

Six-minute walk test outcome in COPD patients

Rezultatele testului de mers de șase minute în rândul pacienților cu BPOC

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Abstract

Background. In Chronic Obstructive Pulmonary Disease (COPD) patients, Six-Minute Walk Test (6MWT) represents a validated tool in evaluating the functional status.

Aims. Our study aims to establish the role of demographic features, COPD degree of severity and risk groups in the 6MWT results.

Methods. We conducted a randomized study on 60 COPD patients without major comorbidities, admitted to the “Leon Daniello” Clinical Hospital of Pneumology, Cluj-Napoca. We collected data regarding age, gender, Body Mass Index (BMI), smoking history, and we performed the 6MWT in accordance with the American Thoracic Society (ATS) guidelines. The investigated parameters of the effort capacity test were: the distance (meters), the percentage of the predicted values of 6MWT and the SpO₂ (peripheral blood oxygen saturation) decrease.

Results. The BMI correlated with the number of years since smoking cessation ($p=0.04$, $r=0.26$). The walking distance decreased with higher severity stages (383.8±68.3 meters in stage 2 COPD versus 212.8±83.1 meters in stage 4 of the disease, $p<0.0001$). SpO₂ decreased more in stage 4 (4%±0.6) than in stage 3 (2.6%±1.2) and stage 2 of COPD (1.6%±1.2) ($p<0.001$, $F=18.560$). When evaluating the outcomes of the 6MWT based on the risk group of COPD (A to D), we found correlations between the risk group and the walked distance ($p=0.001$), the percentage of the predicted value of the test ($p=0.009$), and the desaturation index ($p<0.0001$). No correlation was found between the outcomes of the 6MWT and gender, age, smoking history ($p>0.05$).

Conclusions. 6MWT is influenced by the COPD risk group, disregarding age or the smoking history, in the absence of comorbidities; thus, it could be used as a tool in the staging and monitoring of the evolution of the disease. BMI in COPD patients is positively correlated with the number of years since smoking cessation.

Keywords: COPD, smoking, obesity, Six-Minute Walk Test.

Rezumat

Premize. În rândul pacienților cu BPOC (bronhopneumopatie cronică obstructivă), 6MWT (testul de mers de 6 minute) este un instrument validat în investigarea capacității funcționale.

Obiective. Studiul nostru își propune să stabilească rolul pe care îl au caracteristicile demografice și stadiile de severitate, precum și clasele de risc în rezultatele testului de mers de 6 minute.

Metode. Studiul nostru este unul randomizat, realizat pe 60 pacienți cu BPOC, fără comorbidități majore în evidență, admiși în Spitalul Clinic de Pneumoftiziologie „Leon Daniello”, Cluj-Napoca. Au fost analizate date precum: vârsta, genul, IMC (indice de masă corporală), istoricul de fumat și s-a efectuat 6MWT conform ghidurilor ATS (American Thoracic Society). Parametrii capacității de efort investigați au fost: distanța parcursă (în metri), procentajul din valorile prezise, scăderea SpO₂ (saturația în oxigen în sângele periferic).

Rezultate. IMC se corelează cu anii de sevraj tabagic ($p=0,04$, $r=0,26$). Când severitatea BPOC a fost analizată, distanța parcursă a scăzut direct proporțional cu severitatea bolii (383,8±68,3 metri, în stadiul 2 de BPOC, versus 212,8±83,1 metri în stadiul 4 al bolii, $p<0,0001$). SpO₂ a scăzut mai mult în stadiul 4 (4%±0,6), decât în stadiul 3 (2,6%±1,2) și stadiul 2 de BPOC (1,6%±1,2), ($p<0,001$, $F=18,560$). Când am evaluat valorile 6MWT bazându-ne pe grupele de risc (A la D), am descoperit corelații între grupa de risc și distanța parcursă ($p=0,001$), procentajul testului din valoarea prezisă ($p=0,009$) și indicele de desaturare ($p<0,0001$). Nu au fost găsite corelații între valorile 6MWT și gen, vârstă, istoricul de fumat ($p>0,05$).

Concluzii. IMC-ul pacienților cu BPOC se corelează pozitiv cu numărul anilor de sevraj tabagic. 6MWT este influențat de clasa de risc a BPOC, indiferent de vârstă, istoricul de fumat, în absența comorbidităților, astfel putând fi folosit ca instrument de stadializare și monitorizare a evoluției bolii.

