Respiratory Medicine (2009) **103**, 1430–1435

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Small changes in six-minute walk distance are important in diffuse parenchymal lung disease

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Received 13 November 2008; accepted 26 April 2009
Available online 23 May 2009

KEYWORDS
Exercise test;
Outcome assessment;
Pulmonary fibrosis

Summary
The aim of this study was to determine the minimal important difference for the six-minute walk distance in people with diffuse parenchymal lung disease.
Methods: Forty-eight subjects (24 idiopathic pulmonary fibrosis) undertook the six-minute walk test before and after an 8-week exercise program. The minimal important difference was calculated using a distribution-based and an anchor-based method. A global rating of change scale was used as the external criterion to judge patients as clinically unchanged or changed.
Results: The mean change in six-minute walk distance in improved subjects was 50.0 m, compared to 4.0 m in unchanged subjects and a reduction of 64.3 m in those classified as worse ($p < 0.001$). The receiver operating characteristic curve indicated a cut-off value for meaningful change of 30.5 m (area under the curve 0.89, 95% confidence interval 0.81–0.98) whilst the standard error of the mean method indicated a value of 33 m. Similar values were obtained when only subjects with idiopathic pulmonary fibrosis were included (29 and 34 m, respectively).
Conclusions: Small differences in six-minute walk distance, in the range 29–34 m, may be clinically significant for people with diffuse parenchymal lung disease.

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doi:10.1016/j.rmed.2009.04.024

Introduction

The diffuse parenchymal lung diseases (DPLDs) are a diverse group of chronic lung conditions characterized by exercise limitation and dyspnea on exertion.[1,2] Treatment options are limited and are frequently associated with significant risks and side effects. In this setting, it is important to know whether changes in functional status are associated with sufficient clinical benefit to warrant a change in a patient's medical management. The magnitude of this change is referred to as the minimal important difference (MID).[3]

The six-minute walk distance (6MWD) is a widely used measure of functional status in people with DPLD. The distance walked is closely linked to disease severity and survival across a range of DPLDs[4–6] and is an important outcome measure for clinical trials.[7,8] To date the MID for the 6MWD in DPLD has not been established. Previous investigators have identified a distance of 54 m for the MID in people with COPD,[9] although more recently this value has been questioned and the threshold for clinically important change may be lower.[10] It is likely that differences in pathophysiology between the two conditions preclude the direct adoption of these findings in DPLD. The lack of a description of the MID for this patient group is a major limitation to interpretation of longitudinal change in functional status.

A variety of methodologies have been used to calculate the MID. Although a previous approach has been to examine cross-sectional differences in 6MWD[9] there is evidence that cross-sectional differences (differences between patients at a given time point) do not correspond to longitudinal differences (within one individual over time).[11] It has therefore been suggested that the MID should be determined using methods that focus on change within individuals.[12]

Available methods for determining the MID can be classified as either anchor-based or distribution-based.[13] Anchor-based methods involve comparing a patient's change score to another measure of clinically relevant change, such as a global rating of change score completed by the patient and/or clinician.[14] Some authors suggest that the patient's perspective is the most relevant when assessing change in functional status[3]; however, limitations to patient recall have previously resulted in low correlations between patient-reported anchors and 6MWD.[9] Distribution-based methods, such as the standard error of the measurement (SEM), are built on the statistical properties of the study results. One SEM has been shown to closely approximate the MID.[15] The SEM has the advantages of being independent of the sample characteristics and takes into consideration the possibility that some of the observed change is due to measurement error.[16] Concurrent comparisons using both approaches are recommended to evaluate the effects of the methodology on the final value.[17] The aim of this study was to determine the MID for the 6MWD in people with DPLD using both an anchor-based and a distribution-based method.

Material and methods

Study subjects

Patients with documented DPLD were recruited from two tertiary hospitals. For IPF, the diagnostic criteria were consistent with those outlined in the International Consensus Statement.[18] Patients were eligible to participate if they were ambulant and reported dyspnea on exertion on stable medical therapy. Exclusion criteria were a history of syncope on exertion or any comorbidities which precluded exercise training. All subjects gave written informed consent and the study was approved by the human ethics committees at both sites.

