Characteristics of Alpha-1 Antitrypsin–Deficient Individuals in the Long-term Oxygen Treatment Trial and Comparison with Other Subjects with Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: Alpha-1 antitrypsin deficiency (AATD) predisposes to chronic obstructive pulmonary disease, but is underrecognized. Oxygenation and exercise desaturation in individuals with AATD-associated chronic obstructive pulmonary disease has been sparsely studied. The Long-term Oxygen Treatment Trial (LOTT) permits comparing these features of individuals with AATD with alpha-1 antitrypsin–replete (called "usual chronic obstructive pulmonary disease") LOTT participants.

Objectives: Compare demographic, clinical, baseline oxygenation, and exercise desaturation features in participating AATD subjects with those of other LOTT subjects.

Methods: LOTT is a multicenter randomized controlled trial comparing use of supplemental oxygen versus not in subjects with chronic obstructive pulmonary disease and moderate hypoxemia (resting oxygen saturation as measured by pulse oximetry, 89–93%) or normal oxygen saturation at rest and significant exercise desaturation.

Measurement and Main Results: Among the 597 LOTT participants with nonmissing alpha-1 antitrypsin levels, 11 (1.8%) had severe AATD and 44 (7.4%) had mild/moderate AATD. Comparison of the 11 severely AAT-deficient individuals with the 542 LOTT participants with usual chronic obstructive pulmonary disease showed that the AATD subjects were younger and despite less smoking, had lower FEV_1/FVC (mean post-bronchodilator FEV_1/FVC, 0.38 ± 0.06 vs. 0.46 ± 0.13; $P = 0.002$). Comparison with 27 age-, sex-, and FEV_1-matched alpha-1 antitrypsin–normal LOTT participants showed no baseline difference in resting room air pulse oximetry saturation (AATD, 93.6% ± 2.3% vs. 92.7% ± 2.2%; $P = 0.64$). Exercise-related desaturation was more severe in the individuals with AATD based on desaturation to 88% or less sooner during a 6-minute-walk test, having a higher percentage of desaturation points (e.g., <90%) during exercise, and having a higher distance-saturation product (defined as the distance walked in 6 min multiplied by the nadir saturation achieved during the 6-minute-walk test).

Conclusions: These data suggest that individuals with AATD experience more profound desaturation with exercise than age-, sex-, race-, and FEV_1-matched control subjects with usual chronic obstructive pulmonary disease.

Clinical trial registered with www.clinicaltrials.gov (NCT 00692198)

Keywords: alpha-1 antitrypsin deficiency; oxygenation; Long-term Oxygen Treatment Trial; desaturation

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Alpha-1 antitrypsin (AAT) deficiency (AATD) accounts for 1 to 3% of patients with chronic obstructive pulmonary disease (COPD) and is currently the only well-characterized genetic cause of emphysema. Yet, AATD is generally poorly appreciated (1, 2) and clinically underrecognized (2–5); indeed, individuals with severe deficiency of AAT frequently experience long diagnostic delays before their initial recognition as having AATD and may see multiple physicians before initial diagnosis. Furthermore, as is characteristic of "orphan diseases" more generally, the paucity of recognized AAT-deficient individuals precludes assembly or description of a large cohort in a single center, thereby requiring multicenter studies to characterize the clinical features and natural history or to assess treatment of AATD. As such, only a few large series of AAT-deficient individuals are available, making characterization of these individuals relatively spotty and sparse (6–9). Specifically, although the pulmonary function characteristics of individuals with AATD have been characterized in several studies (6, 9), little attention has been given to describing the oxygenation characteristics or needs of such patients.

In this context, the NHLBI and Centers for Medicare and Medicaid Services Long-term Oxygen Treatment Trial (LOTT) is a multicenter randomized clinical trial comparing use of supplemental oxygen versus no oxygen in individuals with COPD (including AATD) and moderate hypoxemia (resting oxygen saturation as measured by pulse oximetry [Sp_{O_2}], 89–93%) or normal oxygenation at rest and significant exercise desaturation (10). Because AAT levels were measured at baseline in a subset of LOTT subjects, the trial provided an opportunity to compare the baseline features of participating AAT-deficient subjects with other LOTT subjects, thereby characterizing the oxygenation needs and features of LOTT participants with AATD.

