Signs of Gas Trapping in Normal Lung Density Regions in Smokers

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Abstract

Rationale: A substantial proportion of subjects without overt airflow obstruction have significant respiratory morbidity and structural abnormalities as visualized by computed tomography. Whether regions of the lung that appear normal using traditional computed tomography criteria have mild disease is not known.

Objectives: To identify subthreshold structural disease in normal-appearing lung regions in smokers.

Methods: We analyzed 8,034 subjects with complete inspiratory and expiratory computed tomographic data participating in the COPDGene Study, including 103 lifetime nonsmokers. The ratio of the mean lung density at end expiration (E) to end inspiration (I) was calculated in lung regions with normal density (ND) by traditional thresholds for mild emphysema (-910 Hounsfield units) and gas trapping (-856 Hounsfield units) to derive the ND-E/I ratio. Multivariable regression analysis was used to measure the associations between ND-E/I, lung function, and respiratory morbidity.

Measurements and Main Results: The ND-E/I ratio was greater in smokers than in nonsmokers, and it progressively increased from mild to severe chronic obstructive pulmonary disease severity. A proportion of 26.3% of smokers without airflow obstruction had ND-E/I greater than the 90th percentile of normal. ND-E/I was independently associated with FEV₁ (adjusted $\beta = -0.020$; 95% confidence interval [CI], -0.032 to -0.007 ; $P = 0.001$), St. George's Respiratory Questionnaire scores (adjusted $\beta = 0.952$; 95% CI, 0.529 to 1.374 ; $P < 0.001$), 6-minute-walk distance (adjusted $\beta = -10.412$; 95% CI, -12.267 to -8.556 ; $P < 0.001$), and body mass index, airflow obstruction, dyspnea, and

exercise capacity index (adjusted $\beta = 0.169$; 95% CI, 0.148 to 0.190 ; $P < 0.001$), and also with FEV₁ change at follow-up (adjusted $\beta = -3.013$; 95% CI, -4.478 to -1.548 ; $P = 0.001$).

Conclusions: Subthreshold gas trapping representing mild small airway disease is prevalent in normal-appearing lung regions in smokers without airflow obstruction, and it is associated with respiratory morbidity.

Clinical trial registered with www.clinicaltrials.gov (NCT00608764).

Keywords: small airway disease; chronic obstructive pulmonary disease; computed tomography; expiratory/inspiratory mean lung density ratio

At a Glance Commentary

Scientific Knowledge on the Subject: A substantial proportion of subjects without overt airflow obstruction have significant respiratory morbidity and structural abnormalities visualized by computed tomography (CT). Whether regions of the lung that appear normal using traditional CT criteria have mild disease is not known.

What This Study Adds to the Field: Subthreshold gas trapping not detected using traditional CT density thresholds is prevalent in normal-appearing lung regions in smokers without airflow obstruction, is suggestive of mild small airway disease, and is associated with respiratory morbidity.

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Chronic obstructive pulmonary disease (COPD) is characterized by a combination of small airway disease and emphysema. Small airways less than 2 mm in internal diameter are the primary site of airflow obstruction in COPD, and small airway disease likely precedes emphysema (1). Although emphysema can be quantified by computed tomography (CT) using both visual and quantitative methods, the small conducting airways cannot be visualized by clinical CT with currently available image resolution. Gas trapping has traditionally been used as a surrogate for small airway disease, but this measure is also influenced by reduced elastic recoil due to underlying emphysema (2).

Multiple metrics have been proposed to measure small airway disease while minimizing the impact of emphysema (3). Parametric response mapping (PRM) uses image matching to estimate

nonemphysematous gas trapping and provides an estimate of functional small airway disease (fSAD) that is associated with lung function and respiratory morbidity parameters, but it is based on determination of emphysema and gas-trapping regions using fixed lung density thresholds (4–6). Although PRM is a useful tool, the dependence on density thresholds may result in missing detection of mild density abnormalities. In contrast to using fixed-density thresholds, the ratio of expiratory to inspiratory mean lung density (E/I) is a robust alternative measure of small airway disease that partially accounts for underlying emphysema, and it has stronger associations with small airway disease than the fixed-density threshold measures (3, 7).

