Observational Study

Medicine®

OPEN

Computed tomography quantification of pulmonary vessels in chronic obstructive pulmonary disease as identified by 3D automated approach

Nan Yu, MD[b], Xia Wei, MD[c], Yan Li, MD[a], Lei Deng, MD[a], Chen-wang Jin, MD, PhD[a], Youmin Guo, MD, PhD[a,*]

Abstract

The aim of this study was to investigate the vascular alteration of the whole lung and individual lobes in patients with COPD, and assess the association between pulmonary vessels and the extent and distribution of emphysema as well as pulmonary function by a 3-dimensional automated approach.

A total of 83 computed tomography images from COPD patients were analyzed. Automated computerized approach was used to measure the total number of vessels at the fifth generation. The extent of emphysema (%LAA-950) in the whole lung and individual lobes were also calculated automatically. The association between the vascular number and the extent and distribution of emphysema, as well as the pulmonary function were assessed.

Both the vascular number of fifth generation in the upper lobe and in the lower lobe were significantly negatively correlated with % LAA-950 ($P < 0.05$). Furthermore, there were significant, yet weak correlations between the vascular number and FEV1% predicted ($R = 0.556$, $P = 0.039$) and FEV1/FVC ($R = 0.538$, $P = 0.047$). In contrast, the vascular numbers were strongly correlated with DLco ($R = 0.770$, $P = 0.003$). Finally, the vascular number correlated closer with %LAA-950 of upper lobes than with %LAA-950 of lower lobes.

Pulmonary vessel alteration can be measured; it is related to the extent of emphysema rather than the distribution of emphysema.

Abbreviations: 3-D = three-dimensional, COPD = chronic obstructive pulmonarydisease, CSA = cross-sectional area, CT = computed tomography, DLco = diffusing capacity of the lung for carbon dioxide, FEV1% = predicted forced expiatory volume in one second predicted FEV1/FVC % forced vital capacity rate of one second/forced vital capacity, GOLD = Global Initiative for Obstructive Lung Disease, HI = heterogeneity index, HU = Hounsfield unit, LAA = density attenuation area, LAA = low attenuation area, MAV = mean lumen area of pulmonary vessels, PFTs = pulmonary function tests, TNV = total number of pulmonary vessels.

Keywords: chronic obstructive pulmonary disease, computed tomography, emphysema, pulmonary vessels

1. Introduction

It is important to note that pulmonary vascular remodeling is a prominent characteristic feature of chronic obstructive pulmonary disease (COPD).[1–4] It is likely that the alteration of vessels may reflect the severity of lung dysfunction. A new clinical imaging technology to study COPD is being developed[5–6]; however, only a few approaches focus on the alteration of pulmonary vessels. Computed tomography (CT) has been widely used in routine clinical practice for in vivo investigation of COPD. Previous studies have revealed that small pulmonary arteries are reduced at the subsegmental or subsubsegmental levels in patients with emphysema.[2–4] Other studies also revealed a strong correlation between vascular alteration and lung dysfunction. It reported that the total cross sectional area (CSA) of small vessels of subsubsegmental vessels correlated with the mean pulmonary arterial pressure in severe emphysema patients.[7–9] Mastsuoka et al[10] reported that %CSA $< 5\,mm^2$ was significantly negatively correlated with %LAA-950 ($R = -0.83$, $P < 0.0001$) and was weakly correlated with both FEV1% predicted ($R = 0.29$, $P < 0.0000$) and FEV1/FVC ($R = 0.45$, $P < 0.0001$). In addition, pulmonary vascular alterations can also be found in patients with mild COPD.[11–15]

The quantitative CT method used in those studies is a method based on Hounsfield unit (HU) thresholds to identify pulmonary vessels. The ability of the threshold-based method alone to detect and quantify the vessels is reduced in the presence of co-existing abnormalities depicted on CT images as same density as vessel, such as fibrosis, nodule.

Therefore, in this study, a fully automated three-dimensional (3-D) approach is used to identify small pulmonary vessels in COPD patients. This scheme consists of two primary parts. The

Editor: Mariusz Adamek.

This work was supported by funding from the Public Science and Technology research funds of China (No. 201402013).

The authors report no conflicts of interest.

[a] Department of Radiology, the First Affiliated Hospital of Xi'an Jiaotong University, [b] Department of Radiology, The Affiliated Hospital of Shaanxi University of traditional Chinese Medicine, [c] Department of Respiratory Medicine, The Ninth Hospital of Xi'an, Xi'an, China.

[*] Correspondence: Youmin Guo, 277 Yanta Western Road, Xi'an 710061, China (e-mail: guoyoumin163@sina.com).

