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6-Minute Walking Test: Adjusting Reference Equations in COPD and ILD Patients

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Abstract

Background: *Reference equations have been published for different populations. This study aimed to describe 6MWT in two main groups of respiratory diseases (COPD and ILD) and to adjust reference equations of the healthy Caucasian population of a European country in those two groups of patients.*

Methods: *We conducted an observational prospective study that enrolled 186 patients (104 COPD patients and 82 ILD patients) who performed 6MWT between January 2019 and July 2019. Multiple regression models were studied for each group of patients.*

Results: *The mean 6MWD was 462.7 meters in COPD patients and 443.5 meters in ILD patients (p=0.159). Based on the previous multiple regression models of the healthy population, two explanatory models were developed for COPD and ILD patients. The best explanatory power both for COPD and ILD groups (26% and 55%, respectively) was: 6MWD = 743.2 – 3.5 × Age – 3.1 × BMI+1.5 × ΔHR + 2.6 × Sex (COPD group); 6MWD = 642.7 – 2.8 × Age − 4.9 × BMI+3.4 × ΔHR + 70.2 × Sex (ILD group). The impact of each variable in the two groups of chronic respiratory diseases was different. The negative influence of aging is more significant in COPD patients according to the second regression model, which requires individual analysis of each group.*

Conclusion: *This study reinforces the value and validity of reference equations for the 6MWT in the assessment of specific groups of diseases such as COPD and ILD. The regression model which had the best explanatory power was similar between healthy population, COPD and ILD patients and should be used for clinical practice whenever possible.*

Keywords: *Exercise test; Walking; Chronic Obstructive Pulmonary Disease; Interstitial lung diseases; 6MWT*

Background

Exercise capacity may be reduced in certain lung diseases such as chronic obstructive pulmonary disease (COPD) and interstitial lung diseases (ILD).[1] This exercise impairment in respiratory diseases is usually multifactorial and may result from ventilatory dysfunction, pulmonary gas exchange abnormalities, peripheral muscle dysfunction and cardiac dysfunction. [1]

Walking performance is an important issue and factors involved in the choice of self-selected walking speed have already been addressed. In healthy subjects, that choice is related to the cost of transport, as it corresponds to the walking speed in which the energy expenditure is minimal. [2] Both COPD and ILD patients have reduced self-selected walking speed with higher costs of transport. [3,4] The balance of dyspnea sensation and gait stability have an important role in self-selected walking speed in COPD patients, whereas in ILD patients oxygen saturation seems to be more relevant. [3,4]

The 6-minute walking test (6MWT) assesses the global and integrated response of all systems involved during exercise, although it does not provide specific information about the function of each different system or the mechanism involved in exercise impairment. [5, 6] It is a simple test commonly used to assess functional exercise capacity, evaluate treatment responses in both COPD and ILD and it also reflects the capacity of the individual to perform activities of daily living. [7-10] Additionally, 6MWT is important to assess prognosis. Either in COPD or ILD, a lower 6-minute walking distance (6MWD), usually calculated in meters, has been associated with mortality. [11-19] Besides the relationship with clinical outcomes, some studies have also described a correlation between 6MWD (in meters) and respiratory function parameters. [17; 21-25]

The 6MWT guidelines published by the American Thoracic Society (ATS) aimed to standardize this procedure and encourage researchers to establish reference values for different populations.5 Reference equations have been published for different populations. [9, 20]

The aims of this study were: to describe 6MWT in two main groups of respiratory diseases (COPD and ILD); and to adjust reference equations of the healthy Caucasian population of a European country in those two groups of patients. The choice of reference equations is an important issue to better interpret the results of our patients. Our work seeks to improve knowledge about chronic respiratory diseases regarding the impact of some factors, that were previously used in the development of reference equations for 6MWT, in 6MWD.

Methods:

Study design and subjects

This was an observational, descriptive, prospective study, conducted in a Pulmonary Function Testing Laboratory of a central hospital, between January 2019 and July 2019.

Patients with COPD or ILD who performed 6MWT during this period were included in the study. All participants signed the informed consent form. The study was approved by the hospital ethics committee.

