ORIGINAL RESEARCH

Predictors in routine practice of 6-min walking distance and oxygen desaturation in patients with COPD: impact of comorbidities

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Background: The 6-min walk test (6MWT) allows exercise tolerance to be assessed, and it has a significant prognostic value in COPD. The goal of this study was to analyse the determinants (obtained in routine practice) of a low 6-min walking distance (6MWD) and exercise-induced desaturation (EID) in COPD, including comorbidities.

Methods: Patients were recruited from the real-life French COPD cohort "Initiatives BPCO". A low 6MWD was defined as <350 m. EID was defined by a minimum pulse oxygen saturation (SpO2)<90% and delta SpO2≥4% from baseline. Multivariate logistic regression analyses assessed the influence on 6MWD and EID of age, sex, obesity (body mass index, BMI >30 kg/m^2), low BMI (BMI <18.5 kg/m^2), modified Medical Research Council (mMRC) dyspnea scale, FEV1% pred, FVC % pred, hyperinflation and comorbidities including cardiovascular diseases.

Results: Among 440 patients with available 6MWT data, a 6MWD <350 m was found in 146 patients (33%), which was positively associated in multivariate analyses with age and mMRC and negatively with resting SpO2 and FVC % pred (rescaled r^2=0.34), whereas no comorbidity was associated with a low 6WMD. EID was found in 155 patients (35%). This was positively associated with hypertension and negatively with age, obesity, FEV1% pred and resting SpO2 (rescaled r^2=0.37).

Conclusion: 6MWD and EID exhibit different determinants in COPD with a minor impact of comorbidities limited to hypertension in EID and to obesity, which was unexpectedly associated with less EID. Other variables including age, routine resting lung function and SpO2 were weakly associated with 6MWD and EID. Altogether, these results suggest that 6MWT performance remains difficult to predict with routine clinical/functional parameters.

Keywords: 6-min walk test, distance, COPD, obesity, comorbidities, severity

Background

COPD is worldwide a leading cause of mortality and morbidity[1,2] associated with progressive airflow limitation. Until recently, COPD severity was mainly defined by the level of post-bronchodilator FEV$_1$.[3] Dyspnea and exercise limitation are the predominant consequences of COPD in stable condition and appear now as major indexes of disease severity and prominent targets of treatment. The 6-min walk test (6MWT) is a widely used field test to assess exercise performance with an abundant literature supporting its clinical relevance.[4,5] The distance walked at the end of the test (6MWD) is the primary outcome and a strong prognostic factor in COPD, either as a single parameter or as part of a multidimensional index.[6–8] Several studies suggested the

350 m value as a relevant prognostic cutoff.[6,9–11] The multi-dimensional BODE index (BMI, obstruction, dyspnea and exercise) also integrates an upper cutoff of 350 m for 6MWD,[7] and a low baseline value of 6MWD is highly predictive of a worsening in BODE score at 2 to 3 years.[12]

Exercise-induced desaturation (EID) is common in COPD and routinely assessed during the 6MWT. Various definitions have been used to characterize significant EID. The most common definition is a pulse oxygen saturation (SpO2) drop >4% from baseline and/or a lowest SpO2<90% during the 6MWT.[9,13] The predicting factors of EID in COPD are poorly known with conflicting results from different studies, usually demonstrating resting SpO2 and PaO2 as significant predictors.[9,14–16] The negative prognostic value of EID during the 6MWT is confirmed by several studies.[8,13,17]

Comorbidities are frequent in COPD, with a significant impact on symptoms, morbidity and mortality.[18] Among COPD comorbidities, cardiovascular diseases (eg, chronic heart failure [CHF] and coronary heart disease) and mood disorders (eg, depression and anxiety) could contribute to exercise limitation and then impact 6MWT performance.[18,19] Recent results from the ECLIPSE study demonstrated that FEV$_1$, modified Medical Research Council (mMRC) dyspnea score, COPD severity, depression and emphysema score on quantitative CT were associated with a 6MWD <350 m.[10] Individual comorbidities were not specifically assessed, but patient-reported cardiovascular diseases were surprisingly not associated with a low 6MWD.

The purpose of the present study was to analyse the contribution of demographic data, symptoms, lung function, nutritional status and specifically comorbidities including cardiovascular diseases to the 6MWD and EID in a real-life cohort of COPD patients, using only usual parameters obtained in routine practice. A better knowledge of the correlates of 6MWT main variables could help to predict a low performance during the 6MWT and provide a better understanding of the determinants involved in exercise tolerance in COPD.

Methods
The Initiatives BPCO cohort
COPD subjects were recruited from the Initiatives BPCO cohort, a prospective real-life French cohort of clinically and spirometry-diagnosed COPD patients from 20 centers: 17 university hospitals, 2 general hospitals and 1 rehabilitation center. The details of this cohort have been previously described.[20,21] In short, COPD subjects were recruited at stable condition with no history of exacerbation in the previous 4 weeks, and with a diagnosis of COPD based on a post-bronchodilator FEV$_1$/FVC ratio <0.7.[22] Exclusion criteria were a main diagnosis of bronchiectasis, asthma or other chronic respiratory diseases.