Medicine (2016) 95:40(e5095)

Received: 7 January 2016 / Received in final form: 16 August 2016 / Accepted: 15 September 2016

http://dx.doi.org/10.1097/MD.0000000000005095

first is segmentation of the entire lung vascular tree. The second is identification of the number of pulmonary vessels in a cross section. We hypothesized that vascular alteration, as estimated by the 3-D approach, would also be related to the lung dysfunction as defined by both the extent of emphysema as well as pulmonary function measures in COPD patients. Additionally, the distribution patterns of emphysema may be correlated to some extent with clinical implications in COPD patients.[16] Therefore, in this study, we also question whether vascular alteration is related to emphysema heterogeneity in spatial distribution.

2. Methods

2.1. Subjects

The study population was recruited from a lung screening study cohort that took place at a general hospital. Inclusion criteria for enrollment included: being 40 to 75 years' old, smokers with a minimum of a 10-pack-year history of tobacco use. The subjects underwent pulmonary function testing including both ventilation capacity and diffusing capacity measurements and received a chest CT examination. Classifications and diagnoses were made according to the Global Initiative for Obstructive Lung Disease (GOLD) and subjects with the presence of a postbronchodilator FEV1/FVC <0.70 were confirmed as COPD. The classification of severity of airlow limitation in COPD was based on post-bronchodilator FEV1.[17] Subjects who did not meet GOLD criterion were excluded. Other exclusion criteria included: image noise that prevented further image analysis; pleura effusion; and obvious lung parenchymal lesions that prevented image analysis (other than emphysema), such as consolidation, pulmonary nodules, active tuberculosis, or lung destruction (affecting one lobe or more), or interstitial lung disease. Study selection is shown in a flow diagram (Fig. 1).

All subjects were fully informed of the nature of the study, and all gave written consent regarding their participation. Both the study and consent procedure were approved by the local ethical committee of the Xi'an Jiaotong University Institutional Review Board for clinical research. This study was also performed with approval from the Chinese Clinical trials registry center (http://www.chictr.org/en/), and was assigned Registration No: ChiCTR-OCH-14004935.

2.2. Acquisition of thin-section CT examinations

The CT examinations were performed using a 64-detector CT (Philips Gemini TF 64 PET/CT) with subjects holding their breath at full inspiration. The CT datasets were acquired using a helical technique without a contrast medium at the following parameters: 120-kVp tube energy and 200 mA tube current. Images were reconstructed to encompass the entire lung field in a 512 × 512-pixel matrix using "standard" kernel at a 0.625-mm section thickness and a 0.625-mm interval.

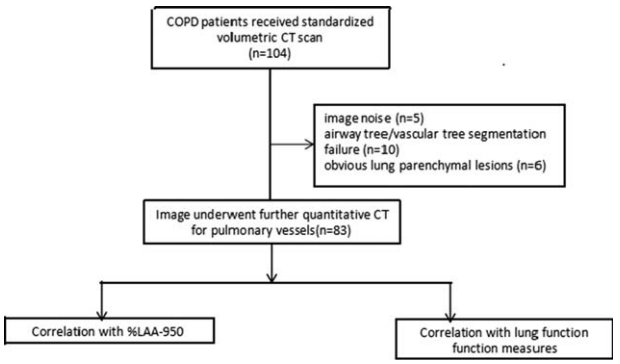

Figure 1. Flow diagram of study population selection.

2.3. Small pulmonary vessels measurement

A 3-D approach was used to measure the small vessels. This scheme consists of 2 primary parts. The first is segmentation of the entire lung vascular tree. The second is identification of total number of vessels (TNV) and mean cross area of vessel (MAV) in each generation (Fig. 2). For the first part, a differential geometric approach is used to automatically segment the vascular tree. The proposed segmentation algorithm consists of 4 basic steps: anatomical structure modeling: to limit the computation space, lung volume segmentation is performed before the vascular tree segmentation.[18] Principal curvature computation: As a concept of geometry, a shape is described of how a surface or a curve "bends" at a given point. And the curvature is defined in terms as the amount of bending and the bending direction. To identify the vascular tree, the schemes estimated the curvatures of the structures in geometric space and exploited both the principal curvatures and the principal directions. Non-airway region filtering: the general shapes of the tissues in lung can be represented by 3 basic categories, spheres (e.g., nodules), planes (e.g., fissures), and cylinders (e.g., vessels and airways). Therefore, knowledge of curvatures should be useful in differentiating these basic shapes. A "puzzle game" procedure acting as a "correction" operation for filtering false identifications. To locate the cross-section, the airway tree was also identified. The segmentation of the airway tree was also performed using the differential geometric approach by changing the signs of the curvatures used for filtering and adjusting the intensity of swept voxels. For the second part, a measurement of vascular number as well as vascular area was taken automatically in certain cross sections that ran at right angles to the labeled airway. 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. Detailed descriptions of these computerized schemes have been reported elsewhere,[18–21] and the vascular segmentation algorithm was shown in Figure 3.

