Original Article

Exercise-induced desaturation in patients with chronic obstructive pulmonary disease on six-minute walk test

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ABSTRACT

Background and Objectives: Exercise-induced desaturation (EID) is associated with increased mortality in chronic obstructive pulmonary disease (COPD). However, the relationship of EID with anthropometric and clinical parameters of resting pulmonary function test and six-minute walk test (6MWT) in COPD remains unclear. The study was designed to assess the correlate of EID and to identify various possible predictors of EID in stable normoxemic patients of COPD. **Materials and Methods:** Sixty patients with stable COPD diagnosed and staged as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines underwent 6MWT. A drop in standard pulse oximetry (SpO_2) of $\geq 4\%$ or nadir up to $\leq 88\%$ was defined as EID. Based on EID during 6MWT, two groups were formed: desaturators (DS) and nondesaturators (NDS). DS and NDS were compared for baseline and clinical characters by the Student's *t*-test while Pearson and Spearman rho correlation coefficient assessed strength of the association of anthropometric and clinical variables with EID. The predictors of EID were identified by logistic regression and receiver operator curve analysis. **Result:** Out of 60 patients with stable COPD, 33 patients desaturated on exercise ($n = 33/60$). DS had significantly lower values of FEV_1 ($P < 0.001$), FVC ($P < 0.01$) FEV_1/FVC ($P < 0.01$) compared to NDS. EID had significant negative correlation with FEV_1 ($r = 0.31$, $P < 0.01$), resting oxygen saturation ($r = 0.549$, $P < 0.001$) and 6MWD ($r = 0.511$, $P < 0.001$). Resting $SpO_2 \leq 93\%$ was found to a predictor of EID with a sensitivity and specificity of 83% and 78%, respectively. **Interpretation and Conclusion:** The 6MWT is a safe and sensitive test to recognize EID in normoxic stable COPD patients. Resting oxygen saturation is a good predictor of EID.

KEY WORDS: Chronic obstructive pulmonary disease, exercise-induced desaturation, predictors, 6-minute walk test

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the leading causes of morbidity and mortality worldwide and is projected to become the third leading cause of death and the fifth leading cause of disability-adjusted life years (DALYs) by 2020.[1] Exercise intolerance in COPD patients is an important development in the natural history of COPD and has important implications on the health-related quality of life, hospitalization rate, and survival.[2,3]

Desaturation with exertion is an important clinical parameter in COPD patients and it portends a poorer prognosis for patients of COPD.[4,5] In our study, we considered exercise-induced desaturation (EID) to be any decrease of oxygen saturation measured by standard pulse oximetry (SpO_2) of 4% or more or to a nadir of 88% or less regardless of the baseline SpO_2.[6] EID has been related to reduced exercise performance, faster decline in FEV_1, and increased mortality in patients with COPD.[5,7]

An earlier recognition of the unrecognized EID in nonhypoxemic COPD patients would be helpful in planning oxygen supplementation to maintain normoxemia. Oxygen supplementation during exertion improves exercise performance, reduces dyspnea, and provides better cardiorespiratory adaptations.[8,9]Recently, the National Heart, Lung, and Blood Institute has advocated

the prescription of oxygen therapy to COPD patients who are normoxemic or only moderately hypoxemic at rest, but who do have substantial EID.[10]

The 6MWT is a standardized self-paced walking test that assesses the cardiovascular response during daily activities; it is a submaximal type of exercise in normal individuals but near-maximal in patients with compromised lung functions.[11] The 6MWT has been observed to be more sensitive to identify EID in patients of COPD compared to cardiopulmonary exercise testing.[12] A perusal of the literature shows that majority of earlier studies[13-15] used maximal exercise testing to determine the predictors of EID. We aimed to
    find correlation of EID with variables in the study study and identify
    identify various possible predictors for EID and determine an optimal cutoff value of the predictor.

MATERIALS AND METHODS

The present study was conducted in the outpatient clinic of the Department of Pulmonary Medicine, Indira Gandhi Medical College and Hospital, Shimla, from May 2012 to June 2013. Institutional ethical clearance was obtained for the study by the Institutional Review Board.Sample size and power sample size calculations are based on outcomes of previous studies.[12-16]

The patients were informed about the study protocol and their written consent was obtained. Inclusion criteria were:
- Moderate to severe patients of COPD as per the Global Initiaitive for Chronic Obstructive Lung Disease (GOLD) guidelines, 2011[17]
- Age 40-75 years
- Stable patients of moderate to severe COPD with no acute exacerbation for the past 6 weeks according to GOLD guidelines, 2011[17]
- COPD patients with baseline $SpO_2 \geq 90\%$.

