Expiratory central airway collapse and symptoms in smokers

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Background

The prevalence and clinical impacts of expiratory central airway collapse (ECAC) in smokers remain controversial. Although studies have shown associations of ECAC with airflow limitation and symptoms, others have shown that higher tracheal collapsibility is associated with lower expiratory-to-inspiratory ratio of lung volume (E/I-LV), but not airflow limitation. This study tested whether ECAC of the trachea and main bronchi could occur exclusively in smokers with lower E/I-LV and affect their symptoms independent of emphysema and intrapulmonary airway disease.

Methods

ECAC was defined as the expiratory-to-inspiratory ratio of cross-sectional lumen area <0.5 for at least one of the three locations, including the trachea, right and left main bronchi on static full-inspiratory, and end-tidal expiratory CT. Symptoms were assessed using the chronic obstructive pulmonary disease (COPD) assessment test (CAT) and modified MRC scale (mMRC).

Results

Out of 241 smokers with and without COPD (n=189 and 52, respectively), ECAC was found in 21 (9%) smokers. No ECAC was found in smokers with E/I-LV ≥0.75. CAT and mMRC in smokers with ECAC were higher than in non-ECAC smokers with E/I-LV <0.75, but comparable to those in non-ECAC smokers with E/I-LV ≥0.75. In the multivariable analysis of smokers with E/I-LV <0.75, ECAC was associated with increased mMRC and CAT independent of CT-emphysema severity, wall area percent of segmental airways, and forced expiratory volume in 1 second.

Conclusions

ECAC is associated with worsening of symptoms independent of emphysema and segmental airway disease in smokers with a lower expiratory-to-inspiratory lung volume ratio.

Keywords

chronic obstructive pulmonary disease, cigarette smoke, computed tomography, airway, symptom

1. Introduction

Cigarette smoke has harmful effects on many organs, including the lungs. Inhalation of cigarette smoke causes damages to the airways and parenchyma and induces symptoms, leading to lung disorders, such as chronic obstructive pulmonary disease (COPD) [1]. However, the susceptibility to cigarette smoke varies among individuals. Only a subgroup of smokers develops COPD, though smokers without COPD may also suffer from respiratory symptoms and carry a higher risk of morbidity and mortality [2-4]. These heterogeneous manifestations stem from complicated structural alterations, including central and peripheral airway disease and emphysema. Thus, detailed structural evaluation of the lungs is essential for improved clinical management in smokers regardless of COPD diagnosis.

Expiratory central airway collapse (ECAC) is an excess reduction in lumen size of central airways, such as the trachea and main bronchi, during expiration, due to weakness in the cartilaginous walls (bronchomalacia) and excessive inward movement of the posterior muscular membrane [5]. While bronchoscopy and dynamic expiratory CT have been regarded as a standard measurement to diagnose ECAC [6-10], Ochs et al. [11] used static full-inspiratory and full-expiratory CT and showed that the tracheal collapse was found in 10.5% of male and 17.1% of female smokers with emphysema. Moreover, a large observational study (n=8820) by Bhatt et al. [12] used static full-inspiratory and end-tidal expiratory CT and showed that the prevalence of ECAC in smokers was approximately 5%, and the presence of ECAC was associated with increased airflow limitation, more severe symptoms, impaired quality of life, and future risk of exacerbations. Subsequently, the same group proposed that paraseptal emphysema near

the trachea might be associated with ECAC in smokers [13]. Meanwhile, Yamashiro et al. showed that expiratory-to-inspiratory ratio of lung volumes (E/I-LV) was associated with physiologically-measured air-trapping [14], and further demonstrated that increased tracheal collapsibility on expiration was associated with lower E/I-LV rather than airflow limitation in smokers [15]. Based on these findings, it was hypothesized that ECAC may have large effects on clinical manifestations in smokers with lower E/I-LV, but these effects disappear in smokers with higher E/I-LV.

The aim of this study was to investigate whether ECAC would be associated with more severe symptoms, assessed using mMRC dyspnea scale and COPD assessment test (CAT) in a subgroup of smokers who were stratified based on E/I-LV. The study further investigated whether the association of ECAC with more severe symptoms could be detected even after adjusting for other CT indices and demographics.

