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Association Between Expiratory Central Airway Collapse and Respiratory Outcomes Among Smokers

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Abstract

Importance—Central airway collapse greater than 50% of luminal area during exhalation (Expiratory Central Airway Collapse, ECAC) is associated with cigarette smoking and chronic obstructive pulmonary disease (COPD). However, its prevalence and clinical significance are unknown.

Objective—To determine whether ECAC is associated with respiratory morbidity in smokers independent of underlying lung disease.

Design, Setting and Participants—We analyzed paired inspiratory-expiratory computerized tomography (CT) images from a large multicenter study (COPDGene) of current and former smokers aged 45–80 years. Participants were enrolled from January 2008 to June 2011, and followed longitudinally till October 2014. Images were screened using a quantitative method to detect at least a 30% reduction in minor axis tracheal diameter from inspiration to end-expiration. From this sample of screen positive scans, cross-sectional area of the trachea was measured manually for confirmation of ECAC at three predetermined levels (aortic arch, carina and bronchus intermedius) in the inspiratory-expiratory scans. Participants with ≥50% reduction in cross-sectional area were diagnosed with ECAC.

Exposure(s)—Expiratory Central Airway Collapse

Main Outcome(s) and Measure(s)—Primary outcome was baseline respiratory quality of life [St George's Respiratory Questionnaire (SGRQ) scale 0 to 100, 100 represents worst health status, minimum clinically important difference MCID 4 units] and secondary outcomes were dyspnea [modified Medical Research Council (mMRC) scale 0 to 4, 4 represents worse dyspnea, MCID 0.7 units] and six minute walk distance [MCID 30 m] at enrollment and exacerbation frequency (events per 100 person-years) on longitudinal follow-up.

Results—8820 current and former smokers with and without COPD were included. The prevalence of ECAC was 5%. On multivariable analyses, ECAC was associated with older age [65.0 vs. 59.4 years, absolute difference = 5.6, 95%CI 4.8 to 6.4, adjusted Odds Ratio, OR for every 1-year increase 1.06,95%CI 1.04–1.07;p<0.001], female sex [297 (67%) vs. 3856 (46%), absolute difference = 21.0%, 95%CI 16.4 to 25.4, OR 2.08,95%CI 1.63–2.63;p<0.001], white race compared to African American [374 (84.4%) vs. 5654 (67.5%), absolute difference = 16.9%, 95%CI 13.1 to 20.2, OR 1.85,95%CI 1.38–2.48;p<0.001], higher BMI [31.2 vs. 28.7, absolute difference = 2.5, 95%CI 1.9 to 3.1, OR for every 1 unit increase 1.07,95%CI 1.06–1.09;p<0.001] and lower FEV_1 [1.82 vs. 2.28 L, absolute difference = −0.46, 95%CI −0.54 to −0.38, OR for every 1L decrease 0.74,95%CI 0.62–0.89;p<0.001]. ECAC was associated with worse SGRQ scores [30.9 vs. 26.5 units, p<0.001, absolute difference =4.4, 95%CI 2.2 to 6.6)] and mMRC [median 2, Interquartile range IQR 0–3 vs. 1, IQR 0–3, p<0.001] and independent of age, sex, race, BMI, FEV_1, smoking burden and emphysema. On follow-up, participants without COPD but with ECAC had increased frequency of total (54 vs. 35 events per 100 person-years, IRR 2.19; 95%CI 1.78 to 2.71;p<0.001) and severe respiratory events requiring hospitalization (16 vs. 10 events per 100 person-years, IRR 2.95; 95%CI 2.20 to 3.95;p<0.001).

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Conclusions and Relevance—In a cross-sectional analysis of current and former smokers, the presence of expiratory central airway collapse was associated with worse respiratory quality of life. Further studies are needed to assess long-term effects on clinical outcomes.

Trial Registration—ClinicalTrials.gov: Identifier: NCT00608764 https://clinicaltrials.gov/ct2/show/NCT00608764?term=copdgene&rank=1

Phase 1 protocol available here: http://www.copdgene.org/sites/default/files/COPDGeneProtocol-5-0_06-19-2009.pdf

Phase 2 protocol available here: http://www.copdgene.org/sites/default/files/CentralStudyProtocol_06%20Oct%202014_Clean.pd

Keywords

Expiratory Central Airway Collapse; CT; lung function; respiratory morbidity

Background

Expiratory Central Airway Collapse (ECAC) is defined by excessive airway collapse during expiration either from cartilaginous weakening or redundancy of the posterior membranous wall.[1] The frequency of ECAC, which includes tracheobronchomalacia and excessive dynamic airway collapse (EDAC), has not been assessed in large studies and the prevalence in people with known respiratory problems using bronchoscopy for diagnosis has ranged from 1% to 53%.[2–4] With increasing use of noninvasive imaging techniques such as computed tomography (CT), ECAC is increasingly recognized in the adult population, especially in association with cigarette smoking and chronic obstructive pulmonary disease (COPD).[4] While the small conducting airways <2 mm in diameter are the major site of resistance to airflow in COPD,[5] central airway collapse greater than 50% of luminal area during exhalation has been hypothesized to cause additional airflow obstruction and respiratory morbidity.[3,6–8] Although ECAC in adults has been associated with cough and dyspnea in previous smaller studies, it is not known if this is due to underlying disease processes or due to ECAC itself.[3,6,7] In addition, there is scant data about its prevalence and correlation with overall respiratory quality of life and other clinical outcomes.

