Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) has generally been thought to be caused by single or recurrent pulmonary emboli arising from deep vein thrombosis (DVT). However, CTEPH patients have not always had clinically apparent acute pulmonary embolic episodes. In addition, both a female predominance and an association of HLA with CTEPH unrelated to deep vein thrombosis are observed in Japan, thus suggesting this condition to be a type of pulmonary vasculopathy. The key for making an accurate diagnosis is to consider CTEPH in any patients with dyspnea on exertion. Perfusion scans provide an excellent noninvasive tool for distinguishing between pulmonary arterial hypertension (PAH) and CTEPH, while CT angiography is useful for differentiating arteritis, tumor, and a congenital anomaly of the pulmonary artery from CTEPH. Pulmonary angiography (PAG) is still considered the gold standard for evaluating CTEPH. No subpleural perfusion in any segments by PAG with high pulmonary vascular resistance is might be related to small vessel disease, thus resulting in a poor outcome after surgery. Recent data suggest a potential therapeutic benefit of antiproliferative therapy for cells isolated from endarterectomized tissue.

Key words: chronic thromboembolic pulmonary hypertension, perfusion scan, pulmonary angiography, HLA, pulmonary vascular remodeling
diagnostic of the surgical outcome. This study also reviews the mechanism and assessment of pulmonary vascular remodeling, and an approach for the treatment of vascular remodeling.

**Pathogenesis and Pulmonary Vascular Remodeling**

The true incidence and prevalence of CTEPH is unknown. From 0.1% to 0.5% of the patients who survive an episode of acute pulmonary embolism have been reported to develop CTEPH.7) A prospective study following survivors of acute pulmonary embolism showed that 3.8% of such patients developed CTEPH within 2 years.8) However, up to 40% of the patients with CTEPH demonstrate no clinically apparent acute embolic episodes.

CTEPH results from a greater than 40% obstruction of the pulmonary vascular bed by unresolved thromboemboli.7) Thrombophilia due to mutations in protein C, protein S, antithrombin, prothrombin, or factor V is not significantly associated with CTEPH. The only factors linked to CTEPH are anticardiolipin antibodies, which are found in 10% to 20% of the patients, and elevated factor VIII.9) Several risk factors associated with CTEPH have so far been identified, including chronic inflammatory disorders, myeloproliferative syndromes, and splenectomy.9) The association with these conditions suggests that chronic inflammatory processes are involved in the pathogenesis of CTEPH.

Patients may remain asymptomatic for months or years (honeymoon period) regardless of the history of acute embolic episodes. The pathological mechanism during this period, however, is unknown. Recurrent thromboembolism and in situ thrombosis may be involved in progressive pulmonary hypertension. However, Galié and Kim suggest that acute pulmonary embolism might be an initiating event and pulmonary hypertension may thus result from pulmonary vascular remodeling (small vessel disease) according to the following evidence:10) First; there is little correlation between the extent of central obstruction visible on pulmonary angiography and the degree of pulmonary hypertension, Second; there is progressive pulmonary hypertension in the absence of recurrent thromboemboli, Third; there is evidence of a redistribution of the pulmonary blood flow from nonoccluded to newly endarterectomized areas after a pulmonary endarterectomy (vascular steal phenomenon), and Fourth; persistent pulmonary hypertension despite successful surgery is observed in approximately 10 to 30% of patients. They also categorized the mechanism for small vessel disease seen in CTEPH into three processes, which may occur alone or in combination as follows: (1) An obstruction of small subsegmental elastic arteries, (2) classical pulmonary arteriopathy in small muscular arteries and arterioles distal to non-obstructed elastic pulmonary arteries, and (3) arteriopathy in small muscular arteries and arterioles distal to obstructed elastic pulmonary arteries. The former 2 processes are also involved in the pathogenesis of pulmonary arterial hypertension (PAH).

In addition, mutations in bone morphogenetic protein receptor type 2 (BMPR-2) have been found in both familial and idiopathic PAH. Several reports suggest that these mutations are related to vascular remodeling in PAH. Although similar mutations have not been found in CTEPH, the expression of BMPR-1A required for BMPR-2 signaling is markedly downregulated in lung tissue specimens from CTEPH patients as well as in other types of pulmonary hypertension.11) Angiopoetin-1, a signaling molecule involved in angiogenesis and smooth muscle cell proliferation linked to pulmonary hypertension, is up-regulated in the lung tissue specimens obtained from CTEPH patients. Angiopoetin-1 cuts off the BMPR-1A expression and thereby blocks BMPR-2 signaling even in the absence of germline BMPR-2 mutations.