2. Materials and methods

2.1. Study subjects

The present study analyzed the baseline data of the Kyoto-Himeji cohort, which is an ongoing prospective observational study conducted at the Kyoto University hospital and Terada clinic [16]. Stable smokers at the age of 40 years or more who had a smoking history of at least 10 pack-years were enrolled from 2018 to 2020. During the exacerbation-free period, spirometry and full inspiratory and end-tidal expiratory chest CT scans were performed. Subjects with either a history of lung resection surgery and lung diseases other than COPD and asthma, or current primary diagnosis of asthma were excluded. A diagnosis of COPD was based on a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) <0.7 on spirometry and respiratory

symptoms [1]. The predicted FVC and FEV_1 were calculated with the Lambda-mu-sigma (LMS) method [17]. This study was performed in accordance with the Declaration of Helsinki, approved by the Ethics Committee of Kyoto University (approval No. C1311, approval date November 8, 2017), and registered with the University Hospital Medical Information Network (UMIN000028387). All participants provided written informed consent.

2.2. Clinical assessments

Respiratory symptoms were evaluated using the mMRC dyspnea scale and CAT score [18, 19]. Exacerbation was defined as an event with worsening of respiratory symptoms requiring the prescription of oral corticosteroids and/or antibiotics or hospitalization [20].

2.3. CT assessments

Volumetric chest CT scans were obtained at full inspiration and end-tidal expiration with Aquilion Precision scanner at Kyoto University and Aquilion lightning scanner at Terada Clinic (Canon Medical Systems, Otawara, Japan) under instruction to hold breath during the scan [16]. The scan was performed with 120 kVp, 0.5 s exposure time, and auto-exposure control. Images with 512 x 512 matrix and 1 mm slice thickness were generated using a soft reconstruction kernel (FC13) for parenchymal density analysis and a sharp reconstruction kernel (FC51) for airway dimension analysis.

The trachea between the level of the aortic arch at the origin of the subclavian artery and the carina, right main bronchus (RMB), and left main bronchus (LMB) were three-dimensionally segmented using Synapse Vincent software (Fujifilm; Tokyo, Japan). Cross-sectional images perpendicular to the longitudinal center line of the lumen were generated, and the lumen areas in the middle third portion were automatically measured and averaged for both inspiratory and expiratory CT. Expiratory-to-inspiratory ratios (E/I)

of cross-sectional lumen area of the trachea, RMB, and LMB were calculated. ECAC was defined as the E/I of lumen areas <0.5 for at least one of the three locations (trachea, RMB, and LMB). The threshold of 0.5 was chosen based on a previous study using static full-inspiratory and end-tidal expiratory CT [12]. The mean and coefficient of variation (CV) of E/I of lumen areas for the trachea, RMB, and LMB were also calculated. Additionally, wall area percent (WA%), the percentage ratio of wall area to the sum of wall and lumen areas, was measured at the segmental airways of the right apical bronchus and lower posterior bronchus as reported [16, 21, 22].

For parenchyma analysis, the lungs were automatically segmented, and lung volumes on inspiratory and expiratory CT were measured to calculate E/I-LV. The volume percentage of low attenuation voxels < -950 HU to the total lungs on inspiratory CT ($iLAV_{950}$%) was measured to evaluate the severity of emphysema [23, 24]. The volume percentage of low attenuation voxels < -856 HU to the total lungs on expiratory CT ($eLAV_{856}$%) was also measured to evaluate air-trapping due to peripheral lung pathologies, such as small airway disease and emphysema [25, 26].

2.4. Statistical analysis

Statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) [27]. Data are expressed as the median (interquartile range) unless otherwise indicated. Dunn test and Fisher exact test with Holm correction were used for multiple comparisons. Multivariable linear and logistic regression models were constructed to explore relative associations of ECAC with CAT score (continuous variable) and mMRC ≥1 and ≥2 (categorical variable), respectively. These multivariable models included ECAC (presence/absence), log-transformed $iLAV_{950}$%, WA%, age, sex, height, weight, smoking pack-years, FEV_1, and institute as independent variables. P<0.05

was considered statistically significant.