Study design

The six-minute walk test was measured on two occasions, eight weeks apart, using a standardised protocol.[19] All subjects undertook two tests on each testing occasion and the best distance was recorded. Use of supplemental oxygen during the test was standardised between subjects and testing occasions as previously described in subjects with DPLD.[4]

Methods

Subjects participated in an eight-week exercise training program conducted according to accepted guidelines for patients with chronic respiratory disease.[20] Some were participants in a randomised controlled trial evaluating the efficacy of exercise training in DPLD.[21] Following the exercise-training period, but before repeating the six-minute walk test, subjects were asked to make a global rating of change in their walking ability by an independent data collector (a physiotherapist who was not known by the participants and had not been involved in their training). Participants were asked 'Has there been any change in your walking ability since you started the pulmonary rehabilitation program?' and could answer either 'worse', 'about the same' or 'better'.[22] If subjects stated that they were worse, they were asked whether they were 'much worse' or 'a little worse'. If subjects stated that they were better, they were asked whether they were 'much better' or 'a little better'. At the same time point, clinicians who trained the participants in the pulmonary rehabilitation class were asked to rate the change in the participant's walking using the same criteria, whilst blinded to the subject's own rating. Both participants and clinicians were therefore blinded to the second 6MWD at the time of undertaking the global rating of change. If participants indicated there had been no change in their walking ability they were classified as 'unchanged'. If participants indicated any degree of improvement or worsening on this scale, they were classified as 'changed'.[22] Comparison of participant and clinician ratings was used to verify patient recall.[14]

Analyses

The MID for the 6MWD was calculated using both anchor-based and distribution-based methods. For the anchor-based method, the sensitivity and specificity for change in 6MWD to discriminate between individuals who had been classified as 'changed' or 'unchanged' were calculated. A receiver operating characteristic (ROC) curve was obtained by plotting the sensitivity (*Y*-axis) against 1-specificity (*X*-axis) for each of the cut-off values.[14] The MID for the 6MWD was determined by visual inspection of the ROC

curve. The 95% confidence interval for the MID was found using the bootstrap.[23] In each case, 1000 bootstrap replicate samples were obtained, by resampling the ''changed'' and ''unchanged'' samples separately. For each replicate sample the optimal cut-point was obtained. The limits of the 95% confidence interval were then taken to be the 2.5th and 97.5th percentile of the 1000 cut-points. Minitab version 15.1 and some associated programming were used to carry out the bootstrapping. For the distribution-based method, the SEM was calculated using the revised Jacobsen formula.[24] Calculations were repeated for the subgroup of participants with IPF. The reliability coefficient for the 6MWD was obtained from a previous study of the 6MWD in subjects with IPF.[25]

Univariate analysis of variance was used to assess the effects of gender, age ($\leq$65 years vs $>$65 years), baseline walking distance ($<$350 vs $\geq$350 m) [26] and disease severity (TLCO $\leq$ 39% predicted vs $>$39% predicted)[27] on change in walk distance. Statistical analysis was undertaken with SPSS version 14.0. Further detail regarding statistical methods is provided in Supplementary data.

Results

Forty-eight subjects with DPLD were recruited. Demographic characteristics of the included subjects are shown in Table 1. There was a wide range of walking ability with 6MWD ranging from 154 to 681 m. Participants reported a moderate degree of dyspnea (median MRC dyspnea score = 3, range 1–5). Twenty-four subjects had a diagnosis of IPF, while 20 subjects had diffuse parenchymal lung disease of known cause (collagen vascular disease, drug or dust-related) and four subjects had granulomatous lung disease. There were no differences between participants with and without IPF in either baseline 6MWD ($p = 0.24$) or the change in 6MWD following the exercise program ($p = 0.61$). Respiratory function did not change over the eight-week study period.

