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Relation of Indices of Lung Hyperinflation to Dyspnea in Patients with Chronic Obstructive Pulmonary Disease: A Physiologic Assessment and Discussion

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Abstract

Background: The severity of COPD is commonly assessed by the reduction in forced expiratory volume at one second (FEV_1), although more recently prognostic factors influencing survival have also incorporated functional capacity, degree of breathlessness on exertion, and body mass index. Increasingly, the reliability of physiological parameters such as FEV_1 to predict patient-centered outcomes has been brought into question. *Objectives*: To evaluate the relationship between dyspnea as assessed by the Modified Medical Council Dyspnea (MMRC) scale, the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2014) staging and indices of lung hyperinflation and spirometry. *Methods*: Data were retrospectively analyzed at a 600-bed tertiary care center including spirometry, plethysmographic lung volumes, single breath carbon monoxide diffusion capacity and dyspnea graded according to MMRC, and GOLD staging. *Results*: Data for 331 patients were analyzed. Differences amongst FEV_1, IC, IC/TLC, FRC and RV/TLC were significant between GOLD I/II and GOLD III/IV groups. The closest relationship to GOLD staging was seen with FEV_1, FVC and slow vital capacity (SVC). FEV_1/FVC, IC, and IC/TLC were inversely associated with MMRC score, while RV/TLC exhibited a positive relation with MMRC score. *Conclusions*: Indices of lung hyperinflation are closely associated, with dyspnea as assessed by MMRC grading with TLC, RV/TLC and IC exhibiting the closest relations, more so than FEV_1. GOLD staging also shows strong correlations with lung volume subdivisions (weakly with TLC), more so than with FEV_1.

That TLC changed little between GOLD stages can be explained by the presence of collateral interalveolar channels and population characteristics different from those of other studies. These findings further support the concept that more than a reduction in FEV_1, lung hyperinflation contributes to the sensation of dyspnea in airflow limitation.

Keywords

Chronic Obstructive Pulmonary Disease, Dyspnea, Expiratory Flow Limitation, Hyperinflation, Inspiratory Capacity

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous group of disorders characterized by incompletely reversible expiratory flow limitation [1]. Its severity is usually characterized by a decrease in forced expiratory volume at one second (FEV_1) [1], although more recently prognostic factors influencing survival have also incorporated functional capacity, degree of breathlessness on exertion, and body mass index [2] [3]. One of the aims of the recent American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement was to investigate the relationship between patient-centered outcomes (such as quality of life and symptomatology) and physiologic outcomes [4]. Increasingly, the reliability of FEV_1 to predict patient-centered outcomes has been brought into question [5]. Lung hyperinflation has been shown to be a major component of physical impairment in patients with airflow limitation [1] [6]. Indeed, the most recent update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2017) de-emphasizes the importance of FEV_1 in favor of symptoms, numbers of exacerbations and exercise capacity in grading the severity of COPD [6].

The main objective of this study was to evaluate the relationship between dyspnea as assessed by the Modified Medical Council Dyspnea (MMRC) scale, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging and indices of lung hyperinflation and spirometry. A secondary objective was to determine lung volume subdivisions most closely related to indices of dyspnea. We discuss these physiologic changes in light of recent imaging findings of ultrastructural changes described in emphysema. Related to this, we discuss a discrepancy between the reduction in vital capacity (VC) and corresponding changes in total lung capacity (TLC) with increase in GOLD and MMRC gradings.

2. Patients and Methods

Data collected at Los Angeles County + University Southern California (USC) Medical Center, a 600-bed tertiary care center were retrospectively analyzed. The investigation was approved by the institutional review board of the USC Health Sciences Center (HS-17-00120). Data were collected in stable patients with

COPD aged 18 - 80 years with a diagnosis of chronic obstructive pulmonary disease based on ATS/ERS criteria [1] [4]. Clinical, physiologic and imaging features were used for confirming the diagnosis of COPD. Patients with post-tuberculosis airflow limitation, infiltrative respiratory diseases, chest wall and neuromuscular disorders, left ventricular heart failure, and those unable to perform lung function testing according to ATS guidelines were excluded. All patients were living in Los Angeles County at the time of evaluation. Pulmonary function testing was performed between 2008 and 2013. Testing was performed in seated patients, consisting of post-bronchodilator spirometry (which included the slow vital capacity, SVC), lung volume subdivisions measured by body plethysmography, and single-breath carbon monoxide diffusion capacity (D_LCO), according to American Thoracic Society guidelines [7]. All cases met inclusion criteria of post-bronchodilator ratio of forced expiratory volume at one second (FEV_1) to forced vital capacity (FVC) less than 0.7 to qualify for the ATS/ERS definition of chronic obstructive pulmonary disease (COPD) [7]. Predicted values for spirometric indices, lung volumes and D_LCO were from Schoenberg *et al.* [8], Crapo *et al.* [9] and Knudson *et al.* [10], respectively. Predicted values for inspiratory capacity (IC) were derived from Bates [11]. In patients with more than one PFT performed in the period studied, the earliest measurement was used for analysis. Dyspnea was graded according to 3 grades of the MMRC scale (0, 2 and 4) based on a questionnaire administered by the laboratory technologist [12]. Severity of COPD was graded based on the GOLD 2014 staging [13].