Methods

Study Design and Participants

The LOTT enrolled patients from 14 participating Regional Clinical Centers and their satellites in the continental United States from January 2009 through August 2014. Patients enrolled in the trial satisfied the following inclusion criteria: COPD-dominated lung disease associated with dyspnea (as judged by the investigator), age 40 years or older, post-bronchodilator FEV_1 less than or equal to 70% predicted, post-bronchodilator FEV_1/FVC less than 0.70, and either a resting Sp_{O_2} of 89 to 93% or the combination of a resting Sp_{O_2} greater than 93% and significant oxyhemoglobin desaturation during exercise, defined as saturation below 90% for at least 10 seconds during the 6-minute-walk test (6MWT). A smoking history of 10 or more pack-years was required for enrollment, but exceptions were made for patients with AATD who had never smoked but otherwise met LOTT eligibility requirements. These exceptions were reviewed and approved by the LOTT Eligibility Review Committee on a case-by-case basis. Patients were randomly assigned to receive supplemental oxygen therapy (tailored to their hypoxemia) or no supplemental oxygen in a 1:1 ratio. A subset of patients who participated in an expanded level of data collection underwent AAT testing during screening. All participating centers' institutional review boards and all subjects granted consent to participate in LOTT.

AAT Determination and Classification

Subjects were considered to have an abnormality of AAT if a phenotype or genotype test was available with a result other than PI*MM (7). Based on the usual lower limit of serum AAT levels using nephelometry, subjects were considered to have AATD if the serum level was indicated to be less than or equal to 100 mg/dl or if an available phenotype or genotype was known to be abnormal (i.e., other than PI*MM). Subjects were stratified into those with severe deficiency of AAT versus mild/moderate AAT deficiency, where severe deficiency was defined by having a known severe deficient genotype/phenotype (e.g., PI*ZZ, PI*Z null, PI* null null, etc.) and/or if an available serum AAT level was less than 57 mg/dl. Mild/moderate deficiency was defined as having a serum AAT level of 57 to 100 mg/dl or having a genotype/phenotype indicating mild or moderate deficiency (e.g., PI*MZ, PI*MS, PI*SS, PI*MP).

Because information regarding the timing of AAT augmentation therapy initiation was not captured, subjects reported to be receiving augmentation therapy were considered to have severe deficiency, recognizing that their phenotype from serum samples could be consistent with mild/moderate deficiency because exogenously administered AAT could contribute M-type protein and raise the serum AAT level. In instances where the reported genotype/phenotype was consistent with severe deficiency but the reported serum level was greater than 100 mg/dl and subjects were recorded to be receiving augmentation therapy, receipt of augmentation therapy before the reported AAT serum level greater than 100 mg/dl was confirmed with individual site investigators or study coordinators. Finally, in instances in which both the serum level and genotype/phenotype were available but discordant and the patient was not said to be on augmentation therapy, subjects were considered "AAT deficient/indeterminate" but counted with the AATD group consistent with the lowest AAT status.

Baseline and Oxygenation Characteristics

Baseline assessment in LOTT (Table 1) included demographic features, medical and smoking history, lung function (spirometry pre- and post-bronchodilator performed at all centers according to ATS guidelines [11, 12]), and oximetry at rest and during a standard 6MWT using standardized oximetry equipment (Masimo Radical 7; Masimo Corp., Irvine, CA). Reference equations were used to determine predicted values of 6MWT distance (13).

Desaturation at rest and during the 6MWT was assessed with the pulse oximeter and Masimo DCI finger or TF-1 forehead sensor and the patient breathing room air for at least 15 minutes before the session. At rest, the sampling rate was once every second, and resting saturation was determined as the mean of the acceptable quality saturation data points obtained in the last 5 minutes of a 6-minute test session; additionally, the coefficient of variation of the data points included in the mean calculation had to be 2.5% or less. If more than 100 of the data points in the last 5 minutes of the test session had unacceptable quality, the test session was considered unacceptable and the mean saturation was not calculated. The oximeter was connected to a laptop; custom-written software developed by LOTT staff implemented this algorithm during the patient test session.

During the 6MWT, staff trailed the patient; the oximeter was either carried by

Table 1. Baseline characteristics of patients with severely deficient, mild/moderately deficient, and normal alpha-1 antitrypsin levels in the Long-term Oxygen Treatment Trial (N = 597)

