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ORIGINAL ARTICLE

Cardio-respiratory responses of the 6-minute walk test in patients with refractory heart failure during the preoperative period for heart transplant surgery

Risposta cardio-respiratoria al Test del cammino dei 6 minuti in pazienti con scompenso cardiaco refrattario nel periodo preoperatorio del trapianto cardiaco

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ABSTRACT: ***Cardio-respiratory responses of the 6-minute walk test in patients with refractory heart failure during the preoperative period for heart transplant surgery. G. Cipriano Jr, G.F. Bernardelli, R. Arena, L.V.F. Oliveira, F. Valdez, J.N.R. Branco.***

Background: The six-minute walk test (6MWT) has been used to assess functional capacity, clinical status and prognosis. There are a very few descriptions in the literature on the safety and metabolic impact of the test, especially in patients with severe heart failure, awaiting cardiac transplantation. Objective: The aim of the present study was to assess the cardiovascular responses and correlate the performance on the 6MWT with clinical status. Method: From 15 initial candidates, twelve patients (10 males) aged 52 ± 8 years were submitted to a comprehensive clinical evaluation. The patients performed the 6MWT with electrocardiographic and perceived exertion monitoring in addition to determination of blood lactate concentration. Patients were followed up for 12 months. Results: The patients walked 399.4±122.5 meters, reaching a perceived exertion (PE) of 14.3±1.5 and an increase of 34% in resting heart rate. Two patients exhibited a greater severity of arrhythmia prior to the 6MWT, which did not increase during exertion. Four patients exhibited a significant increase in blood lactate levels (>5 mmol/dL) and three interrupted the test prematurely. The distance walked (D) revealed a correlation with the ejection fraction (%) and functional classification (NYHA). After 12 months of follow up, three patients died and seven were re-hospitalized due to heart failure decompensation. Conclusion: Clinical and electrocardiographic behavior suggests that the 6MWT is safe, but may be considered of high intensity for some patients with severe heart failure. Variables related to the performance on the 6MWT may be associated to worsening clinical status in this population.

Keywords: exercise, ergometry, heart failure.

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Introduction

Refractory heart failure (HF) is defined as a condition of persistence or deterioration of clinical condition despite intensive therapy. The HF, brought about several forms of heart disease, typically leads to a progressive deterioration of clinical status and ultimately death [1]. The failure of compensatory mechanisms to maintain cardiac output favors protein-energy malnutrition, clinically manifested by a severe reduction in functional capacity [2, 3]. Heart transplantation is a viable therapeutic option for this group, increasing life expectancy, cardiac function and functional capacity (FC). However, after being listed as an appropriate candidate for this surgical procedure, therapeutic management in the pre-transplant phase may be delicate and taxing [4].

Cardiopulmonary exercise testing with ventilatory expired gas analysis is the preferred method for evaluation of functional capacity in patients with HF. However, serial assessments are logistically difficult to execute, which can hinder more detailed control of patients with this clinical condition [5]. In such cases, the six-minute walk test (6MWT) may be indicated as a simplified, reproducible, low-cost alternative for assessment of tolerance to physical exertion, providing insights into clinical status, response to interventions and quality of life, especially in patients with a more pronounced reduction in functional capacity [6-10].

Specific scientific knowledge regarding the safety and the physiologic response to the 6MWT in patients with refractory HF is limited at this time. Given the potential for a profound reduction in functional capacity and for exercise induced arrhythmias and secondary complications, particularly present in conditions of reduced myocardial oxygen supply, often encountered in this population, utilization of the 6MWT may prove to be a

useful clinical assessment. Therefore, the aim of the present study was to assess cardiovascular response to the 6MWT and the possible correlations to clinical status in patients with refractory HF listed for transplantation.

Methods

Participants in the study

Twelve patients (aged 52 ± 8 years, 10 male and 2 female) receiving their care at the heart transplant clinic at the Federal University of Sao Paulo hospital were included in this study. The patients had a clinical diagnosis of refractory HF, and were considered appropriate candidates for heart transplantation. The principal HF etiologies were related to ischemic (58.3%) and idiopathic (25%) cardiomyopathy. Eight patients (67.7%) were in functional classes III and IV (NYHA); ten (83.3%) had associated co-morbidities; and nine (75%) had undergone previous cardiovascular procedures (5 myocardial revascularization surgeries and 4 transluminal angioplasties) (Table 1).

