Dilatation of Bronchial Arteries Correlates With Extent of Central Disease in Patients With Chronic Thromboembolic Pulmonary Hypertension

Hidefumi Shimizu, MD; Nobuhiro Tanabe, MD; Jiro Terada, MD; Masahisa Masuda, MD*; Seiichiro Sakao, MD; Yasunori Kasahara, MD; Yuichi Takiguchi, MD; Koichiro Tatsumi, MD; Takayuki Kuriyama, MD

Background Dilatation of the bronchial arteries is a well-recognized feature in patients with chronic thromboembolic pulmonary hypertension (CTEPH). The purpose of the current study was to use computed tomography (CT) to assess the relationship between dilated bronchial arteries and the extent of thrombi, and to evaluate the predictive value of the former for surgical outcome.

Methods and Results Fifty-nine patients with CTEPH and 16 with pulmonary arterial hypertension (PAH) were retrospectively evaluated. The total cross-sectional area of bronchial arteries was measured by CT and its relationship with the central extent of thrombi or surgical outcome was assessed. The total area of the bronchial arteries in CTEPH patients was significantly larger than that in PAH patients (median [range], 6.9 [1.7–29.5] mm² vs 3.2 [0.8–9.4] mm²), with the total area of bronchial arteries correlating with the central extent of thrombi. In patients who had undergone pulmonary thromboendarterectomy (PTE) (n=22), the change in PaO₂ after surgery had a tendency to correlate with the total area of the bronchial arteries.

Conclusion The total cross-sectional area of the bronchial arteries correlated with the extent of central disease in patients with CTEPH, and it might predict gas exchange improvement after PTE. 

Key Words: Bronchial artery; Chronic thromboembolic pulmonary hypertension; Pulmonary circulation; Pulmonary embolism

In patients with chronic thromboembolic pulmonary hypertension (CTEPH), dilatation of the bronchial arteries (BAs) is a well-recognized feature on conventional angiography and computed tomography (CT) angiography. As the finding of dilated BAs is rarely seen in patients with idiopathic pulmonary arterial hypertension (PAH) or acute pulmonary embolism, it has been suggested that this feature could help distinguish patients with CTEPH from those with other diseases causing pulmonary hypertension.

The presence of dilated BAs represents increased systemic collateral blood supply and it plays a important role in maintaining the viability of ischemic lung parenchyma after pulmonary artery occlusion. However, the mechanisms of bronchial arterial development are not well understood. It is thought that both hemodynamic and nonhemodynamic factors might be involved. In a canine model, Rehulova et al showed that the development of collateral bronchopulmonary circulation depended on the size of the occluded branch of the pulmonary arteries. In patients with CTEPH, the location of thrombi varies between individuals, but to our knowledge no study has evaluated the relationship between the location of thrombi and the dilatation of BAs in humans.

Previous studies showed a lower postoperative mortality rate and lower postoperative pulmonary vascular resistance (PVR) after pulmonary thromboendarterectomy (PTE) in patients with dilated BAs according to the preoperative evaluation, compared with patients without dilated BAs. Those studies classified patients into 2 groups, with (≥1.5 mm) or without (<1.5 mm) dilated BAs. Ley et al showed a correlation between the cross-sectional area of BAs assessed by CT angiography and the bronchopulmonary shunt volume assessed by magnetic resonance imaging. Those results prompted us to use the cross-sectional area of the BAs, instead of their diameters, for assessment of the relationship with surgical outcome after PTE, as the bronchopulmonary shunt volume may contribute directly to supporting ischemic parenchymal tissue caused by occlusion of the pulmonary arteries.

The purpose of our study was to use CT angiography to assess the relationship between the cross-sectional area of the BAs and the central extent of thrombi, as well as to evaluate the predictive value of dilated BAs for surgical outcome.

