original article

Comparison of six-minute walking tests conducted with and without supplemental oxygen in patients with chronic obstructive pulmonary disease and exercise-induced oxygen desaturation

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BACKGROUND: There are contradictory reports in the literature on the effects of supplemental oxygen administered before or after exercise tests. In light of this, we compared the results of 6-minute walking tests performed in room-air conditions (A6MWT) and with supplemental oxygen (O6MWT) in patients with chronic obstructive pulmonary disease (COPD) and exercise-induced oxygen desaturation.

PATIENTS AND METHODS: Thirty-one patients with COPD were included in the study. The A6MWT and O6MWT were performed in randomized order on each patient. During the tests, severity of dyspnea and tiring of the leg were evaluated by the Modified Borg Scale. Heart rate and pulsed oxygen saturation and blood pressure were measured by pulse oximeter.

RESULTS: Walking distance was longer with the O6MWT than with the A6MWT (P=0.001). The O6MWT resulted in a smaller increase in dyspnea, leg fatigue, and heart rate and a smaller drop in pulsed saturation than the A6MWT (P<0.05). The walking distance with the O6MWT correlated with respiratory function and hemodynamic parameters (P<0.05).

CONCLUSION: The O6MWT, which produced less hemodynamic stress and was safer than the A6MWT, might provide more accurate information on exercise limitation for patients with COPD. These results suggest that the O6MWT can be used as a standard walking exercise test for patients with COPD and exercise-induced oxygen desaturation.

Several studies have determined that daily activities, such as walking, are associated with transient oxygen desaturation in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD), even without marked resting hypoxemia.[1-4] It has been reported that patients with low DLCO (diffusion capacity of carbon monoxide) bear a higher risk of oxygen desaturation even during submaximal exercise. Therefore, submaximal exercise tests should be performed in elderly patients with heart failure and pulmonary disease for safety reasons.[4]

As a submaximal exercise test, the 6-minute walking test (6MWT) is a good predictor of functional status for patients with chronic respiratory disease.[5, 6] The 6MWT is easy to perform, well tolerated, and more reflective of activities of daily living than other walking tests and cardiopulmonary exercise tests.[7] Additionally, it is possible to determine exercise-induced oxygen desaturation in patients with COPD, not by the means of cardiopulmonary tests but by means of the 6MWT.[1]

The widespread acceptance of walking tests is due to their convenience, simplicity, lower costs, and presumed easiness of completion. Although these tests are attractive as field tests of function and disability, standardization can be poor. Insufficient and difficult standardization with this test is known to potentially influence the results and could make interpretation and comparison difficult with the results of walking tests obtained at different times or from different testing sites.[8] Especially in severe pulmonary diseases, because of the lack of standardization in the interpretation of the 6MWT and simplicity of measurement, only limited information can be obtained on physiologic and symptomatic changes that occur during exercise.[9]

There are several interrelated factors limiting the exercise capacity of patients with COPD: (1) respiratory (limited ventilation, hypoxemia, dyspnea), (2) cardiac (uncontrolled and unsafe rises in pulmonary artery pressure, heart rate and blood pressure, dyspnea), (3) musculoskeletal (decrease in peripheral muscle strength, osteoporosis, early and enhanced leg fatigue), (4) psychological (fear, dyspnea, social isolation, depression, anxiety), and (5) others (nutritional status, anaemia, fatigue).[9,10] However, 6MWT provides no information on factors limiting exercise other than oxygen-related transport problems. For example, cardiac symptoms can limit the walking distance before respiratory symptoms occur. This is the case especially when cor pulmonale is present or when peripheral muscle strength is lost or fear from effort develops due to prolonged bed rest or inactivity in patients with moderate-to-severe COPD. In those cases, evaluation of the therapeutic effects and interpretation of the test are difficult. On the other hand, in later stages of COPD, increasing severity of respiratory symptoms and high rates of exercise-induced hypoxemia limit the usability of the test. Thus, exercise capacity cannot be evaluated properly with 6MWT alone.

