Original Research

Clinical Differences in COPD Patients with Variable Patterns of Hypoxemia

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) patients enrolled into the Long-term Oxygen Treatment Trial had hypoxemia at rest, hypoxemia on exertion, or hypoxemia both at rest and on exertion. We hypothesized that patients with different patterns of hypoxemia may have significant differences in clinical features.

Methods: All patients had COPD and oxygen saturation measured by pulse oximetry (blood oxygenation [SpO_2]) at rest and during the 6-minute walk test (6MWT). Hypoxemia at rest was defined as resting SpO_2 between 89-93%. $SpO_2 < 90\%$ for at least 10 seconds and $\geq 80\%$ for at least 5 minutes during ambulation characterized hypoxemia on exertion. Severe exercise hypoxemia ($<80\%$ for >1 minute) was exclusionary.

Results: Of 738 patients studied, 133 (18.0%) had mild-moderate hypoxemia at rest only, 319 (43.2%) had hypoxemia on exertion only, and 286 (38.8%) had hypoxemia at both rest and exertion. Patients with hypoxemia at rest only were more likely to be current smokers, had higher body mass index (BMI) and a higher incidence of self-reported diabetes. Patients with hypoxemia on exertion only were more severely obstructed compared to the other groups. General and disease-specific quality of life scores were similarly impaired in all groups. Quality of well-being scores were more impaired in those with hypoxemia at rest only.

Conclusions: COPD patients with mild-moderate hypoxemia have distinct clinical characteristics based on the pattern of oxygen desaturation at rest and with exertion.

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Introduction

Long-term oxygen treatment (LTOT) has been used for more than 70 years in patients with severe lung disease. Patients with chronic obstructive pulmonary disease (COPD) with severe chronic hypoxemia are one group in which LTOT has demonstrated clinical benefit. In patients with severe resting hypoxemia, 2 landmark studies revealed markedly improved survival in patients treated with LTOT.[1,2]

These results were followed by the widespread use of LTOT in patients with COPD, even when severe and persistent hypoxemia was not present. These data, combined with expert opinion, contributed to the development of clinical guidelines, but many questions and controversies still exist regarding the use of LTOT.[3] In the National Emphysema Treatment Trial, the use of continuous oxygen in patients with resting nonhypoxemic emphysema was associated with increased disease severity and mortality. The increase in mortality was associated with a higher prevalence of exercise desaturation in those using continuous oxygen. It was not clear whether a harmful effect of oxygen therapy contributed to the increased mortality, or whether use of continuous oxygen was a marker of more symptomatic patients who had a greater burden of disease.[4] Additionally, the beneficial or harmful effects of using continuous oxygen therapy in this patient group remained unclear.

In 2016, the Long-term Oxygen Treatment Trial (LOTT) investigators reported that the prescription of LTOT did not result in a longer time to death or first hospitalization than no LTOT, nor did it provide sustained benefit to any of the other measured outcomes in patients with stable COPD and resting or exercise-induced moderate desaturation.[3]

The LOTT cohort presents an opportunity to evaluate the clinical characteristics of patients with COPD who have different patterns of hypoxemia. Many factors may contribute to the differences in hypoxemia at rest or with exertion, such as the severity of airflow obstruction, body habitus, gender, race, smoking status and the presence of comorbidities. We retrospectively examined pre-randomization data of LOTT enrolled individuals to determine if the pattern of hypoxemia was associated with distinct differences in the clinical characteristics of the patients with COPD. These results may be useful in helping clinicians to better understand the oxygenation patterns and associated medical problems of patients with COPD.

Materials and Methods

Patient Population

Patients were recruited to the LOTT if they were 40 years of age or older, had a diagnosis of COPD, and had at least a 10 pack-year history of cigarette smoking. The diagnosis was confirmed by the presence of a post-bronchodilator forced expiratory volume in 1 second (FEV_1) less than or equal to 70% of predicted, and a post-bronchodilator FEV_1/forced vital capacity (FVC) ratio less than 0.70. Patients who had an FEV_1 >70% of predicted could still be included if there was radiologic evidence of emphysema present on imaging studies. Eligibility required dyspnea as measured by the modified Medical Research Council (mMRC) dyspnea

scale (i.e., score of at least 1) and that the dyspnea and lung disease process be dominated by COPD in the judgment of the study physician.

