



Prognostic Value of the Six-Minute Walk Test in Heart Failure

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OBJECTIVE

This study aimed to assess the true usefulness of the Six-Minute Walk Test as a prognostic indicator and its contribution to clinical practice with heart failure patients.

METHODS

In order to investigate the actual value of the Six-Minute Walk Test as an objective measure of mortality probability in patients with heart failure, the test was applied to 179 stable patients (120 men and 59 women, mean age 58.32 ± 12.7 years, with NYHA class II and III heart failure and an ejection fraction (LVEF) of $34.91 \pm 12.4\%$). Patients were instructed to walk for 6 minutes and then, four hours later, underwent a conventional exercise stress test (as per Naughton Protocol). Patients were followed for an average of eighteen months.

RESULTS

The average distance walked was 521.11 ± 76.1 meters. During the follow-up period, 66 patients (36.9%) died. There was a significant correlation between the distance walked during the test and mortality ($p < 0.0001$). The logistic regression model identified the distance walked during the test as the most important independent predictor of mortality ($p = 0.0001$). A distance shorter than 520 meters identified the patients with an increased probability of death. There was a significant correlation between the number of metabolic equivalents (METs) measured during the conventional exercise stress testing and mortality rate ($p = 0.0001$).

CONCLUSION

The Six-Minute Walk test is a simple, safe and powerful method to assess the prognosis of patients with NYHA class II and III heart failure. It is an objective examination that may replace the conventional ergometric test for the prognostic evaluation of these patients.

KEY WORDS

Six-Minute Walk test, heart failure, prognosis

Heart failure (HF) constitutes an ever increasing public health problem. In Brazil, according to the *Sistema de Informações Hospitalares (SIH)* of the *Sistema Único de Saúde (SUS)* (Hospital Information System of the Unified Health System – SIH/SUS), among cardiovascular diseases HF was the leading cause of medical admissions to hospitals with 418,620 cases in 2001¹. Consequently, HF has an enormous economic impact on society.

The six-minute walk test (T6') is a simple, easily applied and inexpensive method to objectively assess the level of functional capacity²⁻⁵ and obtain prognostic stratifications in HF⁶⁻⁹.

In 1976, McGavin et al¹⁰ introduced the T6' test as a tool to determine the functional capacity of patients with chronic obstructive pulmonary disease. Recently, Troosters et al¹¹ corroborated its role in this disease.

Since 1980, the T6' test has been utilized more and more in clinical practice, especially in HF. In the SOLVD (Studies of Left Ventricular Dysfunction) study⁸ the distance walked during the six-minute walk test was recognized as an independent variable indicating mortality and morbidity in patients with class II and III heart failure.

The type of exertion put forth during T6' in HF has been considered similar to that of daily activities^{12,13}, i.e., the six-minute walk is a submaximal¹⁴ exercise test. Carreira et al¹⁵ concluded that T6' identifies significant hemodynamic stress and a large number of severe arrhythmias, in spite of being a better reflection of daily activities than a maximal oxygen uptake test.

The main objective of this study has been to determine if the distance walked during T6' is an independent prognostic indicator of mortality. An analysis was also made of whether or not T6' can be considered a submaximal test representative of daily activities. The safety of the method, as well as a potential association between the arrhythmias recorded during the test and mortality, were also assessed.

METHODS

This study prospectively analyzed HF patients who underwent the T6' test and were followed for an average of eighteen months (twelve to twenty-four months). Patients were being treated in the outpatient clinic setting or were hospitalized for diagnostic investigation.

Patients excluded from the study were those with decompensated HF, limitation of physical activity due to factors other than exertional dyspnea and fatigue such as intermittent claudication, lower limb arthrosis and arthritis, psychiatric diseases that could keep the patients from understanding the methodology of the examination, rheumatic *orovalvular* disease (valve disease secondary to oral foci of infection), anemia, chronic obstructive pulmonary disease, and any febrile condition or infectious disease.

