Quantitative CT Measurement of Cross-sectional Area of Small Pulmonary Vessel in COPD:

Correlations with Emphysema and Airflow Limitation

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Rationale and Objectives: Pulmonary vascular alteration is one of the characteristic features of chronic obstructive pulmonary disease (COPD). Recent studies suggest that vascular alteration is closely related to endothelial dysfunction and may be further influenced by emphysema. However, the relationship between morphological alteration of small pulmonary vessels and the extent of emphysema has not been assessed in vivo. The objectives of this study are: to evaluate the correlation of total cross-sectional area (CSA) of small pulmonary vessels with the extent of emphysema and airflow obstruction using CT scans and to assess the difference of total CSA between COPD phenotypes.

Materials and Methods: We measured CSA less than 5 mm^2 and 5–10 mm^2, and calculated the percentage of the total CSA for the lung area (%CSA < 5, and %CSA5–10, respectively) using CT scans in 191 subjects. The extent of emphysema (%LAA-950) was calculated, and the correlations of %CSA < 5 and %CSA5–10 with %LAA-950 and results of pulmonary function tests (PFTs) were evaluated. The differences in %CSA between COPD phenotypes were also assessed.

Results: The %CSA < 5 had significant negative correlations with %LAA-950 (r = -0.83, P < .0001). There was a weak but statistically significant correlation of %CSA < 5 with forced expiratory volume in 1 second (FEV1)% predicted (r = 0.29, P < .0001) and FEV1/forced vital capacity (r = 0.45, P < .0001). A %CSA 5–10 had weak correlations with %LAA-950 and results of PFTs. %CSA < 5 was significantly higher in bronchitis phenotype than in the emphysema phenotype (P < .0001).

Conclusions: Total CSA of small pulmonary vessels at sub-subsegmental levels strongly correlates with the extent of emphysema (%LAA-950) and reflects differences between COPD phenotypes.

Key Words: Pulmonary disease; chronic obstructive; emphysema; endothelial dysfunction; computed tomography.

Pulmonary vascular alteration is a characteristic feature of chronic obstructive pulmonary disease (COPD). Early angiographic studies in patients with emphysema showed narrowing and reduction in the number of small pulmonary arteries at subsegmental or sub-subsegmental levels (1–3). Passive vascular compression by emphysema and hypoxic vasoconstriction has been considered the major pathogenesis of vascular alteration in COPD. Histologically, pulmonary vascular alterations are not exclusive to advanced COPD, however, because they are present in patients with mild COPD and even in smokers with normal pulmonary function (4–10). Recent studies suggest that both pulmonary and extrapulmonary vascular alterations in patients with COPD closely relate to endothelial dysfunction (10–13). Because of the important role played by the endothelium in regulating vascular tone and controlling cell growth, pulmonary arteries with endothelial dysfunction have a diminished ability to dilate (14). Consequently, the pulmonary vascular bed decreases, and structural vascular alterations lead to the functional impairments.

Recently, several researchers demonstrated the relationship between endothelial dysfunction and emphysema (11–13,15–24). Endothelial dysfunction results from changes in the expression and release of vasoactive mediators. In several vasoactive mediators, vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of both vascular

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alteration and emphysema (11–13,21–24). Kasahara et al (11) demonstrated that the blockade of the VEGF receptor caused emphysema, and they simultaneously showed a pruning and decrease of the pulmonary arteries on angiography. More recently, Barr et al (13) suggested that the extent of emphysema, rather than airway obstruction, is responsible for endothelial dysfunction in COPD. Considering these previous reports, we hypothesized that the vascular alteration, as estimated by the reduction in cross-sectional area (CSA) of small pulmonary vessels in patients with COPD, would be related to the extent of emphysema, and predicted a stronger correlation than that with decline of airflow obstruction. To test this hypothesis, we measured CSA of subsegmental and sub-subsegmental pulmonary vessels with CT images, and evaluated the correlation of total CSA with emphysema and airflow obstruction. In addition, previous studies showed the differences in the level of VEGF and vascular alteration between COPD phenotypes (16,25). We hypothesized that a difference in vascular alteration between COPD phenotypes existed and sought to measure it.