Statistical Analysis

Multivariable ordered logistic regression was used to identify patient characteristics and lung function values associated with MMRC and GOLD 2014 staging [14]. The initial ordered multivariable logistic regression model included all variables from the univariate analyses that were associated with MMRC at a significance level of $p \leq 0.10$. All continuous predictors were standardized. The score chi-square test was used to assess the proportional odds assumption; because the proportional odds assumption was rejected at $p < 0.05$, model assumptions for an ordered logistic regression were not met. Variables were then removed and added in a stepwise fashion until a final model with all variables jointly significant at $p < 0.15$ was arrived at. Significances in differences between lung function variables amongst MMRC and GOLD staging were determined by analysis of variance.

3. Results

3.1. Patient Characteristics

Data for 331 patients. Median (IQR) age, history of smoking, and BMI for the entire cohort was 58(11) years, 21(42) pack-years, and 27(10) kg/m^2, respectively. **Table 1** lists anthropometric and physiologic data for the 331 patients, divided into 3 subcohorts based on MMRC grades of 0, 2 and 4. As can be seen,

the mean age was 58 years across all 3 cohorts, while approximately two-thirds of the patients were males. The largest ethnic group was Hispanic (42% of all patients). Table 2 shows the breakdown of the same characteristics based on GOLD I-IV, in which their distribution was similar to that in Table 1. Of note, however, was that while the proportion of males tended to decrease as severity of dyspnea (estimated by MMRC) increased, the opposite trend was seen with GOLD stage: the majority of patients in the GOLD IV group was male.

Table 1. Baseline characteristics by MMRC (N = 331)*.

Baseline Characteristic *N*(%)	MMRC			
	(0) No Dyspnea	(2) Moderate Dyspnea	(4) Severe Dyspnea	P-value†
Number of PFTs	76 (23.0%)	147 (44.4%)	108 (32.6%)	-
Male	56 (73.7%)	96 (65.3%)	64 (59.3%)	0.13
Age, *years* (*mean* ± *SD*)	58.3 ± 1.0	58.1 ± 10.7	58.1 ± 10.6	0.99
BMI, kg/m^2 (*mean* ± *SD*)	26.4 ± 5.6	28.5 ± 7.4	27.9 ± 8.1	0.11
Race				
White	18 (23.7%)	34 (23.1%)	20 (18.5%)	
Hispanic	33 (43.4%)	61 (41.5%)	45 (41.7%)	
Black	11 (14.5%)	36 (24.5%)	24 (22.2%)	0.52
Asian	12 (15.8%)	15 (10.2%)	18 (16.7%)	
Other	2 (2.6%)	1 (0.7%)	1 (0.9%)	

*See text for additional sociodemographic and clinical details of patients. †See text for details of statistical analysis.

Table 2. Baseline characteristics and exacerbation category by GOLD stage (N = 331).

Baseline Characteristic *N*(%)	GOLD Stage				P-value†
	1	2	3	4	
Number of PFTs	98 (29.6%)	150 (45.3%)	60 (18.1%)	23 (7.0%)	-
Male	66 (67.4%)	95 (63.3%)	35 (58.3%)	20 (87.0%)	0.09
Age, *years* (*mean* ± *SD*)	59.7 ± 10.4	57.9 ± 10.7	57.2 ± 10.4	54.9 ± 9.3	0.17
BMI, kg/m^2 (*mean* ± *SD*)	26.5 ± 5.1	28.9 ± 7.3	29.2 ± 9.8	22.9 ± 4.9	<0.001
Race					
White	21 (21.4%)	32 (21.3%)	15 (25.0%)	4 (17.4%)	
Hispanic	41 (41.8%)	70 (46.7%)	21 (35.0%)	7 (30.4%)	
Black	19 (19.4%)	31 (20.7%)	14 (23.3%)	7 (30.4%)	0.63
Asian	16 (16.3%)	14 (9.3%)	10 (16.7%)	5 (21.7%)	
Other	1 (1.0%)	3 (2.0%)	0	0	

*See text for additional sociodemographic and clinical details of patients. †See text for details of statistical analysis.

3.2. Lung Volume Subdivisions and Their Relation to MMRC and GOLD Grades

Table 3 and Table 4 list lung volume subdivisions according to MMRC and GOLD gradings, respectively; they show significant differences amongst most lung volume subdivisions between MMRC and GOLD stages. In particular, differences amongst SVC, FEV_1, IC, IC/TLC, FRC, RV/TLC and D_LCO were significant between GOLD I/II and GOLD III/IV groups as well as between MMRC 0 and 4 grades. However, FEV_1 did not exhibit as strong a relationship with GOLD staging as did plethysmographic lung volumes. By contrast, differences amongst TLC values between GOLD stages were weakly statistically significant.