3. Results

Out of 256 smokers undergoing inspiratory and expiratory CT for the initial assessment, 15 were excluded due to abnormal shadows other than COPD-associated changes and insufficient quality of CT images. Thus, a total of 241 smokers (COPD, n=189; non-COPD, n=52) were enrolled in the present study, and 4, 12, and 10 smokers showed E/I of lumen area of the trachea, RMB, and LMB <0.5, respectively. ECAC, defined as E/I of lumen areas for at least one of the three locations, was found in 21 (9%) smokers. No smokers showed central airway collapse on inspiratory CT. The workflow of this study is described in Supplementary Figure S1. Figure 1 shows that overall, E/I-LV and E/I of lumen areas for the three locations were positively correlated ($r=0.47$, $p<0.001$ for trachea; $r=0.50$, $p<0.001$ for RMB; and $r=0.41$, $p<0.001$ for LMB), but smokers with ECAC were outliers in the linear regression. In addition, no ECAC was found in subjects with E/I-LV ≥0.75. Based on these results, the following analyses were performed by categorizing the smokers into three groups: ECAC with E/I-LV <0.75 (ECAC group), no ECAC with E/I-LV <0.75 (non-ECAC-control group), and no ECAC with E/I-LV ≥0.75 (non-ECAC-Airtrap group). Figure 2 shows examples of subjects with and without ECAC in the trachea while they showed similar E/I-LV (0.47 and 0.46, respectively). Figure 3 shows examples of ECAC in the right and left main bronchi.

Table 1 summarizes the demographics, and physiological and CT indices for the three groups. The non-ECAC-Airtrap group showed more severe impairments of FEV_1, FVC, and FEV_1/FVC, as well as greater $iLAV_{950}$% and $eLAV_{856}$% than the ECAC and

non-ECAC-control groups. $iLAV_{950}$%, but not $eLAV_{856}$%, was larger in the ECAC group than the non-ECAC-control group. Supplementary Figure S2 shows that in a sub-analysis of smokers whose lung sub-volumes were physiologically measured (n=138), residual volume (% predicted) and functional residual capacity (% predicted) did not differ between the ECAC and non-ECAC control groups. As shown in Figure 4, in 210 smokers with available CAT and mMRC data, CAT in the ECAC group was higher than in the non-ECAC-control group but comparable to that in the non-ECAC-Airtrap group. The distributions of mMRC scores differed between the ECAC and non-ECAC-control groups. Supplementary Figure S3 shows that CAT scores for item 3 (chest tightness) and item 5 (limited activities) in the ECAC group were higher than in the non-ECAC-control group.

Moreover, as shown in Table 2, multivariable analyses were performed to explore the relative impacts of ECAC on symptoms in 169 smokers with E/I-LV <0.75 and the available data of CAT and mMRC. In the models that included ECAC (yes/no), age, sex, height, weight, smoking pack-years, and institute as independent variables, the presence of ECAC was associated with an increase in CAT score and increased odds ratio for mMRC scale ≥1 and mMRC scale ≥2. Moreover, in the models that further included $iLAV_{950}$%, WA%, and FEV_1 as additional independent variables, the presence of ECAC was also independently associated with an increase in CAT score and increased odds ratio for mMRC scale ≥1.

4. Discussion

In the present cohort, including both COPD and non-COPD smokers, approximately 9% of smokers showed ECAC, and all the smokers with ECAC showed E/I-LV <0.75.

Moreover, CAT and mMRC in the ECAC group were higher than in the non-ECAC-control group (E/I-LV <0.75) and comparable to those in the non-ECAC-Airtrap group (E/I-LV ≥0.75). The multivariable analysis of smokers with E/I-LV <0.75 showed that ECAC was associated with increased mMRC and CAT, independent of emphysema severity, the extent of airway disease, and FEV_1. These findings suggest that ECAC is common and has impacts on clinical symptoms in smokers with relatively low E/I-LV.