We analyzed paired inspiratory-expiratory computed tomography (CT) images of participants in a cohort of current and former smokers enrolled in the COPDGene study to determine the prevalence and clinical significance of ECAC. We hypothesized that ECAC is common in COPD and smokers without airflow obstruction, and that it is associated with respiratory morbidity independent of underlying lung disease.

Methods

Study population

Current and former smokers aged 45 to 80 years from a large multi-center cohort study (COPDGene) were included in the study, details of which have been previously published.[9] The COPDGene study was approved by the institutional review boards of all 21 participating centers, and all participants gave written informed consent prior to participation

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in the study. Participants were enrolled from local communities across the United States, and those with known lung disease other than COPD and asthma were excluded. Demographic characteristics such as age and sex were collected at the time of enrollment. We collected information on race based on participants' self-identification as non-Hispanic white or non-Hispanic African American race. Participants from these races were specifically recruited to COPDGene to meet the requirements for the planned GWAS analyses of genetic susceptibility to cigarette smoke. Spirometry was performed pre- and post- bronchodilator in accordance with the American Thoracic Society (ATS) criteria.[10] Computed tomographic scans were performed at maximal inspiration (total lung capacity, TLC) and end-tidal expiration (functional residual capacity, FRC), and at one center at residual volume (RV). Emphysema (percentage of lung volume at TLC with attenuation less than -950 Hounsfield Units (HU) (low attenuation area, %LAA950insp) and gas trapping (percentage of lung volume at FRC (or RV) with attenuation less than -856 HU ($\%LAA856_{exp}$) were quantitated using 3D Slicer software (www.airwayinspector.org), and airway dimensions were measured using Pulmonary Workstation 2 (VIDA Diagnostics, Coralville, IA, USA).[9] Wall area percentage of segmental airways (Wall area pct) was used to quantify airway disease.[9] One center acquired expiratory CT scans at residual volume (RV), and these cases were separately analyzed (Supplemental Tables 1 and 2).

Outcomes

The primary outcome was respiratory disease related health impairment and quality of life assessed using St George's Respiratory Questionnaire (SGRQ) scores.[11] SGRQ ranges from 0 to 100 and the minimum clinically important difference (MCID) is 4 units with higher scores indicating worse respiratory quality of life. The secondary outcomes were dyspnea, exercise capacity and exacerbation frequency. Dyspnea was measured using the modified Medical Research Council (mMRC) dyspnea score.[12] mMRC ranges from 0 for minimal symptoms to 4 for severe dyspnea. There is no accepted MCID for the mMRC score. However, based on the dispersal of this score in our cohort, we used distribution methods to define the MCID for mMRC as 0.5 SD, which is 0.7 units.[13] Six minute walk distance was assessed according to ATS guidelines, with an MCID of 30 meters.[9,14] Follow-up data was obtained by contacting participants every 3 to 6 months through an automated telecommunication system using a validated questionnaire.[15] Respiratory events and exacerbations were defined using a modified version of the Epidemiology Standardization Project questionnaire (American Thoracic Society–Division of Lung Diseases [ATS-DLD]-78).[16,17] We defined exacerbations as respiratory worsening (increase in dyspnea, cough or sputum production) lasting at least 48 hours and requiring use of either antibiotics and/or systemic steroids, as reported by the participants on follow-up contact encounters. The respiratory events were classified as "severe" when they resulted in hospitalization. All-cause mortality was also compared by ECAC status at enrollment. Study participants and coordinators were blinded to the presence or absence of ECAC.

CT Analysis of ECAC

We performed CT analysis of ECAC in two stages (Supplemental Figure 1). Measurements were performed on baseline CT scans by investigators blinded to the participants' clinical characteristics. Participants with paired inspiratory-expiratory scans that passed quality