Forty-three of the 48 subjects completed the exercise program; 4 of the 5 participants who did not complete had IPF. Followup data were obtained from all participants regardless of completion. The range of differences in 6MWD between the beginning and the end of the program ranged from an improvement of 128 m to a decrease of 115 m. The patient-completed global rating of change score indicated improvement in 26 subjects, whilst 15 subjects were classified as unchanged and 7 subjects were classified as worse. The mean change in 6MWD in those subjects who were classified as improved was 50.0 m, compared to a mean change of 4.0 m in those classified as unchanged and a mean reduction of 64.3 m in those who were classified as worse ($p < 0.001$, Fig. 1). There were no differences in the degree of change in 6MWD that was classified as clinically important related to gender ($p = 0.98$), severity of lung disease ($p = 0.55$) or age ($p = 0.86$, Fig. 2). There was a trend towards larger changes in walking distance being required to specify that clinically important change had occurred in those with a baseline 6MWD of less than 350 m ($p = 0.1$).

Table 1 Demographic characteristics of subjects at baseline ($n = 48$).

	Mean (standard deviation)	Range
Age, years	69 (9)	48–84
FVC %pred	78 (16)	32–119
TLCO %pred	51 (18)	19–91
TLC %pred	76 (16)	47–101
RVSP (mmHg)	37 (13)	16–71
6MWD m	403 (118)	154–681

Data are mean (standard deviation). FVC – forced vital capacity; %pred – percentage predicted; TLCO – diffusing capacity for carbon monoxide; TLC – total lung capacity; RVSP – right ventricular systolic pressure; 6MWD – six-minute walk distance.

The ROC curve for all participants is depicted in Fig. 3a. The area under the curve was 0.89 (95% confidence interval 0.81–0.98). Visual inspection indicates that the cut-off value at the upper left corner representing the best balance between sensitivity and specificity for this test to reflect meaningful change in the 6MWD is 30.5 m (95% confidence interval 19–45 m). This point corresponds to a sensitivity of 0.73 and a specificity of 0.94. When the analysis was repeated including only subjects with IPF, the area under the curve was 0.93 (95% confidence interval 0.83–1.03) with a cut-off value of 29 m (95% confidence interval 19–45 m, Fig. 3b).

Using the baseline standard deviation for the 6MWD and the reliability coefficient for the 6MWD ($r = 0.96$), the SEM for 6MWD in all participants was calculated to be 33 m. When only participants with IPF were included, the SEM was 34 m. There was excellent agreement between the number of participants who were classified as changed under the ROC and SEM methods (kappa = 0.96 for all participants, 95% confidence interval 0.88–1.0; kappa = 0.92 for IPF participants, 95% confidence interval 0.80–1.0).

There was good agreement between patients and clinicians regarding clinical change, with consensus occurring in 38 subjects (79%). There were no differences in diagnoses, respiratory function, baseline 6MWD or change in 6MWD following the exercise program between those subjects in whom consensus was or was not observed. The ROC curve

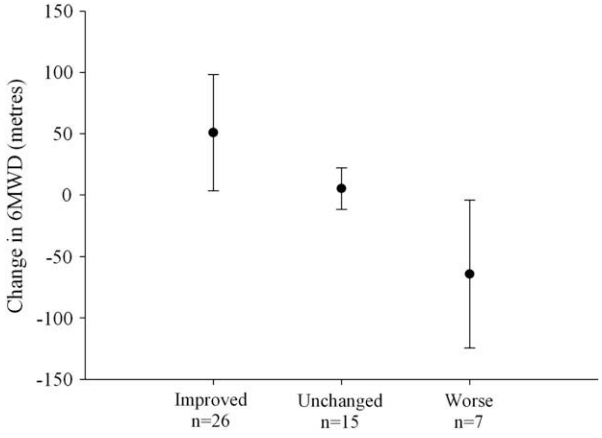

Figure 1 Relationship between change in six-minute walk distance and global rating of change in walking ability following exercise training. Data are means and standard deviations. 6MWD – six-minute walk distance. Univariate analysis of variance indicates a significant difference between groups ($p < 0.001$).