Recent studies suggest that subjects without overt airflow obstruction on spirometry have a substantial symptom burden, and these subjects have evidence of

airway disease (8, 9). These subjects are also likely to have “silent” small airway disease (10). We recently showed that by spatially separating areas of seemingly normal lung regions from areas with established structural lung disease, we can detect abnormalities that are above established thresholds for disease (“subthreshold disease”) that have important clinical consequences (11). We hypothesized that the regions with normal lung density defined by traditional fixed-density thresholds (voxels greater than −910 Hounsfield units (HU) at end inspiration and greater than −856 HU at end expiration) contain regions with subthreshold gas trapping, and by measuring the E/I ratio in these regions with normal density (normal-density E/I [ND-E/I]), we aimed to detect small airway disease not detected using traditional CT density thresholds.

Figure 1. Estimation of the normal-density ratio of expiratory to inspiratory mean lung density in a representative subject. First, the lung parenchyma was delineated into regions with disease and normal regions on the basis of traditional fixed-density thresholds for mild emphysema (−910 Hounsfield units [HU]) and gas trapping (−856 HU), as shown by the **bold vertical lines**. All voxels with density greater than −910 HU on inspiratory scans were classified as normal lung parenchyma at inspiration, and all voxels greater than −856 HU on expiratory scans were classified as normal at expiration. We then separately calculated the mean lung density of these normal regions at expiration (E) and inspiration (I), as shown by the **red dashed lines**. The ratio of E over I was referred to as ND-E/I, where ND represents the normal-density regions in the lung. CT = computed tomography.

Methods

Study Population

We included 10,300 subjects enrolled in phase I of the COPDGene (Genetic Epidemiology of COPD) Study. Subject inclusion is summarized in the Consolidated Standards of Reporting Trials diagram provided in Figure E1 in the online supplement. Study details were published previously (12). Briefly, COPDGene is a large multicenter trial involving 21 centers across the United States, and participants enrolled were current or former smokers between ages 45 and 80 years with a smoking history of at least 10 pack-years. All subjects underwent a standard visit that included spirometry, measurement of exercise capacity using the 6-minute-walk test (6-min-walk distance [6MWD]) (13), and questionnaires to assess medical history and respiratory symptoms. The modified Medical Research Council dyspnea scale score was used to quantify dyspnea (14). Disease-specific influence on subjects' quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ) (15). Total scores range from 0 to 100, where higher scores indicate worse quality of life. We also calculated the body mass index (BMI), airflow obstruction, dyspnea, and exercise capacity (BODE) index, a multidimensional index that predicts all-cause and respiratory-specific

mortality in COPD (16). The index ranges from 0 to 10, with greater scores associated with an increased risk of mortality. We calculated lung function change in the first 5,000 participants who returned for a follow-up visit at approximately 5 years after enrollment.

COPD was diagnosed if the post-bronchodilator ratio of FEV₁ to FVC was less than 0.70, and disease severity was determined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report (17). We excluded participants with FEV₁/FVC greater than or equal to 0.70 and FEV₁ percent predicted less than 0.80 (preserved ratio but impaired spirometry) (18). All participants provided written informed consent, and the study protocol was approved by the institutional review boards of all participating centers.

Computed Tomographic Image Analysis

Volumetric computed tomographic scans were obtained at full inspiration (total lung capacity) and end expiration (FRC or residual volume [RV]). Detailed CT protocols were previously published (12). The voxels less than −910 HU on inspiratory scans were labeled as emphysematous regions, and voxels less than −856 HU on expiratory scans were labeled as regions affected by gas trapping (19). The morphological changes to

segmental airways were quantified using the percentage of wall area (WA %) (20).

