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Emphysema and DL_{CO} predict a clinically important difference for 6MWD decline in COPD

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Summary
Background: Exercise impairment is a central feature of chronic obstructive pulmonary disease (COPD), and a minimal clinically important difference (MCID) for 6-min walk distance (6MWD) decline (>30 m) has been associated with increased mortality. The predictors of the MCID are not fully known. We hypothesize that physiological factors and radiographic measures predict the MCID.
Methods: We assessed 121 COPD subjects during 2 years using clinical variables, computed tomographic (CT) measures of emphysema, and functional measures including diffusion lung capacity for carbon monoxide (DL_{CO}). The association between an MCID for 6MWD and clinical, CT, and physiologic predictors was assessed using logistic analysis. The C-statistic was used to assess the predictive ability of the models.
Results: Forty seven (39%) subjects had an MCID. In an imaging-based model, log emphysema and age were the best predictors of MCID (emphysema Odds Ratio [OR] 2.47 95%CI [1.28

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−4.76]). In a physiologic model, DL_{CO}, age, and male gender were selected the best predictors (DL_{CO} OR 1.19 [1.08−1.31]). The C-statistic for the ability of these models to predict an MCID was 0.71 and 0.75, respectively.
Conclusion: In COPD patients the burden of emphysema on CT scan and DL_{CO} predict a clinically meaningful decline in exercise capacity.

Introduction

The 6-min walk distance (6MWD) is commonly used to assess exercise capacity in COPD patients and exercise impairment is associated with increased risk for hospitalization and death [1−3]. The 6-min walk testing is easy-to-do and widely available, which also make it practical to assess interventions such as rehabilitation [4,5]. Given the importance this test has gained as a functional outcome in COPD, a minimal clinically important difference (MCID) for 6MWD decline of >30 m has been proposed [6]. While the prognostic value of a decline in 6MWD is becoming clear, the predictors of such MCID have yet to be fully defined but once identified would become an integral part of a COPD patient's evaluation.

In longitudinal studies in subjects with COPD a number of determinants are associated with a decline in exercise capacity including lung function [2,7], physical activity [8], and hospitalizations [9]. Greater burden of emphysema on computed tomography (CT) scans is also associated with lower exercise response following lung volume reduction surgery [10] and reduced 6MWD in cross sectional studies [4,11]. Additionally, a low diffusion capacity of the lung for carbon monoxide (DL_{CO}), a functional measure that reflects the quality of alveolar-capillary gas transfer [12], has been linked to decreased 6MWD in cross sectional studies [13,14] and to a blood marker (endothelial microparticles) of early lung destruction [15]. Identification of additional CT and functional predictors can refine a clinician's ability to predict this outcome. For example, emphysema on CT scan has been demonstrated to identify smokers at risk for an accelerated decline in FEV_1 [16] and may also have similar prognostic value for change in exercise capacity.

The aim of this study was to assess physiologic and imaging-based features and identify factors that potentially predict the MCID for 6MWD decline in subjects with Global Initiative for Obstructive Lung Disease (GOLD) [17] COPD stages 1−4 followed for 2 years. We hypothesize that physiological factors and radiographic measures predict the MCID.

Material and methods

Subject selection

We used data from the PELE (Proyecto de Evaluación Longitudinal de la Enfermedad Pulmonar Obstructiva Crónica) Study conducted in Chile [18]. Briefly, this a single-center, population-based, longitudinal study aimed to assess clinical, physiological, and imaging-based determinants of the decline in exercise capacity in smokers with COPD (defined as post-bronchodilator forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] <0.7) [17]. Inclusion criteria were age ≥45 years, ≥20 pack-years smoked, and no history of chronic lung diseases other than COPD. Exclusion criteria were the following: use of supplemental oxygen, current enrollment in pulmonary rehabilitation, and history of chronic heart failure, severe chronic renal failure, and other comorbidities that prevent the subjects from performing a 6MWD (e.g. vascular peripheral disease, neuromuscular compromise following stroke, and severe arthritis/arthrosis). Subjects were assessed at baseline and at years 1 and 2 of follow-up. Because of recruitment issues, criteria for both age and number of pack years were relaxed. As a consequence, among selected subjects there was 1 younger than 45 years and 5 with less than 20 pack-years. The study was approved by the institutional review board of the Catholic University of Chile, University of Chile, and the Brigham and Women's Hospital (protocol #2014P000411). Written informed consent was obtained from all participants.