Previous studies have shown that the increased tracheal collapsibility on expiration is associated with lower E/I-LV but not with worsening of airflow limitation or air-trapping in smokers [15] and patients with COPD [28]. The present data confirm and extend those findings by showing that ECAC was found only in smokers with E/I-LV <0.75. Moreover, as shown in Table 2, the non-ECAC-Airtrap group showed substantial decreases in FEV_1, FVC, and FEV_1/FVC and increases in $iLAV_{950}$% and $eLAV_{856}$%, compared to the ECAC and non-ECAC-control groups. We postulate that in smokers with severe emphysema, airflow limitation, and air-trapping, a reduction in volume change from inspiration to expiration could decrease the change in intrathoracic pressure and make ECAC less likely to occur.

CAT and mMRC scores were higher in the ECAC and non-ECAC-Airtrap groups than in the non-ECAC-control group, but did not differ between the ECAC and non-ECAC-Airtrap groups, even though %FEV_1 and %FVC were higher and $iLAV_{950}$% and $eLAV_{856}$% were lower in the ECAC than in the non-ECAC-Airtrap group. This suggests that the symptomatic impact of ECAC was comparable to that of emphysema and air-trapping in smokers. Moreover, in the multivariable analysis of smokers with E/I-LV <0.75, ECAC was associated with increased CAT and mMRC independent of emphysema, airway disease, and FEV_1. These findings are in line with previous reports

showing that ECAC is associated with symptoms such as cough and dyspnea, impaired health-related quality of life, and decreased 6-minute walking distance [12, 29]. Ernst et al. [30] showed that central airway stabilization for tracheobronchomalacia using tracheal stenting and tracheobronchoplasty could improve patient-reported outcomes in COPD. Therefore, the possibility of ECAC should be considered, particularly when smokers suffer from substantial symptoms and impaired quality of life despite relatively mild impairments of pulmonary function.

iLAV$_{950}$% was higher in the ECAC group than in the non-ECAC-control group, which is consistent with a previous study by Bhatt et al. [12], who showed that ECAC was associated with emphysema severity. In contrast, the finding that FEV$_1$/FVC and %FEV$_1$ did not differ between the two groups is discordant with the study, showing that ECAC was also associated with airflow limitation in smokers. This might be because the study included more non-COPD smokers compared to the present study. It should also be noted that different involvement of airway disease between the two studies might have generated the inconsistency because FEV$_1$ could be determined by a combination of emphysema and the disease of airways, ranging from segmental airways down to the terminal and respiratory bronchioles [22, 25, 31-34].

This study used static inspiratory and expiratory CT to identify ECAC and found that the prevalence was 9% in smokers, which is consistent with previous reports using static CT [11, 12]. Although dynamic expiratory CT has been used to diagnose ECAC and may be more sensitive than static inspiratory and expiratory CT [35], we believe that the use of static CT scans to detect ECAC is clinically relevant because static CT is widely used and the probability of false positives may be lower than dynamic CT. Indeed, studies have shown that even healthy non-smokers with no

symptoms showed tracheal collapse during dynamic expiration [7, 9]. Because smokers generally perform daily activities using tidal breathing but not deep breathing, the present definition of ECAC using end-tidal expiratory CT, but not full-expiratory CT, might more appropriately account for symptomatic burdens in smokers.

E/I of lumen areas was calculated for the trachea, RMB, and LMB, and ECAC was defined as E/I of lumen area <0.5 for at least one of these three locations. The data revealed the association of ECAC with clinical symptoms. Meanwhile, the mean and coefficient of variance (CV) of E/I of lumen areas were also evaluated, as shown in Supplementary Figure S4. The results show that E/I-LV did not differ between the ECAC and non-ECAC-control groups, but the ECAC group showed a lower mean and higher CV of E/I of lumen areas compared to the other two groups. This suggests that the extent of collapse of different central airways in each smoker might be heterogeneous, and further studies including many smokers are needed to explore whether the heterogeneity of E/I of lumen areas for multiple central airways could be associated with pulmonary function and clinical outcomes in smokers.