Table 3. Lung volume subdivisions by MMRC (N = 331).

Lung Volume Subdivisions	MMRC			
	0 (n = 76)	2 (n = 147)	4 (n = 108)	P-value†
FVC, *liters*	3.6 ± 1.1	3.2 ± 1.0	2.6 ± 0.9	0.002
FVC, % *pred*	93.6 ± 19.6	87.5 ± 19.2	73.8 ± 22.6	<0.001
SVC, *liters*	3.8 ± 1.0	3.3 ± 1.1	2.9 ± 0.9	0.009
SVC, % *pred*	100.0 ± 18.6	90.9 ± 20.1	79.9 ± 19.6	<0.001
FEV1, *liters*	2.1 ± 0.7	1.8 ± 0.7	1.5 ± 0.7	0.005
FEV1, % *pred*	77.5 ± 19.9	67.5 ± 22.1	56.6 ± 24.1	0.01
FEV1/FVC	0.60 ± 0.09	0.55 ± 0.13	0.54 ± 0.11	<0.001
TLC, *liters*	6.1 ± 1.2	6.1 ± 1.5	5.6 ± 1.5	<0.001
TLC, % *pred*	104.9 ± 21.4	110.4 ± 18.3	103.2 ± 20.7	<0.001
FRC, *liters*	3.6 ± 0.8	3.8 ± 1.1	3.7 ± 1.3	<0.001
FRC, % *pred*	113.7 ± 24.7	122.0 ± 30.3	121.1 ± 35.7	<0.001
RV, *liters*	2.5 ± 0.8	2.9 ± 1.1	2.9 ± 1.2	<0.001
RV, % *pred*	126.3 ± 37.6	151.9 ± 50.6	157.2 ± 57.6	<0.001
IC, *liters*	2.5 ± 0.8	2.4 ± 0.8	1.9 ± 0.7	<0.001
IC, % *pred*	96.1 ± 23.8	95.4 ± 22.9	80.6 ± 25.2	<0.001
IC/SVC	0.67 ± 0.11	0.73 ± 0.12	0.71 ± 0.14	<0.001
IC/TLC	0.40 ± 0.07	0.39 ± 0.09	0.35 ± 0.10	<0.001
FRC/TLC	0.60 ± 0.07	0.61 ± 0.09	0.65 ± 0.10	<0.001
RV/TLC	0.41 ± 0.10	0.47 ± 0.11	0.51 ± 0.12	<0.001
SVC/FVC	1.02 ± 0.06	1.02 ± 0.11	1.03 ± 0.08	<0.001

See list of abbreviations at beginning of text. †Analysis of variance.

Table 4. Lung volume subdivisions by GOLD Stage (N = 331).

Lung Volume Subdivisions	GOLD Stage				P-value†
	1 (n = 98)	2 (n = 150)	3 (n = 60)	4 (n = 23)	
FVC, *liters*	3.8 ± 0.9	3.1 ± 0.9	2.3 ± 0.7	1.9 ± 0.7	<0.001
FVC, % *pred*	104.2 ± 12.6	84.8 ± 14.6	64.9 ± 14.3	48.1 ± 16.8	<0.001
SVC, *liters*	3.9 ± 1.0	3.2 ± 0.8	2.6 ± 0.8	2.3 ± 0.6	<0.001
SVC, % *pred*	106.5 ± 14.6	87.6 ± 14.2	71.5 ± 16.1	55.8 ± 14.1	<0.001
FEV1, *liters*	2.5 ± 0.6	1.7 ± 0.5	1.1 ± 0.3	0.7 ± 0.2	<0.001
FEV1, % *pred*	93.5 ± 10.6	65.7 ± 8.6	39.6 ± 5.7	22.9 ± 5	<0.001
FEV1/FVC	0.65 ± 0.04	0.58 ± 0.08	0.45 ± 0.11	0.35 ± 0.13	<0.001
TLC, *liters*	6.2 ± 1.3	5.8 ± 1.3	5.8 ± 1.7	6.6 ± 2.1	0.04
TLC, % *pred*	111.2 ± 17.1	104.4 ± 18.9	105.8 ± 23.4	106.9 ± 28.6	0.07
FRC, *liters*	3.5 ± 0.8	3.5 ± 0.9	3.9 ± 1.3	5.3 ± 1.8	<0.001
FRC, % *pred*	113.3 ± 26.3	115.0 ± 25.7	131.4 ± 35.4	153.6 ± 44.7	<0.001
RV, *liters*	2.3 ± 0.7	2.7 ± 0.8	3.2 ± 1.2	4.4 ± 1.6	<0.001
RV, % *pred*	122.4 ± 38.3	141.8 ± 39.8	172.3 ± 54.9	221.2 ± 70.9	<0.001
IC, *liters*	2.7 ± 0.8	2.3 ± 0.6	1.8 ± 0.6	1.3 ± 0.4	<0.001
IC, % *pred*	107.9 ± 21.3	92.4 ± 18.1	73.9 ± 18.6	48.5 ± 13.1	<0.001
IC/SVC	0.70 ± 0.11	0.74 ± 0.13	0.72 ± 0.11	0.60 ± 0.14	0.002
IC/TLC	0.43 ± 0.07	0.39 ± 0.07	0.31 ± 0.07	0.20 ± 0.04	<0.001
FRC/TLC	0.57 ± 0.07	0.61 ± 0.07	0.69 ± 0.07	0.80 ± 0.04	<0.001
RV/TLC	0.38 ± 0.09	0.46 ± 0.09	0.57 ± 0.08	0.67 ± 0.06	<0.001
SVC/FVC	1.01 ± 0.07	1.01 ± 0.09	1.06 ± 0.11	1.02 ± 0.13	<0.001

