Recent progress in the diagnosis and management of chronic thromboembolic pulmonary hypertension

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A B S T R A C T

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension caused by non-resolving thromboembolisms of the pulmonary arteries. In Japan, in contrast to Western countries, CTEPH is more prevalent in women. A Japanese multicenter study reported that a form of CTEPH unrelated to deep vein thrombosis is associated with HLA-B*5201, suggesting that this form of CTEPH may be associated with vasculopathy. CTEPH can be cured by pulmonary endarterectomy, provided that the thrombi are surgically accessible; thus, early diagnosis is important, and all patients with exertional dyspnea should be evaluated for pulmonary hypertension. Ventilation/perfusion scans provide an excellent non-invasive means to distinguish CTEPH from pulmonary arterial hypertension. Similarly, computed tomographic pulmonary angiograms allow for the detection of thrombi and evaluation of pulmonary hemodynamics in a minimally invasive manner. Importantly, the absence of subpleural perfusion on pulmonary angiograms can suggest the presence of small vessel disease. Small vessel disease might be involved in the pathogenesis of CTEPH, and its detection is essential in preventing operative death. Although no modern therapies for pulmonary arterial hypertension have been approved for treatment of CTEPH, a recent randomized control trial of riociguat in patients with CTEPH demonstrated that riociguat significantly improved 6-min walking distance. Further investigations into treatments that target endothelial dysfunction and hyperproliferative CTEPH cells are needed. Recently, balloon pulmonary angioplasty has emerged as a promising treatment modality in Japan. A specialized medical team, including at least one expert surgeon, should make decisions regarding patients’ candidacy for pulmonary endarterectomy and/or balloon pulmonary angioplasty.

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Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; PH, pulmonary hypertension; DVT, deep vein thrombosis; PE, pulmonary embolism; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; BPA, balloon pulmonary angioplasty; Ppa, pulmonary arterial pressure; CT, computed tomographic; CTPA, computed tomographic pulmonary angiography; PVR, pulmonary vascular resistance; SPECT, single-photon emission computed tomography; MR, magnetic resonance; RCT, randomized controlled trial; MD, 6-min walk distance

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1. **Introduction**

Chronic thromboembolic pulmonary hypertension (CTEPH) has traditionally been defined as pulmonary hypertension (PH) caused by single or recurrent pulmonary emboli arising from deep vein thrombosis (DVT). These embolic events are not always clinically apparent. In such cases, a silent acute pulmonary embolism (PE) is the initiating event, and subsequent pulmonary vascular remodeling (small vessel disease) causes progression to PH. Hence, modern therapies for pulmonary arterial hypertension (PAH) may be efficacious in patients with CTEPH [1,2].

Accurate diagnosis of CTEPH is very important because certain procedures have been shown to improve outcome. For example, CTEPH can be cured by pulmonary endarterectomy (PEA) [3–9], and balloon pulmonary angioplasty (BPA) may improve pulmonary hemodynamics and survival in patients with distal-type disease [10–13].

Here, we review recent progress in the diagnosis and management of CTEPH.

2. **Definition**

CTEPH develops because of chronic occlusion of pulmonary arteries by organized thrombi. It is defined as a mean pulmonary arterial pressure (Ppa) ≥25 mmHg and normal pulmonary capillary wedge pressure despite anticoagulation therapy for more than 3 months [14,15]. In patients who meet these criteria and have segmental defects on perfusion scans, the diagnosis of CTEPH should be confirmed by chronic embolic findings on pulmonary angiography or computed tomographic (CT) pulmonary angiography.

3. **Epidemiology**

In the United States, it is estimated that an acute PE occurs in 0.5 to 0.6 million individuals each year, and CTEPH develops in approximately 0.1% to 0.5% of patients surviving the acute phase of PE [3,16]. However, the incidence of CTEPH may be higher; a recent study showed that CTEPH occurs in 3.8% of patients with a history of acute PE [17]. Another study revealed that the cumulative incidence of CTEPH is 0.57% in all patients with PE and 1.5% in patients with unprovoked PE [18]. Thus, physicians should be aware of the risk of progression to CTEPH when treating patients with acute PE. In Japan, the Respiratory Failure Research Group from the Ministry of Health, Labor and Welfare (MHLW) established criteria for the diagnosis of CTEPH during a nationwide survey in 1997. The number of patients with CTEPH was estimated to be 450 (95%...
confident interval, 360–530) [19], which designated it as a specified rare and intractable disease. The MHLW has since conducted annual epidemiological surveys of CTEPH. In 2010, 1288 patients with CTEPH were registered as having this specified rare and intractable disease [20].