Study eligibility required at least 1 of 2 oxygen saturation criteria:

1) Blood oxygenation (SpO_2) of at least 89% and no greater than 93% while sitting quietly on room air, without pursed lips or hyperventilation during oximetry

2) Resting SpO_2 of 94% or greater and desaturation during exercise as defined by saturation below 90% for at least 10 seconds during the 6-minute walk test (6MWT)

Severe exercise hypoxemia defined as SpO_2 below 80% for at least 1 minute during the 6MWT was exclusionary.

All patients had to be Medicare beneficiaries with both Part A and Part B coverage, be served by the Veteran's Administration, or have insurance or other resources to cover the costs of the trial that would have been typically covered by Medicare. Patients were approved for entry into either treatment group by the study physician, provided informed consent, and were randomized within 60 days of initiating evaluation for eligibility.

Data Collection

The study received approval by the institutional review boards at each of the participating institutions, the LOTT Steering Committee and the National Heart Lung and Blood Institute (IRB Approval #21874). Baseline pre-randomization data were collected for each patient, including room air resting oximetry, room air 6MWT, age, gender, race, spirometry, symptom scores, tobacco and oxygen exposures, the Epworth Sleepiness Score (ESS), and comorbidities.

Data Analysis

For the purposes of this analysis, patients were divided into 3 groups using data collected during the room air resting and room air 6MWT oximetry evaluations. Patients having a resting SpO_2 of at least 89% and no greater than 93% without desaturation below 90% for 10 seconds during the 6MWT were placed in "the hypoxemia at rest only group." Patients with a resting SpO_2 of 89%-93% and saturation below 90% for at least 10 seconds were placed in the "hypoxemia at rest and with exertion group." Patients having a resting oxygen saturation of 94% or greater and desaturation

during exercise as defined by saturation below 90% for at least 10 seconds during the 6MWT were placed in the "hypoxemia on exercise only group."

Characteristics were compared across the 3 hypoxemia groups using the Fisher's exact test for categorical measures and the analysis of variance (ANOVA) for continuous measures. Data are presented using percentages and mean±standard deviation (SD). We present 42 different measures, including demographic, clinical, self-reported comorbidities, and symptom scores. Though p-values are presented primarily for descriptive purposes, a Bonferroni-adjusted significance threshold for these comparisons is $p=0.05/42=0.001$. Analyses were completed using R version 3.3.2 (https://www.r-project.org/) or SAS (Cary, North Carolina).[4]

Results

Of the 738 patients studied, 133 (18.0%) had mild-moderate hypoxemia at rest only, 319 (43.2%) had hypoxemia on exertion only, and 286 (38.8%) had hypoxemia at rest and on exertion. Demographics were similar between groups (Table 1). All 3 groups had a mean 6MWT distance greater than 1000 feet. Patients with hypoxemia on exercise only walked further than patients in the other 2 groups but this was not statistically significant. As expected, resting SpO_2 was different between the groups; patients in the "hypoxemia at rest and with exertion" and "hypoxemia at rest only" groups had lower mean resting SpO_2 (91.8±1.2% and 92.4±0.9%) than patients with hypoxemia on exercise only (95.3±1.3%, p-value <0.001). Mean body mass index (BMI) was elevated in the "hypoxemia at rest only" group compared to the other 2 groups.