There are contradictory statements in the literature on the effects of supplemental oxygen administered before or after exercise tests; some of reported that it decreases symptoms and increases exercise capacity while others do not.[2,11-16] In the light of this, we investigated the effect of supplemental oxygen in the 6MWT and of the test stress in patients having moderate-to-severe COPD with exercise-induced oxygen desaturation. We also assessed whether it was possible to get more information on the type of the factors limiting exercise by comparing the results obtained with 6MWTs conducted in room air conditions.

PATIENTS AND METHODS

Thirty-one patients (25 male, 6 female) between 52 and 83 years of age with moderate-to-severe COPD (mean forced expiratory volume in one second [FEV_1], 43.55% of predicted, FEV_1/forced vital capacity [FVC], 58.55%) defined by the GOLD 2003 criteria [17] were recruited at the outpatient clinic for respiratory diseases (University of Dokuz Eylul). All patients were in a clinically stable state for at least 6 weeks and had no recent infectious exacerbations.

The inclusion criteria to this study were: (1) being able to complete the 6MWT; (2) having an FEV_1 less than 70% of the predicted value for all measurements made during the previous 6 months, (3) maintaining a stable standard medical treatment and oxygen therapy, (4) being an ex-smoker; (5) having an exertional desaturation of at least 4% on pulse oximeter during submaximal exertion (corridor walking). The exclusion criteria were symptomatic cardiac dysfunction, angina pectoris, and locomotor disability. All patients underwent two 6MWTs, while breathing room air and breathing supplemental oxygen. Patients were familiar with application of the Modified Borg Scale (MBS) for measurement of severity of dyspnea and leg tiring.[7] The local ethical committee approved the protocol and participants gave informed consent.

We conducted the 6MWT as described by Guyatt and colleagues.[18] Before the test, the patient was seated on a chair in front of the corridor and rested for 15 minutes. Patients were instructed to walk the corridor of the hospital (40 meters length) at their own pace, while attempting to cover as much distance as possible within the 6 minutes allotted to them with and without supplemental oxygen. To eliminate a learning effect, first a normal (without oxygen) 6MWT was performed by all patients. A small 5-kg oxygen cylinder was placed in the middle of the corridor with a 0.5 inch diameter and a tube of 45 meters connected to it. The other end of this tube was connected to the patient's own nasal cannule. To eliminate discomfort, all patients performed both tests with this apparatus. During the test, a supervisor holding the tube walked 2 meters behind the patients to prevent disconnection and discomfort. The 6MWT in room air conditions (A6MWT) was performed without supplemental oxygen and with supplemental oxygen (oxygen dose 4 L/min) (O6MWT) for all patients. Administration of the tests was randomized and single blinded to the study groups. Patients were told that the two walking tests were the same and the patient chose the initial test. During the O6MWT, oxygen was administered for the first 15 minutes prior to the test, during the test and for 5 minutes following the test. Tests were performed in the morning hours on alternate days. During the walking tests, standard phrases of encouragement were delivered with time intervals of 1 minute.[7] The 6MWT was not performed if SpO_2 was lower than 90% before the test and the test was terminated if there were complaints of fatigue in the legs and/or severe dyspnea or at their request.[19] A research assistant timed the walk and recorded the distance travelled.

Besides the walking distance, pulsed oxygen saturation and heart rate were measured by a portable pulse oximeter (Palco model 400, Palco Labs, Santa Cruz, CA, USA). The blood pressure was also evaluated. The severity of dyspnea and leg fatigue was assessed by the Modified Borg Scale (MBS). All measurements were recorded before (baseline), and at the end of the walking test, and 5 minutes after the test. Spirometry was performed by an expert using a Sensor medics Vmax22 machine (SensorMedics Inc, Anaheim, CA, USA). in accordance with the ATS criteria.[20] FVC, FEV_1 and FEV_1/FVC values were recorded. Arterial blood gas analysis was performed using arterialized capillary samples from the radial artery to obtain pH, arterial carbon dioxide pressure ($PaCO_2$) and arterial oxygen pressure (PaO_2) from patients receiving oxygen support for 15 minutes at rest (Model Nova Biomedical Stat-9 Profile (Nova Biomedical, Germany).

