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# Six-minute walking test in cystic fibrosis adults with mild to moderate lung disease: comparison to healthy subjects

A. CHETTA*, G. PISI†, A. ZANINI*, A. FORESI‡, G. L. GRZINCICH†, M. AIELLO*, A. BATTISTINI†, AND D. OLIVIERI*

*Department of Respiratory Diseases and †Cystic Fibrosis Centre, University of Parma, Parma; ‡Respiratory Physiology Unit, Sesto S. Giovanni Hospital, Milan, Italy

**Abstract** The six-minute walking test (6MWT) has been widely utilized to evaluate global exercise capacity in patients with cystic fibrosis. The aim of this study was to assess the exercise capacity by 6MWT, measuring four outcome measures: walk distance, oxygen saturation and pulse rate during the walk, and breathlessness perception after the walk, in a group of cystic fibrosis adults with mild to moderate lung disease, and in healthy volunteers, as the control group. Moreover, the study examined the relationship between 6MWT outcome measures and pulmonary function in patients. Twenty-five adults (15 females, age range 18–39 years) with cystic fibrosis and 22 healthy volunteers (14 females, age range 20–45 years) performed a 6MWT following a standard protocol. Walk distance, oxygen saturation ($SpO_2$) and pulse rate at rest and during walk, and breathlessness perception after walk assessed by visual analogue scale (VAS) were measured. Cystic fibrosis patients did not differ from healthy volunteers in walk distance (626 ± 49 m *vs.* 652 ± 46 m) and pulse rate. Patients significantly differed from healthy volunteers in $SpO_2$ during the walk (mean $SpO_2$) ($P < 0{\cdot}0001$) and VAS ($P < 0{\cdot}0001$). In patients, $SpO_2$ during the walk significantly correlated with forced expiratory volume in 1 sec ($FEV_1$) ($P < 0{\cdot}0001$), residual volume (RV) ($P < 0{\cdot}001$), resting $SpO_2$ (base $SpO_2$) ($P < 0{\cdot}001$), and inspiratory capacity (IC) ($P < 0{\cdot}01$). In addition, VAS significantly correlated with resting $SpO_2$ ($P < 0{\cdot}01$) and IC ($P < 0{\cdot}01$). On the basis of regression equations by stepwise multiple regression analysis, $SpO_2$ during walk was predicted by $FEV_1$ ($r^2 = 0{\cdot}60$) and VAS by IC ($r^2 = 0{\cdot}31$), whereas walk distance was not reliably predicted by any assessed variables. This study showed that cystic fibrosis adults with mild to moderate lung disease covered a normal walk distance with unimpaired cardiac adaptation, but experienced a significant fall in oxygen saturation and an increased breathlessness perception during exercise. Resting pulmonary function was related to oxygen saturation and breathlessness perception during walk, but contributed significantly only to the prediction of oxygen saturation. We suggest that 6MWT could be valuable for identifying patients who might experience oxygen desaturation and dyspnoea during demanding daily activities. 
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**Keywords** six-minute walk test; cystic fibrosis; exercise-induced desaturation.

## INTRODUCTION

In the last decade, the six-minute walking test (6MWT) has been widely utilized to evaluate global exercise capacity in patients with cystic fibrosis (CF) (1–9). Walk distance was used to assess the beneficial effects of lung transplantation on exercise capacity (1,2), and it is usually considered as a parameter-guide to list patients for the procedure (5).

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Correspondence should be addressed to: Dr. Alfredo Chetta, Istituto di Malattie Respiratorie, Azienda Ospedaliera Universitaria di Parma, Viale G. Rasori, 10 - 43100, Parma, Italy. Fax: +39 0521 292 615; E-mail: chetta@unipr.it

In addition, in patients with CF, the walk distance was highly reproducible (4,8) and related to maximum workload (4) and maximum oxygen uptake (3,4) measured during a standardized maximum incremental exercise testing on a cycle ergometer. Thus, the 6MWT has also been proposed as a simple and reliable test for the periodic evaluation of CF patients' exercise programmes (4). Furthermore, the exercise performed during the 6MWT is more relevant to the everyday lives of patients than that performed during other forms of exercise test, such as treadmill or cycle ergometer, and may more accurately reflect what occurs during demanding daily activities.