Pre-bronchodilator spirometry (Table 1) revealed more severe obstruction in patients with hypoxemia on exercise only compared to the other groups. These patients also were more likely to be using oxygen at the start of LOTT (Figure 1), but this relationship was not significant after Bonferroni adjustment for multiple comparisons. However, they were less likely to be current smokers. ESS revealed that patients with hypoxemia at rest only were more likely to report symptoms of daytime hypersomnolence (Table 2). Similarly, Pittsburgh Sleep Quality Index (PSQI) scores tended to be more impaired in the patients with hypoxemia at rest only group. Although these variables

Table 1. Demographic and Clinical Characteristics

Characteristic	Hypoxemia at Rest Only (N=133)	Hypoxemia at Rest and on Exertion (N=286)	Hypoxemia on Exertion Only (N=319)	P-value
Age (years)	68.5 ± 7.7	68.4 ± 7.0	69.2 ± 7.8	0.36
Male Gender	103 (77%)	213 (74%)	226 (71%)	0.32
BMI (mean)	30.5 ± 6.6	29.5 ± 6.6	27.0 ± 5.9	<0.001
Pack Years Smoked (mean)	64.1 ± 33.7	64.3 ± 37.3	57.7 ± 27.7	0.03
Current Smoker	59 (44%)	79 (28%)	64 (20%)	<0.001
COPD Exacerbation within 3 months	21 (16%)	47 (16%)	70 (22%)	0.15
Race				
Black, African American	9 (7%)	28 (10%)	43 (13%)	0.09
White	122 (92%)	250 (87%)	267 (84%)	0.06
Pre-bronchodilator Spirometry				
FVC (% predicted)	71 ± 19	71 ± 19	71 ± 20	0.89
FEV_1 (% predicted)	46 ± 17	44 ± 16	41 ± 16	0.02
FEV_1/FVC	0.49 ± 0.13	0.46 ± 0.12	0.43 ± 0.13	<0.001
6MWT				
6 Minute Walk Distance (feet)	1004 ± 299	1028 ± 332	1074 ± 328	0.07
Oximetry				
Resting Saturation (%)	92.4 ± 0.9	91.8 ± 1.2	95.3 ± 1.3	<0.001

BMI=body mass index; COPD=chronic obstructive pulmonary disease; FVC=forced vital capacity; FEV_1=forced expiratory volume in 1 second; 6MWT=6 Minute Walk Test

Figure 1. Oxygen Use Prior to LOTT Randomization
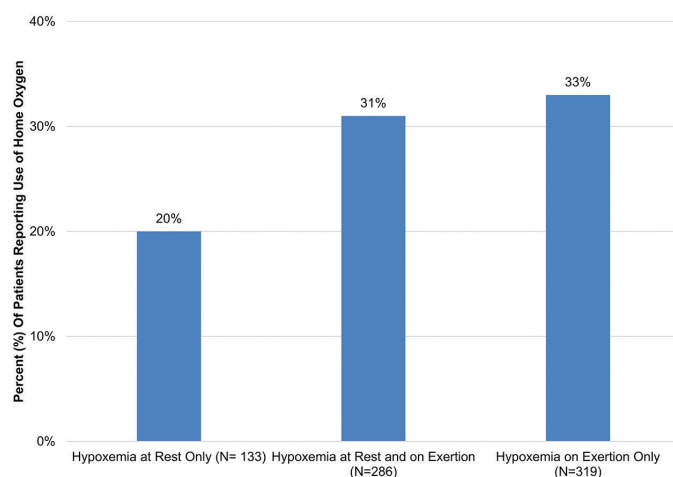
P-value 0.03, but not significant after Bonferroni adjustment for multiple comparisons. LOTT=Long-Term Oxygen Treatment Trial

consistently revealed a trend toward an increased likelihood of sleep-disordered breathing in this group, this relationship was not significant after Bonferroni correction for multiple comparisons.

Other differences existed between the groups

regarding self-reported comorbid diagnoses (Table 3). Patients with hypoxemia at rest only were more likely to suffer from hypertension, hyperlipidemia, diabetes, heart failure, and cardiovascular disease based on a composite variable including myocardial infarction, coronary artery disease, angina, heart failure, and revascularization. Patients with hypoxemia on exercise only were more likely to report a history of anemia. However, after Bonferroni adjustment for multiple comparisons, only a self-reported history of diabetes remained significant.

Symptom scores, as assessed by the mMRC, the St George's Respiratory Questionnaire (SGRQ), the Short Form-36 (SF-36) physical and mental components, and the Hospital Anxiety and Depression Scale (HADS) scores were similarly impaired in all 3 groups (Table 2). However, the Quality of Well-Being average daily score was significantly more impaired in the hypoxemia at rest only group.