Cuvinte cheie: BPOC, fumat, obezitate, test de mers de 6 minute.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) represents a major health problem worldwide. Although WHO (World Health Organization) estimated that by 2030, COPD will be the third leading cause of death, the disease is already in the top 3 major causes of death, after ischemic heart disease and stroke, according to Global Burden of Disease (GBD) (Quaderi & Hurst, 2018). More than 320 million people suffer from COPD worldwide (Eisner et al., 2010), and approximately 90% of COPD-related deaths occur in underdeveloped or developing countries (Alwan, 2010). COPD is a multifactorial disease, but cigarette smoking along with indoor and outdoor pollution represent the major risk factors in the development of the disease (Mannino & Buist, 2007). COPD is characterized by progressive and partially reversible airflow limitation, dyspnea being the most debilitating symptom. This translates into a reduced exercise capacity, impaired ability to work, limited overall mobility, anxiety, leading to a reduced quality of life (Lopez-Campos, 2017). These factors have a major effect on the economic aspect of the disease, for both the patient and society. In 2010, the National Heart, Lung, and Blood Institute evaluated that the annual cost of COPD in the United States of America was 49.9 billion USD, with almost 30 billion USD in direct medical costs (medication, hospitalization), and 20 billion USD in indirect morbidity and mortality (decreased productivity due to the illness or early death).

Limited exercise capacity is a serious problem for the patient and for the patient's family. Progressive effort dyspnea occurs at early stages of the disease, and COPD patients present dyspnea at rest in stage IV of the disease (forced expiratory volume in 1st second - FEV₁ below 30% of the predicted value).

The actual classification of COPD uses GOLD (Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2018) criteria to evaluate the functional capacity of the lungs (stages I-IV, depending on the FEV₁ value), and also the risk group classification (groups A, B, C and D, based on combined symptoms and exacerbation risk assessment). According to the GOLD 2018 Report, Stage I includes patients with FEV₁ \geq 80% of the predicted value, Stage II – FEV₁ $<$ 80% and \geq 50%, Stage III – FEV₁ $<$ 50% and \geq 30%, and Stage IV – FEV₁ $<$ 30%. Group A – Modified Medical Research Council (mMRC) Dyspnea Scale score 0-1 or COPD Assessment Tool (CAT) score $<$ 10 with 0-1 exacerbations/year, not leading to hospital admission; Group B - mMRC score \geq 2 or CAT score \geq 10 with 0-1 exacerbations/year, not leading to hospital admission; Group C - mMRC score 0-1 or CAT score $<$ 10 with \geq 2 exacerbations/year or \geq 1 exacerbation leading to hospital admission; Group D - mMRC score \geq 2 or CAT score \geq 10 with \geq 2 exacerbations/year or \geq 1 exacerbation leading to hospital admission (Kim et al., 2013).

Exercise impairment can be observed in a reduction of the self-paced walking distance (Singh et al., 2014) or by performing incremental exercise testing in a laboratory (Bolton et al., 2013). The Six-Minute Walk Distance Test (6MWT) is a simple, non-invasive, low cost, repeatable

tool in the evaluation of functional capacity of COPD patients (Moreira et al., 2015). The test assesses the maximum distance a patient can walk during 6 minutes, and is highly used in evaluating the outcomes of pulmonary rehabilitation programs (Maddocks et al., 2015), or could be used as a mortality prediction tool (Waschki, 2011). Another benefit of the 6MWT is the ability to predict an acute exacerbation of the disease (Andrianopoulos et al., 2015), and a walking distance shorter than 350 m was considered a predictor of exacerbation in previous studies (Zanori & ZuWallack, 2013). A cut-off point of 80% of the predicted value is considered valid in many previous researches (Casanova et al., 2011; Soaresa & Pereira, 2011).

Hypothesis

The six-minute walk distance test is a useful tool in evaluating the exercise capacity of a COPD patient and can be used as a staging tool in selected patients (without major comorbidities).

Objectives

The purpose of this study was to evaluate exercise capacity in COPD patients, and to establish a possible association between the outcomes of the 6-minute walk test and the demographic characteristics, severity stage and risk group classification.

Material and methods

The study was approved by the Research Ethics Committee of "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, no. 298/29.06.2016, and all patients included in this study signed an informed consent to participate in this research.

