CHEST

How Common Is Airflow Limitation in Patients With Emphysema on CT Scan of the Chest?

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BACKGROUND: COPD has traditionally been defined by the presence of irreversible airflow limitation on spirometry using either the GOLD (Global Initiative for Chronic Obstructive Lung Disease) or American Thoracic Society/European Respiratory Society criteria (lower limit of normal [LLN]). We have observed that some patients with clinical COPD and emphysema on chest CT scan have no obstruction on spirometry. The purpose of this study was to assess the prevalence of obstruction by GOLD and LLN criteria in patients with emphysema on CT scan and determine which radiographic criteria were associated with a clinical diagnosis of COPD.

METHODS: We retrospectively analyzed the clinical records and spirometry of all patients who had radiographically defined emphysema on chest CT scans completed at the University of Vermont in 2011. We compared spirometric criteria and CT scan factors with the presence of clinical COPD based on chart review.

RESULTS: We identified 274 patients with CT scan-defined emphysema. GOLD criteria detected obstruction in 228 patients (83%), and LLN detected obstruction in 206 patients (75%). However, GOLD failed to correctly identify 19 patients (6.9%) and LLN failed to identify 38 patients (13.9%) (average 10.4%) who had radiographic emphysema and a clinical diagnosis of COPD. Obese patients had a lower prevalence of obstruction whether classified by LLN or GOLD. Among patients with spirometric obstruction, there were greater degrees of emphysema and more severely increased airway wall thickness. Factors that were independently associated with clinical COPD were lower FVC % predicted, lower FEV_1/FVC ratio, and increasing airway wall thickness.

CONCLUSIONS: Spirometry missed 10.4% of patients with clinical COPD who have significant emphysema on chest CT scan.

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ABBREVIATIONS: AWT = airway wall thickness; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LAA = low attenuation area; LLN = lower limit of normal; SGRQ = St. George's Respiratory Questionnaire

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COPD is characterized by incompletely reversible airflow limitation related to pathologic changes caused by emphysema, chronic bronchitis, or both.[1] Traditionally, COPD has been graded and defined solely on clinical and physiologic parameters.[2] The GOLD (Global Initiative for Chronic Obstructive Lung Disease) classification system for COPD was revised, stratifying based on symptoms, lung function, and exacerbation history for disease severity.[3] GOLD has promoted the use of a fixed cutoff of FEV_1/FVC ratio $< 70\%$ to diagnose airflow limitation in COPD.[3] Alternatively, the American Thoracic Society and European Respiratory Society have advocated the use of the lower limit of normal (LLN) based on lung function in a healthy population to diagnose airflow limitation[4] and consequently COPD. A diagnosis of COPD is usually delayed until the onset of self-reported clinical symptoms together with findings of airflow obstruction on pulmonary function tests using either the LLN or GOLD criteria.[5,6]

COPD is now recognized as a heterogeneous disorder, and clinical assessment has become increasingly multidimensional.[5,7] There is growing consensus that FEV_1 by itself does not adequately describe the complexity of the disease and that lung function testing alone cannot be used by itself for diagnosis, assessment, and management. Both airway wall thickness (AWT) and emphysema have been shown to make independent contributions to airflow obstruction in COPD.[8] Quantitative assessment of emphysema by CT scan provides objective measures of parenchymal lung disease that correlate well with histopathologic findings[9] and also correlate with the degree of expiratory airflow obstruction.[10] Similarly, objective measures of proximal AWT obtained by CT scan are inversely correlated with lung function.[11]

The clinical implications of CT scan-detected emphysema and airways disease have become clearer as emphysema has been shown to have a strong association with more rapid disease progression[12] and mortality,[13] whereas airways disease appears to have a strong relationship with symptoms as measured by the St. George's Respiratory Questionnaire (SGRQ).[14] In an analysis of the COPDGene cohort, both emphysema and airways disease demonstrated significant associations with symptoms as measured by SGRQ and mortality as predicted by the BMI, airflow obstruction, dyspnea, exercise capacity (BODE) index.[15]

We have observed that many patients with clinical symptoms of COPD and emphysema on chest CT scan have no obstruction on spirometry, which may lead to an underdiagnosis of patients who truly do have COPD. To confirm and quantify this observation, we conducted the current study to test the hypothesis that there are some patients who, despite having clinical COPD and emphysema on CT scan, have normal spirometry, whether interpreted by GOLD or LLN criteria. In addition, we suspected that obesity might account, in part, for the lack of sensitivity of detection of airflow in some patients. We were also interested in determining which information obtained from CT imaging of the chest, if any, would be associated with clinical evidence of COPD in this cohort of patients.