Table 1. - Initial characteristics of patients in preoperative heart transplantation period submitted to the six-minute walk test (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/m2)	23.50	±	4.15	17.64
W/H R	0.97	±	0.06	6.51
Quality of Life (Minnesota QOL)	31.00	±	3.33	37.21
Ejection fraction (%)	26.33	±	4.51	17.16
Time since diagnosis of CHF (months)	98.75	±	822.92	31.55
Respiratory Muscle Strength				
$P_{i\text{-}max}$ (cmH_2O)	–89	±	25.79	29.09
$P_{i\text{-}max}$ (% of predicted)	80	±	27.23	34.03
$P_{e\text{-}max}$ (cmH2O)	83	±	26.08	31.43
$P_{e\text{-}max}$ (% of predicted)	109	±	31.03	28.53
	Nº		**(%)**	
Gender				
Male	10		(83.3)	
Functional Class (NYHA)				
II	4		(33.3)	
III	5		(41.7)	
IV	3		(25.0)	
Etiology of CHF				
Ischemic myocardiopathy	7		(58.3)	
Idiopathic myocardiopathy	3		(25.0)	
Congenital heart disease	2		(16.7)	
Co-morbidities				
Kidney 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				
Smoking	7		(58.3)	
Arterial Hypertension	7		(58.3)	
Previous heart procedures				
Myocardium revascularization	5		(41.7)	
Use of 2 grafts [b]	3		(60.0)	
Use of 3 grafts [b]	2		(40.0)	
Angioplasty	4		(33.3)	
Medications in use				
ACE inhibitor	10		(83.3)	
Digitalis	6		(50.0)	
Diuretic	12		(100.0)	
β-blocker	10		(83.3)	
Vasodilator	2		(16.7)	
Ca^{2+} channel blocker	0		0.0	
Anti-arrhythmia agent	1		(8.3)	
Anticoagulant	0		0.0	

Abbreviations: BMI, body mass index; W/H R, waist/hip ratio; NYHA, New York Heart Association; CHF, congestive heart failure; ACE, angiotensin-converting enzyme; $P_{i\text{-}max}$, maximum inspiratory pressure; $P_{e\text{-}max}$, maximum expiratory pressure.
Continuous parametric data represented as mean ± standard deviation; categorical or continuous data represented as N^O, number of patients (% of total) [a], frequency in 8 patients with acute myocardial infarction, [b], frequency in 5 patients with revascularization of the myocardium.

This study was approved by the local research ethics committee and informed consent was obtained from all patients prior to study.

Design and protocol

This was a prospective cohort study initially carried out on fifteen patients. Three were excluded due to cardiovascular decompensation before performed the 6MWT and twelve were submitted to the protocol, which was comprised of an initial clinical evaluation with information on clinical status, followed by the six-minute walk test (6MWT). The patients were then followed up for a period of 12 months following the 6MWT.

Initial clinical evaluation

Clinical and echocardiographic information [11, 12], such as etiology, presence of co-morbidities, previous cardiovascular procedures, clinical treatment, cardiovascular function - ejection fraction (EF) (%) and functional class (FC) (NYHA) [13] was collected for all patients. The patients were also assessed as to the impact of HF on quality of life and respiratory strength, using the Minessota Living with Heart Failure Questionare (MLHF) [14] and digital manuvacuometer.

Six-minute walk test

The patients were initially submitted to an electrocardiogram at rest to determine the existence of arrhythmias. The 6MWT was carried out in compliance with the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines [15]. Specifically, the test was performed on a circular track, 30 meters in length, with no accompaniment other than standardized vocal orientations at one-minute intervals. The patients were monitored with regard to heart rate (HR, bpm), heart rate recovery at two minutes following test termination (HRR, bpm), blood pressure (BP, mmHg), peripheral oxygen saturation (SpO_2, %) and perceived exertion (PE) using the 6-20 Borg scale [16]. Continuous variables were also monitored through electrocardiogram telemetry (QUARK T12, model CO9055-32-99, Cosmed®, Italy), enabling the instantaneous monitoring of arrhythmic events that. Peripheral lactate levels and blood glucose levels were measured prior to and following the 6MWT, was measured for each fasting subject by capillary finger-stick using the AC monitor. The basal peripheral measurement was taken after a minimum of one hour without any exercise and/or exertion and the final measurement was taken immediately upon finishing the test.