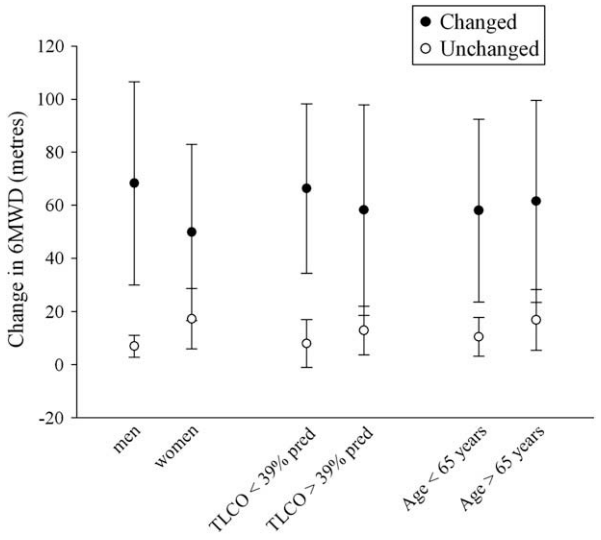

Figure 2 Change in six-minute walk distance according to gender, disease severity, age and baseline walk distance. No effect of baseline demographic variables was found in participants who were rated as either changed or unchanged on the global rating of change score. Data are means and standard deviations. TLCO — diffusing capacity for carbon monoxide; 6MWD — six-minute walk distance.

including only those participants in whom consensus occurred revealed a cut-off for meaningful change of 30.5 m whilst the SEM method was 32 m. When the analyses were repeated excluding those participants who reported deterioration, the ROC and SEM estimates of the MID were slightly lower (28.5 and 24 m, respectively).

Discussion

This study demonstrates that small changes in 6MWD are perceived by both patients and clinicians to be clinically significant for patients with DPLD. Using a longitudinal model that focuses on important change within individuals, we have determined that the difference in 6MWD which is associated with noticeable change in functional status is between 29 and 34 m. The threshold for clinically significant change was not different when only subjects with IPF were included.

This study used both anchor-based and distribution-based methods to calculate the MID and found a difference of only 3 m between approaches. Both methods have desirable features. The anchor-based method we selected[14] takes into account both patient and clinician perspectives, thus strengthening the criterion for change. The ROC curve provides a measure of both sensitivity and specificity, allowing clinicians to determine whether the cut-off point is appropriate for any given therapeutic intervention. This may be important where the risks associated with false positives are high (e.g. where treatment has toxic side effects). The high specificity of our estimates indicates that false negatives are very unlikely using the threshold of 30.5 m (Fig. 3). Based on these data, clinicians can be confident that if the change in 6MWD does not achieve the threshold then it is very unlikely that any significant change has occurred. The distribution-based method has the advantage of consistency across samples and thus can be applied across all but the extremes of a given population's ability levels.[16] The similar result from these two approaches is encouraging and suggests that the estimate is robust.

The MID for the 6MWD determined here for patients with DPLD is similar to the threshold for important change recently reported in patients with COPD[10] but lower than the estimated MID for patients with pulmonary arterial hypertension.[28] Using data sets from previous trials which were analysed using distribution-based methods, a threshold value of 35 m was identified as representing an important effect in patients with COPD.[28] However, an anchor-based estimate was not obtained from that study due to poor correlations between patient-reported outcomes and walking distance. In contrast, we found a strong relationship between patient assessments and change in walking distance. These differences may indicate that walking ability is a more important measure of change to patients with DPLD than it is to those with COPD, perhaps due to differences in pathophysiology and rapid disease progression in the former group.[5,29–31] However, it is more likely to be related to the patient outcomes selected. Whereas previous authors used quality of life measures which assess the broader impact of lung disease on well-being, our prospective study used a global rating of change scale specifically designed to assess walking ability. An MID of 41 m has been reported for patients