The final segmentation results were inspected and verified by 2 radiologists. If the computerized schemes failed to accurately identify the airway tree (>10 generation airways with leakage and/or obstruction in the entire airway tree,[18] or the airway cannot be segmented into ≥5 generations in any lobe), then these CT datasets were excluded from any further quantitative analysis of the lumen dimensions.

2.4. Quantification of the extent of emphysema and its distribution in different lobes

The extent of emphysema at both the entire lung and each lobe was quantified (Fig. 4). The low attenuation area (LAA) was defined as below a threshold of −950 HU.[22] The percentage of the LAA (% LAA) was used as an index of the extent of emphysema. The % LAA of whole lung and individual lobe was calculated. The whole lung %LAA-950 in whole lung and individual lobe was represented as $\%LAA_{whole}$, $\%LAA_{RUL}$, $\%LAA_{RML}$, $\%LAA_{RLL}$, $\%LAA_{LUL}$, and $\%LAA_{LLL}$. After quantifying the extent of emphysema in the individual lobes, an emphysema heterogeneity

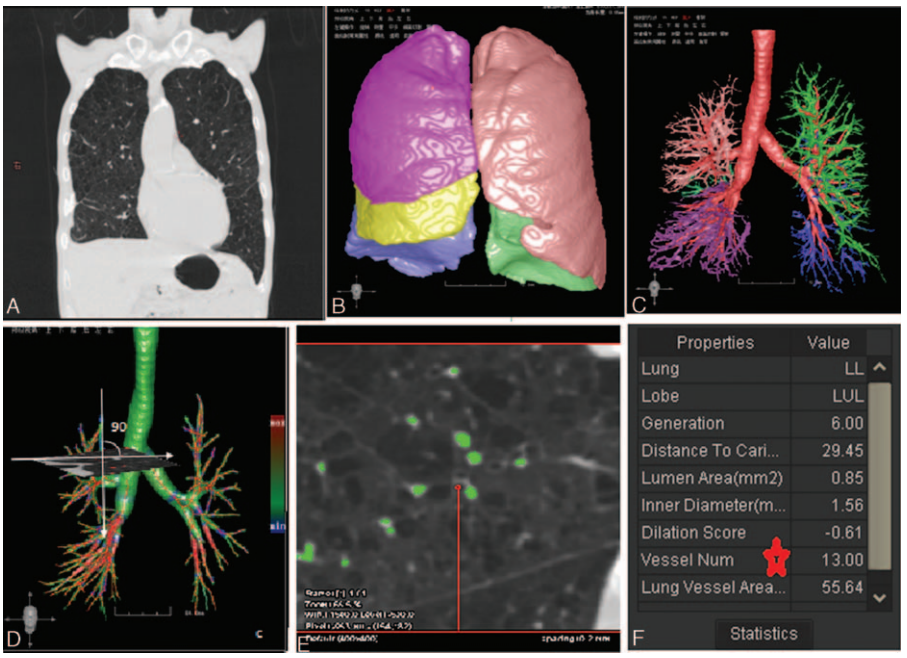

Figure 2. An example of the small vessels segmentation and measurement as well as its 3-D surface model. The original chest CT scan was shown (A); lung volume segmentation is performed before the vascular tree segmentation, and individual lobes were shown in different color (B); vessels tree (shown in different color in each lobe) and airway tree (red) were segmented and represented as 3-D surface model (C); the cross-section was located around the airway, and with the right angle to the airway center line (right upper lobe (D); the vessels in the cross-section were labeled in blue (E); the number of vessels in the cross-section were measured automatically (red star, F).

index (HI) between the upper and lower lobes was computed. The %LAA upper was computed as the summation of the emphysema in the left upper, right upper, and right middle lobes, whereas % LAA lower was the summation of the values for the left lower and right lower lobes. HI is a value ranging from −1 to +1. When emphysema is equally distributed among the lobes or the full extent in the whole lung is <1%, HI is near zero.[2,3]

$$HI\% = \begin{cases} 0\%, & \text{if the total LAA\% is } <1\% \\ \dfrac{\%LAA_{upper} - \%LAA_{lower}}{\%LAA_{upper} + \%LAA_{lower}} \times 100\%, & \text{otherwise} \end{cases}$$

2.5. Pulmonary function tests

Pulmonary function tests were performed after the CT scan. The forced expiatory volume in 1 second predicted (FEV1% predicted), forced vital capacity rate of 1 second/forced vital capacity (FEV1/FVC %), and diffusing capacity of the lung for carbon dioxide (DLco) were each measured after inhalation of a bronchodilator.