12-month follow-up after the 6MWT

The patients were followed for 12 months after performing the 6MWT in order to gather information on their clinical evolution, such as re-hospitalization secondary to HF decompensation and/or death.

Statistical methods

Continuous parametric data are presented as mean and standard deviation and compared over time using ANOVA for repeated measurements, with the Newman-Keuls post hoc test and the Student's t-test. Non-parametric data were represented as median and percentile and compared over time using the Friedman test, with the Muller-Dunn post hoc test and the Wilcoxon rank sum test. Categorical data are presented as absolute frequency (n) and relative frequency (%) and compared over time using McNemar's test and chi-square test (independent groups). Pearson's linear correlation coefficient was used to determine associations between the test variables and clinical status, considering the following agreement values: > 0.75 excellent; between 0.40 and 0.75 moderate; and < 0.40 poor. An alpha risk less than or equal to 5% and a beta risk less than or equal to 20% were considered throughout the study. All statistical tests with a p-value <0.05 were considered significant.

Results

Occurrence of arrhythmias

The occurrence of arrhythmias was assessed in three manners during the 6MWT. Descriptive analysis (represented by the type of arrhythmia) revealed no exacerbation during the 6MWT (p=0.228). Likewise, qualitative analysis regarding a change in risk status during the test revealed no exacerbation, using classifications of origin (p=0.546) or type (0.735) (Table 2).

Systemic adjustments during the 6MWT

Unlike the SpO_2 and BP, which demonstrated no significant alterations during exertion, there was a significant increase in HR (Figure 1), proving to be the main element responsible for the positive adjustment of the double heart product (Table 3).

The average distance walked was 399.4 ± 122.5 meters, with an increase in perceived exertion (14 ± 1.5) and evident variation in lactate level. Four individuals reached lactate levels above 4 mmol/L, thereby suggesting greater use of the anaerobic metabolism during the test. Another three individuals interrupted the test prematurely - the first at 285 seconds due to dyspnea, dizziness, palpitation and pain in the lower limbs; the second at 242 seconds due to pain; and the third at 180 seconds due to precordial pain. The latter two exhibited no electrocardiogram alterations characteristic of ischemia (Table 3). After interruption, the patients were allowed to continue the test until the pre-established 360 seconds had elapsed, which was when the total distance walked was recorded.

Clinical status and cardiovascular follow-up

Three patients died during the 12-month follow-up period - two while awaiting transplant surgery after re-hospitalization due to cardiovascular decompensation and one due to delayed rejection following cardiovascular transplant surgery. All patients were maintained under periodic outpatient follow up, but only two underwent transplant surgery during the study period, as the average time on the waiting list was 21.5 ± 4.95 months. During the period, six patients (50%) manifested episodes of deterioraton in clinical status and required hospitalization - five (41.67%) for HF decompensation and one (8.33%) for kidney failure. Despite of the severe

Table 2. - Comparison of frequency, characteristic and severity of arrhythmia during the 6MWT monitored instantaneously by telemetry at rest, during and after the 6MWT in patients in the preoperative period for heart transplant surgery (n=12)

Electrocardiogram behavior	Rest		During 6MWT		After 6MWT		*p* value
Type of arrhythmia (descriptive)	Nº	(%)	Nº	(%)	Nº	(%)	
Isolated extra-systole	5	(41.7)	6	(50.0)	3	(25.0)	
Unifocal ventricular extra-systole	2	(16.7)	2	(16.7)	1	(8.3)	
Divisional block	2	(16.7)	1	(8.3)	1	(8.3)	
Atrium fibrillation	3	(25.0)	3	(25.0)	3	(25.0)	
Complete block of right branch	1	(8.3)	1	(8.3)	1	(8.3)	
Sinus pause	0	0.0	1	(8.3)	0	0.0	
Multifocal ventricular extra-systole	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*
Arrhythmia severity [a] (based on 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)	
Arrhythmia severity (Lown classification)							
Grade 0, no extra-systoles	6	(50.0)	6	(50.0)	8	(66.7)	
Grade 1, < 30 extra-systoles per hour	4	(33.3)	5	(41.7)	2	(16.7)	
Grade 2, > 30 extra-systoles per hour	0	0.0	0	0.0	0	0.0	
Grade 3, polymorphic extra-systoles	1	(8.3)	1	(8.3)	2	(16.7)	
Grade 4A, coupled extra-systoles	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 phenomenon on T.	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*

Abbreviation: 6MWT, six-minute walk test.
Categorical or continuous data represented as N^{O}, number of patients (% of total); non-parametric continuous data represented as median (percentile 25%-75%). [a] Friedman; [b] McNemar.

