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Determination of vascular alteration in smokers by quantitative computed tomography measurements

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Abstract

A new method of quantitative computed tomography (CT) measurements of pulmonary vessels are applicable to morphological studies and may be helpful in defining the progression of emphysema in smokers. However, limited data are available on the relationship between the smoking status and pulmonary vessels alteration established in longitudinal observations. Therefore, we investigated the change of pulmonary vessels on CTs in a longitudinal cohort of smokers.

Chest CTs were available for 287 current smokers, 439 non-smokers, and 80 former smokers who quit smoking at least 2 years after the baseline CT. CT images obtained at the baseline and 1 year later were assessed by a new quantitative CT measurement method, computing the total number of pulmonary vessels (TNV), mean lung density (MLD), and the percentage of low-attenuation areas at a threshold of −950 (density attenuation area [LAA]%$_{950}$). Analysis of variance (ANOVA) and the independent sample *t* test were used to estimate the influence of the baseline parameters. The *t* paired test was employed to evaluate the change between the baseline and follow-up results.

The current smokers related to have higher whole-lung MLD, as well as less and lower TNV values than the non-smokers ($P < .05$). But no significant differences in LAA%$_{950}$ were found between smokers and non-smokers. After one year, the increase in LAA%$_{950}$ was more rapid in the current (additional 0.3% per year, $P <$. 05–.01) than in the former smokers (additional 0.2% per year, $P = .3$). Additionally, the decline in TNV was faster in the current (additional −1.3 per year, $P <$.05–.01) than that in the former smokers (additional −0.2 per year, $P = .6$). Current smoke, pack-years, weight, and lung volume independently predicted TNV at baseline ($P <$.001) in multivariate analysis.

The findings of this study reveal that the decline in the pulmonary vessels in smokers can be measured and related to their smoking status.

Abbreviations: COPD = chronic obstructive pulmonary disease, CSA = Cross-sectional area, CT = computed tomography, FEV1% = predicted forced expiatory volume in 1 second predicted, LAA = density attenuation area, MLD = mean lung density, QCT = quantitative measures of CT, TNV = total number of pulmonary vessels.

Keywords: COPD, CT, emphysema, pulmonary vascular disease

1. Introduction

A method of quantitative measures of computed tomography (QCT) examinations based on Hounsfield unit (HU) measurements is suitable for the qualitative evaluation of parenchymal disorders caused by smoke in chronic obstructive pulmonary disease (COPD) patients. The main related features such as airway remodeling and emphysema can be present on QCT, displayed as a decrease in lung density and airway wall thickening. Pulmonary vascular alteration is also a key feature in patients with COPD,[1–4] in whom pulmonary vascular alterations are closely related to airflow limitation and may be associated with increased pulmonary vascular resistance. Moreover, pulmonary vascular alteration can also be found in smokers with normal pulmonary function.[5] Previous evidence[6] exists that chronic cigarette smoke exposure caused changes in pulmonary vessels, including arteriolar muscularization, and intima fibrosis. This finding is consistent with the results of other investigations reporting that the altered pulmonary vascular morphology in emphysema is attributable to cigarette smoking.[7] Yamato et al[8] found that cigarette smoke exposure of guinea pigs induced emphysema associated with a diffusely reduced lung capillary density. Altogether, these earlier findings have indicated that inhaled cigarette smoke can seriously injure the lung vessels.

QCT enabled a more detailed analysis of pulmonary vessels.[9–12] Matsuoka et al[13] reported a close relationship between vascular alteration and the degree of pulmonary hypertension in severe emphysema, established by measurements

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Y-mG contribute equal work to the corresponding author.

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The data sets used and/or analyzed during the present study are available upon a reasonable request to the corresponding author.