However, up to now, no 6MWT studies have compared outcome measures of CF patients to those of age

and sex-matched healthy subjects. Moreover, no study has been specifically addressed to assess walk tolerance in adults suffering from CF, nor to evaluate the relationships between outcome measures of 6MWT and pulmonary function. The aim of the present study was therefore to assess the exercise capacity by 6MWT, measuring four outcome measures: walk distance, oxygen saturation and pulse rate during the walk, and breathlessness perception after the walk, in a group of CF adults with mild to moderate lung disease, and in healthy volunteers, as a control group. Moreover, the study examined the relationship between 6MWT outcome measures and pulmonary function in CF patients.

# METHODS

## Subjects

We studied 25 adults (15 females, age range 18–39 years), diagnosed as having CF by the sweat test. Severity of disease was evaluated by a modified version of the Schwachman scoring system (10), which is a 0–100 score, based on the general activity of the patient, physical examination, nutritional status and chest X-ray. We only included non-smoking patients in clinically stable conditions, defined as an absence of re-exacerbation for at least 4 weeks and as therapeutic stability. Moreover, no patients included in the study had histories of concomitant anaemia or locomotion problems, nor did any patients need current oxygen therapy or had a resting oxygen saturation ($SpO_2$, %) less than 90%.

As a control group we studied 22 healthy volunteers (14 females, age range 20–45 years). None of the healthy subjects had history of respiratory disorders and they were lifetime non-smokers. All subjects gave informed consent to participate in the study.

## Lung function test

Pulmonary function was measured by a flow-sensing spirometer and a body pletismograph connected to a computer for data analysis (Vmax 22 and 6200, Sensor Medics, Yorba Linda, U.S.A.). Baseline total lung capacity (TLC), residual volume (RV), RV/TLC ratio, forced expiratory volume in 1 sec ($FEV_1$), forced vital capacity (FVC), $FEV_1$/FVC ratio and inspiratory capacity (IC) were recorded. Carbon monoxide transfer capacity ($TL_{co}$) was measured by the single breath method and considered valid only if the inspiratory volume was at least 90% of FVC. At least three measurements were made for each lung function variable to ensure reproducibility. Predicted values of lung volumes and expiratory flows as well as carbon monoxide transfer capacity were obtained from regression equations by Quanjer *et al.* (11) and Cotes *et al*. (12), respectively.

## Six-minute walk test

After lung function testing, patients and volunteers performed two 6MWTs according to a standard protocol (13). All subjects received the same instructions before the walk and were encouraged by the investigator who repeated set phrases every 30 sec during the walk. The 6MWTs were symptom limited, so patients were allowed to stop if necessary, though they were instructed to resume walking as soon as possible. The second 6MWT was performed in the same manner as the first, following a rest of at least 60 min.

The walk distance covered during the test was recorded in meters. Results from the second walk only were used for analysis to allow for any learning effect (14).

Before and immediately after 6MWT, patients and volunteers rated the magnitude of their perceived breathlessness on an interval scale, which was a 100-mm horizontal visual analogue scale (15). The visual analogue scale (VAS) consisted of a horizontal ruler without any mark on the patient's side with the words 'not at all breathless' and 'extremely breathless' on the left and right end, respectively. The subject had to indicate his breathlessness perception at the moment of the assessment, by moving a marker along the ruler. Breathlessness perception ratings were expressed in mm from 0 to 100 and corresponded to the distance of the marker from the left end of the visual analogue scale.

## Oximetry and pulse rate

The $SpO_2$ and the pulse rate (PR, bpm) were continuously monitored from 5 min before the walk until the test completion, as well as 5 min after completion, or until recovery of the baseline value by using a light weight (0.3 kg) portable pulse oximeter (Healthdyne, Model 920M, Marietta, GA, U.S.A.). This device was carried by each subject with a shoulder strap and a finger probe and was applied to the non-dominant hand. The oxygen saturation and heart rate readings were recorded in the oximeter memory every 10 sec.

For each subject, the resting $SpO_2$ values (base $SpO_2$, %), such as the average of the $SpO_2$ readings taken before the walk, and the mean saturation recorded during the walk (mean $SpO_2$, %) were noted.

