



The 6-min walking distance: long-term follow up in patients with COPD

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ABSTRACT: The 6-min walking distance (6MWD) test is used in clinical practice and research into patients with chronic obstructive pulmonary disease (COPD). However, little is known about natural long-term change in this parameter.

The 6MWD was measured at baseline and then annually for 5 yrs in 294 patients with COPD and its annual rate of decline was determined. Forced expiratory volume in one second (FEV₁) was also measured and the relationship between changes in both markers was explored.

At baseline, the median 6MWD was 380 m (range 160–600 m). It declined by 19% (16 m·yr⁻¹) over the 5 yrs compared with baseline in patients with American Thoracic Society/European Respiratory Society stage III COPD (FEV₁ 30–50% predicted) and by 26% (15 m·yr⁻¹) in patients with stage IV COPD (FEV₁ <30% pred). Over the 5-yr follow-up, the proportion of patients with a minimal clinically significant decline of 54 m increased with the severity of the disease. It was 24% in stage II, 45% in stage III, and 63% in stage IV disease. In contrast, the rate of decline of FEV₁ was greater in patients with milder airflow obstruction and lesser in patients with lower absolute FEV₁ values.

In conclusion, the 6-min walking distance test provides increasingly useful information as the severity of chronic obstructive pulmonary disease increases.

KEYWORDS: Chronic obstructive pulmonary disease, 6-min walking distance

The 6-min walking distance (6MWD) test has gained importance in the assessment of functional exercise capacity in patients with chronic obstructive pulmonary disease (COPD) [1, 2] and other respiratory diseases, such as pulmonary hypertension [3], interstitial lung disease [4], cystic fibrosis [5] and post-acute respiratory distress syndrome [6]. The test evaluates the global and integrated responses of the pulmonary, cardiovascular and muscular component and reflects the functional exercise level for daily physical activities [7].

Introduced in 1976 as a 12-min walk test to measure the exercise capacity of patients with COPD, the abbreviated 6MWD has proved to be reliable, inexpensive, safe and easy to apply [7–10]. Furthermore, it correlates well with other important outcomes in COPD patients such as dyspnoea, airway obstruction and lung hyperinflation [11]. The test has been shown to be an important prognostic factor for outcome independent of the forced expiratory volume in one second (FEV₁) [12]. The 6MWD is a submaximal exercise test, but it correlates well with the maximal cardiopulmonary exercise test [13–15],

and appears to be better tolerated and more reflective of the activities of daily living than other walk tests [16, 17].

While there is plenty of data concerning the natural history of FEV₁ over time, little information has been published regarding the temporal behaviour of the 6MWD. This is a significant omission, as the 6MWD test is frequently used to evaluate the long-term impact of interventions. Changes in 6MWD over time have been addressed in one published study [12], but it was limited to patients with severe COPD, the follow-up time was relatively short (1 yr) and the decline trend was established with only two measurements.

As part of the large body mass index, degree of obstruction, dyspnoea and exercise capacity (BODE) cohort, the present authors have evaluated the 6MWD systematically as one of several variables included in the evaluation of patients. Thus, subjects in the present study had a wide range of severity of COPD. The results are expressed both as absolute change and in terms of the reference equations derived for 6MWD in healthy populations [18, 19].

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Received:

May 30 2006

Accepted after revision:

November 06 2006

STATEMENT OF INTEREST

None declared.

