Pulmonary Hypertension and Computed Tomography Measurement of Small Pulmonary Vessels in Severe Emphysema

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Rationale: Vascular alteration of small pulmonary vessels is one of the characteristic features of pulmonary hypertension in chronic obstructive pulmonary disease. The in vivo relationship between pulmonary hypertension and morphological alteration of the small pulmonary vessels has not been assessed in patients with severe emphysema.

Objectives: We evaluated the correlation of total cross-sectional area of small pulmonary vessels (CSA) assessed on computed tomography (CT) scans with the degree of pulmonary hypertension estimated by right heart catheterization.

Methods: In 79 patients with severe emphysema enrolled in the National Emphysema Treatment Trial (NETT), we measured CSA less than 5 mm\(^2\) (CSA\(_{<5}\)) and 5 to 10 mm\(^2\) (CSA\(_{5–10}\)), and calculated the percentage of total CSA for the lung area (%CSA\(_{<5}\) and %CSA\(_{5–10}\), respectively). The correlations of %CSA\(_{<5}\) and %CSA\(_{5–10}\) with pulmonary arterial mean pressure (Ppa) obtained by right heart catheterization were evaluated. Multiple linear regression analysis using Ppa as the dependent outcome was also performed.

Measurements and Main Results: The %CSA\(_{<5}\) had a significant negative correlation with Ppa (r = -0.512, P < 0.0001), whereas the correlation between %CSA\(_{5–10}\) and Ppa did not reach statistical significance (r = -0.196, P = 0.083). Multiple linear regression analysis showed that %CSA\(_{<5}\) and diffusing capacity of carbon monoxide (D\(_{CO}\)) % predicted were independent predictors of Ppa (r\(^2\) = 0.541); %CSA\(_{<5}\) (P < 0.0001), and D\(_{CO}\) % predicted (P = 0.022).

Conclusions: The %CSA\(_{<5}\) measured on CT images is significantly correlated to Ppa in severe emphysema and can estimate the degree of pulmonary hypertension.

Keywords: chronic obstructive pulmonary disease; emphysema; pulmonary hypertension; CT

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Pulmonary hypertension is an important predictor of mortality in chronic obstructive pulmonary disease (COPD) (1–3). Various factors, including endothelial dysfunction, inflammation, and hypoxia, have been recognized as potential contributors to the development of secondary pulmonary hypertension in emphysema, but its pathogenesis has not been fully clarified. Nevertheless, it is generally recognized that vascular remodeling of small pulmonary arteries is an essential morphological feature of pulmonary hypertension; narrowing and diminution of the small pulmonary vessels have been shown on conventional angiography in emphysema (4–6). However, to our knowledge, the in vivo relationship between pulmonary hypertension and the magnitude of small pulmonary vessel morphological change has not been quantitatively assessed in severe emphysema.

A recent histological study suggested that vascular remodeling leads to reduced distensibility of small pulmonary vessels and that this remodeling is closely related to pulmonary hypertension (7). Such a decrease in distensibility of small pulmonary vessels may lead to increased pulmonary vascular resistance and elevated pulmonary vascular pressure. Therefore, we hypothesized that measurements of the total cross-sectional area of small pulmonary vessels (CSA) using noncontrast chest computed tomography (CT) scans (8) could be used to show a correlation of the relationship with the degree of pulmonary hypertension in patients with emphysema. The principal purpose of this study was to evaluate the relationship between the total CSA on CT images and the degree of pulmonary hypertension in patients.
with COPD. For comparison, we also evaluated the correlation of mean pulmonary arterial pressure (Ppa) with other variables previously described useful in diagnosing pulmonary hypertension, such as the diameter of the main pulmonary artery (MPAD) measured by CT scan. Additional multiple linear regression analysis using Ppa as the dependent outcome was also performed to evaluate the impact of the total CSA on CT images.