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of the total cross-sectional area (CSA) of the small pulmonary vessels using non-contrast chest computed tomography (CT) scans. Additionally, Coste et al[14] found that %CSA <5 and airway wall thickness were the optimal predictors of mean pulmonary arterial pressure (mPAP). In a previous study,[15] employing a 3D QCT method, the authors discovered that the 5th-generation vessels in a cross-section exhibited a positive correlation with the extent of emphysema in COPD patients. However, limited data are available of longitudinal observations on the relationship between the smoking status and pulmonary vessels alteration. Therefore, we hypothesized that the pulmonary vessels alteration in smokers can be measured by the 3D QCT method and may be associated with the smoking status.

We used data from the CT-based lung cancer screening in smokers to determine the vascular alteration and the extent of emphysema at baseline and 1 year later.

2. Methods

2.1. Study design

The data of participants received chest CT for lung cancer screening were collected from July 2014 to November 2016. The inclusion criteria were being 40 to 75 years' old male and underwent chest CT. Chest CTs were performed at the baseline and follow-up examinations. Since the QCT analysis was based on the examinations of CT images, the following exclusive criteria were applied:

(1) obvious abnormal lung lesions on CT, such as lobar consolidation, bronchial carcinoma, active tuberculosis, lung destruction (affecting 1 lobe or more), or interstitial lung disease; pleura effusion;
(2) with any active lung disease at the time of receiving CT scan, including COPD, asthma, bronchial carcinoma, pulmonary tuberculosis, interstitial pneumonia, and bronchiectasis,
(3) image noise preventing further image analysis.

The baseline characteristics were surveyed by a standardized questionnaire, distributed to all subjects at inclusion and repetitively at the follow-up. The baseline characteristics included age, height, weight, and smoking history (including no-smoking, current and past smoking status and habits, numbers of cigarettes per day and total years of smoking. If the subjects had quit smoking, they were asked to record the duration of the period after smoking cessation. The duration was categorized in the following classes: <1 year, 1 to 2 years, 3 to 5 years, 5 to 10 years, and >10 years. The "smoking history" was quantified by the number of "pack-years", calculated by multiplying the number of the packs of cigarettes smoked per day by the number of years the person had smoked. Data of self-reported presence of respiratory symptoms in the recent 1 month (including cough, hemoptysis, and shortness of breath, chest pain, fever, fatigue, or weight loss) were also collected. "Current smokers" were defined as subjects who actively smoked at baseline; "former smokers" were defined as subjects who had quit smoking more than "1 to 2 years" at baseline, and did not start smoking again during the whole observation time. Next, "nonsmokers" were defined as subjects who had never smoked, or their total years of smoking were <1 month. Therefore, we had classified the subjects into 3 baseline subgroups: nonsmokers, former smokers, and current smokers at baseline. Of the 912 patients initially recruited for the study, n=806 patients fulfilled the criteria at baseline, including 439 non-smokers, and 287 current smokers and 80 former smokers. One hundred six patients were excluded from baseline (n=6 for image noise, n=16 for airway tree/vascular tree segmentation failure, n=18 for obvious lung parenchymal lesions and n=66 for incomplete questionnaire).

After 1 year, the former and the current smokers were followed up. The deadline of following-up was within 2 years. The study selection is presented in a flow diagram (Fig. 1). Among 367 enrolled smokers, the 103 smokers had subsequent visit after 1 year, including 55 current smokers and 48 former smokers. Those sample visit after 2 years (n=58), or fail to complete the questionnaire (n=32), or without qualified CT image at subsequent visit (n=10), or received chest CT at other hospital (n=103), or chest CT was not available (n=61) were defined as failed cases of follow-up.

All subjects were fully informed about the nature of the study, and all gave written consent for participation. The local Ethical Committee of the Hospital Institutional Review Board approved this study, which was also performed after the approval by the Chinese Clinical Trials Registry Center (http://www.chictr.org/en/) and was assigned Registration No: ChiCTR-OCH-14004935. All methods were performed in accordance with the relevant guidelines.

2.2. Acquisition of HRCT examinations

The CT examinations were performed using a volumetric CT protocol on a 64-channel CT scanner. The following parameters were used: tube energy of 120-kVp and a tube current of 200 mA, rotation time of 0.5 seconds, and detector collimation of 0.6 mm. Images were reconstructed to encompass the entire lung field in a 512×512-pixel matrix using a standard algorithm at a 0.625-mm section thickness and a 0.625-mm interval.