Methods

Study Population For this retrospective study, we searched the computer database of Chiba University Hospital to identify patients...
with CTEPH (n=74) and PAH (n=19) who had undergone CT angiography between January 2002 and August 2007. All patients, except 1 with PAH, had undergone right-heart catheterization. The diagnosis of CTEPH or PAH was made on the basis of multiple diagnostic tests, including a detailed history, physical examination, pulmonary function testing, perfusion scanning, CT scanning, echocardiogram, right-heart catheterization and serologic tests.

Fourteen patients (11 with CTEPH, 3 with PAH) were excluded because of suboptimal contrast material delivery for evaluation of the BAs. Four patients with CTEPH were also excluded because the duration between CT angiography and right-heart catheterization was more than 3 months. Finally, 59 patients with CTEPH (CTEPH group) and 16 patients with PAH (PAH group: 8 with idiopathic PAH, 4 with PAH associated with collagen vascular disease, 2 with arterial septal defect and 2 with PAH associated with portal hypertension) were evaluated. Right-heart catheterization and selective pulmonary angiography were performed in all patients of the CTEPH group.

Twenty-four patients in the CTEPH group had undergone PTE; 2 of them died in the early postoperative period, and the remainder, except 1 patient (n=21), underwent postoperative CT angiography within 3 months (median [range], 1 [1–3]) after PTE. Postoperative blood gas analyses were performed for all patients and compared with preoperative blood gas levels.

As for the control of the total area of the BAs, we evaluated 12 patients who had acute pulmonary thromboembolism (APTE), whose thrombi were treated and resolved almost completely (post-APTE group).

The Human Subject Committee of Chiba University approved the study, and written informed consent was given by all patients at the time of diagnosis.

### CT Protocol

All CT scans were obtained with a 16-row multidetector CT scanner (LightSpeed Ultra16; General Electric Medical Systems, Milwaukee, WI, USA) with 1.25-mm slice thickness. Patients were injected with 100 ml of contrast material with 350 mg of iodine/ml at 3 ml/s. All CT examinations were performed for a normal workup to diagnose or evaluate CTEPH or PAH, with a scanning delay of 20–30 s for optimal pulmonary artery visualization.

### Image Interpretation

CT images were reviewed by 2 investigators using a cine-mode display on a computer workstation, and final evaluations were achieved by consensus. All BAs arising from the descending aorta in each patient as depicted by CT angiography were identified. At the mediastinal window setting of the axial images, right and/or left BAs were identified as contrast material-enhanced round or curvilinear structures (Fig 1). Their diameters were measured at the most proximal site from their origin. We calculated the cross-sectional area of each BA based on its diameter, and then summed the cross-sectional areas in each patient to yield the total area of the BAs.

The CTEPH group was divided into 3 subgroups, main type, lobar type and segmental type, according to the most proximal location of thrombi observed on CT angiography. The main type (n=9) was defined as thrombi of main arteries with or without more distal thrombi location, the lobar type (n=29) was defined as thrombi of lobar arteries with or without more distal thrombi location, and the segmental type (n=21) was defined as thrombi in segmental arteries or distal location.

We also evaluated pulmonary infarction by the peripheral scar score as described by Heinrich et al9. In short, CT scan images at the lung window settings were analyzed for peripheral, irregular, wedge-shaped or linear densities. By adding up the number of involved lobes (lingual was regarded as a lobe), the peripheral scar score was obtained up to a maximum score of 6.

### Statistical Analysis

Group comparisons were performed by Mann-Whitney U-test or 1-way analysis of variance on ranks (Kruskal-Wallis method) with post-hoc test using the Steel-Dwass method. When data were normally distributed with constant variance, correlations were measured using Pearson’s correlation. Otherwise, the Spearman rank sum correlation was used. Comparison of the total areas of the BAs between before and after PTE was performed by Wilcoxon matched-pairs signed-ranks test. For all comparisons, a p-value of less than 0.05 was considered to indicate a statistically significant difference.