Figure 1 depicts the estimation of the normal-density E/I (ND-E/I) ratio in a representative subject. First, the lung parenchyma was delineated into regions, with diseased and normal regions based on traditional fixed-density thresholds for mild emphysema (−910 HU) and gas trapping (−856 HU). Vessels were excluded by thresholding at −700 HU. All voxels with density greater than −910 HU on inspiratory scans were classified as normal lung parenchyma at inspiration, and all voxels greater than −856 HU on expiratory scans were classified as normal at expiration. We then separately calculated the mean lung density of these normal regions at expiration (E) and inspiration (I). The ratio of E over I was referred to as ND-E/I, where ND represents the normal-density regions in the lung.

Statistical Analyses

Pearson's test was performed to report the correlations between ND-E/I and spirometric measures. Univariate and multivariable associations with FEV₁ were tested for CT emphysema, CT gas trapping, and ND-E/I ratio separately after adjusting for age, race, sex, body mass index, current smoking status, pack-years of smoking, CT scanner type, and WA %. We then created an additional model to test the association

Table 1. Baseline Demographics (n = 8,021)

Parameters	COPD Severity Stages					Nonsmokers
	GOLD 0	GOLD 1	GOLD 2	GOLD 3	GOLD 4	
Subjects, n	3,904	710	1,730	1,034	540	103
Age, yr	56.6 (8.3)	61.7 (9.0)	62.5 (8.8)	64.4 (8.2)	64.1 (7.5)	62.4 (9.2)
Female sex, n (%)	1,850 (47%)	303 (42%)	806 (46%)	427 (41%)	219 (40%)	70 (63%)
African American race, n (%)	1,587 (41%)	157 (22%)	408 (24%)	210 (20%)	96 (18%)	5 (5%)
Body mass index, kg/m ²	28.9 (5.8)	27.0 (5.0)	28.7 (6.0)	28.0 (6.3)	25.2 (5.5)	28.0 (5.0)
Smoking, pack-years	37.1 (20.1)	44.9 (24.4)	50.9 (26.8)	55.0 (27.1)	56.7 (28.8)	—
Current smokers, n (%)	2,320 (59%)	394 (55%)	839 (48%)	370 (35%)	126 (23%)	—
FEV ₁ , L	2.8 (0.6)	2.6 (0.6)	1.8 (0.5)	1.1 (0.2)	0.6 (0.1)	2.8 (0.6)
FEV ₁ , % predicted	97.5 (11.5)	90.8 (8.9)	65.0 (8.4)	40.2 (5.6)	22.6 (4.8)	103 (13.8)
FVC, L	3.6 (0.8)	4.1 (1.0)	3.2 (0.8)	2.6 (0.7)	2.1 (0.6)	3.5 (0.8)
FVC, % predicted	96.6 (11.9)	107 (12.3)	86.1 (12.9)	71.4 (13.1)	56.1 (13.6)	98.9 (12.2)
FEV ₁ /FVC	0.78 (0.05)	0.64 (0.04)	0.58 (0.08)	0.43 (0.09)	0.31 (0.07)	0.79 (0.04)
CT emphysema, %	17.0 (13.6)	27.5 (15.6)	27.8 (16.0)	40.3 (17.8)	52.9 (14.5)	22.0 (14.5)
CT gas trapping, %	10.9 (9.7)	20.2 (12.3)	27.3 (15.5)	46.9 (17.3)	62.9 (13.5)	9.8 (8.9)
CT airway wall area thickness, WA %	60.0 (2.8)	60.3 (2.7)	62.4 (3.0)	63.4 (3.0)	63.5 (2.9)	58.3 (2.0)
ND-E/I ratio, scaled to 100	93.5 (1.6)	93.4 (1.1)	93.9 (1.0)	94.4 (0.7)	94.6 (0.3)	92.5 (1.2)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ND-E/I = expiratory-to-inspiratory mean lung density of voxels greater than −856 Hounsfield units at expiration and greater than −910 Hounsfield units at inspiration, multiplied by 100; WA % = percentage of wall area of segmental bronchi. All values are expressed as mean (SD) unless specified otherwise.