A standardized case report form was used to record demographic data, risk factors including tobacco history, respiratory symptoms, history of acute exacerbations of COPD during the previous year, health-related quality of life, anxiety and depression, spirometry and plethysmographic lung volumes according to American Thoracic Society/European Respiratory Society (ATS/ERS) standards,[23] 6MWT and comorbidities including sleep apnea syndrome, congestive HF, coronary artery disease, hypertension and diabetes mellitus. Physician investigators identified comorbidities from clinical assessment and patient files. Dyspnea was assessed by the mMRC scale[24] ranging from 0 to 4. Health-related quality of life was evaluated by the Saint George's Respiratory Questionnaire (SGRQ) ranging from 0 to 100. Anxiety and depression were assessed by the Hospital Anxiety Depression (HAD) questionnaire.[25,26] The ADO score (age, dyspnea and obstruction) was calculated according to the original description.[27] The 6MWT was performed by experienced respiratoy nurses according to ATS guidelines except for duplication, and the following variables were collected: end of 6MWT dyspnea assessed by a modified Borg scale from 0 to 10, baseline SpO2, SpO2 minimal value and distance. This study was conducted in accordance with the Declaration of Helsinki. The procedures of this study were approved by the Ethics Committee of Versailles (France). All subjects provided informed written consent.

Selection of COPD subjects
Due to the real-life design of the Initiatives BPCO cohort, datasets do not have to be complete to include a patient. Demographic characteristics and spirometry only are mandatory at inclusion. At the time of the analysis, 1.194 COPD subjects were included in the Initiatives BPCO cohort. Because our goal was to study the impact of both lung function and comorbidities on exercise tolerance assessed by the 6MWT, we selected subjects with complete data for 6MWT, spirometry, plethysmography, comorbidities including coronary artery disease, CHF, thromboembolic history, diabetes, hypertension and

exacerbation history during the previous year. A comparison between subjects with complete data and those with incomplete data was performed.

Statistical analyses

As 6MWT parameters did not exhibit a normal distribution according to the Kolmogorov–Smirnov test, nonparametric tests were used, and distributions were described using medians and IQRs.

Univariate analyses

The comparisons of qualitative and quantitative variables between 6MWD and EID categories were compared using Chi^2 or Wilcoxon tests, respectively. The variables considered in the univariate analyses were age, sex, body mass index (BMI), mMRC dyspnea scale, FEV1% pred, forced vital capacity (FVC) % pred, lung volumes (residual volume (RV), total lung capacity (TLC), RV/TLC), SpO2 at rest, exacerbation frequency, chronic bronchitis, nutritional status and physician-diagnosed comorbidities.

Multivariate analyses

Variables explaining 6MWD and EID were explored using the LOGISTIC procedure from SAS® 9.2 statistical software, with significant levels for entry and stay of 15% and 10%, respectively, to introduce or remove a covariate. For each score, two stepwise ordinal logistic regressions were performed starting from no and all variables. The two stepwise analyses converged to the same model. Seventeen variables were used as covariates including lung function variables as continuous variables (FEV$_1$ % pred, FVC % pred, RV/TLC), comorbidities as individual variables and BMI as a categorical variable (low <18.5 kg/m^2; obesity >30 kg/m^2). The mMRC dyspnea scale was also used. The SGRQ and HAD scores were not entered in the models due to too many missing data. A multivariate analysis with the same 17 variables was performed for 6MWD in absolute value (meters).

Results

Patients

Among 1,194 COPD subjects included from January 2005 to October 2015, 440 subjects had complete data for the variables of interest. The characteristics of these patients are reported in Table 1. Compared to patients with incomplete data, subjects with complete data had a lower age (62 [56–70] vs 65 [58–73]; $p<0.0001$) and a lower prevalence of diabetes (10.2% vs 14.9%, $p=0.02$), with no other

Table 1 Clinical and lung function data

Variable	N=440
Comorbidities (present)	
Sex male/female	72.7% (320)/ 27.3% (120)
Age	62 [56–70]
Low BMI ≤18.5 kg/m²	9.1% (40)
Obesity BMI >30 kg/m²	18.9% (83)
Smoking history (pack-years) **Current/ex smokers**	38.0 [23.8–55.0] 31.2% (135)/65.8% (285)
Hypertension	36.4% (160)
Ischemic heart disease	13.4% (59)
Chronic heart failure	12.5% (55)
Diabetes	10.2% (45)
Mechanical limitation	20.9% (92)
Sleep apnea	8.4% (37)
FEV1 (L)	1.41 [0.97–1.87]
FEV1% pred	51 [36–68]
GOLD 2007 severity	
1 2 3 4	8.4% (37) 42.5% (187) 32.7% (144) 16.4% (72)
FEV1/FVC	0.51 [0.42–0.61]
FVC % pred	86 [71–102]
RV % pred	167 [131–208]
TLC % pred	114 [103–128]
RV/TLC %	55 [47–64]
mMRC (0–4)	2 [1–2]
Chronic bronchitis	66.6% (293)
Exacerbations/year	1 [0–3]
BODE score	3 [1–4]
ADO score	3 [2–5]