4. Etiology and characteristics of Japanese CTEPH

The pathogenic mechanisms that cause CTEPH are still uncertain. CTEPH is considered as a chronic condition occurring in patients with a history of acute PE caused by DVT. However, up to 40% of patients with CTEPH have not had clinically apparent acute embolic episodes [21].

CTEPH results from obstruction of more than 40% of the pulmonary vascular bed by unresolved thromboemboli [22]. Thrombophilia due to mutations in protein C, protein S, antithrombin, prothrombin, or factor V has not been significantly associated with CTEPH. Factors that have been linked to CTEPH include anti-cardiolipin antibodies, which are found in 10% to 20% of patients, and elevated factor VIII [23,24]. Several additional risk factors have been associated with CTEPH, including chronic inflammatory disorders, myeloproliferative syndromes, and splenectomy [25]. The association of CTEPH with these conditions suggests that chronic inflammatory processes are involved in its pathogenesis.

Patients with CTEPH may remain asymptomatic for months or years (“honeymoon period”) regardless of whether or not they have a history of acute embolic episodes. The pathological mechanisms that occur during this asymptomatic period are unknown. It is possible that recurrent thromboembolism and in situ thrombosis are involved in the progression to symptomatic PH. However, several investigators have suggested that PH results from pulmonary vascular remodeling (small vessel disease) that occur secondary to the initial PE event. If CTEPH is indeed a small vessel disease, it may develop in a manner similar to PAH [1,2,26].

Analysis of a subset of 519 patients among the 1288 patients in the MHLW CTEPH registry in 2011 revealed that female patients outnumbered male patients (2.6:1), and the mean age was 64 ± 13 years. Interestingly, while no gender difference was observed in younger patients, the female-to-male ratio increased in patients older than 40 years of age [27].

A comparison of important clinical characteristics between patients in the Japanese MHLW registry and those in the international registry is shown in Table 1 [28]. Japanese patients were predominantly female, had better World Health Organization (WHO) functional status, mild hemodynamic impairment, fewer incidents of acute PE, and fewer coagulopathies. Significantly fewer patients in the Japanese registry underwent PEA, which may be related to the fact that patients who improved after surgery were excluded from the registry until 2009. Nonetheless, fewer patients in the Japanese registry underwent surgical treatment. Similar to patients in the international registry, however, half of the Japanese patients underwent operations at Chiba University Hospital, one of the PEA referral centers in Japan [29]. Japanese patients were more likely to have an inferior vena cava filter, even in medically treated cases. In addition, Japanese patients were more likely to be prescribed modern PAH therapies, even in surgically treated cases [27].

Shigeta et al. reported a Japanese series in which female patients with CTEPH were more likely to be elderly, have fewer occurrences of DVT or acute embolic episodes, and have different clinical characteristics than male patients with CTEPH [30].

Tanabe et al. found a significantly higher frequency of HLA-B*5201 in Japanese patients with CTEPH (40%) than in normal controls (24%) or in patients with acute PE (10%), and HLA-B*5201—positive patients were predominantly female (83%) [24]. The frequency of HLA-B*5201 in patients with CTEPH was similar to that reported in patients with Takayasu arteritis (41.3%), a chronic vasculitis involving the aorta and its major branches as well as the coronary and pulmonary arteries. Multicenter Japanese studies have revealed a strong