Patients

Patients aged >18 years with a diagnosis of COPD or ILD proposed to 6MWT were enrolled (tests prescribed by the patients physician according to usual follow-up). COPD was defined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. [26] ILD is a heterogeneous group of diseases sometimes difficult to differentiate and final disease classification was established by the multidisciplinary committee of the hospital (including pulmonologists, chest radiologists and lung pathologists) according to international guidelines. [27-31] Data from each patient before undergoing 6MWT included: sex, age, height, weight, smoking history, medication use and medical history. Body mass index (BMI) was calculated by the standard formula. [32]

The exclusion criteria were: history of chronic disease that could influence the ability to perform the 6MWT and/or walking (e.g., impaired cognition or use of walking aids); other known respiratory, metabolic, neuromuscular or musculoskeletal diseases that could affect exercise performance; the presence of acute respiratory disease in the past 4 weeks; resting blood pressures higher than 180/100mmHg; resting heart rate (HR) higher than 120 beats per minute; ethnicity other than Caucasian.

Data collection

Data were collected by the pulmonology attendings and residents (authors) and 6MWT was performed by the Pulmonary Function Testing Laboratory cardiopulmonary technicians.

Before the 6MWT age was confirmed and height, weight and blood pressure were evaluated.

6MWT

Each patient did one 6MWT due to practical reasons. The use of oxygen during the test was standardized if required. 5 COPD patients and 14 ILD patients performed the 6MWT with supplemental oxygen. Participants were permitted to stop during the test if their symptoms became intolerable but were encouraged to resume the walking as soon as possible. All patients have finished the test. The 6MWTs were performed along a straight, flat, 30-m long corridor, with marks at 3 m intervals. The 6MWTs were monitored by a single operator who recorded the 6MWD at the same time. Oxygen saturation and HR were monitored by wearable finger pulse oximetry. At the end of each minute, subjects were given feedback on the elapsed time and standardized encouragement in the form of statements. Before and after each 6MWT, pulse rate, blood pressure, oxygen saturation, and Borg value were recorded. The distance walked in the test was reported in meters and as a percentage of predicted value using reference equations previously developed for a healthy population. [20]

Statistical analysis

Quantitative variables were reported as mean and standard deviation (SD) or median and interquartile range. Groups of patients were compared using independent samples Student's t-test or the Mann-Whitney nonparametric test. Multiple regression models were studied for each group of patients; gender was included as a binary variable (female = 0, male = 1) and all remaining variables as continuous.

Collinearity was investigated based on the variable inflation factors. The normality of the residuals was evaluated through the Kolmogorov-Smirnov test. All statistics were calculated using the IBM SPSS Statistics (version 24.0) software. A p-value was declared as significant for $p < 0.05$.

Results:

186 patients were enrolled in this study, 104 COPD patients (56.9%) and 82 (44.1%) ILD patients. The characteristics of both groups of patients are summarized in table 1.

Table 1. Characteristics of COPD and ILD patients of the study and 6MWT measures.

	All patients	COPD	ILD	p-value
Sex - male, n (%)	134 (72.0)	90 (86.5)	44 (53.7)	< 0.001
Age (years-old), mean (SD)	66.7 (10.8)	67.3 (8.9)	66.0 (12.9)	0.424
Smoking history				
Current smokers, n (%)	43 (22.8)	32 (29.9)	11 (13.4)	0.007
Former smokers. n (%)	99 (52.4)	67 (62.6)	32 (39.0)	
Height (cm), mean (SD)	163.8 (8.3)	165.0 (7.7)	162.3 (8.8)	0.024
Body mass (kg), mean (SD)	71.1 (13.2)	71.1 (13.1)	71.0 (13.4)	0.962
BMI (kg/m^2), mean (SD)	26.6 (4.6)	26.1 (4.2)	27.2 (4.9)	0.092
FEV1 (L), median (P25-P75)	1.6 (1.2-2.3)	1.3 (1.0-1.8)	2.0 (1.4-2.6)	< 0.001
FEV1 %, median (P25-P75)	66.5 (44.8-82.0)	48.5 (38.0-68.3)	80.5 (68.3-91.8)	< 0.001
FVC (L), median (P25-P75)	2.9 (2.2-3.5)	2.9 (2.4-3.5)	2.7 (1.9-3.4)	0.149
FVC %, median (P25-P75)	81.0 (68.8-92.0)	80.0 (68.5-91.3)	82.0 (68.9-92.0)	0.744
TLC (L), median (P25-P75)	6.2 (5.0-7.1)	7.0 (6.2-8.0)	4.9 (3.9-6.0)	< 0.001
TLC %, median (P25-P75)	106.0 (92.0-119.8)	115.0 (105.3-129.8)	91.0 (79.3-103.0)	< 0.001

