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ORIGINAL RESEARCH

Significances of spirometry and impulse oscillometry for detecting small airway disorders assessed with endobronchial optical coherence tomography in COPD

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Background: Spirometry confers limited value for identifying small-airway disorders (SADs) in early-stage COPD, which can be detected with impulse oscillometry (IOS) and endobronchial optical coherence tomography (EB-OCT). Whether IOS is useful for reflecting small-airway morphological abnormalities in COPD remains unclear.

Objectives: To compare the diagnostic value of spirometry and IOS for identifying SADs in heavy-smokers and COPD based on the objective assessment with EB-OCT.

Methods: We recruited 59 COPD patients (stage I, n=17; stage II, n=18; stage III–IV, n=24), 26 heavy-smokers and 21 never-smokers. Assessments of clinical characteristics, spirometry, IOS and EB-OCT were performed. Receiver operation characteristic curve was employed to demonstrate the diagnostic value of IOS and spirometric parameters.

Results: More advanced staging of COPD was associated with greater abnormality of IOS and spirometric parameters. Resonant frequency (Fres) and peripheral airway resistance (R_5–R_{20}) conferred greater diagnostic values than forced expiratory volume in one second (FEV_1%) and maximal (mid-)expiratory flow (MMEF%) predicted in discriminating SADs in never-smokers from heavy-smokers (area under curve [AUC]: 0.771 and 0.753 vs 0.570 and 0.558, respectively), and heavy-smokers from patients with stage I COPD (AUC: 0.726 and 0.633 vs 0.548 and 0.567, respectively). The combination of IOS (Fres and R_5–R_{20}) and spirometric parameters (FEV_1% and MMEF% predicted) contributed to a further increase in the diagnostic value for identifying SADs in early-stage COPD. Small airway wall area percentage (Aw% 7–9), an EB-OCT parameter, correlated significantly with Fres and R_5–R_{20} in COPD and heavy-smokers, whereas EB-OCT parameters correlated with FEV_1% and MMEF% in advanced, rather than early-stage, COPD.

Conclusions: IOS parameters correlated with the degree of morphologic abnormalities of small airways assessed with EB-OCT in COPD and heavy-smokers. Fres and R_5–R_{20} might be sensitive parameters that reliably reflect SADs in heavy-smokers and early-stage COPD.

Keywords: chronic obstructive pulmonary disease, optical coherence tomography, diagnostic value, impulse oscillometry, small airway disorder

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airway chronic inflammation and incompletely reversible airflow limitation. Airway structural changes in COPD are characterized by airway luminal narrowing, mucus gland hypertrophy, airway wall fibrosis and collagen deposition, which are more evident in small airways

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than in large and medium-sized airways.[1,2] Small airways (diameter <2 mm) are major sites contributing to airway resistance and the disorders are frequently implicated in early-stage COPD.[2] Small-airway resistance only comprises 10%–25% of the total airway resistance in healthy subjects,[3,4] but can be markedly increased in COPD[5,6] due to airway wall thickening and luminal obstruction. To date, few diagnostic approaches are available for assessing small-airway disorders (SADs) in COPD.

Impulse oscillometry (IOS) is an effort-independent non-invasive measurement which, during spontaneous breathing, simultaneously assesses airway resistance at different sites and with various physical properties. IOS parameters were reportedly more sensitive than spirometry in detecting SADs in early-stage COPD.[7–10] In patients with obstructive airway diseases, resonant frequency (Fres) and peripheral airway resistance (R_5–R_{20}) correlated positively with airflow limitation.[6,11,12] However, the interpretation of IOS findings has been based on inference from physiologic perspectives,[12,13] therefore the lack of morphological or imaging evidence has made it challenging to verify their usefulness for assessing SADs.

Endobronchial optical coherence tomography (EB-OCT) provides objective high-resolution images and accurate measurements of small airways (from seventh to ninth generation bronchi the diameter of which was less than 2 mm[3,14–16]) structure in vivo, which correlates well with computed tomographic images and histopathology.[17,18] We have previously confirmed the diagnostic value of EB-OCT in assessing SADs in heavy-smokers and patients with different stages of COPD.[15]

We further hypothesized that spirometry has limited diagnostic value for detecting SADs which can be readily assessed with EB-OCT, and that IOS parameters may complement spirometry in identifying SADs in heavy-smokers and patients with early-stage COPD. Therefore, the aim of this study was to compare the diagnostic value of spirometry and IOS parameters in evaluating SADs (validated with EB-OCT), and determine whether and which IOS parameters are more sensitive than spirometry for assessing SADs in heavy-smokers and patients with early-stage COPD.

Methods

Subjects

We recruited 106 consecutive subjects from the outpatient clinic of The First Affiliated Hospital of Guangzhou Medical University between April 2014 and January 2017. We defined COPD as a post-bronchodilator FEV_1/FVC ratio less than 0.70, according to 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[19] The severity of airflow limitation categories was defined according to GOLD 2017 criteria: I (mild): FEV_1 ≥80% predicted; II (moderate): FEV_1 50%–79% predicted; III (severe): FEV_1 30%–49% predicted; and IV (very severe): FEV_1 <30% predicted. This cohort consisted of 59 COPD patients (GOLD stage I, n=17; stage II, n=18; stage III–IV, n=24), 26 heavy-smokers with normal lung function (FEV_1 ≥80% predicted and FEV_1/FVC ≥0.7) and 21 never-smokers. We excluded patients with exacerbations within 4 weeks and concomitant pulmonary diseases.

This study was approved by the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University (Medical Ethics [Year 2014] No 51). All subjects gave written informed consent.

Study design

In this cross-sectional study, we performed IOS, and subsequently, spirometry (Masterscreen IOS, Jaeger, Hoechberg, Germany) according to the international guidelines.[20] Short- and long-acting bronchodilators were withheld for at least 8 and 24 hours, respectively. For IOS, we recorded respiratory impedance at 5 Hz (Z_5), resonant frequency (Fres), airway resistance at 5 Hz (R_5) and 20 Hz (R_{20}), the difference in airway resistance at 5 Hz and 20 Hz (R_5–R_{20}), reactance at 5 Hz (X_5) and area of reactance (AX).[12,21] For spirometry, maximal mid-expiratory flow (MMEF) were selected from the maneuver with the highest sum of FVC and FEV_1.[20] Chest CT images were analyzed using lung computer-aided graphic software. Total low attenuation areas (TLAAs) were defined as lung voxels with attenuation ≤950 Hounsfield units (HU).[22]

EB-OCT analysis

We performed EB-OCT scans, which is an objective assessment of airway morphological changes, by using Lightlabs C7XR OCT system (St Jude Medical, St Paul, MN, USA), with the probe's outer diameter of 0.9 mm[15]. The EB-OCT probe was advanced to the right lower lobe bronchus (RB9) segment under the guidance of ultrafine flexible bronchoscope (B260F, Olympus, Tokyo, Japan). Patients held their breath following full inspiration. The generation of bronchi was determined based on the airway branch-points in longitudinal section.[23] EB-OCT parameters included mean luminal diameter (D_{mean}), inner airway area (Ai) and airway wall area (Aw) from the seventh to ninth generation.

The airway wall area percentage (Aw%) was calculated as [Aw/(Ai + Aw)]×100%, and Ai was corrected for the body surface area (BSA).[24–28] Each EB-OCT parameter from the seventh to ninth generation of bronchi was averaged to reflect the magnitude of morphological changes of the small airways.