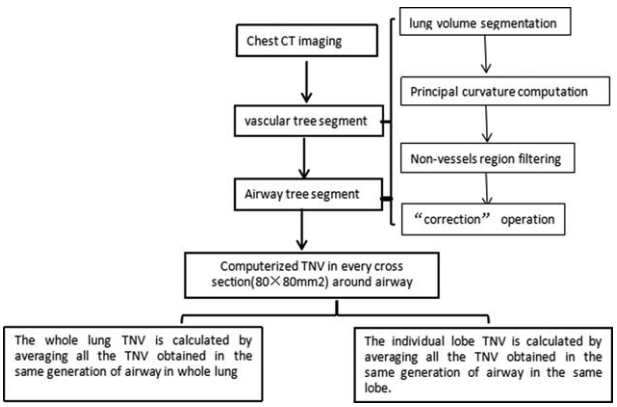

Figure 3. Schematic flowchart of the vascular segmentation algorithm.

2.6. Statistical analysis

Pearson correlation analysis was used to evaluate the relationship between the total number of small pulmonary vessels in the cross-sectional and the extent of emphysema in the whole lung and individual lobes. Correlations of the total number of small pulmonary vessels in the cross-sectional and pulmonary function parameters (FEV1% predicted, FEV1/FVC %, and DLco) were also evaluated by Pearson correlation analysis. Variables were summarized with number or percentage. The emphysema distribution was compared between each group using χ^2 test. Independent t test was used to investigate the number of small vessels in each group. Data were expressed as mean ± standard deviation. For all statistical analyses, a P value <0.05 was considered significant. All statistical analyses were performed using SPSS 17.0 (version 17.0; SPSS Inc, Chicago, IL).

3. Results

3.1. Characteristics of the study population

The involved COPD subject demographics are summarized in Table 1. Twenty-one cases were excluded (n = 5 for image noise, n = 10 for airway tree/vascular tree segmentation failure, n = 6 for obvious lung parenchymal lesions). Finally, this study included 83 patients with a mean age of 68 ± 7 years (55–79). All subjects were classified using GOLD criteria. The values of both TNA and MAV were tested at the fifth and sixth

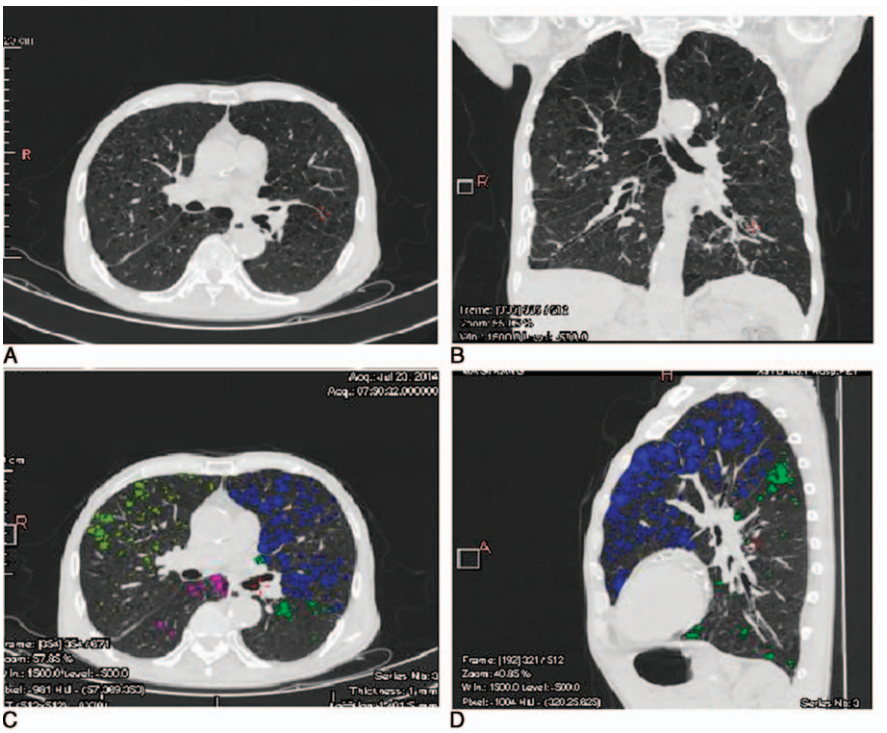

Figure 4. A 3-D surface model of the extent and distribution of emphysema: original CT image in transverse view (A); original CT image in coronal view (B); the LAA area is highlighted in different color in each lobe (C, D). CT = computed tomography, LAA = low attenuation area.

Table 1

Subject demographics.

