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

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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 pulmonary disease, CSA = cross-sectional area, CT = computed tomography, DLco = diffusing capacity of the lung for carbon dioxide, FEV1% = predicted forced expiratory 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). 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; 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. 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. Matsuoka et al reported that %CSA <5mm² 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.

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
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. 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 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 airflow 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 64PET/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 200mA tube current. Images were reconstructed to encompass the entire lung field in a 512 x 512-pixel matrix using “standard” kernel at a 0.625-mm section thickness and a 0.625-mm interval.

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.[16] 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 scheme 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 %LAAin whole %LAAinLUL, %LAAinLLL, %LAAinRUL, and %LAAinLLL. After quantifying the extent of emphysema in the individual lobes, an emphysema heterogeneity...
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.\(^{23}\)

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

2.5. Pulmonary function tests

Pulmonary function tests were performed after the CT scan. The forced expiratory 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.

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 \(\chi^2\) 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
generation of bronchus. According to the results, the fifth generation was chosen for assessing vascular alteration because of the MAV < 5 mm².[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 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%)                  |

TNV₅th (number) 12.12 ± 4.53
MAV₅th, mm 4.92 ± 2.12
Inner diameter of bronchus in fifth generation, mm 1.65 ± 0.42

TNV₆th (number) 13.48 ± 3.06
MAV₆th, mm² 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, MAV₅th = the mean cross area of vessels in fifth generation, TNV₅th = the total number of vessels in fifth generation, TNV₆th = the total number of vessels in sixth generation.

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

| 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      | −0.529      | −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 5. The Correlation between value of TNV and pulmonary function test measurements. TNV = total number of vessels. 

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 $21.21 \pm 5.6$ (%) and $19.43 \pm 8.7$ (%) 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 ($13.05 \pm 3.48$ vs. $10.72 \pm 4.02$, $r = -1.05$, $P = 0.40$). 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-950$_{upper}$ than with %LAA-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 airflow 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.\textsuperscript{[24]} One study showed a negative correlation between %CSA and the extent of emphysema at subsubsegmental levels in COPD patients.\textsuperscript{[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 ($5-10 \text{mm}^2$ at the subsegmental level and $5 \text{mm}^2$ 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.\textsuperscript{[25]} Additionally, the MAV in fifth generation is $4.92 \pm 2.12 \text{mm}^2$ ($<5 \text{mm}^2$), which accord with the definition of small pulmonary vessels.\textsuperscript{[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,\textsuperscript{[26-27]} and when endothelial dysfunction occurs, the pulmonary arteries may have a diminished ability to dilate, and then, the pulmonary vascular bed decreases.\textsuperscript{[24]} Second, the vasoactive mediator VEGF plays an important role in both vascular alteration and airspace enlargement,\textsuperscript{[28]} and a study found that VEGF and its receptor are significantly reduced in humans with emphysema.\textsuperscript{[30]} In addition, we also investigated the correlation of small pulmonary vessels with the distribution of emphysema relating 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.\textsuperscript{[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,\textsuperscript{[32]} which was found to be more related to the number of small vessels in our study. Atushi et al.\textsuperscript{[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.\textsuperscript{[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.