Statistical analysis

Statistical analysis was performed using SPSS, version 20.0 (IBM Corporation, Armonk, NY, USA). The sample size calculation was based on the two-sided significance level (α) of 5%, and power (1-β) of 80%, with the effect size and SD of Aw% 7–9 adopted from our previous study.[15] The minimal sample size for each group was 12 (N=60 for all groups). We determined quality of study using the Standards for Reporting Diagnostic Accuracy Studies (STARD) checklist.[29] The Bland-Altman plot was applied to compare the difference and the limits of agreement between two observers' measurements of EB-OCT to assess reproducibility (see Supplementary data). Chi-squared and Fisher's exact test were used in the analysis of categorical data. Comparison among different groups was made by using one-way analysis of variance for normally distributed variables and by using the Kruskal-Wallis test for non-normally distributed variables. The association between EB-OCT and IOS and spirometry was determined with correlation analysis. Receiver operation characteristic curve (ROC) (MedCalc Software, Mariakerke, Belgium) was constructed to compare the diagnostic performances. No imputation was made to the missing data. $P<0.05$ was deemed statistically significant for all analyses unless otherwise stated.

Results

Baseline characteristics

There were no significant among-group differences in terms of age, height, weight, and BSA (all $P>0.05$, Table 1). Smoking pack-years were not significantly different among heavy-smokers and patients with different stages of COPD ($P>0.05$). Patients with stages III–IV COPD demonstrated more severe pulmonary emphysema (TLAA%) than did heavy-smokers or never-smokers (both $P<0.001$). Patients with COPD had significantly lower levels of spirometric parameters than heavy-smokers and never-smokers (all $P<0.05$), whereas spirometric parameters in heavy-smokers were comparable to those in never-smokers ($P>0.05$). The information regarding symptoms, treatment and comorbidities of COPD patients is described in Table S1.

EB-OCT small-airway parameters among COPD patients, never-smokers and heavy-smokers

The Bland-Altman analysis demonstrated a high degree of concordance of EB-OCT measurement (D7–9, Ai7–9 and Aw7–9) and a negligible bias between two observers' measurements (Figure S1).

Compared with never-smokers, Aw% 7–9 was significantly greater whereas Ai7–9/BSA was markedly lower in COPD patients (both $P<0.05$, Figure 1C and D). More advanced COPD was associated with greater magnitudes of small-airway obstruction (progressively decreasing Ai7–9/BSA) and airway wall thickening (progressively greater Aw% 7–9) (all $P<0.05$, Figures 1 and 2). Compared with never-smokers, Ai7–9/BSA was markedly lower whereas

Table 1 Baseline characteristics

Parameters	Never-smokers	Heavy-smokers	COPD patients		
			Stage I	Stage II	Stage III–IV
Gender (male/female)	13/8	25/1[a]	16/1[a]	17/1[a]	23/1[a]
Age (years)	50.5±12.4	52.8±9.4	56.1±9.1	55.9±4.8	56.2±6.4
Height (cm)	163.9±8.1	165.4±7.3	166.0±5.4	167.2±7.8	164.6±6.3
Weight (kg)	62.2±11.5	63.9±10.6	64.8±8.2	65.2±4.6	60.4±8.1
BSA (m^2)	1.7±0.2	1.7±0.2	1.7±0.1	1.7±0.1	1.7±0.1
Smoking pack-years[b]	0	34.0±22.2	30.5±20.9	33.4±17.3	38.9±22.9
TLAA%[c]	2.3±4.4	5.0±7.1	11.4±12.4	12.0±11.6[a]	25.8±19.2[a,d]
FEV_1% predicted	98.6±9.4	94.1±9.1	88.3±8.3[a]	64.7±9.1[a,d,e]	34.5±8.8[a,d,f]
FEV_1/FVC%	79.2±5.3	76.9±4.3	65.4±3.1[a,d]	55.9±9.4[a,d,e]	39.1±10.0[a,d,f]
MMEF% predicted	68.8±15.5	62.2±13.0	38.9±6.6[a,d]	23.1±7.4[a,d,e]	8.9±3.6[a,d,f]

Notes: Continuous data were expressed as mean (SD). Comparisons between different groups were made by one-way analysis-of-variance or Kruskal-Wallis test, with subjected to Bonferroni correction. [a]Compared with never-smokers, $P<0.05$; [b]Comparison among heavy-smokers, stage I, stage II and stages III–IV COPD; [c]17/21 never-smokers, 22/26 heavy-smokers, 16/17 stage I COPD, 17/18 stage II COPD and 24/24 stages III–IV COPD patients received CT examination; [d]Compared with heavy-smokers, $P<0.05$; [e]Compared with stage I COPD, $P<0.05$; [f]Compared with stage II COPD, $P<0.05$.

Abbreviations: BSA, body surface area; TLAA, total low-attenuation area; MMEF, maximal mid-expiratory flow.

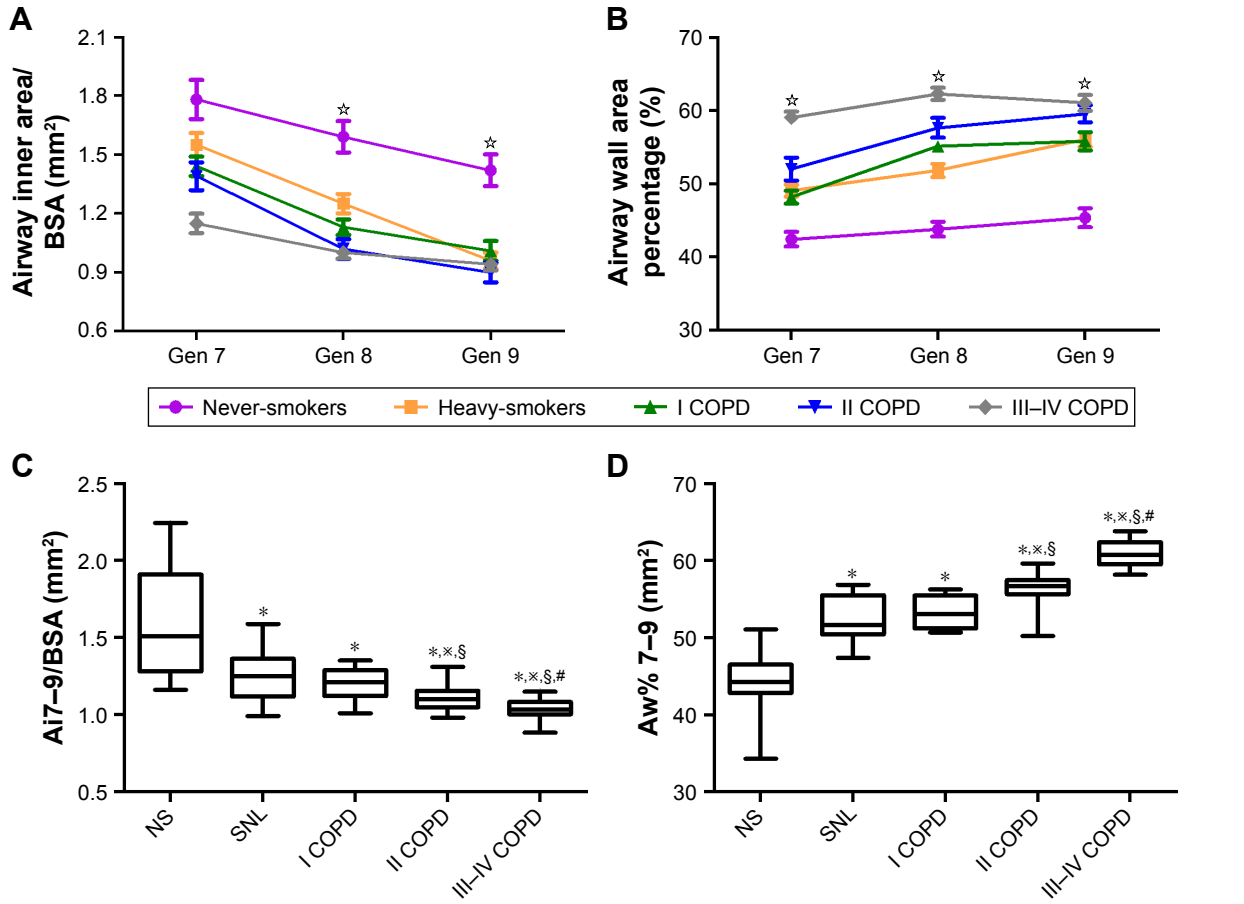

Figure 1 Comparisons of endobronchial optical coherence tomography (EB-OCT) parameters of the seventh to ninth generation of bronchi among never-smokers, heavy-smokers and patients with stages I–IV COPD.