One hundred seventy-nine patients with HF of different etiologies were evaluated by means of the T6'. Seventy-seven patients were hospital in-patients who underwent the test a short time before hospital discharge. Ninety-six percent (n = 173) were identified as NYHA functional class II. Patients' mean age was 58.3 ± 12.73 years, and 67% (n = 120) of them were men. The mean ejection fraction was 34.91% ± 12.40%. Table 1 displays the clinical characteristics of the patients enrolled in the study.

Table 1 - Clinical characteristics of patients enrolled in the study

| Characteristics | n | % |
|--------------------------------|----------|------------|
| Number of patients | 179 | 100 |
| Gender M/F | 120 / 59 | 67 / 33 |
| NYHA FC II/III | 173 / 6 | 96.6 / 3.4 |
| Origin: OPT / IPT | 102 / 77 | 57 / 43 |
| Left bundle branch block (LBB) | 28 | 15.6 |
| Atrial fibrillation | 33 | 18.5 |
| Etiology: | | |
| Ischemic | 57 | 31.8 |
| Hypertensive | 32 | 17.8 |
| Idiopathic | 45 | 25.1 |
| Other * | 45 | 25.1 |
| Mitral insufficiency | 119 | 66.5 |
| Mild | 60 | 33.5 |
| Moderate | 44 | 24.6 |
| Severe | 15 | 8.4 |

n- Number of patients; M- male; FC- functional class; OPT- outpatient; F- female; NYHA- New York Heart Association; IPT- inpatient [hospitalized];
* other- ischemic + arterial hypertension / peripartum / alcoholic / Chagas' disease

Patients were being medicated with diuretics, digoxin and angiotensin-converting enzyme inhibitors, with doses adjusted according to their symptoms and renal function. None of them was using beta blockers.

The ejection fraction was obtained by echocardiography using the Teichholz¹⁶ method (Caris equipment, model 7200/serial number 00353). In order to get T6' results representative of mild-to-moderate activities, the test was based on the principles of Wasserman et al¹⁷, which consider this exertional intensity as representing up to 79% of the predicted maximal heart frequency for the patient's age (220-age).

On the same day, patients underwent the T6' test and, four hours later, the conventional exercise stress test as per the symptom-limited Naughton protocol¹⁸. On the day before the tests, patients were introduced to the T6' by means of a 'preparatory' T6' test, so that they could become familiar with the methodology and adapt to it.

The examinations were performed on a 60-meter course under the supervision of one single technician, accompanied by one of the department's physicians. Patients were instructed to walk at their own pace according to their tolerance to exercise for six minutes.

Encouraging comments were made during the test. The T6' final result was the total distance in meters covered in six minutes. Heart rate was measured using a heart rate meter. Forty-four participants were randomly allocated to the T6' test and were Holter-monitored.

Statistical analysis was performed using Student's *t* test or Mann-Whitney test, chi-square test, Fischer's exact test, Pearson's correlation coefficient, variance analysis and Tukey's multiple comparisons procedure. The logistic regression analysis was used to evaluate the simultaneous influence of prognostic factors on mortality, and the optimum cut-off value was obtained through the use of a ROC curve (*Receiver Operator Characteristic Curve*). The level of statistical significance was set at 5%. Statistical analysis was performed with the SAS® *Systen* software.

RESULTS

Not all patients were able to complete the T6' test without stopping or interrupting it. Four patients (2.2%) did not complete the examination due to angina, and 5.5% (n = 10) needed to have the test interrupted for a short while due to precordial pain, resuming the walk as the angina was relieved. Fatigue was the most common complaint (n = 108 / 60.3%); however, dyspnea (n = 26 / 14.5%), leg pain and fatigue (n = 24 / 13.4%), and dizziness (n = 7 / 3.9%) were also reported. No other clinical event was registered during the course of the examinations.

Of the 179 patients, 66 (36.9%) died during the follow-up period. Deaths were due to deterioration of the myocardial function or to unknown reasons (there was/were eve case(s) of sudden death). Table 2 shows the descriptive analysis of the variables considered for the prognostic evaluation of the death and non-death groups.

The average distance covered by patients who died was significantly shorter (487.3 m x 540.9 m) (p < 0.0001).

When considering the average number of METs reached in the ET (ergometric test) by both groups, a significant difference was noticed, i.e., the mean number of METs in the death group is smaller than in the non-death group (3.3 x 5.3) (p = 0.0001). The mean ejection fraction of patients who died was also significantly smaller (31.3 x 37) (p = 0.002).

