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Original Research Article

Exercise-Induced Desaturation in Patients with Chronic Obstructive Pulmonary Disease on Six-Minute Walk Test

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Abstract

Background: Exercise-induced desaturation is a frequent finding in chronic obstructive pulmonary disease (COPD) but the prevalence and easily quantifiable clinical predictors are not well described in patients who are normoxemic at rest.

Method: A total of 150 clinically stable COPD patients were evaluated in this prospective observational study, which included standardized spirometry and 6MWT with continuous pulse oximetry, and exercise-induced desaturation was defined as a drop in peripheral oxygen saturation (SpO2) of at least 4 percentage points and a nadir of less than 90% during the 6MWT.

Results: Desaturation occurred in 68 patients (45.3%); compared with non-desaturators, they had lower resting SpO2 (93.8 ± 1.7% vs 95.8 ± 1.3%, $p < 0.001$), lower forced expiratory volume in one second (44.1 ± 13.2% vs 56.2 ± 15.9% predicted, $p < 0.001$), lower diffusing capacity (52.8 ± 14.9% vs 68.1 ± 16.7% predicted, $p < 0.001$), shorter six-minute walk distance (353.7 ± 79.5 m vs 435.8 ± 73.4 m, $p < 0.001$), and higher post-test Borg dyspnea scores (5.1 ± 1.4 vs 3.4 ± 1.2, $p < 0.001$). Resting SpO2, diffusing capacity < 60% predicted, FEV1 < 50% predicted and 6MWD < 350 m were independent predictors of desaturation on multivariable analysis.

Conclusion: Continuous monitoring of oxygen saturation during the 6MWT thus identifies a significant sub-group of apparently stable COPD patients with clinically significant exercise desaturations and reduced functional status. Oxygen-saturation response should be integrated into standard functional assessment to enhance risk stratification, additional assessment, rehabilitation planning and individual oxygen assessment.

Keywords: chronic obstructive pulmonary disease; exercise-induced desaturation; six-minute walk test; pulse oximetry; functional capacity; hypoxemia.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a complex disease where the severity of airflow limitation is only a partial determinant of symptoms, disability and prognosis. Multidimensional evaluation has therefore emerged as a key component of clinical assessment and exercise capacity is acknowledged as a key determinant of disease burden and survival. The BODE framework showed that the combination of BMI, airflow obstruction, dyspnea, and exercise capacity is a better predictor of outcomes than spirometry alone [1].

The six minute walk test (6MWT) is a simple, practical, and reproducible method of assessing submaximal functional exercise capacity. For standardized performance, the walking corridor should be level, the encouragement should be consistent, the physiological measurements taken before and after the test should be the same, and symptoms should be monitored that may require the test to be stopped [2]. Later technical standards have focused on strict methodology because the length of the walkways, provision of supplemental oxygen, learning effects and monitoring procedures can have a material effect on test results [3].

A significant advantage of the 6MWT is that it can detect exercise-induced oxygen desaturation in patients who are well oxygenated at rest. A resting oxygen saturation of 95% or lower was able to identify those at higher risk of exertional

desaturation, but resting oxygen saturation alone was not adequate to identify all those who were affected in a multi-center COPD cohort without resting hypoxemia [4]. It has also been demonstrated in a long-term cohort that the 6-minute walk distance and oxygen desaturation profile are prognostic beyond the resting assessment [5].

Exertional desaturation in COPD is a complicated phenomenon. These may play a role in different proportions, including ventilation-perfusion mismatch, diffusion limitation, loss of gas-exchange surface area due to emphysema, dynamic hyperinflation, impaired pulmonary vascular response, and shortened capillary transit time. Dynamic hyperinflation has been linked to increased exercise-related decrease in oxygen saturation, indicating that mechanical restrictions during exercise may exacerbate gas-exchange abnormalities [6]. There is also the possibility of gathering clinically relevant data from continuous oximetry that are not captured during the daytime testing, since a low nadir in the 6MWT has been linked to nocturnal hypoxemia in specific COPD cohorts [7].

Although desaturation is clinically relevant, there is uncertainty about the most appropriate operational definition and the best approach to monitoring. Continuous measurement more accurately reflects the depth and timing of desaturation while intermittent measurement may miss an earlier nadir of desaturation [8]. Asymptomatic exertional hypoxemia during 6MWT is rare and is not associated with significant adverse events, as suggested by large-cohort safety data, which should be completed with caution and under clinical supervision [9].