Spirometric examination was done in all the patients by using an electronic portable PC-based spirometer with printer (Vitalograph Compact, Buckingham, England). Spirometric data was recorded as absolute measures and percentages predicted for age, sex, and height indices that were measured in the study. It included FVC (in liters), FEV_1 (in liters), FEV_1/FVC percent predicted (ratio) and peak expiratory flow rate (PEFR) (L/sec). At least three measurements were made for each lung function variable to ensure that reproducibility and best measurement was accepted for final analysis. The patients were staged as per GOLD guidelines[17] (postbronchodilator FEV_1/FVC ratio <70% predicted), mild ($FEV_1 \geq 80\%$ predicted), moderate ($50\% \leq FEV_1 < 80\%$ predicted), severe ($30\% \leq FEV_1 < 50\%$ predicted), and very severe ($FEV_1 < 30\%$ predicted) or $FEV_1 < 50\%$ predicted plus the presence of the signs of chronic respiratory failure.

Those patients with historic or clinical evidence of pulmonary diseases other than COPD, for example, pulmonary hypertension, obstructive sleep/central apnea, were excluded. Since 6MWT is a submaximal exercise testing, the patients with history of unstable angina or myocardial infarction during the previous 1 month and resting heart rate of more than 120 beats/min were excluded.

COPD patients who were having symptomatic neuromuscular, musculoskeletal, and peripheral vascular diseases were not included in the study as it limited the ability to perform the 6MWT, which would lead to erroneous interpretation of 6MWT.

All the patients were screened for the study by a thorough medical examination and routine biochemical investigations such as complete blood count, lipid profile, blood sugar, serum protein, blood urea, serum creatinine, and serum electrolyte profile. Plain chest radiograph, resting electrocardiogram, and echocardiography were also performed to rule out any comorbidity and complications of COPD.

The final study group included 60 normoxic moderate to severe stable COPD patients with 36 males and 24 females. All the patients were subject to detailed demographic history, occupational history, history of smoking habits, biomass exposure, history of disease with treatment history, and history of any comorbidities and complications. The assessment of smoking was done based on the mode of smoking (bidi, cigarette, or hookah), daily consumption, and total number of years smoked.

The 6MWT was performed according to American Thoracic Society (ATS) guidelines, 2002.[11] The subjects were asked to walk at their own pace, along a 30-m long and straight hospital hallway marked at intervals of meter each. Each patient was instructed to walk as much distance as possible in 6 min. No other encouragement was offered to speed up, but the patients were instructed by standardized verbal phrase of encouragement.

The patient was allowed to stop if symptoms of significant distress occurred, like severe dyspnea, chest pain, dizziness, diaphoresis, or leg cramps. However, the patient was asked to resume walking as soon as possible, if he or she could. Oxygen saturation measured as standard pulse oximetry (SpO_2) continuously during the walk byhandheld pulse oximeter (Nonin 8500 M, USA).

Both prewalk and postwalk measurements of oxygen saturation, blood pressure, heart rate, the 6MWT distance, dyspnea, and fatigue were recorded. The dyspnea and fatigue were scored on the Borg scale that has scoring from 0 to 10.[11] The patients were asked to be observed for a 10-15-min period after the test, to assess any possible complications.

Two groups emerged in the study population based on the criteria for EID[6] during the 6MWT; one group was of desaturators (DS) with the change in arterial saturation of ≥4% or nadir of 88% and the second group was of non desaturators (NDS) with a fall in oxygen saturation <4%. We then compared DS with NDS patients of 6MWT.

Statistical analysis

Statistical analysis was done using SPSS version 16 statistical software (SPSS, Inc., Chicago, IL, USA). The DS and NDS groups were compared by the independent Student *t*-test, Chi-square test. Pearson correlation (parametric data) and the Spearman rho test (nonparametric data) were used to assess correlation of EID with demographic and clinical parameters. The binary logistic regression analysis was done for the desaturation and independent variables. The most significant variable of this analysis was subjected to the receiver operating characteristic (ROC) curve from which the area under curve (AUC), sensitivity, specificity, and positive and negative predictive values were determined. Statistical significance was accepted at a $P < 0.05$.