Materials and Methods

Study Design

We retrospectively analyzed all chest CT scans with radiologist-defined emphysema in the interpretation report that were completed in 2011 at the University of Vermont Medical Center, the teaching hospital of the University of Vermont College of Medicine. The subsequent analysis was on the cohort of patients for whom spirometry was available. When multiple spirometry results were available, we focused on the results that were closest in time to the CT scan. Data were collected after approval by the institutional review board at the University of Vermont, M12-310. All pulmonary function tests were performed according to current American Thoracic Society/European Respiratory Society guidelines.[16] Normative values for spirometry were based on National Health and Nutrition Examination Survey III data.[17] Exclusion criteria included lack of visible emphysema on CT imaging (when reviewed by the radiologist), concomitant fibrosis of any cause, significant bronchiectasis (requiring airway clearance therapy), extensive infiltrate or lung mass, moderate or large pleural effusions, or previous surgical resection. Subsequent complete quantitative and qualitative CT scan analysis was performed on the resulting 274 patients (Fig 1).

Chest CT scan was performed with or without iodinated contrast using 16-, 40-, 64-, 128-, and 256-slice scanners (Brilliance and iCT; Koninklijke Philips NV) for a variety of clinical reasons (as described in the Results section). All CT scans included submillimeter volumetric technique with a high spatial frequency algorithm filter technique and were reviewed by two independent thoracic radiologists (R. R. W., G. E. G.) blinded to the spirometric or clinical criteria defining COPD. Emphysema was then evaluated using a hybrid of both quantitative and qualitative analyses.[18]

We conducted a chart review of all patients with emphysema defined by quantitative CT scan analysis for whom spirometry was available to determine if there was evidence of clinical COPD. We used the following inclusion criteria to define COPD clinically, all of which had to be fulfilled: symptoms including cough, sputum production, wheezing, and dyspnea; a smoking history (although pack-year exposure could not be ascertained on all patients); a physician diagnosis of COPD; medication use including the need for a long-acting β-agonist, a long-acting muscarinic antagonist, and/or inhaled corticosteroids; and no other diagnosis or reason to suspect another disease besides COPD. In particular, we searched for and excluded asthma, significant cardiovascular disease, pulmonary hypertension, and any bronchiectasis requiring airway clearance therapy. Patients may or may not have had emergency room visits or hospitalizations related to an exacerbation or additional need for steroid therapy. Obesity was defined as a BMI ≥ 30 kg/m^2.

Quantitative Analysis of Emphysema

The extent of emphysematous involvement of both lungs was semiautomatically quantified using the dedicated CT Lung Density module of the Philips IntelliSpace PACS software suite (Philips Healthcare). Low attenuation area (LAA) representing emphysematous involvement as a percentage of entire lung volume was calculated using lung attenuation software with an initial default threshold of −950 Hounsfield units[19-22] and subsequently adjusted to best conform with qualitative areas of emphysema. We defined significant emphysema as ≥ 5% LAA.[23]

Qualitative Analysis of Emphysema

The distribution of emphysema was qualitatively classified as central, peripheral, or both defined by a theoretical line dividing the outer and inner portion of the lung into equal volumes. Similarly, emphysema location was classified as either predominantly within the upper or lower lungs or both using the level of the carina as a landmark.[24]

Qualitative Analysis of Airways Disease

Airways were qualitatively analyzed. AWT was categorized as mild (scattered regions of peribronchial thickening and wall thickness > 1 mm in any airway), moderate (diffuse airway wall thickening with nearly all AWT greater than 1 mm), and severe (diffuse airway wall thickening and the presence of mucous plugging).[24]