between ND-E/I and FEV₁ with inclusion of CT emphysema and CT gas trapping as covariates. Similar models were estimated to measure associations between ND-E/I and respiratory morbidity (SGRQ and 6MWD), with additional adjustment for FEV₁. Because multiple participants had zero BODE scores, we zero-inflated Poisson regression analyses to test the association between ND-E/I and the BODE index after adjustment for the above-mentioned variables. In these models, we did not adjust for FEV₁ and BMI, because they are used in the calculation of the BODE index. We also tested the association between ND-E/I and annualized FEV₁ change over time in linear regression models, with adjustment for age, race, sex, BMI, current smoking status, pack-years of smoking, CT scanner type, CT emphysema, and WA %. An α -level of 0.05 was considered statistically significant, and all analyses were performed using IBM SPSS Statistics software (version 22.0; IBM, Armonk, NY) and the R statistical software package (version 3.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Subject Characteristics

We included 8,021 subjects with complete inspiratory and expiratory CT data (Figure E1). The baseline characteristics of participants are shown in Table 1. Among the sample, 3,904 (48.7%) had GOLD stage 0 COPD, 710 (8.8%) were classified as GOLD stage 1, 1,730 (21.5%) as GOLD stage 2, 1,034 (12.8%) as GOLD stage 3, and 540 (6.7%) as GOLD stage 4. One hundred three (1.2%) were lifetime nonsmokers. The average smoking pack-year history was 44.5 (SD, 25.0), and 4,060 subjects (50.5%) were active smokers. The mean SGRQ score was 26.8 (SD, 22.8), and scores ranged from 0.0 to 98.4. Six-minute-walk distance ranged from 100 to 2,690 m, with a mean of 1,370.9 m (SD, 400.3). Participants had a median BODE index of 1.0 (interquartile range, 0–3).

ND-E/I and FEV₁

Figure 2 shows that the mean ND-E/I ratio in participants progressively increases from nonsmoking control subjects to GOLD stages 0 through 4. There were modest but statistically significant correlations between ND-E/I ratio and FEV₁/FVC ($\rho = -0.21$; $P < 0.001$), FEV₁ ($\rho = -0.34$; $P < 0.001$),

Figure 2. Mean normal-density ratio of expiratory to inspiratory mean lung density (ND-E/I) ratio in lifelong nonsmoking control subjects and in participants by Global Initiative for Chronic Obstructive Lung Disease (GOLD, G) stage. Box plots show means and 95% confidence intervals.

and FEV₁ percent predicted ($\rho = -0.30$; $P < 0.001$). The mean ND-E/I in current and former smokers was 0.93 (SD, 0.13), and it ranged from 0.83 to 1.00. In lifetime nonsmoking control subjects, this ratio was 0.92 (SD, 0.14), and it ranged from 0.90 to 0.98. The 90th percentile for this ratio in control subjects was 0.94. Among all GOLD stages, a substantial proportion of subjects had ND-E/I ratios above the 90th percentile of normal: 1,013 (26.1%), 117 (16.4%), 509 (29.4%), 558 (53.9%), and 433 (80.1%), respectively, for GOLD stages 0–4 (Figure 3).

In univariate regression, ND-E/I was significantly associated with FEV₁ ($\beta = -0.247$; 95% CI, -0.261 to -0.232 ; $P < 0.001$). After adjustment for age, sex, race, BMI, pack-years of smoking, current smoking status, CT scanner type, and airway WA %, the ND-E/I ratio remained

significantly associated with FEV₁ (adjusted $\beta = -0.121$; 95% CI, -0.133 to -0.110 ; $P < 0.001$) (Table 2, model A). When CT measures of emphysema and gas trapping were added to the model, the ND-E/I ratio was still independently associated with FEV₁ (adjusted $\beta = -0.020$; 95% CI, -0.032 to -0.007 ; $P = 0.001$) (Table 2, model B).

