Evaluation of organized thrombus in pulmonary arteries in patients with chronic thromboembolic pulmonary hypertension; imaging with cone beam computed tomography during pulmonary angiography

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Purpose

Chronic thromboembolic pulmonary hypertension (CTEPH) is thought to be one of the leading causes of severe pulmonary hypertension. The pathophysiology of this condition is related to the increased resistance to flow through the pulmonary arteries that result initially from obstruction of pulmonary arterial vessels by organized thromboembolic material, and subsequently from vascular remodeling in unobstructed vessels. The consequence is an increased pulmonary vascular resistance resulting in pulmonary hypertension and progressive right heart failure.\(^1\), \(^2\) Surgical correction by pulmonary endarterectomy (PEA) has been the preferred treatment for patients with CTEPH,\(^3\) but not all patients have surgically accessible disease. Recently, an alternative interventional strategy of balloon pulmonary angioplasty (BPA) reduces pulmonary artery hypertension in patients with CTEPH.\(^4\) Previous pathological studies\(^5\),\(^6\) described that intra-arterial organized thrombus so called 'bands' and 'webs' were most frequently observed in major lobar segmental arteries and succeeding orders of the arteries. Among these lesions, BPA can mainly treat the lesions at the subsegmental pulmonary arteries. Though the pre-treatment image diagnosis of the lesions in pulmonary artery is usually performed by digital subtraction pulmonary angiography and CT pulmonary angiography (CTPA), it has not been sufficient to evaluate the intra-arterial lesions within the peripheral pulmonary arteries precisely. During BPA procedures, angiography frequently performed with injecting contrast materials from the catheter wedged at the segmental artery may result in increasing the use of contrast enhanced material, and such a complicated procedure may increase the risk of injury of the pulmonary arteries.

The purpose of this study is to assess the usefulness of CBCT using the flat panel detectors (FPD) during pulmonary angiography comparing with CTPA for characterizing various forms of organized thrombus in segmental and subsegmental arteries in patients with CTEPH.
Methods and Materials

Patients:

Between April 2010 and September 2012, 13 patients (2 men and 11 women; age range, 44-79 years; mean age, 64.1 years) with CTEPH were evaluated in this study. All patients referred for CTEPH were evaluated with a medical history, physical examination, measurement of exercise limitation (6-minute walking test), chest radiography, echocardiography, nuclear lung scintigraphy, right heart catheterization, pulmonary angiography, and CTPA. Among 13 patients, 3 patients have a history of an acute thromboembolic pulmonary embolism, and 6 patients have a history of deep venous thrombosis.

Imaging System:

Angiographic examinations such as pulmonary angiography and CBCT were performed by using an angiography system with a FPD on a motorized C-arms (Infinix Celeve-i INFX-8000V; Toshiba Medical Systems, Tokyo, Japan). This detector has a sampling pitch of 291 × 291 µm and an array format of 1024 × 1024 pixels. The CBCT acquisition consists of synchronized x-ray exposure and a panel readout under the continuous rotation of the C-arm. The 3D datasets were obtained from single rotation with a FOV of 298 × 298 mm using the floor-mounted C-arm. This series covers a total angular range of 200° around patients, with the rotation of 50° per second during administration of contrast material. A total of 108 projections were acquired at 27 frames per second with 1024 × 1024 matrices. The source image-receptor distance (SID) was fixed at 110 cm. The obtained image datasets were transferred to a workstation (Zio station Z800; Ziosoft inc, Japan), where a volume data was reconstructed in a CT-type dataset consisting of many sections with resized sampling pitch of 582 × 582 µm with 512 × 512 matrices, and visualized with volume-rendering technique as 3D, multiplanar reconstruction (MPR), and curved planar reconstruction (CPR).

Angiography and CBCT Protocol:

Under ultrasonographic guide, 7 Fr. catheter was introduced from the right internal carotid vein to the superior vena cava. All of the patients underwent right heart catheterization to evaluate the degree of pulmonary hypertension and oxidization. Then, we underwent pulmonary angiography and CBCT with the use of a 5 Fr. pigtail catheter. For both pulmonary angiography and CBCT, the contrast material (Iopamidol 300; KonicaMinolta, Japan) containing 200mg I/m#, which was diluted with saline was automatically administered using a power injector. For CBCT with rotational angiography, the catheter placed in the descending portions of the right lower lobe, and a total of 48 mL of the contrast material containing 200 mg/mL of iodine was automatically administered.
at a rate of 8 mL/sec during the entire acquisition time of 4 seconds with a scanning delay of 2 seconds.

**Image Analysis of CBCT:**

Segmental vessels were defined according to the standard Boyden classification system. Lesions in 5 segmental and 12 subsegmental pulmonary arteries in right lower lobes were analyzed for each patient.