Statistical Analysis

All data were tabulated in a spreadsheet and analyzed for distribution using standard statistical software (JMP version 11.0; SAS Institute Inc). All data are expressed as mean ± SD, unless otherwise specified. We calculated the sensitivity and specificity of the LLN and GOLD criteria to diagnose clinical COPD based on chart review. One-way analysis of variance was used to compare different variables with the presence or absence of clinical COPD. Multifactor logistic regression analysis using a backward-stepwise modeling procedure was performed to determine the association of demographic (age, sex, BMI) and spirometric (FEV_1 % predicted, FVC % predicted, FEV_1/FVC ratio) variables and CT scan factors (% emphysema, upper-lower and central-peripheral distribution of emphysema, and AWT) with clinical COPD. We analyzed the association between FEV_1 (% predicted) and % emphysema using Spearman rank correlation and AWT using one-way analysis of variance. For all statistical analysis, a P value < .05 was considered statistically significant.

Results

A total of 2,125 patients had CT scans of the chest with the word "emphysema" noted in the interpretation report between January and December 2011. Of these, we identified 560 patients with thoracic CT scan and spirometry available for review, but 286 were subsequently found to be ineligible as they met exclusion criteria. The average time between the CT scan and spirometry was 211 days (interquartile range, 91-465 days). Complete quantitative and qualitative CT scan analysis was performed on 274 patients who had emphysema defined as ≥ 5% LAA.[23] The most common indications for the CT scan study were to assess lung mass (30%), follow up lung nodule (23%), rule out pulmonary embolus (14%), and evaluate shortness of breath (10%), with < 5% each for hemoptysis, infection, pleural effusion, interstitial lung disease, lymphadenopathy, pulmonary hypertension, or preoperative evaluation.

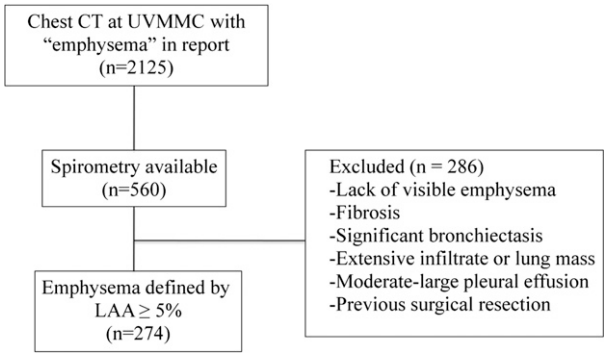

Figure 1 – *Flow diagram of identifying patients with emphysema as defined by ≥ 5% LAA on thoracic CT scan. LAA = low attenuation area; UVMMC = University of Vermont Medical Center.*

Of the 274 patients, the mean age was 66.9 ± 10.4 years, and 55% were men. There were 78 patients (28.1%) with obesity, with a mean BMI of 26.8 kg/m^2. Obese patients had a lower prevalence of obstruction compared with nonobese individuals, whether classified by LLN (63% vs 79%) or GOLD (74% vs 86%) criteria. Comparing the obese to the nonobese patients, the FEV_1 % predicted was 64.5 ± 25.1 vs 56.6 ± 23.2 (P = .02), FVC % predicted was 82.2 ± 20.5 vs 79.7 ± 18.5 (P = .33), and the FEV_1/FVC was 0.58 ± 0.14 vs 0.52 ± 0.15 (P = .01). A low BMI was correlated with increased emphysema (Spearman ρ = −0.31, P < .01).

Further demographic, spirometric, and radiologic characteristics of these patients are shown in Table 1. The GOLD criteria (fixed ratio FEV_1/FVC < 0.70) detected obstruction in 228 patients (83%), and the LLN criteria detected obstruction in 206 patients (75%) (Fig 2). Both GOLD and LLN correctly identified patients with clinical COPD, with a sensitivity of 92% and 84%, and a specificity of 77% and 91%, respectively. However, GOLD criteria failed to correctly classify 19 patients (6.9%) and LLN failed to capture 38 patients (13.9%) with no airflow limitation who had radiographic emphysema and a clinical diagnosis of COPD.

