Analysis of 6-Minute Walk Test Safety in Pre-Heart Transplantation Patients

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Summary

Background: The 6-minute walk test (6WT) has been used as a means of assessment of the functional capacity, clinical staging and cardiovascular prognosis. Its safety and metabolic impact have not been frequently described in the literature, especially in patients with severe heart failure with clinical indication for cardiovascular transplantation.

Objective: To evaluate the occurrence of arrhythmias and cardiovascular changes during 6WT. To correlate 6WT performance with clinical staging and cardiovascular prognosis.

Methods: Twelve patients, 10 of whom males, aged 52±8 years were evaluated at baseline. 6WT was performed with telemetry electrocardiography, vital signs and lactate monitoring. The patients were followed-up for 12 months.

Results: The patients walked 399.4±122.5 (D, m), reaching a perceived exertion (PE) of 14.3±1.5 and a 34% baseline heart rate variation. Two patients presented more severe pre-6WT arrhythmia which did not worsen with the exercice, four patients presented a significant increase of blood lactate levels (>5 mmol/dl), and three interrupted the test. The distance walked correlated with the ejection fraction (%) and functional class (NYHA). After 12-month follow-up, three patients died and seven were rehospitalized for cardiac decompensation. The D/PE ratio and 2-minute heart rate recovery (HRR2, bpm) were lower in the death group.

Conclusion: The clinical and electrocardiographic behaviors suggest that the method is safe, but it may be considered too strenuous for some patients with severe heart failure. Variables related to 6WT performance may be associated with the one-year follow-up mortality. (Arq Bras Cardiol 2009;92(4):294-300)

Key words: Walking; health evaluation; effectiveness; heart failure.

Introduction

Refractory heart failure is an end-stage condition in several heart diseases and is characterized by deterioration of the clinical conditions and mortality[1]. Failure of compensatory mechanisms for maintenance of the cardiac output facilitates protein-energy malnutrition and reduction of the vascular bed and functional capacity[2,3]. Heart transplantation has been an efficient therapeutic option, improving survival and functional capacity (FC). However, after clinical indication, the therapeutical follow-up in the pre-transplantation phase is delicate and costly[4,5].

Cardiopulmonary evaluation is the most accurate method in the assessment and follow-up of the functional capacity. However, it is difficult to be performed periodically, and this may impair a more detailed control of patients with this clinical condition[6,7]. In these cases, the 6-minute walk test (6WT) may be indicated as an alternative simplified low-cost reproducible method[8], for the assessment of exercice tolerance, providing an indirect estimate of different aspects such as clinical staging[9-16], response to interventions, and quality of life[17,18], especially in patients with a greater reduction of the functional capacity[19-24].

The more specific scientific knowledge regarding safety and major systemic adjustments in response to 6WT in patients with refractory heart failure (HF) could minimize the occurrence of adverse clinical responses[25] such as signs of exercice intolerance, arrhythmias, and secondary complications, especially found when reduced myocardial oxygen supply is present, which is very frequent among this population[26,27].

The objective of the present study is to evaluate the cardiovascular responses to 6WT and their possible correlations with clinical staging and cardiovascular prognosis. Thereby we believe we will contribute to the improvement of intervention control and prescription in this population of heart disease patients who await heart transplantation.

Methods

Study participants

Twelve patients (aged 52 ± 8 years, 10 men, 2 women) seen in the heart transplantation outpatient clinic of the university

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hospital of *Universidade Federal de São Paulo* comprised the study group. The patients were clinically diagnosed with refractory heart failure with elective indication for heart transplantation. The main causes of heart failure were related to ischemic (58.3%) and idiopathic (25%) cardiomyopathies. Eight patients (67.7%) were in functional class III and IV (NYHA), 10 (83.3%) had associated comorbidities, and nine (75%) had already undergone previous cardiovascular procedures (five coronary artery bypass graftings and four transluminal angioplasties) (Table 1). Consent was obtained from all patients, and the study was approved by the Research Ethics Committee.

Design and protocol

This was a prospective cohort of 15 patients, of whom three were excluded for cardiovascular decompensation; therefore 12 remained in the protocol. The study comprised a baseline clinical assessment with information on clinical and cardiovascular staging, followed by a 6-minute walk test (6WT). The patients were then clinically followed-up for 12 months after 6WT.