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control were included. In the first stage, a quantitative method using Pulmonary Workstation 2 (VIDA Diagnostics, Coralville, IA) was employed to screen paired inspiratory-expiratory scans to assess percent change in minor axis diameter of the trachea. Measurements were made for the inner diameter of the trachea, including major- and minor-axis diameters, at every 10 mm from the carina caudocranially. Those with at least 30% reduction in minor axis diameter from inspiration to expiration were categorized as screen positive for ECAC, assuming that a 30% reduction in diameter corresponds geometrically to a 50% reduction in cross-sectional area (CSA). In addition, to screen in more patients, participants diagnosed as having tracheobronchomalacia on visual reading either by local radiologists at each site of enrollment, or during a CT workshop were also included.[18] This workshop involved 58 radiologists and pulmonologists evaluating chest CT scans in cigarette smokers to describe CT abnormalities as well as to evaluate concordance between visual and quantitative measurements on chest CT. In the second stage, screen positive scans were evaluated for confirmation of ECAC by three readers (two chest radiologists and one pulmonologist). Those participants with negative scans on screening were deemed to be controls without ECAC. Window levels were set at −550 to −700 HU, and window width at 1200–1500 HU. CSA was measured manually using standard DICOM software at three levels in both inspiratory and expiratory scans: at the level of the aortic arch (at the origin of the subclavian artery), at the level of the carina and at the level of the bronchus intermedius, just distal to the origin of the right upper lobe bronchus (Figure 1). Percent collapse was assessed by [(CSA at end-inspiration – CSA at end-expiration)/CSA at end-inspiration]. ECAC was defined as > 50% reduction in CSA at any level based on the final manual reading. We selected a 50% threshold for defining ECAC based on previous studies as well as our data showing that differences in SGRQ meet the MCID of 4 units at and beyond this threshold (Supplemental Figure 2). All readers scanned the entire length of the trachea to assess qualitatively if there was a greater than 50% reduction in CSA at any other level. Those without a 50% reduction in CSA at any level on manual measurement were deemed controls. A subset of 300 overlapping scans (n=100 each) were read by each reader to calculate inter- and intra-observer variability. The original reader's measurement of collapse was used in the analysis.

Statistical Analyses

Baseline data are expressed as means with standard deviations for normally distributed values. Intra- and inter-observer agreements for diagnosis of ECAC were calculated using Cohen's kappa. The intraclass correlation coefficient (ICC) was calculated to assess inter-rater reliability for measurements at the three pre-determined levels. Bivariable comparisons were made between those with and without ECAC using chi-squared test for categorical variables and two-tailed independent t-tests for continuous variables. Variables significant on bivariable analyses at two-sided alpha of 0.05 were included in a multivariable model, and logistic regression performed to identify variables independently associated with ECAC. Multivariable linear regression analyses were performed to assess relationships between ECAC and respiratory morbidity indices such as MMRC, SGRQ and 6MWD, using age, sex, race, body mass index (BMI), forced expiratory volume in the first second (FEV_1), smoking burden, emphysema, gas trapping and segmental wall area% as covariates. To assess the differences in exacerbations on follow-up, negative binomial regression models

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were created with adjustment for age, race, sex, BMI, smoking burden, FEV_1 and emphysema. To assess the robustness of the negative binomial models, we also compared the time to first contact at which an exacerbation was captured by the longitudinal follow-up system using Cox Proportional hazards models. Cox proportional hazards analyses were also performed to compare mortality by ECAC status after adjustment for age, race, sex, BMI, smoking pack-years, FEV_1, CT emphysema, CT gas trapping and segmental wall area%. Two-sided p value <0.05 was considered statistically significant. Participants who agreed to be part of the long term follow-up cohort were analyzed for exacerbations and mortality. Patients were censored at the time they last reported outcomes in the long term follow-up system. We controlled for multiple comparisons within the entire cohort as well as the COPD and non-COPD subgroups using the false discovery rate procedure.[19] All analyses were performed using Statistical Package for the Social Sciences (SPSS 22.0, SPSS Inc., Chicago, IL, USA).

Results

Participant Characteristics

8820 participants were included with a mean age of 59.7 (SD 9.0) years (Derivation of the Analytic Cohort, Supplemental Figure 1). Males constituted 56.7% (4667 of 8820) of the cohort; 66.0% (5428 of 8820) were White race and 34.0% (2792 of 8820) were African American. 4559 (51.7 %) were active smokers and 3856 (43.7 %) had COPD diagnosed by $FEV_1/FVC<0.70$. The kappa values for intraobserver and interobserver agreement for detecting ECAC were 0.77 (95% confidence interval [CI], 0.71 to 0.83) and 0.73 (95% CI, 0.67 to 0.79), respectively. ICC between raters at the aortic arch, carina and bronchus intermedius was 0.95 (95%CI 0.92 to 0.96), 0.91 (95%CI 0.88 to 0.93), and 0.92 (95%CI 0.88 to 0.94), respectively.