Plasma macrophage chemoattractant protein-1 (MCP-1) is elevated in patients with CTEPH and correlates with pulmonary vascular resistance (PVR).12) Elevations of IL 6, IL1, TNF-α and MCP-1 have also been reported in patients with idiopathic PAH. The plasma levels of endothelin-1 are elevated in CTEPH, and the upregulation of type B endothelin receptors on pulmonary arterial smooth muscle cells has been reported in CTEPH as well as efficacy of bosentan for patients with CTEPH.13) The molecular mechanisms involved in pulmonary vascular remodeling in CTEPH thus appear to be similar to those in PAH.

**Clinical Characteristics of CTEPH in Japan**

According to an annual report on CTEPH in Japan, the total number of CTEPH patients in Japan was 800 in 2007, and approximately 100 patients were newly registered, while another study reported that the estimated total number of new patients with pulmonary embolism was 4106, much less than the 630,000 reported in the US.14)
An analysis of 520 cases of 800 registered patients with CTEPH showed a remarkable female predominance (female to male ratio of 3.1) in comparison to that of 0.7 in the USA. The average age was 62 ± 13 yrs, and a female predominance was not observed in younger patients (< 40 yrs; Fig. 1). The frequency of DVT was 32.1%, lower than that in Western countries (35 to 45%).

Another study of 150 patients with CTEPH reported the female patients to be elderly and have less deep vein thrombosis, less acute embolic episodes, a better cardiac function, lower arterial oxygen tension, and more peripheral thrombi, thus resulting in a smaller improvement in PVR by surgery than that observed in males. The clinical phenotype of female CTEPH is thus considered to be different from that of male CTEPH.14)

ASSOCIATION OF HLA WITH CTEPH

Genetic screening was conducted to identify a possible genetic factor related to the difference in phenotype of CTEPH between the USA and Japan. The frequencies of HLA-B*5201 (40 versus 24%) and DPB1*0202 (19 versus 6%) are significantly higher in the patients. HLA-B*5201 positive patients show a significant female predominance (83%). These HLA alleles are not related to acute pulmonary embolism.5) Takayasu arteritis is a chronic type of vasculitis, mainly involving the aorta and its major branches, as well as the coronary and pulmonary arteries. This disease is also epidemiologically known for both its female predominance and an association with HLA-B*5201. The frequency of HLA-B*5201 (40%) in CTEPH was similar to that reported in Takayasu arteritis (41.3%).

Japanese multicenter studies have revealed a strong association between HLA markers and DVT-negative CTEPH, DPB1*0202 [odds ratio (OR) = 5.07, 95% confidence interval (CI) = 2.52–10.19, p = 0.00000075, corrected p-value (Pc) = 0.00014], IKBL-p*03 (OR = 2.33, 95% CI = 1.49–3.66, p = 0.00017, pc = 0.033) and B*5201 (OR = 2.47, 95% CI = 1.56–3.90, p = 0.000086, pc = 0.016), whereas no significant association has been observed for DVT-positive CTEPH.15) [IKBL-p*03 is one of the promoter polymorphism of NF-κB inhibitor like protein gene (IKBL p allele).] There is also an association of HLA-B*5201 and IKBL-P*03 with Takayasu arteritis and an association of IKBL-p*01 with rheumatic arteritis.16) The HLA region contains a number of genes that control inflammation and immune responsiveness to antigens, which might therefore underlie the process of susceptibility to immune-related disorders. The observation that the susceptibility genes to CTEPH were mapped within the HLA region suggested that the pathogenesis of DVT-negative, but not DVT-positive, CTEPH, occurred through an inflammatory process.15)

Bergin reported a higher central disease score to predict a better surgical outcome, while it is quantitated by adding the number of abnormal central portions (right main, right descending, left main, left descending pulmonary arteries) in each patient up to a maximum score of
4,7) There is a positive correlation between the central disease score and the percent decrease in PVR after surgery. However, when the patients are divide into HLA-B*5201 positive and–negative types, this correlation is observed in only the HLA-B*5201 negative type (Fig. 2). Takayasu arteritis was excluded from the series and it was confirmed intraoperatively, but pulmonary vasculopathy type might be involved in residual pulmonary hypertension after surgery in the Japanese series.