Baseline clinical assessment

The baseline clinical assessment included information on the clinical and echocardiographic evaluations, such as etiology, presence of comorbidities, previous cardiovascular procedures, clinical treatment, cardiovascular function (% ejection fraction) and functional class (NYHA)[28]. The patients were also evaluated as to the impact of heart failure on their quality of life, by means of a specific questionnaire for heart failure known as Minnesota Living with Heart Failure questionnaire (MLHF)[18].

6-minute walk test

Rest electrocardiogram was initially obtained from the patients in order to detect the existence of arrhythmias. The 6WT was performed according to the Guidelines of the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR)[29] and guidelines for the performance of exercice tests of the Brazilian Society of Cardiology (SBC)[7], in a 30-m-long circular track with the patients unaccompanied and receiving only standardized advices every minute. The following parameters were monitored: heart rate (HR, bpm), heart rate recovery (HRR, bpm), blood pressure (BP, mmHg), peripheral oxygen saturation (SpO_2, %) and perceived exertion (PE) scale[30]. Continuous telemetry electrocardiography (QUARK T12, model CO9055-32-99, Cosmed™, Italy) was also performed and allowed instant monitorization of events that could indicate the need for test interruption. Also, peripheral lactate values before and after 6WT were determined. The baseline peripheral measurement was determined after a minimum one-hour period without the performance of exercices and/or exertion activities, and the final measurement was determined right after the end of the test.

12-month post-6WT follow-up

The patients were followed-up for a 12-month period after 6WT so that parameters regarding the clinical outcome

Table 1 - Baseline characteristics in the pre-heart transplantation period of patients undergoing 6-minute walk (n=12)

Characteristics	Mean	±	SD	CV (%)
Age (years)	52	±	8.20	15.56
Weight (Kg)	67.83	±	12.89	19.01
Height (m)	1.64	±	0.10	6.08
BMI (Kg/m^2)	23.50	±	4.15	17.64
W/HR	0.97	±	0.06	6.51
Quality of life (QLS) Minnesota	31.00	±	3.33	37.21
Ejection fraction (%)	26.33	±	4.51	17.16
Time of diagnosis of CHF (months)	98.75	±	22.92	31.55
Respiratory muscle strength				
Pi-max (cmH_2O)	-89	±	25.79	29.09
Pi-max (% of expected)	80	±	27.23	34.03
Pe-max (cmH_2O)	83	±	26.08	31.43
Pe-max (% of expected)	109	±	31.03	28.53
	No		**(%)**	
Gender				
Male	10		(83.3)	
Female	2		(16.7)	
Functional class (NYHA)				
II	4		(33.3)	
III	5		(41.7)	
IV	3		(25.0)	
Cause of CHF				
Ischemic cardiomyopathy	7		(58.3)	
Idiopathic cardiomyopathy	3		(25.0)	
Congenital heart disease	2		(16.7)	
Presence of comorbidities				
Pulmonary disease	0		0.0	
Renal failure	1		(8.3)	
Diabetes Mellitus	1		(8.3)	
Myocardial infarction	8		(66.7)	
1 event[a]	2		(25.0)	
2 events[a]	4		(50.0)	
3 events[a]	1		(12.5)	
4 events[a]	1		(12.5)	
Risk factors				
Cigarette smoking	7		(58.3)	
Hypertension	7		(58.3)	
Previous cardiac procedures				
Coronary artery bypass grafting	5		(41.7)	
Use of 2 grafts[b]	3		(60.0)	
Use of 3 grafts[b]	2		(40.0)	
Angioplastiy	4		(33.3)	

Continuation: Table 1 - **Baseline characteristics in the pre-heart transplantation period of patients undergoing 6-minute walk (n=12)**

Medications used		
ACE inhibitor	10	(83.3)
Digitalis	6	(50.0)
Diuretics	12	(100.0)
β-blocker	10	(83.3)
Vasodilator	2	(16.7)
Ca^{2+} channel blocker	0	0.0
Antiarrhythmic drugs	1	(8.3)
Anticoagulation drugs	0	0.0

BMI - body mass index; CV - coefficient of variation; W/HR - waist/ hip ratio; NYHA - New York Heart Association; CHF - congestive heart failure; ACE - angiotensin converting enzyme; Pi-max - peak inspiratory pressure; Pe-max - peak expiratory pressure. Continuous parametric data are expressed as mean ± standard deviation; categorical or continuous data are expressed as Nº - number of patients (% of total) a, frequency in 8 patients with acute myocardial infarction, b, frequency in 5 patients with coronary artery bypass grafting.

such as rehospitalization, decompensation of the clinical manifestations and mortality could be observed.