2.3. QCT analysis

QCT analysis was performed of all data obtained from baseline as well as from after year. A 3-D approach was employed to measure the quantitative parameters including mean lung density (MLD), density attenuation area (LAA)$\%_{950}$ and total number of pulmonary vessels (TNV). All analytical processes were automatic. The first is segmentation of the entire lung. The total lung volume was calculated by summing the CT voxels that the lung contained (Fig. 2). The density of each lung voxel was collected and averaged as the value of MLD. If the density was equal to or lower than −950 HU, the low-attenuation area (LAA) was defined as emphysema. Then, the percentage of the LAA volume and the volume of the whole lung was used as an index (LAA$\%_{950}$) of the extent of emphysema. [15] The second is segmentation of bronchovascular bundle. A differential geometric approach was applied to automatically segment the vascular tree. A "puzzle game" procedure acting as a "correction" operation for filtering false identifications was utilized. Then the identification of the total number of pulmonary vessels in a cross-section was performed as TNV. The cross-section was defined as an area of $80 \times 80\,mm^2$ around the airway, which formed a right angle to the labeled airway (Fig. 3). The value of TNV for each generation was counted by averaging all the results obtained in the same generation. One generation is defined as a continuous airway beginning and ending at 2 bifurcations. According to the findings of our previous study,[16] the value of TNV in the 5th generation of airway were consistent with those obtained by using a semi-automatic tool; this value was also inversely related to the LAA$\%_{950}$. Therefore, the TNV in the 5th generation was

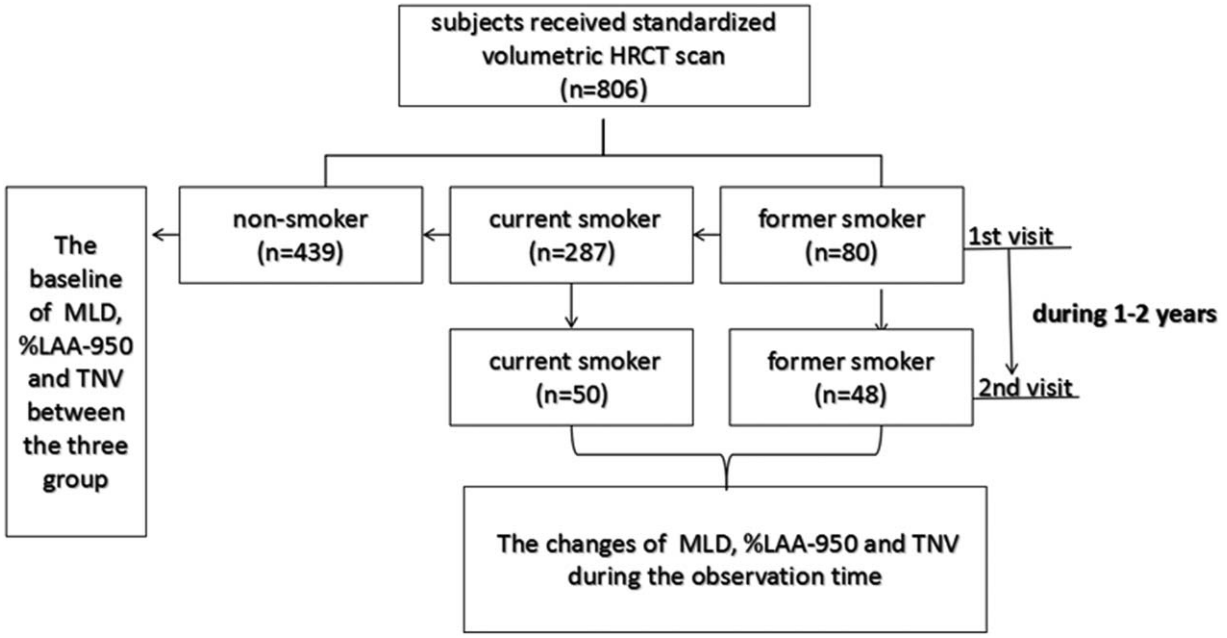

Figure 1. Flow diagram of study.