The mean age of patients who died was significantly higher (p = 0.0002). The death rate was significantly higher in the group over sixty years of age.

Other study variables correlated with the patient's clinical outcome. The presence of LBB (n = 12 / 42.85%) did not significantly correlate with mortality (p = 0.47). Atrial fibrillation (n = 14 / 42.42%) did not significantly interfere with the clinical outcome (p = 0.43). No significant correlation was observed (p = 0.73) between ischemic (n = 24 / 42.10%), hypertensive (n = 11 / 34.37), and idiopathic etiologies (n = 19 / 42.22%) and death. Mitral insufficiency was predominant (p = 0.008) among those patients who died (n = 52 / 43.69%). The combined correlation between the absent-to-mild mitral insufficiency (n = 32 / 26.66%) and moderate-to-severe mitral insufficiency (n = 34 / 57.62%) showed that patients in the death group had a significantly higher rate of moderate-to-severe mitral insufficiency. The statistical analysis was hindered when the functional classification was taken into consideration because of the small number of class III patients (n = 6 / 3.4%).

The T6' walking exertion was considered intense by 65% (n = 43) of the patients who died (p = 0.033). Regarding the Holter-recorded arrhythmias, the statistical analysis was hindered with respect to the clinical outcome. Overall, the exertion-induced arrhythmias that occurred during the ET were not significantly associated with death (p = 0.32). Even when more complex arrhythmias were considered, this connection did not exist.

A logistic regression analysis was used to evaluate the simultaneous influence of prognostic factors on mortality. Factors considered for the regression analysis were: age, gender, patient origin (outpatient / inpatient),

Table 2 - Descriptive analysis of the numerical variables according to clinical evolution

| Variable | Clinical Evolution | Mean | SD | Median | Minimum | Maximum | p |
|-------------|--------------------|-------|------|--------|---------|---------|----------|
| T6' (m) | Death | 487.3 | 75.9 | 480 | 277 | 685 | < 0.0001 |
| | Noan-death | 540.9 | 69.4 | 540 | 264 | 670 | |
| No. of METs | Death | 3.3 | 1.8 | 2.85 | 1.1 | 8.50 | 0.0001 |
| | Non-death | 5.3 | 2.3 | 5.30 | 1.3 | 8.78 | |
| EF (%) | Death | 31.3 | 11.9 | 33 | 9 | 38 | 0.002 |
| | Non-death | 37.0 | 12.3 | 35 | 12 | 40 | |
| Age (years) | Death | 62.9 | 11.4 | 64 | 33 | 85 | 0.0002 |
| | Non-death | 55.7 | 12.8 | 56 | 20 | 79 | |

T6' – Six-minute walk test; METs – metabolic equivalents; SD – standard deviation; m- meters; N° number; p- level of significance; EF- ejection fraction (%)

distance covered during the T6' test, number of METs, ejection fraction, mitral insufficiency, as well as general and specific arrhythmias during the ergometric test. Table 3 displays the parameters of the model selected by the logistic regression method, with a significance level set at 5% for each significant prognostic factor. When analyzed simultaneously, it was noted that the distance walked during the T6', mitral insufficiency, age and ejection fraction factors were significant enough to predict mortality, in this order, and that the highest probability of death was related to the shortest distance covered during the T6' test, greatest mitral insufficiency severity, the most advanced age and the smallest ejection fraction.

Table 3 – Logistic regression analysis for mortality

| Prognostic Factors | Coefficient | Standard Error | p | C-statistic of the model |
|--------------------|-------------|----------------|--------|--------------------------|
| Intercept | 2.0261 | 1.8279 | | 0.796 |
| T6' Distance | -0.0081 | 0.0026 | 0.0001 | |
| Mod/Severe MI | 1.2699 | 0.3788 | 0.0001 | |
| Age | 0.0414 | 0.0166 | 0.0200 | |
| EF | -0.0375 | 0.0166 | 0.0310 | |

MI- mitral Insufficiency; EF- ejection fraction; T6'- six-minute walk test; Mod- moderate; p- significance level

According to the ROC curve, the optimum cut-off value for the distance walked was 520 meters, for age it was 58 years, and for the ejection fraction, 35%. This means that a patient who walked a distance shorter than 520 meters, was 58 years of age or older, or who has an ejection fraction below 35% has a higher probability of death.