Note: Data reported as numbers (percentages) or median [IQRQ1–Q3].
Abbreviations: BMI, body mass index; RV, residual volume; TLC, total lung capacity; mMRC, modified Medical Research Council scale for dyspnea; BODE, body mass index, obstruction, dyspnea and exercise score; ADO, age, dyspnea and obstruction score.

difference regarding clinical and lung function variables. Among the 440 subjects included in the analyses, all GOLD spirometry grades were represented (Table 1)

with a median FEV_1 of 51% pred and an mMRC score at 2 [1; 3]. A low BMI was found in 50 subjects and obesity in 83 subjects. Previously diagnosed comorbidities were found across all GOLD grades.

6MWT

Median 6MWD was 404 m [318–480] and 146 patients (33%) walked a distance <350 m (Figure 1). End of 6MWT-related dyspnea was higher in those with a low 6MWD. Significant EID was found in 155 patients (35%). Of note, EID and low 6MWD were unrelated (Figure 2).

Univariate associations with 6MWD and EID

Several categorical and continuous variables were related to 6MWD and EID (Tables 2 and 4, Tables S1 and S2) including age, mMRC stage, SGRQ global score, exacerbation frequency, FEV1% pred, FVC % pred and hyperinflation at rest (RV and RV/TLC).

Baseline SpO2 was lower in patients with a low 6MWD or EID. The prevalence of cardiovascular comorbidities was similar in patients with low or preserved 6MWD, and between those with and without EID. Obesity was inversely associated with EID, whereas the prevalence of obesity was not significantly different in patients with and without a low 6MWD.

Multivariate determinants of 6MWD and desaturations

The main determinants (as indicated by significant Wald Chi-square values) were different for 6MWD and EID (Table 3A and B). The mMRC scale was predictive of a low 6MWD only. The first functional covariate was FVC for 6MWD and FEV_1 for EID. Baseline SpO2 was significantly associated with both 6MWD and EID. Age had a positive predictive value for a low 6MWD and negative for EID. Only hypertension appeared as a positive cardiovascular predictor of EID, whereas obesity was significantly associated with less EID. Altogether, considering all independent and significant
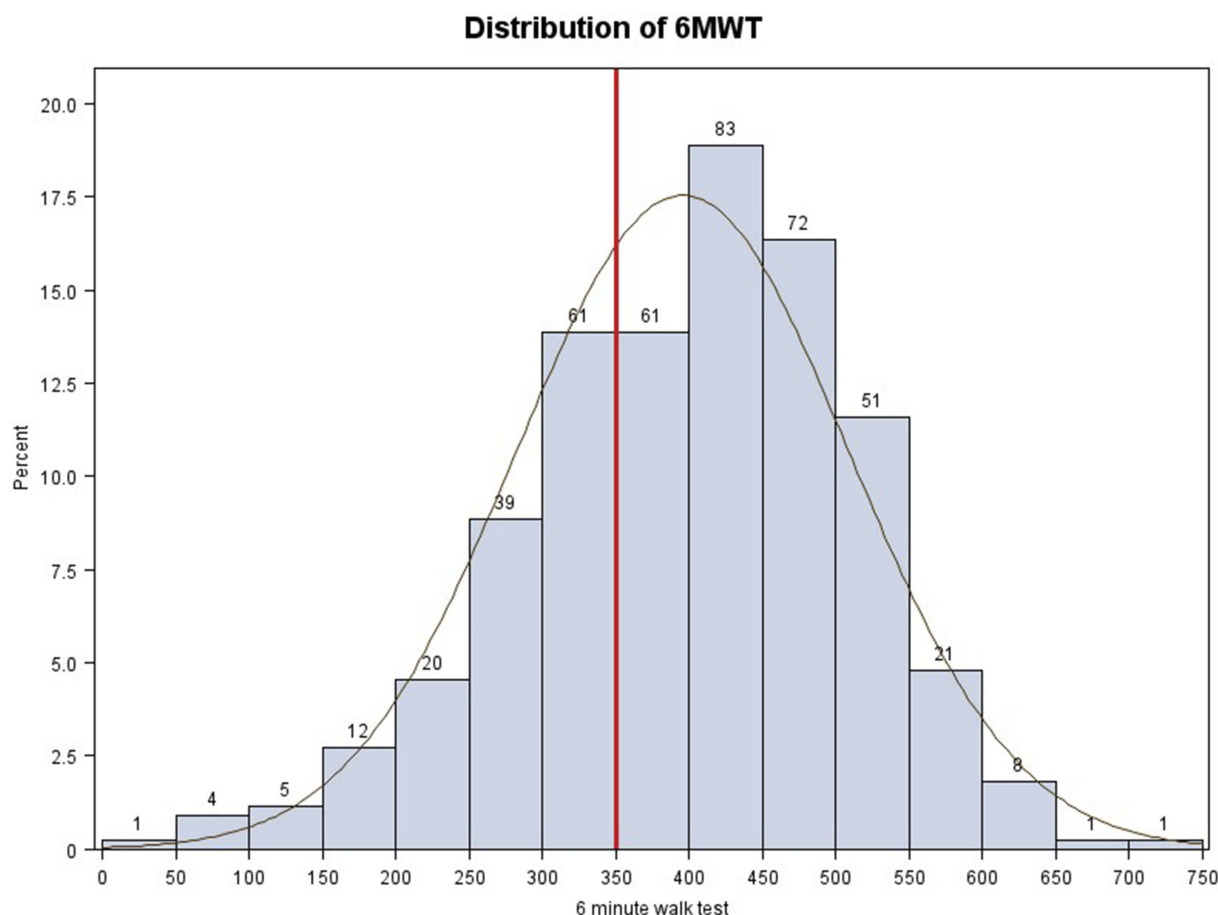