ND-E/I and Respiratory Morbidity

SGRQ. ND-E/I was significantly associated with SGRQ scores in both univariate ($\beta = 5.294$; 95% CI, 4.950 to 5.638; $P < 0.001$) and multivariable analyses (adjusted $\beta = 1.208$; 95% CI, 0.873 to 1.543; $P < 0.001$) after adjusting for age, sex, race, BMI, pack-years of smoking, active smoking status, CT scanner type, airway WA%, and FEV₁. This relationship held true even after adjusting for CT measures of emphysema and gas

Figure 3. The proportion of participants in each Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage with normal-density ratio of expiratory to inspiratory mean lung density (calculated as mean lung density of voxels greater than -856 HU at expiration and greater than -910 HU at inspiration, multiplied by 100) above the 90th percentile of normal (0.94).

trapping (adjusted $\beta = 0.952$; 95% CI, 0.529 to 1.374; $P < 0.001$) (Table 3).

6MWD. In univariate regression, ND-E/I was significantly associated with 6MWD ($\beta = -32.790$; 95% CI, -34.607 to -30.973 ; $P < 0.001$). After multivariable adjustment as described above, the ND-E/I ratio remained significantly associated with 6MWD (adjusted $\beta = -10.412$; 95% CI, -12.267 to -8.556 ; $P < 0.001$). This association was significant when CT emphysema and gas trapping were added to the model (adjusted $\beta = -7.329$; 95% CI, -9.706 to -4.953 ; $P < 0.001$) (Table 3).

BODE index. The ND-E/I ratio was significantly associated with the BODE index in both univariate ($\beta = 0.257$; 95% CI, 0.246 to 0.269; $P < 0.001$) and multivariable analyses (adjusted $\beta = 0.188$;

95% CI, 0.173 to 0.202; $P < 0.001$) adjusted for age, sex, race, pack-years of smoking, active smoking status, CT scanner type, and airway WA %. Even after adjustment for CT emphysema and CT gas trapping, this relationship remained significant (adjusted $\beta = 0.169$; 95% CI, 0.148 to 0.190; $P < 0.001$) (Table 3).

FEV₁ change. We had complete follow-up data for 4,905 participants. The annualized FEV₁ changes were -39.6 (SD, 54.8) ml/yr in the overall cohort and -41.2 (48.2), -51.8 (51.8), -41.1 (59.8), -26.4 (51.3), and -9.7 (91.2) ml/yr in GOLD stages 0–4, respectively. After adjustment for age, race, sex, BMI, current smoking status, pack-years of smoking, CT scanner type, CT emphysema, and WA %, we found a significant association between ND-E/I

ratio and change in FEV₁ ($\beta = -3.013$; 95% CI, -4.478 to -1.548 ; $P = 0.001$). This association was also seen in those with mild disease (GOLD stages 0 and 1 participants; $\beta = -1.611$; 95% CI, -3.126 to -0.096 ; $P = 0.037$).

Scans Acquired at RV

Expiratory scans were acquired at RV at one center. Tables E1 and E2 show that the associations between ND-E/I measured on scans at RV remained significantly associated with respiratory morbidity indices.

ND-E/I in Smokers without Airflow Obstruction

We also analyzed smokers without airflow obstruction (GOLD stage 0). ND-E/I was independently associated with FEV₁, SGRQ, 6MWD, and BODE index after adjustment for the same variables as described above (Table E3).

Discussion

We have demonstrated that in current and former smokers, lung regions considered normal as visualized by CT using traditional fixed-density thresholds show signs of gas trapping not detected using traditional CT density thresholds, suggesting presence of small airway disease. The extent of involvement increases with progressive disease severity, and this subthreshold gas trapping is independently associated with important patient outcomes, including respiratory quality of life, functional exercise capacity, and the BODE index.