METHODS

A total of 294 outpatients with COPD from the original BODE cohort [1] with a wide range of airflow obstruction, from clinics in the USA (Bay Pines Veterans Affairs Medical Center, Bay Pines, FL), Spain (Hospital Universitario La Candelaria, Tenerife, and Hospital Miguel Servet, Zaragoza), and Venezuela (Hospital Jose I Baldo, Caracas), participated in the study, which was approved by the human review boards at each centre. Patients were enrolled from December 1995 to September 2004 and had ≥ 3 yrs follow-up time. After the initial 3 yrs, the cohort was followed up to 5 yrs. Deaths occurring during this time were confirmed by review of the records. COPD was defined by a smoking history of >20 pack-yrs and a post-bronchodilator FEV₁/forced vital capacity (FVC) <0.7 . Patients were clinically stable for ≥ 6 weeks and were receiving optimal medical therapy according to current guidelines. Exclusion criteria were: uncontrolled comorbidities likely to affect mortality within 3 yrs, such as malignant disorders or cardiovascular disease; history of asthma; inability to perform the lung function and 6-min walk tests; and involvement in pulmonary rehabilitation.

After ≥ 6 weeks of clinical stability, patients were tested with pulmonary function tests, spirometry and lung volume measurements according to American Thoracic Society guidelines [20]. The severity of the obstruction was classified using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and ATS/European Respiratory Society classification. All patients had an FEV₁/FVC <0.7 . Patients in stage I have an FEV₁ $>80\%$ predicted; stage II patients have an FEV₁ 50–80% pred; stage III patients have an FEV₁ 30–49% pred; and stage IV patients have an FEV₁ $<30\%$ pred.

The 6MWD was measured using the best of two 6-min walk tests separated by ≥ 30 min [1, 7, 21]. The 6MWD was expressed in absolute values and as per cent pred using two published reference values [18, 19]. Inspiratory fraction, or ratio of inspiratory capacity (IC) to total lung capacity (TLC) was used as a measure of static lung hyperinflation [11]. The combined Charlson index was used to determine the degree of comorbidity [22]. Patients were re-evaluated every 12 months for ≥ 3 yrs.

Statistical analysis

Qualitative variables are expressed as relative frequencies of categories. Numerical values are expressed as median (5th–95th percentile) because of their skewed distribution. Differences between groups were tested using the Chi-squared test for categorical variables or the Mann–Whitney U-test for numerical variables. Correlations were estimated using Spearman's rank coefficient. The slopes of 6MWD decline were estimated by means trend modelling based on median annual values, with 95% confidence intervals (CI). To estimate possible differences in progression owing to the differential loss between patients who dropped out and those who remained between 3 and 5 yrs, general linear modelling was performed for repeated measures. Significance was defined as a two-tailed p-value <0.05 .

RESULTS

The cohort of 294 patients was distributed as follows: 200 (68%) from the USA; 84 (29%) from Spain (56 from Tenerife; 28 from

Zaragoza); and 10 (3%) from Venezuela. Patient characteristics are presented in table 1. The median age was 66 yrs (51–79 yrs), and the majority of subjects (97%) were male. At the time of entry to the study, their disease states were as follows. GOLD and ATS/ERS stage I: 1% (n=4); stage II: 28% (n=81); stage III: 46% (n=136); stage IV: 25% (n=73).

After the initial 3 yrs and during the follow-up period, 194 patients were lost to the study. Of these losses, 69 were due to deaths and 125 due to other causes. No statistically significant difference in the 6MWD decline progression between those patients lost from the study and those who remained at 3 yrs (131 *versus* 163 patients) and 4 yrs follow-up time (63 *versus* 100 patients). However, compared with the survivors, those who died underwent a steeper 6MWD decline, of 25 m·yr⁻¹ (95% CI 10–40 m·yr⁻¹).

The median (5th–95th percentile) 6MWD at baseline was 388 m (160–600 m). It declined by 12.5 m·yr⁻¹ (95% CI 8–17 m·yr⁻¹) for up to 5 yrs (p=0.001; fig. 1). The baseline 6MWD expressed as per cent pred using the equations of ENRIGHT and SHERRILL [18] and TROOSTERS *et al.* [19] were 75% (47–99%), and 58% (39–77%; fig. 2), respectively. Of note, 6MWD declined significantly only in patients with FEV₁ $<50\%$ pred (fig. 3). In patients with GOLD and ATS/ERS stage III COPD, 6MWD decreased by 19% compared with baseline (16 m·yr⁻¹ (95% CI 8–24 m·yr⁻¹); p <0.006) and in patients with stage IV COPD it decreased by 26% compared with baseline (15 m·yr⁻¹ (95% CI 7–22 m·yr⁻¹); p=0.005). The decline did not reach statistical significance in patients with stage II COPD (2% compared with baseline; 6 m·yr⁻¹ (95% CI -4–16 m·yr⁻¹); p=0.16; fig. 4).