The Statistical Package for Social Sciences (SPSS 11.0) program was used for statistical analyses. All results were presented as mean±standard deviation. Variables of both tests were compared by means of the Student's paired t test with a significance level of 95%. The correlation between variables was tested by calculating the Pearson's Correlation Coefficient (r). *P* values of less than 0.05 were considered statistically significant.

RESULTS

Twenty-eight (90.32%) of the patients (n=31) exhibited desaturation during the A6MWT, with pulsed saturation decreasing 4% below the limit of 90% saturation. The subjects having normal pulsed saturation (98% to 100%) were not included in the present study. For purposes of homogeneity, only those patients who exhibited desaturation during the A6MWT were included. Hemodynamic measurements made 5 minutes after finishing the test were within the normal range in all subjects. The characteristics of the 28 patients (22 male, 6 female) are described in Table 1. Congestive heart failure and hypertension was present in 17.9% of the subjects (n=5) and 78.6% (n=22) had mild hypoxemia (PaO_2 < 80 mm Hg). Seventeen patients chose the A6MWT first. In a separate analysis, we found that the order of the tests did not affect the results. Two patients who selected the A6MWT first and one patient who chose the O6MWT first were excluded from the study since they showed normal oxygen peripheral saturation during the test.

The walking distance was longer in the O6MWT than in the A6MWT (*P*=0.001, Table 2). At the beginning of the test, the severity of dyspnea was found to be higher in A6MWT than O6MWT (*P*=0.004). The severity of tiring of the leg and values of blood pressure, heart rate, and pulsed saturation were similar at the initiation of both tests (*P* > 0.05). However, at the end of the tests, the increase in severity of dyspnea, leg tiring and heart rate were found to be statistically significant in the A6MWT compared with the O6MWT (*P*=0.001). In addition, the pulsed saturation at the end of the test showed a statistically significant decrease in A6MWT compared with the O6MWT (*P*=0.001). On the other hand, the blood pressure did not change significantly during either test (*P*>0.05, Table 2).

The walking distance during both tests showed a statistically significant correlation (r=0.87, *P*=0.0001). There was no significant correlation between the walking distance and clinical and demographic parameters of the patients in either test (*P*> 0.05); only the walking distance of the O6WMT showed a significant correlation with respiratory function (r=0 37, -0.38, *P*<0.05, Table 3). The A6MWT correlated with the severity of dyspnea at baseline and at the end of the test (r=0.55, -0.65, *P*<0.05), whereas the O6MWT correlated with severity of dyspnea and leg tiring and pulsed saturation at baseline and at the end of the test and with heart rate at the end of the test (*P*<0.05, Table 4).

Table 1. The physical and clinical characteristics of the population studied.

N = 28	Mean±SD	Range
Age (years)	68.9 ± 8.1	52 - 83
BMI (kg/m²)	24.1 ± 5.3	19.5 - 28.6
FVC,% predicted	62.2 ± 12.0	61.4 - 68.8
FEV_1,% predicted	41.2 ± 2.8	32 – 45
FEV_1/FVC	60.15 ± 13.08	43 – 70
$PaCO_2$ (mm Hg) resting, on air	47.57 ± 1.00	35.4 - 76.4
PaO_2 (mm Hg) resting, on air	78.8 ± 14.7	66 – 87
SaO_2 (%) resting, on air	93.0 ± 5.9	82.3 - 97.7

BMI: body mass index, FVC: forced vital capacity, FEV_1: expiratory volume in one second, $PaCO_2$: arterial carbon dioxide pressure, PaO_2: arterial oxygen pressure, SaO_2: arterial oxygen saturation.