METHODS

Subjects

All subjects in our study were enrolled in the National Lung Screening Trial (NLST), a full description for which is available on the website (http://www.cancer.gov/nlst). Subjects were eligible to participate in the NLST if they were between the ages of 55 and 74 and had a history of at least 30 pack-years of cigarette smoking. All subjects in the trial gave written informed consent. This study and manuscript were reviewed and approved according to the NLST/Lung Screening Study Publications, Presentations, and Associated Studies Working Group's Review Procedures and Authorship Guidelines. A previous publication described the enrollment procedures and baseline characteristics of the cohort that served as a source of participants in this study (26), which consists of 303 consecutively enrolled participants at a single NLST screening center (University of Alabama at Birmingham). After undergoing computed tomography (CT) imaging per the NLST protocol, subjects underwent pre-bronchodilator spirometry according to American Thoracic Society standards (27), for which additional informed consent was obtained. In this study, subjects who underwent CT scanning with a field of view between 300 and 400 mm and a tube current of 60 mA were included, with parameters based on each subject's physique. Other exclusion criteria included: obvious abnormal lung parenchymal lesions, other than emphysema; pleural effusion or cardiomegaly that suggested cardiac failure; or image noise that prevented image analysis. This study was performed with the approval from the Institutional Review Board at University of Alabama at Birmingham; subsequent data analysis was performed at Brigham and Women's Hospital with the approval of the Institutional Review Board.

Multislice CT Scanning

All subjects were scanned with a four-detector CT (QXi; GE Medical Systems, Milwaukee, WI) at full inspiration. None received contrast medium. Images were obtained using 120 kV and 60 mA. CT images were reconstructed with 2.5-mm slice thickness at 2-mm intervals, using standard algorithm (standard).

CT Measurement of Small Pulmonary Vessels

For the measurements of pulmonary vascular cross-sectional area, three CT slices were selected. The upper cranial slice was taken ~1 cm above the upper margin of the aortic arch, the middle slice was taken ~1 cm below the carina, and the lower caudal slice was taken ~1 cm below the right inferior pulmonary vein. The CT images were analyzed using a semiautomatic image-processing program (ImageJ Version 1.39, a public domain Java image processing program available on the Web at http://rsb.info.nih.gov/ij/). Using the "Analyze Particles" function of ImageJ software that can count and measure objects on binary images, the number and CSA of each vessel on each CT slice can be obtained. Vessels that ran at an oblique angle to the axial image were excluded using the "Circularity" function in ImageJ where "circularity" was calculated by the $4\pi \times (\text{area} / \text{perimeter}^2)$ of the structure of interest. Circularity ranges from 0 (straight line) to 1.0 (circle). In this way, only those vessels whose long axis was orthogonal to the scanning plane were included in the CSA measurements.

CSA measurements were conducted as follows (Fig. 1). First, the lung field was segmented using threshold technique with all pixels between -500 and -1024 HU on each CT image. Next, segmented images were converted into binary images with window level of -720 HU, and vessels were then displayed in black on the binary image. We separately measured the CSA at both the subsegmental level and sub-subsegmental level: the range of CSA of each vessel was defined less than 5 mm^2 at the sub-subsegmental level, and 5–10 mm^2 at the subsegmental level (28). The range of circularity was set from 0.9 to 1.0. After these settings, CSA for each vessel was calculated. Finally, we totaled the CSA of vessels measured on each set of three CT slices, and those totals were abbreviated as follows: CSA < 5 for the total CSA of vessels that were less than 5 mm^2 in CSA each and CSA5–10 for the total CSA of vessels that were between 5 and 10 mm^2 in CSA each. Total area of the lung in selected three slices was obtained using threshold values between -500 HU and -1024 HU, and the percentages of CSA <5 (%CSA < 5) and CSA5–10 (%CSA5–10) for the total area of the lung were calculated.

Pulmonary Function Tests

After the CT scan, prebronchodilator spirometry was performed according to American Thoracic Society standards. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) were measured, and expressed as percentages of predicted values.

