The relation between repeated 6-minute walk test performance and outcome in patients with chronic heart failure

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Abstract

Objective: To assess the prognostic implications of the 6-minute walk test (6-MWT) distance measured twice, one year apart, in a large sample of patients with chronic heart failure (CHF) followed for an extended period (>8 years from baseline).

Material and Methods: Patients undertook a 6-MWT at baseline and at one year, and were followed up for 8 years from baseline.

Results: 600 patients (median [inter-quartile range, IQR]) (age 78 [72-84] years; 75% males; body mass index 27 [25-31] $kg \cdot m^{-2}$; left ventricular ejection fraction 34 [26-38] %) were included. At baseline, median 6-MWT distance was 232 (60-386) m. There was no significant change in 6-MWT distance at one year (change -12m; *P*=0.533). During a median follow up of 8.0 years in survivors, 396 patients had died (66%). Four variables were independent predictors of all-cause mortality in a multivariable Cox model (adjusted for body mass index, age, QRS duration, left ventricular ejection fraction); increasing NT pro-BNP, decreasing 6-MWT distance at one year, decreasing haemoglobin, and increasing urea.

Conclusions: Distance walked during the 6-MWT is an independent predictor of all-cause mortality in patients with CHF. In survivors, the 6-MWT distance is stable at one year. The 6-MWT distance at one year carries similar prognostic information.

Keywords: repeat testing, 6 minute walk test, risk, chronic heart failure

Introduction

Cardiopulmonary exercise testing (CPET) is perhaps the "gold standard" method for assessing exercise capacity in patients with chronic heart failure (CHF), but it is not widely available. More simple tests of functional capacity are commonly used [9]. The distance walked during a six-minute walk test (6-MWT) is reproducible and sensitive to changes in quality of life [10, 12, 18]. It is a self-paced, sub-maximal test, and exercise intensity mimics activities of daily living in patients with mild-to-moderate CHF [4, 2, 13]. The 6-MWT can be affected by a number of factors including: severity of heart failure, extent of co-morbidities [12], verbal encouragement provided by the healthcare professional [13], track layout, and the number of walk tests performed and their proximity to each other [4, 9].

We have previously showed agreement between repeated 6-MWTs (12 months apart) in 74 patients with HF with unchanged symptoms (intra-class correlation coefficient =0.80; 95% CI = 0.69–0.87) [10]. However, in practice, symptoms and functional capacity may change over time. Studies suggest that 6-MWT distance increases with repeat testing [4]. This "learning effect" is likely to be affected by changes in symptoms and medication usage but also other factors such as patient motivation, familiarity with the test requirements, and psycho-social factors (including confidence and anxiety levels) [4, 8, 14].

The prognostic implication of 6-MWT distance from repeated tests is unclear. The aim of the present study was to assess the prognostic implications of 6-MWT distance measured twice, one year apart, in a large sample of patients with CHF followed for an extended period (>8 years from baseline).

Methods

The Hull and East Riding Ethics Committee approved the study, and all patients provided informed consent for participation. Clinical information obtained included past medical history and drug and smoking history. Clinical examination included assessment of body mass index (BMI), heart rate, rhythm, and blood pressure (BP). Heart failure was defined as current symptoms of heart failure, or a history of symptoms controlled by ongoing therapy, in the presence of reduced left ventricular (LV) systolic function on echocardiography and in the absence of any other cause for symptoms [18, 23]. 2D-echocardiography was carried out by one of three trained operators. LV function was assessed by estimation on a scale of normal, mild, mild-to-moderate, moderate, moderate-to-severe, and severe impairment. LV ejection fraction (LVEF) was calculated using the Simpson's formula, where possible, from measurements of end-diastolic and end-systolic volumes on apical 2D views, following the guidelines of Schiller and colleagues [23] and LVSD was diagnosed if LVEF was <45%.

The 6-MWT was conducted following a standardised protocol [14]. A 15 m flat, obstacle-free corridor, with chairs placed at either end was used. Patients were

instructed to walk as far as possible at a self-selected pace, turning 180° every 15 m in the allotted time of 6 min. Patients were able to rest, if needed, and the time remaining was called every second minute [4]. Patients were excluded if they were unable to walk without assistance from another person (not including mobility aids), or if they were unable to exercise because of non-cardiac limitations. Patients walked unaccompanied so as not to influence walking speed. After 6 min, patients were instructed to stop and the total distance covered was measured to the nearest metre. Standardised verbal encouragement was provided to patients at 2 min and 4 min in a neutral tone. If a patient could not undertake the 6-MWT a distance of 0 m was recorded. The 6-MWT was repeated 12 months later.

