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Use of 6-minute walk test for assessing severity of interstitial lung disease: an observational study

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Abstract. *Background:* The 6-minute walk test (6MWT) is a potential tool for assessing the severity of interstitial lung disease (ILD). *Objectives:* To explore the relationship between 6MWT results and traditional measures including pulmonary function and chest computed tomography(CT) and to determine factors that might influence the 6-minute walk distance (6MWD). *Methods:* Seventy-three patients with ILD were enrolled at Peking University First Hospital. All patients underwent 6MWT, pulmonary CT, and pulmonary function tests and their correlations were analyzed. Multivariate regression analysis was used to identify factors that might impact 6MWD. *Results:* Thirty (41.4%) of the patients were female and the mean age was 66.1 ± 9.6 years. 6MWD was correlated with forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), diffusing capacity for carbon monoxide (DLCO) and DLCO%pred. The decrease in oxygen saturation (SpO2) after the test was correlated with FEV1%pred, FVC%pred, TLC, TLC%pred, DLCO, DLCO%pred and the percentage of normal lung calculated by quantitative CT. The increase in Borg dyspnea scale was correlated with FEV1, DLCO and the percentage of normal lung. The backward multivariate model ($F = 15.257$, $P < 0.001$, adjusted $R^2 = 0.498$) indicated that 6MWD was predicted by age, height, body weight, increase in heart rate, and DLCO. *Conclusions:* The 6MWT results were closely correlated with pulmonary function and quantitative CT in patients with ILD. However, in addition to disease severity, 6MWD was also influenced by individual characteristics and the degree of patient effort, which should thus be considered by clinicians when interpreting 6WMT results.

Key words: Interstitial lung disease, pulmonary function test, quantitative CT, 6-minute walk test

Introduction

Interstitial lung disease (ILD) comprises more than 200 different diseases. The disease behavior of the specific ILD is a key factor affecting treatment decisions; however, this can vary, with some patients experiencing remission and stabilization, while others might deteriorate at various rates or develop acute exacerbations. The American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines for idiopathic interstitial lung pneumonias recommend a method of classification based on disease behavior(1), including long-term observation to guide therapeutic targets. However, there are currently no standard recommendations concerning the methods and frequency of monitoring the severity of ILD. According to a recent survey, physicians in Japan, the United States, and Europe performed pulmonary function tests (PFTs) and pulse oxygen saturation (SpO2) tests at least twice a year, while Japanese doctors tended to use imaging examinations more frequently and doctors in the United States and Europe preferred physiologic tests (such as the 6-minute walk test, 6MWT), and only increased the frequency of imaging examinations when deterioration was detected(2).

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PFTs and chest computed tomography (CT) are the most commonly used methods for assessing the severity of ILD. Compared with PFTs and chest CT, the 6MWT has the advantages of low cost, ease of access, and being radiation-free. In patients with ILD, 6-minute walk distance (6MWD) was found to be associated with forced vital capacity (FVC), and the decrease in SpO2 after the 6MWT was correlated with patients' diffusing capacity for carbon monoxide (DLCO)(3). Furthermore, the 6MWT was also found to be a potential predictor of mortality risk in patients with ILD(4, 5). However, previous studies failed to demonstrate any correlations between 6MWT results and other pulmonary function indices, and the relationship between 6MWT and quantitative chest CT remains unclear. Notably, various confounding factors might influence the results of the 6MWT in patients with ILD, and it is therefore important to understand the roles of these different factors. This study aimed to explore the correlations between 6MWT results and traditional measurements of ILD severity, including PFT and quantitative chest CT results, and to determine the factors affecting 6MWD.

Methods

Ethical approval

This study conformed to the requirements of the Declaration of Helsinki and was approved by the Ethics Committee of Peking University First Hospital (approval number: 2019 research 133). Written informed consent was obtained from all participants. This manuscript conformed to the STROBE guidelines.

Study design and patient recruitment

Patients with ILD were recruited prospectively and enrolled at Peking University First Hospital from 2015 to 2020. The inclusion criteria were: age 35–85 years, ILD confirmed by chest CT, and independent of oxygen therapy in daily life. The exclusion criteria were an inability to perform 6MWT or PFT due to any cause, and comorbidities that might influence the 6MWT, including but not limited to lower limb movement disorders, heart failure, pulmonary hypertension, pulmonary embolism, and neuromuscular diseases.