Among the patients with emphysema defined as ≥ 5% LAA, the FEV_1, FVC, FEV_1 % predicted, FVC % predicted, and FEV_1/FVC ratio were statistically lower in those with as compared with those without obstruction defined by LLN and GOLD, as expected (Table 1). The percentage of total emphysema was significantly greater in those with obstruction defined by either GOLD or

TABLE 1] Baseline Characteristics: 274 Patients With Emphysema Defined by ≥5% LAA on CT Scan

Characteristic	Obstruction by LLN	No Obstruction by LLN	*P* Value[a]	Obstruction by GOLD	No Obstruction by GOLD	*P* Value[b]
Patient, No. (%)	206 (75%)	68 (25%)	…	228 (83%)	46 (17%)	…
Age, y	67 ± 10	67 ± 12	.93	67 ± 10	65 ± 11	.12
Sex, %						
Male	52	64	.07	54	61	.39
Female	48	35	…	46	39	…
BMI, kg/m^2	26 ± 6	30 ± 7	< .01	26 ± 6	29 ± 6	< .01
FEV_1, L	1.34 ± 0.61	2.2 ± 0.63	< .01	1.41 ± 0.65	2.44 ± 0.63	< .01
FEV_1 % predicted	50 ± 19	85 ± 18	< .01	53 ± 21	88 ± 18	< .01
FVC, L	2.79 ± 0.96	3.21 ± 0.81	< .01	2.82 ± 0.95	3.26 ± 0.81	.003
FVC % predicted	78 ± 19	88 ± 18	< .01	79 ± 19	88 ± 18	< .01
FEV_1/FVC	47.4 ± 11.7	72.2 ± 4.9	< .001	49.3 ± 12.5	74.7 ± 3.7	< .01
Total emphysema, %	23.9 ± 13.2	12.9 ± 6.6	< .01	22.7 ± 13.2	14.1 ± 7.1	< .01
AWT, %			χ^2 P < .01			χ^2 P < .01
Mild	6.8	20.6		7.0	26.1	
Moderate	71.4	76.5		72.4	73.9	
Severe	21.8	2.9		20.6	0 (0)	
Emphysema distribution, %			χ^2 P < .01			χ^2 P = .04
Both	77.7	58.8		75.0	63.0	
Central only	18.0	26.5		19.7	21.7	
Peripheral only	4.4	14.7		5.3	15.2	
Emphysema location, %			χ^2 P < .01			χ^2 P < .01
Both only	45.2	19.0		51.8	15.2	
Upper only	54.8	81.0		48.2	84.8	

Data are presented as mean ± SD unless otherwise noted. AWT = airway wall thickness; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN = lower limit of normal.
[a]*P* value is for LLN comparison.
[b]*P* value is for GOLD comparison.

LLN (Table 1). There were significant correlations between the FEV_1 % predicted and FEV_1/FVC and CT scan findings (% emphysema and AWT), as shown in Figure 3. Obstruction on spirometry by either GOLD or LLN criteria was further associated with more combined central and peripheral emphysema that was located in both upper and lower lung zones and more moderate and severe AWT.

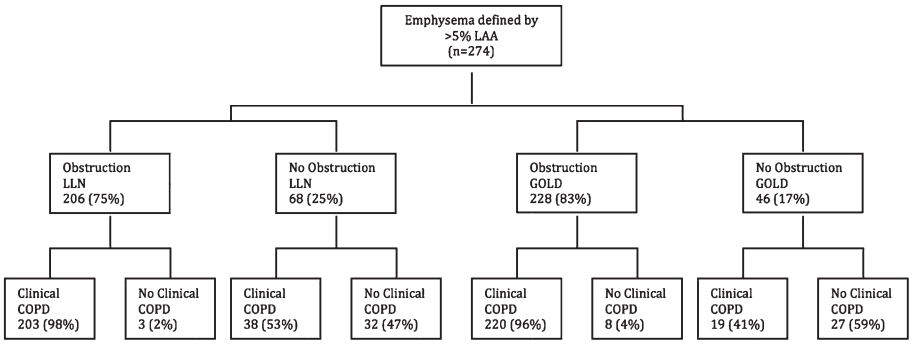

Figure 2 – *Flow diagram of identifying patients with COPD as defined by LLN and GOLD criteria and defined clinically among those with emphysema on thoracic CT scan. GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN = lower limit of normal. See Figure 1 legend for expansion of other abbreviation.*