Six-minute walk testing

At baseline, subjects performed first two practice 6MWDs followed by two additional ones in a separate visit and then two 6MWDs at years 1 and 2 [18,19]. The subjects performed the test in a 20 m corridor, were requested to walk at the maximum tolerated speed, and verbally encouraged every 1 min. For each subject the greater of the two 6MWDs was selected for analysis. The MCID for 6MWD was defined as a decrement of more than 30 m between baseline and year 2 [6]. We used this cut off point because the derivation cohort [6] for the MCID was comparable to our study population in terms of lung function and age.

Lung function

Subjects performed spirometric testing before and after 200 μg the administration of albuterol, single-breath DL_{CO}, and lung volume assessment according to international guidelines [20−22]. Spirometric, $DL_{CO,}$ and lung volume measurements were standardized as percentages of predicted values as described previously [23−25]. Inspiratory capacity (IC) was measured as described elsewhere [18] and the IC/TLC (total lung capacity) ratio was also calculated.

Clinical assessment and blood testing

Clinical data including smoking history, dyspnea, acute exacerbations of COPD, and comorbidities were collected with standardized instruments. A blood sample was drawn to measure arterial blood gas, hemoglobin, cholesterol, and glucose. Dyspnea was scored with the modified Medical Research Council (mMRC) Dyspnea scale and the score was dichotomized as <2 or ≥ 2. Self-reported exacerbations in the year prior to enrollment were based on a questionnaire. During follow-up subjects were asked to contact the investigator team if they had changes in their respiratory symptoms (increasing cough, shortness of breath, phlegm, or reporting new purulent sputum) for 2 consecutive days. An exacerbation was recorded only if the subject's primary care provider or a physician of the research team prescribed antibiotics and/or systemic corticosteroids for or an episode required hospitalization [26]. The frequency of such events in the year prior to enrollment was dichotomized about 2 (<2 or ≥ 2) episodes [26]. Assessment of comorbidities at baseline was based on subject's self-report data, chart review, and objective measurements. Myocardial infarction was defined as self-reported history of heart attack verified on chart review. Hypertension was defined based on the presence of one of the following criteria: 1) self-reported physician diagnosis of high blood pressure and use of antihypertensive medication; 2) diastolic blood pressure ≥ 90 mm Hg or systolic blood pressure ≥ 140 mm Hg. Diabetes was considered based on 1) self-reported history of diabetes and use of diabetes medication or 2) fasting blood glucose ≥ 126 mg/dl. Obesity was defined as BMI ≥ 30 kg/m^2. Anemia was present if hemoglobin level was <13 g/dL in males and females. Hypercholesterolemia was defined as fasting total cholesterol level >200 mg/dL or use of lipid-lowering agents. Depression was considered if the subject self-reported a physician diagnosis and was using medication for depression. The presence of gastroesophageal reflux disease (GERD) was based on the Frequency Scale for the Symptoms of GERD (FSSG) questionnaire, which has been used in COPD [27]. Briefly, this is a 12-item questionnaire where each question has a score ranging from 0 (no symptoms) to 4 (always with symptoms). GERD was defined as being present in those subjects who reported a symptom score of ≥ 8 points. The total number of comorbidities was calculated for each subject and grouped as 0, 1–2, and ≥ 3 for the analyses.

CT imaging

A volumetric CT scan examination of the chest at full inflation and the thigh muscle was performed as previously detailed [18]. Briefly, subjects were imaged in a 64-row multidetector scanner (Somatom Sensation 64; Siemens Healthcare; Erlangen, Germany), which was calibrated daily for air, and every 3 months for water. Chest CT acquisition protocol was as follows: 120 kVp, 200 mAs, and 0.33 s rotation time. Images were reconstructed using an algorithm (B45f) at 1 mm slice thickness and 0.5 mm interval. Emphysema was defined as percent of low attenuation areas less than -960 Hounsfield Units (%LAA-960) [18]. CT cross-sectional area of the right thigh muscle was determined following a method described elsewhere [28].