Discussion

Patients were included in the LOTT if they met one of the following criteria: moderate hypoxemia at rest

Table 2. Symptom Scores

Symptom Scores	Hypoxemia at Rest Only (N=133)	Hypoxemia at Rest and on Exertion (N=286)	Hypoxemia on Exertion Only (N=319)	*P*-value
Quality of Well-Being Score (range 0-1, MCID 0.03)	0.52 ± 0.12	0.56 ± 0.13	0.57 ± 0.13	<0.001
SGRQ (range 0-100, MCID 4)	52.6 ± 20.1	49.4 ± 18.1	49.5 ± 16.8	0.19
SF-36 Physical Component (range 0-100, MCID 0.5)[a]	33.1 ± 10.1 (N=110)	34.3 ± 8.9 (N=249)	33.6 ± 8.9 (N=257)	0.52
SF-36 Mental Component (range 0-100, MCID 0.5)[a]	48.2 ± 13.3 (N=110)	51.1 ± 12.8 (N=249)	50.8 ± 11.3 (N=257)	0.10
HADS Anxiety ≤ 10[a]	90 (68%) (N=110)	217 (76%) (N=249)	225 (71%) (N=257)	0.31
HADS Depression ≤10[a]	100 (75%) (N=110)	224 (78%) (N=249)	236 (74%) (N=257)	0.77
PSQI (range 0-21, MCID 3)[a]	8.8 ± 4.0 (N=110)	7.5 ± 4.3 (N=249)	7.5 ± 3.9 (N=255)	0.01
Epworth Sleepiness Score				
0-5	46 (35%)	124 (43%)	160 (50%)	0.002
6-10	62 (47%)	99 (35%)	119 (37%)	
11-15	25 (19%)	60 (21%)	40 (13%)	
>15	0 (0%)	3 (1%)	0 (0%)	
modified Medical Research Council Score				
1	30 (23%)	86 (30%)	84 (26%)	0.53
2	46 (35%)	78 (27%)	91 (29%)	
3	46 (35%)	99 (35%)	123 (39%)	
4	11 (8%)	23 (8%)	21 (7%)	

MCID=minimal clinically important difference; SGRQ=St George's Respiratory Questionnaire; SF-36= Short Form 36; HADS=Hospital Anxiety and Depression Score; PSQI=Pittsburgh Sleep Quality Index

[a]Not all sites completed SF-36, HADS and PSQI questionnaires, scores are collected only for patients in the advanced data set.

only, moderate hypoxemia at rest and on exercise, or moderate hypoxemia on exercise only. This patient cohort differs from others in the literature as it included patients with medical comorbidities and patients with hypoxemia at rest or with ambulation, providing a patient cohort more representative of COPD patients encountered by the practicing physician.

Analysis of pre-randomization data of the 738 patients recruited for LOTT revealed significant differences between patients with the 3 patterns of oxygen desaturation. Patients with hypoxemia at rest only were more likely to be current smokers, have a higher BMI, and have a comorbid diagnosis of diabetes than patients in the exercise and resting hypoxemia group and the exercise hypoxemia only group. Cumulative tobacco exposure based on pack years was similar between groups. ESS and PSQI scores also revealed a

trend toward an increase in daytime hypersomnolence. Conversely, patients with hypoxemia on exercise only had more severe obstruction.

There is no firm consensus on the relationship between BMI and smoking, although several trials have linked increased BMI and current heavy smoking.[5-9] These findings corroborate a relationship between increased BMI and current smoking.

The mechanism of hypoxemia in COPD is primarily related to the mismatch of ventilation and perfusion due to airflow obstruction and emphysema.[10] This mechanism is exacerbated during sleep and exercise and causes tissue hypoxemia, which exacerbates or contributes to greater symptom burden.