Notes: The comparisons of airway inner area (**A**), and airway wall area percentage (**B**), average value (**C**), average value (**D**), from 7 to 9 generation of bronchi among five groups. Multiple-group comparisons were made by using one-way ANOVA. ☆Indicates a significant difference ($P<0.05$) between heavy-smokers and never-smokers. *Compared with never-smokers, $P<0.05$; ×Compared with heavy-smokers, $P<0.05$; §compared with stage I COPD, $P<0.05$; #compared with stage II COPD, $P<0.05$.

Abbreviations: Gen 7–9, from the seventh to ninth generation bronchi; Ai, airway internal area; Aw, airway wall area; Aw%, airway wall area percentage, calculated with the formula of [Aw/(Aw + Ai)×100%]; BSA, body surface area; NS, never-smokers; SNL, heavy-smokers with normal lung function.

Aw% 7–9 was significantly higher in heavy-smokers (both $P<0.05$). The degree of morphological/structural changes was more evident in the eighth and ninth generation of bronchi (Figure 1A and B). Ai7–9/BSA and Aw% 7–9 were comparable between heavy-smokers and patients with stage I COPD ($P>0.05$).

IOS parameters among never-smokers, heavy-smokers and COPD patients

The magnitude of abnormality of IOS parameters was greater in patients with COPD than in never-smokers (Figure 3). The magnitudes of abnormality of R_5–R_{20} were notably higher in heavy-smokers and stage I COPD than those in never-smokers (both $P<0.05$), whereas Fres, R_5, R_{20}, Z_5 X_5 and AX were comparable among never-smokers, heavy-smokers and stage I COPD.

Diagnostic performances of spirometric and IOS parameters in assessing small-airway disorders among never-smokers, heavy-smokers and COPD patients

COPD has been conventionally diagnosed based on spirometry, the "gold standard" as recommended by the previous version of international guidelines. To minimize the bias towards equivocal or inferior diagnostic value of IOS parameters compared with FEV_1 and MMEF predicted% in differentiating the presence from the absence of SADs, we explored the cut-off value for Aw% 7–9 for ROC analysis. According to our previous study,[15] ROC analysis was performed to differentiate never-smokers from COPD patients, and the cut-off value was 51.0% for Aw% 7–9 (AUC: 0.971, 95% CI: 0.895–0.997, sensitivity: 89.6%,

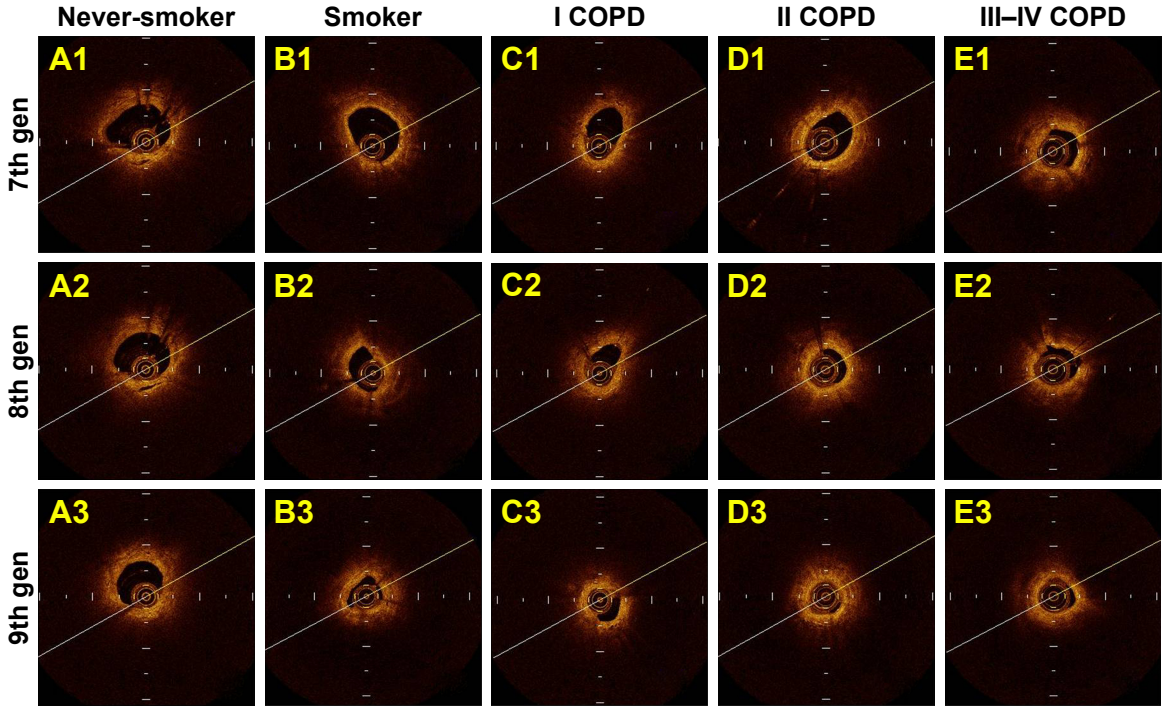

Figure 2 Cross-sectional endobronchial optical coherence tomography (EB-OCT) images of the seventh, eighth, and ninth generation of bronchi.
Notes: Compared with never-smokers (**A1**–**A3**), patients with COPD are characterized by significant small-airway wall thickening and luminal narrowing (panel **C**–**E**). Despite the abnormality to a lesser extent, heavy-smokers also displayed small-airway wall thickening and luminal narrowing compared with never-smokers (**B1**–**B3**).

specificity: 100.0%), which was comparable with the cut-off value of 50.5% derived from the current study (AUC: 0.995, 95% CI: 0.946–1.000, sensitivity: 98.3%, specificity: 95.2%), for discriminating the presence from the absence of SADs (Figure S2). By using this cut-off value, we have identified SADs in one out of 21 never-smokers (4.8%), 17 out of 26 heavy-smokers (65.4%), 15 out of 17 patients with stage I COPD (88.2%), and 17 out of 18 patients with stage II COPD