See list of abbreviations at beginning of text. †Analysis of variance.

Between GOLD I and GOLD IV, FVC and FEV_1 decreased from a mean of 3.8 L to 1.9 L, and from 2.5 L to 0.7 L, respectively (decreases of 50% and 72%, respectively (both $p < 0.001$). In addition, the slow vital capacity (SVC) decreased from 3.9 L to 2.3 L, a change of 41% ($p < 0.001$). Relative differences between the slow and forced VCs increased sharply at GOLD III and IV (by 0.1 L and 0.4 L respectively). Residual volume increased by 91%. By contrast, TLC (in L) increased slightly between GOLD I and GOLD IV (from 6.2 L to 6.6 L, an increase of 6%; $p < 0.04$). Figures 1-3 show more significant differences amongst FEV_1 and RV as compared to TLC according to GOLD (2014) staging. By contrast, using the MMRC grading, TLC decreased between MMRC 0 and MMRC 4 (by 8%, $p > 0.04$), explained by the marked reduction in FVC.

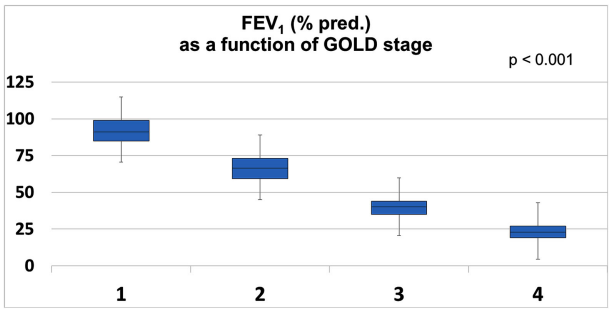

Figure 1. Forced expiratory volume in one second (FEV_1) as a function of GOLD stage. Values represent median (IQR). Differences amongst GOLD stages by ANOVA.

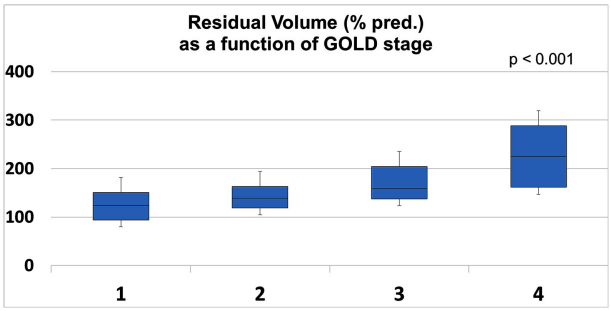

Figure 2. Residual volume as a function of GOLD stage. Values represent median (IQR). Differences amongst GOLD stage by ANOVA.

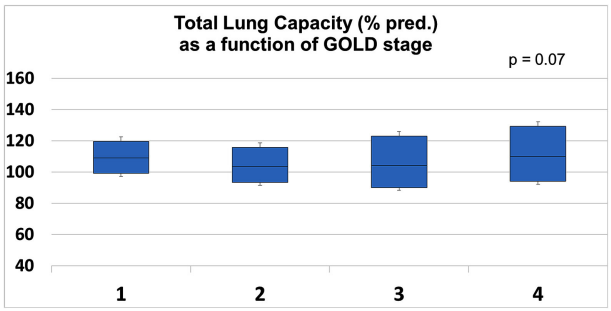

Figure 3. Total lung capacity as a function of GOLD stage. Values represent median (IQR). Differences by ANOVA.

4. Discussion

The main findings in this study are that: 1) several lung volume subdivisions are associated with the MMRC score, with the fewest variables exhibiting the closest relation when combined to be RV/TLC and IC (% predicted); 2) both MMRC and GOLD staging showed strong correlation with lung volume subdivisions (when corrected for TLC), more so than did FEV_1. We discuss these findings in the contexts of dyspnea and hyperinflation. We also discuss some of the discrepancies in changes amongst lung volume divisions in light of recent imaging reports using advanced CT scanning methods to assess the magnitude and distribution of emphysema.