The rate of decline was not influenced by the age of the patients (14 m·yr⁻¹ in patients aged >65 yrs and 13 m·yr⁻¹ in patients aged <65 yrs). The rate of decline was greater in

TABLE 1 Baseline characteristics of the patients

Subjects n	294
Sex M/F	285/9
Age yrs	66 (51–79)
Current smokers %	18
BMI kg·m ⁻²	27 (19–36)
6MWD m	388 (160–600)
FEV ₁ L	1.13 (0.64–2.22)
FEV ₁ % pred	39 (20–70)
GOLD and ATS/ERS staging	
Stage I	4 (1)
Stage II	81 (28)
Stage III	136 (46)
Stage IV	73 (25)
IC/TLC	0.28 (0.16–0.42)
Charlson index	4 (1–7)

Data are presented as n, median (5th–95th percentile) or n (%), unless otherwise stated. M: male; F: female; BMI: body mass index; 6MWD: 6-min walking distance; FEV₁: forced expiratory volume in one second; % pred: % predicted; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ATS: American Thoracic Society; ERS: European Respiratory Society; IC: inspiratory capacity; TLC: total lung capacity.

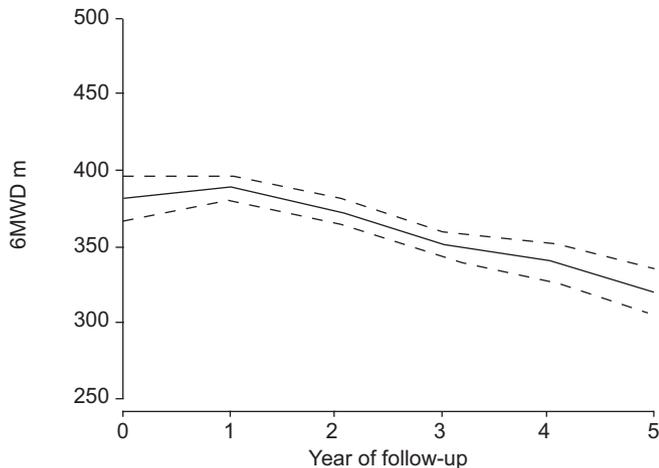


FIGURE 1. Median 6-min walking distance (6MWD) over 5 yrs. Baseline median (range) 6MWD was 388 m (161–600 m; n=294). It declined at $12.5\text{ m}\cdot\text{yr}^{-1}$ (95% confidence interval $8\text{--}17\text{ m}\cdot\text{yr}^{-1}$) for up to 5 yrs ($p=0.001$). —: median; -----: 95% confidence intervals. Year 4: n=163; year 5: n=100.

patients from the USA ($14\text{ m}\cdot\text{yr}^{-1}$ (95% CI $6\text{--}21\text{ m}\cdot\text{yr}^{-1}$); $p=0.008$) than in patients from the other regions ($7\text{ m}\cdot\text{yr}^{-1}$ (95% CI $0\text{--}15\text{ m}\cdot\text{yr}^{-1}$); $p=0.05$). This is in agreement with the fact that patients from the USA had higher degrees of obstruction and comorbidity.

The proportion of patients with a minimal clinically significant decline ($\geq 54\text{ m}$) in 6MWD over the 5-yr period increased with the severity of the disease (stage II: 24%; stage III: 45%; stage IV: 63%; $p=0.025$).