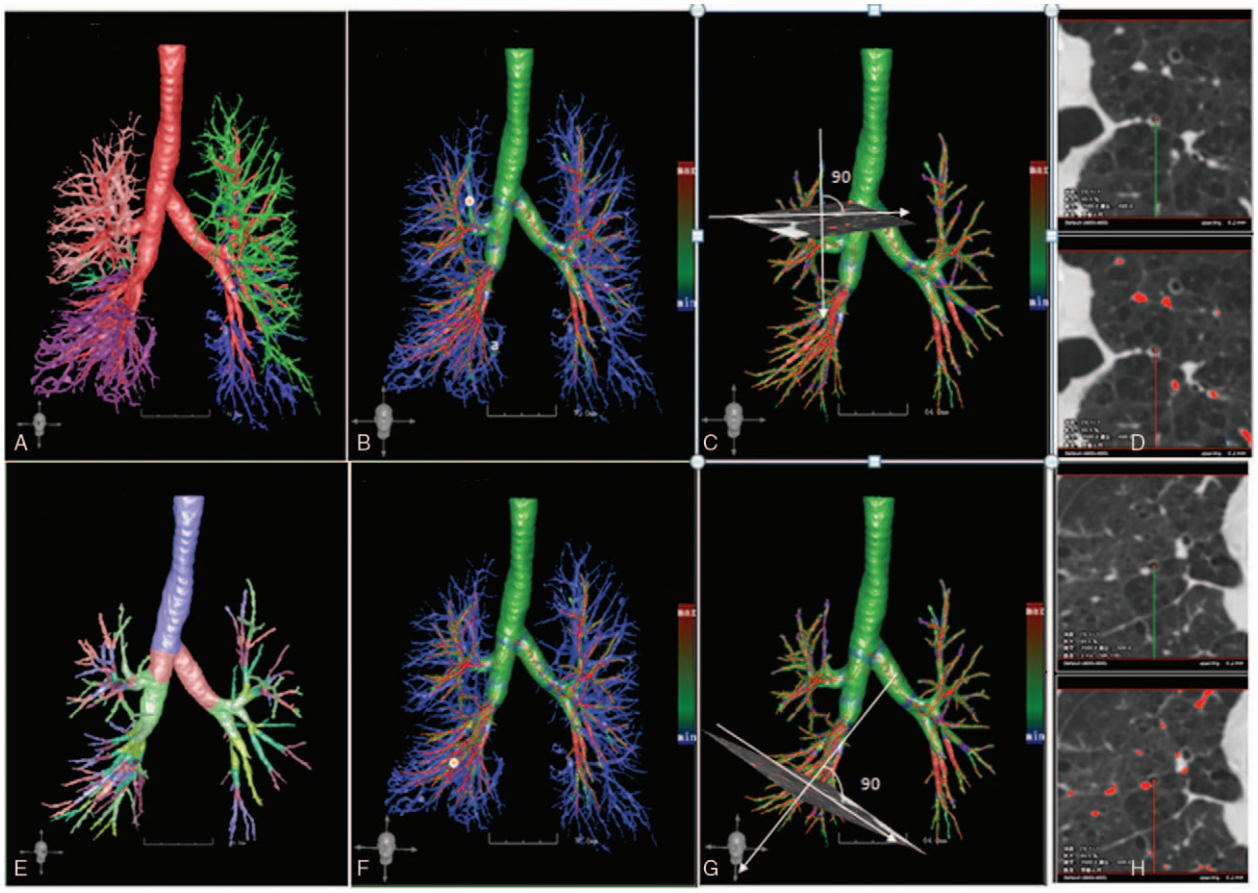

Figure 2. Small vessels segmentation and measurement as well as its 3-D surface model at the right upper lobe (A, B, C, and D) and the right lower lobe (E, F, G, H). (A) airway (red) and vessels (difference color in each lobe) segmentation were performed automatically; (B) the center-line of vascular tree (blue); (C) the location of cross area (right upper lobe) was around the airway (green); (D) small vessels measurement are presented in red in the cross area (right upper lobe); (E) airway segmentation in the individual generation, presented in different color; (F) the center-line of the vascular tree (blue); (G) location of the cross area (right lower lobe); (H) small vessels measurement results, shown in red (right upper lobe).