Skeletal muscle dysfunction associated with tissue hypoxemia specifically exacerbates sleep-disordered breathing, a mechanism that is promoted by the

Table 3. Self-Reported Comorbidities

Characteristic	Hypoxemia at Rest Only (N=133)	Hypoxemia at Rest and on Exertion (N=286)	Hypoxemia on Exertion Only (N=319)	P-value
Diagnosis of OSA	32 (24%)	73 (26%)	60 (19%)	0.12
Prescribed CPAP for OSA	23 (72%)	47 (64%)	41 (68%)	0.75
Cancer	25 (19%)	54 (19%)	64 (20%)	0.93
Anemia	13 (10%)	47 (16%)	60 (19%)	0.05
Depression	46 (35%)	110 (38%)	98 (31%)	0.14
GERD or PUD	59 (44%)	125 (44%)	139 (44%)	0.99
Kidney Disease	10 (8%)	34 (12%)	27 (8%)	0.26
Liver Disease	15 (11%)	37 (13%)	26 (8%)	0.15
Diabetes	40 (30%)	62 (22%)	47 (15%)	<0.001
Cerebrovascular Disease / Stroke	12 (9%)	20 (7%)	25 (8%)	0.75
Angina	22 (17%)	27 (9%)	35 (11%)	0.11
Connective Tissue Disease	18 (14%)	25 (9%)	21 (7%)	0.06
Coronary Artery Disease	39 (29%)	60 (21%)	67 (21%)	0.12
Coronary Artery Revascularization	25 (19%)	43 (15%)	47 (15%)	0.53
Heart Failure	20 (15%)	26 (9%)	22 (7%)	0.03
Hyperlipidemia	71 (53%)	138 (48%)	150 (47%)	0.01
Hypertension	97 (73%)	176 (62%)	181 (57%)	0.005
Myocardial Infarction	25 (19%)	37 (13%)	35 (11%)	0.09
Peripheral Vascular Disease	14 (11%)	25 (9%)	29 (9%)	0.84
Cardiovascular Disease[a]	58 (44%)	89 (31%)	88 (28%)	0.004

OSA=obstructive sleep apnea; CPAP=continuous positive airway pressure; GERD= gastro-esophageal reflux disease; PUD=peptic ulcer disease

[a]Composite variable of the following: angina, coronary artery disease, coronary artery revascularization, heart failure, congestive heart failure, and myocardial infarction.

worsening of hypoxemia during sleep, particularly rapid-eye-movement sleep.[11]

Alveolar hypoxemia also contributes to the development of pulmonary hypertension, which increases in prevalence with increasing obstruction.[12] Pulmonary hypertension can then progress to overt right heart failure, or cor pulmonale. This reduces cardiac function and increases peripheral edema, which contributes to respiratory skeletal muscle dysfunction that is already present due to other factors such as hyperinflation, disuse atrophy, undernutrition, hypoxemia and hypercapnia. Together these factors can contribute to the development of hypoventilation.[13]

The population of patients included in LOTT differs from the population of patients with mild to moderate hypoxemia previously described. Table 4 compares baseline characteristics between the resting hypoxemia only group in the LOTT population and patients from 3 previously published cohorts of patients with mild to moderate hypoxemia at rest.[14-16] The LOTT subgroup had a higher mean BMI and a lower mean degree of airway obstruction, but on average, had a similar degree of resting hypoxemia. In the LOTT group, the likelihood of hypoventilation as a result of BMI and an increased incidence of cardiovascular disease is greater and may be a significant factor in the development of hypoxemia compared to patient populations with lower BMI but more obstruction where ventilation/perfusion mismatch may be the predominant cause of hypoxemia.