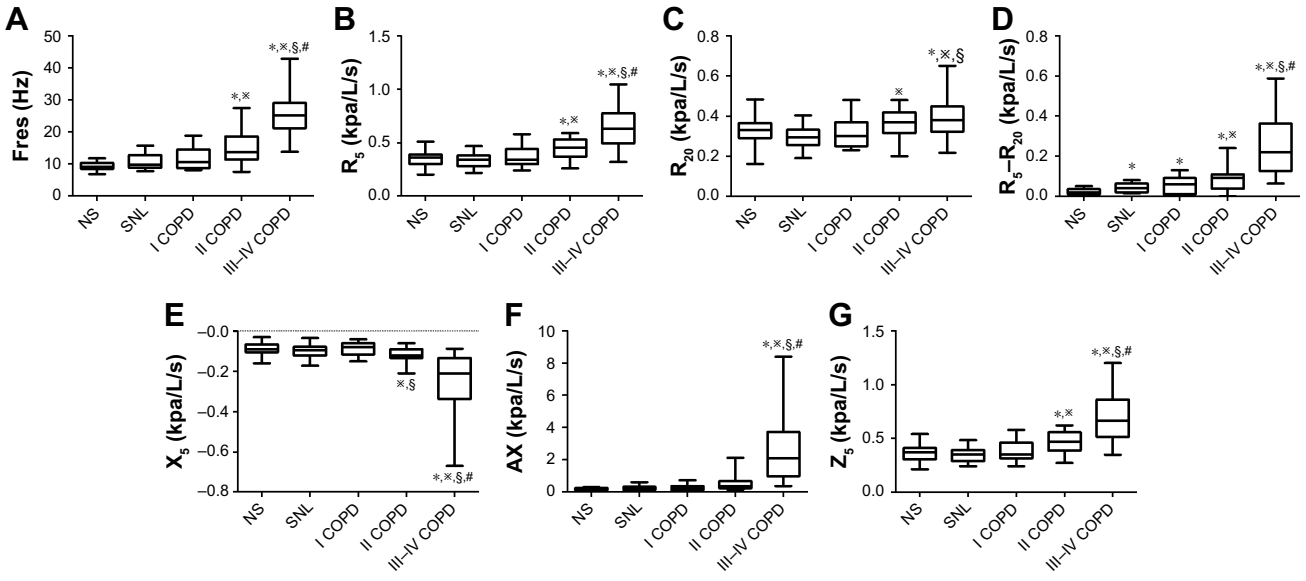

Figure 3 Comparison of impulse oscillometry (IOS) parameters in never-smokers, heavy-smokers and patients with stages I–IV COPD.
Notes: The magnitude of Fres (**A**), R_5 (**B**), R_{20} (**C**), R_5–R_{20} (**D**), X_5 (**E**), AX (**F**) and Z_5 (**G**) in five groups. Multiple-group comparisons were made by using one-way ANOVA. *Compared with never-smokers (NS), $P<0.05$; *compared with heavy-smokers, $P<0.05$; §compared with stage I COPD, $P<0.05$; #compared with stage II COPD, $P<0.05$.
Abbreviations: Fres, resonance frequency; R_5, airway resistance at 5 Hz; R_{20}, airway resistance at 20 Hz; R_5–R_{20}, the difference between airway resistance at 5 Hz and 20 Hz; X_5, pulmonary reactance at 5 Hz; AX, reactance area; Z, impedance; NS, never-smokers; SNL, smokers with normal lung function.

(94.4%) (χ^2=41.88, P<0.001, see Figure S3). Therefore, both Fres and R_5–R_{20} had higher AUC compared with FEV_1% and MMEF% predicted for identifying SADs in never-smokers and heavy-smokers (AUC: Fres: 0.771, R_5–R_{20}: 0.753, FEV_1% predicted: 0.570, MMEF% predicted: 0.558). Fres presented with a significantly greater diagnostic value than that of MMEF% predicted (AUC: 0.771 vs 0.558, P<0.05) (Figure 4A and Table S2). Furthermore, the combination of Fres, R_5–R_{20}, FEV_1% and MMEF% predicted contributed to a further increase in the discriminative power for identifying SADs in never-smokers and heavy-smokers compared with FEV_1% and MMEF% predicted alone, respectively (AUC: 0.825 vs 0.570 and 0.558, respectively, both P<0.05).

Establishment of the cut-off value for Aw% 7–9 would have contributed to the morphological diagnosis of SADs in early-stage COPD. To this end, ROC analysis with the cut-off of 51.0% for Aw% 7–9 was performed to identify SADs in heavy-smokers and patients with stage I COPD. Despite the lack of statistical significance, Fres and R_5–R_{20} demonstrated numerically higher AUC than FEV_1% and MMEF% predicted (AUC: 0.726 and 0.633 vs 0.548 and 0.567, respectively), whereas the combination of Fres, R_5–R_{20}, FEV_1% and MMEF% predicted contributed to significantly improved diagnostic value compared with FEV_1% and MMEF% predicted alone (AUC: 0.761 vs 0.548 and 0.567, respectively) in identifying SADs in heavy-smokers and patients with stage I COPD (Figure 4B and Table S3).

Correlation between EB-OCT, spirometric and IOS parameters

Fres and R_5–R_{20} correlated negatively with D7–9 and Ai7–9, but positively with Aw7–9 and Aw% 7–9 in heavy-smokers and COPD patients (all P<0.05, Figure S4). Consistently, both Fres and R_5–R_{20} correlated significantly with Aw% 7–9 in heavy-smokers and stage I COPD (Figure 5C and D and Table S4), whereas the correlations between Aw% 7–9 and FEV_1% predicted, and MMEF% predicted, were tempered in heavy-smokers and patients with stage I COPD (Figure 5A and B and Table S4). The correlation coefficients between IOS and EB-OCT small-airway parameters were comparable with those between EB-OCT parameters and FEV_1% and MMEF% predicted in stages II–IV COPD, except that

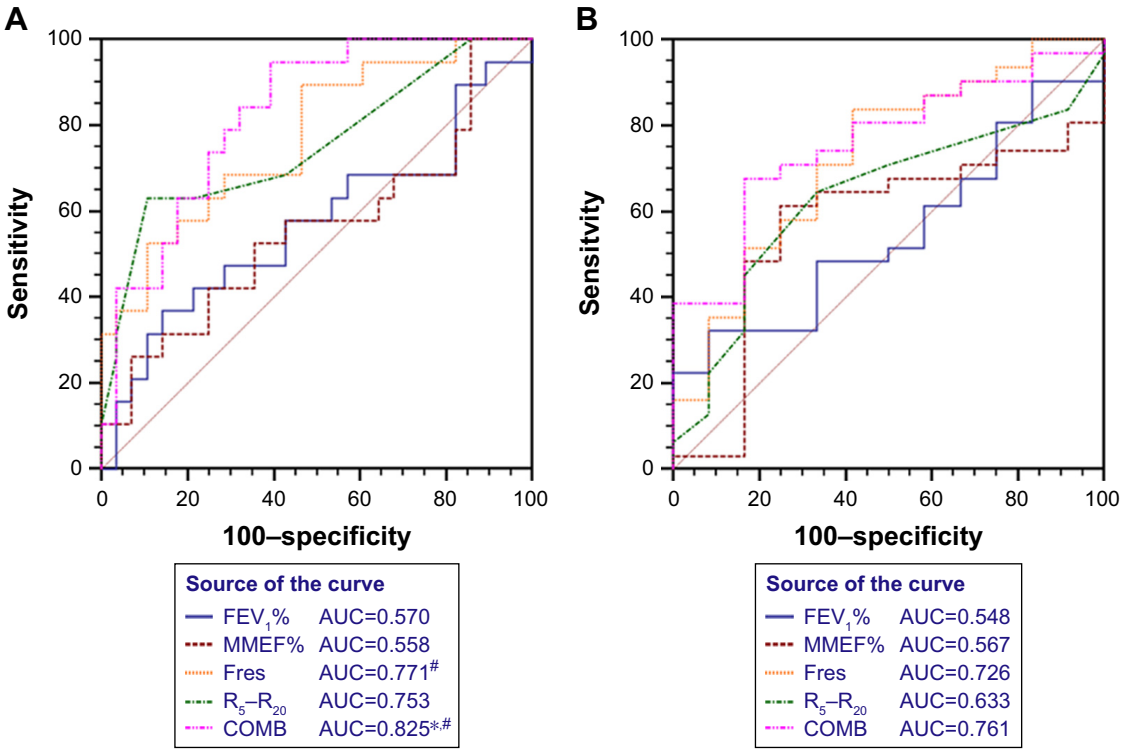

Figure 4 The diagnostic value of spirometric and impulse oscillometry (IOS) parameters in discriminating the presence from the absence of small-airway disorders in never-smokers, heavy-smokers, and patients with stage I COPD.