RESULTS

Subject characteristics

The study group included 60 patients (male/female = 36/24) of moderate to severe stable COPD diagnosed and staged as per GOLD guidelines. The study population was mainly from a rural background (91.3%) and the mean age of the study group was 63.77 years. Out of 60 patients with COPD in the study group, 17 (28.3%) were current smokers and 43 (71.7%) were ex-smokers with each patient having a history of smoking of ≥10 packs/year.

The majority of females (n = 23/26) had exposure to biomass (chulha) and a significant proportion of these females (n = 12/22) were exposed to both biomass smoke and tobacco smoke. Males smoked more than females (mean packs smoked per year of 36.7 ± 14.4 v/s 13.4 ± 7.8, $P < 0.05$). Table 1 summarizes baseline demographic data and the risk factor profile of the study population.

The distribution of clinical parameters (pulmonary function and 6MWT) in DS and NDS is shown in Table 2. Comparison of differences between DS and NDS by the independent student's *t*-test revealed that the group with DS had a significant decrease in FEV_1, FVC, and FEV_1/FVC ratio ($P < 0.01$). It was also observed that during 6MWT, DS had lower baseline oxygen saturation, higher degree of dyspnea, and covered less of distance compared to NDS ($P < 0.001$).

Correlation of EID

Pearson moment-product was done to determine the variables that would show correlation to EID in DS and NDS. In DS, EID was associated inversely with baseline SpO_2 (r = -0.605, $P < 0.001$), 6-min walk distance (r = -0.549, $P < 0.001$) and FEV_1 (r = -0.511, $P < 0.05$) whereas in NDS, there existed only a weak inverse association with baseline oxygen saturation ($P < 0.05$) depicted in Table 3.

Logistic regression analysis

The two variables that remained significant were baseline oxygen saturation with highly statistical significance with odds ratio (OR) of 1.37 (95% CI 0.89-2.12) ($P < 0.001$) and FEV_1 with OR of 3.27 ($P < 0.010$). The model with the most baseline oxygen saturation was sensitive and its performance was quantified by calculating the area under the ROC curve [area under the receiver operating characteristic (AUROC) curve] of 0.85 ($P < 0.001$) [Figure 1]. A cut-off baseline SpO_2 ≤93% was then determined that had sensitivity of 83% and specificity of 78% for predicting EID.

Table 1: Sociodemographic and risk factor profiles of DS and NDS in the study population

	Total (*n*=60)	DS (*n*=33)	NDS (*n*=27)	*P*
Age years, mean±SD	63.0±7.7	63.8±6.8	61.9±8.7	0.34
Males, number (percent)	36	16 (44.4%)	20 (55.5%)	0.79
Females, number (percent)	24	17 (70.8%)	7 (29.2%)	
BMI (Kg/m²) mean±SD	21.1±1.7	21.2±1.8	21.0±1.6	0.73
Moderate COPD, number (percent)*	34 (56.67%)	12 (35.3%)	22 (64.7%)	<0.05
Severe COPD number (percent)	26 (43.34%)	21 (80.8%)	5 (19.2%)	
Current smokers number (percent)	17 (28.3%)	8 (47.1%)	9 (56.3%)	0.63
Ex-smokers number (percent)	43 (71.7%)	25 (58.1%)	18 (41.9%)	
Smoking index, packs/year, mean±SD	477.7±140.0	477.7±135.5	451.1±147.9	0.96
Duration of smoking, years	32±1.7	34±4.6	30±4.8	0.45
Biomass exposure number (percent)	51 (85.2%)	28 (54.9%)	23 (45.1%)	0.76

Results shown in median±standard deviation *$P<0.05$. DS: Desaturators, NDS: Nondesaturators, SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, BMI: Body mass index

**Table 2: Clinical characteristics of the study population**

Pulmonary function parameters	Total (*n*=60) Mean±SD	DS	NDS	*P*
FVC (in liters)	1.5±0.4	1.4±0.3	1.7±0.4	<0.01
FEV_1 (in liters)	0.9±0.4	0.8±0.2	1.2±0.5	<0.01
PEFR (in L/sec)	181.8±107.3	178.9±81.4	184.8±62.4	NS
FEV_1/FVC (percent predicted)	58.6±8.3	55.8±8.3	62.4±7.0	<0.01
Baseline SpO_2, percent	93.5±2.07	92.70±2.1	94.59±1.3	<0.001
Postwalk SpO_2, percent	89.2±4.4	86.91±4.6	92.15±1.7	<0.001
Change in SpO_2, percent	4.2±2.9	5.85±3.1	2.33±0.7	<0.001
6MW distance, meters	312.0±21.2	313.1±175.5	333.3±203.3	<0.001
Change in heart rate beats/min	28.7±3.6	28.21±3.7	29.30±3.6	<0.01
Change in dyspnea (Borg scale)	4.2±2.9	0.318±0.3	0.093±0.1	<0.01
Change in fatigue (Borg scale)	0.289	0.507	0.159	NS