Figure 1 Distribution of the 6MWD (m).
Abbreviations: 6MWD, 6-min walking distance; m, meters.
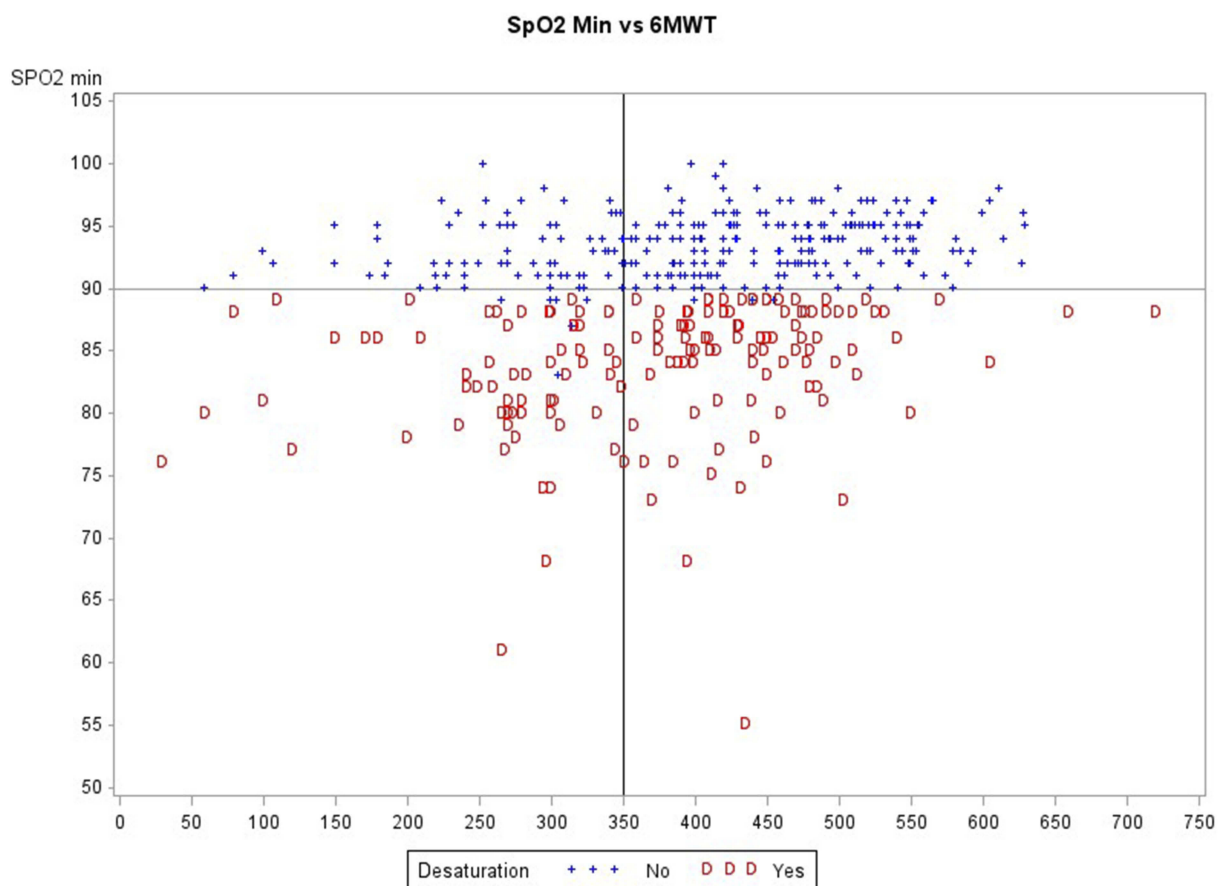
SpO2 Min vs 6MWT