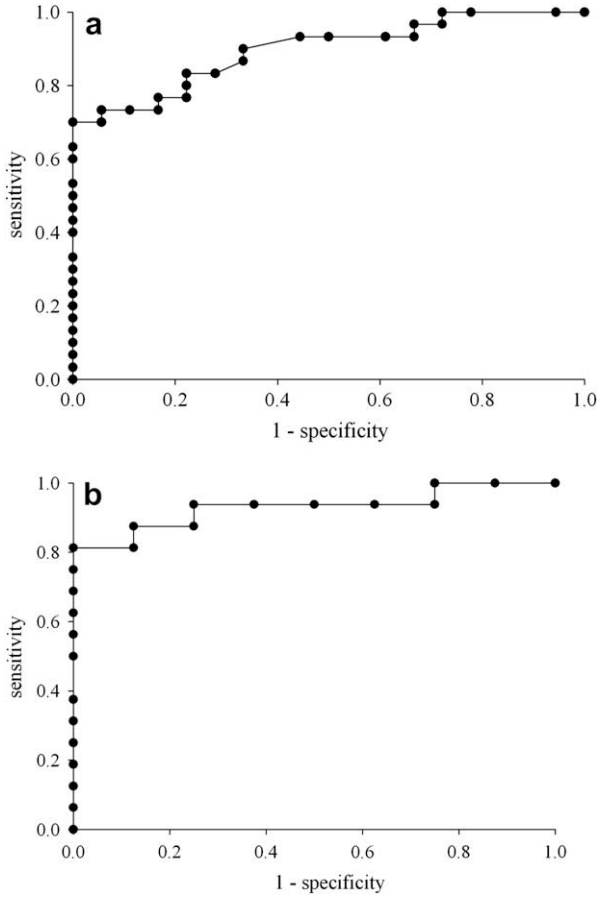

Figure 3 Receiver operating characteristic curves for change in six-minute walk distance; (a) all participants; (b) IPF participants only.

with pulmonary arterial hypertension,[28] representing the average of seven different distribution-based approaches that ranged from 18.7 to 74.15 m. A patient anchor was not available for use in this study. Anchor-based approaches are the preferred method of assessing the MID where possible[32] and provide confidence that the identified changes are meaningful to patients.

Differences in the MID according to gender, age or disease severity were not identified (Fig. 2). This is in accordance with previous authors who have not identified any difference in the MID for 6MWD according to baseline demographic features.[9] However, there was a trend towards a larger difference in 6MWD being required to achieve clinical significance in those with lower baseline walk distances. These results should be interpreted with caution due to the small numbers included in the subgroup analysis ($n = 13$). Larger trials are required to assess this in more detail.

This study has a number of limitations. Firstly, it was conducted in the context of a randomised controlled trial of exercise training for DPLD.[21] Whether the results would be similar in the context of other therapeutic interventions is unclear. However, our sample included participants with a wide range of disease severity and exercise tolerance (Table 1) and thus it is likely that our results are broadly applicable. Our sample did not include sufficient numbers of subjects who deteriorated to assess whether the MID for decline differed from the MID for improvement. Removal of participants who had a 'negative' change in walking distance resulted in slightly lower estimates of the MID that were within the 95% confidence interval for the MID calculated from the whole data set. Although some authors suggest that positive and negative changes are pooled,[22,33] others have indicated that there could be a difference in the perception and meaning of positive and negative changes.[34] Larger samples followed across longer time periods will be required to assess this important component of the MID. Finally, we have focussed on the change in walking distance as the primary indicator of clinically significant change. Although many authors have reported that 6MWD is a critical indicator of prognosis[4,35,36] others have suggested that desaturation during the six-minute walk test may also be an important marker.[2,29] The amplitude of desaturation during exercise is poorly reproducible in this population[25] and we therefore chose not to evaluate this in a study which required repeated measures.

In conclusion, this study demonstrates that the threshold for clinically significant change in 6MWD for people with DPLD is in the range of 30–33 m, and for people with IPF is in the range 29–34 m. These values should be tested further in the context of commonly used therapies for DPLD and over a longer duration of follow-up.

Conflict of interest statement

The authors have no conflict of interest related to this research.

Acknowledgements

This study was supported by the Victorian Tuberculosis and Lung Association. The study sponsors had no role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.rmed.2009.04.024.

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