RV %, median (P25-P75)	126.0 (91.5-164.8)	159.5 (127.0-186.8)	90.0 (77.0-109.8)	< 0.001
RV/TLC %, median (P25-P75)	48.9 (39.7-56.9)	55.0 (47.1-61.8)	40.7 (35.4-48.5)	< 0.001
DL_{CO} %, median (P25-P75)	57.0 (46.0-72.0)	58.0 (48.8-73.0)	56.0 (42.9-68.8)	0.134
6MWT				
6MWD (meters), mean (SD)	454.2 (89.1)	462.7 (76.0)	443.5 (102.8)	0.159
6MWD (% predicted)*, mean (SD)	78.5 (13.7)	79.1 (12.4)	78.1 (15.2)	0.626
6MWD (% predicted)**, mean (SD)	79.2 (13.5)	79.7 (12.3)	78.5 (14.9)	0.569
ΔHR, mean (SD)	22.0 (15.0-32.0)	21.5 (15.0-31.5)	22.5 (17.0-32.0)	0.268
ΔSpO2, mean (SD)	5.7 (4.4)	5.5 (3.9)	6.0 (5.1)	0.446
Supplemental oxygen during 6MWT, n (%)	19 (10.1)	5 (4.7)	14 (17.1)	0.005

*Values based on the first multiple regression model developed for a healthy population

** Values based on the second multiple regression model developed for a healthy population

6MWD: six-minute walk distance; 6MWT: six-minute walk test; BMI: body mass index; cm: centimeters; COPD: Chronic Obstructive Pulmonary Disease; DLco: diffusion capacity for carbon monoxide; ΔHR: the difference between heart rate at the end and the beginning of 6MWT; ILD: Interstitial Lung Disease; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; kg: kilograms; L: liters; RV: residual volume; SD: standard deviation; SpO2: peripheral oxygen saturation; TLC: total lung capacity;

There was a significantly greater proportion of males in the COPD group (86%) as compared to the ILD group (54%). There were no statistically significant differences in age between the two groups of patients and both COPD and ILD patients had a mean BMI in the overweight range. COPD patients had a higher proportion of current and former smokers than the ILD group (30% vs 13% and 63% vs 39%, respectively).

Regarding the pulmonary function tests, in the COPD group, the FEV1% was significantly lower and lung hyperinflation was also present, as opposed to the ILD group. Either in COPD and ILD patients, a reduction in DLCO % was observed.

The mean 6MWD was 462.7 meters in COPD patients and 443.5 meters in ILD patients (p=0.159). In percentage of predicted (based on the first multiple regression model developed for the healthy population20), the mean 6MWD was 79.1% and 78.1% in COPD and ILD groups, respectively (p=0.626). There were no statistically significant differences in ΔHR and ΔSpO2 during the 6WMT between the two groups but a significantly higher number of patients with supplemental oxygen during 6MWT in ILD group was observed (p=0.005).

In the COPD group, the mean 6MWD of patients with FEV1 < 50% was 447.4 meters as opposed to 483.4 meters in patients with FEV1 ≥ 50% (p=0.022).

Three multiple regression models were previously developed for 6MWT for the healthy population. 20 Based on those results, explanatory models were developed for COPD and ILD patients, using measurements of both groups (table S1)

The first model had an explanatory power of 34% on the healthy population and included the following variables: age, BMI and sex. Using this model in COPD and ILD patients, the explanatory power was 18% and 41%, respectively.

6MWD = 787.2 − 2.0 × Age − 4.4 × BMI + 54.8 × Sex (healthy population)

6MWD = 780.8 – 3.6 × Age – 2.9 × BMI + 3.1 × Sex (COPD group)

6MWD = 820.6 − 4.0 × Age − 5.4 × BMI + 59.2 × Sex (ILD group)

For COPD patients, only age was statistically significant and the 6MWD decreased 3.6 m per year of age. Therefore, an increase in age effect in 6MWD was observed in relation to the healthy population model (slope of -3.6 vs -2.0).