Figure 2 Relationship between 6MWD and EID (SpO2 min).
Abbreviations: 6MWD, 6-min walking distance; EID, exercise induced desaturation.

determinants identified by our analyses, only a low-to-moderate proportion of the 6MWD and EID results were explained with a maximal rescaled r^2 of 0.34 and 0.37, respectively. The prediction of 6MWD in absolute value (Table 4) retained age, FEV1% pred, mMRC and baseline SpO2, with obesity, hypertension and diabetes as additional factors of borderline significance. Adjusted r^2 of the whole model was similar at 0.33.

Discussion

In this real-life cohort of COPD patients, a low 6MWD and/or EID occurred in approximately one-third of patients (33% and 35%, respectively). Low 6MWD and the presence of EID were unrelated, and their major determinants were different but with limited predictive values. Of note, the influence of comorbidities was low.

Determinants of a low 6MWD

Our results regarding the prevalence of a 6MWD <350 m are consistent with other COPD populations, especially the ECLIPSE cohort which exhibited a 6MWD <350m in 41%

of the patients.[10] The identification of determinants associated with decreased walking distance might be useful for prognosis assessment and to identify a risk of reduced physical activity,[5] although the relationships between the amount or intensity of daytime activity and 6MWT performance remain variable among studies.[28] Our results from a cohort of stable COPD patients show that age, FVC, mMRC scale and baseline SpO2 were the main determinants of a poor performance.[29,30] Although very easy to obtain in clinical practice, these clinical and lung function correlates of 6MWD were relatively poor predictors (rescaled r^2 0.34), insufficient to reliably estimate the presence of a low 6MWD in the individual patient. FEV$_1$ and mMRC were significant predictors in the multivariate analyses of the Bergen cohort by Waatevik et al,[31] but physical activity (>1–2 hrs per week) and comorbidities assessed by the Charlson index were additional predictive factors of a better 6MWD.

Contrary to what could be expected RV/TLC was unrelated to 6MWD, a finding suggesting a moderate relationship between resting and exercise-induced dynamic hyperinflation, mainly related to the level of expiratoy

Table 2 Univariate comparisons for low vs high 6MWD

Variable	6MWD ≤350 m N=146	6MWD >350 m N=294	p	Desaturation N=155	No desaturation N=285	p
Sex male/female	70.5% (103)/29.5% (43)	73.8% (217)/26.2% (77)	0.469	69.0% (107)/31.0% (48)	74.7% (213)/25.3% (72)	0.199
Age	65 [58–74]	60 [54–67]	**<0.0001**	60 [54–67]	62 [56–71]	**0.0410**
BMI ≤18.5	10.3% (15)	8.5% (25)	0.543	11.6% (18)	7.7% (22)	0.175
Obesity BMI >30	23.3% (34)	16.7% (49)	0.095	13.5% (21)	21.8% (62)	0.036
Hypertension	41.8% (61)	33.7% (99)	0.096	40.0% (62)	34.4% (98)	0.242
Chronic heart failure	16.4% (24)	10.5% (31)	0.078	11.0% (17)	13.3% (38)	0.474
Ischemic heart disease	16.4% (24)	11.9% (35)	0.189	10.3% (16)	15.1% (43)	0.161
Diabetes	11.0% (16)	9.9% (29)	0.721	9.0% (14)	10.9% (31)	0.542
Exacerbations/year	2 [0–3]	1 [0–2]	**0.0021**	1 [0–3]	1 [0–2]	**0.0235**
mMRC stage	2 [1–3]	1 [1–2]	**<0.0001**	2 [1–3]	1 [1–2]	**<0.0001**
SGRQ global score	53 [42–64]	39 [27–53]	**<0.0001**	49 [35–59]	42 [28–56]	**0.0066**
	missing 19	missing 46		missing 20	missing 45	
BODE	5 [3–6]	2 [1–3]	**<0.0001**	4 [2–5]	2 [1–4]	**<0.0001**
ADO	5 [4–6]	3 [2–4]	**<0.0001**	4 [3–5]	3 [2–4]	**<0.0001**
HAD anxiety ≥10	26.7% (39)	23.8% (70)	0.414	25.2% (39)	24.6% (70)	0.864
	missing 18	missing 50		missing 22	missing 46	
HAD depression ≥10	20.5% (30)	13.6% (40)	0.169	18.1% (28)	14.7% (42)	0.649
	missing 20	missing 46		missing 22	missing 44	
FEV_1 % pred	42 [31–54]	56 [41–71]	**<0.0001**	38 [29–52]	57 [43–71]	**<0.0001**
FVC % pred	74 [61–89]	90 [76–106]	**<0.0001**	76 [62–91]	89 [75–106]	**<0.0001**
RV % pred	175 [137–223]	161 [131–199]	**0.0364**	189 [147–238]	156 [127–187]	**<0.0001**
TLC % pred	113 [98–127]	115 [104–128]	0.3958	118 [106–132]	112 [100–124]	**0.0012**
RV/TLC %	60 [52–67]	53 [44–61]	**<0.0001**	61 [51–66]	53 [46–61]	**<0.0001**
SpO2 at rest	95 [92–96]	96 [94–97]	**<0.0001**	94 [92–96]	96 [95–98]	**<0.0001**