**METHODS**

**Subjects**

We retrospectively evaluated patients who were screened for participation in the National Emphysema Treatment Trial (NETT) at three institutions. The NETT was a prospective, multicenter, randomized, controlled study comparing optimal medical therapy to lung volume reduction surgery for the treatment of severe emphysema. Inclusion criteria for the NETT have been described elsewhere (9). In 3 of the 17 clinical centers, subjects underwent measurements of central pulmonary hemodynamics during right heart catheterization (RHC). Results have been reported elsewhere (10). All data reported were collected before randomization. The institutional review boards at each participating institution as well as the sponsor (National Institutes of Health) approved the main trial and the substudies. In accordance with the policies at each participating institution, all patients signed informed consent for the main trial and for each of the individual substudies. Exclusion criteria included (1) obvious abnormal lung parenchymal lesions other than emphysema, (2) pleural effusion or cardiomegaly that suggested cardiac failure, and (3) excessive image noise that prevented image analysis.

Pulmonary function tests (PFTs) as defined in NETT were performed using American Thoracic Society guidelines (11–14). PaO2 was measured with subjects breathing room air.

**Multislice CT Scanning**

CT scans were performed on one of three types of scanners as published previously (15). CT images were obtained with 120 kV, 150 to 300 mA, and 1- to 1.5-mm slice thickness for the high-resolution CT (HRCT) images, and 120 kV, 200 to 225 mA, and 5- to 7-mm slice thickness for conventional CT images.

**CT Measurement of Small Pulmonary Vessels and Main Pulmonary Artery**

For the measurements of the pulmonary CSA, three CT slices were selected from HRCT images. The upper cranial slice was taken approximately 1 cm above the upper margin of the aortic arch, the middle slice was taken approximately 1 cm below the carina, and the lower caudal slice was taken approximately 1 cm below the right inferior pulmonary vein. These CT images were analyzed using a semi-automated image-processing program (ImageJ Version 1.40 g, a public domain Java image processing program available at http://rsb.info.nih.gov/ij/).

Using the ImageJ software “Analyze Particles” function, which can count and measure objects on binary images, the number of vessels of a specified size and the CSA of each size range on every CT slice were obtained (8). Simultaneously, vessels that ran obliquely or parallel to the slice were excluded using the ImageJ software “Circularity” function (8) and only those vessels that ran closest to perpendicular to the CT slice based on their shape in the image were analyzed.

CSA measurements were conducted as follows: First, selected CT images were smoothed by performing Gaussian blurring to eliminate image noise because those CT images were reconstructed with a lung or bone algorithm. The lung field was then segmented using a threshold technique with all pixels between –500 and –1,024 Hounsfield units (HU) on each CT image (Figure 1A). Next, segmented images were converted into binary images with a window level of –720 HU. Vessels including pulmonary arteries and veins were displayed in black on the binary image (Figure 1B). We measured CSA at both the subsegmental and subsubsegmental levels separately, defined as those vessels with a cross-sectional area of 5 to 10 mm2 for subsegmental and less than 5 mm2 for subsubsegmental (16). After these settings, CSA of each vessel was calculated (Figure 1C). Finally, we totaled the CSA of vessels measured on each set of three CT slices, and those totals were abbreviated as follows: CSA-S (for the total cross-sectional area of the subsegmental vessels that ranged less than 5 mm2 and CSAS,S for the total cross-sectional area of the subsegmental vessels that ranged from 5 to 10 mm2. Total lung area of the three selected slices was obtained using threshold values between –500 HU and –1,024 HU, and the percentages of CSA-S (CSA-S) and CSAS,S (CSAS,S) for the total lung area were calculated.

For the evaluation of the dimensions of the central pulmonary vessels, the diameter of the main pulmonary artery (MPAD) was measured at its widest portion within 3 cm of the bifurcation on the conventional CT image (17). On the same slice, the diameter of the ascending aorta (AoD) was measured. The ratio of MPAD to AoD (MPAD/AoD) was calculated. Measurements were performed by a single observer in a blinded fashion. All measurements were made three times, and the mean values were recorded.