| Table 1 |

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Japanese registry</th>
<th>International registry</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>519</td>
<td>679</td>
<td>NA</td>
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<tr>
<td>Gender, % male</td>
<td>28.1</td>
<td>50.1</td>
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</tr>
<tr>
<td>Age, y, median [Q1; Q3]</td>
<td>67 [53;75]</td>
<td>63 [51;72]</td>
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</tr>
<tr>
<td>World Health Organization class, % I/II/III/IV</td>
<td>5.2/41.9/47.7/5.2</td>
<td>0.7/17.8/68.6/12.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6-min walk distance, m, median [Q1; Q3]</td>
<td>330 [248;410]</td>
<td>329 [245;427]</td>
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</tr>
<tr>
<td>History of deep vein thrombosis, %</td>
<td>50.4</td>
<td>56.1</td>
<td>ns</td>
</tr>
<tr>
<td>History of acute pulmonary embolism, %</td>
<td>37.2</td>
<td>74.8</td>
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</tr>
<tr>
<td>Coagulopathies, %</td>
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<td>31.9</td>
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<tr>
<td>Cancer, %</td>
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<td>12.7</td>
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<td>Mean pulmonary arterial pressure, mmHg, median [Q1; Q3]</td>
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<td>47 [38;55]</td>
<td>NA</td>
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<tr>
<td>Pulmonary vascular resistance, dyne s cm⁻⁵, median [Q1; Q3]</td>
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<td>709 [480;988]</td>
<td>NA</td>
</tr>
<tr>
<td>Pulmonary endarterectomy, %</td>
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<tr>
<td>Inferior vena cava filter, %</td>
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<td>12.4</td>
<td>&lt;0.0001</td>
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<tr>
<td>Modern pulmonary arterial hypertension therapy, %</td>
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<td>37.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are expressed as medians with first and third quartiles [Q1; Q3] or percentages. Data are from new cases in the Japanese Registry (n = 138).

NA, not assessed.

* p value obtained from the chi-square test.
association of IKBL^p03 (odds ratio, 2.33; 95% confidence interval, 1.49–3.66; p=0.00017; pc=0.033) and B^s5201 (odds ratio, 2.47; 95% CI, 1.56–3.90; p=0.000086; pc=0.016) with DVT-negative CTEPH [31]. IKBL^p03 is a polymorphism in the promoter region of the gene coding for nuclear factor κB inhibitor-like protein (IKK-p allele), and it has been associated with Takayasu arteritis [32]. Hence, inflammatory processes may be involved in the pathogenesis of DVT-negative CTEPH in Japanese populations. It should be noted that Takayasu arteritis was differentiated from CTEPH in this study by CT angiography and by the absence of macroscopic findings during surgery. We have observed thrombus growth into the proximal side of the pulmonary artery in 3 HLA-B^s5201-positive patients whose C-reactive protein levels were <0.3 mg/dL. The results of one autopsy showed diffuse inflammatory cell infiltrates in the media of the large elastic pulmonary arteries to which thrombi were attached. Those findings mimicked Takayasu arteritis but were differentiated from this entity based on the lack of adventitial lesions. It is possible that more cases of undiagnosed pulmonary arteritis secondary to thrombi have occurred in HLA-B^s5201-positive patients with CTEPH [24].

4.1. Clinical presentations

Progressive exertional dyspnea and exercise intolerance are common in patients with CTEPH, whether or not they have a history of clinically relevant acute PE. A “honeymoon period” between the acute episode and the diagnosis of CTEPH is common and may last from months to years [2,16,22]. In patients who do not have a known history of acute PE, progressive exertional dyspnea and fatigue appear to be caused by elevated Ppa and decreased maximal cardiac output, similar to patients with PAH. As the disease progresses, patients develop exertional chest pain, syncope, and lower extremity edema, which are indicative of decreased cardiac output at rest and right heart failure.

In a study of patients with inoperable CTEPH, patients with a mean Ppa ≥40 mmHg had a poor prognosis (5-year survival, ~30%) but those with a mean Ppa <30 mmHg did not [33]. Hence, precise evaluation and surgical intervention, when appropriate, are essential to survival.

Physical findings of CTEPH are often subtle but may include a prominent pulmonary component of S2 and a systolic murmur reflecting tricuspid regurgitation. Signs of right heart failure (dilated neck veins, edema, ascites, and acrocyanosis) occur later in the course of the disease. Approximately 30% of patients have a bruit somewhere in the lung fields. These flow murmurs originate from turbulent blood flow through partially occluded vessels or through recanalized thrombi [2].