### Results

#### Clinical and Hemodynamic Characteristics of the Patients

Table 1 summarizes the clinical and hemodynamic data from the 75 patients included in the current study. No statistically significant differences were found in terms of age, mean pulmonary artery pressure, cardiac index and PVR among the groups and subgroups.

#### Comparisons Between Patient Groups

The median total area of the BAs in the CTEPH group was significantly larger than that in the PAH group and the post-APTE group (Fig 2a; median [range], 6.9 [1.7–29.5] mm² vs 3.2 [0.8–9.4] mm² vs 2.0 [0.9–5.1] mm²). When the CTEPH group was divided into 3 subgroups according to the most proximal location of thrombi, the median total area of the BAs in the segmental type was significantly smaller than in the other 2 types (Fig 2b). No significant difference in
total area of the BAs was observed between the PAH group and the segmental type of CTEPH. In the CTEPH group, the total area of the BAs showed a slight correlation with the peripheral scar score, but it did not reach statistical significance (Fig 3; \( r_s = -0.26 \), \( p = 0.08 \)).

**Correlation With Total Area of BAs and Preoperative Hemodynamics**

The total area of the BAs was significantly correlated with the preoperative cardiac index (Fig 4; \( r = -0.324 \), \( p < 0.05 \)). No significant correlation was found between the total area of the BAs and preoperative mean pulmonary artery pressure (\( r = -0.05 \), \( p = 0.72 \)) or PVR (\( r = 0.12 \), \( p = 0.37 \)).
Correlation of Total Cross-Sectional Area of BAs With Outcome and its Change After PTE

Twenty-two patients (10 men, 12 women), mean 51.5 years (range, 18–69 years), underwent PTE and postoperative right-heart catheterization, and the relationship between the total cross-sectional area of the BAs and surgical outcome was evaluated. In this subgroup, the median total area of the BAs was 14.8 mm² (range, 3.6–29.5 mm²). Every patient, except 1, had at least 1 BA with a diameter ≥1.5 mm. Based on the location of thrombi, 7 patients were classified as main type of CTEPH, 14 as lobar type, and only 1 patient was classified as the segmental type. Table 2 summarizes the surgical outcomes of the 22 patients. The total area of the BAs showed a slight correlation with changes in PaO₂, but it did not reach statistical significance (r=0.40, p=0.06). Other parameters regarding surgical outcome showed no correlation with the total area of the BAs. The total area of the BAs after PTE was significantly reduced compared with before PTE (Fig 5; median [range], 7.7 [2.3–18.9] mm² vs 11.2 [3.6–17.5] mm²).

Discussion

The current study demonstrated that the location of thrombi is related to the total cross-sectional area of the BAs in CTEPH patients. Although the BAs in the CTEPH patients were significantly dilated compared with those in the PAH patients, there was no significant difference in the total area of the BAs in the segmental type of CTEPH group and those in the PAH group. We also showed that the total area of the BAs in patients with CTEPH significantly decreased after PTE and might predict surgical outcome. With the advances in CT, the potential of CT angiography for diagnosing CTEPH has been demonstrated by a number of studies. Moreover, CT angiography is also being recognized as a useful test for evaluating the development of systemic collateral supply to the lung. Remy-Jardin et al showed that multidetector row helical CT angiography depicts the BAs more precisely than conventional angiography. Therefore, in the present study we also used multidetector row helical CT angiography to evaluate the dilatation of the BAs.

Consistent with previous studies, dilated BAs were frequently seen in the patients with CTEPH in the present study. The total area of the BAs in the CTEPH patients was significantly larger than that in the PAH patients. In the CTEPH group, as in earlier studies, we did not find any significant correlation between the total area of the BAs and the preoperative mean pulmonary artery pressure or the PVR, meaning that the severity of pulmonary hypertension was not a stimulus for the development of dilated BAs.