The resting PR values (base PR, bpm), such as the average of the PR readings taken before the walk, the mean pulse rate recorded during the walk (mean PR, bpm) and the maximum pulse rate sustained for more than 10 sec (max PR, bpm) during the walk were also noted. The predicted maximum pulse rate was calculated by the following equation:

$$210 - 0.66 \times \text{age (16)}.$$

### Statistical analysis

All pulmonary function test results are expressed as per cent of predicted value or as absolute value. The patients were also studied with reference to mean $SpO_2$ values and divided in two groups, choosing one reference point: 90 % or less and more than 90%. Data are reported as mean ± standard deviation (SD) and differences in numerical data between groups were determined by unpaired *t*-test. Differences in qualitative data were analysed by Fisher exact test. Also, relationships were estimated by the Pearson correlation coefficient ($r$).

We chose $FEV_1 \leq 65\%$ and base $SpO_2 \leq 96\%$ as values for detecting a mean $SpO_2 \leq 90\%$. Sensitivity, specificity and predictive values for $FEV_1$ and base $SpO_2$ to determine mean $SpO_2$ were calculated by standard methods (17). Stepwise multiple regression analysis was used to determine the best predictor variables for the dependent variables walk distance, breathlessness perception ratings after walk, mean $SpO_2$ and mean PR. Percentage of total variance in the dependent variable, accounted for by the predictors variables is expressed as the adjusted square of the multiple correlation coefficient ($r^2$). A P-value of less than 0·05 was taken as significant, however, only those results with a significance level of less than 0·01 are given for correlations.

## RESULTS

Personal details of patients and healthy volunteers are reported in Table 1. Patients had CF of varying severity. The mean Schwachman score was 67 ± 13 (range 40–90). All CF patients were able to complete a 6MWT.

There were no significant differences between patients and healthy subjects when age, sex and BMI were considered. Patients differed from healthy volunteers in $FEV_1$ ($P < 0{\cdot}001$), FVC ($P < 0{\cdot}001$), RV ($P < 0{\cdot}001$), IC ($P < 0{\cdot}05$), $TL_{CO}$ ($P < 0{\cdot}001$), base $SpO_2$ ($P < 0{\cdot}001$) and base PR ($P < 0{\cdot}001$) (Table 1).

The walk distance was 626 ± 49 m, ranging from 500 to 725 m, and 652 ± 46 m, ranging from 544 to 738 m, in patients and healthy volunteers, respectively (Table 2). There was no significant difference between males and females in patients (646 ± 51 m and 613 ± 44 m) and in healthy volunteers (670 ± 62 m and 641 ± 33 m). CF patients and healthy volunteers did not also differ in mean PR values and in max PR (Table 2). The time course of mean PR during 6MWT was also similar in CF patients and controls (Fig. 1).

CF patients significantly differed from healthy volunteers in mean $SpO_2$ ($P < 0{\cdot}0001$) and VAS ($P < 0{\cdot}0001$) (Table 2). Furthermore, a mean $SpO_2 \leq 90\%$ occurred in nine out of 25 patients. In patients with mean $SpO_2 \leq 90\%$, $FEV_1$, RV and base $SpO_2$ significantly differed, when compared to those of patients with mean $SpO_2 > 90\%$. However, the walk distance covered by

**TABLE 1.** Characteristics of 25 patients with cystic fibrosis and 22 healthy volunteers

| | Cystic fibrosis patients | Healthy volunteers |
|---|---|---|
| Age (years) | 25 ± 5 | 26 ± 6 |
| Gender (F/M) | 15/10 | 14/8 |
| BMI (kg $m^{-2}$) | 21 ± 2 | 23 ± 2 |
| $FEV_1$ (% of pred) | 69 ± 23 | 121 ± 16** |
| FVC (% of pred) | 85 ± 20 | 124 ± 17** |
| RV (% of pred) | 162 ± 52 | 82 ± 27**$^*$ |
| TLC (% of pred) | 107 ± 15 | 113 ± 11 |
| IC (l) | 2·7 ± 0·9 | 3·3 ± 0·9* |
| $TL_{CO}$ (% of pred) | 82 ± 15 | 105 ± 13** |
| Base $SpO_2$ (%) | 96 ± 1 | 98 ± 1** |
| Base PR (bpm) | 87 ± 14 | 76 ± 6** |

Values are expressed as mean ± SD.
*$P < 0{\cdot}05$, **$P < 0{\cdot}001$.