Statistical methods

Continuous parametric data were expressed as mean and standard deviation and compared throughout time using ANOVA for repeated measurements with Newman-Keuls post-test for more than two timepoints or, otherwise, with Sudent's t test. Non-parametric data were expressed as median and percentile and compared throughout time using Friedman's test with Muller-Dunn post-test for more than two timepoints or, otherwise, with Wilcoxon's test. Categorical data were expressed as absolute frequency (n) and relative frequency (%) and compared throughout time using Mc'Nemar's test, or the chi-square test for independent groups. Pearson's linear correlation analysis was used to verify the association between the test variables with clinical and cardiovascular staging, with values set at > 0.75, <0.40, and between 0.40 and 0.75 for excellent, poor and moderate concordance, respectively. For the entire study, the alpha risk was set at equal to or lower than 5%, and beta risk at equal to or lower than 20%.

Results

Occurrence of arrhythmias

The occurrence of arrhythmia was evaluated in three ways during 6WT. The descriptive analysis, represented by the type of arrhythmia, did not show exacerbation with 6WT ($p=0.228$). Qualitative analysis regarding change in risk stratification during the test did not show exacerbation either, and classifications were used regarding the origin ($p=0.546$) or type ($p=0.735$) (Table 2).

Maximum performance in 6WT

Unlike SpO_2 and BP, which did not change significantly with exercice, HR adjusted efficiently and physiologically, and was the major responsible for the positive adjustment of the double product (Table 3).

The mean distance walked was 399.4 ± 122.5, with significant increase in the perceived exertion (14 ± 1.5)[31] and evident variation in lactate levels. Greater than 4mmol/L lactate levels were reached in four individuals, thus suggesting higher utilization of anaerobic metabolism during the exercise. Other three individuals interrupted the test early, the first one due to dyspnea, dizziness, palpitation, and leg pain at 285 seconds; the second due to leg pain at 242 seconds; and the third due to chest pain at 180 seconds, both with no electrocardiographic changes characteristic of ischemia (Table 3). After interruption, the patients could continue the test so as to complete the 360 seconds planned, and only then the total distance walked was calculated.

Clinical staging and cardiovascular prognosis

Three patients died within the 12-month follow-up period, two of them after rehospitalization for cardiovascular decompensation while awaiting cardiovascular transplantation, and one of late rejection following cardiovascular transplantation. Conventional periodic outpatient clinical follow-up was carried out, but only two patients underwent transplantation during the follow-up period, and the mean waiting time was 21.5 ± 4.95 months. Within this period, six (50%) patients had episodes of deterioration of the clinical staging and required hospitalization, five (41.67%) of them for heart failure decompensation and one (8.33%) for renal failure.

The analysis of correlation of all variables obtained in 6WT showed association only between the distance walked and severity of arrhythmia at the end of 6WT, with EF (Ejection fraction) (R: 0.7 and -0.83) and FC (Functional class) (R: 0.73 and 0.73) (Figure 1). Quality of life was moderately reduced (31 ± 3.33 out of 105 points); however, no correlation was demonstrated in the comparison with the variables obtained in the walk test.

Paired analysis of the characteristics studied before and during the walk test showed a significant difference between individuals who died within the 12 subsequent months and the group of survivors in relation to characteristics such as weight, waist/hip ratio, respiratory muscle strength ($P_{i\text{-}max}$ and $P_{e\text{-}max}$) ,PE (Perceived Exertion), and 2-minute heart rate recovery (Table 4).