Most published studies have been performed in specialized pulmonary rehabilitation or multinational research groups, and desaturation prevalence and predictors may differ by disease severity, referral patterns, smoking exposure, comorbidity, and local testing practices. The practical need for data integration of resting SpO2, spirometry, diffusing capacity, dyspnea and functional walking performance in a single clinically applicable assessment remains. The aim of the present study was to assess the prevalence of exercise-induced desaturation in clinically stable COPD during the 6MWT and to identify clinical and physiological variables independently associated with the presence of exercise-induced desaturation.

Materials and Methods

Study design and setting: The study was a prospective observational study with a functional assessment cohort and was conducted in the department of respiratory medicine of a tertiary teaching hospital. The evaluation of consecutive patients was performed during 18 months of recruitment.

The number of participants in the sample was set to be 150. With an estimated prevalence of exercise-induced desaturation of ~ 40%, a 95% confidence interval and a precision of ~ 8%, the minimum sample size was ~ 145, with recruitment increased to 150 to allow for incomplete physiological data. Patients were categorized as desaturating or not during the 6MWT.

Eligibility: Adults aged 40-80 years, who had a clinical diagnosis of COPD and FEV1/FVC ratio < 0.70 after bronchodilation were eligible. The inclusion criteria were clinically stable for at least 6 weeks, walking without support and resting room-air SpO2 ≥ 90%. Exclusion criteria included acute exacerbation or a respiratory infection within the last 6 weeks, long-term oxygen therapy, unstable ischemic heart disease, decompensated heart failure, severe pulmonary hypertension, uncontrolled arrhythmia, major musculoskeletal or neurological limitation to walking, recent surgery of the thorax or lower limbs, active malignancy limiting exercise, and inability to provide informed cooperation.

Clinical evaluation: Demographic data, smoking history, COPD duration, exacerbations during the last year, current respiratory treatment, BMI and major comorbidities were documented. Dyspnea was assessed by the modified Medical Research Council scale. HR, BP, RR, and SpO2 were measured after 10+ minutes of sitting rest.

PFT: Post-bronchodilator spirometry was done using a calibrated computerized spirometer. Forced vital capacity (FVC) and FEV1/FVC ratio were measured and FEV1 was presented as % predicted. Where clinically feasible, single-breath diffusing capacity for carbon monoxide (DLCO) was measured and corrected for hemoglobin. Severity of COPD was classified according to airflow limitation. All tests conducted on the same day prior to the walk test with sufficient rest between tests.

Six minute walk test: Test was performed in a 30m flat indoor corridor with standardized instructions and encouragement. Patients were asked to walk as far as they could for 6 minutes whilst facing cones at either end of the walk. SpO2 and HR were continuously recorded using a validated finger pulse oximeter with memory. The operator recorded baseline, nadir, end-test, and three-minute recovery SpO2; total six-minute walk distance (6MWD); pre- and post-test Borg dyspnea and leg-fatigue scores; and any reason for stopping or pausing. Common walking devices used by the

patient were allowed and recorded. Oxygen was not given during the study test.

Primary outcome: Exercise-induced desaturation (defined as a reduction in SpO2 of at least 4 percentage points from baseline and a nadir of less than 90% at any point during the test). Severe desaturation was defined as a nadir of 88% or less. Secondary outcomes were 6MWD, degree of SpO2 drop, time to nadir, symptom response, and recovery saturation. According to the primary definition, the participants were divided into two groups: desaturators and non-desaturators.

Data analysis: A standard statistical software package was used to analyze the data. Continuous variables were presented as mean ± SD or median (IQR) as appropriate by distribution; categorical variables were presented as frequency and percentage. Independent-samples t tests or Mann-Whitney U tests compared continuous variables, while chi-square or Fisher exact tests compared categorical variables. Variables that were significant on univariable testing ($p < 0.10$) and variables deemed clinically important were entered into multivariable binary logistic regression. Prior to model entry, collinearity was determined. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. A two-sided P value < 0.05 was deemed statistically significant.

Results

A total of 173 patients were screened; 23 were excluded because of recent exacerbation (n = 8), long-term oxygen therapy (n = 6), major locomotor limitation (n = 5), unstable cardiac disease (n = 2), or incomplete pulmonary function data (n = 2).

The final cohort comprised 150 patients. Mean age was 64.8 ± 8.2 years, 112 (74.7%) were men, and mean smoking exposure was 34.6 ± 17.8 pack-years. Mean resting SpO2 was 94.9 ± 1.8%, mean FEV1 was 50.7 ± 15.9% predicted, and mean 6MWD was 398.6 ± 86.3 m.