**TABLE 2.** Differences in outcome measure of six-minute walking test between 25 patients with cystic fibrosis and 22 healthy volunteers

| | Cystic fibrosis patients | Healthy volunteers |
|---|---|---|
| Walk distance (m) | 626 ± 49 | 652 ± 46 |
| Mean PR (bpm) | 121 ± 21 | 114 ± 18 |
| Max PR (bpm) | 143 ± 18 | 136 ± 17 |
| Max PR (% pred) | 74 ± 10 | 71 ± 8 |
| Mean $SpO_2$ (%) | 92 ± 4 | 97 ± 1** |
| VAS (mm) | 64 ± 24 | 27 ± 19** |

Values are expressed as (mean ± SD).
**P < 0.001.

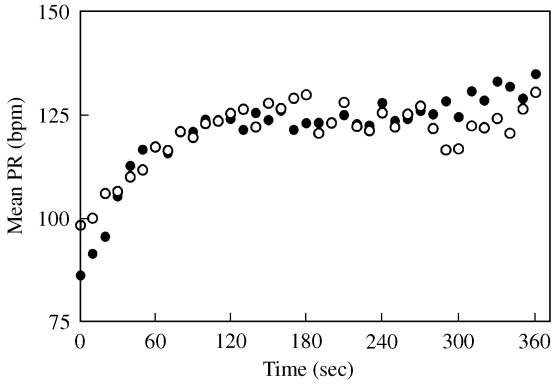


**FIG. 1.** Time course of mean pulse rate during walk (mean PR) in 25 patients with cystic fibrosis (○) and in 22 healthy volunteers (●).

patients with mean $SpO_2 \leq 90\%$ did not differ from that of patients with mean $SpO_2 > 90\%$ ($620 \pm 64$ m *vs.* $629 \pm 39$ m). Furthermore, the VAS measured in patients with mean $SpO_2 \leq 90\%$ did not differ from that of patients with mean $SpO_2 > 90\%$ ($77 \pm 15$ mm *vs.* $56 \pm 26$ mm).

In CF patients, mean $SpO_2$ significantly correlated with $FEV_1$ ($r=0.69$, $P<0.0001$), RV ($r=-0.68$, $P<0.001$), Base $SpO_2$ ($r=0.68$, $P<0.001$), and IC ($r=0.55$, $P<0.01$) (Fig. 2). In addition, VAS significantly correlated with Base $SpO_2$ ($r=-0.58$, $P<0.01$) and IC ($r=-0.52$, $P<0.01$).

Results of sensitivity, specificity and predictive value calculations for $FEV_1 \leq 65\%$ and base $SpO_2 \leq 96\%$ as values for detecting a mean $SpO_2 \leq 90\%$ are presented in Table 3. The regression equation generated by stepwise multiple regression analysis for mean $SpO_2$ included $FEV_1$: mean $SpO_2$ (%)=83·7+0·12 ($FEV_1$); $r^2=0.60$.

Moreover, IC was chosen by multiple regression analysis as the main predictor variable for VAS. The regression equation for VAS was: VAS (mm)=107.3−15.6 (IC); ($r^2=0.31$).

Lastly, multiple regression analysis for walk distance could not account for more than 20% of the total variance ($r^2=0.19$), the main predictor variable being IC.

## Discussion

Our study showed that CF patients with mild to moderate lung disease, when compared to controls, did not differ in walk distance and in pulse rate during the walk, but

**Table 3.** $FEV_1$ and base $SpO_2$ as screening parameters for detecting a mean $SpO_2 \leq 90\%$ in 25 patients with cystic fibrosis

| | Mean $SpO_2 \leq 90\%$ |
|---|---|
| Sensitivity | |
| $FEV_1 \leq 65\%$ pred | 89% |
| Base $SpO_2 \leq 96\%$ | 89% |
| Specificity | |
| $FEV_1 \leq 65\%$ pred | 94% |
| Base $SpO_2 \leq 96\%$ | 87% |
| Positive predicted value | |
| $FEV_1 \leq 65\%$ pred | 94% |
| Base $SpO_2 \leq 96\%$ | 82% |
| Negative predicted value | |
| $FEV_1 \leq 65\%$ pred | 89% |
| Base $SpO_2 \leq 96\%$ | 100% |