Increased body weight, as measured by BMI, results in decreased functional residual capacity (FRC) and expiratory reserve volume as movement of the respiratory muscles and diaphragm is impaired by increased adiposity of the thorax and abdomen.[17,18] This is detectable even with small increases in BMI, and as BMI increases, premature airway closure during tidal breathing is also affected. Both mechanisms are

Table 4. Comparisons of Baseline Characteristics of the Hypoxemia at Rest Only Group with Previously Studied Populations

Characteristic	LOTT Hypoxemia at Rest Only (n=133)	Chaouat et al (n=35)	Ringbaek et al (n=23)	Górecka et al (n=67)
Age (years)	68.5 ± 7.7	63 ± 8	68.6 ± 7.8	62.4 ± 8.2
Male Gender	103 (77%)		10 (44%)	52 (78%)
BMI (mean)	30.5 ± 6.6	26.4 ± 4.9	25.6 ± 6.1	23.3 ± 4.0
Pack Years Smoked (mean)	64.1 ± 33.7		36.3 ± 14.0	
Current Smoker	59 (44%)		3 (14%)	
Prebronchodilator Spirometry				
FVC (% predicted)	71 ± 19	72 ± 19		50.0 ± 11.6
FEV_1 (% predicted)	46 ± 17	39 ± 16	31 ± 12	29.8 ± 10.3
FEV_1/FVC	0.49 ± 0.13	0.41 ± 0.13		40.8 ± 12.1
6MWT				
Resting Saturation (%)	92.4 ± 0.9		93.7 ± 1.9	

Populations: Chaouat et al,[14] Ringbaek et al,[15] Górecka et al[16]

associated with hypoxemia in patients with increased BMI.[19]

Our findings show that patients with hypoxemia at rest only have increased BMI, which may contribute to resting hypoxemia via the mechanisms described above, when compared to patients with exercise hypoxemia with or without resting hypoxemia. Patients with cardiovascular disease (especially congestive heart failure with reduced ejection fraction and pulmonary hypertension) are likely to be less able to compensate for gas exchange abnormalities caused by coexisting COPD. This study differs from previous cohorts in that these patients were not excluded, thus providing relevant information for patients treated in general clinical practice. This group, having less severe obstruction than the other groups, is equally impaired due to the mechanisms discussed above.

COPD patients with hypoxemia on exercise only have been shown in prior studies to have increasing respiratory limitation during exercise testing with increasing obstruction.[20] Worsened hypoxemia on exercise has been correlated with increased emphysema.[21] Our findings did not assess the degree of emphysema, but did corroborate the correlation between exercise-induced hypoxemia and increased airway obstruction.

Study Limitations
A limitation of this study is that it does not include more comprehensive physiologic data (e.g., lung volumes, arterial blood gases and diffusion capacity) to provide more information on the differences between these groups. Self-reported cardiac comorbidities, while a trend was present between groups, are less informative than more objective data. These data would provide direct evidence of cardiac function, which is unknown in these groups. Additional data could also elucidate the prevalence and severity of pulmonary hypertension and cor pulmonale in these groups. Similarly, although the degree of expiratory airflow obstruction was different between groups, the degree of emphysema, as measured by computed tomography, lung volumes, and diffusion capacity, is not known. Further research should address these questions.

Increased indices of sleep-disordered breathing as measured by questionnaires had a trend towards association with hypoxemia at rest only in this study. However, polysomnography was not available for this analysis. Therefore, the true prevalence of untreated obstructive sleep apnea is unknown. Patients with obstructive sleep apnea are likely to have increased oxygen needs during sleep, which were not assessed by the study and could be clinically important.[22] The prevalence of Obesity Hypoventilation Syndrome, which also would be an important contributor to gas exchange abnormalities, is not known in this cohort.

Measurement of oxygen saturations at rest and with exertion is required to distinguish these groups;

further studies including pulmonary function tests and chest imaging will be required to better determine distinguishing clinical characteristics between them.

Conclusion

Patients with COPD enrolled in LOTT with hypoxemia at rest only were more likely to be current smokers and had more comorbid diagnoses of obesity and diabetes than patients with hypoxemia on exercise only. Patients with hypoxemia on exercise only had more severe obstruction than patients with hypoxemia at rest only. General and disease-specific quality of life scores including the HADS, SGRQ, and the SF-36 were impaired but similar between groups, except that quality of well-being scores were more impaired in the hypoxemia at rest only group. Differences in clinical, demographic, and physiologic parameters exist between COPD patients with different patterns of hypoxemia.

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Declaration of Interest
None of the authors have real or apparent conflicts of interest including financial and consulting relationships to declare.

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