No association between the distance covered during the T6' test and the ejection fraction was observed ($p = 0.27$; $r = 0.082$).

When arrhythmias occurring during the T6' and ET tests were correlated, 86.4% ($n = 38$) and 84.4% ($n = 151$) of the patients showed cardiac rhythm disturbances, respectively.

Ninety-eight patients (54.7%) reached a heart rate higher than 79% of the maximum heart rate predicted for the T6' walk test, whereas 81 patients (45.3%) failed to reach this limit.

The average distance walked during the preparatory T6' test (486.8 ± 85.2) which took place the day before the examination was significantly shorter ($p = 0.0001$) than the average distance covered during the T6' itself (521.1 ± 76.1 meters).

DISCUSSION

SOLVD⁸ was the first study to demonstrate, in a group of 898 patients with class II and class III HF, a

strong connection between the distance walked during the T6' test and mortality. Medical literature shows that this prognostic value is controversial. In a study with 315 moderate and severe HF patients, Opasich et al⁵ reported that the distance walked during the T6' test does not provide prognostic information that can complement or replace VO_2 (oxygen consumption) or the classic clinical functional class grading system. However, despite the fact that patients in this study had undergone two T6' tests each, one of which the preparatory T6' test, the encouraging remarks technique was not used. Therefore, such results may have been influenced by the lack of encouragement to patients during the walking exercise, since they did not approach their anaerobic threshold.

The present study showed that the distance walked during the T6' test was a reliable prognostic indicator of mortality for HF patients ($p < 0.0001$). The four variables selected for the logistic regression model, i.e., distance covered during the test, moderate-to-severe mitral insufficiency, age and ejection fraction, accounted for approximately 80% of the deaths, as shown by the model C-statistic value (0.796). When death is considered, it was noted that the distance walked ($p < 0.0001$) and the number of METs reached in the ergometric test ($p = 0.0001$) are strongly related. For this reason, the distance walked during the T6' test was the only variable included in the subset of the proposed model, as both variables would provide approximately the same information.

The ROC curve determined the optimum cut-off value for the numerical variables selected by the logistic regression method, and it was clear that the distance covered during the T6' can determine and participate with other parameters in the prognostic stratification of HF patients. The average distance walked, which was greater than that reported in medical literature, was attributed to the fact that the condition of the population studied was less severe (most of the patients were HF II) and the group of patients received verbal encouragement during the examination (T6' test with encouragement). Recently, Rostagno et al¹⁹ reported similar results when comparing T6' in HF with other methods used to assess functional capacity.

In this study, other factors showed a significant association with the clinical outcome of HF patients. Exertion tolerance, measured by the number of METs reached in the ET, showed a significant association similar to that observed during the T6' test ($p = 0.0001$ x $p < 0.0001$). This information is of utmost importance, since T6' is a simpler test, is easily applied, is inexpensive and has greater acceptance compared to the ET test. Up until now, no other study has compared these two methods as to the clinical outcome of HF patients.

The left ventricle ejection fraction is one of the strongest indicators of mortality in HF²⁰⁻²². According to Haass et al²³, the prognostic value of the distance walked during the T6' does not depend on the ejection fraction and other

potential prognostic parameters. In this study we observed that the ejection fraction is a good prognostic indicator of mortality ($p = 0.031$), although less significant than the distance walked during the T6' test ($p = 0.0001$), the moderate-to-severe mitral insufficiency ($p = 0.0001$) and the patient's age ($p = 0.0001$) as observed after the model adjustment.

Taking into consideration the NYHA functional class and the clinical evolution of patients, it was noted that the small number of class III patients ($n = 6$) did not allow a verification of the discriminative power of the T6' test between functional classes II and III.