Statistical analysis

Analysis was performed with SAS 9.3 (SAS Institute, Cary, NC). Baseline variables were compared using parametric and non-parametric tests based on the variable distribution. The association of clinical, physiologic, and imaging-based factors with MCID for 6MWD decline was assessed using logistic regression analysis. Model building was performed in 3 steps. First, variables were selected based on statistical significance ($P < 0.05$) in univariate analysis shown in Table 2 (age and gender were excluded from input list and forced in the last step). Second, the four selected variables (mMRC dyspnea score ≥ 2, FEV_1, IC/TLC ratio, arterial oxygen tension [PaO_2]) were then combined with % LAA-960 in one model (imaging-based model) and with DL_{CO} (to make it comparable with %LAA-960 it is expressed as observed maximum DL_{CO}-subject's DL_{CO}) in a separate model (physiologic model). We used this approach because these parameters are highly correlated with each other with one providing morphologic and the other physiologic information on the gas-exchanging surface of the lungs. In the second step variable selection was performed using stepwise method. We then assessed the predictive accuracy of these models using the C-statistic, an estimate of the area under the receiver operating characteristic (ROC) curve [29]. Finally, age and gender were added to the models obtained in step 2 based on a P value of <0.05 and/or a change in C-statistic >0.01. Since %LAA-960 was skewed it was log transformed for logistic analysis. Secondary analyses using four predictions equations [24,30–32] for DL_{CO} and hemoglobin-adjusted [33] DL_{CO} values were also conducted. We used these equations since the lack of reference values for the Chilean population.

Results

At enrollment 140 subjects had COPD and 121 (86%) had a 6MWD at baseline and year 2. Nineteen subjects had missing data on 6MWD at year 2 due to death ($n = 11$) or lost to follow-up ($n = 8$). GOLD COPD stage distribution was as follows: I, 37 (31%); II, 41 (34%); III, 26 (21%); and IV, 17 (14%). Table 1 shows subjects' characteristics at baseline by MCID status. Compared to the subjects who did not meet the criterion for MCID for 6MWD, those who met the MCID were more likely to be older and report higher frequency of dyspnea. These subjects had significantly greater expiratory airflow obstruction and static hyperinflation as measured by IC/TLC. Decliners had higher indices of lung parenchyma destruction as measured by DL_{CO} and %LAA-960 on CT scan along with lower PaO_2. They also tended to have more exacerbations prior to enrollment ($P = 0.06$). Decliners were more likely to use short-acting bronchodilators and long-acting bronchodilators. We found no differences in body mass index, smoking intensity, lung volume, thigh muscle wasting, inhaled corticosteroids use, 6MWD, and the number of comorbidities between the two groups. During a median follow-up of 2.1 years 90 (74%) subjects experienced one or more exacerbations and 17 exacerbation

Table 1 Demographic, clinical, physiologic, and CT imaging data by the MCID for 6MWD status in COPD subjects.

Characteristic	With MCID (N = 47)	Without MCID (N = 74)	P Value
Age, yr	69 ± 9	64 ± 8	0.003
Male gender, n (%)	29 (62)	39 (53)	0.33
BMI, kg/m^2	27 ± 4	27 ± 4	0.42
Pack years smoked	44 (32–62)	42 (34–60)	0.87
Current smoking status, n (%)	10 (21)	27 (36)	0.08
mMRC dyspnea score ≥2, n (%)	32 (68)	31 (42)	0.005
FEV_1, L	1.4 ± 0.7	1.8 ± 0.8	0.009
FEV_1 % predicted	56 ± 22	68 ± 24	0.01
IC, L	2.1 (1.7–2.9)	2.4 (1.8–3.1)	0.22
IC % predicted	93 ± 23	88 ± 24	0.24
TLC, L	6.4 ± 1.5	6.5 ± 1.5	0.72
TLC % predicted	118 ± 20	118 ± 17	0.97
IC/TLC, %	38 ± 11	44 ± 10	0.04
DL_{CO}, ml CO min	15.2 ± 5.7	19.2 ± 6	<0.0001
DL_{CO} % predicted	63 ± 17	77 ± 21	<0.0001
PaO_2, mm Hg	71.7 ± 10.8	75.9 ± 10.5	0.009
$PaCO_2$, mm Hg	39.8 ± 5.1	39.5 ± 4.4	0.77
CT %LAA-960	10.4 (5.5–17.9)	16.8 (10.3–25.8)	0.002
CT Cross sectional area of right thigh muscle, cm^2	61 ± 18	66 ± 18	0.16
Six-minute walk distance, m	472 ± 70	496 ± 103	0.14
Two or more exacerbations the year prior to enrollment, n (%)	24 (51)	25 (34)	0.06
Comorbidities, n (%)			0.34
0	5 (11)	15 (20)	
1–2	29 (62)	34 (46)	
≥3	13 (28)	25 (34)	
Treatment, n (%)			
Short-acting bronchodilator	40 (85)	44 (59)	0.003
Long-acting bronchodilator	37 (79)	41 (55)	0.009
Inhaled corticosteroid	33 (70)	40 (54)	0.08