DISCUSSION

The short-term benefits of oxygen administration during exercise have been reported in many articles, have described improvements in the dyspnea index and in exercise performance when oxygen was administered only during exercise. Some reports have described the difficulties in predicting the lack of a relationship between short-term oxygen effects and desaturation during exercise.[3,21,22]

The most important factor for exercise capacity in patients with COPD is impaired gas exchange. In early stage of COPD, oxygen saturation is maintained at rest, but when the lung is challenged with increasing demand (exercise), oxygen desaturation may occur.[4] However, patients with more severe COPD are prone to arterial hypoxemia during exercise and routine activi-

Table 2. Clinical characteristics of patients during the six-minute walk tests with supplemental oxygen and room air.

	A6MWT	O6MWT	*P* Value
Walking Distance	174.7 ± 30.4	222.1 ± 12.4	0.001
The severity of dyspnoea			
Baseline	1.4 ± 1.7	0.45 ± 0.9	0.004
End	3.8 ± 2.4	1.6 ± 1.8	0.001
Heart rate, beats/minute			
Baseline	84.1 ± 15.3	85.7 ± 13.1	0.33
End	102.4 ± 17.1	98.8 ± 14.6	0.01
Systolic blood pressure (mm Hg)			
Baseline	139.5 ± 1.6	138.8 ± 0.6	0.94
End	142.2 ± 4.4	143.5 ± 8.5	0.17
Diagnostic blood pressure (mm Hg)			
Baseline	90.5 ± 3.9	90.2 ± 24.4	0.84
End	92.5 ± 7.4	90.0 ± 10.9	0.36
SpO_2, (%)			
Baseline	91.5 ± 3.4	94.9 ± 2.8	0.08
End	88.8 ± 5.7	94.2 ± 4.7	0.001
The severity of leg fatigue			
Baseline	0.3 ± 0.1	0.2 ± 0.1	0.49
End	2.0 ± 1.1	0.8 ± 0.4	0.001

A6MWT: 6MWT in room air, O6MWT: 6MWT with supplemental oxygen, SpO_2: Pulsed oxygen saturation.

Table 3. Correlations between patient characteristics and the six-minute walk test with supplemental oxygen and room air.

	A6MWT r	O6MWT r
Walking distance of O6MWT	0.87**	-
Age	-0.17	-0.23
BMI	0.03	0.08
FVC % predicted	0.32	0.38*
FEV_1 % predicted	0.33	0.37*
FEV_1/FVC	0.32	0.34
$PaCO_2$	-0.26	-0.21
PaO_2	0.14	0.15
SaO_2	0.12	0.10

* Significant at the 0.05 level ($0.01 \geq P < 0.05$), ** $P < 0.0001$, r: Pearson correlation,
A6MWT: 6MWT in room-air, O6MWT: 6MWT with supplemental oxygen, BMI: body mass index, FVC: forced vital capacity, FEV_1: expiratory volume in one second, $PaCO_2$: arterial carbon dioxide pressure, PaO_2: arterial oxygen pressure, SaO_2: arterial oxygen saturation

ties. Exercise hypoxemia may limit exercise capacity in these patients.[11]

In the present study, the exercise capacity of patients with moderate-to-severe COPD was evaluated by the 6MWT with oxygen. As is reported in the literature, we found oxygen desaturation during 6MWT in 90% of the subjects. When the 6MWT was performed with supplemental oxygen, dyspnea scores were lower and exercise desaturation did not develop. Moreover, O6MWT produced less hemodynamic stress and higher exercise capacity. Eliminating the impairment in oxygen transport and respiratory symptoms, we expected to uncover other possible factors limiting exercise. We found that cardiac function, peripheral muscle strength and psychological factors were sufficient to limit exercise, although the most important factors limiting exercise were respiratory symptoms and limited respiratory capacity. In our opinion, the functional capacity would be misunderstood with the 6MWT if the walking distance was taken as the only outcome parameter for exercise. The 6MWT should be interpreted with supplemental oxygen and in room air. This information is important to give a more complete picture of limited exercise capacity.

