Pulmonary vessel volume can help to differentiate fibrotic lung diseases

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ABSTRACT

Objectives: Idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), and chronic hypersensitivity pneumonitis (CHP) are diffuse fibrosing lung diseases that are sometimes difficult to differentiate by only visual evaluation of CT images. We aimed to find if pulmonary vessel volume (PVV), a new quantitative CT measure, can help to differentiate these diseases at the time of diagnosis.

Methods: We retrospectively measured PVV values of IPF, NSIP, and CHP patients diagnosed within the last five years in our institution, by using their CT images at the time of diagnosis. We used CALIPER-technology (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) for the quantification of CT images. We compared the PVV values of disease groups by the Kruskal-Wallis test and performed ROC curve analysis to evaluate the ability of PVV to differentiate these diseases.

Results: We measured the PVV values of 152 patients, 113 of them were diagnosed with IPF, 16 with NSIP, and 23 with CHP. The PVV value of the NSIP group was significantly lower than that of both IPF ($p = 0.028$) and CHP ($p = 0.013$) groups. However, there was no significant difference between IPF and CHP groups ($p = 0.924$). Selected cut-off values of PVV were found to differentiate NSIP from IPF with a specificity of 88%, and NSIP from CHP with a specificity of 91%.

Conclusions: PVV measured by CALIPER at the time of diagnosis can help to differentiate NSIP from both IPF and CHP.

Keywords: Hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, non-specific interstitial pneumonia, pulmonary vessel volume, quantitative computed tomography

Idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), and chronic hypersensitivity pneumonitis (CHP) are diffuse fibrosing lung diseases that may show some overlapping features on computed tomography (CT) images which may sometimes make it very difficult to differentiate them [1]. Visual evaluation of CT features is prone to subjectivity and sometimes a considerable inter-observer variation is seen between the opinions of even expert thoracic radiologists [2,3]. Automated computer-based quantification of parenchymal CT findings of these diseases may help to differentiate them [4].

Pulmonary vessel volume (PVV), a novel quantitative computed tomographic (QCT) parameter that is measured by using volumetric CT data, is the total CT volume of intraparenchymal arteries and veins, including their walls. It excludes extraparenchymal (hilar and mediastinal) portions of the vessels. PVV is a
purely computer-based parameter that cannot be evaluated by the human eye. CT scans obtained without intravenous contrast administration are used and intraparenchymal vessels, that are visible and tractable as connected tubular structures on CT slices, are automatically detected by a computer and then the total volume of these tubular structures is calculated [3]. Instead of the “PVV” term, it is sometimes alternatively mentioned as “volume of pulmonary vessel-related (or vascular-related) structures”.

PVV was reported to be a good measure of disease severity and a strong predictor of mortality in some interstitial lung diseases, in addition to its significant correlations with pulmonary function indices [4-13]. It was shown that increased PVV is strongly linked to the extent of IPF and PVV value is a very good independent CT-derived parameter that predicts pulmonary function tests, and also it is a very powerful predictor of mortality [5, 10]. In systemic sclerosis patients, PVV was reported to increase progressively in follow-up chest CT scans [7]. It was found that PVV is an independent predictor of mortality in patients with connective tissue disease-related interstitial lung disease [8]. In CHP patients, a higher PVV value was reported to indicate a more aggressive disease and an IPF-like outcome [9].

In this study, we aimed to find if we can use PVV value to differentiate IPF, NSIP, and CHP at the time of diagnosis.

METHODS

In this retrospective study, we investigated all consecutive IPF, NSIP, and CHP patients diagnosed by our Institutional Council of Interstitial Lung Diseases from 2017 to 2021. We extracted a total of 242 patients from the hospital records with final diagnoses of 169 IPF, 48 CHP, and 25 NSIP. Those patients diagnosed without referral to the Council were not included. This multidisciplinary council consisted of a radiologist, a pathologist, a thoracic surgeon, and at least three respiratory clinicians, reviewed the clinical and chest CT findings of all patients that were referred to the council because of either a diagnostic difficulty and/or a request of biopsy-decision of the council that was mandatory in our institution for surgical lung biopsies of suspected interstitial lung disease patients. For all three diseases, the council established a final diagnosis after a multidisciplinary evaluation of all clinical and CT findings of patients, and pathological findings if existed. The American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guideline criteria were used by the council to establish IPF diagnoses.