Parameter	Mean (±SD) or count (%)
Male	80 (96.38%)
Age	68 ± 7
Pack years	56 ± 21
FEV1	1.13 ± 0.63
FEV1% predicted	41.22 ± 19.86
FEV1/FVC%	51.08 ± 13.04
DLCO % predicted	59.69 ± 21.66
Four-category classification	
GOLD 1	0 (0%)
GOLD 2	30 (38.55)
GOLD 3	29 (34.94)
GOLD 4	22 (26.51)
The extent of emphysema	
<10%	44 (53.30%)
10%–30%	22 (26.65%)
30%–50%	17 (19.99%)
>50%	0 (0%)
TNV_{5th} (number)	12.12 ± 4.53
MAV_{5th}, mm	4.92 ± 2.12
Inner diameter of bronchus in fifth generation, mm	1.65 ± 0.42
TNV_{6th} (number)	13.48 ± 3.06
MAV_{6th}, mm^2	4.28 ± 3.43
Inner diameter of bronchus in sixth generation, mm	1.54 ± 0.39

DLCO = diffusing lung capacity of carbon monoxide, FEV1 = forced expiratory volume in 1 s, FVC = functional vital capacity, MAV_{5th} = the mean cross area of vessels in fifth generation, TNV5th = the total number of vessels in fifth generation, TNV_{6th} = the total number of vessels in sixth generation.

generation of bronchus. According to the results, the fifth generation was chosen for assessing vascular alteration because of the MAV $<5\,mm^2$.[10]

3.2. Correlation between small pulmonary vessels and pulmonary function tests

After the pulmonary function tests (PFTs), correlations between the TNV in whole lung and individual lobes and the PFTs results were analyzed. The correlation between TNV and PFTs was similar for whole lung and individual lobe: there were significant (but weak) positive correlations between the value of TNV and both the FEV1% predicted and the FEV1/FVC. However, the value of TNV was strongly positively correlated with DLco (Table 2, Fig. 5)

Table 2

Correlation between value of TNV and pulmonary function test measurements.

	Pulmonary function test measurements		
	FEV1% predicted	FEV1/FVC (%)	DLco%
RUL	0.502	0.527	0.663
RML	0.498	0.512	0.708
RLL	0.551	0.465	0.698
LUL	0.611	0.477	0.771
LLL	0.419	0.533	0.720
Whole lung	0.556	0.538	0.770

LLL = left lower lobe, LUL = left upper lobe, RLL = right lower lobe, RML = right middle lobe, RUL = right upper lobe. All rho values have $P < 0.05$.

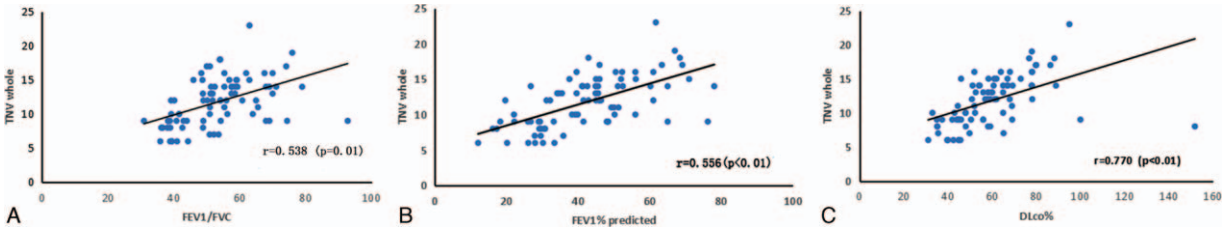

Figure 5. The Correlation between value of TNV and pulmonary function test measurements. TNV = total number of vessels.

3.3. Correlation between small pulmonary vessel and extent and distribution of emphysema

To investigate the association between small pulmonary vessels and the extent and distribution of emphysema, the TNVs of whole lung and individual lobe were tested. The %LAA-950 of the whole lung and individual lobes were also calculated. The TNVs of whole lung and individual lobe were both significantly correlated with the extent of emphysema in the whole lung and individual lobes (Table 3). However, the relationship is closer between each TNV and $\%LAA_{upper}$ than that between TNV and $\%LAA_{lower}$ (Fig. 6).

The emphysema distribution was classified as upper lobe dominant emphysema (HI% >0%, n = 65) and lower lobe dominant emphysema (HI% <0% n = 18). The mean extent of

Table 3

Correlation between value of TNV and the extent of emphysema.

	The extent of emphysema					
	$\%LAA_{RUL}$	$\%LAA_{RML}$	$\%LAA_{RLL}$	$\%LAA_{LUL}$	$\%LAA_{LLL}$	$\%LAA_{whole}$
RUL	−0.735	−0.721	−0.512	−0.730	−0.543	−0.710
RML	−0.712	−0.685	−0.449	−0.692	−0.464	−0.698
RLL	−0.745	−0.703	−0.539	−0.745	−0.639	−0.723
LUL	−0.699	−0.663	−0.612	−0.664	−0.553	−0.812
LLL	−0.728	−0.612	−0.698	−0.782	−0.425	−0.700
Whole lung	−0.712	−0.663	−0.650	−0.752	−0.603	−0.738

LLL = left lower lobe, LUL = left upper lobe, RLL = right lower lobe, RML = right middle lobe, RUL = right upper lobe. All rho values have $P < 0.05$.