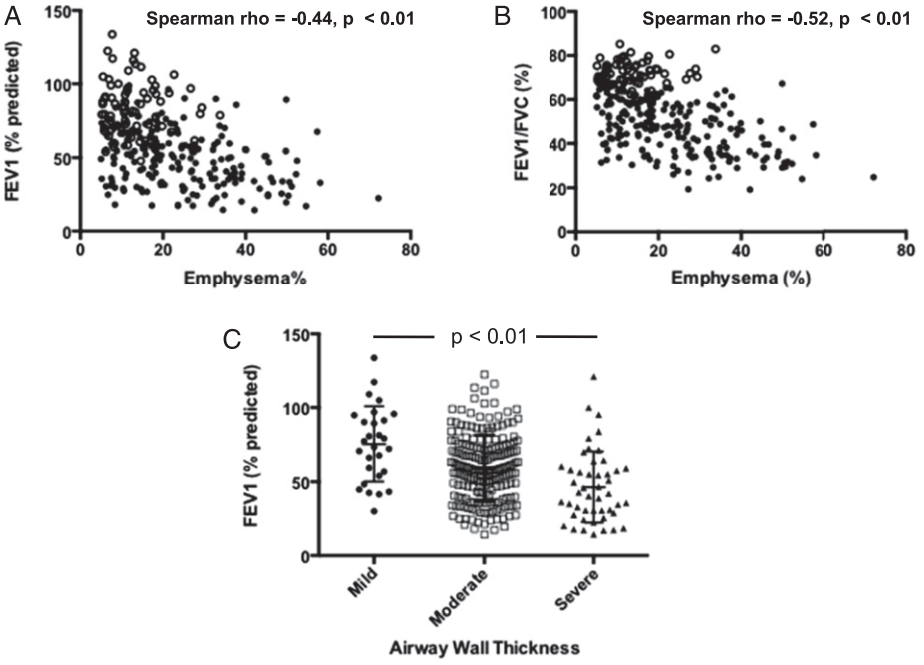

Figure 3 – *A, Correlation between FEV_1 % predicted and % emphysema. B, Correlation between FEV_1/FVC and % emphysema. C, Correlation between FEV_1 % predicted and airway wall thickness. In A and B, open circles indicate patients with normal spirometry by LLN; filled circles indicate patients with airflow limitation by LLN. In C, horizontal lines indicate the mean and one SD above and below the mean. See Figure 2 legend for expansion of abbreviation.*

Of the 68 patients with emphysema and normal lung function tests by LLN, 53% had COPD clinically and 47% did not (Table 2). Comparing these two groups, we found patients with clinical COPD had a lower FEV_1/FVC ratio and near significantly lower FEV_1 % predicted and more moderate to severe AWT. The amount and distribution of emphysema was not significantly different between those with and without a clinical diagnosis of COPD. A multifactor logistic regression model identified that the factors that independently associated with clinical COPD were lower FVC % predicted, lower FEV_1/FVC ratio, and increased AWT (Table 3).

Discussion

We examined the prevalence of airflow limitation by GOLD and LLN criteria among patients with radiographic emphysema seen on chest CT scan. Both the GOLD and LLN criteria performed well, with significant agreement between the two methods in diagnosing COPD in the majority of patients with emphysema on CT scan. We demonstrate, however, that both GOLD and LLN misclassified 6.9% and 13.9% (mean, 10.4%) of this population, respectively, as normal when clinical COPD was present. The GOLD criteria would be expected to overdiagnose airway obstruction in older individuals (> 60 years) and underdiagnose it in younger individuals (< 40 years).[25] Accordingly, among our study population of older patients (mean age, 67 years) we would expect that GOLD would have greater sensitivity in detecting clinical COPD in older patients than LLN, which is what we found. The LLN criteria, however, were more specific than GOLD in detecting clinical COPD in the presence of radiographic emphysema. Our findings are similar to those reported from cohorts of older patients relating spirometry to clinical COPD[26] or to CT scan emphysema.[23]