Baseline Characteristics	AAT Deficiency Category			*P* Value*		
	Severe† (*n* = 11)	Mild/Moderate (*n* = 44)	Normal (*n* = 542)	Severe vs. Normal	Mild/Moderate vs. Normal	Severe vs. Mild/ Moderate
Demographic features						
Sex				0.48	1.00	0.47
Male	7 (63.6)	33 (75.0)	406 (74.9)			
Female	4 (36.4)	11 (25.0)	136 (25.1)			
Race				0.70	**0.005**	0.36
White, non-Hispanic	10 (90.9)	43 (97.7)	445 (82.1)			
Other	1 (9.1)	1 (2.3)	97 (17.9)			
Age, yr	61.2 ± 10.8	70.1 ± 9.2	69.1 ± 7.3	**0.04**	0.47	**0.007**
Education				0.35	1.00	0.50
H.S. diploma or less	6 (54.6)	17 (38.6)	208 (38.4)			
Some college or higher	5 (45.5)	27 (61.4)	334 (61.6)			
Marital status				0.14	0.35	0.50
Currently married	8 (72.7)	25 (56.8)	267 (49.3)			
Not married	3 (27.3)	19 (43.2)	275 (50.7)			
Income				1.00	0.40	0.72
<$50,000	5 (50.0)	22 (59.5)	246 (51.8)			
⩾$50,000	5 (50.0)	15 (40.5)	229 (48.2)			
Smoking history						
Pack-years	28.3 ± 26.6	57.6 ± 25.1	61.6 ± 34.6	**0.002**	0.33	**0.001**
Current smoker	2 (18.2)	10 (22.7)	145 (26.8)	0.74	0.72	1.00
Ever used home oxygen	2 (18.2)	16 (36.4)	171 (31.6)	0.52	0.51	0.31
Lung function and 6MWT						
Pre-BD FEV_1 % pred	40.8 ± 15.5	39.7 ± 14.8	43.9 ± 16.7	0.54	0.12	0.84
Pre-BD FVC % pred	82.4 ± 25.8	71.2 ± 22.1	72.3 ± 19.6	0.09	0.73	0.16
Pre-BD FEV_1/FVC	0.37 ± 0.08	0.41 ± 0.10	0.46 ± 0.13	**0.03**	**0.04**	0.26
Post-BD FEV_1 % pred	43.6 ± 16.4	43.3 ± 16.4	47.0 ± 16.6	0.49	0.15	0.95
Post-BD FVC % pred	86.0 ± 27.3	76.7 ± 23.2	76.9 ± 19.4	0.13	0.95	0.26
Post-BD FEV_1/FVC	0.38 ± 0.06	0.42 ± 0.11	0.46 ± 0.13	**0.002**	**0.05**	0.25
Resting saturation, %	93.6 ± 2.3	93.0 ± 1.8	93.4 ± 2.0	0.69	0.28	0.36
6MWT distance, % pred	74.7 ± 10.4	60.2 ± 21.7	65.4 ± 19.9	**0.01**	0.13	**0.003**
GOLD lung function level				0.75	0.52	1.00
I/II	3 (27.3)	14 (31.8)	203 (37.5)			
III/IV	8 (72.7)	30 (68.2)	339 (62.6)			
Desaturation qualifying for LOTT				1.00	1.00	1.00
At rest only/at rest and on 6MWT	6 (54.6)	26 (59.1)	316 (58.3)			
On 6MWT only	5 (45.5)	18 (40.9)	226 (41.7)			

Definition of abbreviations: 6MWT = 6-minute-walk test; AAT = alpha-1 antitrypsin; BD = bronchodilator; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LOTT = Long-term Oxygen Treatment Trial.
Values are mean ± SD or n (%). Values in boldface denote values deemed statistically significant ($P < 0.05$).
*P values determined from Fisher exact test for categorical variables and two-sample t tests for continuous variables.
†None of the subjects with severe deficiency of AAT was from a high altitude center (e.g., Utah, Denver).

the staff or the oximeter was placed in a fanny pack worn by the participant. Significant desaturation during the 6MWT was defined as desaturation below 90% for 10 or more seconds. However, if desaturation below 80% lasted for for 1 minute or longer during the 6MWT, the subject was excluded from enrollment. In terms of the 180 data points obtained during the 6 minutes of walking (sampling was every 2 s), the patient had to have at least 5 consecutive good-quality data points with saturation below 90%, and every rolling average of 30 consecutive data points had to have mean saturation of 80% or greater; at least 20 of the 30 points in each rolling average had to be good quality (Figure 1). Custom software developed by LOTT was written to implement these algorithms.

Additional oxygenation characteristics during the 6MWT were determined in two predefined subsets of patients: (*1*) The 11 LOTT participants with severe deficiency of AAT and 27 AAT-normal LOTT patients who were matched on age, sex, race, and prebronchodilator FEV_1 % predicted (a 1:3 case–control ratio was used for six severely AAT-deficient patients, a 1:2 case–control ratio was used for four severely AAT-deficient patients, and a 1:1 case–control ratio for one patient, depending on availability of adequate control subjects); and (*2*) 34 of the 44 LOTT participants with mild/moderate AATD who had oximetry data and 34 similarly matched AAT-replete LOTT patients, hereafter called subjects with "usual COPD." Six-minute walk oximetry files could not be located for 10 of the 44 subjects with mild/moderate AATD. Oxygenation characteristics included: the percent of pulse oximetry saturation values during the 6MWT less than 90%, the