4.2. Diagnostic strategy

PH, including CTEPH, should be suspected in all patients with unexplained dyspnea [14,15]. Suspicion should be even higher in patients who have had a PE and/or DVT. The first objective finding in early CTEPH may be desaturation during exercise [3]. Echocardiography is widely used as an initial test for detecting PH and excluding left heart disease and shunt. Screening echocardiography, performed 6 weeks after the diagnosis of acute PE, can identify patients with persistent PH and may be of value in planning follow-up care [34]. Chest roentgenography may be normal in early CTEPH and is thus not diagnostic, although several abnormalities may occur in later stages of disease [3]. Electrocardiography is also non-diagnostic; however, certain findings are associated with PH, including right ventricular hypertrophy or strain with right axis deviation, complete or incomplete right bundle branch block, and nonspecific ST-T changes in leads V1 to V3. PaO2 may also be normal, although the alveolar–arterial oxygen tension gradient is typically widened.

Ventilation/perfusion (V/Q) scans are excellent noninvasive tests with which to distinguish CTEPH from PAH [14,15], while CT angiography is useful for differentiating CTEPH from arteritis, tumors, and congenital anomalies of the pulmonary arteries [15,21,35]. Pulmonary angiography is still considered the gold standard for evaluation of CTEPH. Right heart catheterization is required to confirm precapillary PH (mean Ppa ≥25 mmHg and pulmonary capillary wedge pressure ≤15 mmHg) after patients have been adequately anticoagulated for more than 3 months [14,15].

5. Imaging

5.1. Chest roentgenography

In patients with CTEPH, chest roentgenography may appear normal and demonstrate clear lung fields, but close examination may reveal areas of hyperperfusion or hypoperfusion with enlargement or asymmetry of the central pulmonary arteries. Right atrial and right ventricular enlargement may occur in PH and will appear on lateral CT views as obliteration of the retrosternal space by the cardiac shadow [3]. Satoh et al. reported that an avascular area or marked dilatation of the right descending pulmonary artery, together with pleuritic changes, suggests the presence of CTEPH [36].

5.2. V/Q scans and single photon emission computed tomography

In patients with unexplained PH, a V/Q scan is recommended to exclude CTEPH [2,21,22,25]. The presence of either normal or mottled perfusion scans can suggest PAH, while even one unmatched perfusion defect suggests CTEPH (Fig. 1). Matched perfusion defects and elevated ventilation-to-perfusion defects suggest PH due to lung disease and/or hypoxemia. In a study of 227 patients that compared detection of CTEPH by V/Q scan with detection by multi-slice computed tomographic pulmonary angiography (CTPA), V/Q scans demonstrated a sensitivity of 96%–97.4% and a specificity of 90%–95% and CTPA demonstrated a sensitivity of 51% and a specificity of 99% [37]. Although V/Q scans demonstrated a higher sensitivity in detection of CTEPH (Fig. 1), V/Q findings have been shown to underestimate the severity of angiographic findings and do not correlate with pulmonary vascular resistance (PVR) or mean Ppa [38].

A recent pilot study comparing single-photon emission computed tomography (SPECT) perfusion scans with CTPA showed that SPECT is more sensitive than CTPA in identifying
obstructed segments [39] (Fig. 2a and b). The investigators suggest that this increased sensitivity might be important not only during initial evaluations but also during postsurgical follow-up care [39].

5.3. CTPA

CTPA is often the first choice for imaging in patients who have had a recent acute embolic episode. CT angiography is also indicated when a V/Q scan is indeterminate or shows perfusion defects. Recently, 64- or 320-detector row CTPA has been shown to be an accurate and reliable noninvasive alternative to pulmonary angiography in evaluating patients with CTEPH. The sensitivity and specificity of CTPA in detecting thromboembolic findings were 97.0%–98.3% and 94.8%–97.1% at the main/lobar level, respectively, and 85.8%–94.1% and 92.9%–94.6% at the segmental level, respectively [40,41]. Three-dimensional CT angiography reveals chronic embolic findings consistent with those in pulmonary angiography (Fig. 3); however, poor correlation between the CT-derived obstruction index and PVR has been reported [42]. Pulmonary vascular remodeling may result in a disproportionately elevated PVR compared with that produced by proximal thrombi. Recently, the development of electrocardiography-gated CTPA has allowed for the simultaneous evaluation of thrombi location and right ventricular function. Sugiuira et al. reported good correlation between bowing of the interventricular septum (expressed as curvature) and systolic Ppa (r = 0.79, p < 0.001) and mean Ppa (r = −0.86, p < 0.001) [41] (Fig. 4). Liu et al. reported that the Cobb angle (the angle between the interventricular septum and the line between the sternal midpoint and thoracic vertebral spinous process, measured during diastole) on transverse images is a reliable tool for estimating PVR [42].