![Figure 1.](image-url)
The extent of emphysema was obtained by calculating the mean percentage of low attenuation values lower than −950 HU (%LAA<sub>-950</sub>) on each CT slice using the ImageJ software (18).

### Pulmonary Arterial Pressure Measurements

Right heart catheterizations (RHC) were performed as detailed previously (10). All hemodynamic measurements are reported as the mean of three measurements taken at end-expiration. The P<sub>p</sub><sub>a</sub> was calculated as the pulmonary artery diastolic pressure plus one-third of the pulse pressure.

### Statistical Analysis

For the main object of this study, the correlations of P<sub>p</sub><sub>a</sub> and CT measurements, including %CSA<sub>5</sub> and %CSA<sub>5.10</sub>, were tested using Spearman rank correlation analysis. We also used Spearman correlation coefficients to express the relationship between P<sub>p</sub><sub>a</sub> and PFTs, %LAA<sub>-950</sub>, P<sub>O</sub><sub>2</sub>, and other variables previously described as indicators of pulmonary arterial pressure, including MPAD and MPAD/AoD (17, 19–21).

Multiple linear regression analysis using P<sub>p</sub><sub>a</sub> as the dependent outcome was performed to evaluate the impact of measured CT values, lung function, and subject characteristics including age, sex, and body mass index (BMI). Data were expressed as the mean ± standard deviation for all normally distributed variables. For all statistical analyses, the null hypothesis was rejected at the 5% level. All statistical analyses were performed using JMP 5.0 software (SAS Institute, Cary, NC).

### RESULTS

#### Characteristics of the Study Subjects

Characteristics of the patients, including the results of PFTs, are presented in Table 1. The cardiovascular substudy enrolled 163 patients from the NETT, including those who were screened but not found eligible for randomization. Ninety-three of the 163 patients from the NETT, including those who were screened but not found eligible for randomization. Ninety-three of the 163 patients had both analyzable chest CT and RHC data that were available for the current study. According to the CT criteria in this study, 14 subjects were excluded because of extensive old inflammatory changes (n = 3) or image noise (n = 11). Thus, 79 patients (mean age, 65 ± 7 yr; range, 47–70 yr; 33 women, 64 ± 6 yr; 46 men, 66 ± 7 yr) were included in this study. Table 2 shows the variables measured at RHC. P<sub>p</sub><sub>a</sub> was 25.8 ± 5.0 mm Hg, and the range was from 12.7 to 40.7 mm Hg.

### Correlations between P<sub>p</sub><sub>a</sub> and CT Measurements

The results of CT measurements and correlations with P<sub>p</sub><sub>a</sub> are shown in Table 3. Mean %CSA<sub>5</sub> was 0.55 ± 0.14%, and mean %CSA<sub>5.10</sub> was 0.20 ± 0.05%. The %CSA<sub>5</sub> had a significant negative correlation with P<sub>p</sub><sub>a</sub> (r = −0.512, P < 0.0001), whereas the correlation between %CSA<sub>5.10</sub> and P<sub>p</sub><sub>a</sub> did not reach statistical significance (r = −0.196, P = 0.083) (Figure 2). P<sub>p</sub><sub>a</sub> had a significant correlation with D<sub>lCO</sub>% predicted (r = −0.387, P = 0.0004), whereas P<sub>p</sub><sub>a</sub> did not have significant correlations with P<sub>O</sub><sub>2</sub> (r = −0.201, P = 0.075) or %LAA<sub>-950</sub> (r = 0.12, P = 0.29).

Mean MPAD was 28.6 ± 3.3 mm, and mean MPAD/AoD was 0.81 ± 0.11. The correlation between these CT dimensions of the central pulmonary vessels and P<sub>p</sub><sub>a</sub> did not reach statistical significance (MPAD: r = 0.210, P = 0.063; MPAD/AoD: r = 0.099, P = 0.384) (Figure 3).