Table 3. - Characteristics and relative variations between end of exercise and rest

Characteristics after 6MWT	Mean	±	SD	CV (%)
Maximum distance (m)	399.4	±	122.50	30.67
Maximum perceived exertion (PE)	14.3	±	1.55	10.86
Exertion/Max. Dist. Ratio (PE/m)	0.0	±	0.01	87.50
Peak HR after 6MWT (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 6MWT	3.2	±	1.04	32.75
Δ Lactate variation, pre and post 6MWT (mmol/L)	1.3	±	1.15	91.28
Δ Glycemia variation, pre and post 6MWT	–10.7	±	27.91	31.25
	Nº		(%)	
Lactate > 4 (mmol/L) post 6MWT	4		(33.3)	
Test interrupted prematurely	3		(25.0)	

Abbreviation: 6MWT, six-minute walk test; PE, perceived exertion scale; Max. Dist., maximum distance walked in meters; HR_{max}, maximum heart rate.
Parametric continuous data represented as mean ± standard deviation; categorical data represented as N^{O}, number of patients (% of total).

cardiac condition this specific group has only 20% reduction in inspiratory muscle strengh and normal values in expiratory evaluation.

The analysis of the correlation of the variables obtained on the 6MWT only revealed an association of the distance walked and arrhythmia severity at the end of the 6MWT with EF (r=0.70 and –0.83) and FC (r=0.73 and 0.73) ($p < 0.05$). Quality of life was moderately reduced (31 ± 3.33 in a total of 105 points), but there was no correlation with the variables obtained on the 6MWT.

Discussion

The present study demonstrates that the 6MWT (without accompaniment) is a safe measure with regard to the hemodynamic and electrocardiographic response in patients with refractory heart failure. These findings furthermore reinforce the importance of a clinical evaluation during physical exertion in this patient population, as variables related to performance on the 6MWT appear to be associated to current clinical status and possibly with the cardiovascular prognosis.

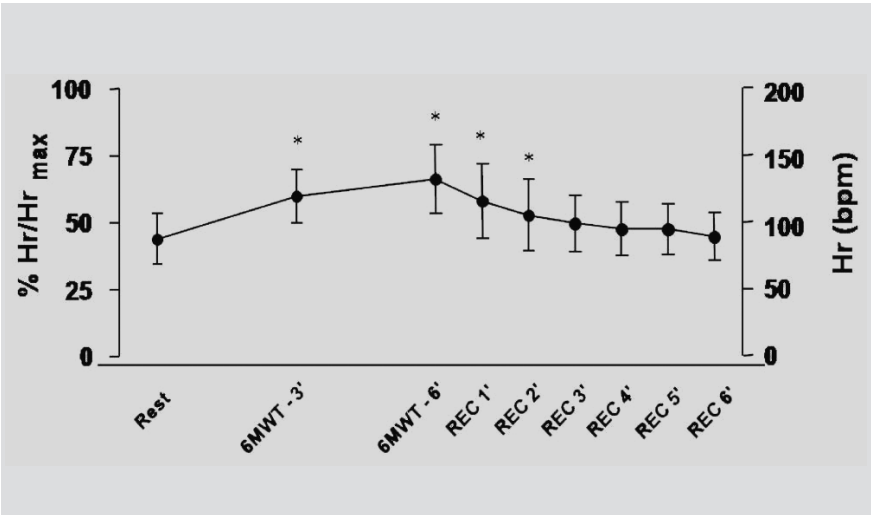

Figura 1. - Cardiovascular responses during 6MWT.

Abbreviations: 6MWT, six-minute walk test; REC, recovery period; HR, heart rate (bpm). Parametric continuous data represented as mean ± standard deviation. Longitudinal analysis: ANOVA with DMS post hoc test. (*$p < 0.05$).

The 6MWT is a simple, reproducible, low-cost exam with low operational difficulty and has important correlations with clinical variables such as exercise capacity, cardiopulmonary health, functional class, quality of life and prognosis [4-11, 17]. The present study was the first to use electrocardiogram telemetry monitoring during the unaccompanied 6MWT, thereby allowing the real-time determination of possible arrhythmia or signs suggestive of ischemia that may warrant test termination. A simplified analysis of peripheral lactate was also performed in order to gather information on alterations in the energy metabolism.