Smokers with ECAC were divided into those with ECAC in the trachea (n=4) and those with ECAC in the main bronchus, but not the trachea (n=17). Supplementary Table S1 shows that there were no significant differences in age, BMI, lung function, CT indices, and CAT scores between the two ECAC groups, although the small sample size precludes a definite conclusion. Regarding the mechanism of ECAC trachea, Copeland et al. [13] proposed that paraseptal emphysema adjacent to the trachea could be involved in tracheal collapse on expiration. We speculate that the main right and left bronchi might be compressed by adjacent structural components such as the

thoracic vertebra, esophagus, and heart, when lungs and thoracic cage shrink on expiration, which induces ECAC in the main bronchus in smokers.

There are some limitations to this study. First, the sample size was relatively small. The absence of statistical significance for the association between ECAC and mMRC ≥2 in the multivariable analysis (Table 2) might be due to the small number of ECAC. Second, this study did not control the opening/closing of the glottis during CT scans. The tracheal collapsibility in smokers with closed glottis could be affected by expiratory-to-inspiratory lung volume change more strongly than that in those with opened glottis [36]. Third, the number of smokers without COPD is smaller than that of smokers with COPD. However, there was no significant difference in the percentages of non-COPD between the ECAC and non-ECAC control groups (80 and 74%, respectively). This suggests that ECAC could occur even in smokers without COPD and indicates the importance of screening for ECAC in both COPD and non-COPD smokers. Fourth, no ECAC was found in the smokers with E/I-LV ≥0.75. Whether ECAC could be detected in these smokers when using dynamic expiratory CT instead of the present static expiratory CT remains unclear. Fifth, this study did not include non-smoking healthy controls, and the normal range of E/I-LV could not be obtained. Alternatively, based on the present data that the range of E/I-LV in smokers with ECAC was 0.40 to 0.74, E/I-LV ≥0.75 was used to identify smokers with air-trapping. Since E/I-LV <0.6 was used as the threshold of sufficient expiration during CT scan in healthy subjects in a previous study [37], the cut-off value of 0.75 in this study might be higher than the normal range of E/I-EV. Finally, many smokers were male. Since sex difference affects tracheal collapsibility [9], whether the present findings could be applied to female smokers is not known.

5. Conclusion

The present data show that ECAC is common in smokers with low expiratory lung volume relative to inspiratory lung volume. In such smokers, ECAC is associated with worsening of symptoms independent of emphysema and FEV_1. Therefore, identifying ECAC in smokers is important for understanding the underlying mechanism of impaired subjects-reported outcomes and improve clinical management in smokers with and without COPD.

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Conflict of interest

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Table 1. Clinical features and CT measures in smokers with and without expiratory central airway collapse

	ECAC (E/I-LV <0.75) N=21	Non-ECAC control (E/I-LV <0.75) N= 175	Non-ECAC Air-trap (E/I-LV ≥0.75) N=45
Age, year	75 (69, 81)	73 (68, 78)	74 (69, 79)
Male, %	100%	94%	89%
BMI	23.2 (21.1, 26.7)†	23.9 (21.5, 26.0)†	21.0 (18.9, 24.2)
Current smoker, %	24%	26%	29%
Pack-Years	54.0 (35.0, 73.8)	50.0 (38.0, 76.5)	55.0 (42.1, 70.3)
FEV_1, %pred	73.9 (52.3, 91.2)†	76.5 (59.8, 93.7)†	42.0 (30.0, 58.5)
FVC, %pred	95.8 (82.2, 110.1)†	100.4 (84.7, 112.0)†	75.0 (54.7, 88.0)
FEV_1/FVC	0.58 (0.42, 0.69)†	0.62 (0.53, 0.70)†	0.43 (0.35, 0.55)
COPD, %	80%	74%†	96%
$iLAV_{950}$%	10.8 (4.2, 22.3)*†	5.3 (2.5, 15.3)†	24.1 (11.2, 34.4)
$eLAV_{856}$%	36.2 (14.9, 49.4)†	34.9 (21.1, 48.9)†	66.2 (55.3, 71.8)
WA%	57.7 (55.4, 61.2)	56.9 (54.3, 61.3)	58.2 (55.3, 63.7)
CAT	13 (6, 18)*	9 (5, 15)†	13 (10, 26)
mMRC (0,1, ≥2), %	16%, 53%, 32%*	48%, 38%, 14%†	20%, 32%, 49%
No. exacerbation (0, 1, ≥2 /yr), %	74%, 26%, 0%	82%, 16%, 2%†	65%, 20%, 15%