Post-bronchodilator FEV₁ values declined significantly, with a mean rate of decline of $23\text{ mL}\cdot\text{yr}^{-1}$ (95% CI $14\text{--}32\text{ mL}\cdot\text{yr}^{-1}$; $p=0.002$). The decline differed by disease stage, in the opposite way to the 6MWD (fig. 4). FEV₁ declined in stage II patients by $40\text{ mL}\cdot\text{yr}^{-1}$ (95% CI $20\text{--}70\text{ mL}\cdot\text{yr}^{-1}$; $p=0.011$), whereas the fall was smaller in patients with stage III disease ($10\text{ mL}\cdot\text{yr}^{-1}$

(95% CI $4\text{--}20\text{ mL}\cdot\text{yr}^{-1}$); $p=0.017$) and FEV₁ did not decline in patients with stage IV COPD ($p=0.73$). The pattern was similar when only patients who had been followed for 5 yrs were included in the analysis (n=99; stage II: $46\text{ mL}\cdot\text{yr}^{-1}$ (95% CI $22\text{--}70\text{ mL}\cdot\text{yr}^{-1}$), $p=0.006$; stage III: $31\text{ mL}\cdot\text{yr}^{-1}$ (95% CI $-18\text{--}80\text{ mL}\cdot\text{yr}^{-1}$) $p=0.158$; stage IV: $27\text{ mL}\cdot\text{yr}^{-1}$ (95% CI $1\text{--}53\text{ mL}\cdot\text{yr}^{-1}$) $p=0.047$).

IC/TLC did not change significantly over the period of study. There were no significant differences in comorbidity score between the different GOLD and ATS/ERS stages (stage II: 4 (5th–95th percentile 1–8); stage III: 4 (1–8); stage IV: 4 (1–7)). However, over time there was some worsening of comorbidity, with the Charlson score increasing from 4 (1–7) to 5 (2–12; $p<0.001$).

The characteristics of the cohort by region are presented in table 2. COPD patients from Spain walked more (463 m (336–635 m)) than those from the USA (350 m (146–503 m)). FEV₁ was slightly lower and comorbidity was higher among patients from the USA than those from Spain. These variables partially explained the differences in 6MWD ($r^2=0.36$; $p<0.001$). There was no difference in 6MWD between the patients from Tenerife, Zaragoza and Venezuela.

DISCUSSION

To the present authors' knowledge, this is the first prospective large long-term cohort study evaluating the temporal change of 6MWD in patients with COPD and a wide range of airflow obstruction. The most important finding is that the 6MWD declines over time, but that the decline is really significant only in patients with severe airflow limitation (FEV₁ $<50\%$ pred). In addition, the decline worsened with disease severity. This contrasted with the rate of FEV₁ loss over time, which was lower at the more severe stages of the disease.

The impairment of patients with COPD is more comprehensively described if pulmonary function tests are complemented with an evaluation of exercise performance [2]. The latter is usually carried out *via* a cardiopulmonary test in a specialised