### Multivariate Linear Regression Analysis

In multiple linear regression analysis with P<sub>p</sub><sub>a</sub> as the dependent variable, age, sex, BMI, P<sub>O</sub><sub>2</sub>, FEV<sub>1</sub>% predicted, D<sub>lCO</sub>% predicted, %LAA<sub>-950</sub>, and %CSA<sub>5</sub> as the independent variables, only the following two variables were independent predictors of P<sub>p</sub><sub>a</sub> (r<sup>2</sup> = 0.541): %CSA<sub>5</sub> (r < 0.0001) and predicted D<sub>lCO</sub>% (r = 0.022) (Table 4).

### Additional Analysis

We evaluated the relationships between %CSA<sub>5</sub> and the extent of emphysema, pulmonary function, and P<sub>O</sub><sub>2</sub> using Spearman rank correlation analysis. Table 5 shows the correlations between %CSA<sub>5</sub> and PFT results, P<sub>O</sub><sub>2</sub>, and %LAA<sub>-950</sub>. These correlations are graphed in the online data supplement, Figure E1. The %CSA<sub>5</sub> had significant correlations with %LAA<sub>-950</sub> (r = −0.507, P < 0.0001), FEV<sub>1</sub>% (% predicted) (r = 0.330, P = 0.0029), and D<sub>lCO</sub>% (% predicted) (r = 0.389, P = 0.0004), whereas no significant correlation with P<sub>O</sub><sub>2</sub> (r = 0.064, P = 0.955) was found.

### DISCUSSION

In the present study, we found that %CSA<sub>5</sub> correlated inversely with P<sub>p</sub><sub>a</sub> in severe emphysema. To our knowledge, this is the first report to quantitatively evaluate the in vivo relation-
ship between pulmonary arterial pressure and small vessel morphology in severe emphysema. Vascular remodeling of small pulmonary vessels, which mainly consists of intimal thickening of the pulmonary muscular artery, is believed to be the most important factor in the development of pulmonary hypertension in severe emphysema, although the relationship between vascular alteration and pulmonary hypertension is not yet proved. However, pulmonary vascular remodeling is not exclusively a characteristic of severe emphysema; it has also been shown in patients with mild COPD and in smokers with normal pulmonary function (22–28). Previous authors have not found a significant correlation between vascular remodeling and $P_{\text{pa}}$ at rest (29, 30). In contrast, Kubo and colleagues (7) found that pulmonary vascular remodeling assessed histologically in severe emphysema led to reduced distensibility of pulmonary vessels and was closely correlated to $P_{\text{pa}}$ during exercise, but not at rest. Wright and colleagues (31) demonstrated that $P_{\text{pa}}$ correlates with vascular mediators that control vasoconstriction or vasodilation of pulmonary vessels. Thus, the degree of pulmonary arterial pressure in COPD may be related to the dynamic morphological change in the pulmonary vascular bed rather than static or histological vascular alteration. The $\%\text{CSA}_{<5}$ may reflect the effects of the vascular distensibility and vasoactive mediators because it is measured in vivo; this may explain the significant correlation between $\%\text{CSA}_{<5}$ and $P_{\text{pa}}$ in our study, although decrease in total capillary bed may be associated with $P_{\text{pa}}$ because $P_{\text{pa}}$ had a significant correlation with $D_{L\text{CO}}$.

We confirmed that the relationship between vascular alteration and $P_{\text{pa}}$ depends on vessel size. A significant correlation

![Figure 2](image1).