Notes: The cut-off value was 51.0% for Aw% 7–9, according to our previous study.[15] *Compared with FEV_1% predicted, P<0.05; #compared with MMEF% predicted, P<0.05. The diagnostic value of spirometric and IOS was compared for discriminating the presence from the absence of small-airway disorders in never-smokers and heavy-smokers (**A**), and discriminating the presence from the absence of small-airway disorders in heavy-smokers and patients with stage I COPD (**B**), respectively.

Abbreviations: MMEF, maximal mid-expiratory flow; Fres, resonant frequency; R_5–R_{20}, peripheral airway resistance; AUC, area under the curve; COMB, Combination of Fres, R_5–R_{20}, FEV_1% and MMEF% predicted.

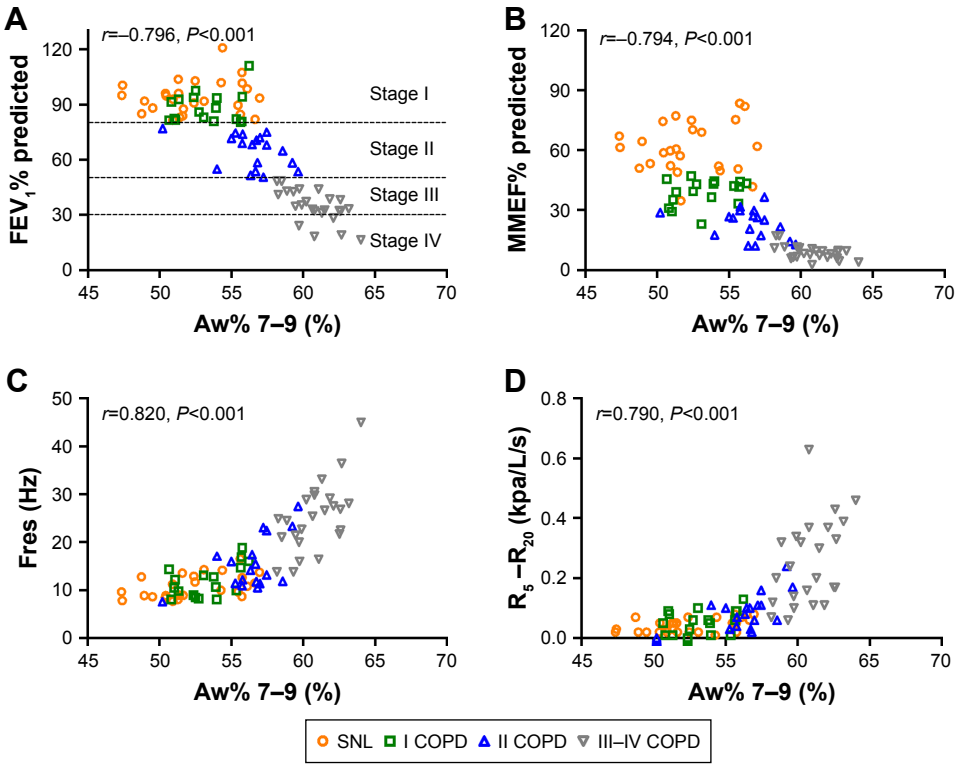

Figure 5 Correlation among FEV_1% predicted, MMEF% predicted, Aw% 7–9, Fres and R_5–R_{20} in COPD patients and heavy-smokers.
Notes: The correlations between FEV_1% predicted and Aw%7–9 (**A**), MMEF% predicted and Aw%7–9 (**B**), Fres and Aw%7–9 (**C**), R5–R20 and Aw%7–9 (**D**). All *r* values denoted the Spearman's correlation coefficient of each parameter in both patients with COPD and heavy-smokers. The dashed line was not shown in Figure **B**–**D** for the measurements of MMEF% predicted, Fres and R_5–R_{20} were overlapped in COPD staging based on the conventional classification with the reduction in FEV_1. The different colors indicated the five individual groups, including heavy-smokers (yellow circles), patients with stage I COPD (green rectangles), patients with stage II COPD (dark blue triangles), and patients with stages III–IV COPD (gray inverse triangles).
Abbreviations: MMEF, maximal mid-expiratory flow; Fres, resonant frequency; R_5–R_{20}, peripheral airway resistance; Aw%, airway wall area percentage.

R_5–R_{20} correlated significantly with Aw% 7–9 in patients with stage II COPD (Table S4).

Discussion

Although the clinical significance of IOS small-airway parameters has been deduced mostly from physiologic and/or mathematical models, no data have directly been derived from morphological investigations that lent support to the hypothesis. Since our previous report showed that small airways (inner diameter <2 mm) denoted the seventh generation of bronchi or more distal airways in never-smokers,[15] we selected and averaged the EB-OCT parameter from the seventh to ninth generation of bronchi to reflect small airway morphology. We have demonstrated a significant correlation between IOS small-airway parameters and the caliber and wall thickness of small airways detected with EB-OCT in COPD patients and heavy-smokers. Fres and R_5–R_{20} had significantly greater diagnostic performance compared with FEV_1% and MMEF% predicted in discriminating the presence from the absence of SADs. Therefore, Fres and R_5–R_{20} might be sensitive markers for reflecting SADs in heavy-smokers and patients with early-stage COPD.

Structural changes of the airway in COPD is characterized by airway luminal narrowing, airway wall fibrosis and collagen deposition, which are more evident in small airways.[1,2] The previous EB-OCT study indicated that more advanced stages of COPD were characterized by greater abnormality in airway architecture (tapering airway caliber and greater airway wall thickness); however, SADs were present in some heavy-smokers without airflow limitation.[15] Spirometry has been the "gold standard" for the diagnosis and severity grading of COPD, according to the previous version of international guidelines. FEV_1 mainly reflects obstruction of large and medium-sized airways, and confers limited value for identifying SADs in early-stage COPD. Whilst not being recognized as a marker of peripheral airway obstruction, the changes of MMEF% predicted would be non-specific and vary considerably among different individuals. Hence, MMEF measurements can be misleading and unreliable to reflect the airway structural changes.[30–32] By contrast, IOS offers a global measure of airway resistance and reactance at different frequencies and provides greater insights into regional heterogeneity and lung periphery.[13] Theoretically, Fres reflects the inertial properties of airways and the

capacitance of lung periphery, whereas R_5–R_{20} indicates small-airway caliber and ventilation heterogeneity.[33,34] In this study, we noted that the greater magnitude of abnormality of IOS parameters reflected more severe COPD, Fres and R_5–R_{20} significantly correlated with EB-OCT measurements of lumen and wall area even in stage I COPD and heavy-smokers. Consistently, respiratory resistance could detect airway obstruction in early-stage COPD,[11] and isolated abnormality in IOS parameters possibly reflected the latent chronic airway disease which is undiagnosed by spirometry.[35]

Heavy smoking has been a risk factor for developing COPD, and there has been a significant lag starting from the development of SADs to the onset of clinically notable FEV_1 decline. Because some heavy-smokers may have developed SADs which are reminiscent of COPD, proper identification of SADs in patients with early-stage COPD and heavy-smokers may be of clinical importance for ensuring early diagnosis. Some studies[36,37] have documented that IOS parameters had greater sensitivity in detecting SADs among subjects exposed to environmental hazards and asymptomatic heavy-smokers, therefore IOS presumably would be more sensitive in identifying early-stage COPD. However, since the diagnosis of COPD is largely based upon airflow limitation assessed primarily with spirometry, it is difficult to directly compare the discriminative power of IOS and spirometric parameters. The EB-OCT parameter Aw%, in which Ai and Aw have been taken into account, is a sensitive indicator of airway morphological changes[24–26,28] and may serve as a novel tool for assessing SADs in early-stage COPD. Our findings demonstrated that both spirometric parameters and IOS small-airway parameters correlated with small-airway morphological changes detected with EB-OCT in COPD. The magnitude of correlation between spirometric and EB-OCT small-airway parameters was greater in more advanced COPD but progressively tempered in early-stage COPD, whereas the correlation between IOS and EB-OCT small-airway parameters remained significant in stage I COPD and heavy-smokers. Hence, IOS parameters, rather than spirometry, may contribute to the great value for detecting small-airway morphological changes and predicting the development of early-stage COPD in some, if not all, of the heavy-smokers. Extra-fine ICS, which is capable of reaching to the small airways,[38] might provide greater therapeutic effect in terms of bronchodilation, improve lung function and reduce rate of exacerbations in patients with COPD.[39,40] Based on the correlation with morphological changes detected by EB-OCT measurement, IOS small-airway parameters might serve as the surrogate markers for the assessment of therapeutic effects of inhaled corticosteroids, bronchodilators and anti-inflammatory agents in patients with COPD.