CBCT images for CTEPH patients showed organized thrombus with various forms. Considering the forms of the organized thrombus, we classified representative forms of organized thrombus in pulmonary segmental and/or subsegmental arteries such as secondary and tertiary branches into 4 types as follows: type 1: webs, type 2: web and slits, type 3: slits, and type 4: narrowing or complete occlusion (Figure 1). Figure 2 shows the typical structure of 'web' and 'slit'. Typical CPR images of CBCT reconstructed volume data for type 1, 2, and 3 were shown in figures 3, 4, and 5, respectively. Based on the classification, the distribution and frequency of organized thrombus were evaluated.

Single lesion extended to multiple segmental and subsegmental branches, especially in type 2 lesions, was counted twice or more in the evaluation of the number of involved branches. An abrupt decrease in vessel diameter and absence of contrast material are found in the vessel segment distal to the proximal total occlusion were counted as type 4. Abrupt vessel narrowing included in type 4 may be associated with recanalization within a thrombus or stenosis due to an organized thrombus and intimal thickening related to the organization process.

**Comparison with CTPA:**

Finally, we assessed the diagnostic values of CBCT images in comparison with CTPA. The detectability of CTPA for the type 1, 2, and 3 lesions observed by CBCT was evaluated. The CBCT was displayed on a diagnostic monitor, and radiologists could examine the desired cross-sectional images including MPR and CPR images. Axial images (slice thickness 1mm) of CTPA were retrospectively reviewed in comparison with CBCT for each lesions. CTPA was performed with multi-detector low CT (Somatom Definition Flash CT scanner; Siemens Healthcare, Forchheim, Germany) for all patients within 1 month. Contrast materials (370mg l/ml) were injected for 30 seconds via an antecubital vein with a weight-adapted injection protocol (1.3ml per kg body weight) followed by a saline injection for 10 seconds at the same rate. CTPA images were reconstructed with a 1-mm slice thickness, 1mm increment, as previously reported.
Fig. 1: Schematic figures of classified representative forms of organized thrombus such as; type 1: webs, type 2: web+slits, type 3: slits, and type 4: narrowing or complete occlusion. Type 1 'webs' appeared in a great variety of forms, ranged from fenestrated membranes to relatively thick eccentrically situated branching mass structures frequently observed at the bifurcation. Type 2 'web+slits' consists of a proximal web at a bifurcation or orifices of branches, and distal intravascular fibrous septa which we call 'slits'. An intravascular slit alone is defined as type 3. Narrowing or complete occlusion is defined as type 4.
Fig. 2: 70-year-old woman with CTEPH. reconstructed image obtained by CBCT during pulmonary angiography of right lower lobe, showing ‘web and slits’ which we call type 2 lesion. (a) (d) CPR images of different rotation angle. (b) (c) cross sectional images of ‘web’ at the bifurcation of A9 and 10. (e) (f) cross sectional images of ‘slit’ at the mid to distal portion of A10. (g) and (h) shows schematical cross sectional images of web and slit, respectively.

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**Fig. 3:** 44-year-old woman with CTEPH. Reconstructed images obtained by CBCT during pulmonary angiography of right lower lobe, showing the 'web' astriding the bifurcation of right A9b and A10b+c branches. (a) a 3D image with centerline of CPR (b),(c),(d) CPR images of different rotation angle. At around the web, irregular intimal surface of pulmonary artery was observed.

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Fig. 4: 70-year-old woman with CTEPH. Reconstructed images obtained by CBCT during pulmonary angiography of right lower lobe, showing 'web and slits' (a) a 3D image with centerline of CPR (b),(c),(d) CPR images of different rotation angle. There were thin flap structure in distal A10 extending distally from the web astriding on a bifurcation of A9 and A10.

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Fig. 5: 72-year-old woman with CTEPH. Reconstructed images obtained by CBCT during pulmonary angiography of right lower lobe, showing ‘slits’ (a) a 3D image with centerline of CPR (b),(c),(d) CPR images of different rotation angle. A slit alone was observed at a mid to distal portion of A10c. Another slit was also observed at a distal portion of A10b. There was no mass structure at the attachment sites of these lesions. Note that significant stenosis was observed at the ostiums of the proximal branches as shown in the 3D image.

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Results

*Image Analysis of CBCT:*

In the CBCT images of pulmonary arterial trees, there were any of the type 1 to 4 lesions in all segments. Table 1 showed the number of lesions and involved branches in segmental and subsegmental pulmonary arteries found in the CBCT images of 13 patients with CTEPH.

Frequency of type 1 lesions observed in segmental and subsegmental branches was 30/65 (46%) and 72/156 (46%), respectively. 'Webs' tend to astride a bifurcation of segmental or subsegmental branches, and severe stenosis was frequently found at the ostiums of the branching vessels (fig 3).