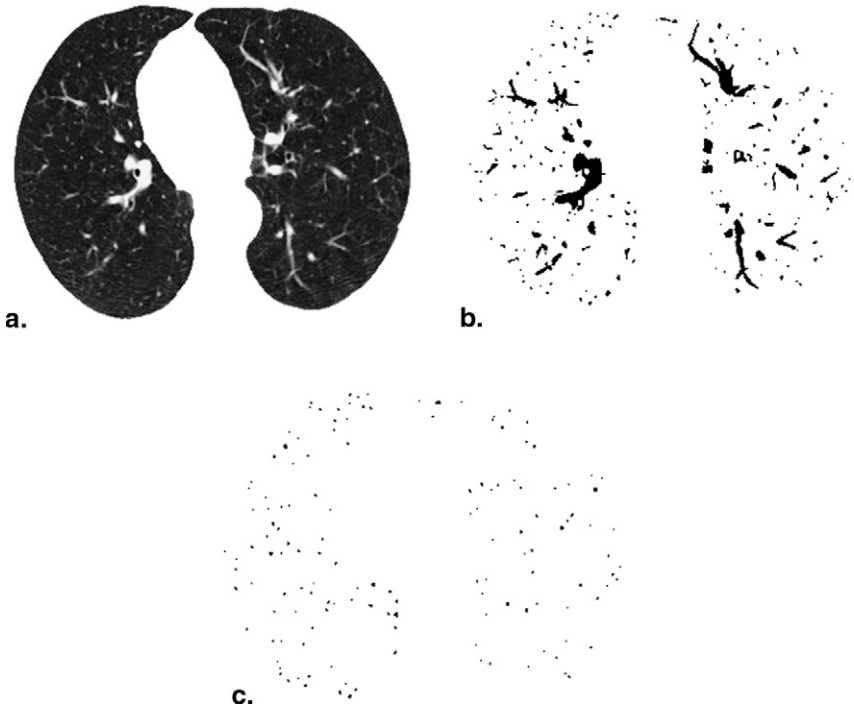

Figure 1. The method of measuring the cross-sectional area of small pulmonary vessels using ImageJ software. **(a)** Computed tomography image of lung field segmented within the threshold values from -500 Hounsfield units (HU) to -1024 HU. **(b)** Binary image converted from segmented image **(a)** with window level of -720 HU. Pulmonary vessels are displayed in black. **(c)** Mask image for the particle analysis after setting vessel size within 0–5 mm^2, and circularity within 0.9–1.0.

Statistical Analysis

To evaluate the relation between %CSA and the extent of emphysema, percentage of low attenuation values lower than -950 HU was measured on each slice using ImageJ software, and mean percentage low attenuation area was obtained (%LAA-950) as the extent of emphysema (29). Correlations of %CSA with %LAA-950 and airflow obstruction (FEV1% predicted and FEV1/FVC ratio) were evaluated by Spearman's rank correlation analysis. Correlations of %LAA-950 with FEV1% predicted and FEV1/FVC ratio were also evaluated by Spearman's rank correlation analysis.

For the evaluation of the difference in %CSA between COPD phenotypes, subjects in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 1, 2, 3, and 4 were divided into two groups according to the extent of emphysema as follows: emphysema phenotype (%LAA-950 $\geq$ 5%), and bronchitis phenotype (%LAA-950 < 5%). The difference in CSA between the two COPD phenotypes was assessed in each GOLD stage group with a two-way analysis of variance and Tukey-Kramer test. Data were expressed as mean $\pm$ standard deviation. For all statistical analyses, a *P* value less than .001 was considered significant. All statistical analyses were performed using SAS 8.0 software (Cary, NC).

RESULTS

Characteristics of the Study Subjects

Characteristics of the patients including the results of PFT are presented in Table 1. According to the CT criteria in this study, 68 subjects were excluded. In addition, 44 subjects were excluded because of obvious abnormal parenchymal lesions other than emphysema (n = 2 for interstitial pneumonia, n = 1 for multiple nodules, n = 1 for atelectasis), pleural effusion (n = 1), and image noise (n = 39). Thus 191 patients (mean age, 62 $\pm$ 5 years; range, 56–74 years; 78 women, 61 $\pm$ 4 years and 113 men, 63 $\pm$ 5 years) were included in this study. All patients had a smoking history, and mean number of pack-years was 52 $\pm$ 29. Subjects were classified using GOLD criteria for disease severity (smoker with normal lung function [formally GOLD stage 0], n = 61; stage 1, n = 36; stage 2, n = 63; stage 3, n = 30, and stage 4, n = 1).