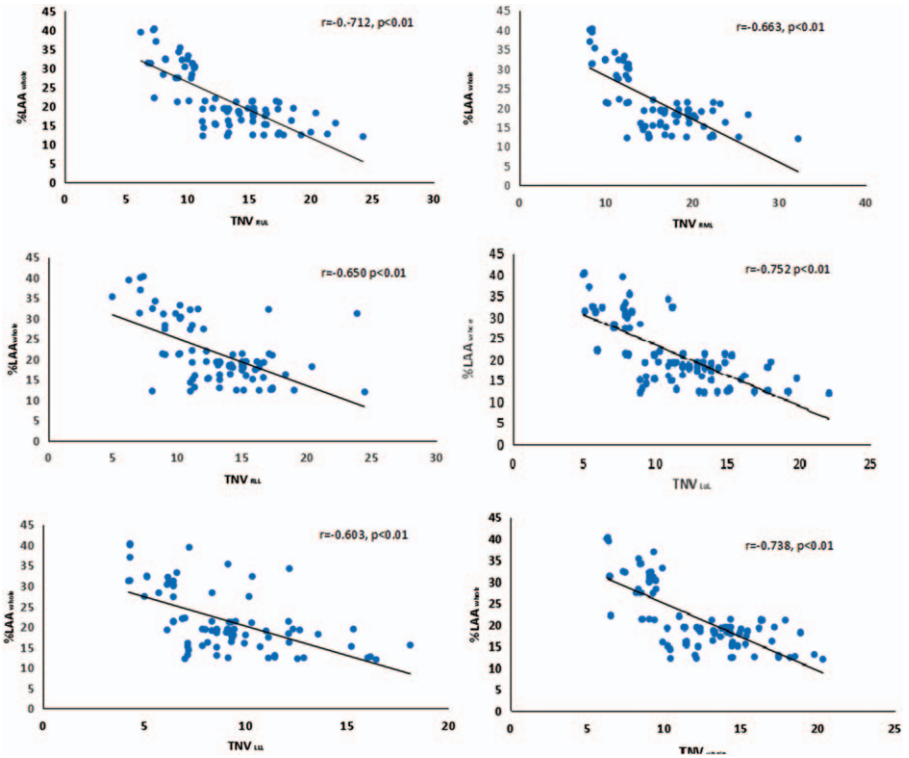

Figure 6. The correlation between value of TNV and the extent of emphysema. LLL = left lower lobe, LUL = left upper lobe, RLL = right lower lobe, RML = right middle lobe, RUL = right upper lobe, TNV = total number of vessels, Whole = whole lung.

emphysema was 21.21 ± 5.6 (%) and 19.45 ± 8.7 (%) separately ($P < 0.05$). The TNV of whole lung was not significantly different between the upper lobe dominant emphysema group and the lower lobe dominant emphysema group (13.05 ± 3.48 vs. 10.72 ± 4.02, $t = -1.05$, $P = 0.40$). In addition, there was not a statistically significant correlation between the HI absolute value and the number of small vessels ($r = -0.314$, $P = 0.275$).

4. Discussion

In the present study, the number of small vessels was found to be significantly correlated with both the FEV1% predicted and FEV1/FVC, but these correlations were weak. In contrast, there was a strong significant correlation between the number of small vessels and DLco. Meanwhile, it was also found that the TNV around the fifth-generation bronchus had a strong negative correlation with %LAA-950 in whole lung and individual lobe. The TNV correlated closer with $\%LAA\text{-}950_{upper}$ than with $\%LAA\text{-}950_{lower}$, regardless of whether the number of small vessels was measured in the upper lobe or the lower lobe. In contrast, there was not a significant correlation between the number of small vessels and HI. These results suggest that vessel alteration is more closely related to the extent of emphysema rather than to airway obstruction. In addition, there was no association between the interlobar heterogeneity of emphysema and the number of small vessels. These results were consistent with some early studies.[24] One study showed a negative correlation between %CSA and the extent of emphysema at subsubsegmental levels in COPD patients.[10]

The CSA method is the first method focused on the alteration of pulmonary vessels in COPD patients. The CSA method is an easy means of evaluating the alteration of small pulmonary vessels using CT images without contrast material. The premise of CSA based on the following facts: vessels can be separated from lung parenchyma and airways by using the threshold technique in a CT image and the size and location of the vessels can be separated by defining the cross-sectional area of vessels ($5-10\,mm^2$ at the subsegmental level and $5\,mm^2$ at the subsubsegmental level). As previously mentioned, although this method can be advantageous, there are also several limitations that should be noted. First, the results are easily impacted by the threshold value. Image noise may increase under a lower threshold. Second, the 2-D representation can locate vessels whose long axis is orthogonal to the scanning plane; however, most vessels do not form in this manner. Therefore, we developed a 3-D computerized scheme to automatically identify small pulmonary vessels. The scheme offers a number of advantages. First, this scheme extracts small vessels structures firstly; thus, no other related tissues are included. Second, with labeled geometric segmented airways, this scheme can easily identify small pulmonary vessels in any location. Third, unlike previous approaches, the cross-section chosen in this study forms a right angle with vessels, not with the scanning plane. Therefore, this method may potentially be suitable for evaluating pulmonary small vascular alteration.