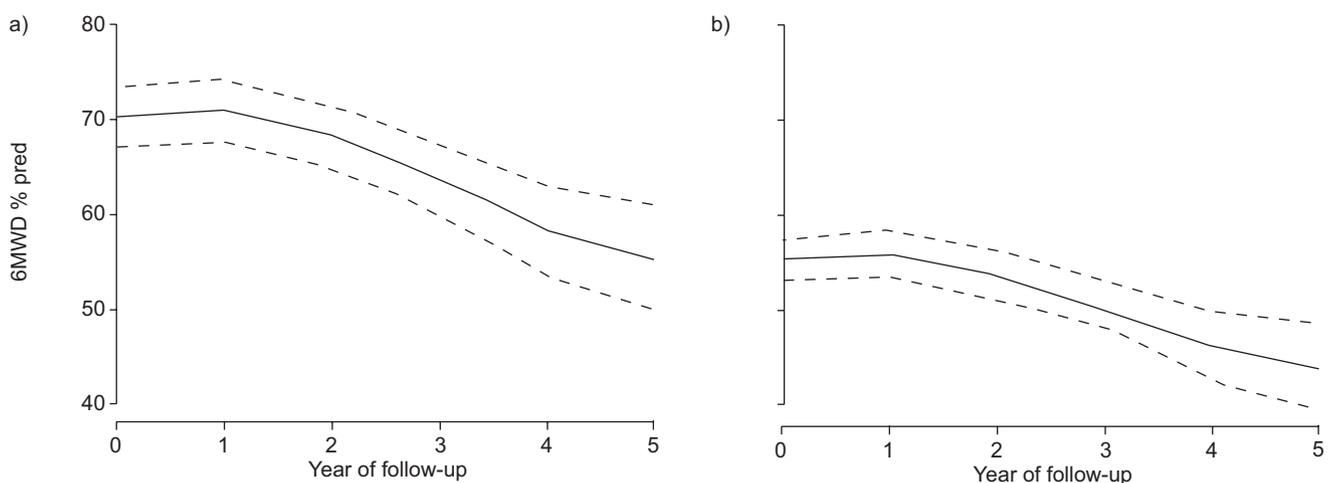


FIGURE 2. Change in 6-min walking distance (6MWD) over time as a percentage of the predicted values (% pred) as reported by a) ENRIGHT and SHERRILL [18] ($2.1\text{ m}\cdot\text{yr}^{-1}$ (95% confidence interval (CI) $1.6\text{--}2.7\text{ m}\cdot\text{yr}^{-1}$); $p<0.001$); and b) TROOSTERS *et al.* [19] ($1.6\text{ m}\cdot\text{yr}^{-1}$ (95% CI $1.1\text{--}2.1\text{ m}\cdot\text{yr}^{-1}$); $p<0.001$). —: median; -----: 95% CI. Baseline, years 1–3: n=294; year 4: n=163; year 5: n=100.

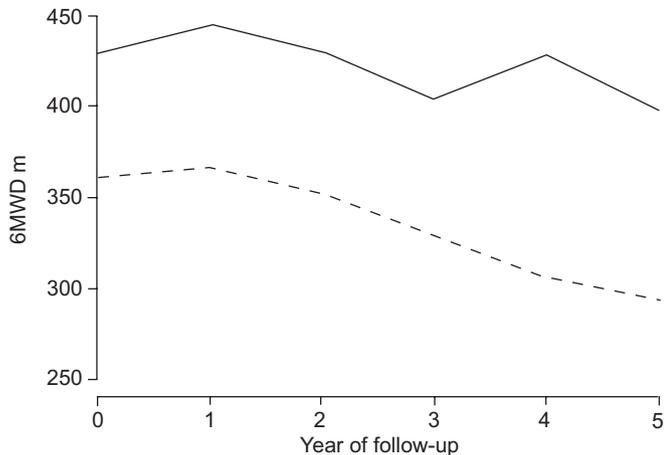


FIGURE 3. The 6-min walking distance (6MWD) declines significantly in patients with a forced expiratory volume in one second (FEV₁) <50% predicted (-----; 15.3 m·yr⁻¹ (95% confidence interval (CI) 9.1–21.4 m·yr⁻¹); p=0.002). —: FEV₁ >50% pred, years 0–3: n=85; year 4: n=44; year 5: n=25). FEV₁ <50% pred, years 0–3: n=209; year 4: n=119; year 5: n=75).