Notes: Data reported as percentages (numbers) or median [IQR Q1–Q3]. Significant (P< 0.05) shown in bold.
Abbreviations: 6MWD, 6-min walking distance; ADO, age, dyspnea and obstruction score; BMI, body mass index; BODE, obstruction, dyspnea and exercise score; HAD, Hospital anxiety and depression scale; mMRC, modified Medical Research Council scale for dyspnea; RV, residual volume; SGRQ, Saint George's Respiratory Questionnaire; SpO2, transcutaneous oxygen saturation; TLC, total lung capacity.

Table 3 (A) Multivariate analysis for low vs high 6MWD. (B) Multivariate analysis for the presence of desaturations

OR estimates		
Effect	**Point estimate**	**95% Wald confidence limits**
A		
Age/10 years	1.953	1.510	2.527
FVC/10% pred	0.794	0.707	0.890
mMRC	1.954	1.541	2.477
SpO2 at rest	0.857	0.787	0.933
B		
Age/10 years	0.661	0.507	0.861
Obesity yes vs no	0.457	0.242	0.864
Hypertension yes vs no	1.690	1.020	2.800
FEV1/10% pred	0.674	0.590	0.770
SpO2 at rest	0.701	0.632	0.778

Abbreviations: 6MWD, 6-min walking distance; mMRC, modified Medical Research Council scale for dyspnea; SpO2, transcutaneous oxygen saturation.

flow limitation and ventilatory pattern during the test. Interestingly, hyperinflation was also unrelated to EID, probably due to the major confounding effect and contribution of FEV_1. Age represents a major confounder, as it is present in all reference equations. As a consequence, it was present in the multivariate 6MWD model.

Previous studies also focused on the impact of comorbidities. Waatevik et al demonstrated a mean 60 m reduction of 6MWD in patients with at least 2 comorbidities, using the Charlson comorbidity score.[31] Impact of individual comorbidities was on the contrary rather modest in our model.

Unexpectedly, important comorbidities including CHF were unrelated to 6MWD. This result is in accordance with those of Spruit et al, in which pooled cardiovascular comorbidities were unrelated to the presence of a poor 6MWD.[32] Conversely, a markedly lower 6MWD was recently found in COPD patients with a reduced (<50%) left ventricular ejection fraction (397 m vs 456 m) vs those with similar GOLD severity but preserved left ventricular contractility.[33] A 30% reduction in cycle endurance time was also reported in COPD patients with coexisting CHF.[34] CHF is a frequent comorbidity in COPD and contributes to dyspnea, although it is often difficult to determine its specific impact in individual patients. In our study, we cannot exclude an underdiagnosis of CHF, particularly diastolic or with preserved ejection fraction, especially because of the lack of systematic echocardiography. A recent study in the CHANCE cohort from Netherlands demonstrated a significant contribution of echocardiographic right ventricular systolic pressure, timed up and go test and quadriceps endurance work in the multivariate analysis of 6MWD.[35] With the addition of GOLD stage, SGRQ activity, mMRC and resting lung function (FEV1, FEV1/FVC, diffusing capacity of the lung for carbon monoxide (DLCO) and PaO2), the model explained 72% of 6MWD variance. However, echocardiography and quadriceps assessment are not performed in routine practice for COPD evaluation. In addition, timed up and go test is rather considered as a surrogate than as a determinant of 6MWT. Peripheral artery disease was also associated with a lower 6MWD in the COSICONET cohort, as objectively defined by a low ankle-brachial index.[36]

One significant limitation of the present study regarding the 6MWD data is the lack of duplicate 6MWT. This was also the case in recent large-scale studies such as ECLIPSE.[10] In clinical practice, a second test is rarely performed due to time constraints. In addition, the mean gain induced by the second test is around 26 m.[5] When

Table 4 Multivariate analysis for 6MWD in absolute value (m)