To get rid of any diagnostic uncertainties, we excluded those patients without a surgical lung biopsy. Therefore, 17 patients were excluded from the CHP and 9 from the NSIP group. But, since the ATS/ERS/JRS/ALAT Guideline, used by the Council, stated that, in IPF diagnosis, “surgical lung biopsy is not required for patients with a CT pattern consistent with usual interstitial pneumonia (UIP)”, non-biopsied patients were not excluded from the IPF group.

For quantification of the lung parenchyma, we included only those CT scans performed in our institution within a period of three months before the diagnosis, obtained without intravenous contrast administration and by volumetric technique with a slice-thickness of 1 mm. Since they do not comply with the CT criteria mentioned above, 49 patients were excluded from the IPF, and 5 from the CHP group.

All CT scans were performed by using the same acquisition parameters (by using Philips Ingenuity 128 slice CT scanner, with a tube voltage of 120 kV, a pitch of 1, a rotation time of 0.4 seconds, and a reconstruction thickness of 1 mm).

From the axial image series of patients, only those with a relatively “soft” reconstruction filter (kernel B) were used for quantification. CT images with this kernel are recommended to be used in quantification because this kind of so-called “soft” or “neutral” kernels have relatively low signal-noise ratios, provide the most accurate CT attenuation values, and hence they are better than other kernels for quantification purposes [14, 15].

PVV measurements were performed by using a software called Lung Texture Analysis (Imbio, Minneapolis, Minnesota, USA) (this is an ‘investigational use only’ software in the USA). This software is based
on the CALIPER-technology (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) developed by the Mayo Clinic. For quantification purposes, this software extracted (segmented) only the parenchymal areas of both lungs automatically. Occasionally this segmentation process has been terminated by the software with a “segmentation fault” message, mainly as a result of motion artifacts or gastric/colonic air content just beneath the diaphragm that confuses the computer to segment the air as the lung parenchyma. The software reported segmentation fault for 6 of the patients in the IPF and 2 of the patients in the CHP group and these patients were excluded from the study.

For each patient, following the CALIPER’s segmentation sessions, all segmented axial images were reviewed by a 20-year experienced chest radiologist to ensure that the entire lung parenchyma was segmented correctly. In two of the patients (one in the IPF and another one in the CHP group), the radiologist detected that only one of the two lungs was segmented by the software, and these two patients were excluded from the study.

After segmenting the lungs, the software then segmented the intrapulmonary vessels by using a mathematical method of an optimized multi-scale tubular structure enhancement filter that determines the likelihood of a voxel belonging to a vessel as a dense tubular structure [3]. Then the absolute intrapulmonary vessel volume is measured by the computer. To make more reliable comparisons between patients with different body size parameters (such as height, weight, and body surface area), we divided this absolute vessel volume by the total lung volume (CALIPER-derived) and obtained a “normalized” PVV value as a percentage of the total lung volume.

This study was approved by our Institutional Review Board and written informed consent was waived because of its retrospective nature.

**Statistical Analysis**

SPSS Statistics software (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY) was used to perform a non-parametric Kruskal-Wallis test to make PVV and age comparisons between disease groups. This non-parametric test was preferred because of the small numbers of patients in two of the three disease groups (CHP and NSIP), and the lack of normal distribution of PVV values in the CHP group and age values in IPF and NSIP groups. The normality of distributions were evaluated by using histograms and Q-Q plots. All significance values have been adjusted by the Bonferroni correction and a p-value less than 0.05 was considered to be statistically significant. Fisher’s exact test was used to compare the gender proportions of the groups. The diagnostic performance of PVV in distinguishing IPF, NSIP, and CHP was assessed by using Receiver Operating Characteristic (ROC) curve analysis and optimal cut-off points were determined by using the Youden index.

**RESULTS**

The PVV measurements were performed on a total number of 152 patients in this study; 113 of them were diagnosed with IPF, 23 with CHP, and 16 with NSIP.

The demographic data of the patients are summarized in Table 1. The median age of the IPF group was higher than that of both CHP ($p = 0.005$) and NSIP groups ($p = 0.002$) and there was no significant differ-

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
<th>Median age (IQR)</th>
<th>Male, n (%)</th>
<th>Female, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF</td>
<td>113</td>
<td>61 (57-69)</td>
<td>92 (81.4)</td>
<td>21 (18.6)</td>
</tr>
<tr>
<td>CHP</td>
<td>23</td>
<td>52 (32-62)</td>
<td>10 (43.5)</td>
<td>13 (56.5)</td>
</tr>
<tr>
<td>NSIP</td>
<td>16</td>
<td>51 (34-62)</td>
<td>11 (68.8)</td>
<td>5 (31.2)</td>
</tr>
<tr>
<td>Total</td>
<td>152</td>
<td>61 (51-67)</td>
<td>113 (74.3)</td>
<td>39 (25.7)</td>
</tr>
</tbody>
</table>