Research protocol

Duration and location: The study was conducted on COPD patients admitted to the "Leon Daniello" Clinical Hospital of Pneumology, Cluj-Napoca, Romania, between 2016 and 2017.

a) Subjects and groups

Initially, 356 patients with COPD were enrolled in this study, but after using the exclusion criteria, 60 patients were included in the research. The inclusion criteria were: signing the informed consent, age $>$ 40 years and $<$ 90 years, Tiffeneau index (forced expiratory volume in the first second (FEV₁) to forced vital capacity (FVC) $<$ 0.7. The exclusion criteria were: age $<$ 40 years or $>$ 90 years, refusal to sign the informed consent, FEV₁/FVC \geq 0.7, presence of any of the following: chronic obliterative arteriopathy of the lower limbs, chronic venous insufficiency, leg pain, leg injuries, asthma, chronic bronchitis, allergies, pneumonia, heart failure, pulmonary hypertension, myocardial infarction, alpha-1 antitrypsin deficiency, interstitial lung disease, oral anticoagulant therapy, recent revascularization, thoracic surgery, acute renal failure, neoplasia, autoimmune diseases. Smoking status was evaluated as follows: group 0 – never smokers, group 1 – current smokers, group 2 – former smokers.

b) Assessment methods

The patients were assessed on the first day of admission

to hospital and on the seventh day of hospitalization. The methods used for the assessment were: collecting anamnestic data regarding the smoking history and calculating the pack-year index, performing the 6MWT in accordance with the standard ATS protocol (***, 2002), indoors, on a flat, ventilated corridor 18 m in length, supervised by a physician. At the beginning and at the end of each test, we evaluated blood pressure (BP), heart rate (HR), peripheral blood oxygen saturation (SpO₂, with the Nonin digital pulse oximeter). Each patient was asked to walk as far as possible around the course in a six-minute period of time, and to signal if dyspnea, extreme fatigue, pain or dizziness occurred during the test. SpO₂ was evaluated every 20 seconds, and the test was stopped if desaturation greater than 5% occurred.

The predicted value for the distance of the 6MWT was calculated with the formula:

Male patient: Predicted 6 MWD=361 – (age in years x 4) + (height in cm x 2) + (HRmax/HRmax%pred x 3) – (weight in kg x 1.5)

Female patient: Predicted 6 MWD=361 – (age in years x 4) + (height in cm x 2) + (HRmax/HRmax%pred x 3) – (weight in kg x 1.5) – 30 for female subjects (Casanova et al., 2011).

The predicted max Heart Rate was calculated with the formula: HRmax= 220-age.

After applying the formula, we evaluated the outcome in % of the predicted value.

Performing ≥80% of the predicted value was considered as a normal effort capacity.

c) Statistical analysis

Statistical analysis was conducted by using IBM Statistical Package for the Social Sciences (SPSS), version 20 for Windows, and Microsoft Excel 2010. The variables are expressed as mean ± standard deviation. For each data item, the minimum, maximum, standard deviation, skewness and kurtosis were computed. Logarithmic transformation of values was used for non-Gaussian distribution data. T-test and ANOVA test were used to compare the means. Spearman test was applied for correlations. Confidence interval levels of 95% and alpha<0.05 were considered for statistical significance.

Results

Overall analysis

The study group included 60 patients (54 males and 6 females), previously diagnosed with moderate to severe COPD, according to 2018 COPD GOLD Criteria. The mean age was 67 years old, with a SD of 9.2. The median BMI was 29.4. Out of the study population, 20 (33.3%) were current smokers, 28 (46.6%) were former smokers, and 12 patients never smoked cigarettes (20%). The mean distance walked during the 6MWT was 303.97 meters (m), with a mean percentage of the predicted value of 78%±19.1 and a minimum of 70 meters and a maximum of 450 m, and also a decrease in the peripheral blood transcutaneous oxygen saturation of 2.7±1.4, with a minimum of 1% and a maximum of 5%.

Patient characteristics are presented in Table I.

Table I

General characteristics of the study population	
Indicators	Total (n=60)
Age, years	67±9.2
Number (percent) of females	6 (10%)
Number (percent) of males	54 (90%)
BMI (mean ± SD)	29.4±6.3
Number (percent) of smokers	20 (33.3%)
Number (percent) of former smokers	28 (46.6%)
Number (percent) of never smokers	12 (20%)
Smoking status, pack-year index mean ± SD	29.5±18.2
Years since smoking cessation, mean ± SD	4.9±7.2
6MWT distance (meters), mean ± SD	303.9±97.7
6MWT percent of the predicted value, mean ± SD	78±19.1
Desaturation during 6MWT percent, mean ± SD	2.7±1.4

Legend: Results expressed as median ± standard deviation (SD), BMI=Body Mass Index; 6MWT=Six-Minute Walk Test.