4.1. Dyspnea

Using multivariate ordered logistic regression analysis of several lung function variables, we found that several lung volume subdivisions showed significant correlations with the MMRC scale. In fact, using the MMRC scale, FRC, TLC and RV showed closer associations with dyspnea rating than did FEV_1, although the latter was still closely related to dyspnea rating. Using GOLD staging alone, TLC showed the weakest correlation with severity. Patients with the most severe airflow limitation, as reflected by the FEV_1, might be expected to exhibit the most dyspnea. Yet, some patients with severe airflow limitation, as reflected by the FEV_1, have few symptoms, while others with minimal or no flow limitation experience dyspnea [3] [15]. Although FEV_1 has been considered important in the staging of COPD [13], other variables provide useful information in its evaluation, including age, gender, smoking history, functional vital capacity, dyspnea assessed by the Medical Research Council (MRC) and CAT scales, BMI, FRC, IC, hematocrit, and albumin level [3]. With specific reference to exertional dyspnea, Marin *et al.* [16] assessed the association between breathlessness or the six-minute walk test (6 MWT) and age, BMI, resting function and dynamic lung volumes using Pearson's correlation coefficient and stepwise multiple linear regression. The change in Borg dyspnea rating from resting to the end of a 6 MWT correlated with MRC scale and showed a small but significant correlation with change in IC during the 6 MWT ($r^2 = 0.24$, $p < 0.00001$), but was independent of age, BMI, resting IC/TLC, FEV_1 or arterial blood gas measurements. In this connection, we also found a similarity between MMRC and GOLD staging, but our findings varied from those of Marin *et al.* [16] in that we were able to show associations between the MMRC and most lung volumes (when corrected for age, BMI and gender), including IC (% predicted) and IC/TLC, and may reflect differences in population characteristics between Los Angeles and Boston. In this connection, our BMIs were comparable to those reported by other investigators, which ranged 24 - 26 kg/m^2 [16] [17] [18].

4.2. Hyperinflation

The SVC, FVC and IC exhibited similar magnitudes of decrement between GOLD 0-I and IV. By contrast, the TLC barely changed between GOLD and MMRC gradings. The contrasting changes in TLC between GOLD and MMRC severity, albeit slight, can be explained by the different methods by which each is subdivided: GOLD (2014) severity was categorized by FEV_1 only, while the MMRC is determined by severity of dyspnea while performing a task. One would have, instead, expected reciprocal changes between SVC (and FVC), and plethysmographic lung volume subdivisions, with TLC increasing with GOLD stage along with the RV. What would account for these discrepancies?

In chronic airflow limitation, tobacco exposure and aging contribute to small airway closure; this leads to closing volume exceeding FRC [19] [20]. Low volume mechanical ventilation in animal models produces injury to small airways

and increase in airway resistance within a few hours [21] [22] [23], similar to findings of histopathologic changes in peripheral airways of smokers [24]. Hogg and colleagues [25] provided a more detailed explanation of small airway obstruction in COPD, based on work by others employing micro-computed tomography (CT) and MRI imaging. Inflammatory changes in the terminal and respiratory bronchioles lead to formation of centrilobular lesions. The entire lung lobule is destroyed, and its coalescence with other destroyed lobules leads to formation of bullous lesions. McDonough *et al.* [26] found that lungs from patients with very severe COPD (GOLD IV) exhibited only 10% to 25% of the number of terminal bronchioles as contained in normal lungs, depending on the COPD phenotype (centrilobular type exhibiting the more severe deficit as compared to the panlobular form). They also showed that the number of terminal bronchioles per milliliter lung tissue was reduced before alveolar tissue developed emphysematous changes. In a more recent study, the same group, using multi-detector CT scans, determined morphologic characteristics of preterminal bronchioles in the same lung samples reported in the earlier investigation plus 64 new samples [27]. They found that bronchiolar length, wall volume, total volume, lumen circularity, and number of alveolar attachments were reduced in both types of emphysema compared with normal lungs, with changes being more severe and heterogeneous in the centrilobular form. CT imaging with three-dimensional (3D) computational model of the lungs has been employed to assess structural changes in emphysema [28]. Mondonedo *et al.* [29] recently showed that CT-based 3D low-attenuation super clusters (outliers of low-attenuation areas) were associated with disease severity and inversely related to FEV_1 and D_LCO, changes that may reflect destruction of small airways within the super cluster [26].

Given the magnitude of alveolar destruction in the most severely involved lungs (GOLD IV) described by Hogg *et al.* [25] and Tanabe [27], the increase in RV should reciprocate an equivalent reduction in the SVC and FEV_1. That is, if, according to Hogg *et al.* [25], in GOLD IV patients, close to 80% of terminal bronchioles are destroyed, the RV, representing trapped gas, should comprise 80% of the TLC. In fact, in our GOLD IV patients RV/TLC amounted to only 67%. Moreover, TLC hardly changed between GOLD I and GOLD IV. To account for this discrepancy, Hogg *et al.* [25] have suggested that some of the trapped gas may not be measurable. Our findings indicate that gas trapping may not be as severe as one would expect, a finding that can be explained by the presence of interalveolar collateral channels [25] [26] [27] and differences between our population and that of Hogg *et al.* [25]. While non-Hispanic Caucasians comprise 29% and 46% the populations of Los Angeles County and the Vancouver metropolitan area, respectively, Latinos of any race make up 48% and 1.6%, respectively, African-Americans constitute 8.6% and 1%, respectively, and Asians comprise 14% and 40%, respectively [30] [31]. The prevalence of emphysema (and hence, air trapping) in the Hispanic population is known to be less than in individuals of non-Hispanic European origin [32] [33].