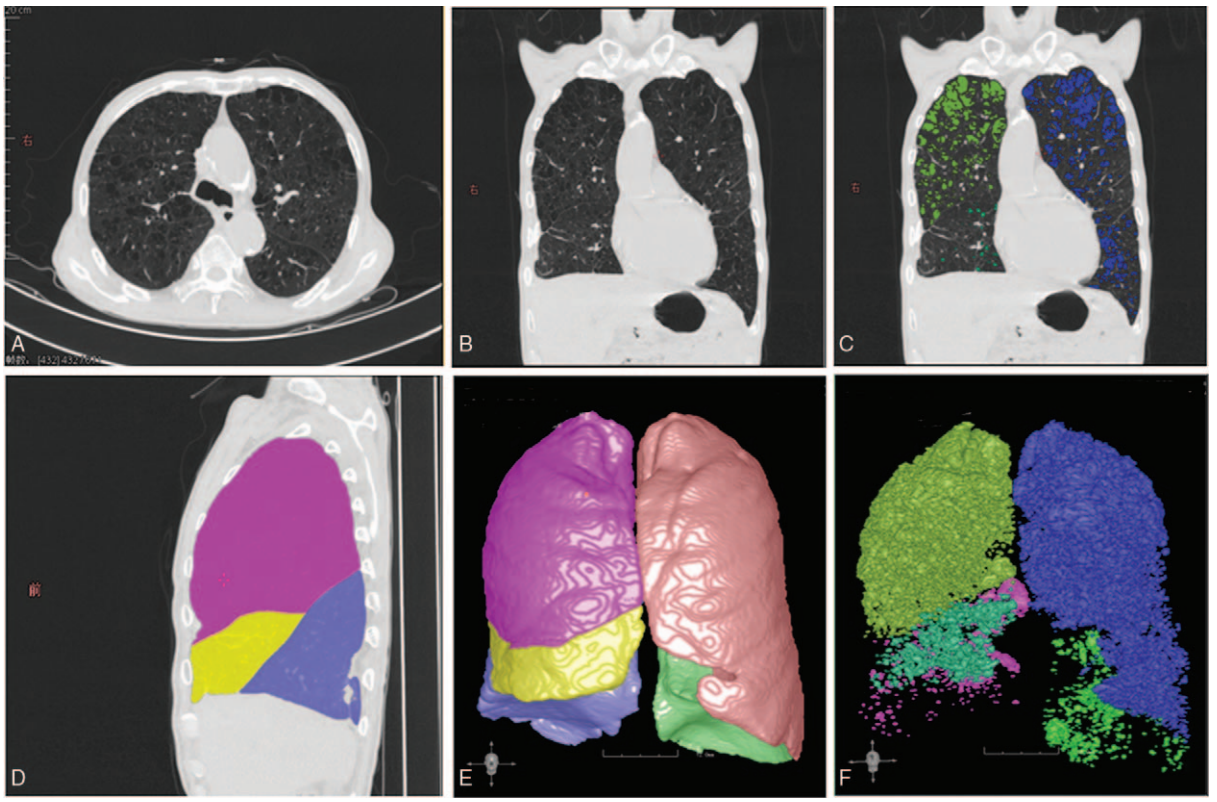

Figure 3. A 3-D surface model of the extent and distribution of emphysema. (A) a transverse view of the original CT image; (B) a coronal view of the original CT image; (C) LAA area is highlighted; (D) automatic segmentation of the pulmonary lobes from chest CT scans based on fissures; (E) 3-D surface model of the pulmonary lobes segmentation; (F) 3-D surface model of the distribution of emphysema in the whole lung and individual lobe (the LAA in individual lobe showing in different color). CT = computed tomography, LAA = density attenuation area.

calculated by averaging all the results automatically obtained in the same generation. Detailed descriptions of these computerized schemes have been reported elsewhere.[16–20]

The segmentation results were reviewed and verified by 2 radiologists. If the software failed to identify the airway tree (>10 generation airways with leakage and/or obstruction in the entire airway tree, or the airway could not be segmented into ≥5 generations in any lobe), these CT datasets were excluded from any further quantitative analysis of the TNV.