Results shown in median±standard deviation as on student's *t*-test. $P<0.01$ is significant, $P<0.001$ is highly significant, NS: Not significant, $P>0.05$. FVC: Forced vital capacity, FEV_1: Forced expiratory volume in one second, PEFR: Peak expiratory flow rate

Table 3: Trends depicting correlates of EID with anthropometric and clinical variables in the study population

Parameters	COPD (*n*=60)	DS (*n*=33)	NDS (*n*=27)
Age, years	0.064	0.052	0.064
Sex,	0.0034	0.038	0.543
Biomass exposure	0.342	0.413	0.131
BMI , Kg/m^2	−0.125	−0.221	−0.24
FVC, in liters	−0.334[†]	−0.240	0.157
FEV$_1$, in liters	−0.324[†]	−0.351[†]	0.266
PEFR, L/sec	−0.249	−0.288	0.057
FEV$_1$/FVC ratio, percent predicted	−0.348[†]	−0.241	−0.065
Baseline SpO$_2$, percent	−0.605[†]	−0.549*	−0.043[†]
6MW distance, meters	−0.579[†]	−0.511*	−0.313
Δ Dyspnea, borg scale	0.223[†]	0.279*	0.301
Δ Fatigue in borg scale	0.289	0.507	0.5
Δ heart rate, beats/min	−0.122	−0.111	0.037

Δ refers to change (postwalk value-prewalk value). [†]*P* is significant at <0.01, *P*<0.001 significance (two-tailed)
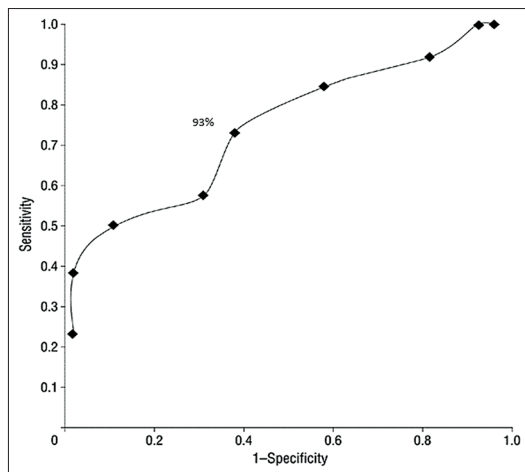
Figure 1: ROC for baseline oxygen saturation via pulse oximetry as a screening test for EID AUROC is 0.85 (95%CI 0.62-0.89); *P* < 0.001

DISCUSSION

Impaired gas exchange is the most commonly encountered functional abnormality in COPD patients. Initially, oxygen desaturation occurs during exercise but with progression of disease, it occurs eventually at rest. EID is frequently observed among patients with COPD. Gestel *et al.*[18] reported a high prevalence of EID of 61.7% among 154 patients with COPD. The mean FEV$_1$ was 43.0% predicted in the study population.

Schenkel *et al.*[19] measured oxygen desaturation in a group of 30 patients with moderate to severe COPD (mean FEV$_1$ 37% of predicted and mean PaO$_2$ 68 mmHg). Oxygen desaturation was defined as a ≥4% decrease in the SaO$_2$. The largest number of desaturations was seen during walking (13.1 desaturations per hour), washing (12.6 desaturations per hour), and eating (9.2 desaturations per hour) than at rest (5.3 desaturations per hour).

Our study also reported a very high frequency of EID. Out of 60 patients in our study, 33 patients (*n* = 33/60), i.e. 55% patients desaturated on 6MWT.

However, the prevalence of EID differs widely in previously established studies.[9,12,15,16,18] This could be explained because of the lack of a uniform definition of EID in patients with COPD or the lack of a standardized exercise protocol to elicit decreases in oxygen levels in individuals with COPD.