443 cases of ECAC were identified (prevalence 5.0%). The prevalence was higher in those with COPD than in those without COPD (5.9%, 229 of 3856 vs. 4.3%, 205 of 4964,p=0.001, absolute difference 1.6%, 95%CI 0.9 to 2.7), and increased with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage[20] [4.8% (33 of 683), 5.6% (93 of 1666), 6.6% (66 of 995) and 7.2% (37 of 512) for stages 1 to 4 respectively; p<0.001). Compared with controls, participants with ECAC were older [65(8.6) vs. 59.4(9) years; p<0.001, absolute difference 5.6, 95%CI 4.8 to 6.4]. Prevalence of ECAC was greater in females than in males [7.2% (297 of 4153) vs. 3.1% (146 of 4667); p<0.001, absolute difference 4.2%, 95%CI 3.1 to 5.0] and in White race than in African Americans [6.2% (374 of 6028) vs. 2.5% (69 of 2792); p<0.001, absolute difference 3.7%, 95%CI 2.9 to 4.6]. Table 1 shows a comparison of baseline demographics in participants with and without ECAC. Those with ECAC also had a higher BMI [31.2(6.6) vs. 28.7(6.2) kg/m^2; p<0.001, absolute difference 2.5, 95%CI 1.9 to 3.1], greater frequency of chronic bronchitis [24.6% (109 of 443) vs. 15.3% (1283 of 8377); p<0.001, absolute difference 9.3%, 95%CI 5.4 to 13.6], and a greater smoking burden [47.9(26.7) vs. 44.2(24.8) pack years; p=0.002, absolute difference 3.7, 95%CI 1.2 to 6.2]. Participants with ECAC also had greater baseline airflow obstruction [FEV_1 1.82(0.79) vs. 2.28(0.92) L; p<0.001, absolute difference of 460 ml, 95%CI −0.540 to −380].

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Variables associated with ECAC

Participants with ECAC had a greater degree of %emphysema on CT [7.4(10.7)% vs. 6.1(9.6)%; p = 0.005, absolute difference 1.3, 95%CI 0.3 to 2.3] compared to controls; however there were no differences in percent gas trapping and airway wall thickness of either segmental or sub segmental airways (Table 1). While on bivariable analysis, emphysema and smoking burden were associated with ECAC, on multivariable analyses ECAC was independently associated with older age, female sex, White race, higher BMI and greater airflow obstruction (Table 2).

Primary outcome

Respiratory quality of life (SGRQ)—Compared to controls, participants with ECAC had worse respiratory quality of life [SGRQ 30.9(22.4) vs. 26.5(22.8); p<0.001] at enrollment, an absolute difference of 4.4 units (95%CI 2.2 to 6.6). After adjustment for age, sex, race, BMI, smoking burden, airflow obstruction on spirometry and %emphysema, %gas trapping and wall area of segmental airways on CT, ECAC was associated with worse respiratory quality of life (unstandardized regression coefficient for SGRQ = 2.90, 95%CI 1.10 to 4.69; p<0.01).

Secondary outcomes

Dyspnea and six minute walk distance—Those with ECAC had greater dyspnea [mMRC mean 1.7(1.5) vs. 1.3(1.4); p<0.001, absolute difference of 0.4 unit mean, 95%CI 0.3 to 0.5; and median 2.0, interquartile range IQR 0 to 3 vs. 1.0, IQR 0 to 3, absolute difference of 1.0 unit median], and worse functional capacity as measured by lower six minute walk distance [399(123) vs. 417(121) m.; p=0.003, absolute difference of 18 m, 95%CI 6 to 30]. After adjustment for age, sex, race, BMI, smoking burden, airflow obstruction on spirometry and %emphysema, %gas trapping and wall area of segmental airways on CT, ECAC was associated with greater dyspnea (regression coefficient for mMRC = 0.18, 95%CI = 0.06 to 0.29; p<0.01), see Table 3. ECAC was not associated with six minute walk distance (regression coefficient = 17.0, 95%CI = −15.43 to 49.43; p = 0.304).

Acute respiratory events—We had follow-up data on 7456 participants (median 4.3 years, range 0.2 to 6.7 years). For participants with COPD (n=3388), we had data for exacerbations for a median duration of follow-up of 4.3 years (interquartile range IQR 3.3 to 5.0). After adjustment for age, sex, race, smoking burden, FEV_1 and emphysema, ECAC was not associated with total number of exacerbations (68 vs. 56 events per 100 person-years, Incidence risk ratio, IRR 1.12; 95% CI, 0.92 to 1.35; p = 0.27), but with a significantly greater frequency of severe exacerbations (21 vs. 17 events per 100 person-years IRR 1.39; 95% CI, 1.08 to 1.78; p = 0.01). Amongst those without COPD (n=4068, median follow up 4.2 years, IQR 3.0 to 4.9), ECAC was associated with increased frequency of both total number of respiratory events (54 vs. 35 events per 100 person-years, IRR 2.19; 95%CI 1.78 to 2.71;p<0.001) and with severe respiratory events requiring hospitalization (16 vs. 10 events per 100 person-years, IRR 2.95; 95%CI 2.20 to 3.95;p<0.001).[21]

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In participants with COPD, after adjustment for age, sex, race, BMI, smoking burden, CT emphysema, CT gas trapping, segmental wall area% and FEV_1, there was no association between the presence of ECAC and the time to first severe exacerbation (adjusted HR = 1.281, 95%CI 1.00 to 1.640; p = 0.050). ECAC was also not associated with the time to first total exacerbation (adjusted HR = 1.097, 95%CI 0.940 to 1.281; p = 0.238). In participants without COPD, ECAC was associated with a shorter time to first severe exacerbation (HR = 1.349, 95%CI 1.006 to 1.810; p = 0.046, see Supplemental Figure 3) but with no difference in time to first total exacerbation (HR = 1.090, 95%CI 0.90 to 1.321; p = 0.378).