Data are expressed as median (IQR). Smokers were classified based on expiratory-to-inspiratory lung volume ratio (E/I-LV). Expiratory central airway collapse (ECAC) was found only in smokers with E/I-LV <0.75. Smokers without ECAC were divided into those with E/I-LV <0.75 (Non-ECAC control group) and those with E/I-LV ≥0.75 (Non-ECAC Air-trap group). * and †$p<0.05$ indicates significance of Non-ECAC control and Non-ECAC groups, respectively, based on Dunn and Fisher exact tests with the Holm correction.

Table 2. Multivariable analysis to explore associations of expiratory central airway collapse with symptoms in smokers with lower expiratory-to-inspiratory lung volume ratio

Models 1		**ECAC**		
#1-1 CAT	Estimate (95%CI)	3.80 (0.43, 7.18)		
	p-value	0.03		
#1-2 mMRC ≥1	Odds ratio (95%CI)	4.98 (1.37, 18.0)		
	p-value	0.01		
#1-3 mMRC ≥2	Odds ratio (95%CI)	3.19 (1.01, 10.03)		
	p-value	0.047		
Models 2		**ECAC**	**iLAV$_{950}$%**	**WA%**
#2-1 CAT	Estimate (95%CI)	3.48 (0.10, 6.86)	1.98 (-0.50, 4.15)	-0.07 (-0.33, 0.20)
	p-value	0.04	0.12	0.64
#2-2 mMRC ≥1	Odds ratio (95%CI)	6.15 (1.47, 25.70)	2.66 (1.25, 5.64)	0.97 (0.89, 1.06)
	p-value	0.01	0.01	0.50
#2-3 mMRC ≥2	Odds ratio (95%CI)	2.54 (0.74, 8.80)	5.74 (1.62, 20.37)	0.97 (0.86, 1.09)
	p-value	0.14	0.007	0.60

Of smokers with expiratory-to-inspiratory lung volume ratio <0.75, 169 whose COPD assessment test (CAT) and mMRC were available were included. ECAC = expiratory central airway collapse, iLAV950% = low attenuation volume percent <-950HU on inspiratory CT, WA% = wall area percent of segmental airways. Multivariable linear regression and logistic regression models were used for CAT (continuous variable) and mMRC ≥1 and ≥2 (categorical variable), respectively. Each of models 1 included ECAC (yes/no), age, sex, height, weight, smoking pack-years, and institute as independent variables. Each of models 2 included ECAC (yes/no), iLAV$_{950}$%, WA%, age, sex, height, weight, smoking pack-years, institute, and forced expiratory volume in 1 sec as independent variables. iLAV950% was log-transformed.

Figure legends

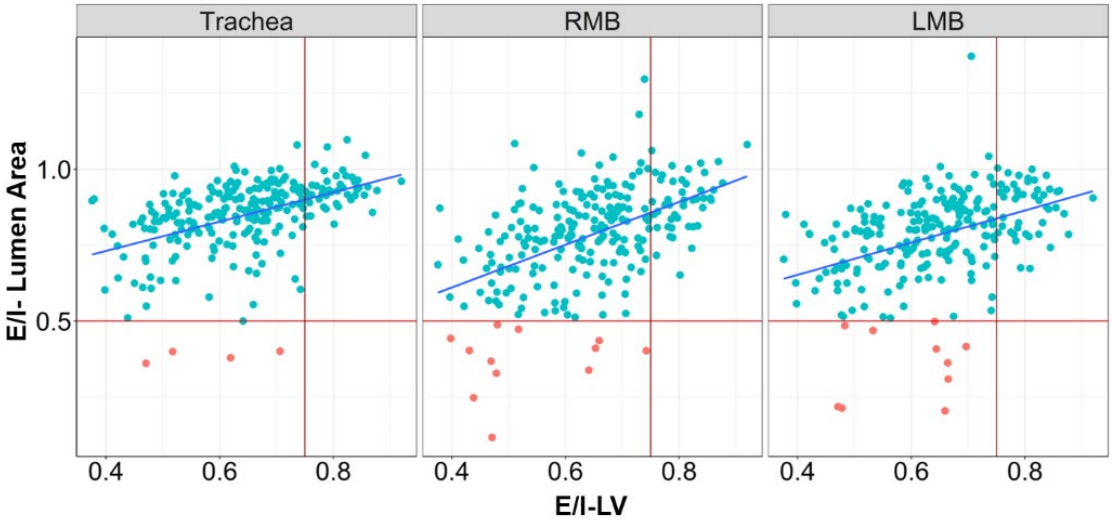

Figure 1. Relationships between expiratory-to-inspiratory ratios of lung volume and cross-sectional lumen area for central airways