The relationship between the pulmonary arterial mean pressure ($P_{\text{pa}}$) and (A) the percentage of the area taken up by the cross-sectional area (CSA) of pulmonary vessels smaller than 5 mm$^2$ ($\%\text{CSA}_{<5}$), and (B) the percentage of the area taken up by the CSA of pulmonary vessels between 5 mm$^2$ and 10 mm$^2$ ($\%\text{CSA}_{5–10}$). $P_{\text{pa}}$ has a significant negative correlation with $\%\text{CSA}_{<5}$ ($r = -0.512, p < 0.0001$), whereas there is no significant correlation between $P_{\text{pa}}$ and $\%\text{CSA}_{5–10}$ ($r = -0.196, p = 0.083$).

![Figure 3](image2).

The relationship between the pulmonary arterial mean pressure ($P_{\text{pa}}$) and (A) the diameter of main pulmonary artery (MPAD), and (B) the ratio of MPAD to the diameter of ascending aorta (MPAD/AoD). There is no significant correlation between $P_{\text{pa}}$ and MPAD or MPAD/AoD.

**TABLE 4. PREDICTORS OF PULMONARY MEAN ARTERIAL PRESSURE FROM MULTIPLE REGRESSION ANALYSIS ($N = 79$)**

<table>
<thead>
<tr>
<th>Partial Regression Coefficient</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$%\text{CSA}_{&lt;5}$ (%)</td>
<td>-23.88</td>
</tr>
<tr>
<td>$%\text{LAA}_{&lt;950}$ (%)</td>
<td>-0.09</td>
</tr>
<tr>
<td>$\text{FEV}_1$, % predicted</td>
<td>-0.04</td>
</tr>
<tr>
<td>$D_{L\text{CO}}$, % predicted</td>
<td>-0.13</td>
</tr>
<tr>
<td>$P_{\text{AO}_2}$</td>
<td>-0.08</td>
</tr>
<tr>
<td>Age</td>
<td>-0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.37</td>
</tr>
<tr>
<td>BMI</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** BMI = body mass index; $D_{L\text{CO}}$ = diffusing capacity of the lung for carbon monoxide; $P_{\text{pa}}$ = pulmonary arterial mean pressure; $\%\text{LAA}_{<950}$ = CT measurement of the percentage of low attenuation area less than $-950$ HU, defined as emphysema.
was found between $P_{pa}$ and $% CSA_{<5}$, but not $% CSA_{5-10}$. The degree of histological vascular alteration in COPD varies according to vessel size (22). In patients with pulmonary hypertension in COPD, histological vascular alteration can be found mainly in muscular pulmonary arteries (21–24). In this study, the lower limit of detection of cross-sectional area of pulmonary vessel is defined by the size of the CT pixel (approximately 0.6 mm in this study). Thus, $% CSA_{<5}$ included both elastic and relatively large muscular vessels, whereas $% CSA_{5-10}$ was composed of mostly elastic vessels. Therefore, the difference in correlations between the two CSA groups and $P_{pa}$ may reflect the difference between the proportions of elastic versus muscular pulmonary vessels in each group. Characteristics of central large vessels, such as the measured MPAD or MPAD/AoD, correlated poorly if at all with $P_{pa}$, a finding in agreement with previous work (17).

Although earlier studies suggested that emphysema, and consequent tissue destruction, leads to pulmonary hypertension, this contention is not supported by recent studies (10, 32, 33). Likewise, we found no significant correlation between the extent of emphysema and $P_{pa}$ at least in patients with severe emphysema. However, there was a significant correlation between the extent of emphysema and $% CSA_{<5}$ as well as the relationship between $P_{pa}$ and $% CSA_{<5}$. The correlations among the extent of emphysema, $% CSA_{<5}$, and $P_{pa}$ suggest that the increase in emphysema itself does not induce the decrease in $% CSA_{<5}$. Recently, several researchers have demonstrated the relationship between vascular alteration and emphysema from the viewpoint of endothelial dysfunction (34–42). Thus, the negative correlation between the decrease in $% CSA_{<5}$ and the extent of emphysema could be related to endothelial dysfunction. Meanwhile, the decrease in $% CSA_{<5}$ might result from the passive vascular compression by emphysema. However, previous study has shown that a significant correlation between $% CSA_{<5}$ and the extent of emphysema was found even in patients with relatively mild emphysema. Thus, the association of the passive vascular compression by emphysema to $% CSA_{<5}$ may be relatively minimal.