Parameter	DF	Parameterestimate	SE	t value	Pr > |t|
Intercept	1	100.46004	168.52394	0.60	0.5514
Age	1	−3.22696	0.46779	−6.90	**<0.0001**
Obesity	1	−24.05947	11.73060	−2.05	**0.0409**
Hypertension	1	−20.54332	9.78203	−2.10	**0.0363**
Diabetes	1	33.89135	15.15119	2.24	**0.0258**
FEV1% pred	1	1.25108	0.25561	4.89	**<0.0001**
mMRC	1	−31.07953	4.65525	−6.68	**<0.0001**
SpO2 at rest	1	5.17758	1.73057	2.99	**0.0029**

Note: Significant (*P*< 0.05) shown in bold.
Abbreviations: 6MWD, 6-min walking distance; mMRC, modified Medical Research Council scale for dyspnea; SpO2, transcutaneous oxygen saturation.

considering the distribution of 6MWD in our cohort, the risk of misclassification (ie, classification of a patient below the cutoff value of 350 m instead of above this cutoff value) would be limited to those who were in the 300–349 m group: as shown in Figure 2, this group contained only 61 patients. Even assuming a high (50%) rate of misclassification, this would affect <7% (30/440) of patients in our study and thus be of little influence on the multivariate analysis results. A second test is currently mainly recommended for comparison over time, according to the latest ATS/ERS technical standards.[37]

Determinants of EID

Although the criteria used to define significant EID in the literature are heterogeneous, recent studies concur in finding a frequency of 21–39% for these events.[13,15] The proportion of EID was in the same range in our study. Several studies demonstrated the pejorative prognostic value of EID in COPD. The most extensive analysis was performed in the Bergen COPD cohort,[13] using EID criteria similar to ours. Their evaluation also comprised a Charlson index, arterial blood gases and bioelectrical impedance. The HR for death was 2 among patients with EID and 2.4 after adjustment for clinical data (including Charlson index), FEV1, baseline PaO2 and 6MWD. Other recent studies demonstrated a significantly worse survival in COPD subjects with EID.[8,38,39]

A number of predictors of EID during the 6MWT have been described. Abnormal resting gas exchange is a major determinant in most studies. A baseline SpO2 value ≤95% appeared to have a high predictive value, together with female sex, a DLCO <50% pred, FEV1<45% pred and PaO2<10 kPa.[14] A lower resting SpO2 threshold (93%) was found in the ECLIPSE cohort. Resting SpO2 was also present in our multivariate model with a significant OR (0.7).

Moderate-to-severe emphysema on quantified CT has also been found to be a significant predictor of EID,[15] but at present quantitative CT is not routinely used to assess emphysema in COPD patients. Unexpectedly, obesity was negatively related to EID in our cohort. Obesity was found to be a positive predictive factor of EID in a recent multivariate analysis in the ECLIPSE cohort.[15] Conversely, it was recently suggested that moderate obesity could improve dyspnea during exercise in COPD, by limiting the degree of dynamic hyperinflation during exercise.[40] Thus, the relation between obesity, exercise hyperinflation and EIDs remains to be elucidated.

Age had a moderate negative predictive value (OR 0.66 per 10 years) of EID in our patients. This finding is opposite to the reduction of 6MWD with age, which may be explained by less desaturation due to lower distance.

The only cardiovascular comorbidity significantly associated with 6MWT variables was hypertension with a 1.6 OR for EID. Hypertension could be associated with subclinical left heart diastolic dysfunction. However, no difference in 6MWT-induced desaturation was found recently in COPD patients with HF and reduced left ventricular ejection fraction.[33]

In our patients, hyperinflation (RV/TLC) was not a significant determinant of 6MWT or desaturation, which was likely related to a major interaction with FEV_1. Dynamic hyperinflation during exercise is currently considered as a major limiting factor, but recent data suggest a predominant role of ventilatory constraint per se (low inspiratory reserve volume), similar in patients with or without dynamic hyperinflation.[41]

One important strength of our study is the systematic assessment of clinical variables including comorbidities together with lung function parameters, including lung volumes. The present study has also some limitations. Most of our patients were recruited in university hospitals and therefore may not represent the global COPD population, with a lower proportion of spirometric stage I patients. The 6MWT was not performed in duplicate, which is also true for other large previous series including ECLIPSE.[10] An average learning effect of 26 m has been previously observed.[5] This small increment is unlikely to change the predictive value of our models if a second test had been performed in our cohort. A significant limitation of the present study is that the diagnosis of comorbidities was identified by physicians based on clinical evaluation and taking into account the medical history with no systematic assessment of the presence/absence and severity (for instance left ventricular ejection fraction, diastolic parameters and/or BNP measurement for CHF) of these comorbidities. However, it must be pointed out that the frequency of comorbidities in the present study is in line with other large observational studies in COPD. The Charlson index was unavailable but is obviously not used for the routine assessment of COPD patients. Furthermore, DLCO was not assessed in the present study, whereas it was found to be a significant predictor of 6MWD and desaturations in previous studies.[14] It is, however, not a standard assessment tool in recent guidelines[2] and clinical practice.