Mortality—Mortality data was available for 7389 participants of whom 707 (9.6%) died over the period of follow-up. Of those with ECAC, 38 (9.9%) died on follow-up, compared with those without ECAC (669, 9.6%). After adjustment for demographics including age, race, sex, smoking burden in pack-years, BMI and FEV_1 and CT measures of COPD, ECAC was not associated with mortality (adjusted hazards ratio, HR 1.09, 95%CI 0.77 to 1.54;p=0.639)

Scans obtained at RV

Expiratory scans were acquired at RV at a single center and the results for these participants are presented separately in Supplemental Tables 1 and 2. Overall, the prevalence of ECAC was expectedly higher in these participants compared to those who had FRC scans (9.4% vs. 4.3%; p<0.001, absolute difference 5.1%, 95%CI 3.4 to 6.9). However, the relationships between respiratory morbidity and ECAC remained similar regardless of the level of expiration at which the scans were acquired (Supplemental Tables 1 and 2).

Discussion

Our analysis of CT scans from a cohort of current and former smokers shows that the prevalence of ECAC in this high risk group was five percent, and that it was associated with worse respiratory quality of life. While previous smaller studies have ascribed respiratory symptoms to the presence of ECAC, we demonstrated that ECAC is associated with respiratory morbidity independent of the degree of airflow obstruction and emphysema.

The prevalence of ECAC has not been extensively investigated, and previous studies were limited either by selection bias of patients with known respiratory problems who underwent bronchoscopy,[2–4,22] or by small sample size.[4,23–26] ECAC has long been recognized to be associated with respiratory symptoms; these range from chronic cough, dyspnea, stridor and wheezing that are resistant to corticosteroids, impaired clearance of secretions, and respiratory failure.[7,27–29] However, these symptoms are non-specific and have been variously ascribed to the underlying disease. We found that after adjustment for demographics, structural lung disease and FEV_1, ECAC was associated with greater dyspnea and worse respiratory quality of life. These findings add another dimension to the evaluation of respiratory symptoms in smokers, and we speculate that ECAC might explain some cases of dyspnea disproportionate to apparent obstructive airways disease by CT and/or spirometric measures.[8]

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We also found that ECAC was associated with the incidence of acute respiratory events on follow-up in those without COPD, and with greater incidence of severe exacerbations in those with airflow obstruction. This is a new finding, and merits further investigation as to whether this is due to a continuum of peripheral airway inflammation along the central airways, or is an independent cause of respiratory decompensation. While ECAC may be a marker of poorer outcomes in patients with COPD, that ECAC is associated with increased frequency of mild-moderate as well as severe respiratory events in those without airflow obstruction is noteworthy. Recent large population studies have reported “exacerbation like” events in participants without airflow obstruction.[21,30] Whether some of these represent decompensated ECAC or whether ECAC is a marker for future respiratory events needs to be investigated. Our results suggest that ECAC might contribute to symptoms independent of underlying disease and may also serve as a CT based biomarker of poor respiratory outcomes.

ECAC occurring in association with COPD has previously been attributed to a combination of the proximal extension of the inflammatory process of the peripheral airways,[31] weakening of membranous trachea from inflammation and cough,[32] wall instability due to loss of parenchymal tissue,[33] and increased pressure changes during exhalation.[1] We found no association between ECAC and any of the CT measures of COPD, suggesting that ECAC can occur without co-existing emphysema. However, the frequency of ECAC increased with COPD GOLD stage, suggesting that there is some association with worsening lung disease, likely not discernible with existing CT protocols. We found a higher prevalence of chronic bronchitis in participants with ECAC than in controls. Alternatively, this finding could reflect a lower FEV_1 associated with ECAC. Airflow obstruction in smokers has traditionally been thought to occur in the distal smaller airways <2mm in diameter.[5] However, when central airway collapse is severe, it is plausible that this is associated with additional airflow obstruction.[34] There was no association between ECAC and gas trapping, a mechanism that could potentially lead to elevated intrathoracic pressures and collapse of weakened airway walls. That gas trapping does not play a major role in central airway collapse is supported by Lee et al who reported improvement in symptoms with tracheoplasty independent of the degree of air trapping.[35] Previous reviews have suggested a link between cigarette smoking and ECAC.[7,22] While smoking burden was significantly associated with ECAC on bivariable analyses, this relationship did not persist after consideration of underlying smoking related disease. Greater BMI was associated with a greater frequency of ECAC. Obesity has been shown to affect the degree of tracheal collapse in COPD,[8] likely due to added pressure changes, similar to the mechanisms of increased small airway disease in obesity.[36]