CTPA is also used to differentiate CTEPH from other pulmonary vascular diseases in patients with perfusion defects. Unilateral obstruction on perfusion scans is rare in CTEPH but suggests the presence of other diseases, such as sarcoma of the pulmonary artery (Fig. 5c), Takayasu arteritis (Fig. 5d), cancer, or mediastinal fibrosis [15,21,35]. In addition, 3-dimensional CTPA is used to differentiate CTEPH from congenital anomalies of the pulmonary arteries [43]. High-resolution CT of the lung shows a diagnostic pattern of mosaic attenuation (mixed hyperperfused and hypoperfused areas) in CTEPH, independent of the presence of contrast media (Fig. 2d) [35].

Dual-energy CTPA allows for evaluation of lung perfusion and thrombus location. Simultaneous acquisition of data sets at 80 and 140 kV can be used to visualize iodine distribution maps (lung perfusion blood volume images) in the pulmonary parenchyma, which reflect lung perfusion. Imaging of lung perfusion blood volume by dual-energy CT has been reported to be comparable to SPECT perfusion scans in establishing a diagnosis of CTEPH [44].

5.4. Magnetic resonance imaging

Magnetic resonance (MR) imaging may also provide a clear diagnosis of CTEPH [33], but a recent report suggested that it is less effective than multidetector CTPA in assessing the pulmonary arteries of patients with CTEPH [45]. However, contrast-enhanced MR angiography may be useful in discriminating central thromboembolic lesions from tumors; with contrast-enhanced MR, the latter are enhanced with gadolinium, whereas the former are not [2]. Moreover, MR imaging is the gold standard for quantifying right ventricular function and dimensions in patients with PAH or CTEPH [35]. This is important because Reesink et al. reported that after PEA, changes in total PVR correlate with changes in right ventricular ejection fraction, right ventricular mass, and leftward ventricular septal bowing [46].

5.5. Pulmonary angiography

Pulmonary angiography is the gold standard for diagnosing CTEPH and assessing operability [14,15,21]. Five distinct angiographic findings correlate with the presence of organized thromboemboli: pouch defects, webs or bands, intimal irregularities, abrupt narrowing, and complete obstruction [47]. Pulmonary angiography allows for visualization of proximal and distal thromboembolic findings in the elastic pulmonary arteries. It also helps to determine if thromboemboli are surgically accessible by providing an assessment of capillary perfusion (Fig. 6) [48]. Pulmonary angiography can be performed safely in patients with severe CTEPH and is often performed in conjunction with a diagnostic right heart catheterization [49]. Selective nonionic contrast injections into the right and left main pulmonary arteries should be performed on a biplane digital subtraction system. It should be noted that, unlike CTPA, pulmonary angiography cannot fully assess the pulmonary trunk [45].

6. Classic therapy

Patients with CTEPH, whether treated medically or with PEA, must receive lifelong anticoagulant therapy to avoid a recurrence of venous thromboembolism and to prevent progression of thrombus growth within the pulmonary arteries [14,15,21]. Warfarin is the most commonly used anticoagulant and is generally administered to achieve a prothrombin time/international normalized ratio of 2 to 3 (1.5 to 2.5 according to Japanese guidelines) [14,15]. Patients who experienced an acute embolic episode show rapid disease progression. When D-dimer levels are high during disease progression, thrombolytic therapy may improve outcome [15]. Finally, although there is no conclusive evidence regarding the utility of oxygen therapy in patients with CTEPH, it is believed to improve both quality of life and prognosis [15].

7. PEA

PEA, a standard surgical procedure for removal of surgically accessible central thrombi, is performed worldwide, usually at expert centers [3–9]. PEA offers early and significant decreases in both mean Ppa and PVR and later improvements in gas exchange [50].
7.1. Indication for surgery

The selection criteria for PEA include (1) mean Ppa $>30\,\text{mmHg}^{2}$ (resulting in a calculated PVR of $>300\,\text{dyn s cm}^{-5}$) even after oral anticoagulant therapy for $>6\,\text{months}$, (2) WHO functional class $\geq 2$, (3) thrombi that are accessible to current surgical techniques (i.e., located in the main, lobar, or segmental arteries), and (4) absence of severe associated disease [15,51].
In symptomatic young patients who want to improve their daily activity, surgery should be considered even in those with mild resting PH and exercise-induced PH [3,26].