After enrollment, all patients underwent 6MWT, chest CT, and PFTs during one visit.- The 6MWT was performed according to the ATS instructions(6). To guarantee reproducibility, the tests were all performed by designated physicians in the research team, using standard encouragements and in a 30-m-long corridor. In addition to the 6MWD, we also recorded heart rate, respiratory rate, SpO2, Borg dyspnea scale (range 0–10), and fatigue scale (range 0–10) before and immediately after the test. CT images were analyzed using software specifically designed for this study by the Academy for Advanced Interdisciplinary Studies of Peking University. The software first extracted areas of lung tissues from CT images, excluding the mediastinum, broncho-vascular bundles, and chest wall. The lung was then divided into normal (−950 to −700HU), low-density (<−950HU), and high-density areas (>−700HU) based on the CT values of each pixel(7). Total lung volume (TLV) and the volume of each area were then calculated. PFTs were performed by experienced technicians using the Jaeger Master Screen PFT system (Germany) following ATS guidelines. All procedures conformed to the acceptability and repeatability criteria(8), and the results included forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), and DLCO. DLCO was measured using the single-breath method. Both measured values and percentages of predicted values of pulmonary function indices were used in the study. In order to distinguish the two kinds of values in the text, the suffix "%pred" is used to indicate percent of predicted.

Statistical analysis

Statistical analyses were carried out using SPSS Statistics for Windows (Version 22.0; IBM Corp., Armonk, NY, USA). Continuous data with a normal distribution were expressed as mean ± standard deviation. Non-normally distributed data (checked by Kolmogorov-Smirnov test) were expressed as median (first quartile, third quartile). Correlations were analyzed using Pearson's correlation test (for normally distributed data) or Spearman's rank correlation test (for skewed data). Backward stepwise multivariate linear regression analysis was used to determine factors affecting the 6MWD. For correlation tests, both measured values and percentages of predicted values of pulmonary function indices were analyzed. For regression analysis, only measured values were used to avoid multicollinearity. P values < 0.05 were considered statistically significant.

Results

Seventy-three patients with ILD were enrolled in the study, including 30 (41.1%) females. The mean age was 66.1 ± 9.6 years, the mean height was 162.7 ± 8.2 cm, and the mean body weight was 67.5 ± 9.9 kg. The cohort included five patients with sarcoidosis, four with connective tissue disease-associated ILD, two with eosinophilic pneumonia, one with hypersensitivity pneumonitis, and one with organizing pneumonia. The remaining 60 patients had idiopathic interstitial pneumonias. Thirteen patients (17.8%) were receiving glucocorticoids and/or immunosuppressants, one was receiving an anti-fibrotic agent (pirfenidone), and the others were not receiving any treatment.

Table 1: The 6MWT, quantitative CT and PFT results of the 73 patients with ILD.

Items	Results
6MWT	
6MWD (meters)	538 ± 56
Baseline SpO2 (%)	96 (95, 97)
Decrease in SpO2 after the test (%)	2 (1, 5)
Baseline heart rate (bpm)	76.7 ± 11.1
Increase in heart rate after the test (bpm)	38.8 ± 15.5
Baseline respiratory rate (times per minute)	18 (16, 20)
Increase in respiratory rate after the test (times per minute)	6 (4, 9)
Baseline Borg dyspnea scale (range 0–10)	1 (0, 2)
Increase in Borg dyspnea scale after the test	1 (1, 3)
Baseline fatigue scale (range 0–10)	1 (0, 2)
Increase in fatigue scale after the test	1 (0, 1)
Quantitative CT	
Total lung volume (liters)	4.09 ± 0.97
Percentage of normal lung area (%)	85.61 (80.40, 88.02)
Percentage of low-density area (%)	1.06 (0.70, 2.41)
Percentage of high-density area (%)	11.89 (9.64, 18.07)
PFT	
FEV1 (liters)	2.29 ± 0.57
FEV1(%pred)	98.96 ± 20.66
FVC (liters)	2.97 ± 0.71
FVC(%pred)	101.93 ± 19.63
FEV1/FVC (%)	77.17 ± 6.85
TLC (liters)	4.63 ± 0.93
TLC(%pred)	85.02 ± 13.11
DLCO (mmol/min/kPa)	5.50 ± 1.29
DLCO(%pred)	74.21 ± 17.63

Data are presented as mean ± SD or median (Q1, Q3) as appropriate. 6MWT = 6-minute walk test; 6MWD = 6-minute walk distance; ILD = interstitial lung disease; PFT = pulmonary function test; SpO2 = pulse oxygen saturation; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; TLC = total lung capacity; DLCO = diffusing capacity for carbon monoxide; Q1 = first quartile; Q3 = third quartile.

All 73 patients completed the three tests and the 6MWT, quantitative CT, and PFT results are summarized in Table 1.