Concerning ILD group, all variables were statistically significant. The 6MWD decreased 4 m per year of age and 5.4 m per unit of BMI. On the other hand, it was 59.2 m higher in males. Compared to the healthy population model, there was an increase in the effect of age (slope of -4.0 vs -2.0), BMI (slope of -5.4 vs -4.4) and sex (slope of +59.2 vs +54.76). Additionally, compared to the COPD group, the effect of age and BMI was also more pronounced (slope of -4.0 vs -3.6 and -5.4 vs -2.9).

Concerning the second model, the explanatory power was 38% on the healthy population and it had an additional variable: ΔHR. In COPD and ILD groups the explanatory power was 25.7% and 54.6%, respectively.

6MWD = 721.7 − 1.6 × Age − 4.0 × BMI+0.9 × ΔHR + 58.4 × Sex (healthy population)

$$6MWD = 743.2 - 3.5 \times Age - 3.1 \times BMI + 1.5 \times \Delta HR + 2.6 \times Sex \text{ (COPD group)}$$

$$6MWD = 642.7 - 2.8 \times Age - 4.9 \times BMI + 3.4 \times \Delta HR + 70.2 \times Sex \text{ (ILD group)}$$

In the COPD model all variables were statistically significant, except for sex; it should be noted that the sample was mostly male (86.5%). The 6MWD decreased 3.5 m per year of age and 3.1 m per unit of BMI and increased 1.5 m per beat per minute. Compared to the healthy population model, there was an increase in the effect of age (slope of -3.5 vs -1.6) and ΔHR (slope of +1.5 vs +0.5), and a decrease in the effect of BMI (-3.1 vs -4.0). Regarding the ILD model, all variables were statistically significant. The 6MWD decreased 2.8 m per year of age and 4.9 m per unit of BMI; on the other hand, it increased 3.4 m per beat per minute and was 70.2 m higher in males. Compared to the healthy population model, there was a higher effect of age (slope of -2.8 vs -1.6), BMI (slope of -4.9 vs -4.0), ΔHR (slope of +3.4 vs +0.9) and sex (slope of 70.2 vs 58.4). Furthermore, compared to the COPD group, the effect of BMI and ΔHR was higher (slope of -4.9 vs 3.1 and +3.4 vs +0.9) in ILD patients and less pronounced for age (slope of -2.8 vs -3.5).

The third model developed to a healthy population, which included age categorized in decades, was not considered for our COPD and ILD groups due to the low number of patients under 50 years old.

In Figures 1 and 2 we present the difference between the expected 6MWD as healthy individuals and the same distance as ILD or COPD patients according to age. We can observe that the difference between those distances increases with age. In the ILD group, that difference is approximately 80 meters at 50 years old and it increases to 160 meters at 90 years old. On the other hand, in the COPD group that difference is about 100 meters at 50 years old and it increases to 150 meters with aging. Figures 1 and 2 are based on the first multiple regression model. Figures 3 and 4 are based on the second multiple regression model.