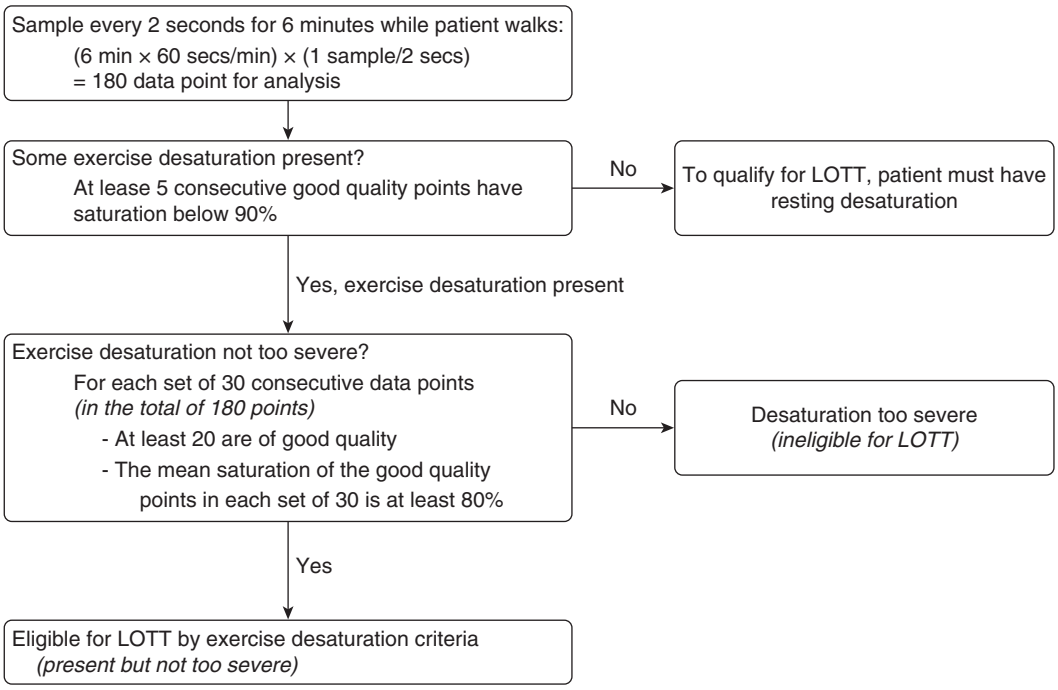

Figure 1. Exercise desaturation eligibility evaluation using oximetry data from the 6-minute-walk. LOTT = Long-term Oxygen Treatment Trial.

time to attain an Sp_{O_2} value less than or equal to 90% and less than or equal to 88% during the 6MWT, the nadir Sp_{O_2} value reached during the 6MWT (defined as the lowest Sp_{O_2} value replicated at least twice), and the distance-saturation product ([DSP], defined as the distance walked in 6 min multiplied by the nadir saturation achieved during the 6MWT), as proposed by Lettieri and colleagues (14).

Statistical Methods

Baseline characteristics of all LOTT patients with available AAT results are reported as mean ± SD or number and percentage. Pairwise *P* values comparing severely deficient AAT versus usual COPD, severely versus mildly deficient AAT, and mildly deficient AAT versus usual COPD were determined by Fisher exact test for 2 × 2 categorical variables and by two-sample *t* tests for continuous variables. Baseline characteristics of the patients with severe or mild AATD and their matched control subjects with usual COPD were also compared. Because patients with AAT deficiency were individually matched to control patients with usual COPD, we used conditional logistic regression models to compare categorical baseline characteristics and mixed effects linear regression models to compare continuous baseline characteristics; both types of regression models account for within matched sets correlations. The fixed effect in the mixed-effects linear regression model was the binary variable for severely deficient AAT versus usual COPD or mildly deficient AAT versus usual COPD, and the random effect was for the random intercepts for each matched set. Oxygenation characteristics comparing these matched groups are presented as mean ± SD. *P* values for difference in time to desaturation were determined by interval regression to account for right-censoring of patients who did not reach the cut-point for desaturation (either 90 or 88%). All other *P* values were determined from mixed-effects linear regression models, as described above. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and Stata version 13 (StataCorp, College Station, TX). Nominal two-sided *P* values are presented and are not adjusted for multiplicity.