We also made some interesting observations in patients with obesity. The effects of obesity on spirometry in otherwise healthy subjects are well described, with reduction in FEV_1 and FVC but preservation of FEV_1/FVC being associated with high levels of BMI (typically > 30 kg/m^2).[27] With the increasing prevalence of obesity, the interaction between increasing BMI and lung volumes in patients with underlying airway obstruction has been an area of increasing interest.[28,29] In a cohort of patients with COPD defined by GOLD criteria, O'Donnell et al[28] showed that with increasing BMI, patients with airway obstruction had consistent reductions in lung hyperinflation, with significant improvements in the FEV_1/FVC ratio across all GOLD stages. Our results show that although the obese patients had a higher FEV_1, they had no significant differences in FVC and so had a higher FEV_1/FVC ratio than the nonobese group. This is reflected in the obese group having a lower incidence of obstruction by both LLN (63% vs 79%) and GOLD (74% vs 86%). We speculate that in our population of obese patients the higher FEV_1 may be due to enhanced elastic recoil causing faster lung emptying on forced expiration. Such an effect may be even more

TABLE 2] Patients With Emphysema and No Obstruction by LLN

Characteristic	COPD		*P* Value
	Yes	No	
Patient, No. (%)	36 (53)	32 (47)	…
Age, y	68 ± 12	66 ± 11	.39
Sex, %			.72
Male	67	62	
Female	33	38	
BMI, kg/m^2	30 ± 7	29 ± 7	.40
FEV_1 % predicted	81.5 ± 18.1	89.0 ± 17.7	.09
FVC % predicted	86.0 ± 18.2	89.9 ± 18.4	.39
FEV_1/FVC, %	70.3 ± 3.9	74.4 ± 5.0	< .01
AWT, %			χ^2 *P* = .06
Mild	11.1	31.2	
Moderate	83.3	68.8	
Severe	5.6	0	
Emphysema, total %	11.9 ± 6.6	14.1 ± 6.4	.16
Emphysema distribution, %			χ^2 *P* = .28
Both central and peripheral	50.0	68.8	
Central only	33.3	18.8	
Peripheral only	16.7	12.5	
Emphysema location, %			χ^2 *P* = .82
Both upper and lower	16.7	18.8	
Upper only	83.3	81.2	

Data are presented as mean ± SD unless otherwise noted. See Table 1 legend for expansion of abbreviations.

pronounced in patients with higher BMI than the relatively mild elevation seen in our population (mean BMI = 26.8 kg/m^2). Interestingly, the association of low BMI with increased emphysema measured by quantitative CT scan has been well established in patients with COPD.[28-30] A similar correlation was observed in our cohort of patients between BMI and percent emphysema on CT scan. These findings suggest that spirometry alone may not be sufficient to diagnose COPD in obese patients and that further diagnostic tests, such as chest CT scan, may be helpful.

TABLE 3] Factors Associated With Clinical COPD

Factor	β-Coefficient	*P* Value
FVC % predicted	0.236	.04
FEV_1/FVC ratio	0.533	< .002
AWT	0.743	.021

R^2 = 0.562; *P* < .001. See Table 1 legend for expansion of abbreviation.

Our results demonstrate that although airflow limitation was associated with both emphysema and airway wall thickening, the latter seemed to be the more important factor. As shown in Figures 3A and 3B, many patients with severe airflow limitation had mild emphysema, and yet this same group of patient had more severe airway wall thickening (Fig 3C). We believe this reflects the important role of airway narrowing in explaining airflow limitation.[31-33] However, as expected, there was more emphysema among the patients with airflow obstruction,[32] by either GOLD or LLN criteria. The distribution of emphysema was also different, with patients with airflow obstruction having more combined central and peripheral involvement and more involvement of both upper and lower lobes. These findings are compatible with other reports.[34,35]