As a result of the organization process including the recanalization process after thromboembolism in pulmonary arteries, 'webs' appeared in a great variety of forms, ranged from fenestrated membranes to relatively thick eccentrically situated branching mass structures. They sometimes branched themselves and formed networks of variable complexity. Based on these various forms, some of these types of structures have been called 'cords', 'bands', and 'webs' in previous pathological reports.\(^5,6\) Therefore, 'cords' and 'bands' anchored to the arterial intima at its two ends, bridging the orifices of subsidiary channels,\(^5\) can be regarded as a simple form of 'webs', and were classified as 'webs' and are included in type 1 in this study. According to the previous pathological studies, intimal ridge-like thickenings are frequently formed and an eccentric plaque of fibro elastic tissues were observed at the attachment sites of the 'webs'.\(^5\) These lesions are thought to be firm and type 1 lesions seemed to be correlated with such lesions.

Type 2 lesions consists of a proximal web at a bifurcation or orifices of segmental or subsegmental branches, and distal intravascular fibrous septa which we call 'slits'. Slit was shown as a flap-like thin membrane attached to the arterial wall at its both two sides, and oriented in the direction of blood flow along the axis of the arteries. Most of the distal attachment sites were found to be a bifurcation of the subsidiary branches as shown in Fig. 4.

Frequency of type 2 lesions in segmental and subsegmental branches were 13/65 (20%) and 29/156 (19%), respectively. Each type 2 lesion tend to extend two or more subsegmental branches in pulmonary arterial trees. The size of the proximal webs and length of continuous slits have a variety of range, from a large web with short slits to a small web with long slits. Length of these lesions along the long axis of the vessel was reported to be 0.3 to 2cm in a previous pathological examination.\(^5\) In the present study, CPR images of CBCT showed type 2 lesions longer than 2cm is observed. Irregularity
of the vessel wall was rarely observed at around the 'slits' as previously reported by the pathological study. 5)

Type 3 lesions was defined as slit alone as shown in fig. 5. Type 3 lesions were observed in subsegmental branches as a thin flap in 9 of 156 lesions (6%). Though severe stenosis caused by intimal ridge-like thickening at the orifice of segmental branches was also observed in fig.5, the 'slit' does not connect to the proximal intimal thickening. Intraluminal irregularity is not observed at around the slit . Type 3 lesions are shown as a flap-like thin membrane alone and oriented in the direction of blood flow along the axis of the arteries. This form is thought to be similar to the 'slits' observed at the distal portion of type 2 lesions, and is quite different from the 'cords' or 'bands' at the proximal bifurcation of the branches.

Type 4 lesions including narrowing and complete obstruction were observed in 38.5% (60/156) of subsegmental branches. Among these subsegmental 60 branches, 23 subsegmental branches were completely obstructed at the orifices of the branches or at the proximal segmental branches resulting in total occlusion of the succeeding orders of subsegmental branches. 37 branches other than total occlusion are narrowing and obstruction at distal portion of the branches.

**Diagnostic values of CBCT in comparison with CTPA:**

Structures of 'webs' formed at the segmental branches are reported to be observed by using CTPA.8) However, fine structures of the webs and slits formed at the subsegmental branches can hardly be evaluated sufficiently by using CPTA. Therefore, we assessed the diagnostic values of CBCT images in comparison with CTPA. Number of the type 1-3 lesions, in which webs and/or slits were observed by the CBCTs, were 40 in segmental branches and 90 in subsegmental branches as listed in table 1. Among these lesions all 40 lesions in segmental branches were detectable in CTPA, whereas the only 62 lesions (62/90=69%) in subsegmental lesions were observed in CTPA. This indicates that detectability of CBCT for organized thrombus in subsegmental branches was superior to that of CTPA. Though all the lesions in segmental branches found in CBCT images could be observed by CTPA, resolution of the CBCT images are superior to that of CTPA as shown in fig.6.

CBCT was found to be superior to CTPA for the diagnosis of intra-arterial organized thrombus within the peripheral pulmonary arteries. We think that the CBCT during pulmonary angiography is useful for the pre-treatment diagnosis of subsegmental lesions before BPA.
### Table 1

Number of lesions and involved branches in segmental and subsegmental pulmonary arteries.

<table>
<thead>
<tr>
<th>Type</th>
<th>Segmental Lesions</th>
<th>Involved br.</th>
<th>Subsegmental Lesions</th>
<th>Involved br.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>28</td>
<td>30</td>
<td>64</td>
<td>72</td>
</tr>
<tr>
<td>Type 2</td>
<td>12</td>
<td>13</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Type 3</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Type 4</td>
<td>7</td>
<td>7</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

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Fig. 6: 70-year-old woman with CTEPH. (a) and (c) show reconstructed axial images obtained by CBCT during pulmonary angiography, (b) and (d) show axial images of CTPA at the same lesions as (a) and (c), respectively. An organized thrombus at A10 segmental branch is shown in (a) and (b), whereas 'slit' at A10c subsegmental branch is shown in (c) and (d). As shown in (d), the 'slit' could not be observed in A10c subsegmental branch.

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Conclusion

Organized thrombus at subsegmental pulmonary arteries in patients with CTEPH could be precisely evaluated by CBCT during pulmonary angiography. Considering not only the forms of the organized thrombus but also the indication of BPA, CBCT was found to be superior to the conventional CTPA.
References


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