Statistical Analysis

Continuous variables are presented as medians with inter-quartile ranges (IQR); categorical data as percentages. Continuous variables were assessed for normality by the Kolmogorov–Smirnov test. NT pro-BNP was normalised by log-transformation for analysis. No survivor was followed for fewer than 8 years from baseline. We used receiver operating characteristic (ROC) curves to assess the relation between variables at baseline and survival at 8 years from baseline, and report the area under the curve (AUC) with 95% confidence intervals (CI), sensitivity, specificity, and optimal cut-points. To define the optimal cut-point, we used the point closest to the upper left corner of the ROC curve, often known as the (0, 1) criterion.

Cox regression models (univariable and multivariable) were used to develop predictor models using all baseline variables. We used multivariable Cox

proportional hazards model using the backward likelihood ratio method (*P* value for entry was <0.05; *P* value for removal >0.1) to identify independent predictors of all-cause mortality from candidate predictor variables. The assumption of proportionality was tested for each variable using the method of Grambsch and Therneau [7]. To minimise the risk of 'overfitting' we were guided by Peduzzi and colleagues [19, 26] who suggested an events per variable ratio of 10:1. To determine the robustness of our model(s) we performed bootstrapping based on 1,000 stratified samples. SPSS version 19.0 (IBM, New York, USA) was used to analyse the data. An arbitrary level of 5% statistical significance was used throughout (two-tailed). We followed the guidance of Perneger [20] and did not adjust for multiple testing in order to avoid the inflation of type I error. The primary outcome measure was all-cause mortality.

Results

600 patients (median [inter-quartile range, IQR]) (age 78 [72-84] years; 75% males; body mass index 27 [25-31]kg·m^{-2}; left ventricular ejection fraction 34 [26-38]%) with heart failure due to left ventricular systolic impairment were included in the study (Table 1). At baseline, median 6-MWT distance was 232 (60-386) m, and quartile ranges for 6-MWT distance were <60m, 61-270m, 271-365m, and >365m. After a median follow up of 374 (21-45) days the 6-MWT was repeated and walking distance was unchanged (change -12m; *P*=0.533). Figure 1 shows limits of agreement for difference in walking distance between baseline and one year (y=-0.0784x + 27.663; R^2=0.0068; *P*=0.657). During a median follow up of 8.0 years in survivors, 396 patients had died (66%).

Ten variables were significantly associated with all-cause mortality following the one year test in univariable Cox analysis (Table 2) including baseline 6-MWT distance (χ^2 = 61.1; P<0.0001) and one year 6-MWT distance (χ^2 = 59.5; P<0.0001). After bootstrapping, 11 variables remained statistically significant (Table 3) including baseline 6-MWT and 1-year 6-MWT distance.

All variables in Table 2 were included in a final multivariable Cox model, and four were independent predictors of all-cause mortality when adjusted for body mass index, age, QRS duration, and left ventricular ejection fraction; increasing NT pro-BNP, decreasing 6-MWT distance at one year, decreasing haemoglobin, and increasing urea (Table 4). We re-ran the multivariable model by forcing baseline 6-MWT distance into it instead of 6-MWT distance at one year; we noted that the overall Chi-square value for the model remained unchanged.

Receiver operating characteristic curve analysis of the relation between the two 6-MWT distances and all-cause mortality at 8 years from baseline is shown in Figure 2. For baseline distance, AUC= 0.67; *P*<0.0001; 95% CI = 0.63–0.71; the optimal cut-point for baseline 6-MWT distance was 325m with sensitivity 0.75 and specificity 0.54); and for one year distance AUC= 0.66; *P*<0.0001; 95% CI = 0.62–0.70; sensitivity 0.73; specificity 0.53; optimal cut-point 327m).