laboratory or, more commonly, in the field, using a timed walk test. Owing to its ease of administration and value as a predictor of functional capacity and mortality, the 6MWD has gained wide acceptance [12, 23]. Surprisingly, compared with the FEV₁ [24, 25], there is very little information regarding the natural evolution of exercise capacity in general or the 6MWD more specifically, probably reflecting the belief that airflow obstruction represents the most important determinant of the natural history of COPD. Recently, OGA *et al.* [26], studying patients with COPD, have shown a progressive deterioration in exercise capacity over time when evaluated by maximal oxygen intake ($V'O_{2,max}$) during maximal cycle ergometry. OGA *et al.* [26] described a weak correlation between $V'O_{2,max}$ and decline in FEV₁. Interestingly, they observed a stronger

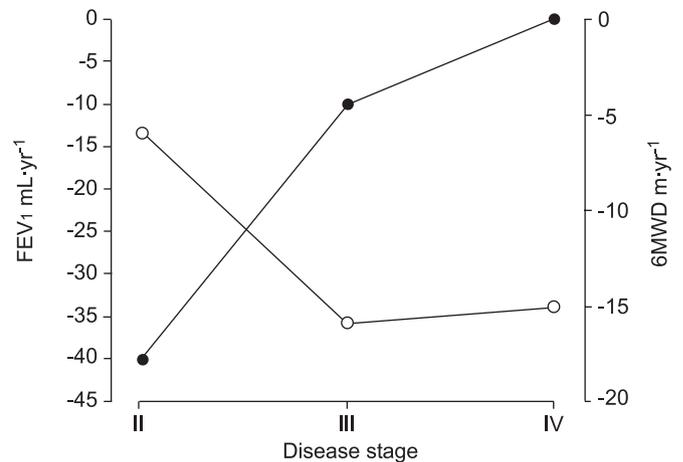


FIGURE 4. The decline in 6-min walk distance (○) was greater in patients with more severe airflow obstruction, as determined by Global initiative for Chronic Obstructive Lung Disease and American Thoracic Society/European Respiratory Society staging criteria. In contrast forced expiratory volume in one second (FEV₁; ●) changed less in those patients with more severe airflow limitation. Δ: change. Stage II: n=81; stage III: n=136; stage IV: n=73.

correlation between $V'O_{2,max}$ and the dynamic ventilatory constraints of dynamic hyperinflation, which in their patients progressed over time. They speculated that hyperinflation contributed to the longitudinal decline in exercise capacity. However, there was no adjustment for comorbidity, hence the involvement of other organs could have influenced their overall results. Similarly, the current authors did not observe an association between 6MWD decline and FEV₁. However, no change in static hyperinflation, estimated by the rate of change of IC/TLC, was detected over the 5 yrs of the present study. The differences between the two studies may relate to methodology: OGA *et al.* [26] used a symptoms-limited exercise test and dynamic hyperinflation, whereas the present authors used the 6MWD and static hyperinflation. More studies using similar methodology may help resolve these differences.

After short-term interventions, such as 3 months' pulmonary rehabilitation, the estimated threshold for clinically significant change in the 6MWD is thought to be ~50 m [27], but there is very limited information about the predicted decline over a longer period in COPD [12]. The present results show that the annual decline in 6MWD is relatively small, at 12.5 m·yr⁻¹. The decline was low in patients with moderate obstruction, but larger in patients with FEV₁ <50% pred. In this group, the proportion of patients with changes in 6MWD greater than the minimal clinically important difference increased with increasing airflow obstruction (fig. 4). This is significant, because at that level of disease severity, the FEV₁ behaves as a more rigid and less sensitive parameter to detect clinical changes. Thus, the present results can clarify the role of the 6MWD in the long-term evaluation of patients with COPD, with it being shown to be of most help when evaluating patients with FEV₁ <50% pred.