Our study has several limitations. First, we used paired inspiratory-expiratory scans that were not obtained during dynamic expiration. Dynamic maneuvers cause greater collapse of the tracheobronchial walls.[37–39] However, we used a stringent 50% cutoff for CSA reduction despite scan acquisition with tidal exhalation, and thus detected the more severe cases. Recent studies have shown that with dynamic scans, even normal volunteers can have significant airway collapse,[38,39] and our measurements at tidal exhalation might be clinically more meaningful. Second, COPDGene includes smokers with an oversampling of participants with COPD. Therefore, these findings may not be generalizable to the general

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population. Third, many participants with COPD were receiving medications and though the effect of medications on respiratory outcomes is modest, this may have influenced our results. We did not control for medication use as only baseline information was known and we cannot control for changing prescriptions, a particular issue for our assessment of exacerbations over time. We did observe that ECAC was associated with respiratory morbidity even in patients without COPD who had lower rates of use of rescue and controller medications. Fourth, some participants were lost to follow-up. Fifth, we analyzed intrathoracic trachea alone and might have missed cases of upper airway malacia. Further, each scan was read by a single reader with subsequent calculation of interobserver agreement which was fair to good. Sixth, we did not adjust for the change in lung volume with exhalation. However, this is difficult to control as it is affected by both patient effort as well as underlying patient characteristics such as air trapping and lung elasticity. Spirometric gating was not used during the CT examinations. However, since ECAC is frequently underdiagnosed and is associated with respiratory symptoms, paired inspiratory-expiratory scans offer a simple method to diagnose ECAC, and screen for severe cases.

Conclusions

In a cross-sectional analysis of current and former smokers, the presence of expiratory central airway collapse was associated with worse respiratory quality of life. Further studies are needed to assess long-term effects on clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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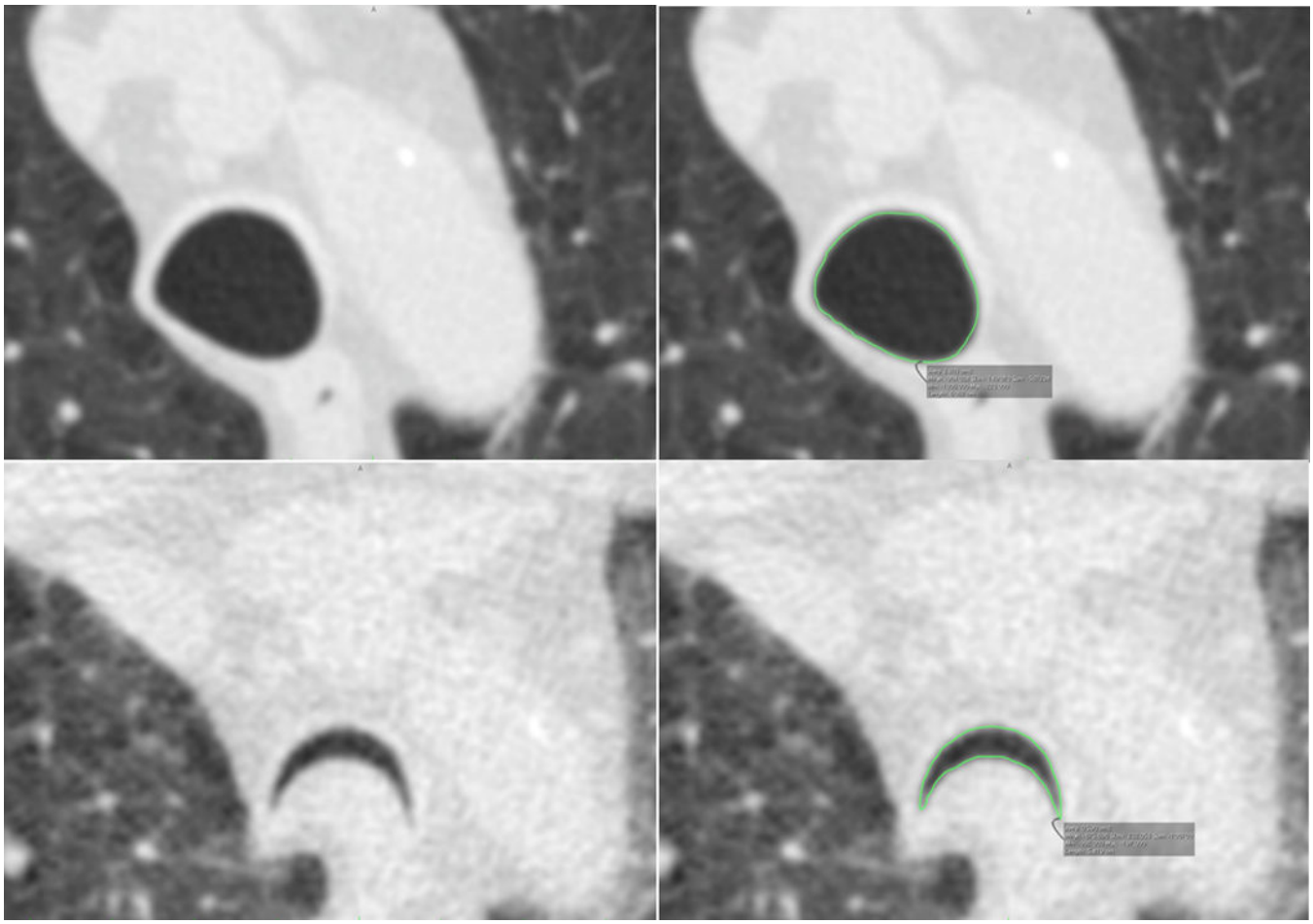

Figure 1.