Discussion

The present study showed that unaccompanied 6WT is a safe measurement regarding the electrocardiografic and cardiovascular changes in the assessment of patients with refractory heart failure, but underscores the importance of preliminary clinical and functional assessment for risk stratification. Additionally, some variables related to 6WT performance seem to be indeed associated with the current clinical staging and with one-year follow-up mortality.

6WT is a simple, reproducible, low-cost, easy-to-operate test that has a significant correlation with clinical variables such as functional capacity, cardiorespiratory conditioning, functional class, quality of life, and cardiovascular

Table 2 - Comparison between frequency, characteristic and severity of arrhythmias instantly monitored by telemetry at rest, during and after 6WT of patients in the pre-heart transplantation period. (n=12)

Electrocardiographic behavior	Rest		During 6WT		After 6WT		p value
Type of Arrhythmia (descriptive)	**No**	**(%)**	**No**	**(%)**	**No**	**(%)**	
Single extrasystole	5	(41.7)	6	(50.0)	3	(25.0)	
Unifocal ventricular extrasystole	2	(16.7)	2	(16.7)	1	(8.3)	
Fascilar block	2	(16.7)	1	(8.3)	1	(8.3)	
Atrial fibrilation	3	(25.0)	3	(25.0)	3	(25.0)	
Complete right bundle branch block	1	(8.3)	1	(8.3)	1	(8.3)	
Sinus pause	0	0.0	1	(8.3)	0	0.0	
Multifocal ventricular extrasystole	1	(8.3)	2	(16.7)	2	(16.7)	
Non-sustained ventricular tachycardia	1	(8.3)	0	0.0	0	0.0	
Total of Patients with arrhythmia[a]	9	(75.0)	9	(75.0)	8	(66.7)	0.228
Severity of Arrhythmia a (based on the origin)							0.546
0, Absent	3	(25.0)	3	(25.0)	4	(33.3)	
1, Supraventricular	2	(16.7)	2	(16.7)	1	(8.3)	
2, Ventricular	7	(58.3)	7	(58.3)	6	(50.0)	
Severity of Arrhythmia (Low's classification)							
Grade 0, no extrasystoles	6	(50.0)	6	(50.0)	8	(66.7)	
Grade 1, < 30 extrasystoles per hour	4	(33.3)	5	(41.7)	2	(16.7)	
Grade 2, > 30 extrasystoles per hour	0	0.0	0	0.0	0	0.0	
Grade 3, polymorphic extrasystoles	1	(8.3)	1	(8.3)	2	(16.7)	
Grade 4A, coupled extrasystoles	0	0.0	0	0.0	0	0.0	
Grade 4B, ventricular tachycardia (> 3)	1	(8.3)	0	0.0	0	0.0	
Grade 5, R-on-T phenomenon	0	0.0	0	0.0	0	0.0	
Total of arrhythmias	0,5	(0-1.0)	0,5	(0-1.0)	0,0	(0-1.0)	0.7351

6WT - 6-minute walk test. Categorical or continuous data are expressed as Nº, number of patients (% of total), continuous non-parametric data are expressed as median (25th-75th percentile). [a] Friedman; [b] Mc'Nemar.

prognosis[4,6,8-13,17,19-24]. The present study was the first to use a telemetry electrocardiographic monitoring system during 6WT on the floor, thus permitting real-time observation of possible arrhythmias or signs suggestive of ischemia that could indicate the need for test interruption. Additionally, a simplified analysis of peripheral lactate was also carried out in order to obtain acute information on modulations of the energy metabolism.

The individuals had a common history of presence of risk factors, previous procedures and associated comorbidities, as well as a significant reduction of the cardiovascular function, and were concentrated mainly in functional classes III and IV, whose main cause was myocardial ischemic diseases. Historically, one third of hospitalized patients diagnosed with heart failure spend approximately 55 billion US dollars anually in ambulatory treatment[1], and these expenses concentrate mainly in functional class III and IV patients. Thus, simple, reproducible and efficient measures for the assessment of and support to cardiovascular treatment seem very relevant and could minimize these costs and provide a more qualified follow-up. Quality of life was only moderately reduced in this study, and did not correlate with 6WT variables, unlike what was demonstrated in other studies. This is probably due to the fact that we evaluated only a small number of patients in different functional classes[10].