In this connection, in current and former smokers without airflow limitation, the detection of even mild emphysema on chest CT imaging can be associated with impairment in quality of life, an abnormal D_LCO value, a higher number of exacerbations, and exercise-induced oxygen desaturation [34]. These findings support the concept that destruction and remodeling of peripheral airways leads to gas trapping long before airway resistance is increased (and before FEV_1 declines) in COPD. In many cases, as likely occurred in our cohort, the disappearance of peripheral airways would also explain why a decrease in IC and increases in FRC and TLC are more prominent than the reduction in the FEV_1 as emphysematous changes develop before airway resistance increases. Based on earlier GOLD classifications [1] [13], such changes occur even in stage 0, when FEV_1 and FEV_1/FVC are normal, but when patients experience productive cough. Thus, the further staging of GOLD based on FEV_1 is not justified because FEV_1 has proven to be only weakly related to dyspnea, exercise capacity and quality of life in COPD [3] [34]; it is for this reason that the latter 3 components are now the main components of the most recent staging of GOLD [6]. In addition, IC and IC/TLC have been shown to be associated with increased exacerbations [17] and mortality [17] [18] [34] [35] [36]. Hyperinflation may also influence exercise tolerance and mortality by reducing cardiac chamber size and impairing function of the right and left ventricles [37].

Our study has several strengths. Most important, approximately 80% of our study population was comprised of non-Caucasian minority groups, of which the largest was Hispanic, a group in which such a physiologic analysis has not been reported. Second, while this was a single center study, we assessed lung function data in a relatively large number of patients. There were also limitations to this study. We did not subdivide COPD into separate phenotypes such as chronic bronchitis or emphysema. We were primarily interested in the relation of dyspnea to airflow limitation in general and hyperinflation. Such an analysis should apply to most forms of airflow limitation. The numbers of exacerbations and deaths documented during the study recorded were limited as it is likely that such events were managed or occurred at outside facilities; hence we do not report them. Another limitation was the absence of availability of indices of dynamic hyperinflation as measured during exercise [38]. We also used the GOLD 2014 to classify severity of airflow limitation in our patients as data were analyzed between 2008 and 2013. Finally, data from the 6-minute walk test (6 MWT) or cardiopulmonary exercise testing (CPET) were available in only a few patients and are not included here.

5. Conclusion

In conclusion, markers of lung hyperinflation are associated with dyspnea as assessed by MMRC grading, with RV/TLC and IC exhibiting the closest relation. GOLD staging is more strongly correlated with lung volume subdivisions (except for TLC) than with FEV_1. These findings further support the concept that,

compared to FEV_1, lung hyperinflation contributes at least as much, if not more, to the sensation of dyspnea than does airflow limitation per sé. That TLC and FRC alone were not related to dyspnea or to GOLD staging can be attributed to collateral channels between alveolar spaces and differences between our population and those reported by others.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Pauwels, R.A., Buist, A.S., Calverley, P.M., Jenkins, C.R. and Hurd, S.S. (2001) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. *American Journal of Respiratory and Critical Care Medicine*, **163**, 1256-1276. https://doi.org/10.1164/ajrccm.163.5.2101039

[2] Casanova, C., de Torres, J.P., Aguirre-Jaíme, A., Pinto-Plata, V., Marin, J.M., Cordoba, E., Baz, R., Cote, C. and Celli, B.R. (2011) The Progression of Chronic Obstructive Pulmonary Disease Is Heterogeneous: The Experience of the BODE Cohort. *American Journal of Respiratory and Critical Care Medicine*, **184**, 1015-1021. https://doi.org/10.1164/rccm.201105-0831OC

[3] Celli, B.R., Cote, C.G., Marin, J.M., Casanova, C., Montes de Oca, M., Mendez, R.A., Pinto Plata, V. and Cabral, H.J. (2004) The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. *The New England Journal of Medicine*, **350**, 1005-1012. https://doi.org/10.1056/NEJMoa021322

[4] Celli, B.R., Decramer, M., Wedzicha, J.A., *et al.* (2015) ATS/ERS Task Force for COPD Research. An Official American Thoracic Society/European Respiratory Society Statement: Research Questions in COPD. *European Respiratory Review*, **24**, 159-172. https://doi.org/10.1183/16000617.00000315

[5] Jones, P., Miravitlles, M., van der Molen, T. and Kulich, K. (2012) Beyond FEV_1 in COPD: A Review of Patient-Reported Outcomes and Their Measurement. *International Journal of Chronic Obstructive Pulmonary Disease*, **7**, 697-709. https://doi.org/10.2147/COPD.S32675