The detection of EID is an important event in the natural history of COPD. An earlier mortality has been reported in patients who are normoxic at rest but desaturated on exercise.[20,21] EID is associated with impaired daily physical activity and poor health-related quality of life.[22] Oxygen desaturation during 6MWT is also found to be a predictor of nocturnal hypoxemia.[23] COPD patients with exertional desaturation are at a higher risk of rapid decline in FEV$_1$.[7]

Our study documented that DS had a significant inverse correlation with FEV$_1$, baseline oxygen saturation, and 6-min walk distance [Table 3], signifying a higher degree of airflow obstruction and a lower resting SpO$_2$ limited exercise tolerance evidenced by lesser distance covered during the walk. Other investigators have also documented similar findings.[12-18]

Our study also revealed that dyspnea score was significantly higher in the DS compared to the NDS and it correlated inversely to EID [Table 2]. A similar observation was made by Torres *et al.*;[24] they stated that mMRC dyspnea score negatively correlated with PaO$_2$ (r =-0.59, P < 0.001), and PaCO$_2$ (r = 0.27, P = 0.05) in patients with COPD, suggesting that a higher dyspnea score leads to a greater possibility of exercise desaturation.

The causes for EID in patients with COPD are multifactorial with ventilation-perfusion mismatching, diffusion-type limitation, shunting, and reduced oxygen content of mixed venous blood, all of which contribute to some degree.[4] The increasing severity of COPD and consequently decreasing lung functions contribute to the worsening of SpO$_2$ levels that is further worsened with exercise. Hence, oxygen supplementation has been documented to improve the functional capacity and quality of life of COPD patients.[8]

However, continuous oxygen supplementation is advocated for patients of COPD with resting nonhypoxemia having oxygen saturation ≤88% by the Centers for Medicare and Medicaid Services.[25] Therefore, identifying those nonhypoxemic COPD patients who will be desaturated on exertion is important to prevent the potential adverse effects of hypoxemia.

Therefore, several researchers have tried to determine various predictors of EID, including FEV$_1$, diffusing

capacity of the lung for carbon monoxide (DLCO), and baseline-SpO_2.[12,13,16,18] Owen *et al.*[15] evaluated that a DLCO cutoff of >55% of predicted had 82% sensitivity and 100% specificity for excluding EID. They reported that FEV_1 had 82% specificity for FEV_1, above 55% of predicted. The sensitivity of diffusing capacity with this cutoff point was 68% as compared to 46% for FEV_1. Van Gestel *et al.* observed that the only independent predictor of EID was FEV_1 and the optimal cutoff of FEV_1 was 50% or lower for predicting EID in patients with COPD.

Crisafulli *et al.*[26] indicated FEV_1 <45% predicted in association with resting SpO_2 <95% and PaO_2 <10.0 kPa as determinants of EID. Multivariate regression between anthropometric and functional variables and SpO_2 nadir as the dependent variable indicated that resting saturation of arterial oxygen - SO_2 ($r = 0.65$), PaO_2 ($r = 0.50$), and FEV_1% predicted ($r = 0.41$) significantly predict EID in COPD. They showed that both the resting saturation of arterial oxygen ($r = 0.65$) and FEV_1% ($r = 0.41$) can significantly predict EID in COPD.

Andrianopoulos *et al.*[27] found on a multivariate model that DLCO <50%, FEV_1 <45%, PaO_2 <10 kPa, baseline-SpO_2 <95%, and female sex were the strongest determinants of EID. Baseline oxygen saturation of SpO_2 ≤95% solely was inaccurate to predict EID occurrence among COPD patients but a combination of clinical characteristics increases the odds for EID in COPD.

This observation stands in contrast with our study where we found baseline SpO_2 levels as an independent predictor of EID in patients of COPD. In our study, we found the optimal cutoff of baseline SpO_2 ≤93% with sensitivity of 83% and specificity of 78%.

However, our study is consistent with the study by Knower[16] and colleagues who suggested that a resting SpO_2 of 95% or less is a good screening test for the detection of EID during a 6MWT (sensitivity: 73%; negative predictive value: 84%), especially in patients with a DLCO >36% of the predicted value (sensitivity: 100%; negative predictive value: 100%). Similarly, Khaled and colleagues[28] reported that a baseline SaO_2 <95% had 92.9% sensitivity of predicting EID.

In our study, we also found baseline oxygen saturation as a good predictor of EID; routine use of pulse oximetry on outpatient basis would help to screen all the COPD patients for unrecognized EID, which enhances the validity of our study.

CONCLUSIONS

It is sufficiently evident that desaturation during the 6MWT is a simple and accessible screening test for patients with COPD. Pulse oximetry can be utilized to screen such patients and identify those who might benefit from long-term oxygen therapy. Screening of patients of unrecognized EID in COPD could possibly result in prevention of hypoxemia and its adverse consequences. These results merit further study in a larger prospective patient cohort.

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