CSA Measurements and Correlation with %LAA-950 and results of PFTs

The results of %CSA measurements and correlation with %LAA-950 and the results of PFTs are shown in Table 2. The %CSA < 5 had a significant negative correlation with the %LAA-950 (r = -0.83, P < .0001) (Fig. 2), and the %CSA5–10 had a significant but weak negative correlation with %LAA-950 (r = -0.25, P = .0004). Although there were statistically significant correlations of %CSA < 5 with FEV1% predicted (r = 0.29, P < .0001) and FEV1/FVC (r = 0.45, P < .0001) (Fig. 2), these were relatively low when compared with the correlation with %LAA-950. Likewise, %CSA 5–10 had significant but weak positive correlations with FEV1% predicted and FEV1/FVC. Extent of emphysema (%LAA-950) had significant correlations with FEV1% predicted and FEV1/FVC (r = -0.37, P < .0001,

TABLE 1. Patient Characteristics and Results of Pulmonary Function Tests (*n* = 191)

	Mean ± SD
Age (y)	62 ± 5
Age (y): female	61 ± 4
Age (y): male	63 ± 5
Pack-years	52 ± 29
Current smokers (%)	56.0
FEV_1 (L)	2.3 ± 0.8
FEV_1 % predicted (%)	74.2 ± 20.5
FVC (L)	3.7 ± 0.9
FEV_1/FVC	0.63 ± 0.13

SD, standard deviation; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

and $r = -0.54$, $P < .0001$, respectively), but these correlations were lower than the correlation between %LAA-950 and %CSA < 5.

CSA Measurements and COPD Phenotypes

Mean %LAA-950 was 9.6% ± 7.6 in 130 subjects with GOLD stages 1, 2, 3, and 4. Forty-seven subjects were classified into bronchitis phenotype (mean %LAA-950: 2.6% ± 1.2), and 83 subjects were classified into emphysema phenotype (mean %LAA-950: 13.6% ± 6.9). There was no statistical significance of the interaction between COPD phenotype and GOLD group ($P = .835$). A %CSA < 5 was significantly lower in subjects with emphysema phenotype (0.35 % ± 0.08) than in subjects with bronchitis phenotype (0.53 % ± 0.10) ($P < .0001$). All subjects with emphysema phenotype had a value of %CSA < 5 lower than 0.6%. The results of the difference of %CSA < 5 between COPD phenotypes in each GOLD stage are summarized in Table 3. In each GOLD stage, %CSA < 5 was significantly higher in subjects with bronchitis phenotype than in subjects with emphysema phenotype (Fig. 3).

DISCUSSION

In the present study, we found that %CSA < 5 had a negative strong correlation with the extent of emphysema. Meanwhile, the correlations of %CSA < 5 with FEV1 % predicted and FEV1/FVC were significant but weak. These results support the concept that the vascular alteration closely correlates with the extent of emphysema rather than airway obstruction (13). Moreover, %CSA < 5 was significantly higher in subjects with bronchitis phenotype than in emphysema phenotype. In addition, this difference was significant regardless of the GOLD staging.

Some early histologic studies showed a relationship between vascular alteration and the extent of emphysema (4,5). Several recent studies on the pathogenesis of COPD suggest that endothelial dysfunction plays an important role in both vascular alteration and emphysema (11–13,15–24). The impairment of vasoactive mediator such as VEGF leads to endothelial dysfunction. Decreased expression of VEGF caused vascular alteration and airspace enlargement in a rat model (11), and VEGF and its receptor were found to be significantly reduced in emphysema in humans (15). A more recent study suggested an association between endothelial dysfunction and an increase in the extent of emphysema on CT scans (13). Moreover, the relationship between the extent of emphysema and systemic vascular function has been reported (18,19). Although we did not assess the endothelial dysfunction, our observed negative correlation of %CSA < 5 with the extent of emphysema might be related to endothelial dysfunction.