Various other factors have been recognized as potential association to the development of pulmonary hypertension in emphysema. Hypoxia-induced vasoconstriction and vascular remodeling have been considered as causes of pulmonary hypertension in COPD. However, when accounting for other factors, previous study (10) showed that $PaO_2$ was not a significant predictor for $P_{pa}$, although there was a limitation with a narrow range of $PaO_2$ in this study. Likewise, although we found significant correlations between $P_{pa}$ and $D_{14CO}$ % predicted, or FEV$_1$ % predicted as reported in previous studies (10, 43, 44), these significant correlations were not corroborated by another previous study (45). In multiple linear regression analysis, $D_{14CO}$ % predicted was a significant but weak predictor of $P_{pa}$, which may be due to destruction of pulmonary microvessels. The $% CSA_{<5}$, which can reflect morphological vascular alteration, was by far the best predictor of $P_{pa}$. However, further evaluation, including reproducibility of the relationship between $% CSA$ and $P_{pa}$, may be required to use this method to estimate $P_{pa}$.

### Limitations of the CSA Method

Echocardiography has been used to evaluate pulmonary hypertension; however, a recent study showed that the estimation of pulmonary hypertension with echocardiography was not reliable in patients with COPD (46). The measurement of the peripheral vessel CSA may be an alternative diagnostic method that can evaluate pulmonary vascular alteration and pulmonary hypertension without a particular CT scanning technique or injection of contrast material. However, there are still several issues that should be resolved: First, we used the threshold value of $-720$ HU to identify vascular structure on CT images because using a threshold lower than $-720$ HU led to an increase in image noise. In the future, the appropriate threshold value should be assessed. Second, this method cannot evaluate the pulmonary arteries and veins separately; however, we believe that three-dimensional reconstruction from multislice CT images in conjunction with innovative image analysis software might overcome this limitation. In addition, with recent developments in CT technology, each CT image can be obtained in less than 1 second. Thus, CSA may be influenced by the cardiac cycle. Respiratory phases, including inspiration and expiration, also may affect CSA measurements. These effects should be evaluated with each respiratory phase and cardiac gating in the future. Other confounding variables that may affect the correlations of lung function and CT morphological measurements of small vessel dimensions could be the influence of posture and lung volume on measurements made in the upright and supine postures, respectively. Decreased lung volume and increased venous return in the supine posture during CT performance could limit the ability to correlate measurements of small pulmonary vessel dimensions with lung function measurements made during relative conditions of a higher lung volume and decreased venous return in the upright posture.

### Study Limitations

There are some limitations of this study, first, because this is a retrospective study, and because of the characteristics of this cohort, the majority of patients have severe emphysema. In some patients with COPD, pulmonary hypertension can also develop without emphysema. Thus, the relationship between pulmonary vascular alteration and pulmonary hypertension remains unclear in subjects with COPD who do not have such severe parenchymal disease as found in the NETT cohort. Likewise, the majority of patients have mild to moderate pulmonary hypertension. Thus, the relationship between pulmonary vascular alteration and pulmonary hypertension remains unclear in severe pulmonary hypertension. Further evaluation in patients with severe pulmonary hypertension is necessary. Second, we did not measure the cross-sectional area of pulmonary vessels histologically; therefore, there might be some differences between CSA measured on CT image and actual cross-sectional area of pulmonary vessels. Further evaluation is necessary.

### Conclusion

We found that $P_{pa}$ in severe emphysema is significantly correlated to a decrease in the $% CSA$ less than $5 \text{ mm}^2$. In
addition, this parameter is a strong predictor of the degree of pulmonary hypertension in patients with COPD.

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