The presence of small airway disease is an early finding in COPD; however, limitations in existing CT resolution preclude direct visualization of small airways. Gas trapping seen by expiratory CT provides an indirect estimate of small airway involvement, but this metric is also influenced by reduced lung elastic recoil due to emphysema. Because the density of normal lung tissue is expected to increase homogeneously from inspiration to expiration, a lower-than-expected increase in density suggests trapping of air. An alternative measure of gas trapping, the E/I ratio, adjusts for emphysema and has stronger correlations with spirometric measures of airflow obstruction than density threshold-based measures of gas trapping (3, 21). Hersh and colleagues showed that

Table 2. Multivariable Associations with FEV₁ (n = 7,918)

Parameter	β Regression Coefficient (95% CI)	P Value
Model A*		
CT emphysema, %	-0.019 (-0.020 to -0.018)	<0.001
CT gas trapping, %	-0.024 (-0.025 to -0.024)	<0.001
ND-E/I ratio, scaled to 100	-0.121 (-0.133 to -0.110)	<0.001
Model B†		
ND-E/I ratio, scaled to 100	-0.020 (-0.032 to -0.007)	0.001

Definition of abbreviations: CI = confidence interval; CT = computed tomography; ND-E/I = expiratory-to-inspiratory mean lung density of voxels above -856 Hounsfield units at expiration and above -910 Hounsfield units at inspiration.

*Model A was adjusted for age, race, sex, smoking status, pack-years, body mass index, CT scanner type, and airway wall area (%).

†Model B was adjusted for age, race, sex, smoking status, pack-years, body mass index, CT scanner type, airway wall area (%), CT emphysema (%), and CT gas trapping (%). Adjusted R^2 for Model B = 0.714.

Table 3. Multivariable Associations with Respiratory Morbidity (n = 7,918)

Parameter	Multivariable Regression					
	SGRQ		6MWD		BODE Index	
	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
CT emphysema, %	0.197 (0.167 to 0.227)	<0.001	−0.398 (−0.566 to −0.230)	<0.001	0.029 (0.028 to 0.030)	<0.001
CT gas trapping, %	0.284 (0.253 to 0.316)	<0.001	−1.187 (−1.303 to −1.010)	<0.001	0.030 (0.030 to 0.031)	<0.001
ND-E/I ratio, scaled to 100	1.208 (0.873 to 1.543)	<0.001	−10.412 (−12.267 to −8.556)	<0.001	0.188 (0.173 to 0.202)	<0.001
ND-E/I ratio*, scaled to 100	0.952 (0.529 to 1.374)	<0.001	−7.329 (−9.706 to −4.953)	<0.001	0.169 (0.148 to 0.190)	<0.001

Definition of abbreviations: 6MWD = 6-minute-walk distance; BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity; CI = confidence interval; CT = computed tomography; ND-E/I = expiratory-to-inspiratory mean lung density of voxels greater than −856 Hounsfield units at expiration and greater than −910 Hounsfield units at inspiration, multiplied by 100; SGRQ = St. George's Respiratory Questionnaire. All models are adjusted for age, race, sex, smoking status, pack-years, body mass index, CT scanner type, FEV₁, and segmental airway wall area (%). FEV₁ and body mass index are not included in the BODE regression model, because they are used in the calculation of the BODE index.