Red and blue dots indicate smokers with and without expiratory central airway collapse, respectively. Expiratory-to-inspiratory ratio of lung volumes (E/I-LV) was positively associated with expiratory-to-inspiratory ratio of lumen areas (E/I-Lumen Area) of the trachea, and right and left main bronchus (RMB and LMB). No smokers with ECAC were found at E/I-LV ≥0.75 (dark red vertical lines).

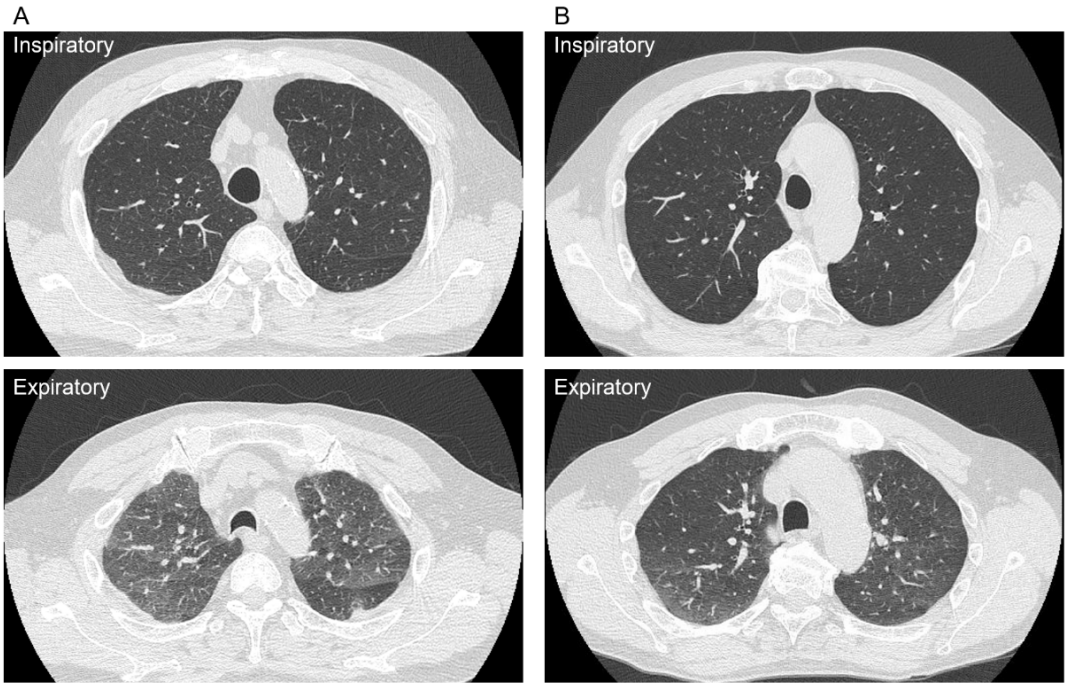

Figure 2. Examples of computed tomography images of smokers with and without expiratory central airway collapse in trachea

A. Case with expiratory central airway collapse (ECAC). Expiratory-to-inspiratory ratio (E/I) of mean tracheal lumen area was 36%. B. Case without ECAC. E/I of mean tracheal lumen area was 84%. Of note, despite the distinct difference in tracheal collapsibility, both cases showed similar expiratory-to-inspiratory ratios of lung volumes (E/I-LV=0.47 and 0.46, for A and B, respectively).