Data is presented as mean ± standard deviation, median (interquantile range), or number (%) as appropriate. Missing data: PaO_2 2, $PaCO_2$ 2.

Abbreviations: CT, Computed Tomography; MCID, Minimal Clinically Important Difference; 6MWD, Six-minute Walk Distance; COPD, Chronic Obstructive Pulmonary Disease; BMI, Body Mass Index; mMRC, modified Medical Research Council; FEV_1, Forced Expiratory Volume in 1 Second; IC, Inspiratory Capacity: TLC, Total Lung Capacity; DL_{CO}, Diffusing Lung Capacity for Carbon Monoxide; PaO_2, Arterial Oxygen Tension; $PaCO_2$, Arterial Carbon Dioxide Tension; %LAA-960 HU, Percent of Low-attenuation Areas Less Than −960 Hounsfield Units.

episodes required hospitalization (exacerbation-related hospitalization rate 0.10/yr). There was no difference in the annual exacerbation rate between decliners and non-decliners (1.52/yr vs. 1.44/yr P = 0.81).

Decline in 6MWD

The mean ± SD 6MWD decline over two years was 21.8 ± 46.1 m and its distribution is shown in Fig. 1. The MCID for 6MWD decline was observed in 47 (39%) subjects. Thirty eight (31%) subjects had a decline ≤30 m or no change and 36 (30%) increased their walked distance. The MCID was observed more often in subjects with severe and very severe COPD than those with mild and moderate COPD (51% vs. 32%, P = 0.04).

Association of CT and physiologic predictors to MCID for 6MWD

Univariate analyses (Table 2) showed that increasing age, log %LAA-960 on CT scan, and DL_{CO} (expressed as maximum DL_{CO}-subject's DL_{CO}), and mMRC dyspnea score ≥2 statistically significantly increased the odds of an MCID. In contrast, greater FEV_1, IC/TLC, and PaO_2 decreased the odds of an MCID. Among all the 6 significant predictors of Table 2 (excluding age and DL_{CO}) automated stepwise method selected %LAA-960 as the only predictor of the MCID (imaging-based model). Addition of age resulted in a C-statistic increase of 0.04 units (C-statistic, from 0.67 to 0.71) and gender added no predictive ability nor was significant in this model (Fig. 2, Table 3). In this model, %LAA-960 increased the odds for 6MWD (Odds Ratio [OR] 1.19, 95% Confidence Interval [CI] 1.08–1.31). Further adjustment for 6MWD at baseline (P = 0.65) did not increase model C-statistic. When DL_{CO} was used in place of %LAA-960, DL_{CO} was selected as the only variable associated with MCID (physiologic-based model). In the model with DL_{CO} (OR 2.47 [1.28–4.76]), addition of gender and age increased the C-statistic by 0.04 and 0.03 units, respectively (full-model C-statistic, 0.75) (Fig. 2, Table 3). When baseline 6MWD (P = 0.03) was added to the physiologic-based model with age and gender, C-statistic increased 0.036 units. A model with previously identified risk factors [2] including age, BMI, and FEV_1 had a C-statistic of 0.68.

Secondary analyses

Expressed as a percent of predicted rather than as an absolute value, the DL_{CO} % predicted (expressed as 100 − DL_{CO} % predicted) was associated with MCID for 6MWD decline regardless of the equation type (OR range 1.03–1.05; C-statistic range, 0.68 − 0.71; P ≤ 0.002 for all models). Similarly hemoglobin-adjusted DL_{CO} (expressed as maximum hemoglobin-adjusted value-subject's hemoglobin-adjusted DL_{CO}) was selected when used as input variable for the stepwise selection method. In a model along with age and male gender, hemoglobin-

Table 2 Univariate analysis for MCID for 6MWD decline in COPD subjects.