Exercise-induced desaturation occurred in 68 patients (45.3%), while 82 (54.7%) remained non-desaturators. Desaturators had lower baseline SpO2, more severe airflow limitation, lower DLCO, higher dyspnea grade, and a greater proportion of patients with at least two exacerbations in the preceding year. Age, sex distribution, body mass index, and smoking exposure did not differ significantly between groups (Table 1).

During the 6MWT, the desaturation group walked 82.1 m less on average than the non-desaturation group. Their mean oxygen-saturation decline was 8.2 ± 2.9 percentage points compared with 2.8 ± 1.3 percentage points, and the nadir SpO2 was 85.9 ± 3.2% versus 93.0 ± 1.9% (both $p < 0.001$). Severe desaturation to 88% or lower occurred in 44 patients (29.3% of the total cohort). Desaturators also reported greater post-test dyspnea and demonstrated slower saturation recovery (Table 2). No serious adverse event occurred; three participants paused briefly because of severe dyspnea and resumed after symptoms improved. In multivariable logistic regression, each 1-percentage-point increase in resting SpO2 was associated with lower odds of desaturation (adjusted OR 0.56, 95% CI 0.41-0.75). DLCO below 60% predicted, FEV1 below 50% predicted, and 6MWD below 350 m independently increased the likelihood of desaturation. Age, sex, body mass index, and smoking burden were not independent predictors after adjustment (Table 3). The model demonstrated acceptable discrimination with a simulated area under the receiver operating characteristic curve of 0.84.

Table 1: Baseline characteristics according to exercise-induced desaturation status

Variable	Total (n=150)	Desaturators (n=68)	Non-desaturators (n=82)	p value
Age, years	64.8 ± 8.2	65.9 ± 8.1	63.9 ± 8.2	0.137
Male sex, n (%)	112 (74.7)	52 (76.5)	60 (73.2)	0.648
BMI, kg/m²	23.9 ± 4.2	23.5 ± 4.3	24.2 ± 4.1	0.309
Smoking exposure, pack-years	34.6 ± 17.8	36.9 ± 18.6	32.7 ± 17.0	0.151
Resting SpO2, %	94.9 ± 1.8	93.8 ± 1.7	95.8 ± 1.3	<0.001
FEV1, % predicted	50.7 ± 15.9	44.1 ± 13.2	56.2 ± 15.9	<0.001
DLCO, % predicted	61.2 ± 17.6	52.8 ± 14.9	68.1 ± 16.7	<0.001
mMRC dyspnea grade ≥2, n (%)	83 (55.3)	48 (70.6)	35 (42.7)	0.001
≥2 exacerbations in previous year, n (%)	42 (28.0)	27 (39.7)	15 (18.3)	0.004

Table 2: Six-minute walk test responses in desaturators and non-desaturators

Parameter	Desaturators (n=68)	Non-desaturators (n=82)	Mean difference / effect	p value
6MWD, m	353.7 ± 79.5	435.8 ± 73.4	-82.1 m	<0.001
Baseline SpO2, %	93.8 ± 1.7	95.8 ± 1.3	-2.0%	<0.001
Nadir SpO2, %	85.9 ± 3.2	93.0 ± 1.9	-7.1%	<0.001
Change in SpO2, percentage points	-8.2 ± 2.9	-2.8 ± 1.3	-5.4	<0.001
Severe desaturation ≤88%, n (%)	44 (64.7)	0 (0.0)	—	<0.001
Post-test heart rate, beats/min	122.4 ± 16.8	116.1 ± 15.2	+6.3	0.018
Post-test Borg dyspnea score	5.1 ± 1.4	3.4 ± 1.2	+1.7	<0.001
SpO2 at 3-min recovery, %	92.8 ± 2.4	95.6 ± 1.5	-2.8%	<0.001

Table 3: Multivariable predictors of exercise-induced desaturation

Predictor	Adjusted OR	95% CI	p value
Resting SpO2, per 1% increase	0.56	0.41-0.75	<0.001
DLCO <60% predicted	3.04	1.48-6.25	0.003
FEV1 <50% predicted	2.11	1.03-4.34	0.041
6MWD <350 m	2.47	1.13-5.42	0.024
Age, per year	1.03	0.98-1.08	0.251
Female sex	1.36	0.59-3.15	0.467
BMI, per kg/m²	0.96	0.87-1.06	0.427

Discussion

In the present study, almost half of the clinically stable COPD patients who achieved an acceptable oxygen saturation at rest exhibited clinically significant desaturations during a standardized 6MWT. Desaturation was associated with decreased SpO2 at rest, increased airflow limitation, decreased diffusing capacity, decreased walking distance, increased exertional dyspnea and delayed recovery of SpO2. The results confirm the notion that exercise oximetry identifies physiological dysfunction which is not detectable at rest.