In the death group ($n = 66$), there was a significantly greater number ($n = 43$ -65%) of patients with a heart rate higher than 79% of the maximal heart rate ($p = 0.03$). This means that for patients with the worst prognoses, according to Wasserman et al¹⁷, T6' represents an intense activity. Roul et al⁶ observed that patients with the worst prognoses have a daily activity level relatively close to their maximum exertion tolerance.

Zugck et al²⁴ verified that the prognostic power of the distance walked during the T6' test in HF is similar to the VO_2 peak in ergospirometry. VO_2 peak is an important and established prognostic variable determined by ergospirometry; a method that should only be performed by experienced professionals especially for its interpretation. When serial evaluations are performed, costs increase even more, placing ergospirometry out of our reach. In light of this, ergospirometry is not a technique that just any healthcare institution in the country can afford to perform. The T6' test can in no way substitute for the information provided by ergospirometry in HF, but it is an important method in those cases where the analysis of respiratory gases is not feasible.

Lately, medical literature has reported on several prognostic indicators in HF. In our country, Silva²⁵ reported in his thesis on the prognostic value of CRP as an independent predictor of survival for patients with decompensated HF. In a recent publication, De Groote et al²⁶ demonstrated that for patients with stable HF, type B natriuretic peptide (BNP) plasma levels and maximal VO_2 provide independent information for prognostic risk stratification. Despite recent laboratory prognostic indicators described for HF, the distance walked in the T6' test remains a low cost indicator that is easy to perform and apply.

Faggiano et al²⁷ observed that the walking exercise exertion frequently demands a contribution from anaerobic metabolism (exertional effort above the anaerobic threshold). For 73% of the patients, physical exertion during the T6' reached the anaerobic threshold with a respiratory quotient greater than or equal to 1. That is, in these patients, T6' proved to be the maximal exertion test to be applied. Despite all tests on the population analyzed having been performed in one single hospital, on one single course, and according to the same methodology

(T6' test with encouragement) and under the supervision of only one technician, the maximum heart rate reached did not define the level of intensity that the T6' walking represents for this population.

Patient familiarity with the T6' test was fundamental for the results. The comparison between the average distance walked during the preparatory T6' with that of the T6' itself, showed a significant increase in the average distance walked in the T6' test ($p = 0.0001$). This better performance during the test itself was attributed to the information the patient acquired about the test the day before, reducing the usual psychological stress of undergoing an examination. Therefore, this analysis confirmed the importance of patient familiarity with the test before undergoing it. In a recent study²⁸, the importance of this familiarity with the T6' test was evident in fifty healthy patients.

The T6' methodology adopted varies from one study to another accounting for, at least in part, the divergences in results found in medical literature. T6' methodology should be standardized, and careful interpretation is necessary in studies where such standardization is not clearly defined. The methodology standardization is essential for the reproduction of results.

When the arrhythmogenic potential of the T6' and ET tests was analyzed for the population studied, both methods showed a high tendency to induce arrhythmias (86.4% and 84.4%, respectively). Therefore, arrhythmias may compromise the safety of both methods, mainly that of the T6' test as the patient is not under continuous cardiac monitoring¹⁵. According to the SOLVD⁸ study, no complications were recorded for the 833 T6' tests performed. Despite the great number of arrhythmias detected during the T6' test in the present study, there was no complication recorded. A total of 460 examinations were carried out without any adverse events: 281 T6' tests performed in 179 patients (102 examinations were disregarded since they were the second test done by the same patient), 179 preparatory T6' tests performed. No clinical complication was recorded within the five-hour period following the tests. Therefore, it can be said that T6' is a safe method for assessing these patients.

CONCLUSION

The degree of left ventricle dysfunction has been considered the main determinant of prognosis for HF. This study demonstrated that the distance walked during the T6' test is a highly reliable and independent predictor of mortality.

Depending on the heart rate, T6' cannot be considered a method representative of daily activities; nevertheless, it is an intense exertional activity for those patients with the worst prognosis. Despite the fact that T6' induces frequent complex arrhythmias, the test proved to be safe in evaluating this group of patients. It was not possible to correlate

arrhythmias induced by the T6' test with mortality.

On the other hand, considering that the study was performed with left ventricle dysfunction HF patients,

further investigations will be necessary to assess HF patients whose systolic function was preserved during the test.

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