Discussion

We have shown that distance walked during a 6-MWT both at baseline and at one year is an independent predictor of subsequent all-cause mortality in patients with CHF. The 6-MWT distance at one year carries similar prognostic information to baseline values. We believe ours is the first study which has considered the prognostic implications of 6-MWT distance measured twice, one year apart in patients with CHF. We have shown that in survivors, the 6-MWT distance is stable at one year. There is thus little to be gained from repeating the 6-MWT at one year in clinical practice.

We have previously shown that 6-MWT distance is an independent predictor of all-cause mortality. In 1 592 patients, 212 died representing a crude death rate of 13.3%. Five independent predictors of all-cause mortality were identified including decreasing 6-MWT distance [14]. Few studies have reported serial follow up of 6-MWT distance in cardiac patients. Cheetham and colleagues [6] conducted repeated 6-MWTs at baseline, 6 weeks, 12 weeks, and 18 weeks in patients awaiting heart transplantation (all patients had a history of at least 6 months of symptomatic heart failure). Distance walked ranged from 457 ± 28m to 470± 30m across the four time points (greatest distance being at the second time point). Although the mean distance at each time-point was greater than in our study, the mean change of 13m over 18 weeks was similar to our findings (-12m), albeit over 52 weeks. Cheetham and co-workers [6] did not perform a survival analysis but they concluded that the 6-MWT had limited utility in terms of repeated assessment of clinical status in patients with advanced heart failure.

Alison and colleagues [2] conducted repeated 6-MWTs after 6 months in 173 patients with significant pulmonary disease, and reported a mean increase of 119 m compared to baseline. Our follow up period was longer (1 year) and it is possible that any learning effect is lost over this period as other factors such as increasing age and severity of disease may become more significant drivers of walking performance.

The reproducibility of repeated 6-MWTs has been questioned due to inconsistencies in testing protocol. There is little agreement regarding the length or shape of the test course, whether a practice walk should be conducted, and which test result should be reported (i.e. first test, final test, best test, mean test score). Each of these issues is of particular importance when comparing serial data from multicentre trials. A 7 to 14% improvement in the second 6-MWT has been reported in patients with COPD [21, 24]. Sciurba and co-workers [24] reported that 761 patients with severe emphysema walked further (363m) during a second 6-MWT than during a first test one day before (343m). They argued that this was due to patients becoming familiar with the walking course, more motivated or using better pacing strategies. Similar short term improvement in 6-MWT distance has also been reported in older, apparently healthy individuals [27], and patients with heart failure [21].

Adsett and co-workers [1] investigated whether repeated performance of 6-MWTs was related to the time interval between tests or the baseline performance in 88 patients with stable CHF. The authors reported a mean difference of 12 metres between the first and second tests and concluded that this would be clinically insignificant. Patients with a poor baseline 6-MWT distance showed no learning

effect, and Adsett *et al* [1] concluded that repeated testing was unnecessary in their cohort of patients with CHF.

The optimum cut-point in our study was 325m, patients walking less than this distance were at an increased risk of all-cause mortality. Our findings our similar to a previous study which reported a cut off <300m for predicting increased likelihood of death or pre-transplant hospital admission in 45 patients with more advanced heart failure [5] than those recruited to our study.

Study Limitations

We acknowledge that a number of confounding variables may affect performance in repeated 6-MWT over a period of 12 months including changes in lifestyle, medication usage, deterioration or improvement in symptom severity, or surgical intervention. The American Thoracic Society [3] recommended that corridor distance should be 30m. Our corridor was 15m meaning that patients must turn more frequently during the 6-minute period. Therefore, the distance "norms" we report are likely to underestimate walking performance in this cohort of patients. The 6-MWT is not a test of maximal exercise capacity but is a test of submaximal exercise performance [13]. The American Thoracic Society [3] advocates that verbal encouragement should be limited, and tone of voice be controlled during the 6-MWT in an elderly, chronic disease population. We have followed this approach with our patients but different centres will operate different systems. Therefore, findings from our current study should not be extrapolated to other populations, or to other research centres that may use a more aggressive 6-MWT coaching style.

Furthermore, patients who had a poorer 6-MWT distance may preferentially have died before the second measurement. The effect is to dilute the relation between baseline 6-MWT and outcome.

Conclusion: In survivors, the 6-MWT distance is stable at one year. Distance walked during the 6-MWT is an independent predictor of all-cause mortality in patients with CHF. The relation is similar when the test is repeated at one year, suggesting that there is limited clinical utility in repeating the 6-MWT.

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