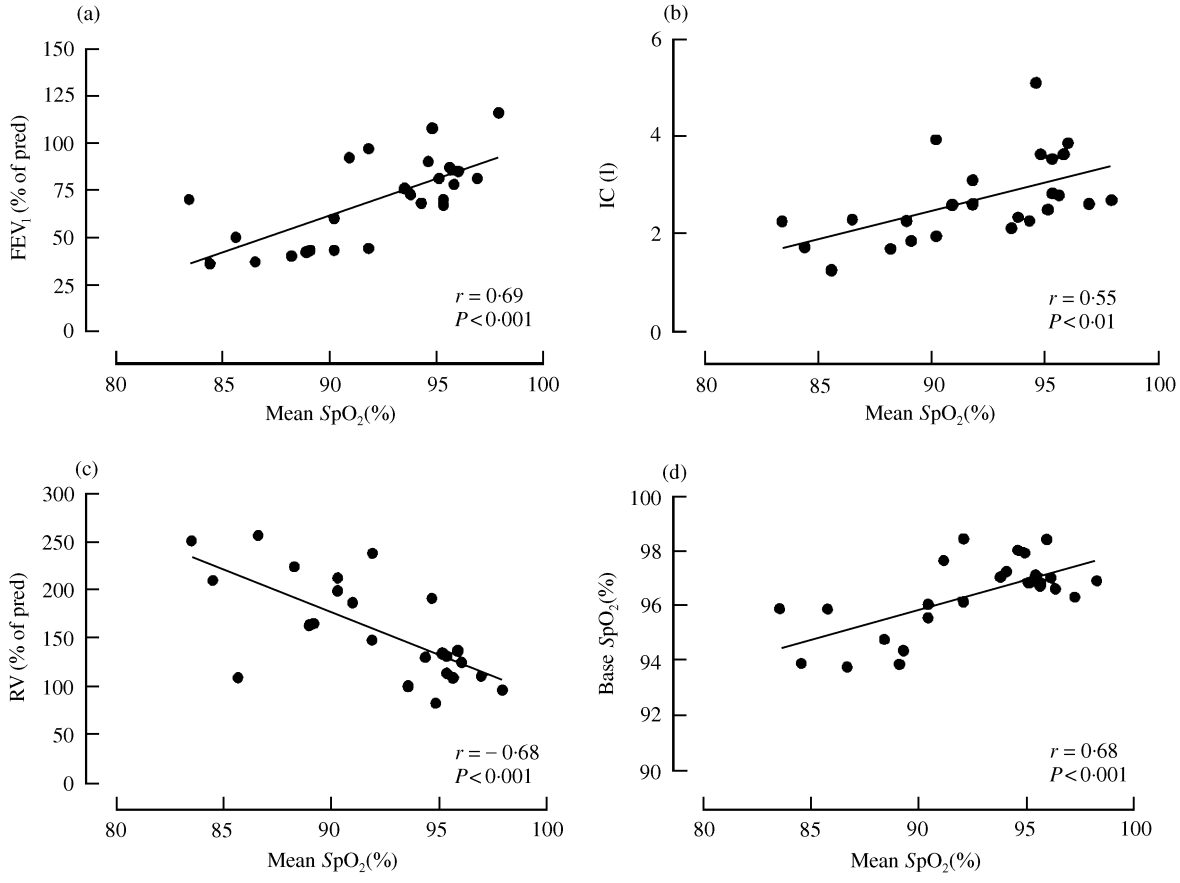


**Fig. 2.** Relationships between mean oxygen saturation during walk (mean $SpO_2$) and $FEV_1$ (a), IC (b), RV (c), and resting oxygen saturation (base $SpO_2$) (d) in 25 patients with cystic fibrosis. $r$=Pearson correlation coefficient.

they differed in oxygen saturation and breathlessness perception during the walk. Furthermore, in CF patients pulmonary function was related to oxygen saturation and breathlessness perception during walk, but contributed significantly only to predict oxygen saturation.

The 6MWT is a simple and non-expensive test that can provide a global evaluation of exercise capacity in patients with respiratory disability and the walk distance is the most popular outcome measure (18). Interestingly, we found that the walk distance covered by young adults with CF and ventilatory impairment was the same as that covered by age- and sex-matched healthy volunteers. Maximum exercise capacity in patients with CF depends on the severity of the impairment in lung function (19,20), however, 6MWT can be considered as an endurance, submaximal exercise test, since it demands the ability to sustain the exercise, rather than the capacity for maximum exercise. Our findings are consistent with a previous report by Freeman *et al*., who demonstrated in adults with cystic fibrosis a normal tolerance to endurance exercise test, defined as the duration of exercise at 80% of each individuals maximum oxygen uptake (21). Moreover, in the present study, the walk distance does not seem to be significantly affected by lung function limitation in CF patients, since it was only barely predicted by the inspiratory capacity. These results are in agreement with those by Foglio *et al*. (22), who recently demonstrated that in adults with chronically stable airway obstruction the walk distance was poorly predicted by baseline lung function measures. Furthermore, Freeman *et al*. (21) did not find any significant relationship between the endurance times of submaximal exercise and baseline lung function. Home exercise training programs, currently followed by patients in their maintenance treatment could explain the tolerance to the sub maximal exercise in CF. In fact, home exercise training programs are effective for improving physical performance and to decrease limitation in activities of daily living in CF patients, even in those with moderate to severe pulmonary impairment (23).