We were also interested in examining which radiologic criteria were specific to this group of patients with radiographic emphysema and clinical COPD but no evidence of airflow obstruction defined by either GOLD or LLN on spirometry. In addition to the FVC % predicted and FEV_1/FVC ratio, we found that AWT was different between patients with emphysema who had clinical COPD compared with those without clinical COPD. Airways disease has also been shown to have a strong relationship with symptoms and health status.[8] Patients with clinical COPD had less mild, and more moderate and severe, AWT. Our results suggest that in those with radiographic emphysema, AWT, but not the amount or distribution of emphysema, predicted clinical COPD, as did FVC and FEV_1/FVC. This implies that the functional effect of increased AWT is to result in not only airway narrowing (reduced FEV_1/FVC) but also air trapping (reduced FVC), which is strongly associated with dyspnea and exercise intolerance in COPD.[36] Indeed, increased AWT[11] and air trapping,[10] rather than emphysema, have been shown to be more closely correlated with lung function in patients with COPD.

We demonstrate that although standard pulmonary function tests (FEV_1 % predicted and FEV_1/FVC ratio) correlate well with AWT and degree of emphysema, they fail to identify clinical COPD in a significant number of patients with emphysema. The unique clinical implications of emphysema and airways disease are becoming clearer, as emphysema has a strong association with more rapid disease progression and mortality.[12,13] Several

studies demonstrated a relationship between symptoms and emphysema; for example, Grydeland et al[37] reported a 1.87 OR for greater Modified Medical Research Council score per 10% increase emphysema. In two separate cohorts, the relationship between health status as measured by the SGRQ and emphysema has been established, demonstrating a 5.3- to 5.8-point increase in SGRQ per 10% increase in emphysema, adjusted for other potential factors that can influence SGRQ, including FEV_1.[13,38] Objective measures of AWT obtained via CT scan have been shown to be inversely correlated with lung function and relate to small airways disease[39] and exacerbation frequency.[38]

An interesting observation in our study is that there are a significant number of patients with quantifiable emphysema on CT scan who have no evidence of airflow obstruction or clinical COPD. We acknowledge that the actual prevalence of this group is uncertain, because it will vary depending on the exact definition of radiographic emphysema (eg, LAA $<$ 950 Hounsfield units vs $<$ 15th percentile)[40] and the percentage of total emphysema believed to be clinically significant.[13,23,41,42] However, we suspect that people in this group either have subclinical COPD that may progress over time[12,21,43] or have a physiologic amount of emphysema that accompanies the normal loss of lung function with age.[44,45]

There are several limitations to our study. This was a retrospective study that examined a cohort of patients with chest CT scans, which were performed for a variety of clinical reasons. As such, the images were not all standardized. The timing between the CT scan and spirometry was highly variable, but on average was $<$ 1 year, which we believe makes the accuracy of lung function testing reasonable in relation to the CT scan data. The diagnosis of COPD was also obtained by chart review, which had inherent limitations including amount of smoking and possible misclassification by other diagnoses including bronchiectasis or asthma. However, we did try to exclude these as well as other diseases, such as cardiovascular disease and pulmonary hypertension, that may have presented with shortness of breath and been diagnosed as COPD. In addition, we did not record comorbidities that might have impacted clinical symptoms and thus contributed to the clinical diagnosis of COPD. Further lung function tests such as diffusing capacity were not available for all patients. A large number of CT scans were not included because of technical factors and confounding pathology. However, a major strength of this study is the real-world applicability of radiologic software and radiologist assessment in quantitative and qualitative thoracic imaging on scans that were previously obtained for reasons not related to the diagnosis of COPD. This underscores the importance of radiologic data, which can add value in the overall assessment of COPD in routine clinical practice.

Conclusions

Despite the importance of spirometry in confirming a diagnosis of COPD, our study supports the clinical view that some patients with clinical COPD and emphysema on CT scan may have normal spirometry. We found that 10.4% of patients with radiographic emphysema and clinical COPD had normal spirometry. The idea that spirometry may need to be supplemented by other manifestations of COPD is the basis of the current GOLD guidelines.[3] Our findings suggest that CT scan assessment of emphysema and airways disease may be useful in characterizing patients with respiratory symptoms and normal spirometry. This may become more important as the obesity epidemic worsens.

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