The other factors might be related to the correlation of %CSA < 5 and %LAA-950. The decrease in %CSA < 5 might result from the passive vascular compression by emphysema. This influence, however, would be minimal because the degree of emphysema in this cohort was relatively mild. The calculation of %CSA < 5 also could be affected by the extent of emphysema. In general, the lung volume increases with emphysema; therefore, this increase in lung volume may affect this calculation. However, absolute value of CSA < 5 also correlated with %LAA in this cohort ($r = -0.55$, $P < .0001$).

Meanwhile, correlations of %CSA with FEV1 % predicted and FEV1/FVC were significant but weak. Several reports demonstrated that pulmonary vascular alteration is identified even in smokers without airflow obstruction (4–10). Noma et al (30) experimentally showed a decrease in pulmonary perfusion in mild emphysema without significant ventilation abnormality. Together, these studies suggest that vascular alteration in COPD is not always associated with the ventilation impairment. Moreover, Barr et al (13) concluded that the association between FEV1% predicted and endothelial dysfunction was entirely attributable to CT percentage of emphysema. This implies that the vascular alteration in COPD is related to the extent of the pulmonary emphysema rather than airflow obstruction, and the weak correlation between CSA and FEV1% predicted in our study appears consistent with this previous report. Furthermore, correlations between the extent of emphysema and results of PFTs were not as good as that between CSA < 5 and the extent of emphysema. This result suggests that assessment of vascular alteration may be more predictive of emphysema than the results of PFT.

Several studies have addressed the relevance of COPD phenotypes including emphysema and bronchitis phenotypes (31,32). In our study, we found that %CSA < 5 was significantly lower in subjects with the emphysema phenotype than in subjects with the bronchitis phenotype. Kanazawa et al (17) reported that the VEGF level in induced sputum was decreased in patients with emphysema relative to the VEGF level in patients with chronic bronchitis. Although the relationship between the VEGF level and morphologic vascular alteration in each phenotype group was not evaluated, our results indicate a potential difference of the VEGF level between bronchitis and emphysema phenotype. Our

TABLE 2. Cross-sectional Area of Pulmonary Vessels and Correlations with %LAA-950 and Pulmonary Function Tests (*n* = 191)

		%LAA-950		FEV1% predicted		FEV1/FVC	
Cross-sectional Area	Mean ± SD (%)	*r*	*P*	*r*	*P*	*r*	*P*
%CSA < 5	0.43 ± 0.11	-0.83	<.0001	0.29	<.0001	0.45	<.0001
%CSA5–10	0.10 ± 0.04	-0.25	.0004	0.26	.0003	0.22	.0025

%LAA-950, the percentage of low attenuation area less than -950 HU (defined as emphysema); FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation; %CSA < 5, percentage total cross-sectional area calculated from pulmonary vessels less than 5 mm^2; %CSA5–10, percentage total cross-sectional area calculated from pulmonary vessel size between 5 and 10 mm^2.

Correlations were assessed using Spearman's rank correlation analysis.