The analysis of the occurrence of arrhythmias was carried out in three ways: using the classification proposed by Low[32], which considers the severity of ventricular arrhythmias; the atrioventricular (AV) classification, which divides arrhythmias into ventricular and supraventricular arrhythmias[27]; and qualitative (descriptive) analysis of the electrocardiographic findings[26]. Both show a higher incidence of arrhythmias in patients with reduced myocardial oxygen supply. In the present study, the analysis showed a high probability of the occurrence of arrhythmias in this population, though without exacerbation with 6WT. This suggests that the method is safe, but we emphasize the need for a preliminary clinical and functional assessment for stratification. However, the routine use of electrocardiographic monitoring systems should be carefully considered, since the principle of the walk test is to be simple and easy to reproduce.

Table 3 - Characteristics and relative changes between the end of the exercise and resting

Characteristics after 6WT	Mean	±	SD	CV (%)
Maximum distance (m)	399.4	±	122.50	30.67
Perceived exertion (PE)	14.3	±	1.55	10.86
Exertion/Max. Dist. ratio (PE/m)	0.036	±	0.013	87.50
Peak HR after 6WT (bpm)	111.4	±	25.13	22.56
% of HRmax (%)	66.3	±	12.83	19.34
HRmax/Max. Dist. Ratio (bpm/m)	0.1	±	0.07	66.22
Maximum lactate after 6WT	3.2	±	1.04	32.75
Pre and post-6WT Δ Lactate variation (mmol/l)	1.3	±	1.15	91.28
Pre and post-6WT Δ Blood glucose variation	-10.7	±	27.91	31.25
	No		(%)	
Lactate > 4 (mmol/l) post-6WT	4		(33.3)	
Tests interrupted early	3		(25.0)	

CV - coefficient of variation; 6WT - 6-minute walk test; PE - perceived exertion scale; Max. Dist - maximum distance walked in meters; HRmax - maximum heart rate. Continuous parametric data are expressed as Mean ± Standard Deviation; Categorical data are expressed as Nº, number of patients (% of total).

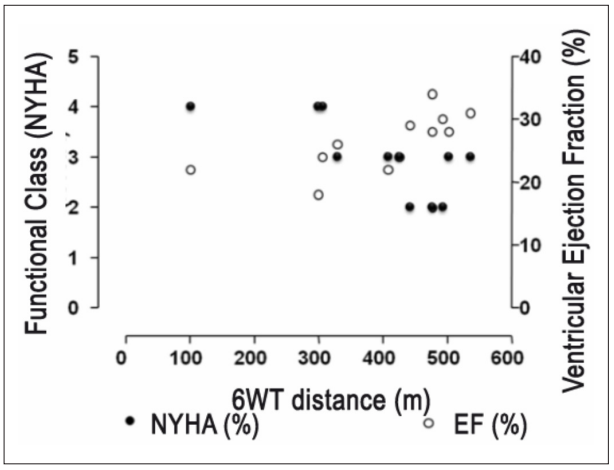

Figure. 1 - *Correlation between maximum distance walked at the end of 6WT and previous clinical characteristics. 6WT - 6-minute walk test; 6WT distance - maximum distance walked in meters; NYHA - New York Heart Association. EF - ejection fraction. Pearson's correlation test, EF (%): 0.70; FC: 0.73.*

In the analysis of the cardiovascular adjustment to 6WT, HR was the variable that showed the most significant adjustment to 6WT. This behavior is translated into the influence of HR on the double product variations, since these patients already present a diminished cardiovascular function, which is evidenced by a reduced ventricular ejection fraction. Thus, as we had expected, the chronotropic response was more important than the inotropic response in this population[15]. HRR2 was higher in the group of patients who died within the 12-month follow-up period. Some studies have described the relationship of the heart rate recovery (HRR) behavior with cardiovascular function, where slower reductions are directly related to function deterioration and cardiovascular mortality, a phenomenon that is linked to an autonomic nervous system imbalance, usually resulting from overstimulation of the sympathetic nervous system and reduction of the vagal activity[21,33], in addition to measuring functional capacity changes after exercise training[34].