Results

Among the cohort of 597 LOTT participants (of 737 total LOTT enrollees) with nonmissing data regarding AAT levels, 11 (1.8%) had severe deficiency of AAT (of the 8 subjects with available genotypes, 4 were PI*ZZ and one was null) and 44 (7.4%) had mild/moderate AATD (of the 40 subjects with available genotypes, 24 were PI*MZ, 14 were PI*MS, and 2 were PI*SZ). Baseline comparison of those with severe AATD and those with usual COPD (Table 1) showed that AAT-deficient individuals were younger and, despite smoking less, had results consistent with more severe airflow obstruction (with a mean post-bronchodilator FEV_1/FVC 0.38 vs. 0.46, $P = 0.002$) and a trend toward lower prebronchodilator FEV_1 % predicted (40.8 vs. 43.9, $P = 0.54$). Subjects with severe AATD walked farther on 6MWT than individuals with usual COPD.

The groups were similar regarding their mean resting pulse oximetry saturation (93.6 vs. 93.4%). To assess the oxygenation features of those 11 individuals with severe AATD versus control subjects with usual COPD, groups matched on age, sex, race, and FEV_1 (Tables 2 and 3) were compared. Based on the metric of "time to desaturate to less than or equal to 88%" during a 6MWT test, those with severe deficiency of AAT desaturated sooner (Table 3, Figure 2). The nadir Sp_{O_2} value reached during the 6MWT (defined as the lowest Sp_{O_2} value replicated at least twice) was lower in those with severe deficiency of

Table 2. Baseline characteristics of patients with severe and mild/moderate alpha-1 antitrypsin deficiency matched to patients with normal alpha-1 antitrypsin serum levels in the Long-term Oxygen Treatment Trial

Baseline Characteristics	AAT Deficiency Category					
	Severe (*n* = 11)	Normal (*n* = 27)	*P* Value*	Mild/Moderate (*n* = 34)	Normal (*n* = 34)	*P* Value*
Demographic features						
Sex			n/a			n/a
Male	7 (63.6)	15 (55.6)		28 (82.4)	28 (82.4)	
Female	4 (36.4)	12 (44.4)		6 (17.7)	6 (17.7)	
Race			n/a			n/a
White, non-Hispanic	10 (90.9)	27 (100.0)		33 (97.1)	34 (100.0)	
Nonwhite, non-Hispanic	1 (9.1)	0 (0.0)		1 (2.9)	0 (0.0)	
Age, yr	61.2 ± 10.8	63.4 ± 7.9	n/a	69.6 ± 9.2	69.6 ± 9.4	n/a
Education			0.13			1.00
H.S. diploma or less	6 (54.6)	7 (25.9)		13 (38.2)	13 (38.2)	
Some college or higher	5 (45.5)	20 (74.1)		21 (61.8)	21 (61.8)	
Marital status			1.00			0.62
Currently married	8 (72.7)	13 (48.2)		15 (44.1)	17 (50.0)	
Not married	3 (27.3)	14 (51.9)		19 (55.9)	17 (50.0)	
Income			0.78			1.00
<$50,000	5 (50.0)	13 (50.0)		18 (64.3)	19 (59.4)	
⩾$50,000	5 (50.0)	13 (50.0)		10 (35.7)	13 (40.6)	
Smoking history						
Pack-years	28.3 ± 26.6	51.6 ± 20.5	**0.02**	57.0 ± 24.8	64.3 ± 31.5	0.24
Current smoker	2 (18.2)	6 (54.6)	1.00	10 (29.4)	11 (32.4)	0.78
Ever used home oxygen	2 (18.2)	3 (27.3)	0.48	11 (32.4)	5 (14.7)	0.12
Lung function and 6MWT						
Pre-BD FEV_1 % pred	40.8 ± 15.5	41.4 ± 14.1	n/a	37.9 ± 14.9	37.0 ± 13.0	n/a
Pre-BD FVC % pred	82.4 ± 25.8	65.9 ± 19.2	**0.01**	67.9 ± 22.4	67.5 ± 20.1	0.78
Pre-BD FEV_1/FVC	0.37 ± 0.08	0.48 ± 0.10	**0.01**	0.41 ± 1.0	0.41 ± 0.12	0.97
Post-BD FEV_1% pred	43.6 ± 16.4	45.3 ± 16.0	0.18	41.9 ± 16.9	40.7 ± 12.5	0.44
Post-BD FVC % pred	86.0 ± 27.3	70.7 ± 18.7	**0.03**	74.7 ± 24.4	72.0 ± 18.6	0.44
Post-BD FEV_1/FVC	0.38 ± 0.06	0.48 ± 0.11	**0.01**	0.42 ± 0.11	0.43 ± 0.12	0.58
Resting saturation, %	93.6 ± 2.3	92.7 ± 2.2	0.87	93.1 ± 1.8	93.5 ± 1.6	0.39
Resting saturation, categorical			0.57			1.00
89–93%	6 (54.6)	8 (72.7)		20 (58.8)	20 (58.8)	
>93%	5 (45.5)	3 (27.3)		14 (41.2)	14 (41.2)	
6MWT distance % predicted	74.7 ± 10.4	65.2 ± 14.9	0.08	56.1 ± 21.1	64.0 ± 19.0	0.07
GOLD lung function level			1.00			0.18
I/II	3 (27.3)	4 (36.4)		9 (26.5)	5 (14.7)	
III/IV	8 (72.7)	7 (63.6)		25 (73.5)	29 (85.3)	
Desaturation qualifying for LOTT			0.57			1.00
At rest only/at rest and on 6MWT	6 (54.6)	8 (72.7)		14 (41.2)	14 (41.2)	
On 6MWT only	5 (45.5)	3 (27.3)		20 (58.8)	20 (58.8)	