Variable	OR (95%CI)	P
Age, yr	1.07 (1.02–1.12)	0.004
Male gender	1.45 (0.69–3.04)	0.33
BMI, kg/m^2	1.04 (0.95–1.13)	0.42
Current smoking status	0.47 (0.20–1.09)	0.08
mMRC dyspnea score ≥2	2.96 (1.37–6.38)	0.006
FEV_1 per 100 ml	0.93 (0.88–0.98)	0.01
IC/TLC ratio	0.96 (0.923–0.998)	0.04
DL_{CO}[a], ml CO min	1.14 (1.06–1.23)	0.0006
PaO_2, mmHg	0.95 (0.92–0.99)	0.01
Log %LAA-960	2.73 (1.45–5.14)	0.002
CT Cross sectional area of right thigh muscle, cm^2	0.98 (0.96–1.00)	0.16
Two or more exacerbations the yr prior to enrollment	2.05 (0.97–4.32)	0.06
Exacerbation rate per yr during follow-up	1.02 (0.86–1.21)	0.82
Comorbidity, n		
0	Ref	
1–2	2.56 (0.83–7.90)	0.10
≥3	1.56 (0.54–2.35)	0.47

[a] DL_{CO} is expressed as the difference between maximum DL_{CO} of the cohort and subject's DL_{CO}.

adjusted DL_{CO} increased the odds of an MCID (OR 1.52 [1.21–1.92]; P = 0.0004) and the C-statistic was 0.75. Finally, when the 6 subjects who did not meet the initial study entry criteria were excluded, results shown in Table 3 were comparable (data not shown).

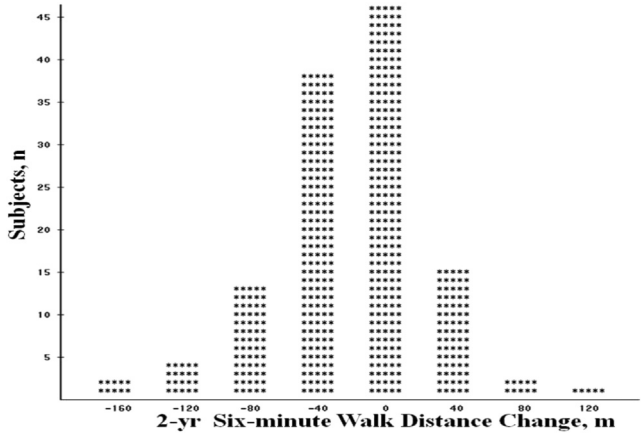

Figure 1 Distribution of the change in 6MWD (meters) over 2 years in COPD subjects.

Table 3 Multivariate analysis for MCID for 6MWD decline in COPD subjects.

Model	Or (95%CI)	P
Model 1		
DL_{CO}[a]	1.19 (1.08–1.31)	0.0005
Male	3.24 (1.24–8.49)	0.02
Age	1.04 (0.98–1.09)	0.18
Model 2		
Log %LAA-960	2.47 (1.28–4.76)	0.007
Age	1.06 (1.01–1.11)	0.02

P = 0.62 for Hosmer and Lemeshow Goodness-of-Fit Tests for Model 1 and Model 2.

[a] DL_{CO} is expressed as the difference between maximum DL_{CO} of the cohort and subject's DL_{CO}.

Discussion

We evaluated the MCID for 6MWD in 121 subjects with COPD over two years using CT, clinical, and physiologic assessments. We found that more than a third of the subjects met criterion of MCID for 6MWD decline (>30 m). We also found that in addition to the factors previously identified as predictors of change in 6MWD, novels factors such as the burden of emphysema on CT scans or DL_{CO} at baseline accurately predicted this clinically relevant functional outcome.