*Adjusted for age, race, sex, smoking status, pack-years, body mass index, CT scanner type, FEV₁, segmental airway wall area (%), CT emphysema (%), and CT gas trapping (%)

the E/I ratio correlated with both FEV₁/FVC ($r = -0.62$) and FEV₁ percent predicted ($r = -0.73$), as well as with respiratory morbidity indices, including dyspnea, respiratory quality of life, and 6MWD (3). Nambu and colleagues showed that the E/I ratio has a stronger correlation with airflow obstruction and spirometric measures of small airway disease than gas trapping measured using the −856 HU threshold (21). Compared with other CT measures, the E/I ratio also has the strongest correlation with RV as well as RV/total lung capacity (22, 23). These findings are corroborated by results of other studies (21, 22, 24, 25). All these studies calculated E/I for the entire lung, including areas with established and readily apparent disease. We extend the findings previously reported in the literature by showing that even in seemingly normal areas of the lung, there is evidence of clinically important gas trapping. Using PRM, we recently showed that fSAD occurs in early stages of the disease and is associated with lung function decline (10). The PRM metric is based on using thresholds of lung density (less than −950 HU for severe emphysema) and gas trapping (less than −856 HU), as well as matching images voxel to voxel, such that nonemphysematous gas trapping (fSAD) can be determined. The lung regions that we included for analysis (normal density) would register as normal areas on PRM, and this precludes direct comparisons with the PRM technique. However, by detecting abnormalities in seemingly normal areas,

we believe our method is sensitive to detecting very mild disease that is not detected by PRM.

The etiology for the elevated E/I in normal lung regions is likely multifactorial. The most likely reason is the presence of mild small airway disease. Although reduced elastic recoil can also contribute to gas trapping, the E/I ratio attenuates the influence of emphysema by adjustment for its presence. In our study, by excluding areas with even mild emphysema using the −910 HU cutoff, we minimized the influence of emphysema in these normal-appearing regions. Multiple small studies have previously shown that even healthy subjects can have some evidence of regional gas trapping, a finding of previously unclear significance. We found that the overall E/I in smokers without apparent airflow obstruction is higher than in healthy nonsmoking control subjects, and we also found that the E/I increases progressively with increasing COPD severity. We also found that this unrecognized but abnormal E/I is associated with additional respiratory morbidity and hence is clinically important. The increasing burden of E/I with worsening disease severity is likely due to a progressively greater involvement of the lung with small airway disease (10). We recently showed that emphysematous voxels can influence the mechanics of surrounding normal voxels (11), and some of the greater E/I in the normal areas of subjects with moderate to severe COPD could also be due to this mechanotransduction (26, 27).

Recent studies suggest that a substantial proportion of smokers without airflow obstruction on spirometry have CT-derived evidence of structural lung disease and respiratory morbidity. Regan and colleagues found that 42.3% of smokers without spirometric obstruction had CT-derived evidence of emphysema or airway disease, and more than half had one or more respiratory symptom or exacerbation (8). Woodruff and coworkers found that approximately 50% of smokers without spirometric obstruction had substantial respiratory symptoms, and these symptomatic smokers had greater airway wall thickening (9). These smokers also had a greater frequency of exacerbations than nonsmoking control subjects. Our study supports the findings of these studies in suggesting early structural disease has an impact on respiratory morbidity. One-fourth of participants without airflow obstruction had evidence of abnormal ND-E/I. In addition, we have shown significant relationships between ND-E/I and respiratory morbidity in GOLD stage 0 participants, in whom respiratory morbidity is less likely to be driven by established disease.

Our study has multiple strengths. First, we analyzed well-characterized subjects with a wide range of disease severity as well as healthy control subjects enrolled in a large cohort with stringent quality control for spirometry and CT. Second, we spatially separated normal voxels from voxels with emphysema or gas trapping, and we

estimated the ND-E/I ratio in lung regions above the threshold for mild emphysema (−910 HU), thus eliminating the direct influence of underlying emphysema. Our study also has several limitations. Computed tomographic image acquisition was not controlled by spirometry gating; however, participants were carefully

coached to full inspiration and end expiration. We had a low number of healthy control subjects; however, the amount of emphysema-like lung in these healthy control subjects was similar to that seen in other studies that included assessment of normative data for CT emphysema (28).

Conclusions

Subthreshold gas trapping is prevalent in normal-appearing lung regions in smokers without airflow obstruction, and it is associated with respiratory morbidity. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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