Ventilatory reserve depends on two main factors: ventilatory demand and ventilatory capacity. Body weight, metabolic demand, deadspace ventilation, hypoxemia, and level of cardiorespiratory fitness affect ventilatory demand whereas airway resistance, elastic and threshold loads on the respiratory system, ventilatory muscle function, muscle mass, age, and age-related comorbid diseases affect ventilatory capacity. Ventilatory capacity also depends on the lung volume.[9] Therefore, we analysed the relationship between the walking distance and age, body mass index (BMI), respiratory parameters, desaturation, and heart rate and blood pressure. Though the exercise capacity is influenced by several factors, Stel et al determined that performance on the 6MWT can be described by four statistically independent and clinically interpretable factors: endurance capacity, heart rate pattern, perceived symptoms, and impairment of oxygen transport. Therefore, we considered these parameters.[6]

In one study, no relationship was found between the benefit of supplemental oxygen and the age, sex, baseline spirometric values, and gas transfer in the individual patient.[14] Similarly, we found no relationships between O6MWT and age, BMI, or arterial blood gas values. This might be explained by the moderate-to-severe degree of obstruction of our patients. We have also observed that our patients were less distressed during the O6MWT than during the A6MWT.

Table 4. Correlations between clinical factors and the six-minute walk test with supplemental oxygen and room air.

	A6MWT r	O6MWT r
Walking Distance		
Severity of dyspnoea		
Baseline	-0.55**	-0.37*
End	-0.65**	-0.46**
Heart rate		
Baseline	-0.30	-0.22
End	0.12	-0.37
Systolic blood pressure		
Baseline	0.08	0.12
End	-0.14	0.20
SpO_2		
Baseline	-0.17	0.47**
End	0.35	0.34*
Severity of leg fatigue		
Baseline	0.22	0.37*
End	0.27	0.42*

* Significant at the 0.05 level ($0.01 \geq P < 0.05$), ** $P \leq 0.002$, r: Pearson correlation, A6MWT: 6MWT in room air, O6MWT: 6MWT with supplemental oxygen, SpO_2: pulsed oxygen saturation.

Some articles have reported that the FEV_1 and/or FEV_1/FVC ratio are sensitive parameters to predict exercise-induced desaturation.[23] It has been found that FEV_1 impairment and perceived breathlessness are correlated with walking distance in patients with COPD.[24] Bauerle et al indicated that expiratory flow rates during expiration were significantly influenced by measurement of the change in FEV_1 and that the ventilatory response to exercise might be helpful in assessing the mechanism of disability in this disease.[10]

Fujimoto et al. found that in patients with COPD of three different obstruction degrees and with mild hypoxemia that the improvement in exercise performance with oxygen was more prominent in the moderate-to-severe groups than in the mild group, and correlated negatively with $\%FEV_1$, but was not associated with PaO_2 at rest or the degree of desaturation during the walking test.[25] In the present study, we found no association between A6MWT and FEV_1, PaO_2 and desaturation parameters. There was no relationship between O6MWT and resting arterial blood gas values (PaO_2, $PaCO_2$), but the fact that O6MWT is correlated with $\%FEV_1$ and %FVC and the desaturation rate appearing during walking led us to conclude that O6MWT is a more appropriate test battery in evaluating exercise capacity in patients with severely limited ventilation capacity.