### 7.2. Surgical technique

The PEA procedure developed at the University of California, San Diego is performed through a median sternotomy and requires intermittent deep hypothermic circulatory arrest [3,51]. This surgical procedure has been described in detail elsewhere [3,51]. Briefly, PEA is performed with intermittent circulatory arrest to avoid bleeding from systemic-to-pulmonary collateral circulation, and deep hypothermia (20 °C) is induced to prevent brain damage. It is important to find the correct dissecting plane during endarterectomy, because the plane is followed all the way to the lobar, segmental, or subsegmental arteries of each lobe.

An inferior vena cava filter should be considered before surgery to prevent recurrent emboli within the perioperative period, particularly in patients with a history of DVT [3,26,51]. Cardiovascular risk should be assessed preoperatively by coronary angiography or CT coronary angiography, and coronary artery bypass surgery, if necessary, can be performed without risk [38,48].

### 7.3. Short-term results

Thistlethwaite et al. reported an overall mortality of 4.7% in 1100 consecutive patients who underwent PEA [51]. Patients with a postoperative PVR > 500 dyn s cm⁻⁵ had significantly higher mortality (5.7%) compared with those with a postoperative PVR < 500 dyn s cm⁻⁵ (1.2%). The investigators classified intraoperative thromboembolic disease into 4 types: type 1, fresh thrombus in the main/lobar pulmonary arteries (37.7%) (Fig. 6b); type 2, intimal thickening and fibrosis proximal to the segmental arteries (42.6%); type 3, disease within distal segmental arteries only (17.5%); and type 4, distal arteriolar vasculopathy without visible thromboembolic disease (2.2%). Patients with distal thromboembolic disease type 3 or type 4 had higher perioperative mortality (6.3% and 16.7%, respectively) than patients with type 1 or type 2 disease (3.9% and 4.7%, respectively) [51]. Results from a prospective international registry revealed that median PVR decreased from 698 dyn s cm⁻⁵ before PEA to 235 dyn s cm⁻⁵ after PEA, and in-hospital mortality was 4.4% [6]. In Japan, similar levels of operative mortality were reported by Ando et al. (8.3% when undergoing elective PEA) [7], Ogino et al. (8.0%) [8], and Ishida et al. (initially 14%, but more recently reduced to 7.5%) [9].

### 7.4. Long-term results

The University of California, San Diego group achieved a 6-year survival rate of 75% in 308 patients who underwent
More recently, Corsico et al. reported a 5-year survival rate of 84% in 157 patients who underwent PEA between 1994 and 2006 [5]. In Japan, Ishida et al. reported that freedom from disease-specific death was 84% and 82% at 5 and 10 years, respectively [9].

7.5. Risk factors for surgery

Several reports have demonstrated that high preoperative PVR is a significant prognostic factor for postsurgical complications [1,2,6,21]. One international registry showed that the mortality rate was 2.8% in patients with PVRs between 400 and 800 dyn s cm\(^{-5}\), 5.8% in patients with PVRs between 800 and 1200 dyn s cm\(^{-5}\), and 10.6% in patients with PVRs >1200 dyn s cm\(^{-5}\) [6]. One explanation for this is that patients with PVRs that are disproportionate to the amount of visible central lesion obstruction are likely to have distal thrombi and severe pulmonary vascular remodeling, which results in poor outcome after PEA [1,2]. Kim et al. used pulmonary arterial occlusion waveform analysis to determine that upstream resistance was inversely correlated to both postoperative total pulmonary vascular index and mean Ppa. Further, all non-survivors had upstream resistance >60%, indicating peripheral-type disease [52]. Tanabe et al. recently used the capillary phase in pulmonary angiography to focus on subpleural perfusion and found that the absence of subpleural perfusion in any segment, coupled with high PVR, might be related to small vessel disease and results in poor outcome after surgery [48].
8. Modern PAH therapy

The progression of CTEPH may be caused by small vessel disease, similar to PAH, but no medications for PAH have been approved for the treatment of CTEPH [1,2]. However, medications for PAH have been used off-label in patients with CTEPH who have inoperable disease or patients with persistent PH after PEA and have been used as therapeutic bridges before PEA [26]. According to the international registry, more than one-third of patients with CTEPH were treated medically. Of those, half received modern PAH therapies such as phosphodiesterase-5 inhibitors and endothelin receptor antagonists [28]. Similarly, a Japanese series showed that more than half of patients with CTEPH were treated with modern PAH medications beraprost, bosentan, or sildenafil [27].