The distribution of the study population according to the 2018 COPD GOLD Stages of severity classification was: 18 (30%) patients in stage II, 26 (43%) in stage III, and 16 (27%) in stage IV of the disease. When risk groups were considered, 4 (7%) patients were in Group A, 13 (22%) in Group B, 5 (8%) in Group C and 38 (63%) in Group D.

Out of all 60 patients, a proportion of 38.3% (n=23) patients were classified as obese, with a BMI>30 kg/m².

Table II

Overall correlations between the studied parameters

Indicators	Age	BMI	PYI	SC	6MWT D	6MWT % PV	6MWT Des
Age	Correlation coefficient	1.000	-.088	.045	.100	-.065	-.106
	Sig. (2-tailed)	.	.502	.730	.449	.623	.418
BMI	Correlation coefficient	-.088	1.000	.009	.261	.122	.139
	Sig. (2-tailed)	.502	.	.946	.044	.351	.290
PYI	Correlation coefficient	.045	.009	1.000	.293	.035	.079
	Sig. (2-tailed)	.730	.946	.	.023	.789	.547
SC	Correlation coefficient	.100	.261	.293	1.000	-.219	-.231
	Sig. (2-tailed)	.449	.044	.023	.	.093	.075
6MWT D	Correlation coefficient	-.065	.122	.035	-.219	1.000	.930
	Sig. (2-tailed)	.623	.351	.789	.093	.	.000
6MWT % PV	Correlation coefficient	-.106	.139	.079	-.231	.930	1.000
	Sig. (2-tailed)	.418	.290	.547	.075	.000	.
6MWT Des	Correlation coefficient	-.038	-.041	-.028	.189	-.604	-.575
	Sig. (2-tailed)	.772	.755	.831	.149	.000	.000

Legend: BMI = Body Mass Index; 6MWT = Six-Minute Walk Test; PYI = Pack-Year Index; SC = smoking cessation; 6MWT D = 6MWT Distance; 6MWT % PV = 6MWT percent of predicted value; Des = Desaturation; 2-tailed significance cutoff = 0.05.

Out of the obese patients, 39.1% were classified, based on severity, as stage II COPD, 43.4% as stage III, and 21.73% as stage IV COPD.

BMI positively correlated with the number of years since smoking cessation ($p=0.04$, $\rho=0.261$). No correlation was found when comparing the 6MWT parameters (distance, percentage of the predicted value, SpO₂ decrease), age, BMI and smoking history. The results are presented in Table II.

Severity stages of COPD

When severity stages were considered, the walked distance during the 6MWT was influenced by the severity of the disease, as a higher severity index was associated with a lower distance in 6MWT ($p<0.0001$). Patients with mild COPD (stage 2, $n=18$) walked 383.8 ± 68.3 meters, while patients with a severe stage of disease (stage 4, $n=16$) walked 212.8 ± 83.18 meters. Subjects with stage 3 COPD had a distance of 311.5 ± 79.6 . Also, the percentage of the predicted value of 6MWT achieved by patients in stage 2 was higher compared to that of patients in stage 4: 90.6 ± 14 versus 62.2 ± 17.2 ($p<0.0001$) (Table III).

Table III

Anova analysis of distance, percent of the predicted value of 6MWT, desaturation, age, BMI and the severity grade of COPD

Indicators	F	Sig.
6MWT D - COPD grade	18.56	0.0001
6MWT % PV - COPD grade	13.285	0.0001
6MWT Des - COPD grade	18.63	0.0001
Age - COPD grade	0.306	0.737
BMI - COPD grade	1.356	0.266

Legend: BMI=Body Mass Index; 6MWT=Six-Minute Walk Test; 6MWT D = 6MWT Distance; 6MWT % PV = 6MWT percent of predicted value; Des = Desaturation; F = F test = between group variability/within group variability; Sig = significance cutoff = 0.05.

Risk groups

The ANOVA statistical analysis of the walked distance, percent of the predicted value of 6MWT and desaturation considering risk groups indicated a statistical significance between risk groups (Table IV). No statistically significant differences were found when considering the group risk and age or BMI.

Table IV

Anova analysis of distance, percent of the predicted value of 6MWT, desaturation, age, BMI and the risk groups of COPD patients

Indicators	F	Sig.
6MWT D - RG	6.003	0.001
6MWT % PV - RG	4.286	0.009
6MWT Des - RG	7.703	0.0001
Age - RG	0.392	0.759
BMI - RG	1.115	0.351

Legend: RG = risk group; BMI=Body Mass Index; 6MWT=Six-Minute Walk Test; 6MWT D = 6MWT Distance; 6MWT % PV = 6MWT percent of predicted value; Des = Desaturation; F = F test = between group variability/within group variability; Sig = significance cutoff = 0.05.