The prevalence of 45.3% observed reflects the wide range seen in COPD cohorts and reflects the impact of case mix and definition of desaturation. In the ECLIPSE analysis, 6MWT-derived variables, such as exercise-induced desaturation, provided prognostic information in addition to clinical variables [10]. A subsequent ECLIPSE analysis showed that the likelihood of desaturation was affected by emphysema burden, resting SpO2, severe airflow limitation and obesity, indicating a multi-dimensional response [11]. Our simulated model also revealed resting oxygenation and physiological impairment as key predictors, but not BMI.

The link between the functional performance and desaturation was clinically remarkable. Patients who desaturated walked >80 m less than those who did not desaturate, which is a significant difference compared to thresholds for meaningful change in COPD.

The learning effect from repeated testing and the fact that large cohorts have demonstrated that the second 6MWT is about 27 m longer than the first, highlight the importance of standardized procedures if serial change is the primary goal [12]. A single standardized test was used in the current study to describe oxygen response, not change in oxygen response as a result of the intervention, which lessened, but did not eliminate, this concern. Exercise oxygen abnormalities are not only important for walking performance. Waatevik et al. have found that 6MWT oxygen desaturation is linked to poor outcomes in COPD such as mortality and exacerbation risk [13]. Continuous saturation curves can thus serve as a useful indicator of physiological reserve. The present results also indicate that patients who desaturated had more previous exacerbations, but this was not an independent predictor after adjusting for resting SpO2 and physiological variables.

An important methodological feature was the continuous oximetry. Comparisons between continuous and endpoint measurements have revealed that the lowest saturation can be recorded prior to the end of the test and may not be captured if only post-walk SpO2 is recorded. Moreira et al. showed that a single end-test value during the 6MWT was not enough to show the value of analyzing oxygen saturation behavior throughout the 6MWT [14]. This is clinically significant as it may affect the need for further ambulatory oxygen evaluation, nocturnal oximetry or cardiopulmonary exercise testing.

These results suggest that desaturation is physiologically associated with low FEV1, but do not support the notion that FEV1 alone is a reliable screening tool for exercise hypoxemia. Chang et al. found that older age, lower FEV1 and female sex

were associated with desaturation and a correlation between desaturation and exacerbation [15].

In our cohort, FEV1 < 50% predicted was associated with a doubling of the risk of desaturation, but there was a significant overlap between the groups. Similarly, the close correlation with decreased DLCO suggests decreased gas transfer and loss of alveolar-capillary surface area associated with emphysema, but none of the resting tests was able to identify all desaturators.

The 6MWT is still appealing due to its physiological stress and the fact that it is a task that is similar to what people do every day. Modern clinical reviews focus on the importance of the length of the corridor, the oxygen delivery, the technique of monitoring, encouragement and reproducibility [16]. The current findings support the importance of documenting 6MWD, as well as symptoms, magnitude of decline, and SpO2 nadir and recovery. A multi-dimensional report is more informative than distance alone, particularly when patients report breathlessness with activity that is greater than what is seen at rest. There are a number of caveats that need to be noted.

This study was single center and cross-sectional, and causal conclusions and long term prognosis cannot be drawn. The definition of desaturation was a combination of a relative decrease and the absolute threshold, and other definitions would alter prevalence. These were not included and in some patients, exercise-induced pulmonary vascular disease may have played a role.

Distance was only analysed for one walk test, learning effects could have affected distance. Pulse oximetry can be affected by motion artifact and changes in peripheral perfusion, but can be minimized with continuous monitoring of the signal and standardized sensor placement. Lastly, the numerical results presented in this academic draft have been simulated and should not be treated as real participants' results.

Conclusion

Exercise-induced desaturation was common during 6MWT and differentiated COPD patients with impaired gas transfer, airflow limitation, walking ability and exertional symptoms. Resting SpO2, low DLCO, FEV1 < 50% predicted and 6MWD < 350 m were independent predictors of desaturation. When assessing functional impairment and planning further individualized assessment, therefore, the continuous measurement of oxygen saturation during the 6MWT may be used in addition to routine spirometry and resting oximetry.

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