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Study has identified age, body mass index, and lung function as factors associated with the decline in 6MWD [2]. Additional investigation in COPD subjects has shown that low physical activity [8] at baseline and all-cause hospitalizations [9] are also associated with 6MWD decline. We and others have also found that greater burden of emphysema on CT scans is associated with decreased exercise capacity following lung volume reduction surgery [10] and lower 6MWD in cross sectional studies [4,11]. Furthermore, a recent study [6] showed that when a subject's 6MWD decline is greater than 30 m he/she has an increased risk for mortality, a finding substantiated by prior investigation [5,34,35]. Although such studies used densitometric measures of emphysema on CT scans or DL_{CO} to characterize their subjects [2,4,9], no information was reported on the association between these measures and the change in 6MWD. We built on this prior knowledge by demonstrating that both an anatomic surrogate (emphysema on CT scan) and a physiologic measure of lung gas-exchanging surface predict the MCID for this functional outcome. The fact that we found comparable results when using hemoglobin-adjusted or % predicted DL_{CO} values substantiate our novel findings. The results of our multivariate models also demonstrate that these measures are additive or complimentary to factors previously identified as predictors of exercise capacity decline. Thus, our analysis suggests that emphysematous destruction of the lung parenchyma as measured by CT scan or DL_{CO} seems not only to be a critical factor predicting an MCID but also provides evidence to use either measure to refine the prediction of the 6MWD decline. Our data is in keeping with a recent study showing

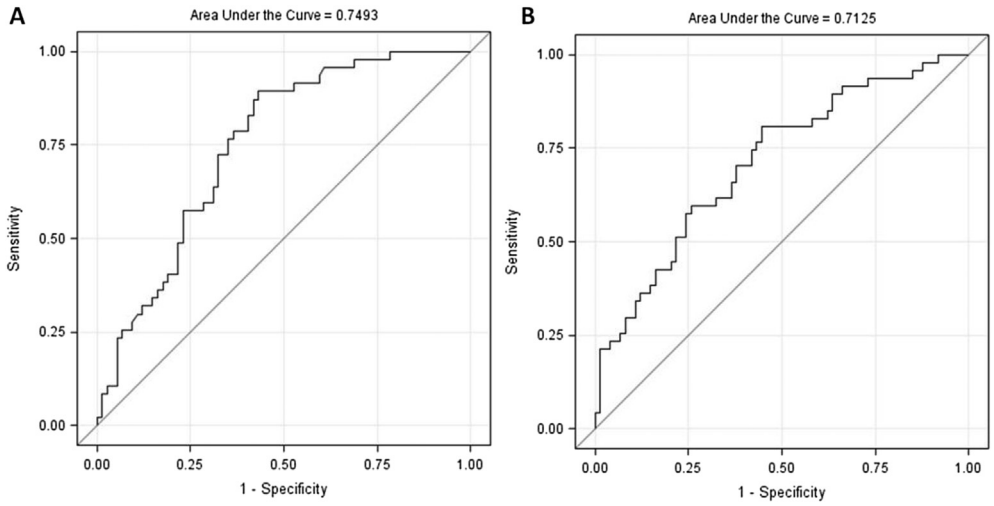

Figure 2 Receiver operating characteristic (ROC) curves for the minimal clinically important difference for 6-min walk distance decline in COPD subjects. Panel **A** shows the curve of a model with DL_{CO}, age, and male gender. Panel **B** depicts the curve of a model with log %LAA960 on CT scan and age.

that even in ex-smokers without airflow obstruction decreased DL_{CO} was associated with lower 6MWD [13]. Our findings may have clinical implications. Using either measure of lung parenchyma destruction may be useful to identify patients at higher risk to decline their 6MWD and design the appropriate interventions. In the light of the increasing use of CT to screen high-risk subjects for lung cancer [36], our data suggest that there are broader clinical applications to this imaging tool including predicting decline in 6MWD. Similarly, using DLCO as part of an initial pulmonary function work up for a COPD patient is supported by our findings.

In our study we found no effect of exacerbations on the MCID for the 6MWD. This is in contrast with a recent study showing that hospital admission and COPD-related hospitalizations are associated with a decrease in 6MWD over 2 year follow-up. One potential explanation may be differences in the respective cohorts. First, Ramon et al. study [9] consisted of subjects with more severe COPD enrolled at the time of hospital admission, while subjects in the PELE study were enrolled from the outpatient community. Compared to PELE, their subjects also had lower 6MWD at baseline (difference, 54 m). These differences in part may explain the differences in the relationship between hospitalization rate and decline in 6MWD between the studies. In particular, we noticed that in our physiologic-based model, the 6MWD at baseline was associated with MCID. Then the question is as to why indices of lung parenchymal destruction are related to the decline in this functional outcome.