2.4. Statistical analysis

All statistical analyses were performed using SPSS 17.0 (SPSS, version 17.0; Chicago, IL). The single-sample K-S and Levene's tests were utilized to test the goodness of fit and the homogeneity of variance of the measurements. The independent samples *t* test was used to test the parameters of the 2 groups which were consistent with normal distribution and homogeneity of variance. Otherwise, the Mann–Whitney *U* test was employed presented as median (min-max). The data were expressed as mean ± standard deviation if they conform normal distribution. And the qualitative variables were presented as absolute numbers and percentages. As we found in experiments, the value of TNV, LAA%950, as well as MLD conformed normal distribution. Therefore, analysis of variance (ANOVA) and independent samples *t* test were used to assess the influence parameters of baseline. The *t* paired test was employed to evaluate the change between the baseline and follow-up results. A P value $<.05$ was considered as significant for all statistical analyses.

Multivariate linear regression analysis was performed with baseline data in order to identify potential predictors of LAA% 950, MLD and TNV. Lung volume, age, weight, height, BMI (kg/m^2), current smoking status, and pack-years were chosen as explanatory variables.

3. Results

3.1. Characteristics of the study population

The characteristics of the subjects included in the study are summarized in Table 1. The smoke history of the current smokers was 27.5 ± 21.4 (pack-years), and 27.1 ± 24.1 (pack-years) of the former smokers. A number of 103 smokers had subsequent visits after 1 year. The subsequent visit time of the current smokers was 1.7 ± 0.9 years after the baseline and 1.8 ± 1.3 years of the former smokers (Table 1).

3.2. QCT results at baseline

The baseline characteristics are presented in Table 1, including the value of TNV, the $LAA\%_{950}$, and MLD in the whole lung. The current smokers had higher whole-lung MLD and lower TNV values than the non-smokers ($P<.05$). But no significant difference of $LAA\%_{950}$ was found between smokers and non-smokers.

Table 1

Characteristics of the participants.

Parameters	Current smoker	Former smoker	Non smoker	*P*
n	287	80	439	
Mean age	59.0±10.3	63.1±8.9	59.6±10.4	n.s.
Smoking history (Pack years)	27.5±21.4	27.1±24.1	—	n.s.
Smoking history >20pack years, n	123 (28.0%)	58 (20.2%)	—	<.05
Smoking cessation time, yr		8.1	—	
Emphysema (LAA%950)	0.9±2.1	1.4±3.0	1.0±1.8	n.s.
TNV	18.0±6.4	17.2±4.2	22.1±6.9	<.01
MLD	−822.3±27.2	−827.8±28.7	−825.6±25.5	<.05

$LAA\%_{950}$ = percentage of low attenuation areas at a threshold of −950, MLD = mean lung density, TNV = total number of pulmonary vessels.

At baseline, multivariate linear regression analysis revealed the following 4 variables to be independent predictors of TNV, in descending order of predictive value as expressed by the standardized regression coefficient: lung volume, weight, current smoker, and pack-year ($P<.001$) (Table 2). The regression model showed a coefficient of determination with $R^2=0.378$. The above-mentioned variables, as well as age, would also significantly predict TNV ($P<.001$), and $LAA\%_{950}$ ($P<.001$).

3.3. Longitudinal changes in QCT

The baseline values of TNV, $LAA\%_{950}$, and MLD and their changes over time are displayed in Table 3. The baseline MLD values did not change during the observation period in both current and former smokers (>0.05). However, TNV declined more rapidly in the current than in the former smokers ($P<.05$), and the extent of emphysema increased faster in the current than in the former smokers ($P<.05$).