We believed that establishing the cut-off value of EB-OCT small-airway parameters, rather than spirometry, would help differentiate patients with from those without SADs. In this study, ROC curve analysis based on Aw% 7–9 was performed to assess the usefulness of spirometry and IOS parameters for identifying SADs. Our findings demonstrated that both Fres and R_5–R_{20} conferred higher AUC than FEV_1% and MMEF% predicted in never-smokers and heavy-smokers, as well as in heavy-smokers and patients with stage I COPD. Furthermore, the combination of IOS (Fres and R_5–R_{20}) and spirometric (FEV_1% and MMEF% predicted) parameters contributed to a further increase in the diagnostic value for identifying SADs in early-stage COPD, as compared with FEV_1% and MMEF% predicted alone. Hence, spirometry may have limited usefulness for detecting SADs in early-stage COPD, whereas IOS parameters might help predict, at least in some heavy-smokers, the development of early-stage COPD. Our findings suggested that heavy-smokers with small-airway disorders (either detected with spirometry, IOS or EB-OCT) would benefit from a regular follow-up in clinical practice.

Some limitations should be acknowledged. Our study was conducted in a tertiary medical center with small sample sizes, which limited the generalizability of our findings. The imbalanced sex ratio in healthy subjects may have biased the results. To minimize the bias of small-airway areas measurements, Ai was adjusted for BSA in this study. The EB-OCT probe could only reach the ninth-generation bronchi that made it impossible to demonstrate the morphological changes of the whole peripheral airways. IOS measurement still suffers from the lack of normal reference values, therefore we were unable to compare the usefulness of absolute vs percentage for IOS parameters. Finally, although this study demonstrated that 65.4% of the heavy-smokers presented with small-airway disorders, we were unable to confirm the predictive role of SADs of future development of COPD. Long-term follow-up studies are needed to confirm the correlation between small airway disorders and the development of COPD.

Conclusion

In summary, spirometry confers limited value for reflecting SADs in early-stage COPD. IOS small-airway parameters correlate better with SADs, as assessed with EB-OCT, in different stages of COPD and heavy-smokers. Both Fres and R_5–R_{20} may sensitively detect small-airway

morphological/structural change in early-stage COPD and heavy-smokers.

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Author contributions

Z-QS and W-JG performed the literature search and drafted the manuscript; Z-QS, YC, C-HZ, C-LT and X-BC were responsible for patient recruitment; Z-QS, YC, X-BC contributed to the data collection, data analysis and data interpretation; Z-QS, W-JG and MJ performed statistical analyses; Z-QS, W-JG, S-YL and N-SZ contributed to study conception; S-YL and N-SZ provided critical review of the manuscript and approved the final submission. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

Prof. Li declared that he had received National Key R&D Program of China (Grant No. 2016YFC1304100) and Special Funds for Public Welfare Research and Capacity Building in Guangdong Province (No.: 2014A020215036). Dr. Guan declared that he had received Pearl River S&T Nova Program of Guangzhou No. 201710010097 and Guangdong Province Universities and Colleges Pearl River Scholar Funded Scheme 2017. All authors report no other conflicts of interest in this work. None of the funding sources had any role on the study.

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Supplementary materials

Reproducibility of endobronchial optical coherence tomography (EB-OCT) measurement

The difference between observer A and observer B measurements of mean luminal diameter D_{mean}, inner airway area (Ai) and airway wall area (Aw) was calculated to assess the reproducibility. The Bland-Altman analysis demonstrated a high concordance of D7–9, Ai7–9, Aw7–9 and a negligible bias between two observers' measurements (Figure S1).

Establishment of cut-off value for EB-OCT measurement in discriminating never-smokers from COPD patients

According to the data (Ai7–9 and Aw7–9) from our previous study[1] and Aw% 7–9 was calculated as: [Aw7–9/(Ai7–9+Aw7–9)]×100%, ROC analysis was performed to

Table S1 Symptoms, treatment and comorbidities in patients with COPD

	Stage I COPD	Stage II COPD	Stage III–IV COPD
Smoking status			
Current smoker	11 (64.7%)	11 (61.1%)	19 (79.2%)
Ex-smoker	4 (23.5%)	5 (27.8%)	3 (12.5%)
Non-smoker	2 (11.8%)	2 (11.1%)	2 (8.3%)
Symptoms			
Cough	10 (58.8%)	12 (66.7%)	18 (75%)
Sputum	8 (47.1%)	10 (55.6%)	17 (70.8%)
Shortness of breath	6 (35.3%)	7 (38.9%)	12 (50%)
Treatment			
ICS+LABA	8 (47.1%)	11 (61.1%)	17 (70.8%)
LAMA	3 (17.6%)	4 (22.2%)	19 (79.2%)
Comorbidities*			
Hypertension and/or Diabetes	3 (17.6%)	6 (33.3%)	10 (41.7%)

Note: *Patients with pulmonary heart disease, pulmonary arterial hypertension, bronchiectasis, pulmonary fibrosis and pneumonia were excluded from this study.
Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting anticholinergic.

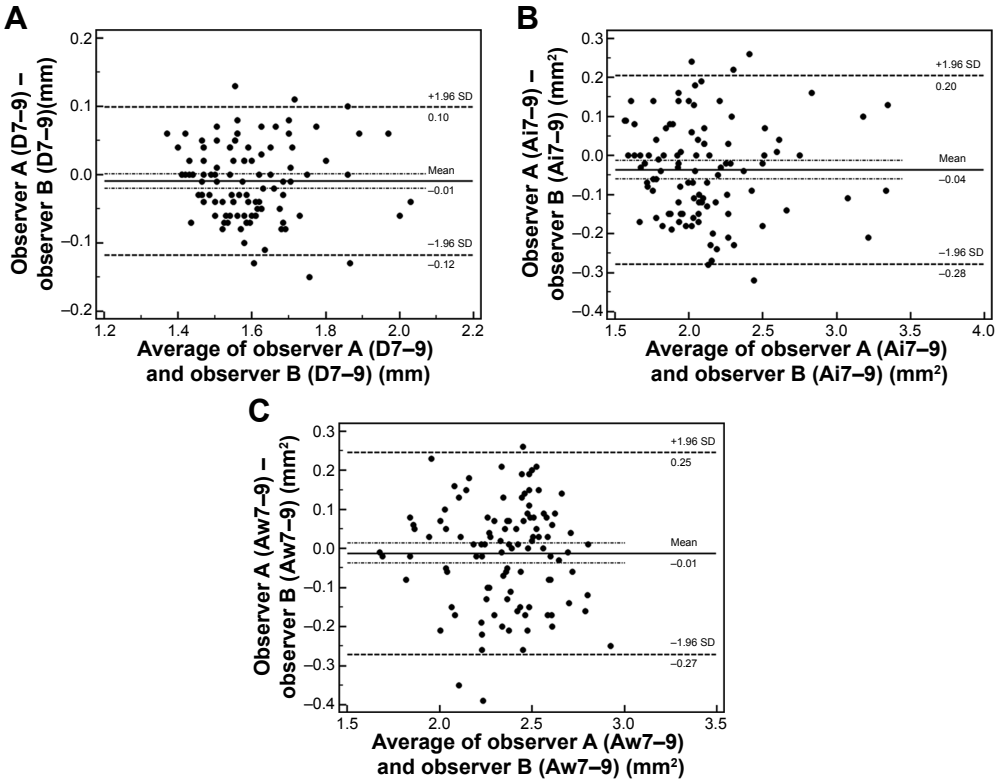

Figure S1 Bland-Altman analysis for endobronchial optical coherence tomography (EB-OCT) measurements by observer A and observer B (n=106).
Note: Bland-Altman analysis for D7–9 (**A**), Ai7–9 (**B**) and Aw7–9 (**C**) as measured by observer A and observer B.
Abbreviations: D7–9, mean diameter from 7th to 9th generation of bronchi; Ai7–9, airway internal area from 7th to 9th generation of bronchi; Aw7–9, airway wall area from 7th to 9th generation of bronchi.