Definition of abbreviations: 6MWT = 6-minute-walk test; AAT = alpha-1 antitrypsin; BD = bronchodilator; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LOTT = Long-term Oxygen Treatment Trial; n/a = not applicable.

Values are mean ± SD or n (%). Values in boldface denote values deemed statistically significant ($P < 0.05$). Matched on age, sex, race/ethnicity, and pre-BD FEV_1 % predicted. One Asian patient with severe AAT matched to white patient due to no Asian patients in the normal AAT group. One female African-American patient with mild AAT matched to female white patient, due to no alternative matches in the normal AAT group.

**P* values determined from conditional logistic regression for categorical variables and single-level mixed-effects linear regression models.

AAT (Table 3). Also, the percent of oximetry desaturation points less than 90, 89, and 88% were all significantly greater in AAT-deficient individuals (Table 3). Finally, the DSP was higher in AAT-deficient than in AAT-normal subjects (348.4 m% vs. 295.4 m%, $P = 0.02$). Similar findings regarding time to desaturate to less than or equal to 88% and desaturation points less than 90% were observed in subjects with mild/moderate AATD ($P = 0.04$ and $P = 0.01$, respectively). Nonsignificant trends were directionally similar in other parameters (Table 3), with the exception of the DSP, which was lower (mean, 243.3 vs. 275.0, $P = 0.10$) in those with mild/moderate AATD than in LOTT subjects with usual COPD.

Discussion

In this study comparing baseline features of LOTT subjects with mild/moderate and severe AATD versus those with normal AAT levels and "usual" COPD, we found that the prevalence of severe AAT deficiency among LOTT subjects (1.8%) was similar to that in other, unselected COPD populations. In comparison to patients with COPD without AATD matched for age, sex, race, and FEV_1, individuals with severe deficiency of AAT desaturated more quickly and generally to a greater extent during exercise. The DSP, a metric first described by Lettieri and

Table 3. Desaturation metrics by alpha-1 antitrypsin deficiency category

Sp_{O_2} Metric	AATD Category*			AATD Category*		
	Severe (*n* = 11)	Normal (*n* = 27)	*P* Value†	Mild/Moderate (*n* = 34)	Normal (*n* = 34)	*P* Value†
Time to desaturation ⩽ 90%, s	58.0 ± 47.5	65.8 ± 56.3	0.16	66.5 ± 53.5	70.6 ± 57.7	0.55
Time to desaturation ⩽ 88%, s	110.0 ± 60.0	143.3 ± 96.9	**0.008**	119.9 ± 64.5	136.3 ± 78.0	**0.04**
Nadir Sp_{O_2}‡	84 ± 3	87 ± 3	**<0.001**	86 ± 3	87 ± 3	0.06
Percentage of Sp_{O_2} points:						
<90	66.6 ± 20.0	27.5 ± 30.6	**<0.001**	47.1 ± 31.4	33.6 ± 28.3	**0.01**
<89	49.8 ± 29.1	18.0 ± 26.7	**<0.001**	34.2 ± 30.6	23.1 ± 28.4	0.05
<88	39.4 ± 32.3	11.2 ± 24.3	**0.001**	24.2 ± 28.9	16.0 ± 27.1	0.14
DSP, m%§	348.4 ± 64.6	295.4 ± 88.6	**0.02**	243.3 ± 94.7	275.0 ± 77.7	0.10

Definition of abbreviations: 6MWT = six-minute walk test; AATD = alpha-1 antitrypsin deficiency; DSP = distance-saturation product; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

Values are mean ± SD or n (%). Values in boldface denote values deemed statistically significant ($P < 0.05$).

*Patients with severe AATD matched to patients with normal AAT and patients with mild AATD matched to patients with normal AAT, matching on age, sex, race, ethnicity, and prebronchodilator FEV_1.

†*P* values for time to desaturation derived from interval regression to account for right censoring, clustering on the unique identifier matching patients with AATD to patients with normal AAT. All other *P* values derived from single-level mixed-effects linear regression models.