The 6MWD was positively correlated with FEV1 ($r = 0.377$, $P = 0.001$), FVC ($r = 0.407$, $P < 0.001$), TLC ($r = 0.360$, $P = 0.002$), DLCO ($r = 0.513$, $P < 0.001$) and DLCO%pred ($r = 0.283$, $P = 0.015$). The correlation between 6MWD and DLCO%pred is shown in Figure 1. The decrease in SpO2 (ΔSpO2) after the test was negatively correlated with FEV1%pred ($\rho = -0.330$, $P = 0.004$), FVC%pred ($\rho = -0.345$, $P = 0.003$), TLC ($\rho = -0.277$, $P = 0.018$), TLC%pred ($\rho = -0.451$, $P < 0.001$), DLCO ($\rho = -0.385$, $P = 0.001$), and DLCO%pred ($\rho = -0.423$, $P < 0.001$). The increase in Borg dyspnea scale after the test was correlated with FEV1 ($\rho = -0.246$, $P = 0.036$) and DLCO ($\rho = -0.248$, $P = 0.034$), but the increase in fatigue scale was not correlated with pulmonary function indices.

TLV calculated by quantitative CT was strongly correlated with TLC ($r = 0.846$, $P < 0.001$)(Figure 2). However, the correlation between TLV and 6MWD was not statistically significant ($r = 0.228$,

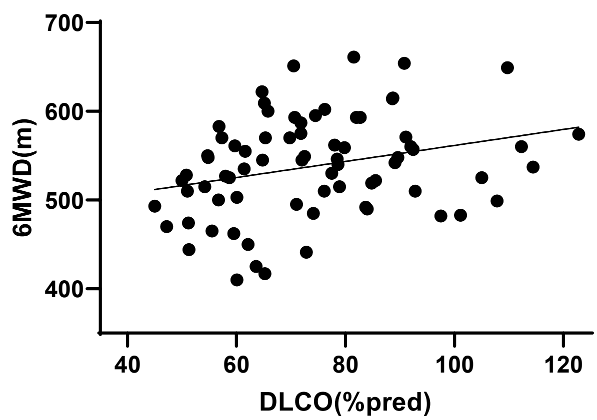

Figure 1. Scatterplot of DLCO%pred and 6MWD. Figure 1 shows the relationship between DLCO%pred and 6MWD in the 73 patients with ILD. DLCO = diffusing capacity for carbon monoxide; 6MWD = 6-minute walk distance; ILD = interstitial lung disease.

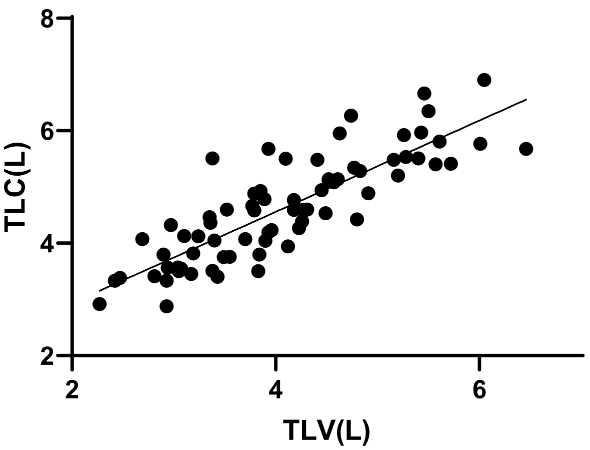

Figure 2. Scatterplot of TLV and TLC. Figure 2 shows the relationship between TLV measured by quantitative CT and TLC measured by pulmonary function test. TLV and TLC were expressed as measured values. TLV = total lung volume; TLC = total lung capacity.

P = 0.053). The percentage of normally aerated lung was positively correlated with DLCO (ρ = 0.334, P = 0.004) and DLCO%pred (ρ = 0.469, P < 0.001), and negatively correlated with ΔSpO2 (ρ = −0.435, P < 0.001) and increase in Borg dyspnea scale (ρ = −0.254, P = 0.030).

Backward stepwise multivariate regression analysis was conducted including age, sex, height, body weight, body mass index, physiologic indices before and after 6MWT, baseline PFT indices, and quantitative CT indices. The multivariate model was statistically significant (F = 15.257, *P* < 0.001, adjusted R^2 = 0.498) and age, height, body weight, increase in heart rate, and DLCO were identified as predictive factors of 6MWD.

Discussion

The current study enrolled 73 patients with ILD and examined the correlations between the results of 6MWT and traditional ILD severity tests, including quantitative CT and PFTs. The results showed that 6MWD, ΔSpO2, and Borg dyspnea scale in 6MWT were correlated with pulmonary function indices, and ΔSpO2 and Borg dyspnea scale were correlated with the percentage of normal lung area calculated by quantitative CT. We also demonstrated that individual characteristics and disease severity affected the results of 6MWD. These results support the wide use of 6MWT for assessing the severity of ILD, but also demonstrate that various factors might influence the 6MWD, indicating that the 6MWT results should be interpreted individually by clinicians.