It was determined that the benefit of supplemental oxygen was higher in patients with severe desaturation and obstruction, but lower in patients with milder COPD.[25] Therefore, we suggest that the effect of oxygen is associated with the degree of obstruction because of the association of O6MWT and $\%FEV_1$ and the pulsed oxygen saturation value, which is related to the severity of the obstruction. Davidson et al. stated that this benefit cannot be clearly predicted by the results of respiratory function tests and blood gas analyses, and that a trial of oxygen is warranted in any severely dyspneic patient.[15] Despite this, we found that the benefits of supplemental oxygen were related to pulmonary function parameters. Consequently, O6MWT results might be a criteria to be considered when prescribing oxygen therapy for patients with moderate-to-severe COPD. Leach et al noted that the walking distance increased and dyspnea decreased and that supplemental oxygen prevented desaturation during the O6MWT ($P<0.001$).[14] Consequently, we found that supplemental oxygen prevented exercise-induced oxygen desaturation.

McDonald et al found that improvement in exercise performance while breathing oxygen could not be predicted by the magnitude of drop in SaO_2 with exercise.[26] In contrast, Stel et al found that the change of walking distance significantly correlated with change in desaturation ($r=0.43$, $P=0.005$), but not with the change in maximal heart rate and dyspnea during the test. Only the change in desaturation remained a significant predictor of change in walking distance in a multiple regression analysis ($R2=0.48$, $P=0.001$).[6]

Dean and co-workers found that two of four patients who had a 100% or greater improvement in endurance exercise on a cycle breathing 40% oxygen exhibited no fall in SaO_2 while exercising in room air.[13] We found no relationship between baseline pulsed oxygen saturation and the 6MWT, but the correlation between the O6MWT and pulsed oxygen saturation suggested the benefit of supplemental oxygen and led us to consider the pulsed saturation measurement as a decision criteria. The severity of dyspnea at the end of the A6MWT was found to be higher in patients with moderate-to-severe COPD, suggesting some relationship between dyspnea and exercise-induced desaturation.[2]

There are numerous studies in the literature indicating that exercise tests performed with supplemental oxygen increase exercise capacity, decreass dyspnea severity and cause small decreases in oxygen saturation in patients with COPD.[11-13,15,26,27] Controversially, Nandi et al noted no increase in exercise capacity or decrease in severity of dyspnea with 6MWT with oxygen administration in patients with COPD and exercise-induced oxygen desaturation.[16] In contrast, we administered supplemental oxygen throughout the test. As the A6MWT showed a relationship with only severity of dyspnea, the O6MWT correlated with dyspnea severity and pulsed saturation, heart rate and leg tiring, which could indicate that this test was more sensitive to the respiratory stresses.

It has been suggested that the mechanisms leading to improvement in exercise tolerance as a consequence of supplemental oxygen are multifactorial. These factors include relief of dyspnea, prevention of desaturation during exercise, improvement in hemodynamic stress, and improved oxygen delivery and oxidative metabolism in respiratory and peripheral muscles during exercise.[28,29] The O6MWT may provide information on limiting factors.

According to our results, the increased exercise capacity obtained with the O6MWT in moderate-to-severe COPD with mild hypoxemia could be related to the fact that (1) supplemental oxygen prevented exercise-induced desaturation by improving oxygen transport, (2) supplemental oxygen decreased severity of dyspnea and hemodynamic stress and thus supported the patient psychologically to overcome their fear of effort, and (3) supplemental oxygen might delay the formation of lactic acid and hence might have had an effect on leg tiring. The results of our study showed that exercise limitation could be attributed to the respiratory system rather than peripheral muscle strength and that by causing lesser hemodynamical stress, the O6MWT accurately determined the exercise capacity in moderate-to-severe COPD with mild hypoxemia.

In summary, the O6MWT can be considered as a submaximal exercise test and used in the routine evaluation of the exercise capacity in patients with moderate-to-severe COPD and/or other cardiopulmonary patients that bear a high risk of oxygen desaturation during exercise and who cannot perform or complete the 6MWT due to their respiratory symptoms.

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