Change in cross-sectional area was manually measured in paired inspiratory-expiratory computed tomography (CT) scans at three predetermined levels, aortic arch at origin of subclavian artery, at level of carina and at bronchus intermedius just distal to origin of right upper lobe bronchus. The figure shows axial images in lung windows at the level of the aortic arch. The panel shows change in cross sectional area from inspiration (upper panel) to expiration (lower panel).

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Table 1

Characteristics of patients by ECAC status

	ECAC (n=443)	Controls (n=8377)	p value	Absolute difference (95%CI)
Age (years)	65 (8.6)	59.4 (9)	<0.001	6.6 (5.8, 7.4)
Sex, female, n(%)	297 (67)	3856(46)	<0.001	21% (16.2, 25.2)
Race			<0.001	
White race, n (%)	374(84.4)	5654 (67.5)		16.9% (13.1, 20.2)
African American, n (%)	69 (15.6)	2723(32.5)		
BMI (kg/m^2)	31.2 (6.6)	28.7 (6.2)	<0.001	2.5 (1.9, 3.1)
Pack-years of smoking	47.9 (26.7)	44.2 (24.8)	0.002	3.7 (1.2, 6.2)
FEV_1 (L)	1.82 (0.79)	2.28 (0.92)	<0.001	−0.46 (−0.54, −0.38)
FEV_1% predicted	70.2 (25.8)	77.2 (25.5)	<0.001	−7.0 (−9.5, −4.5)
FVC (L)	2.82 (0.88)	3.35 (1)	<0.001	−0.53 (−0.63, −0.43)
FVC %predicted	82.6 (18.8)	87.6 (18.1)	<0.001	−5.0 (−6.8, −3.2)
FEV_1/FVC	0.63 (0.17)	0.67 (0.16)	<0.001	−0.04 (−0.06, −0.02)
COPD,%	229 (51.7)	3627 (43.3)	<0.001	8.4% (3.9, 13.4)
GOLD Stage, n(%)			0.002	
0	214 (48.3)	4750 (56.7)		−8.4% (−13.2, −3.5)
I	33 (7.4)	650 (7.8)		−0.4% (2.5, −2.6)
II	93 (21.0)	1573 (18.8)		2.2% (−1.4, 6.3)
III	66 (14.9)	929 (11.1)		3.8% (0.7, 7.5)
IV	37 (8.4)	475 (5.7)		2.7% (0.4, 5.7)
Chronic Bronchitis, n(%)	109 (24.6)	1283 (15.3)	<0.001	9.3 (5.4, 13.6)
Asthma, n(%)	92 (20.8)	1376 (16.4)	0.017	4.4% (7.3, 8.4)
Home O2 therapy, n(%)	89 (20.1)	902 (10.8)	<0.001	9.3% (5.8, 13.4)
TLC (L)	5.3 (1.3)	5.6 (1.4)	<0.001	−0.3 (−0.5, −0.1)
FRC (L)	2.9 (1.1)	3.3 (1.1)	<0.001	−0.4 (−0.6, −0.2)
Emphysema (%LAA<950_{insp})	7.4 (10.7)	6.1 (9.6)	0.005	1.3 (0.3, 2.3)
Gas trapping (%LAA<856_{exp})	21.4 (20.3)	21.8 (19.9)	0.65	−0.4 (−2.3, 1.5)

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	ECAC (n=443)	Controls (n=8377)	p value	Absolute difference (95%CI)
Wall area% segmental	61.2 (3.1)	61.4 (3.3)	0.19	−0.2 (−0.6, 0.2)
Wall area% subsegmental	64.1 (2.4)	64.4 (2.6)	0.19	−0.2 (−0.4, 0.1)
MMRC (median, IQR)	1.7 (1.5) (2.0, 0 to 3.0)	1.3 (1.4) (1.0, 0 to 3.0)	<0.001	0.4 (0.2, 0.6)
SGRQ	30.9 (22.4)	26.5 (22.8)	<0.001	4.4 (2.2, 6.6)
6MWD (m)	399 (123)	417 (121)	0.003	18 (6, 30)

All values expressed as mean (standard deviation), unless otherwise specified.