We found that patients and healthy controls performed the same effort not only in terms of walk distance, but also in terms of cardiac function. At baseline, CF patients showed a pulse rate higher than that of controls. A mild to moderate resting thachycardia is a common feature in CF (24,25) and may represent a right ventricular dysfunction (25). During walk, CF patients experienced a change in pulse rate, as percent of baseline, similar to that of controls (29% *vs.* 33%). In addition, similarly in patients and controls, pulse rate progressively increased during the first 2 min of the walk, then it reached a plateau, which lasted for the remaining 4 min (Fig. 1). Taken together, these findings showed that 6MWT induced a submaximal effort with an appropriate cardiac response in adults with CF. These results are in agreement with a previous report in children with CF, who showed a pulse rate, equal to a 25% change compared to baseline, while performing 6MWT (8). Interestingly, in patients affected by CF, irrespective of the severity of lung disease, the heart rate response was appropriate for work amount, also during a progressive incremental cycle ergometer test (19). Furthermore, even in patients with severe lung involvement and elevated resting heart rate, the cardiovascular response to exercise was normal (19). On the whole, data on cardiac response both to sub maximal and maximal effort support the view that in CF there is no cardiac limitation to exercise.

Although CF patients had a normal performance in terms of walk distance and pulse rate, they showed a significant fall in oxygen saturation during walk, when compared to the control group. Oxygen saturation during walk was strictly related to airway obstruction and hyperinflation, as well as to the baseline oxygen saturation. More specifically, we found that the saturation during walk could be highly predicted by baseline $FEV_1$, which can account for 60% of the total variance. Moreover, the fall in oxygen saturation during walk was clinically significant in a third of CF patients, since in these patients the oxygen saturation reached or exceeded the value of 90%. Our study also showed that patients with a $FEV_1 < 65\%$ predicted or with a resting oxygen saturation $< 96\%$ are highly likely to develop an oxygen saturation during walk less than or equal to 90%. This finding is in agreement to a previous endurance submaximal exercise study, that suggested that patients with a $FEV_1 < 60\%$ predicted or with a resting oxygen saturation $< 95\%$ are vulnerable for exercise oxygen desaturation (21). In this study, patients had mild to moderate impairment in diffusing capacity and did not show any relationship between resting $TL_{co}$ and oxygen saturation during walk. Despite the airway obstruction and hyperinflation, CF patients had a relative preservation of diffusing capacity, measured by the single breath method (26), and measurements of $TL_{co}$ were unreliable for predicting oxygen desaturation induced by submaximal exercise (21). In CF patients, ventilation–perfusion mismatch and alveolar hypoventilation proved to be the physiological causes of the arterial oxygen desaturation during maximal exercise (19).

In this study, CF patients had a significant increase in ratings on the visual analogue scale after walk when compared to controls, however the induced breathlessness could not be reliably predicted by any outcome measure of 6MWT or any variables of resting lung function. Therefore, our results support the view that the underlying mechanisms of exertion dyspnea, a disabling symptom in CF, are elusive, and that subjectivity is inherently involved in the symptom. In this regard, to date, previous reports in CF patients regarding the exertion breathlessness perception reveal various results. De Jong *et al*. showed that though dyspnoea could influence exercise

capacity, breathlessness perception score showed a large inter-individual variation, not strongly related to pulmonary function (27). Additionally, other studies showed significant relationships between exertion dyspnoea score and quality of life (28) or exercise intensity degree (29), but did not report any relationships to baseline lung function.

In summary, we showed that in CF adults with mild to moderate lung disease, walk distance is normal and cardiac adaptation to walk is unimpaired. However, patients experienced a significant fall in oxygen saturation and an increased breathlessness perception during exercise. Our findings suggest that 6MWT can be valuable for identifying patients who might experience oxygen desaturation and dyspnoea during demanding daily activities.

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