Conclusion

In conclusion, this study shows that, although related on a statistical ground, usual clinical data and resting lung function do not adequately predict either 6MWD or desaturations during the test. The present results also confirm the complexity of 6MWT determinants in COPD and suggest a low impact of common comorbidities, particularly clinically defined HF or coronary disease. In clinical practice, 6MWT performance remains difficult to predict with routine clinical and PFT parameters.

Abbreviation list

BMI, body mass index; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; HAD, Hospital Anxiety Depression score; IC, inspiratory capacity; mMRC, Modified Medical Research Council dyspnea scale; RV, residual volume; SpO2, oxygen saturation measured by pulse oximetry; TLC, total lung capacity.

Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Supplementary materials

Table S1 Univariate logistic analysis for low 6MWD

Effect	OR estimates	95% Wald confidence limits		Wald Chi-square	Pr > ChiSq
Female vs male	1.177	0.757	1.828	0.5227	0.4697
Age	1.056	1.034	1.079	24.4536	**<0.0001**
Low BMI yes vs no	1.232	0.628	2.416	0.3690	0.5435
Obesity yes vs no	1.518	0.929	2.481	2.7719	0.0959
Hypertension yes vs No	1.414	0.940	2.126	2.7609	0.0966
Ischemic heart disease yes vs No	1.456	0.830	2.554	1.7137	0.1905
Heart failure yes vs No	1.669	0.940	2.965	3.0538	0.0805
Diabetes yes vs No	1.125	0.590	2.145	0.1273	0.7213
OSAS yes vs No	0.840	0.403	1.751	0.2167	0.6416
Chronic bronchitis yes vs No	1.192	0.779	1.825	0.6567	0.4177
FEV1% pred	0.966	0.955	0.977	35.1247	**<0.0001**
FEV/FVC	0.073	0.015	0.360	10.3363	**0.0013**
FVC % pred	0.971	0.961	0.981	33.2866	**<0.0001**
RV (L)	1.214	1.047	1.409	6.5540	**0.0105**
TLC % pred	1.004	0.990	1.019	0.3466	0.5560
mMRC	2.234	1.798	2.776	52.6517	**<0.0001**
Exacerbations/patient/year	1.148	1.038	1.270	7.2482	**0.0071**

Note: Significant *P*-values shown in bold.
Abbreviations: BMI, body mass index; OSAS, obstructive sleep apnea syndrome; FEV1 % pred, forced expiratory volume in one second, percentage of predicted; FVC % pred, forced vital capacity, percentage of predicted; RV (L), residual volume in liters; TLC (L), total lung capacity in liters; TLC % pred, total lung capacity, percentage of predicted; mMRC, modified Medical Research Council dyspnea scale; 6MWD, 6-min walking distance.

Table S2 Univariate logistic analysis for the presence of significant desaturations

Effect	OR estimates	95% Wald confidence limits		Wald Chi-square	Pr > ChiSq
Sex female vs male	1.327	0.861	2.046	1.6424	0.2000
Age/10 years	0.840	0.690	1.024	2.9788	0.0844
Low BMI yes vs no	1.571	0.815	3.028	1.8185	0.1775
Obesity yes vs no	0.564	0.329	0.967	4.3370	**0.0373**
Hypertension yes vs no	1.272	0.850	1.905	1.3651	0.2427
Ischemic heart disease yes vs no	0.648	0.352	1.193	1.9404	0.1636
Heart failure yes vs no	0.801	0.436	1.472	0.5121	0.4742
Diabetes yes vs no	0.814	0.419	1.580	0.3712	0.5424
OSAS yes vs no	0.480	0.214	1.078	3.1579	0.0756
Chronic bronchitis yes vs no	1.084	0.714	1.643	0.1425	0.7058
FEV1% pred	0.952	0.940	0.964	58.3708	**<0.0001**
FEV1/FVC	0.003	<0.001	0.018	41.5437	**<0.0001**
FVC % pred	0.973	0.964	0.983	29.4992	**<0.0001**
RV (L)	1.346	1.158	1.563	15.0655	**0.0001**
TLC (L)	1.001	0.999	1.004	1.1197	0.2900
RV/TLC %	1.008	0.997	1.019	1.8886	0.1694
mMRC	1.490	1.231	1.804	16.7205	**<0.0001**
Exacerbations/patient/year	1.110	1.005	1.226	4.2674	**0.0388**

Note: Significant *P*-values shown in bold.
Abbreviations: BMI, body mass index; OSAS, obstructive sleep apnea syndrome; FEV1 % pred, forced expiratory volume in one second, percentage of predicted; FVC % pred, forced vital capacity, percentage of predicted; RV (L), residual volume in liters; TLC (L), total lung capacity in liters; mMRC, modified Medical Research Council dyspnea scale.