It is possible to speculate why the decline of the 6MWD is more manifest in patients with more severe airflow limitation. It could simply relate to the deconditioning brought about by a

TABLE 2 Characteristics of the cohort according to country

	USA	Spain	p-value
Subjects	200	84	
Sex M/F	193/7	83/1	0.443
Age yrs	66 (51–79)	67 (47–76)	0.461
BMI kg·m⁻²	27 (18–37)	27 (19–36)	0.658
6MWD m	350 (146–503)	463 (336–635)	<0.001
FEV₁ L	1.20 (0.6–2.1)	1.15 (0.6–2.3)	0.946
FEV₁ % pred	37 (19–67)	43 (21–75)	0.014
IC/TLC	0.29 (0.14–0.42)	0.28 (0.13–0.44)	0.385
Charlson index	4 (2–8)	2 (1–6)	<0.001

Data are presented as n or median (5th–95th percentile). M: male; F: female; BMI: body mass index; 6MWD: 6-min walking distance; FEV₁: forced expiratory volume in one second; % pred: % predicted; IC: inspiratory capacity; TLC: total lung capacity.

more sedentary lifestyle, as more severe COPD is associated with greater dyspnoea. However, it is also possible that the decline results from the development of more advanced systemic involvement of COPD [28]. This hypothesis is further supported by the observations of AGUSTI *et al.* [29], who showed worsening apoptosis in muscle biopsies of patients with COPD, and by MONTES DE OCA *et al.* [30] who described increased levels of markers of oxidative stress and infiltration by macrophages in patients with severe COPD compared with controls. In addition, worsening Charlson comorbidity scores over time in the present study suggest a possible role for increasing comorbidity as the population aged. Taken together, these findings can be clinically important, as the therapy could change depending upon the reason for the decline.

The mean annual decline of the 6MWD in the current study is smaller than that reported by PINTO-PLATA *et al.* [12] ($26 \text{ m}\cdot\text{yr}^{-1}$). These differences may be explained by the fact that the present authors excluded patients who did not complete the first 3 yrs of follow-up. Therefore, the differences are probably due to the fact that PINTO-PLATA *et al.* [12] evaluated the decline in 6MWD in a population of severe COPD patients with a very low baseline 6MWD and high comorbidity, as evidenced by their high (27%) short-term mortality. Indeed, in the current study, patients followed for 3 yrs who subsequently died during the follow-up period had a steeper rate of decline ($25 \text{ m}\cdot\text{yr}^{-1}$), very close to that observed by PINTO-PLATA *et al.* [12]. Taken together, the results of both studies indicate that steep declines in 6MWD are indicative of poor prognosis and should raise concern regarding the wellbeing of the patient.

The current study also observed important variability in the expression of the results as per cent pred values derived from standard equations for healthy individuals [18, 19]. This may be due to differences among the studies that generated the predictive equations in use. ENRIGHT and SHERRILL [18] generated the predicted equation using the values from only one 6MWD, and subjects were instructed to walk at their own pace rather than as quickly as possible. Conversely, the study by TROOSTERS *et al.* [19] was based on a smaller sample of healthy subjects and may not represent the general population at large. This suggests a need to develop new reference values with larger numbers and standard methodology.

The present study has some limitations. First, few females were included. This was not by design, because the opportunity to join the study was independent of sex. However, the large proportion of males may be seen as lending more validity to the findings, because they cannot be attributed to gender bias. Secondly, the current results do not wholly address the issue of individual patient variability, since 6MWD annual decline was interpreted as a mean value of the group. The actual change for an individual may be less or more than the mean and its importance can be judged only in the context of the specific situation in which it is measured.

In summary, the present study shows that the decline in 6-min walking distance over time is most important in patients with more severe obstruction. This contrasted with the smaller changes in forced expiratory volume in one second observed in those patients. The results also suggest that in the regular evaluation of patients with severe obstruction (measured by

forced expiratory volume in one second), repeated measures of 6-min walking distance can help describe clinical changes that cannot be detected easily in the sequential evaluation of pulmonary impairment. These findings have to be taken into account when planning studies using changes in 6-min walking distance over time. In addition, the current study suggests that the 6-min walking distance is of greatest help in the evaluation of patients with severe airflow limitation.

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