler-Echocardiographic left ventricular diastolic function to exercise performance in systolic heart failure: the HF-ACTION study. *Am Heart J* 2009; 158: S45–S52.

60. Bajraktari G, Dini FL, Fontanive P*, et al*. Independent and incremental prognostic value of Doppler-derived left ventricular total isovolumic time in patients with systolic heart failure. *Int J Cardiol* 2011; 148: 271–275.

61. Farag EM, Al-Daydamony MM and Gad MM. What is the association between left ventricular diastolic dysfunction and 6-minute walk test in hypertensive patients? *J Am Soc Hypertens* 2017; 11: 158–164.

62. Wohlfahrt P, Melenovsky V, Redfield MM*, et al*. Aortic waveform analysis to individualize treatment in heart failure. *Circ Heart Fail* 2017; 10: e003516.

63. Arslan S, Erol MK, Gundogdu F*, et al*. Prognostic value of 6-minute walk test in stable outpatients with heart failure. *Tex Heart Inst J* 2007; 34: 166–169.

64. Frankenstein L, Remppis A, Graham J, *et al*. Gender and age related predictive value of walk test in heart failure: do anthropometrics matter in clinical practice? *Int J Cardiol* 2008; 127: 331–336.

65. Boxer R, Kleppinger A, Ahmad A, *et al*. The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure. *Congest Heart Fail* 2010; 16: 208–213.

66. Woo MA, Moser DK, Stevenson LW, *et al*. Six-minute walk test and heart rate variability: lack of association in advanced stages of heart failure. *Am J Crit Care* 1997; 6: 348–354.

67. den Boer SL, Flipse DH, van der Meulen MH, *et al*. Six-minute walk test as a predictor for outcome in children with dilated cardiomyopathy and chronic stable heart failure. *Pediatr Cardiol* 2017; 38: 465–471.

68. Ingle L, Cleland JG and 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: 244–253.

69. Ciani O, Piepoli M, Smart N, *et al*. Validation of exercise capacity as a surrogate endpoint in exercise-based rehabilitation for heart failure: a meta-analysis of randomized controlled trials. *JACC Heart Fail* 2018; 6: 596–604.

70. Ferreira JP, Duarte K, Graves TL, *et al*. Natriuretic peptides, 6-min walk test, and quality-of-life questionnaires as clinically meaningful endpoints in HF trials. *J Am Coll Cardiol* 2016; 68: 2690–2707.

71. McCabe N, Butler J, Dunbar SB, *et al*. Six-minute walk distance predicts 30-day readmission after acute heart failure hospitalization. *Heart Lung* 2017; 46: 287–292.

72. Howie-Esquivel J and Dracup K. Does oxygen saturation or distance walked predict rehospitalization in heart failure? *J Cardiovasc Nurs* 2008; 23: 349–356.

73. Tager T, Hanholz W, Cebola R, *et al*. Minimal important difference for 6-minute walk test distances among patients with chronic heart failure. *Int J Cardiol* 2014; 176: 94–98.

74. Corvera-Tindel T, Doering LV, Woo MA, *et al*. Effects of a home walking exercise program on functional status and symptoms in heart failure. *Am Heart J* 2004; 147: 339–346.

75. Palmer K, Bowles KA, Paton M, *et al*. Chronic heart failure and exercise rehabilitation: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. Epub ahead of print 24 April 2018. DOI: 10.1016/j.apmr.2018.03.015.

76. Olsson LG, Swedberg K, Clark AL, *et al*. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. *Eur Heart J* 2005; 26: 778–793.

77. Brenyo A, Goldenberg I, Moss AJ, *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: 1454–1459.

78. Beltran P, Palau P, Dominguez E, *et al*. Sacubitril/valsartan and short-term changes in the 6-minute walk test: a pilot study. *Int J Cardiol* 2018; 252: 136–139.

79. Mirdamadi A, Arefeh A, Garakyaraghi M, *et al*. Beneficial effects of the treatment of iron deficiency on clinical condition, left ventricular function, and quality of life in patients with chronic heart failure. *Acta Biomed* 2018; 89: 214–218.

80. Gotzmann M, Hehen T, Germing A, *et al*. Short-term effects of transcatheter aortic valve implantation on neurohormonal activation, quality of life and 6-minute walk test in severe and symptomatic aortic stenosis. *Heart* 2010; 96: 1102–1106.

81. D'Ascenzo F, Moretti C, Marra WG, *et al*. Meta-analysis of the usefulness of Mitraclip in patients with functional mitral regurgitation. *Am J Cardiol* 2015; 116: 325–331.