‡Lowest Sp_{O_2}, repeated at least two times.

§DSP = meters walked during 6MWT multiplied by lowest Sp_{O_2}.

colleagues in idiopathic pulmonary fibrosis as a significant correlate of mortality (14), also discriminated between those with severe deficiency of AAT versus AAT-sufficient COPD. In addition, we found that study subjects with severe deficiency of AAT were younger and had lower FEV_1/FVC than AAT-sufficient subjects despite fewer pack-years of smoking.

In general, statistically significant differences with AAT-sufficient subjects did not extend beyond the subjects with severe AATD to those who had mild to moderate deficiency, although most trends in these comparisons were directionally the same as those for individuals with severe deficiency of AAT versus matched control subjects. Baseline resting room air pulse oximetry saturation did not differ between the compared groups.

Although the observations that AAT-deficient individuals were younger and had worse obstruction despite less smoking exposure is not surprising based on the known features of severe AATD as a genetic predisposition to emphysema that may occur in never smokers (6, 8), characterizing oxygenation in AAT-deficient individuals is novel, as the issue has received only scant attention to date. Indeed, only two of the six largest available series of AAT-deficient patients (6, 15–18), whether descriptive or interventional, report any baseline oxygenation characteristics of study participants, and then only in simple descriptive terms. None of the available studies has examined oxygenation during activity.

For example, in the largest available study cohort of AAT-deficient individuals (N = 1,129) in the NHLBI Registry of Individuals with AAT Deficiency (6), baseline arterial blood gas values were available in 599 individuals, but no correlations with other baseline characteristics were provided. For these individuals, the mean baseline Pa_{O_2} was 72.5 ± 14.0 mm Hg, mean Pa_{CO_2} was 37.6 ± 5.5 mm Hg, and the mean pH (available in 598 individuals) was 7.42 ± 0.04. In a description of 164 participants in the Alpha-1 Foundation DNA and Tissue Bank database (18), supplemental oxygen was reportedly used by 50.8% of those receiving augmentation therapy (whose mean FEV_1 was 43% predicted) and by 12.5% of those not receiving augmentation therapy ($P < 0.001$) whose mean FEV_1 was 77% predicted. Neither subjects' arterial blood gas nor pulse oximetry saturation values were reported in that series. Finally, in a series of 102 PI*ZZ subjects with AATD (19), resting room air Pa_{O_2} was higher in subjects with basilar-predominant (mean, 9.0 ± 0.9 kPa) than in those with apical-predominant emphysema (mean, 8.5 ± 1.0 kPa). Oxygenation during activity was not measured.

Notably, the 1.8% prevalence of severe AATD in LOTT is consistent with the estimated prevalence of severe AATD in COPD in general (20, 21), supporting the representativeness of AAT-deficient LOTT subjects. However, the low total number of AAT-deficient individuals in this series invites further study of the oxygenation characteristics of these patients.

Although the mechanism of the greater desaturation in individuals with severe deficiency of AAT is unclear from this study, altered ventilation–perfusion relationships may contribute. For example, Kanner and colleagues (22) showed that along with having more severe airflow obstruction, individuals with severe deficiency of AAT demonstrated altered ventilation–perfusion patterns compared with AAT heterozygotes and to individuals with usual COPD.

A related striking finding in this study is that individuals with severe deficiency of AAT have more pronounced oxygen desaturation during exercise, yet walked a significantly greater distance than matched subjects with usual COPD. Because fewer of the subjects with severe deficiency of AAT than subjects with usual COPD had ever attended pulmonary rehabilitation (45 vs. 69%), this longer walk distance in subjects with AATD cannot easily be ascribed to greater use of pulmonary rehabilitation. Although this finding seems paradoxical, it could reflect the younger age of AAT-deficient subjects. It should also be noted that the acute and chronic consequences of exertional hypoxemia remain unclear. Recent animal data suggest that intermittent hypoxia may have a protective role in attenuating diaphragm fatigue under certain