IPF = idiopathic pulmonary fibrosis, CHP = chronic hypersensitivity pneumonitis, NSIP = non-specific interstitial pneumonia, IQR = interquartile range
Fig. 1. The box-and-whisker chart showing the PVV distributions in the IPF, CHP, and NSIP patient groups with the boxes representing the interquartile ranges, the horizontal lines in the boxes representing the median PVV values, and the whiskers representing the minimum-maximum ranges. PVV = pulmonary vessel volume, IPF = idiopathic pulmonary fibrosis, CHP = chronic hypersensitivity pneumonitis, NSIP = non-specific interstitial pneumonia.

Fig. 2. ROC curve showing the ability of PVV to differentiate NSIP from IPF. AUC is 0.70 (95% confidence interval: lower bound 0.56- upper bound 0.84). PVV = pulmonary vessel volume, AUC = area under the curve, ROC = receiver operating characteristic, NSIP = non-specific interstitial pneumonia, IPF = idiopathic pulmonary fibrosis.
ence between the ages of the CHP and NSIP groups ($p = 1$). Regarding the gender distribution, there was no significant difference between the NSIP group and the other two groups. But the gender proportions were significantly different in the IPF and CHP groups ($p < 0.001$) with male dominance in the IPF group.

The PVV values of the three disease groups, expressed as median (1st quartile - 3rd quartile), were as follows: 4.83% (3.24-6.55) in the IPF, 5.58% (3.81-6.41) in the CHP, and 2.86% (2.32-5.38) in the NSIP group (Fig. 1). There was no significant difference between the PVV values of the IPF and CHP groups ($p = 0.924$). However, the mean PVV value of the NSIP group was significantly lower than that of both IPF ($p = 0.028$) and CHP ($p = 0.013$) groups.

To evaluate the ability of PVV to distinguish NSIP from IPF and CHP we obtained Receiver Operating Characteristic (ROC) curves. The area under curve (AUC) value for the ROC curve showing the ability of PVV to differentiate NSIP from IPF (Fig. 2) was 0.70, and NSIP from CHP (Fig. 3) was 0.78. We determined optimal cut-off points by using the maximum Youden index. A PVV cut-off value of 2.7% was found to differentiate NSIP from IPF with a specificity of 88%, with a sensitivity of 50%. A PVV cut-off value of 3.1% was found to differentiate NSIP from CHP with a specificity of 91%, with a sensitivity of 56%.

**DISCUSSION**

IPF is the most common and lethal form of idiopathic interstitial pneumonia. CHP and NSIP are two of the most common, and also usually the most difficult to differentiate, mimics of IPF [16]. QCT measurements can detect quantitative differences between some diffuse parenchymal lung diseases and hence may help to differentiate them [4, 17]. To our knowledge, this is the first study comparing PVV values of IPF, NSIP, and CHP patient groups in a single study. We found that the PVV is significantly higher in the IPF and CHP patients compared to the NSIP. But there was no significant difference between the IPF and CHP groups regarding the PVV values.

PVV is a relatively new QCT entity. PVV term is used to denote the total volume of intraparenchymal arteries and veins of lungs, including their walls and...
lumens, and it excludes the hilar and mediastinal portions of these vessels. Quantitative evaluation of PVV on CT images by radiologists’ eyes without using quantifying software seems to be impossible. Hence, PVV is a “QCT-only” entity.

PVV value is usually expressed as a percentage of total pulmonary volume and therefore it is sometimes mentioned as “normalized pulmonary vessel volume”.

In IPF patients PVV is correlated with the severity of fibrosis, it is a strong predictor of survival, its increase indicates poor prognosis and it shows a significant difference between treated and untreated patients with antifibotics [6, 10, 11, 18, 19]. It was shown that the extent of lung fibrosis (fibrotic score) and PVV score were associated with the diffusing capacity of the lungs for carbon monoxide (DLCO) in IPF patients [20]. PVV is reported to be the most predictive of IPF progression and mortality which is independent of spirometric parameters [6, 11, 21]. PVV was also reported to predict mortality better than physiological indices and visual CT scores in patients with connective tissue disease-related interstitial lung disease [8]. Jacob et al. [22] demonstrated that CHP patients with a higher CALIPER-PVV had the more aggressive disease and worse prognosis. CHP patients with a PVV value above 6.5% were reported to have a similar clinical course and survival to IPF [9].