In the present study, quality of life was only moderately reduced and had no correlation with the variables measured during the 6MWT. This differs from the findings of preliminary studies demonstrating such a correlation. The discrepancy is likely due to the small number of patients and different functional classes in the present study.

The analysis of the occurrence of arrhythmia was carried out in three manners: The classification proposed by Low [18], which considered the severity of ventricular arrhythmia; the atrioventricular classification (AV), which divides arrhythmia into ventricular and supraventricular [11]; and the qualitative (descriptive) evaluation of the electrocardiogram findings [12]. The latter two report a greater incidence of arrhythmia in patients with a reduced oxygen supply in the myocardium. The analysis revealed a high probability of the occurrence of arrhythmia in this population. However, this condition was not exacerbated during the performance of the 6MWT, which suggests that safety of the method. Nonetheless, the need for clinical and preliminary dysfunction stratifying assessment must be emphasized. The routine use of an electrocardiogram system should be evaluated carefully, as the six-minute walk test is, in principle, a simplified test of easy reproducibility.

Heart rate was the variable that demonstrated the most expressive cardiovascular adjustment during the 6MWT. This response highlights its influence on the variation in the double heart product, which exhibits a loss in cardiovascular function in such patients, as evidenced by the reduced ventricular ejection fraction. Thus, as we could imagine, the chronothropic response was more important than the inotropic response in this population [11,18]. The HRR_2 was apparently higher in the group with poor cardiac function. A number of studies have described a correlation between the behavior of heart rate recovery (HRR) and cardiovascular function, in which slower reductions are directly related to deterioration in cardiovascular function and mortality. This phenomenon is linked to an imbalance in the autonomic nervous system, generally produced by the over-stimulation of the sympathetic nervous system and a reduction in vagal activity, and measures changes in functional capacity following a conditioning program [8, 9].

The simplified assessment of lactate allowed the estimation of additional information regarding the behavior of the energy metabolism during the walking test. Although the maximum heart rate (HR_{max}) reached an average of just 66.3% of the predicted value, four of the patients surpassed 4 mmol/L in the analysis of lactate behavior, suggesting a greater use of the anaerobic metabolism [20]. Following the 6MWT, the individuals reported an average perceived exertion of 14.3 ± 1.55 in a total of 20 points, which corresponds to exertion much closer to weariness and is compatible with the exertion reported in other studies. These findings allow us to infer a possible error in the estimation of maximum heart rate for these patients with an important functional limitation and most of whom (83.3%) made use of β-blocker treatment.

In the initial clinical evaluation, body weight and muscle force production are important markers in this population. With the evolution of heart failure, these variables develop an increased metabolic energy demand associated to perceptible musculoskeletal degradation. This can generate a functional stage denominated cardiac cachexia, interfering negatively on cardiopulmonary conditioning and, consequently, on quality of life and cardiovascular prognosis [2, 3].

The analysis of the 6MWT correlation with clinical status primarily revealed that, despite pertaining to an apparently homogeneous group equally eligible for heart transplant surgery, the individuals exhibited diversified functional capacity, as estimated by the distance walked. This was especially true for the four individuals who walked distances of less than 300 meters. It is currently known that individuals with heart failure who travel less than 300 meters on the 6MWT have a much worse prognosis [5, 10]. In the present study, the maximum distance walked

on the 6MWT demonstrated an important correlation with classic clinical characteristics such as ejection fraction (r=0.70) and functional class (r=0.73). Although some studies question the use of the test as a measure of cardiovascular status, most randomized clinical trials are in favor of its diagnostic value in patients with heart failure [7-9].

The present study has limitations that should be addressed. We evaluated a relatively small sample of patients with an indication for elective heart transplant surgery. Although we have demonstrated relevant results in this study, we must stress the difficulty in access to this population. Thus, the population evaluated in the present study corresponded to 12% of the total number of patients registered in Sao Paulo state, which speaks to the importance of carrying out multi-center studies in the future.

In conclusion, the clinical and electrocardiogram behavior suggests that the six-minute walk test is safe, but may be considered of high intensity for some patients with severe heart failure. Variables related to performance on the 6MWT may be associated with clinical status.

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