4. Discussion

In this study, we report that the extent of emphysema in patients varies considerably and is associated with the differences in their smoking history. The most serious emphysema was more easily represented by older subjects, with a longer cumulative smoking history (pack-years), and by current smokers. Our findings also revealed that the progression of emphysema and pulmonary vessels over time can be detected and correlated with the smoking status. The increased $LAA\%_{950}$ and decreased TNV were associated with the status of current smokers rather than that of former smokers. However, no changes in the mean density were found over the course of the study except for those in the older smokers with a longer cumulative smoking history.

We confirmed the relationship between smoking history and emphysema. In our study, the $LAA\%_{950}$ of smokers was similar to that of non-smokers, with the exception of the over-65-year-old

Table 2

Predictors of QCT parameters based on multiple linear regression analysis.

	MLD				Emphysema (LAA%950)				TNV			
	Coeff.	St. Coeff.	t	*P*	Coeff.	St. Coeff.	*t*	*P*	Coeff.	St. Coeff.	*t*	*P*
Lung volume, mL	−0.23	−0.818	−33.458	<.001	0.001	0.326	8.987	<.001	−0.01	−0.228	−6.378	<.001
Age, yr	−0.220	−0.084	−3.844	<.001	0.014	0.074	2.281	.023				
Weight	0.873	0.315	10.900	<.001	−0.043	−0.212	−4.959	<.001	0.082	0.133	3.150	<.001
Pack years	0.007	0.089	2.986	<.001					−0.002	−0.086	−1.973	<.05
Current smoker									−1.742	−0.168	−3.913	<.001
	$R^2=0.599$				$R^2=0.343$				$R^2=0.378$			

Coeff. regression coefficient.

St. Coeff. Standardized regression coefficient.

LAA%950 = percentage of low attenuation areas at a threshold of −950, MLD = mean lung density, TNV = total number of pulmonary vessels.

Table 3

The changes of pulmonary vessels over time.

Parameters			*t* value	*P* value
Current smoker, n	55			
Parameters	1	2		
LAA-950%whole	0.9±2.4	1.2±2.7	−2.3	<.05
MLD, Hu	−821.0±26.20	−822.9±26.27	0.8	n.s.
TNV, number	17.2±4.2	16.0±3.9	−2.1	<.05
Former smoker, n	48			
Parameters	1	2		
LAA%950	1.0±1.5	1.2±1.7	−1.8	n.s
MLD, Hu	−827.1±31.9	−829.8±27.8	0.7	n.s
TNV, number	17.3±6.1	17.6±5.2	−1.1	n.s

$LAA\%_{950}$ = percentage of low attenuation areas at a threshold of −950, MLD = mean lung density, TNV = total number of pulmonary vessels.

smokers with a smoking history of more than 20 pack-years. The former smokers had a higher extent of emphysema than the current smokers. The interpretation of these results, however, is complex because smoking-related lung inflammation may concurrently increase lung density; meanwhile, emphysema could have been a result of chronic bronchitis. Similar results revealed that the presence and severity of emphysema correlated with smoking history, showing that current smokers had lower $LAA\%_{950}$ than former smokers, as established by QCT.[21–24] The explanation of this phenomenon could be that the inflammation caused by cigarette smoke exposure may affect emphysema by increasing the local lung tissue density in current smokers.[23,24] On the other hand, the more severe emphysema in former smokers may have also been induced by decreasing sputum production or clearing of accumulated soot and tar due to smoking cessation.[24] In our study, we also considered the effect of lung density by comparing the MLD in each sub-group. We found higher MLD values in the former smokers than in the current smokers, which is consistent with the results of the aforementioned earlier study. However, when we a threshold of −910 HU was applied as emphysema quantification, it was easier to obtain the difference in the emphysema extent among the sub-groups.