Jacob et al. [10] postulated that increased PVV in IPF patients can be related to the following reasons: i) Diversion of the blood flow from fibrotic areas to relatively spared lung regions, resulting in dilation of vessels and therefore an increased PVV, ii) Increased negative pressure during inspiration, due to increased lung stiffness in IPF patients, that result in the dilation effect on blood vessels, iii) Increased pleuro-parenchymal and bronchial-pulmonary arterial anastomosis that was previously described in histological lung specimens of IPF patients [23, 24].

In addition to the above explanations, Puxeddu et al. [19] stated one more explanation that vascular alterations might be the first pathological changes in the IPF lung on which fibrosis might build up later on, by an unclear mechanism.

Jee et al. [25] stated that strong correlation of PVV with the extent of interstitial lung disease but not with right ventricular systolic pressure was suggesting that PVV may reflect interstitial damage rather than pulmonary hypertension severity, and hence might provide an additional measure of disease severity not quantifiable on visual assessment.

Chung et al. [17] reported that vessel-related structures detected by CALIPER can differentiate pathological UIP cases from others in those patients with a non-IPF diagnosis CT category.

Crews et al. [4] compared CALIPER’s PVV values between 58 IPF, 67 interstitial pneumonia with autoimmune features (IPAF), 42 connective tissue disease (CTD), and 58 CHP patients, and reported that pulmonary vessel-related structure volumes in IPF and IPAF were greater than those of CTD and CHP. In contrast to their results, a comparison of the PVV values between the IPF and CHP groups yielded no significant difference in our study. This incompatibility between our results and theirs may be just because these two studies compared different entities. They used the absolute PVV values measured by the CALIPER and did not normalize these values by the total lung volume, and as they pointed out in their manuscript since the absolute value could be affected by the body size, it was not quite appropriate for comparison of different patient groups. We divided the total intrapulmonary vessel volume by the total lung volume and obtained the PVV value as a percentage of the lung volume. In other words, we “normalized” our PVV value by the lung size, and hence, minimize the effect of the body size of the patient. Another difference between our study and theirs is that they included CT scans performed within one year of diagnosis, whereas we included only CT scans taken within three months of diagnosis, which can better reflect the PVV value at the time of diagnosis.

We found that a PVV cut-off value of 2.7% could differentiate NSIP from IPF with a specificity of 88%, and similarly a PVV cut-off value of 3.1% could differentiate NSIP from CHP with a specificity of 91%. Therefore, we think that, when it is difficult to differentiate NSIP from IPF or CHP by visual evaluation of parenchymal CT findings, PVV may help to differentiate them at the time of diagnosis. Crews et al. similarly reported that increased PVV seems to be associated with a diagnosis of some interstitial lung diseases [4].

Limitations

Our study has some limitations: i) There were relatively small numbers of patients in NSIP and CHP...
groups. ii) Our institution is a tertiary referral center for lung diseases, and hence, our results may not generalize to the community setting. iii) Only those “difficult to diagnose” patients referred to our Institutional Council of Interstitial Lung Diseases were included in this study and hence our results may not be equally valid for more “typical” cases. iv) Not only a limitation of our study, but also a limitation of quantitative CT measurements is that, since quantitation algorithms as well as scanning and reconstruction parameters, such as slice thickness, reconstruction kernel, pixel size, and CT scanner used, can make radiomics features differ significantly [26], mean PVV values may differ in different institutions using different CT scanning parameters, and our institution’s threshold PVV values may not be valid for others.

We think that further studies should be done with larger series to show the role of pulmonary vessel volume and other quantitative CT parameters in differential diagnosis of interstitial lung diseases. As Weatherley et al. [27] emphasized, machine learning or deep learning techniques may help to find some features that are not perceptible nor reproducibly assessed by humans.

CONCLUSION

In challenging cases, PVV measured by the CALIPER may help to differentiate NSIP from both IPF and CHP, in both of which PVV values at the time of diagnosis are greater than that in NSIP. More research is needed to obtain institution independent thresholds for PVV measurements in interstitial lung diseases.

Authors’ Contribution

Study Conception: AG; Study Design: AG; Supervision: AG; Funding: N/A; Materials: AG; Data Collection and/or Processing: AG; Statistical Analysis and/or Data Interpretation: AG; Literature Review: AG; Manuscript Preparation: AG and Critical Review: AG.

Conflict of interest

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