However, the total area of the BAs was negatively correlated with the cardiac index. Although the onset of CTEPH is difficult to detect, disease duration might correlate with the development of dilated BAs. On the other hand, reduction in the cardiac index occurs in the symptomatic and decompensated phase of pulmonary hypertension so disease duration might lead to this negative correlation between the total area of the BAs and cardiac index.

Of the CTEPH subgroups, the total area of the BAs in the segmental type was significantly smaller than in the other types. To our knowledge, this is the first study to investigate the correlation between BA enlargement and the central extent of thrombi in humans. The inverse relationship between the total area of the BAs and the peripheral scar score, possibly representing prior pulmonary infarction, might support this finding. One study using a dog model showed that the BAs did not become enlarged upon embolization of muscular arteries or arterioles, although enlargement occurred when the elastic branches of the pulmonary arteries were occluded. This suggests that occlusion of the pulmonary arteries at the proximal sites of bronchopulmonary arterial anastomoses might open them up. In humans, preexisting bronchopulmonary arterial anastomoses are commonly seen slightly proximal to the lobular arteries. The pressure gradient between the systemic arteries and the pulmonary arteries distal to the site of occlusion would increase when small distal arteries and arterioles are unaffected in patients with main or lobar type of CTEPH and it would result in systemic arterial blood flow increasing in ischemic areas. Another possibility for the development of dilated BAs is ischemic areas. Another possibility for the development of dilated BAs.

Table 2 Surgical Outcomes of Patients Undergoing PTE (n=22) and Correlation With Total Area of Bronchial Arteries

<table>
<thead>
<tr>
<th>Total area of bronchial arteries</th>
<th>r value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative mean pulmonary artery pressure (mmHg)</td>
<td>26.5±12.5 (12–58)</td>
<td>-0.23</td>
</tr>
<tr>
<td>Postoperative cardiac index (L·min⁻¹·m⁻²)</td>
<td>2.79±0.51 (1.85–3.63)</td>
<td>0.02</td>
</tr>
<tr>
<td>Postoperative pulmonary vascular resistance (dynes·s⁻¹·cm⁻⁵)</td>
<td>388±348 (132–1,168)</td>
<td>-0.23</td>
</tr>
<tr>
<td>%reduction in pulmonary vascular resistance (%)</td>
<td>55±21 (–25–90)</td>
<td>0.16</td>
</tr>
<tr>
<td>Change in PaO₂ after PTE (mmHg)</td>
<td>14±13.6 (–10.9–44.3)</td>
<td>0.40</td>
</tr>
<tr>
<td>Change in AaDO₂ after PTE (mmHg)</td>
<td>–19.9±14.5 (–53.6–4.43)</td>
<td>–0.26</td>
</tr>
</tbody>
</table>

Data are mean±SD (range), unless otherwise stated.

PTE, pulmonary thromboendarterectomy; PaO₂, arterial oxygen tension; AaDO₂, alveolar-arterial oxygen pressure difference.

Fig 5. Comparison of the total area of the bronchial arteries before and after pulmonary thromboendarterectomy. *p<0.05.
systemic arterial supply to an occluded lung, related to the location of thrombi, is hyperplasia of the pulmonary artery vasa vasorum, which is of bronchial arterial origin. In addition, the extent of central disease per se may lead to nonhemodynamic factors, including pro- and anti-angiogenic factors. Our previous study showed that monocyte chemotactrant protein-1 is produced in endothelial cells, mononuclear cells, and smooth muscle cells in the fibrous portion adjacent to the vascular lumen in endarterectomized tissue. Herve and Fadel speculated that macrophages infiltrating the wall of an occluded pulmonary artery stimulate proliferation of the vasa vasorum and lead to delivery of bone marrow-derived endothelial progenitor cells for local vasculogenesis within the nonresolving clots. Other nonhemodynamic factors that are elevated in patients with CTEPH, such as endothelin-1, might play a role in development of dilated BAs.