The benefits of low cost, ease of operation, and radiation-free nature make the 6MWT an ideal alternative to CT and PFT. However, the correlations between 6MWT and PFT in patients with ILD have not been fully studied. In a study of 40 patients with ILD, Chetta *et al*(3)found that 6MWD was correlated with FVC and ΔSpO2 was correlated with DLCO, in accordance with the current study. With a larger sample size, we also showed that 6MWD and ΔSpO2 were both correlated with ventilatory indices and DLCO, which conformed to the mechanism of respiratory physiologic changes in ILD. In the current study, the increase in Borg dyspnea scale was also indicative of the patients' pulmonary function, indicating that this index of 6MWT might provide an additional reference value.

Compared with PFTs, high-resolution CT is an objective test and the gold standard for the diagnosis of ILD. However, traditional qualitative interpretations can vary dramatically among individuals, especially in cases with different changes in different image sections. Quantitative CT has undergone great technical advances and its value for assessing the severity of ILD has been proven in various studies(9,10). The normal lung areas represent the remaining healthy lung, high-density areas represent lesions of ground glass opacities, interlobular/intralobular septal thickening, fibrosis, and consolidations, and low-density areas represent lesions of emphysema, honeycombing, and pulmonary cysts. A recent study demonstrated a positive correlation between the percentage of normal lung and DLCO(11), which was also demonstrated in the current study. Notably however, lung areas with interstitial changes might not totally lose their diffusing capacity. A previous study in patients with idiopathic pulmonary fibrosis compared four different quantitative CT methods, of which the method used in the current study showed the best correlation with the gender-age-physiology (GAP) score, indicating that this method might be a potential mortality-risk predictor in patients with ILD(12). A subsequent study found that <70% of normal lung calculated by quantitative CT was an independent predictor of death in patients with ILD(13). In the current study, we examined CT images of 73 patients with ILD using self-designed quantitative CT software. The volume indices calculated by the software were strongly correlated with PFTs, proving the quality of our software. To the best of our knowledge, few studies have focused on the relationship between 6MWT and quantitative CT in patients with ILD; however, the correlation between the 6WMT results and percentage of normal lung area calculated by quantitative chest CT in the current study verified the value of 6MWT for assessing the severity of ILD.

Although our results support the utility of 6MWT in patients with ILD, the 6MWD can also be influenced by various factors other than the ILD itself. According to previous studies, age, sex, height, and body weight all affected the 6MWD in healthy subjects(14). In the current study of patients with ILD, in addition to individual characteristics and pulmonary function indices, the increase in heart rate also significantly influenced 6MWD, despite the standardized test procedure. Previous studies of healthy adults also noted a relationship between the increase in heart rate and 6MWD(15,16). We suggest that the increase in heart rate may indicate whether or not the patients have exerted themselves enough in the test, and could therefore be considered as a quality control index in the 6MWT. The current results suggests that, despite a standardized procedure, patients' level of exertion may vary and the 6MWD should thus be interpreted individually. Moreover, the results may also be affected by the individual's leg muscle strength and the doctor's instructions(17), which are not easy to quantify. Factors such as heart failure and pulmonary hypertension were excluded in the current study; however, these factors should be considered by doctors interpreting the 6WMT results. Despite these confounding factors, the current study proved that DLCO, which is an important indicator of ILD severity, was an important factor affecting the 6MWT results, indicating that the 6MWT might serve as an alternative test for assessing the severity of ILD.

This study had several limitations. First, the results of PFTs indicated that patients enrolled in this study generally had mild to moderate ILD. This was understandable, given that we did not enroll patients who were dependent on oxygen therapy, due to safety concerns. The results of this study may therefore not represent all patients with ILD. Second, a recent study of patients with ILD showed that 6MWD declined more rapidly in patients with progressive pulmonary fibrosis than in those without(18), proving the clinical value of trajectories of 6MWD. Further follow-up visits are therefore needed to determine if 6MWT is as sensitive as PFTs and CT for detecting deterioration of ILD. Finally, we unfortunately did not acquire long-term prognosis data for the 73 patients, and were therefore unable to analyze the predictive values of 6MWT in patients with ILD.

The 6MWT results are closely correlated with pulmonary function and quantitative CT results in patients with ILD. The 6MWT is an especially useful alternative to CT or PFTs because of its low cost and radiation-free nature; however, in addition to disease severity, 6MWD may also be influenced by individual characteristics and the degree of patient effort, which should be taken into consideration by clinicians interpreting the results of 6WMTs.

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Conflict of Interest: None.

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