[6] Vogelmeier, C.F., Criner, G.J., Martinez, F.J., *et al.* (2017) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *American Journal of Respiratory and Critical Care Medicine*, **195**, 557-582. https://doi.org/10.1164/rccm.201701-0218PP

[7] Pellegrino, R., Viegi, G., Brusasco, V., *et al.* (2005) Interpretative Strategies for Lung Function Tests. *American Journal of Respiratory and Critical Care Medicine*, **26**, 948-968. https://doi.org/10.1183/09031936.05.00035205

[8] Schoenberg, J.B., Beck, G.J. and Bouhuys, A. (1978) Growth and Decay of Pulmonary Function in Healthy Blacks and Whites. *Respiration Physiology*, **33**, 367-393. https://doi.org/10.1016/0034-5687(78)90063-4

[9] Crapo, R.O., Morris, A.H., Clayton, P.D. and Nixon, C.R. (1982) Lung Volumes in Healthy Nonsmoking adults. *Bulletin Européen de Physiopathologie Respiratoire*, **18**, 419-425.

[10] Knudson, R.J., Kaltenborn, W.T., Knudson, D.E. and Burrows, B. (1987) The Single-Breath Carbon Monoxide Diffusing Capacity. Reference Equations Derived from a Healthy Nonsmoking Population and Effects of Hematocrit. *The American Review of Respiratory Disease*, **135**, 805-811. https://doi.org/10.1164/arrd.1987.135.4.805

[11] Bates, D.V. (1989) Respiratory Function in Disease. Saunders, Philadelphia, 108-109.

[12] Fletcher, C.M., Elmes, P.C., Fairbairn, M.B., *et al.* (1959) The Significance of Respiratory Symptoms and the Diagnosis of Chronic Bronchitis in a Working Population. *British Medical Journal*, **2**, 257-266. https://doi.org/10.1136/bmj.2.5147.257

[13] Vestbo, J., Hurd, S.S., Agustí, A.G., Jones, P.W., Vogelmeier, C., Anzueto, A., Barnes, P.J., Fabbri, L.M., Martinez, F.J., Nishimura, M., Stockley, R.A., Sin, D.D. and Rodriguez-Roisin, R. (2013) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary. *American Journal of Respiratory and Critical Care Medicine*, **187**, 347-365. https://doi.org/10.1164/rccm.201204-0596PP

[14] Dixon, W.J. and Massey, F.J. (1983) Introduction to Statistical Analysis. 4th Edition, McGraw-Hill, New York, 385-414.

[15] Woodruff, P.G., Barr, R.G., Bleeker, E., *et al.* (2016) Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *The New England Journal of Medicine*, **374**, 1811-1812. https://doi.org/10.1056/NEJMoa1505971

[16] Marin, J.R., Santiago, J.C., Gascon, M., Sanchez, A., Gallego, B. and Celli, B.R. (2001) Inspiratory Capacity, Dynamic Hyperinflation, Breathlessness, and Exercise Performance during the 6-Minute Walk Test in Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, **163**, 1395-1399. https://doi.org/10.1164/ajrccm.163.6.2003172

[17] Tantucci, C., Donati, C., Nicosia, F., *et al.* (2008) Inspiratory Capacity Predicts Mortality in Patients with Chronic Obstructive Pulmonary Disease. *Respiratory Medicine*, **102**, 613-619. https://doi.org/10.1016/j.rmed.2007.11.004

[18] French, A., Balfe, D., Mirocha, J.M., *et al.* (2015) The Inspiratory/Total Lung Capacity Ratio as a Predictor of Survival in an Emphysematous Phenotype of Chronic Obstructive Pulmonary Disease. *International Journal of Chronic Obstructive Pulmonary Disease*, **10**, 1305-1312. https://doi.org/10.2147/COPD.S76739

[19] McCarthy, D.S., Spencer, R., Greene, R. and Milic-Emili, J. (1972) Measurement of "Closing Volume" as a Simple and Sensitive Test for Early Detection of Small Airway Disease. *The American Journal of Medicine*, **52**, 747-753. https://doi.org/10.1016/0002-9343(72)90080-0

[20] Milic-Emili, J. (2004) Does Mechanical Injury of the Peripheral Airways Play a Role in the Genesis of COPD in Smokers? *COPD*, **1**, 85-92. https://doi.org/10.1081/COPD-120028700

[21] Muscadere, J.G., Mullen, J.B., Gan, K., Bryan, C. and Slutsky, A.S. (1994) Tidal Ventilation at Low Airway Pressures Can Augment Lung Injury. *American Journal of Respiratory and Critical Care Medicine*, **149**, 1327-1334.

https://doi.org/10.1164/ajrccm.149.5.8173774

[22] Saetta, M., Di Stefano, A., Turato, G., Facchini, F.M., Corbino, L., Mapp, C.E., Maestrelli, P., Ciaccia, A. and Fabbbri, L.M. (1998) CD8+ T-Lymphocytes in Peripheral Airways of Smokers with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, **15**, 822-826. https://doi.org/10.1164/ajrccm.157.3.9709027