We also showed that the total area of the BAs was significantly reduced after PTE. However, the total area of the BAs after PTE was greater compared with that in the post-APTE group. A certain number of thrombi remained after PTE, which would keep the BAs dilated. Fadel et al showed that in piglets revascularization after a period of left pulmonary artery occlusion normalized the systemic blood flow to the left lung. Our finding is consistent with their experimental model and we believe that reduction in the total area of the BAs after PTE can prevent hemoptysis, a life-threatening complication of CTEPH.

When we divided the CTEPH group into main type, lobar type and segmental type based on the most proximal location of thrombi, we did not find any significant difference between the total area of the BAs in the segmental type of CTEPH and that in PAH. Some previous studies have indicated that the finding of dilated BAs can help distinguish CTEPH from idiopathic PAH or APTE; however, those studies made no mention of the central extent of thrombi in the CTEPH patients. Although dilatation of the BAs is a common finding in CTEPH, it seems to be relatively limited to the central type of CTEPH.

Although it did not reach statistical significance (p=0.06), the change in PaO2 after PTE moderately correlated with the total area of the BAs. In patients without lung disease, the bronchial circulation supplying the systemic arterial flow is estimated to be 1% of cardiac output. In CTEPH patients, this bronchopulmonary shunt volume can increase up to approximately 30% of cardiac output. Some animal models have confirmed that bronchial circulation supports ischemic parenchymal lung tissue. Besides that support, prolonged lung ischemia damages the pulmonary endothelium and leads to increasing permeability in the lung. In that condition, ischemic–reperfusion injury after PTE could happen to varying degrees. Development of bronchial circulation was shown to attenuate ischemic–reperfusion lung injury in some experimental models and our data also suggest a supportive role of the BAs in the ischemic lung and their importance for gas exchange after PTE.

We did not find any other relationships between surgical outcomes, including %reduction in PVR, and the total area of the BAs. Kauczor et al found a lower postoperative mortality rate in patients with dilated BAs after PTE! In our study, only 2 patients died during the early postoperative period, so we did not evaluate the mortality rate. Heinrich et al reported that the postoperative PVR was significantly lower in patients with dilated BAs than in those without; they classified patients into 2 groups, with (≥1.5 mm) and without (<1.5 mm) dilated BAs. In our study, as 23 of 24 patients undergoing PTE had BAs ≥1.5 mm, it is likely that we performed surgery only for the relatively central type of CTEPH and assessed only the patients with dilated BAs, and thus we could not apply their criterion for determining any correlation between postoperative PVR and bronchial arterial dilatation.

The major difference between the current study and earlier studies is that we used the total cross-sectional area of the BAs to evaluate the development of the systemic collateral supply instead of their diameters. Evaluation of bronchial arterial dilatation in CTEPH is intended for assessment of the role of systemic circulation to the lung, so a method of quantifying the systemic collateral supply would be desirable. In our study we could determine a relationship between the total cross-sectional area of the BAs and the central extent of thrombi or the increase in PaO2 after PTE, and we believe that it is reasonable to use the total area of the BAs to assess the role of systemic circulation to the lung in patients with CTEPH.

Study Limitations

First, none of our patients underwent conventional angiography of the BAs or measurement of the bronchopulmonary shunt volume, so we could not confirm the accuracy of our findings with a “gold standard”. Second, the CT protocol was optimal for pulmonary artery visualization because all CT examinations were performed for a normal workup to diagnose or evaluate CTEPH or PAH. However, we could depict the BAs sufficiently for evaluation, except for 14 cases. Third, the number of patients in each group was small. Larger studies are needed to confirm the relationship between dilated BAs and the central extent of thrombi or surgical outcomes after PTE.

In conclusion, the total cross-sectional area of the BAs correlated with the extent of central disease in patients with CTEPH and it might be useful for predicting gas exchange improvement after PTE.

Acknowledgment

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