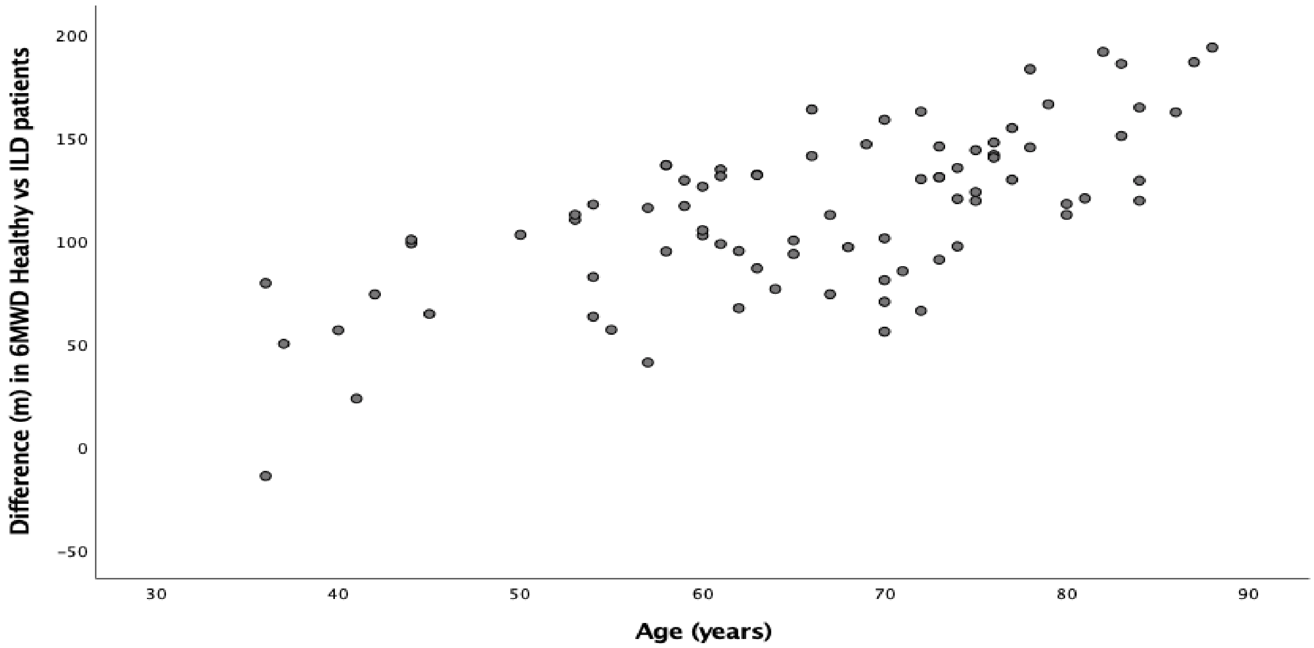

Figure 1

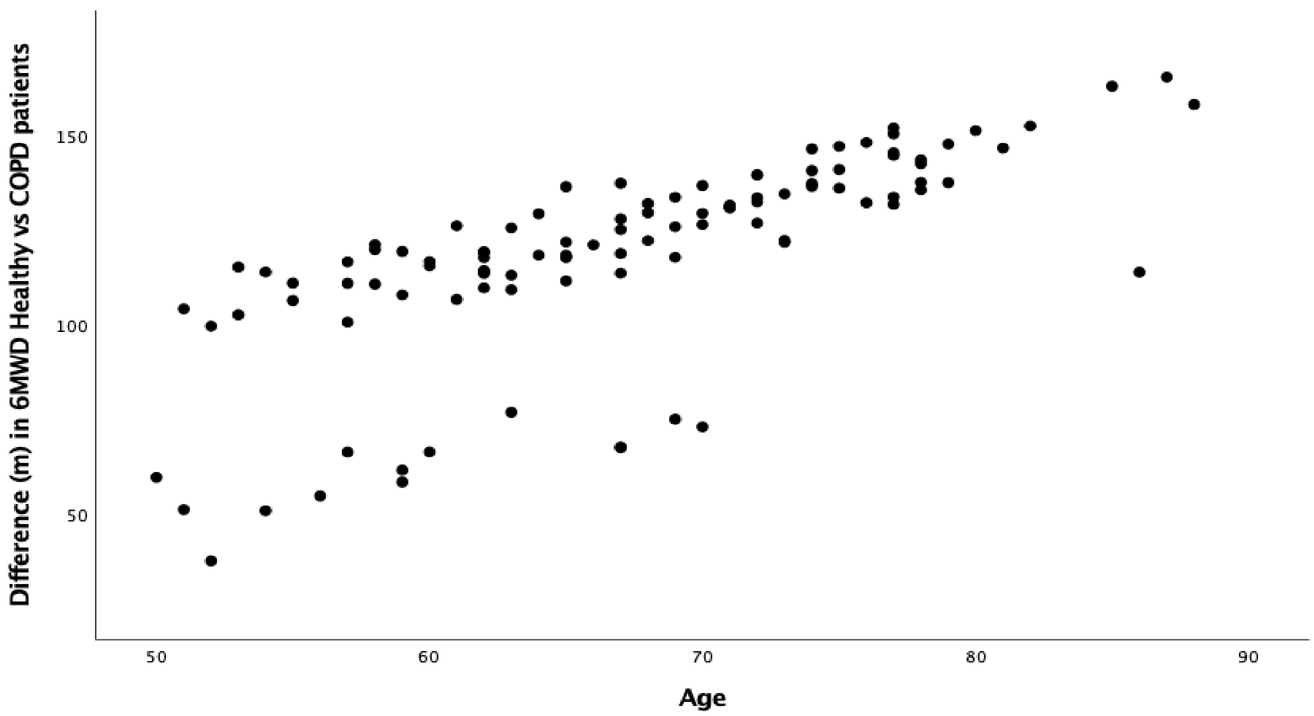

Figure 2

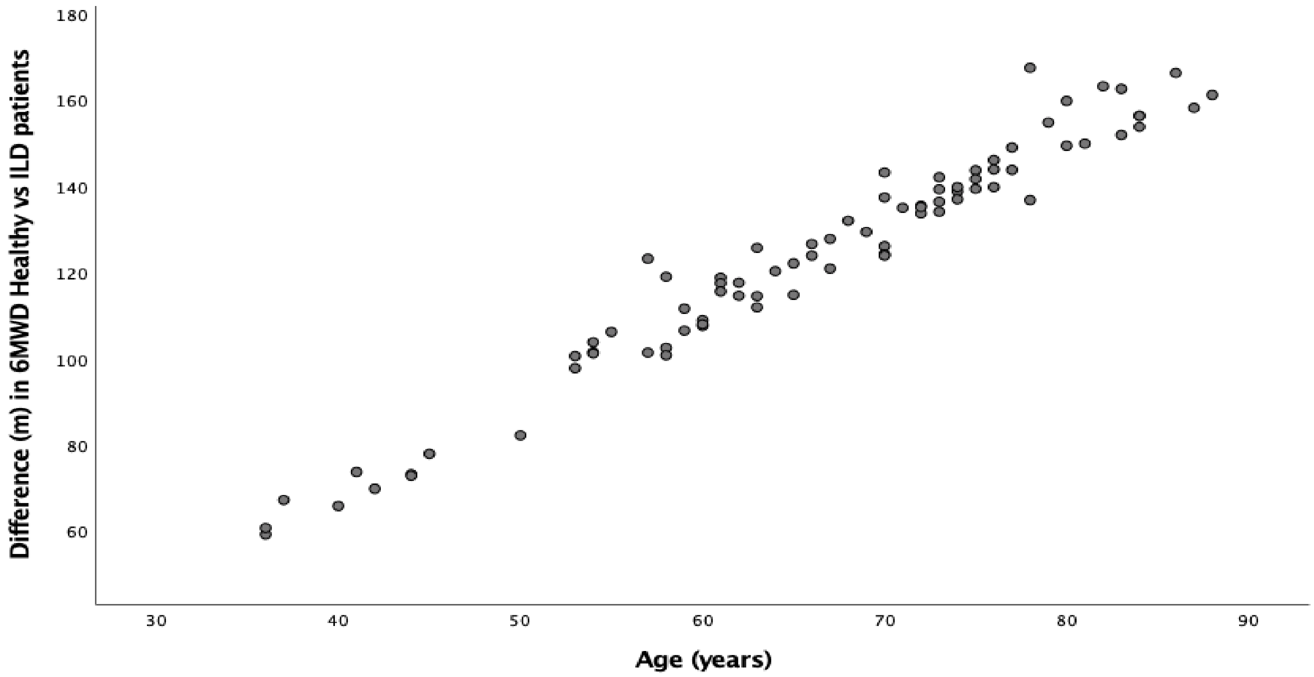

Figure 3

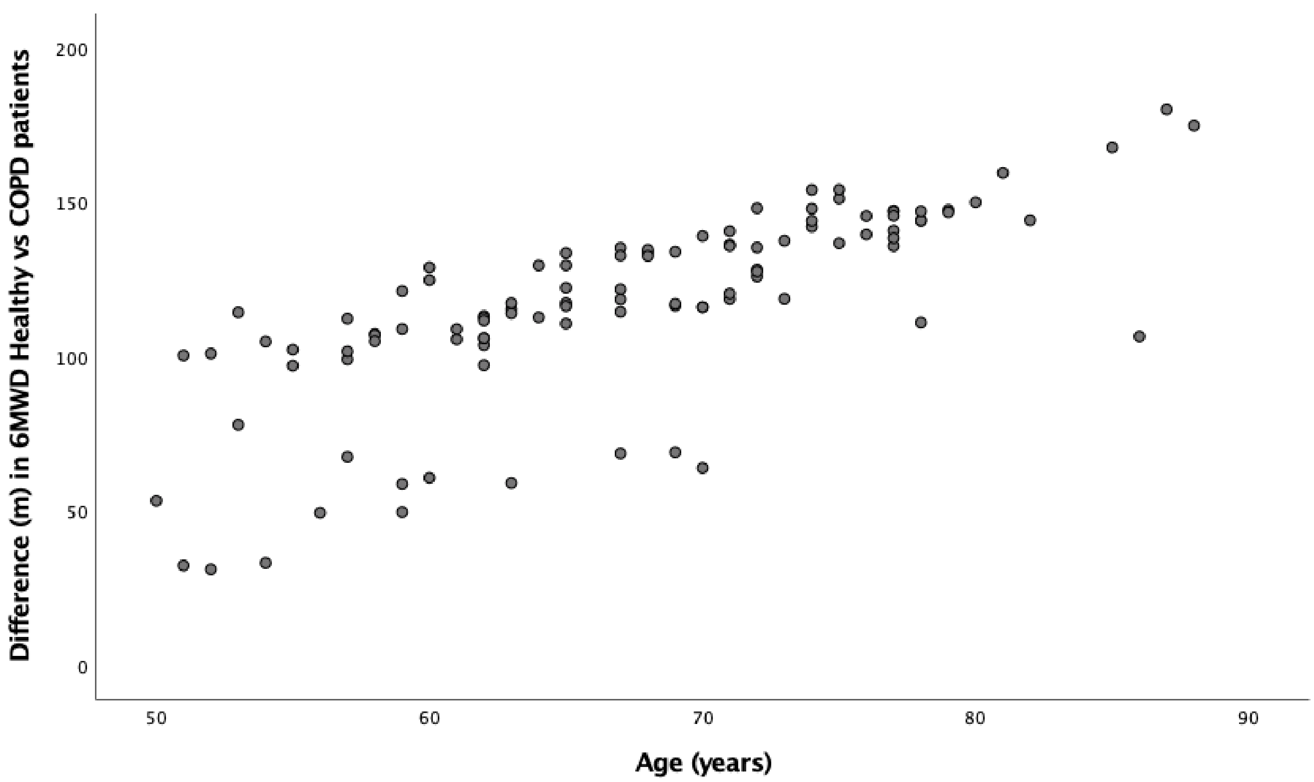

Figure 4

Figures 1 and 2. Difference between the expected 6MWD as healthy individuals and 6MWD as ILD or COPD patients according to age (based on the first multiple regression model).

Figures 3 and 4. Difference between the expected 6MWD as healthy individuals and 6MWD as ILD or COPD patients according to age (based on the second multiple regression model.

Discussion:

The 6MWT reference equations of different populations are developed using healthy subjects. Several 6MWT reference equations have been developed using healthy individuals with different clinical characteristics and, in some cases, with different variables.[33] The choice of 6MWT reference equations is an important issue to avoid misinterpretation of the results. When available reference equations should be specific for the country or region of origin. It is important to analyze their behaviour in specific groups of patients to reinforce their usefulness and applicability and improve our understanding of the differences between specific groups of diseases.

We have used reference equations of the healthy Caucasian population of a European country previously developed [20], to analyse them in COPD and ILD patients. The sample of this study is much older than the healthy subjects used for the development of those reference equations (only 7.7% of patients were under 50 years old). Therefore, the multiple regression model that uses age in categorized ranges of decades was not so suitable for our sample. The greater proportion of males in the COPD sample compared to ILD patients (86.5% vs 53.7%) limited the application and analysis of the different models within the former group.