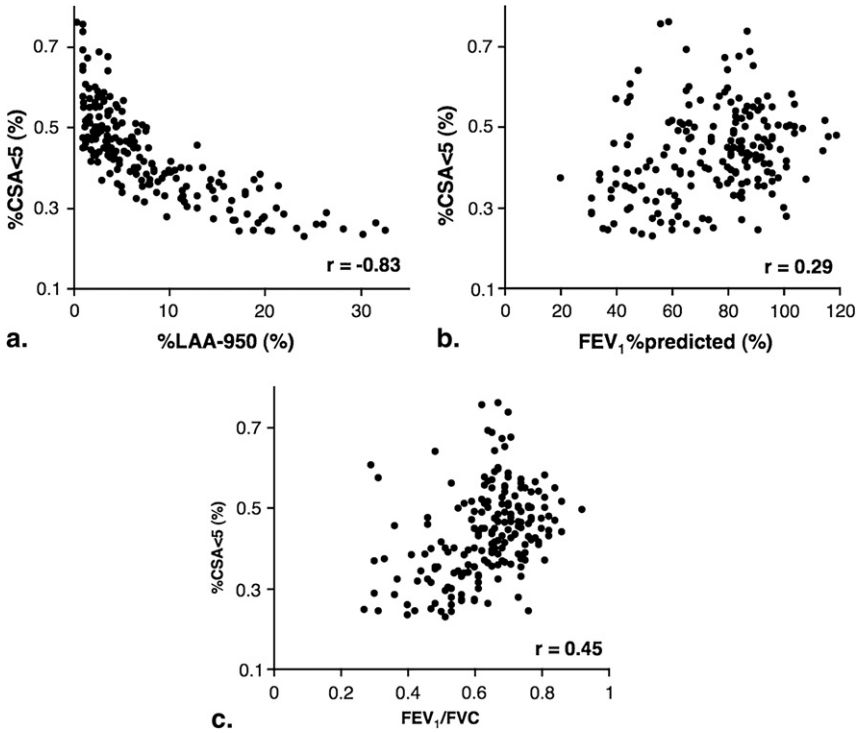

Figure 2. The relationship between the percentage cross-sectional area of pulmonary vessels less than 5 mm^2 (%CSA < 5) and **(a)** the percentage area of emphysema (%LAA-950) estimated by CT, **(b)** forced expiratory volume in 1 second (FEV1)1% predicted, and **(c)** FEV1/forced vital capacity (FVC). The %CSA < 5 had significant negative correlation with the %LAA-950 (r = -0.83, P < .0001), and relatively weak correlation with FEV1% predicted (r = 0.29, P < .0001) or FEV1/FVC (r = 0.45, P < .0001).

results also suggest that vascular alteration might be a useful CT finding for classifying COPD by phenotypes.

Our study also shows that the relationship between %CSA and the extent of emphysema is dependent on vessel size. A strong correlation was found between the extent of emphysema and %CSA < 5, whereas the correlation between %CSA5–10 and the extent of emphysema was statistically significant but weak. The degree of histologic vascular alteration in COPD varies according to vessels size (4). In this study, both elastic vessel and muscular vessel were included in %CSA < 5, whereas pulmonary vessels measured as %CSA5–10 were mostly elastic vessel. In patients with COPD, histologic vascular alteration can be found mainly in muscular pulmonary artery (4–6); therefore, the difference in correlations between total CSA and the extent of emphysema might reflect the difference in the degree of histologic vascular alteration according to the vessel size.

In patients with COPD, some researchers have reported the efficacy of measuring the central large pulmonary arteries for the evaluation of pulmonary hypertension (33–35). However, morphologic alteration of small pulmonary vessel has not been assessed quantitatively in vivo. To our knowledge, this is the first approach to evaluate the alteration of small pulmonary vessels in COPD using CT images. This method is a relatively uncomplicated procedure because special CT scanning techniques and contrast material injection are not necessary. Although this method is potentially suitable for evaluation of pulmonary small vascular structure, there are several issues that should be addressed. First, in this study, we used the threshold value of -720 HU to identify vascular structure on CT images because using a lower threshold than -720 HU led to increased image noise. In fact, even with a relatively higher threshold value, it was necessary to exclude a considerable number of subjects due to image noise. In this NLST cohort, relatively low tube current (60 mA) has been adopted for the reduction of radiation exposure, so we could not examine the suitable CT threshold for the reorganization of small vascular structure. This threshold should be evaluated

TABLE 3. Cross-sectional Area of COPD Phenotypes (n = 130)

	%CSA < 5 (%)		
GOLD Stage	Bronchitis Phenotype	Emphysema Phenotype	*P* Value
All Stage	0.53 ± 0.10	0.35 ± 0.08	<0.0001
GOLD 1	0.52 ± 0.08	0.36 ± 0.05	<0.0001
GOLD 2	0.53 ± 0.10	0.36 ± 0.09	<0.0001
GOLD 3 and 4	0.52 ± 0.11	0.33 ± 0.07	<0.0001

GOLD, Global Initiative for Chronic Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; %CSA < 5, percentage total cross-sectional area calculated from pulmonary vessels less than 5 mm^2.