8.1. Endothelin receptor antagonists

In a randomized controlled trial (RCT) of patients with inoperable disease or persistent PH after surgery, treatment with bosentan led to a significant improvement in PVR (−24.1% of baseline) but did not significantly improve 6-min walk distance (6MD) [53]. In a recent meta-analysis of 11 studies (totaling 269 patients), bosentan was associated with improved pulmonary hemodynamics and exercise capacity [54]. In an uncontrolled study of several types of PH, ambisentan led to a modest increase in 6MD (mean, 17 m) in patients with CTEPH [55].

8.2. Phosphodiesterase-5 inhibitors

Reichenberger et al. showed that sildenafil improved PVR and 6MD in an open-label study of 104 patients with inoperable CTEPH [56]. In a small double-blind RCT of patients with inoperable CTEPH, Suntharalingam et al. reported that sildenafil did not significantly improve 6MD relative to placebo but significantly improved several secondary endpoints at both 3 months (PVR and WHO class) and 12 months (6MD, PVR, WHO class) [57]. They further reported that the change in PVR after 12 months of treatment with sildenafil correlated with the change in PVR during vasoreactivity testing with sildenafil.

8.3. Prostanoids

Olchewski et al. reported the results of a RCT in which inhaled iloprost was tested in 203 patients with PH, including 57 patients with CTEPH. Iloprost improved exercise capacity and pulmonary hemodynamics compared with placebo, but the beneficial effect was less prominent in patients with CTEPH than in patients with PAH [58]. In an uncontrolled study of 28 patients with inoperable CTEPH, subcutaneous treprostinil therapy significantly improved PVR. Furthermore, 5-year survival in patients treated with treprostinil was significantly better than in a historical control group (53% vs. 16%) [59]. In a retrospective study of 27 patients with inoperable CTEPH, epoprostenol improved mean Ppa, total PVR, 6MD, and New York Heart Association class [60]. In an uncontrolled study in Japan, Ono et al. reported that oral beraprost improved New York Heart Association class in 10
patients (50%) and significantly decreased total pulmonary resistance from 18 ± 6 to 15 ± 8 Wood units (p < 0.05). Sixteen patients died of cardiopulmonary causes in the group receiving conventional therapy, while only 3 patients died of cardiopulmonary causes in the group receiving beraprost. Condliffe et al. recently reported improved survival in patients treated with bosentan and sildenafil [29]. Recently, an international RCT showed that patients with CTEPH treated with soluble guanyl cyclase (riociguat) had a statistically significant improvement in 6MD and PVR [63,64]. Jensen et al. have suggested that modern PAH therapy has minimal effect on pre-PEA pulmonary hemodynamics and no effect on post-PEA outcomes/hemodynamics [65]. The guidelines recommend that patients with CTEPH should first be assessed for PEA eligibility at an expert center. Next, their eligibility for clinical studies should be evaluated. In the remaining cases, patients can be treated with off-label modern PAH therapy over a limited period, such as 6 months, and then reevaluated to determine if continuation of therapy is justified [66].

9. **Recommendation for modern PAH therapy**

The clinical efficacy of modern PAH therapy in CTEPH remains to be demonstrated by an RCT. However, Condliffe et al. recently reported improved survival in patients treated with endothelin receptor antagonists and phosphodiesterase-5 inhibitors [62], and Nishimura et al. reported improved survival in patients treated with bosentan and sildenafil [29]. Recently, an international RCT showed that patients with CTEPH treated with soluble guanyl cyclase (riociguat) had a statistically significant improvement in 6MD and PVR [63,64]. Jensen et al. have suggested that modern PAH therapy has minimal effect on pre-PEA pulmonary hemodynamics and no effect on post-PEA outcomes/hemodynamics [65]. The guidelines recommend that patients with CTEPH should first be assessed for PEA eligibility at an expert center. Next, their eligibility for clinical studies should be evaluated. In the remaining cases, patients can be treated with off-label modern PAH therapy over a limited period, such as 6 months, and then reevaluated to determine if continuation of therapy is justified [66].