In this study, the TNV of fifth generation of bronchus was chosen as a measure of small pulmonary vessels in this study based on our previous work, which reported the good correlation of TNV with %LAA-950.[25] Additionally, the MAV in fifth generation is $4.92 \pm 2.12\,mm^2$ ($<5\,mm^2$), which accord with the definition of small pulmonary vessels.[10] The correlation of small pulmonary vessels with the extent of emphysema may be explained by numerous previous studies. First, endothelial dysfunction may be easily found in COPD patients,[26–27] and when endothelial dysfunction occurs, the pulmonary arteries may have a diminished ability to dilate, and then, the pulmonary vascular bed decreases.[28] Second, the vasoactive mediator VEGF plays an important role in both vascular alteration and airspace enlargement,[29] and a study found that VEGF and its receptor are significantly reduced in humans with emphysema.[30] In addition, we also investigated the correlation of small pulmonary vessels with the distribution of emphysema owing to the widely recognized importance of emphysema distribution. In this study, the number of small vessels in a cross-section in the right upper lobe was tested and measured, and the number of small vessels in this cross-section had a strong significant correlation with the LAA%-950 of both the whole lung and individual lobe. There was not a significant difference between the number of small vessels in the upper lobe dominant emphysema group and that of the lower lobe dominant emphysema group. Our findings suggest that the decrease in small vessels seen in COPD may result from endothelial dysfunction rather than from passive vascular compression by emphysema. Therefore, it is not necessary to total the number of vessels measured on each cross-section in the individual lobes, and instead, a single measurement can represent the vascular alteration in the whole lung.

Meanwhile, as was previously mentioned, there was a strong correlation between the number of small vessels and the DLco value; however, the correlations between the small vessels and FEV1% predicted and FEV1/FVC were weak. These results may be explained by some previous studies. It has been reported that pulmonary vascular alteration can be found not only in COPD patients but also in smokers without airflow obstruction. In addition, even in mild emphysema without significant ventilation abnormality, a decrease of pulmonary perfusion can also be found.[31] These results suggest that vascular alteration is not only always correlated with abnormal ventilation but also with the extent of emphysema. The severity of COPD is currently graded by FEV1%, but it is often assessed by measuring DLco,[32] which was found to be more related to the number of small vessels in our study. Atsushi et al[33] found that the extent of emphysema was better correlated to DLco than to FEV1%. COPD involves multiple pathophysiological changes that may cause DLco to decrease, such as a reduction in the alveolar surface area, decreased perfusion, uneven ventilation, or inflammation or fibrosis of the alveolar wall impairing alveolar diffusion.[34] Therefore, the results that demonstrate that the number of small vessels is more closely related to DLco than to FEV1.0% may be explained by the fact that DLco better reflects a reduction in the alveolar surface area caused by emphysema as well as decreased perfusion than FEV1% does.

It should be noted, however, that there are some limitations to this study. First, clinical data were not considered in this study. Second, the alterations of pulmonary vessels we measured were mainly on the number changes, but morphological changes should also be pay attention to. Third, all of our results are based on measurements of CT images, so histological study was limited. Thus, further evaluation is necessary.

In conclusion, by using a full automated 3-D approach, it was found that the number of pulmonary vessels in a cross-section better correlates with the extent of emphysema rather than with airflow obstruction. This finding supports the following statements: pulmonary vessel alteration can be measured, it is related to endothelial dysfunction, and it may reflect differences between COPD phenotypes.

References

[1] Estimates for chronic obstructive pulmonary disease, asthma, pneumonia/influenza and other lung diseases are from Chart Book, 2007, Nat. Heart, Lung Blood Inst., 2007.

[2] Cordasco EM, Beerel FR, Vance JW, et al. Newer aspects of the pulmonary vasculature in chronic lung disease. A comparative study. Angiology 1968;19:399–407.

[3] Scarrow GD. The pulmonary angiogram in chronic bronchitis and emphysema. Proc R Soc Med 1965;58:684–7.

[4] Jacobson G, Turner AF, Balchum OJ, et al. Vascular changes in pulmonary emphysema. The radiologic evaluation by selective and peripheral pulmonary wedge angiography. Am J Roentgenol Radium Ther Nucl Med 1967;100:374–96.

[5] Coxson HO, Mayo J, Lam S, et al. New and current clinical imaging techniques to study chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180:588–97.

[6] Barr RG, Bluemke DA, Ahmed FS, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med 2010;362:217–27.