Also, the simplified lactate assessment permitted the supply of additional information regarding the energy metabolism behavior in response to the walk test. We could observe that although the maximum heart rate (HR_{max}) had reached only 66.3% of the predicted value, on average, four of these patients had higher than 4mmol/l levels of lactate, thus suggesting greater utilization of anaerobic metabolism. Recent studies demonstrated the relationship between anaerobic metabolism and functional capacity as an important predictor of mortality[35,36]. Even so, after 6WT, the individuals reported a mean perceived exertion of 14.3 ± 1.55, with 20 points corresponding to a closer to tiresome exertion, a result that is compatible with the exertion reported in other studies[9]. Based on these findings we can presume a possible error in the estimate of the maximum heart rate for these patients with significant functional limitation who, in their majority (83.3%), were being treated with beta-blockers[37,38].

As we could observe, in the baseline clinical evaluation, the variables showing the most significant differences in the

Table 4 - Characteristics associated with mortality in patients followed-up for 12 months after 6-minute walk test

Characteristics associated with mortality	Survivor (n=9)			Death (n=3)			p
	Mean	±	SD	Mean	±	SD	
Weight (Kg)	70.71	±	13.70	59.17	±	3.75	*
W/HR	0.94	±	0.03	1.05	±	0.07	**
MIP (cmH_2O)	-98.33	±	22.11	-59.67	±	4.51	***
Perceived exertion (PE)	13.67	±	1.00	16.33	±	1.15	*
Exertion/Max.Dist ratio (PE/m)	0.08	±	0.03	0.21	±	0.08	**
HRR2	80.44	±	18.13	113.00	±	27.07	*

*Continuous data are expressed as Mean ± Standard Deviation; Non-paired t test, sig. (2-tailed), * P<0.05; **, P<0.01; ***, P<0.001; W/HR - waist/hip ratio; HRR2 - 2-minute heart rate recovery; MIP - maximum inspiratory pressure.*

individuals who died in the 12 subsequent months in relation to those who survived were weight, muscle strength, and waist/hip ratio. Weight and muscle strength are important markers in this population, since with the progression of heart failure the patients develop an increased metabolic energy demand associated with a noticeable muscle-skeletal deterioration, which can lead to a functional stage known as cardiac cachexia that negatively interferes with the cardiorespiratory conditioning and, consequently, with the quality of life and cardiovascular prognosis[2,3].

The analysis of the relationship between 6WT and the clinical staging and cardiovascular prognosis, in turn, primarily revealed that despite belonging to an apparently homogeneous group, all being equally eligible to heart transplantation, the patients presented very different functional capacities, as estimated by the distance walked, especially the four patients who walked a shorter than 300-m distance. We currently know that individuals with heart failure who walk less than 300 meters have a very poor prognosis[14-16]. Also, in our study, the maximum distance walked in the 6WT showed an important correlation with some classical clinical characteristics such as ejection fraction (r=0.70) and functional class (r=0.73). Although some studies question the usefulness of this test as a measure of cardiovascular clinical staging, most of the randomized clinical trials support its diagnostic value in patients with heart failure[10,15].

Finally, in the comparison between the survivor group and the death group, we could observe that the distance walked and the perceived exertion ratio (meters/PE), perceived exertion (PE) and heart rate recovery (HRR, bpm) were the variables that showed the most significant differences when individuals who died were compared with the survivors.

The present study had some limitations. Initially, we evaluated a relatively small sample of patients with elective indication for a heart transplant. However, although relevant results were shown in this study, we point out the difficulty in reaching this population, since during the entire study period the Brazilian Association of Organ Transplant (*Associação Brasileira de Transplante de Órgãos* - ABTO), registered only 60 heart transplantations in the State of São Paulo, for a total of 98 individuals enrolled[39]. Thus, the population assessed accounted for 12% of the total number of patients enrolled, which shows the importance of further multicenter studies. And the simplified analysis for cross-sectional comparison in place of a detailed analysis on mortality was also justified by the fact that we had a small number of patients, which led to a less affirmative degree of inference, though relevant for reassessment in prospective studies.

In conclusion, the clinical and electrocardiographic behaviors suggest that the method is safe but can be considered strenuous for some patients with severe heart failure. Variables related to the performance in 6WT may be associated with the one-year follow-up mortality.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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