We also found the following variations in emphysema severity associated with age and smoking history: the higher value of $LAA\%_{950}$ was more easily found in the current over-65-year-old smokers with a smoking history of more than 20 pack-years. Moreover, the higher value of $LAA\%_{950}$ was also related to the age of the smokers older than 65 years. However, no significant deference in $LAA\%_{950}$ was established between smokers with a smoking history of more than 20 pack-years and nonsmokers. These results indicated that both the longer cumulative smoking history and the elder age affected the progress of emphysema. However, because the high lung density induced by persistent smoking, the progress of emphysema might be masked due to the density mask method used to assess the extent of emphysema commonly. The number of vessels in the cross area is one of a parameter we used to assess the difference of baseline between each group. We found that the smokers had less TNV than that in nonsmokers, even when the difference of emphysema was not significant. It suggested that the alteration of vessels may be a sensitive parameter to detecting the pulmonary morphologic changes since the vessel segmentation was mildly influenced by the lung density in our study.[16]

Our second most significant result is the correlation of the smoking status with the pulmonary vessels alteration and the extent of emphysema. The decline in the vascular number was more rapid in the current smokers (additional −1.3 per year, $P<.05$) than in the former smokers (additional −0.2 per year, $P=.6$). The role of cigarette smoke in pulmonary vascular remodeling has been previously discussed in several studies. Previous findings indicated that chronic hypoxia was the cause of pulmonary vascular abnormalities due to the pulmonary vascular changes in patients with COPD.[25] However, other researchers challenged this hypothesis by evidencing that pulmonary vascular abnormalities were also found in smokers without chronic hypoxia.[26] These conclusions are consistent with our results in smokers. The cigarette smoke reached the lung vessels by their inner and outer exposure to cigarette smoke. Then, particles of the cigarette that had reached the alveoli could diffuse from the terminal respiratory bronchioles into the surrounding tissue area while also entering the systemic circulation and endothelial cells.[27,28] This is a possible explanation of the higher likelihood of continuous smoking to cause changes in the pulmonary vessels.

The QCT analysis used in this study is a 3-D computerized technique to automatically identify small pulmonary vessels. The scheme offers a number of advantages, including high accuracy in the vascular segmentation, and easiness of operation. This approach was reported in our previous publication, where we found that the TNV of the fifth bronchus generation was correlated with both the predicted forced expiatory volume in 1 second predicted (FEV1%) predicted ($r=0.556$) and FEV1/FVC ($r=0.538$), as well as the %LAA-950 ($r=-0.738$).[15] Therefore, in the present study, we used the TNV of the fifth generation to detect the alterations in pulmonary vessels.

However, some limitations to this study should be acknowledged. First, the alteration in the pulmonary function was not considered in the present investigation. Second, the alterations in the pulmonary vessels we measured were associated mainly with the number of the vessels in the cross area, rather than the morphological changes. Third, since all smokers observed were males, we only chose males as subjects when setting the criteria for enrollment. Fourth, as a longitudinal observation study, there were too many cases of lost follow-up. Nevertheless, we had a relatively strict follow-up time. During the follow-up period, many patients were defined as "failed follow-up cases" due to various reasons, such as inconsistent scanning parameters or equipment, or a poor image quality, all of which affect the QCT analysis results. Finally, we did not detect the annual change in the pulmonary functional parameters in any group, regardless of its smoking status. In our previous study, we found a relationship between TNV and pulmonary function, namely, that TNV values were strongly correlated with the lung diffusing capacity of the lung for carbon dioxide (DLco, $R=0.770$, $P=.003$), and weak correlations between TNV and the predicted forced expiatory volume in 1 second (FEV1% predicted $=0.556$, $P=.039$), as well as between the forced vital capacity rate of 1 second/forced vital capacity (FEV1/FVC, $R=0.538$, $P=.047$)

In conclusion, by using a fully automated 3-D approach, we found that continuous smoking is more likely to lead to a decrease in pulmonary vessels. This finding confirms that the decline in pulmonary vessel function in smokers can be measured and that it is related to the smoking status.

Author contributions

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Investigation: Junchao Ma, Guangming Ma.
Software: Guangming Ma.
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Writing – review & editing: Nan Yu, Fei Wu.

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