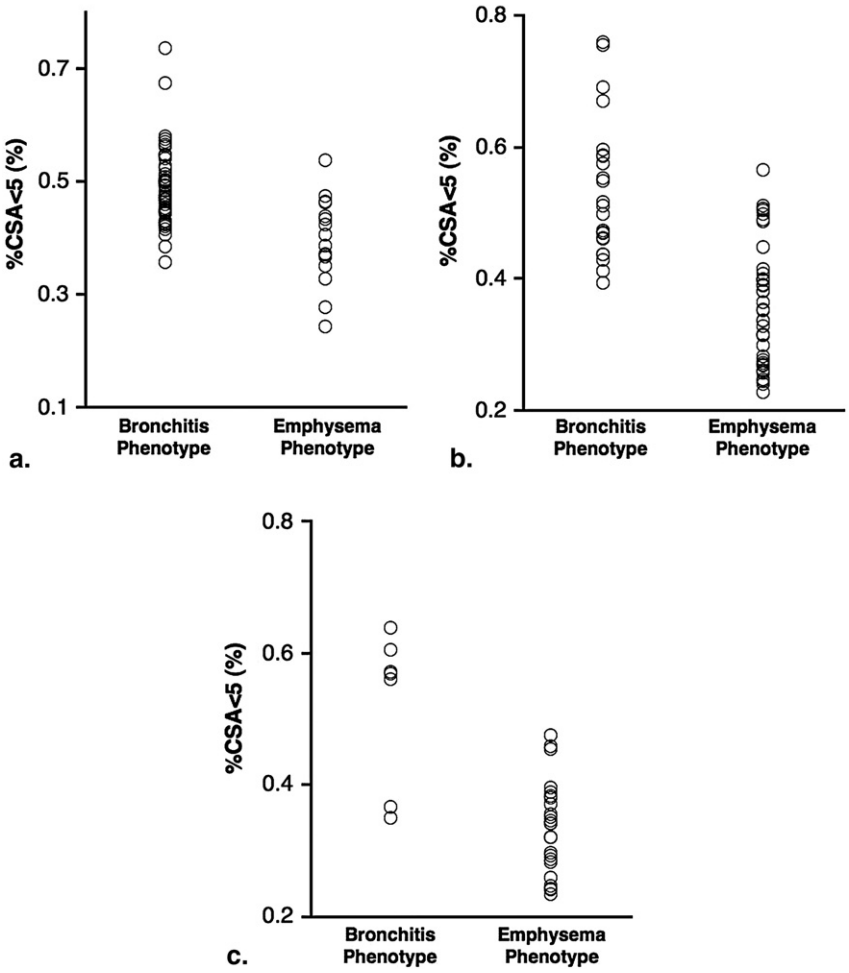

Figure 3. Individual data of the percentage cross-sectional area of pulmonary vessels less than 5 mm^2 (%CSA < 5) of chronic obstructive pulmonary disease phenotypes as defined by the percentage of emphysema (bronchitis type, %LAA-950 < 5% and emphysema type, %LAA-950 > 5%) in each GOLD stage: stage 1 **(a)**, stage 2 **(b)**, and stages 3 and 4 **(c)**. In each Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, %CSA < 5 in the bronchitis type is significantly higher than that in the emphysema type.

in future investigations. Second, this method cannot evaluate the pulmonary artery and vein separately; however, three-dimensional reconstruction of multislice CT images in conjunction with innovative image analysis software might overcome this limitation. Likewise, vascular lumen and vascular wall cannot be measured separately.

There are some limitations of this study. First, pulmonary function test and other clinical data were limited, and did not permit an evaluation of the relationship between small vascular alteration and diffusing capacity of the lung for carbon monoxide. Second, most of our results are considered to relate to endothelial dysfunction; however, we did not assess the degree of endothelial dysfunction. The relationship between %CSA and the deterioration of endothelial function should be assessed. Finally, we did not measure the CSA of pulmonary vessels histologically; therefore, there might be some differences between CSA measured on CT image and actual CSA of pulmonary vessel. Further evaluation is necessary.

In conclusion, we found that the extent of emphysema strongly correlated with the percentage of total CSA for pulmonary vessels less than 5 mm^2, whereas the relation with airflow obstruction was weak. This finding supports the association between emphysema and vascular alteration in COPD, and also suggests that anatomic emphysema, rather than airway obstruction, is responsible for impaired vascular structure. The differences we found in the total CSA for pulmonary vessels less than 5 mm^2 between COPD phenotypes can be understood in light of effects related to endothelial dysfunction.

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