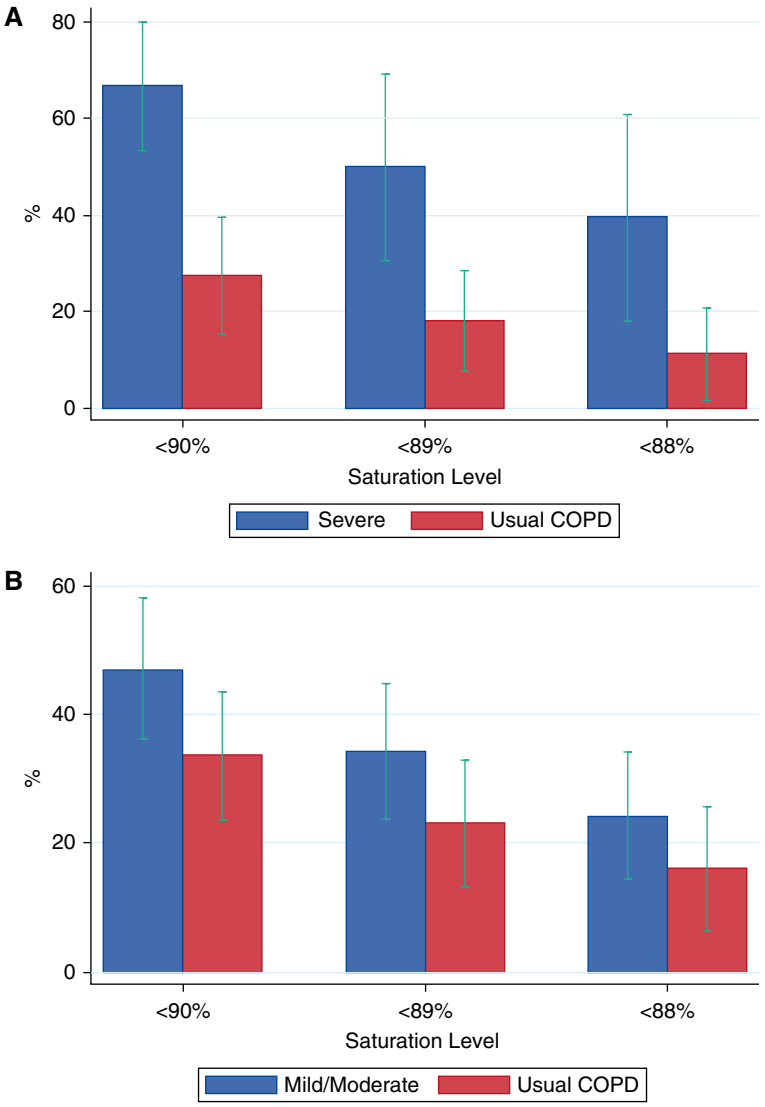

Figure 2. Percent of oxygen saturation as measured by pulse oximetry points below saturation cut points of 90, 89, and 88%. (*A*) Severe alpha-1 antitrypsin deficiency (AATD) (*blue*) versus usual chronic obstructive pulmonary disease (COPD) (*red*). (B) Mild/moderate AATD (*blue*) versus usual COPD (*red*).

conditions (23); this phenomenon may relate to the induction of antioxidant defenses in the working muscle during intermittent hypoxia (1). Whether such a protective mechanism is relevant to patients with COPD with exertional hypoxemia is speculative; however, long-term follow-up from LOTT will provide important insight about the effects of intermittent hypoxemia in humans.

Several other potential limitations of this study warrant comment. First, recognizing the paucity of descriptive information about oxygenation in AAT-deficient individuals, this study was exploratory in identifying oxygenation characteristics that might distinguish subjects with AATD from those with usual COPD in LOTT. Certainly, although novel in studies of COPD, the use of metrics like time to desaturation, percent of oximetry points less than 88%, and the DSP are exploratory in this series and will require analysis of other cohorts of individuals with AATD and COPD to validate their utility; such analyses are anticipated as part of the analysis of the larger LOTT population. Furthermore, the interpretation of the DSP in AAT-deficient subjects must be conditioned by the longer distance they walked than the usual-COPD group (mean, 414 m vs. 328 m); indeed, the fact that the DSP in the AATD group is higher in the face of their earlier and lower saturation values than the usual-COPD group owes to the longer distance walked by AAT-deficient subjects. Although requiring further study, such a composite index may have value in other studies of patients with COPD as it has preliminarily in examining idiopathic pulmonary fibrosis (14).

As another potential shortcoming of the study, because diffusing capacity measurements were not made in the LOTT protocol, we are unable to relate these findings regarding desaturation to the degree of alveolar-capillary integrity in these subjects. Finally, computed tomography imaging was not available in the LOTT; in the context that Parr and colleagues have demonstrated that resting oxygenation was slightly better preserved with basilar-predominant emphysema than with apical-predominant emphysema (19), we cannot easily relate oxygenation characteristics in LOTT participants to their apical-basal distribution of emphysema.

In summary, AAT-deficient subjects in LOTT demonstrated more pronounced exercise desaturation than matched LOTT subjects with usual COPD. Although this observation requires validation in additional studies, these results suggest that clinicians should be more vigilant for desaturation in AAT-deficient individuals. The implications of such exercise desaturation for patient management should be clarified when the results of follow-up and full outcomes in the LOTT are available. ■

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