ECAC = Expiratory Central Airway Collapse. BMI = Body Mass Index. CI = Confidence Intervals. FEV_1 = Forced Expiratory Volume in the first second. FVC = Forced Vital Capacity. COPD = Chronic Obstructive Pulmonary Disease. GOLD = Global Initiative for Chronic Obstructive Lung Disease staging. O2 = Oxygen. TLC = Total Lung Capacity on computed tomography. FRC = Functional Residual Capacity on computed tomography. %LAA<950insp = %Low Attenuation Area below a threshold of −950 Hounsfield Units at end inspiration. %LAA<856exp = %Low Attenuation Area below a threshold of −856 Hounsfield Units at end expiration. Wallarea% = Bronchial wall area. MMRC = Modified Medical Research Council Dyspnea Scale. IQR = Interquartile range. SQRQ = St. George's Respiratory Questionnaire. 6MWD = Six Minute Walk Distance.

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Table 2

Bivariable and Multivariable factors associated with ECAC

	Bivariable Odds Ratio (95% CI)	Adjusted OR (95%CI)
Age (per year increase)	1.07 (1.06 to 1.08), p<0.001	1.06 (1.04 to 1.07), p<0.001
Sex, female (compared to males)	2.39 (1.95 to 2.92), p<0.001	2.08 (1.63 to 2.63), p<0.001
Race, White (compared to African American)	2.65 (2.04 to 3.45), p<0.001	1.85 (1.38 to 2.48), p<0.001
BMI (per 1 kg/m^2 increase)	1.06 (1.04 to 1.07), p<0.001	1.07 (1.06 to 1.09), p<0.001
Pack-years of smoking (for every 1 pack-year increase)	1.006 (1.002 to 1.009), p=0.002	1.0 (0.99 to 1.0), p=0.930
FEV_1 (for every 1 L decrease)	1.79 (1.59 to 2.0), p<0.001	1.35 (1.12 to 1.61), p=0.001
Emphysema (for every 1 %LAA<950insp increase)	1.013 (1.004 to 1.022), p=0.005	1.0 (0.99 to 1.01), p=0.891

ECAC = Expiratory Central Airway Collapse. BMI = Body Mass Index. FEV_1 = Forced Expiratory Volume in the first second. %LAA<950insp = %Low Attenuation Area below a threshold of −950 Hounsfield Units at end inspiration. Multivariable Odds Ratios adjusted for all variables significant on bivariable analyses as shown in the first column.

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Table 3

Multivariable associations between ECAC and respiratory morbidity

	SGRQ	MMRC	6MWD
	Unstandardized regression co-efficient (95% CI)	**Unstandardized regression co-efficient (95% CI)**	**Unstandardized regression co-efficient (95% CI)**
Age (years)	−0.70 (−0.75 to −0.64) p<0.001	−0.029 (−0.032 to −0.025) p<0.001	−1.25 (−2.25 to −0.25) p=0.014
Sex, female	−4.09 (−5.06 to −3.12) p<0.001	−0.09 (−0.16 to −0.30) p=0.004	4.56 (−13.05 to 22.17) p=0.612
Race, White	−1.01 (−1.94 to −0.08) p=0.033	−0.20 (−0.26 to −0.14) p<0.001	−184.67 (−201.40 to −167.95) p<0.001
BMI (kg/m^2)	0.48 (0.41 to 0.54) p<0.001	0.038 (0.034 to 0.043) p<0.001	−11.63 (−12.84 to −10.39) P<0.001
Emphysema ($\%LAA<950_{insp}$)	0.08 (0.01 to 0.15) p=0.035	0.019 (0.014 to 0.024) p<0.001	−2.47 (−3.80 to −1.13) p<0.001
Gas trapping ($\%LAA<856_{exp}$)	0.23 (0.19 to 0.27) p<0.001	0.009 (0.006 to 0.011) p<0.001	−2.09 (−2.81 to −1.36) p<0.001
Wall area% segmental	0.64 (0.50 to 0.78) p<0.001	0.027 (0.018 to 0.036) p<0.001	−13.04 (−15.63 to −10.46) p<0.001
Pack-years	0.14 (0.12 to 0.15) p<0.001	0.007 (0.006 to 0.008) p<0.001	−1.75 (−2.05 to −1.45) p<0.001
FEV_1(L)	−10.57 (−11.32 to −9.81) p<0.001	−0.67 (−0.71 to −0.62) p<0.001	145.39 (131.78 to 159.01) p<0.001
ECAC	2.90 (1.10 to 4.69) p=0.002	0.18 (0.06 to 0.29) p=0.002	17.0 (−15.43 to 49.43) p=0.304

ECAC = Expiratory Central Airway Collapse. FEV_1 = Forced Expiratory Volume in the first second. SQRQ = St. George's Respiratory Questionnaire. MMRC = Modified Medical Research Council Dyspnea Scale. 6MWD = Six Minute Walk Distance. BMI = Body Mass Index. %LAA<950insp = %Low Attenuation Area below a threshold of −950 Hounsfield Units at end inspiration. %LAA<856exp = %Low Attenuation Area below a threshold of −856 Hounsfield Units at end expiration. Wall area% = Segmental bronchial wall area. Multivariable analyses performed with adjustment for age, race, sex, BMI, FEV_1, smoking pack-years, %emphysema, %gas trapping and segmental wall area% on CT.