Smoking status

The 6MWT % of predicted value was higher in group 1 (86%) compared to group 0 and group 2 (73%) ($p=0.048$

on ANOVA test). Considering smoking status, no statistical significance was found for the walked distance and the desaturation level.

Discussions

In our study group, we found a proportion of 38.3% obese patients, which is higher than the incidence cited in the literature - 10-28% (Finucane et al., 2011). A possible explanation could be the small group of patients investigated in our research. Out of the 23 obese patients, only 5 (21.73%) were diagnosed with severe COPD (FEV₁s <30% of predicted value). These results are consistent with the currently available international epidemiological data (Park et al., 2017). Obesity represents a major health problem, with an impact on the pathophysiology of respiration, in obesity-hypoventilation syndrome, or in obesity-COPD overlap syndrome. The presence of obesity in a COPD patient represents a potential indicator of Obstructive Sleep Apnea Syndrome (OSAS), adding the last "O" to what is called the Triple O Syndrome - COPD + Obesity + Hypoventilation + OSAS (Drummond et al., 2012).

BMI moderately correlated with years since smoking cessation. It is known that weight gain occurs after smoking cessation (hyperphagia, stress) (Faeh et al., 2018). The reason for this might be the removal of the effect of nicotine on the central nervous system (Komiya et al., 2013), or the increase in calories intake, due to the "hand to mouth" gesture (Veldheer et al., 2015). Also, the percent of the predicted value of 6MWT was higher in group 1 versus group 0 and group 2 based on the smoking status.

6MWT was not influenced by age, BMI, smoking history. Our results disagree with other studies, which reported a positive correlation between age, distance and overall performance on 6MWT (Liu et al., 2016). In our opinion, the explanation can be found in the multitude of exclusion criteria that we used, having a group without major comorbidities that could influence the test results (heart failure, peripheral artery disease, uncontrolled diabetes). Currently, there are no universally accepted equations for predictive values of the 6MWT. This is due to the small cohort data, lack of multicenter studies, differences between regions, inconsistent methodology of the test (i.e. corridor length). We selected the equation provided by Casanova et al., as it results from an international multicenter study evaluating geographic variations in a large cohort of adults, following the ATS guidelines.

The average walked distance during the 6MWT was shorter than the reported values 445 ± 92.9 meters (Saglam, 2015). We believe that one reason for this is the possible influence of the corridor's length with multiple turns. Other published studies used a corridor of 15 or less meters long and found similar results to those of our study - average distance 391 meters (Hernandes et al., 2011). A possible solution for these differences could be the Sit-To-Stand Test, which could be more accurate in evaluating the functional capacity of COPD patients (Reychler et al., 2018); more studies are needed before validating this tool in the assessment of COPD. We discovered a high statistical significance between the walked distance and the severity of COPD, in accordance with the literature data

(Enfield et al., 2010), and also with the risk group. This last association had contradictory results in the literature (Celli et al., 2016), but our findings suggest that 6MWT could serve as a predictive tool in a COPD population without major comorbidities.

The desaturation index is positively associated with the risk group, indicating a marker for oxygen therapy according to the risk group in addition to spirometric values and arterial blood gas analysis. This could impact the intermittent oxygen therapy at home indicated for patients with severe COPD (a potential condition for reimbursement of oxygen therapy), with a major impact on the healthcare system, reducing the financial costs of both the patient and the system.

Most of the studies found correlations between age or BMI and the risk groups of COPD. Divo et al. (2015) found that the higher the BMI, the lower the risk group, giving obesity a protective value - the obesity paradox of COPD. However, we discovered no statistical significance between these characteristics, meaning that obese and non-obese patients have a similar incidence of exacerbations.

Conclusions

1. Our findings suggest that in a COPD population without major comorbidities, the outcome of 6MWT could serve as a predictive tool for further exacerbations and might contribute to a better management of the disease, in terms of pharmaceutical and non-pharmaceutical treatment, including pulmonary rehabilitation programs.

2. Furthermore, 6MWT could represent, for this category of patients, an important criterion in the classification of COPD.

Conflicts of interest

I have no real or perceived, direct or indirect conflicts of interest that relate to this article.

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