The reference equations of a healthy population are developed to be simple in what respects to data collection. The most important factors that influenced the 6MWD in the healthy population model used were age, sex, BMI and ΔHR. [20] Thus, several factors influence 6MWD that were not included in the development of such reference equations. For instance, muscle power decreases with aging and has a negative and strong impact on mobility. [34] In specific groups of patients, other aspects affect the 6MWD. In COPD patients, many factors can influence the 6MWD including age, sex and BMI but also the degree of airflow limitation, the degree of emphysema and the rate of acute exacerbations. [35-39] In ILD patients, % predicted FVC and % predicted DLco is also correlated with 6MWD. [40] In this study, we have analyzed the influence in 6MWD of variables from the reference equations of a European country in COPD and ILD patients.

In our study, there were no significant differences between 6MWD of COPD and ILD groups. However, the relative influence of age, sex, BMI and ΔHR in 6MWD of both groups of patients should be analyzed to improve the interpretation of results.

The explanatory power of the two models presented above was higher in the ILD group compared to COPD patients and even with a healthy population sample. In the first multiple regression model, both age, for COPD and ILD patients, and BMI and sex, for ILD patients, had a greater effect in the 6MWD compared to the healthy population model; on the other hand, the effect of BMI was smaller in COPD patients. In the ILD group, all variables (age, BMI and sex) had a greater influence in 6MWD than in COPD patients. Regarding the second multiple regression model, which had the best explanatory power across all groups (38% in healthy population, 25.7% in COPD patients and 54.6% in ILD patients), it was observed a more pronounced effect in the 6MWD of the variables age and ΔHR, for COPD and ILD patients, and also of the variables sex and BMI, for ILD patients, about healthy population model; the influence of BMI in the 6MWD of COPD patients was smaller, as in the first model; compared with a healthy population, both samples were more homogeneous and, therefore, the standard deviations were much lower. As opposed to what was observed in the first model, in the second model the negative influence of age in 6MWD was higher in COPD patients when compared to the ILD group (aging had a greater impact on reducing the 6MWD in COPD patients); for the remaining variables, the effect was more pronounced in ILD group about COPD patients.

We also analyzed the difference between the expected 6MWD as healthy individuals and that distance as ILD or COPD patients. As previously mentioned, that difference increases with age, with the most pronounced increase in the ILD group. This increasing difference with age may be related to some factors. Age is negatively associated with 6MWD and this could be explained by the fact that maximal oxygen uptake, muscle mass and muscle strength decrease with age. [41,42] Furthermore, chronic lung diseases are associated with skeletal muscle dysfunction and reduction in fat-free mass. [43,44] In addition, the severity of the disease and comorbidities may play a role in explaining the increase in the 6MWD difference between a healthy population and COPD and ILD patients with age (cardiovascular diseases and other disorders were excluded in the healthy population group) which should be analyzed in further studies. In figure 2 there is a group of COPD patients who have a smaller difference in 6MWD about what would be expected as a healthy population. Of those 14 patients, the majority are female (12 patients) and great variability was found regarding the severity of the disease and the presence of comorbidities. Considering that the variable sex in this model was not statistically significant, and the difference verified in the coefficients, the observed distance results of the lack of fit given the low representation of women in the COPD group of patients.

Patients using supplemental oxygen were allowed in this study, reflecting the real-world function of both COPD and ILD patients. Patients just performed a single 6MWT, so the learning effect and reproducibility of the exam could not be analyzed. [45] However, most patients had performed a previous 6MWT and thus they were familiar with the procedure.

Conclusion

This study reinforces the value and validity of the reference equations for the 6MWT analyzed above in the evaluation of specific groups of diseases such as COPD and ILD. The second regression model, which had the best explanatory power in a healthy population, COPD patients and especially in the ILD group, should be used for clinical practice whenever possible. Nonetheless, our study only included Caucasian patients from one hospital in Portugal and further broader studies will improve our work. It would also be important to study the relationship of % predicted 6MWD values and clinical outcomes in specific groups of patients.

Ethics approval and consent to participate

The study was approved by the hospital ethics committee.

All the experimental protocols for involving human data was following the guidelines Declaration of Helsinki.

Conflicts of Interest:

The authors declare no conflict of interest.

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