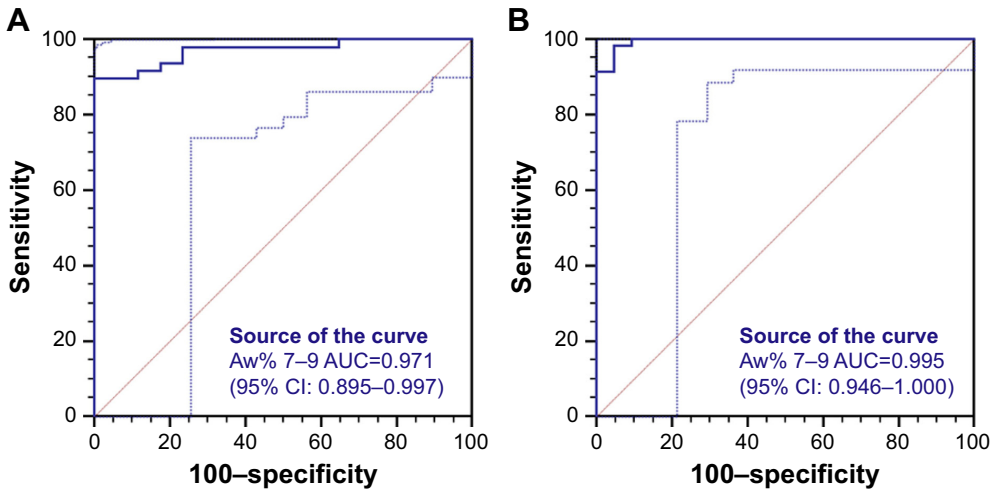

Figure S2 Receiver operating characteristic (ROC) curve analysis of endobronchial optical coherence tomography (EB-OCT) parameter for discriminating never-smokers from patients with COPD.

Notes: The diagnostic value of Aw% 7–9 for discriminating the presence from the absence of small-airway disorders in never-smokers and COPD patients (never-smokers, n=17; COPD patients, n=48) (Figure **A**. Data from the previous study[1]). The diagnostic value of Aw% 7–9 for discriminating the presence from the absence of small-airway disorders in never-smokers and COPD patients (never-smokers, n=21; COPD patients, n=59) (Figure **B**. Data from the current study).

Abbreviations: 7–9, from 7th to 9th generation of bronchi; Aw%, airway wall area percentage.

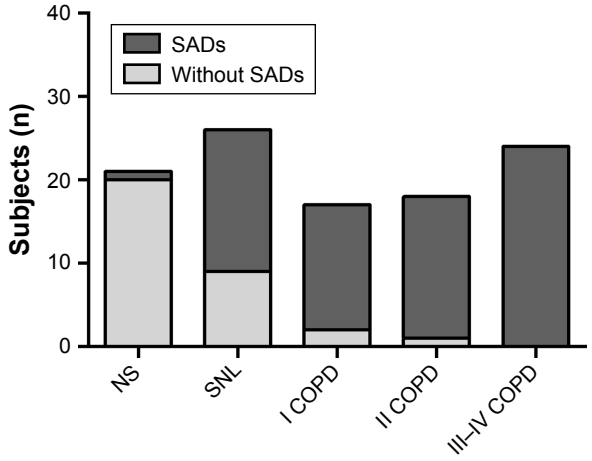

Figure S3 Incidences of small airway disorders (SADs) in never-smokers, heavy-smokers and patients with different stages of COPD.

Notes: By using cut-off value of 51% for Aw% 7–9, SADs were detected in 1/21 (4.8%) never-smokers, 17/26 (65.4%) heavy-smokers, 15/17 (88.2%) stage I, 17/18 (94.4%) stage II and 24/24 (100%) stages III–IV COPD patients.

Abbreviations: NS, never-smokers; SNL, heavy-smokers with normal lung function.

Table S2 Receiver operating characteristic curve of spirometric and IOS parameters in discriminating the presence or absence of small-airway disorders in never-smokers and heavy-smokers

Parameters	AUC	95% CI		Cut-off	Sensitivity (%)	Specificity (%)	PPV	NPV
		Lower limit	Upper limit					
FEV_1% pred	0.570	0.417	0.713	89.7	36.8	85.7	0.64	0.69
MMEF% pred	0.558	0.406	0.703	50.65	26.3	92.9	0.71	0.68
Z_5	0.644	0.491	0.778	0.37	57.9	67.9	0.50	0.70
Fres	0.771[a]	0.625	0.881	8.86	89.5	53.6	0.53	0.88
R_5	0.621	0.468	0.759	0.39	31.6	89.3	0.56	0.66
R_{20}	0.529	0.378	0.676	0.26	84.2	28.6	0.42	0.73
R_5–R_{20}	0.753	0.605	0.867	0.04	63.2	89.3	0.73	0.78
X_5	0.638	0.485	0.773	–0.1	57.9	71.4	0.58	0.75
AX	0.696	0.549	0.822	0.12	89.5	42.9	0.48	0.86
COMB	0.825[a,b]	0.687	0.920	0.25	94.7	60.7	0.59	0.94

Notes: The cut-off value was 51.0% for Aw% 7–9, according to our previous study.[1] [a]Compared with R_5–R_{20}, $P<0.05$. [b]Compared with Fres, $P<0.05$.

Abbreviations: IOS, impulse oscillometry; MMEF, maximal mid-expiratory flow; Fres, resonant frequency; R_5–R_{20}, peripheral airway resistance; AUC, area under curve; AX, area of reactance; COMB, combination of Fres, R_5–R_{20}, FEV_1% and MMEF% predicted; NPV, negative predictive value; PPV, positive predictive value; R_5, airway resistance at 5 Hz; R_{20}, airway resistance at 20 Hz; X_5, pulmonary reactance at 5 Hz; Z, impedance.

Table S3 Receiver operating characteristic curve of spirometric and IOS parameters in discriminating the presence or absence of small-airway disorders in heavy-smokers and patients with stage I COPD

Parameters	AUC	95% CI		Cut-off	Sensitivity (%)	Specificity (%)	PPV	NPV
		Lower limit	Upper limit					
FEV_1% pred	0.548	0.389	0.700	96.06	32.3	91.7	0.69	0.09
MMEF% pred	0.567	0.407	0.717	50.65	61.3	75.0	0.91	0.43
Z_5	0.668	0.508	0.804	0.31	77.4	58.3	0.86	0.50
Fres	0.726	0.569	0.851	8.87	83.9	58.3	0.87	0.58
R_5	0.657	0.497	0.795	0.29	77.4	50.0	0.83	0.46
R_{20}	0.645	0.485	0.785	0.27	71.0	58.3	0.81	0.38
R_5–R_{20}	0.633	0.472	0.775	0.03	64.5	66.7	0.88	0.42
X_5	0.618	0.458	0.762	–0.11	38.7	83.3	0.86	0.31
AX	0.672	0.512	0.807	0.34	29.0	100.0	1.00	0.32
COMB	0.761	0.606	0.877	0.74	67.7	83.3	0.92	0.47

Notes: The cut-off value was 51.0% for Aw% 7–9, according to our previous study.[1] [a]Compared with Fres, $P<0.05$; [b]Compared with R_5–R_{20}, $P<0.05$.