[23] D'Angelo, E., Pecchiari, M., Baraggia, P., Saetta, M., Balestro, E. and Milic-Emili, J. (2002) Low Volume Ventilation Induces Peripheral Airways Injury and Increased Airways Resistance in Normal Open Chest Rabbits. *Journal of Applied Physiology*, **92**, 949-956. https://doi.org/10.1152/japplphysiol.00776.2001

[24] Niewoehner, D.E., Kleinerman, J. and Rice, D.B. (1974) Pathologic Changes in the Peripheral Airways of Young Cigarette Smokers. *The New England Journal of Medicine*, **291**, 755-758. https://doi.org/10.1056/NEJM197410102911503

[25] Hogg, J.C., McDonough, J.E. and Suzuki, M. (2013) Small Airway Obstruction in COPD. New Insights Based on Micro-CT Imaging and MRI Imaging. *Chest*, **143**, 1436-1443. https://doi.org/10.1378/chest.12-1766

[26] McDonough, J.E., Yuan, R., Suzuki, M., *et al.* (2011) Small-Airway Obstruction and Emphysema in Chronic Obstructive Pulmonary Disease. *The New England Journal of Medicine*, **365**, 1567-1575. https://doi.org/10.1056/NEJMoa1106955

[27] Tanabe, N., Vasilescu, D.M., McDonough, J.E., Kinose, D., Suzuki, M., Cooper, J.D., Paré, P.D. and Hogg, J.C. (2017) Micro-Computed Tomography Comparison of Preterminal Bronchioles in Centrilobular and Panlobular Emphysema. *American Journal of Respiratory and Critical Care Medicine*, **195**, 630-638. https://doi.org/10.1164/rccm.201602-0278OC

[28] Parameswaran, H., Majumdar, A. and Suki, B. (2011) Linking Microscopic Spatial Patterns of Tissue Destruction in Emphysema to Macroscopic Decline in Stiffness Using a 3D Computational Model. *PLOS Computational Biology*, **7**, e1001125. https://doi.org/10.1371/journal.pcbi.1001125

[29] Mondonedo, J.R., Sato, S., Oguma, T., *et al.* (2019) CT Imaging-Based Low-Attenuation Super Clusters in Three Dimensions and the Progression of Emphysema. *Chest*, **155**, 79-87. https://doi.org/10.1016/j.chest.2018.09.014

[30] California—Fact Sheet—American FactFinder.

[31] Metro Vancouver Population by Visible Minority. National Household Survey (NHS) Profile, 2011, Canada.

[32] Bruse, S., Sood, A., Petersen, H., *et al.* (2011) New Mexican Hispanic Smokers Have Lower Odds of Chronic Obstructive Pulmonary Disease and Less Decline in Lung Function than Non-Hispanic Whites. *American Journal of Respiratory and Critical Care Medicine*, **184**, 1254-1260. https://doi.org/10.1164/rccm.201103-0568OC

[33] Akinbami, L.J. and Liu, X. (2011) Chronic Obstructive Pulmonary Disease among Adults Aged 18 and over in the United States, 1998-2009. NCHS Data Brief No. 63. National Center for Health Statistics, Hyattsville.

[34] Alcaide, A.B., Sanchez-Salcedo, P., Bastarrika, G., *et al.* (2017) Clinical Features of Smokers with Radiological Emphysema But without Airway Limitation. *Chest*, **151**, 358-365. https://doi.org/10.1016/j.chest.2016.10.044

[35] Casanova, C., Cote, C., de Torres, J.P., *et al.* (2005) Inspiratory-to-Total Lung Capacity Ratio Predicts Mortality in Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, **171**, 591-597. https://doi.org/10.1164/rccm.200407-867OC

[36] Klooster, K., Hartman, J.E., ten Hacken, N.H.T. and Slebos, D.-J. (2017) Improved Predictors of Survival after Endobronchial Valve Treatment in Patients with Severe Emphysema. *American Journal of Respiratory and Critical Care Medicine*, **195**, 1272-1274. https://doi.org/10.1164/rccm.201610-1993LE

[37] Criner, G. (2011) Lung Volume Reduction as an Alternative to Transplantation for COPD. *Clinics in Chest Medicine*, **32**, 379-397. https://doi.org/10.1016/j.ccm.2011.02.014

[38] O'Donnell, D.E. (2006) Hyperinflation, Dyspnea, and Exercise Tolerance in Chronic Obstructive Pulmonary Disease. *Proceedings of the American Thoracic Society*, **3**, 180-184. https://doi.org/10.1513/pats.200508-093DO

Abbreviations

ANOVA: analysis of variance

D_LCO: single-breath carbon monoxide diffusion capacity

FVC: forced vital capacity

SVC: slow vital capacity

FEV_1: forced expiratory volume in 1 second

FRC: functional residual capacity

IC: inspiratory capacity

RV: residual volume

TLC: total lung capacity

PFT: pulmonary function test