Emphysema is associated with loss of elastic recoil leading to airflow limitation and gas trapping which in turn may contribute to reduce exercise capacity. An additional consequence of emphysema is lung hyperinflation, which can also contribute to 6MWD decline [37]. Recently it has been shown that both a greater burden of emphysema on CT scans and lower DL_{CO} are associated with loss of pulmonary vessels lower than 5 mm^2 [38]. The loss of small pulmonary vasculature may increase vascular resistance even in subjects with mild emphysema leading to an increased load on the right ventricle and thus reducing the left heart filling [39], which in turn may compromise oxygen delivery to locomotor muscles. This latter may be an additional factor linking the destruction of gas-exchanging surface and the decline in exercise capacity in COPD subjects. Another link between emphysema and decline in 6MWD might be exertional dyspnea as it has been demonstrated in a cross sectional study [40] and it is supported by the association between mMRC score and decline in 6MWD in univariate analysis we observed. Thus, emphysema might increase the ventilatory demand, which in turn may lead to exertional dyspnea and decline on physical activity.

Another important finding is that 30% of the subjects improved their 6MWD over two years. A prior study in more severe COPD subjects found that 20% had a 6MWD improvement over two years of follow-up [9]. Together these findings highlight the longitudinal variability in this outcome. Potential explanations for increasing exercise capacity are as follows: a) our subjects had a more benign course of the disease with a lower exacerbation-related hospitalization rate as compared with ECLIPSE subjects (0.10 vs. 0.22) [26]; b) improvers may preferentially reflect patients who started or remained on bronchodilator therapy. Prior investigation has demonstrated that bronchodilator therapy improves exercise capacity [41]; and c) subjects may have kept at least a moderate daily physical activity level, which also decreases the odds of 6MWD decline [8]. Note that no subject received rehabilitation during the follow-up.

Strengths of our study are a detailed physiologic and morphologic characterization of their subjects who had a full range of COPD stages as well as its high retention rate at the end of the follow-up. Several limitations should be acknowledged though. First, we could not account for important factors previously associated with 6MWD decline such as all-cause hospitalization [9] and physical activity [8] as we did not collect data on these factors at baseline, which may potentially bias our estimates of the associations observed; however, it is unlikely that those factors dilute

the emphysema or DL_{CO} effects completely. We collected data on COPD exacerbation-related hospitalizations the year prior to enrollment and during follow-up and found that there were 9 and 17 of such events, respectively. Although these are a low number of events it suggests that in our cohort this factor may have not been relevant. It should note that exacerbations were self-reported and thus potential under-reporting and non-differential misclassification is possible. We had morphologic information on thigh muscle but not a measure of its strength. However, prior investigation has shown that cross sectional area of the quadriceps is associated with its strength in COPD subjects validating the use of this morphologic assessment [42]. We used a straight walking course (20 m) at maximal tolerated speed using standardized encouragement prompts. Our course length is shorter than that recommended by international guidelines [19] and potentially underestimated walking distance. However, the effect of course length on distance is controversial. A study demonstrated that course lengths ranging from 15 to 55 m has no significant effect on walking distance [43], while another one using a 10-m straight length course (vs. 30-meter) showed significant lower 6MWD [44]. Because of these differences in walking testing between our and prior studies, which limits external validity, caution should be exercise when comparing our results with prior reports. However, the course length or maximum tolerated pacing we used is not likely to affect the relationships of 6MWD decline with DL_{CO} and %LAA-960 we observed. Finally, we used 6MWD as a binary outcome instead as a continuous one. While using this approach may lead to a loss of statistical power, this allowed us to refine the prediction of a demonstrated clinically relevant decline in 6MWD using CT and physiologic data.

In summary, this study in COPD subjects demonstrates that both emphysema on CT scan and DL_{CO} are predictors of a minimal clinically important difference in 6MWD decline.

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Conflicts of interest statement

Dr. Alejandro A. Díaz, Victor Pinto-Plata, Cristóbal Ramos, Juan C Díaz, Julieta Klaassen, Cecilia M Patino, Fernando Saldías, and Orlando Díaz and Miss Camila Hernandez and Mr. Javier Peña have no conflicts of interest to disclose.

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