Abbreviations: IOS, impulse oscillometry; MMEF, maximal mid-expiratory flow; Fres, resonant frequency; AUC, area under curve; COMB, combination of Fres, R_5–R_{20}, FEV_1% and MMEF% predicted; NPV, negative predictive value; PPV, positive predictive value; R_5, airway resistance at 5 Hz; R_{20}, airway resistance at 20 Hz; X_5, pulmonary reactance at 5 Hz; Z, impedance.

Table S4 Correlation between EB-OCT parameters and IOS and spirometric indices in never-smokers, heavy-smokers and different stages of COPD

	Cases	FEV_1% predicted		MMEF% predicted		Fres		R_5–R_{20}	
		r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
Aw% 7–9									
Never-smokers	21	–0.34	0.130	0.14	0.548	–0.27	0.246	–0.21	0.357
Heavy-smokers	26	0.11	0.589	0.13	0.535	0.54	**0.005**	0.39	**0.047**
Stage I COPD	17	0.09	0.729	0.24	0.348	0.49	**0.047**	0.37	0.141
Stage II COPD	18	–0.37	0.130	–0.30	0.220	0.44	0.067	0.50	**0.033**
Stage III COPD	19	–0.66	**0.002**	–0.45	0.056	0.51	**0.026**	0.37	0.118
Stage IV COPD	5	–0.50	0.391	–0.20	0.747	0.90	**0.037**	0.30	0.624
All COPD	59	–0.90	<**0.001**	–0.86	<**0.001**	0.83	<**0.001**	0.81	<**0.001**

Notes: Data in boldface indicated the correlation with statistical significance. All *r* values denoted the Spearman's correlation coefficients.

Abbreviations: EB-OCT, endobronchial optical coherence tomography; MMEF, maximal mid-expiratory flow; IOS, impulse oscillometry; Aw%, airway wall area percentage = [Aw/(Ai+Aw)]×100%; 7–9, from 7th to 9th generation of bronchi; Fres, resonance frequency; R_5–R_{20}, the difference between airway resistance at 5 Hz and 20 Hz; FEV_1, forced expiratory volume in the first second.

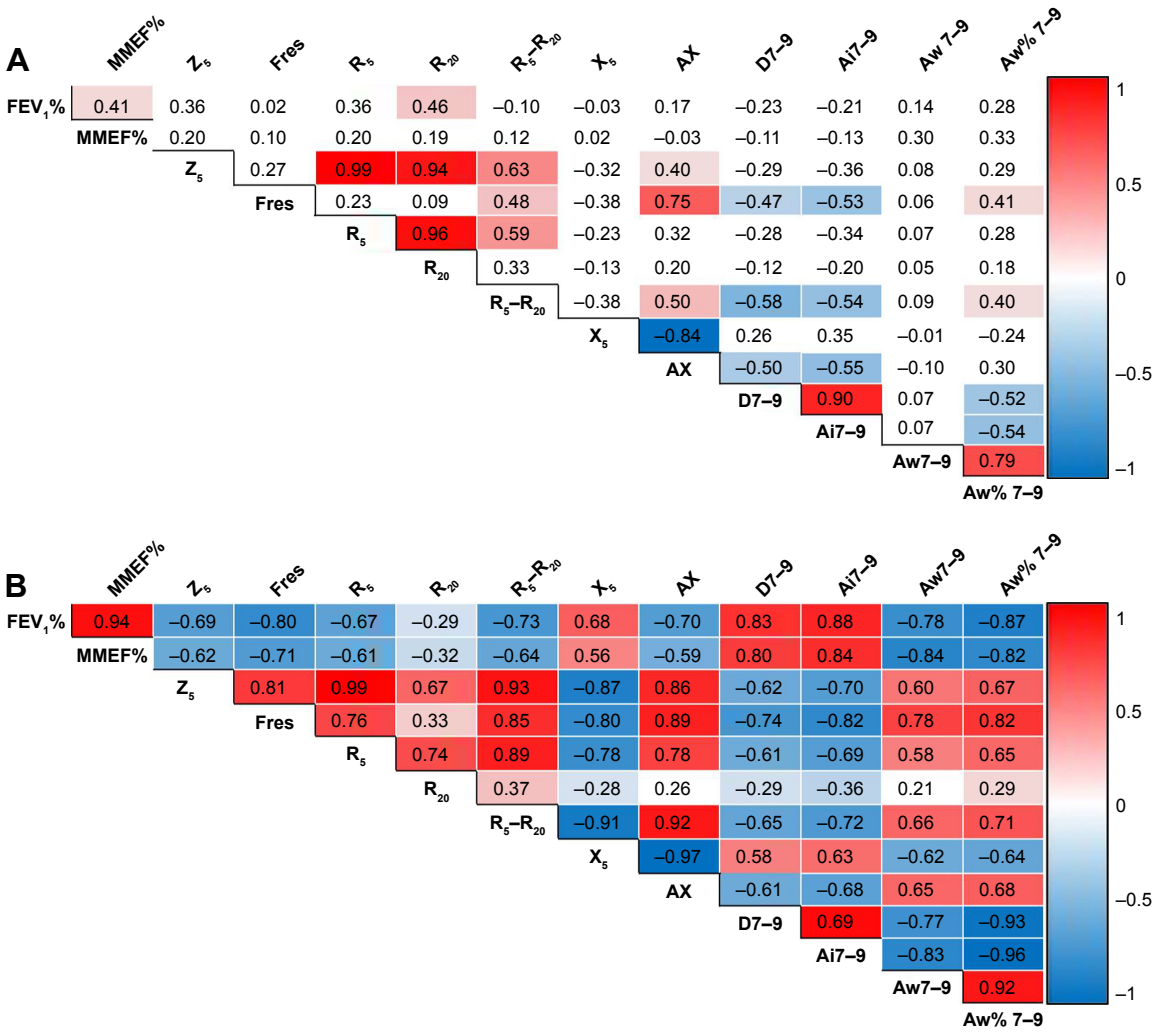

Figure S4 Partial correlation among spirometric, impulse oscillometry (IOS) and endobronchial optical coherence tomography (EB-OCT) parameters in heavy-smokers (**A**) and COPD patients (**B**).

Notes: Partial correlation analysis were performed with controlling for age and height. The color of individual boxes indicated the partial correlation coefficient of two parameters (red fillings indicated significantly positive correlation, whereas blue fillings indicated significantly negative correlation).

Abbreviations: MMEF, maximal mid-expiratory flow; 7–9, from 7th to 9th generation of bronchi; Ai, airway internal area; Aw, airway wall area; Aw%, airway wall area percentage; D, mean diameter; Fres, resonance frequency; R_5, airway resistance at 5 Hz; R_{20}, airway resistance at 20 Hz; R_5–R_{20}, the difference between airway resistance at 5 Hz and 20 Hz; X_5, pulmonary reactance at 5 Hz; AX, reactance area; Z, impedance.

explored the cut-off value of Aw% 7–9 for differentiating never-smokers from COPD patients. Herein, the cut-off value was 51.0% for Aw% 7–9 (AUC: 0.971, 95% CI: 0.895–0.997, sensitivity: 89.6%, specificity: 100.0%), which was comparable with the cut-off value of 50.5% derived from the current study (AUC: 0.995, 95% CI: 0.946–1.000, sensitivity: 98.3%, specificity: 95.2%), for discriminating the presence from the absence of SADs (Figure S2).

Reference

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