[7] Matsuura Y, Kawata N, Yanagawa N, et al. Quantitative assessment of cross-sectional area of small pulmonary vessels in patients with COPD using inspiratory and expiratory MDCT. Eur J Radiol 2013;82:1804–10.

[8] Matsuoka S, Washko GR, Yamashiro T, et al. Pulmonary hypertension and CT measurement of small pulmonary vessels in severe emphysema. Am J Respir Crit Care Med 2010;181:218–25.

[9] Uejima I, Matsuoka S, Yamashiro T, et al. Quantitative computed tomographic measurement of a cross-sectional area of a small pulmonary vessel in nonsmokers without airflow limitation. Jpn J Radiol 2011;29:251–5.

[10] Matsuoka S, Washko GR, Dransfield MT, et al. Quantitative CT measurement of cross-sectional area of small pulmonary vessel in COPD: correlations with emphysema and airflow limitation. Acad Radiol 2010;17:93–9.

[11] Wright JL, Lawson L, Pare PD, et al. The structure function of the pulmonary vasculature in mild chronic obstructive pulmonary disease. The effect of oxygen and exercise. Am Rev Respir Dis 1983;128: 702–7.

[12] Barbera JA, Riverola A, Roca J, et al. Pulmonary vascular abnormalities and ventilation perfusion relationships in mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;149:423–9.

[13] Santos S, Peinado VI, Ramirez J, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. Eur Respir J 2002;19:632–8.

[14] Peinado VI, Barbera JA, Abate P, et al. Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:1605–11.

[15] Peinado VI, Barbera JA, Ramirez J, et al. Endothelial dysfunction in pulmonary arteries of patients with mild COPD. Am J Physiol 1998;274: L908–13.

[16] Castaldi PJ, San Jose' Este' par R , Mendoza CS, et al. Distinct quantitative computed tomography emphysema patterns are associated with physiology and function in smokers. Am J Respir Crit Care Med 2013;188:1083–90.

[17] Marc Decramer. Global strategy for the diagnosis, management, and prevention of chronic obstructive obstructive pulmonary disease (updated 2016), http://goldcopd.org/2016.2.

[18] Pu J, Fuhrman C, Good WF, et al. A differential geometric approach to automated segmentation of human airway tree. IEEE Trans Med Imaging 2011;30:266–78.

[19] Pu J, Roos J, Yi CA, et al. Adaptive border marching algorithm: automatic lung segmentation on chest CT images. Comput Med Imaging Graph 2008;32:452–62.

[20] Pu J, Leader JK, Zheng B, et al. A computational geometry approach to automated pulmonary fissure segmentation in CT examinations. IEEE Tran Med Imaging 2009;28:710–9.

[21] Pu J, Zheng B, Leader JK, et al. Gur D Pulmonary lobe segmentation in CT examinations using implicit surface fitting. IEEE Trans Med Imaging 2009;28:1986–96.

[22] Wang Z, Gu S, Leader JK, et al. Optimal threshold in CT quantification of emphysema. Eur Radiol 2013;23:975–84.

[23] Ju J, Li R, Gu S, et al. Impact of emphysema heterogeneity on pulmonary function. PLOS One 2014;9:e113320.

[24] Petrache I, Natarajan V, Zhen L, et al. Ceramide up regulation causes pulmonary cell apoptosis and emphysema-like disease in mice. Nat Med 2005;11:491–8.

[25] Yu N, Jin C, Li Y, et al. The pulmonary vascular alteration in COPD as determined by quantitative CT measurement: a two-year longitudinal study. Insights into Imaging 2015;6:159–445.

[26] McAllister DA, Maclay JD, Mills NL, et al. Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;176:1208–14.

[27] Mills NL, Miller JJ, Anand A, et al. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. Thorax 2008;63:306–11.

[28] Dinh-Xuan AT, Higenbottam TW, Clelland CA, et al. Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. N Engl J Med 1991;324:1539–47.

[29] Kasahara Y, Tuder RM, Taraseviciene-Stewart L, et al. Inhibition of VEGF receptors causes lung cell apoptosis and emphysema. J Clin Invest 2000;106:1311–9.

[30] Kasahara Y, Tuder RM, Cool CD, et al. Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. Am J Respir Crit Care Med 2001;163:737–44.

[31] Noma S, Moskowitz GW, Herman PG, et al. Pulmonary scintigraphy in elastaseinduced emphysema in pigs. Correlation with high-resolution computed tomography and histology. Invest Radiol 1992;27:429–35.

[32] Gould GA, Redpath AT, Ryan M, et al. Lung CT density correlates with measurements of airflow limitation and the diffusing capacity. Eur Respir J 1991;4:141–6.

[33] Nambu A, Zach J, Schroeder J, et al. Relationships between diffusing capacity for carbon monoxide (DLCO), and quantitative computed tomography measurements and visual assessment for chronic obstructive pulmonary disease. Eur J Radiol 2015;84:980–5.

[34] Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26:720–35.