Fig. 7 – Selective pulmonary angiograms before, during, and after BPA. (a) Pulmonary angiogram before BPA. Mean Ppa was 38 mmHg, and PVR was 632 dyn s cm⁻⁵. (b) Pulmonary angiogram during balloon inflation. (c) Pulmonary angiogram after BPA. After BPA of 7 vessels, mean Ppa decreased to 21 mmHg and PVR decreased to 312 dyn s cm⁻⁵. Pictures of pulmonary angiograms were provided by Professor Toru Satoh and Dr. Takumi Inami with permission. BPA, balloon pulmonary angioplasty; Ppa, pulmonary arterial pressure; PVR, pulmonary vascular resistance.
10. BPA

Many patients with CTEPH have disease that is not amenable to surgery, and other interventions are required. Feinstein et al. performed BPA in 18 patients with CTEPH. Each patient underwent an average of 2.6 procedures (range, 1 to 5) and 6 dilations (range, 1 to 12). Approximately 36 months after BPA, the average WHO class improved from 3.3 to 1.8 (p < 0.001), 6MD increased from 209 to 497 yards (p < 0.0001), and the mean Ppa decreased from 43.0 ± 12.1 to 33.7 ± 10.2 mmHg. However, 11 patients developed reperfusion pulmonary edema, 3 required mechanical ventilation, and 1 died [10].

Recently, Japanese investigators improved upon the traditional BPA technique by using smaller-sized balloons and dilating fewer lobes per procedure under the application of modern PAH therapies and noninvasive positive pressure ventilation. These modifications resulted in improved efficacy and fewer severe complications due to reperfusion injury [11–13] (Fig. 7). Of note, it is possible to perform BPA multiple times in patients who have unresolved PH after PEA. Although the long-term survival benefit of BPA remains uncertain, improved hemodynamics could result in improved survival. It remains unclear, however, if BPA improves gas exchange, and the necessity of modern PAH therapy before and/or after BPA remains controversial.

10.1. Current practical treatment

Recent surgical techniques have decreased the mortality rate during PEA and made it possible to perform endarterectomy in patients with distal-type thrombi (type 3). However, modern PAH therapy and BPA are emerging as alternative treatments for patients with surgically inaccessible disease and in patients who refuse PEA. BPA could be a high-risk procedure in patients with high PVR (which indicates severe pulmonary vascular remodeling), in contrast to patients with mild to moderate PVR (which indicates distal thrombi). However, BPA in combination with modern PAH therapy might be safe and practical in severe cases. We suggest that a specialized medical team, including at least one expert surgeon, should make decisions regarding the patient’s candidacy for PEA and/or BPA.

10.2. Future treatment

Maruoka et al. and Sakao et al. reported that organized thrombotic tissue in CTEPH is composed of myofibroblast-like cells, characterized as hyperproliferative and anchorage independent. Myofibroblast-like cells promote endothelial cell transition to other mesenchymal phenotypes and/or induce endothelial cell dysfunction [67,68]. Ogawa et al. reported that inhibition of mTOR attenuates reduced platelet-derived growth factor-stimulated cell proliferation in CTEPH [69]. Both groups propose that rapamycin may have therapeutic benefit in CTEPH [67,69]. Imatinib and other antiproliferative therapies are being evaluated in PAH [70], but the value of systemic or local antiproliferative therapy in patients with CTEPH requires further investigation.

11. Conclusion

Modern PAH therapies may have beneficial effects in CTEPH, and clinical studies investigating new drugs for patients with inoperable CTEPH are underway. Recent advances in BPA are likely to change the CTEPH treatment algorithm. It is important to diagnose CTEPH early to determine surgical candidacy and reduce surgical risk. To prevent the progression of CTEPH, the mechanisms underlying the chronicity of PH should be elucidated, as well as the role of endothelial dysfunction, inflammation, and hyperproliferative cells.

Conflicts of interest

Nobuhiro Tanabe received lecture fees from Actelion. Koichiro Tatsumi received a grant to the Respiratory Failure Research Group from the Ministry of Health, Labor and Welfare of Japan. Toshihiko Sugiuira has no potential conflict of interests.

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