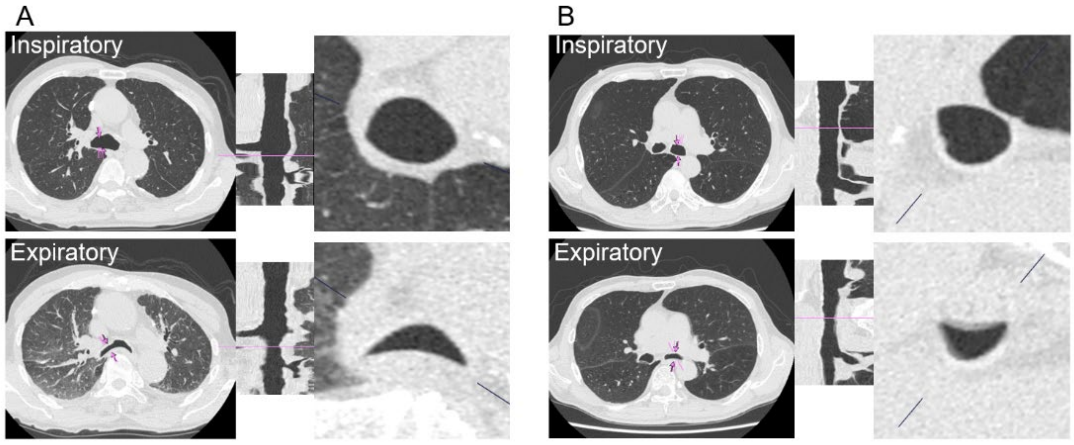

Figure 3. Examples of computed tomography images of smokers with expiratory central airway collapse in the right and left main bronchi

A. Original CT image, multi-planar reconstruction, and cross-section of the right main bronchus (RMB) in a case with expiratory central airway collapse (ECAC) in RMB. B. Original CT image, multi-planar reconstruction, and cross-section of the left main bronchus (LMB) in a case with expiratory central airway collapse (ECAC) in LMB.

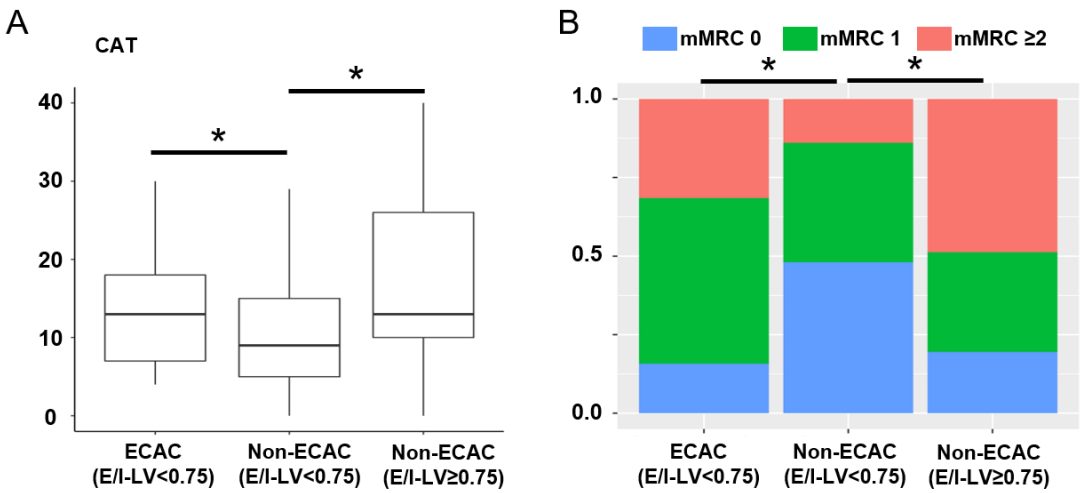

Figure 4. Symptom and dyspnea in smokers with and without expiratory central airway collapse

Symptom and dyspnea were evaluated using COPD assessment test (CAT) and modified MRC dyspnea scale (mMRC). Expiratory central airway collapse (ECAC) was found in smokers with expiratory-to-inspiratory lung volume ratio (E/I-LV) <0.75. The ECAC group was compared to non-ECAC group with E/I-LV <0.75 and E/I ≥0.75. * indicates $p<0.05$ based on Dunn and Fisher exact tests with Holm correction.