**CLINICAL PRESENTATION**

Progressive exertional dyspnea and exercise intolerance are common in patients with CTEPH whether the patients have had acute embolic episodes or not. A “ honeymoon period” between the acute episodes and the development of CTEPH is common and may last from months to years.4,7) Patients with no history of acute pulmonary embolism, present with only progressive exertional dyspnea and fatigue due to elevated pulmonary arterial pressure and decreased maximal cardiac output, similar to PAH. Exertional chest pain, presyncope or syncope, and lower extremity edema may develop late in the course of disease, thus suggesting both a decreased cardiac output at rest and right heart failure.

The physical findings are often subtle and may include a prominent pulmonary component of S2, and a systolic murmur of tricuspid regurgitation. Signs of right heart failure (extended neck veins, edema, ascites, and acrocyanosis) occur late in the course of the disease. Approximately 10% of all patients have an audible bruit over the lung fields, which originates from the turbulent flow through partially occluded or recanalized thrombi.3)

**DIAGNOSIS**

Any patients with unexplained exertional dyspnea should therefore be evaluated for the presence of CTEPH. Suspicion should be high when the patients had a history of venous thromboembolism. Chest X-rays, although often normal, may disclose either an enlargement of the bilateral main pulmonary arteries or asymmetry in the size of pulmonary arteries, hypoperfused area, pleural disease, and right cardiac enlargement. Although PaO2 may be within the normal limits, the alveolar-arterial oxygen gradient is widened. Echocardiography is usually used as the initial diagnostic tool when pulmonary hypertension is suspected. Right atrial and ventricular enlargement, tricuspid regurgitation, flatterting and displacement of interventricular septum, and pericardial effusion may be seen depending on the stage of this disease.

A ventilation/perfusion scan is recommended to rule out CTEPH in patients with unexplained PH.4,7,10) A normal ventilation/perfusion scan excludes CTEPH. CT angiography is indicated when the ventilation/perfusion scan is indeterminate or shows perfusion defects (Fig. 3). CT is particularly useful in the evaluation of the main pulmonary arteries and of unilateral pulmonary vascular obstruction, as determined by ventilation/perfusion scan.7,10) Under these circumstances, the probability of another disease, such as pulmonary-artery sarcoma, Takayasu arteritis, and other causes of pulmonary hypertension should be high.

**Fig. 2** Relationship between the central disease score and percent decrease in PVR (%ΔPVR) after an endarterectomy %ΔPVR after surgery correlated with central disease score in only the HLA-B5201-negative type.
teritis (Fig. 5), cancer, or mediastinal fibrosis, is thus considered to increase. In addition, 3D CT angiography is useful for differentiating a congenital anomaly of pulmonary artery from CTEPH (Fig. 6). CT easily assesses RV dilatation, even without ECG gating, by the comparing RV and LV diameters at the midventricular level, and an RV/LV diameter ratio greater than 1:1 indicates RV dilatation. A high-resolution CT of the lung shows a mosaic pattern (mixed hypoperfused area and hyperperfused area) in CTEPH that is thought to be diagnostic (Fig. 3).\(^1\)

MRI may also provide a clear diagnosis of CTEPH, but this technique is infrequently used for this indication. However, contrast-enhanced magnetic resonance angiography may be very useful for distinguishing central thromboembolic lesions from tumors because the latter

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**Fig. 3** Ventilation-Perfusion scan and CT angiograms in CTEPH.

**Fig. 4** Pulmonary angiograms and right cardiac catheterization data in CTEPH.
Fig. 5  Perfusion scans and CT angiograms in isolated involvement of pulmonary arteries by Takayasu arteritis.

Fig. 6  Ventilation/perfusion scans, PAG, and 3D CT angiograms in peripheral pulmonary artery branch stenosis.
are enhanced with gadolinium, whereas the former are not.\textsuperscript{1)}

Even now, pulmonary angiography is the gold standard technique in the assessment of patients with CTEPH both to establish the diagnosis and to assess surgical indications.\textsuperscript{18)} Five distinct findings have been described, that correlate with the finding of organized thromboemboli, ex. pouch defects, webs or bands, intimal irregularities, abrupt narrowing, complete obstruction.\textsuperscript{20)} This modality allows for the visualization of both the proximal as well as distal pathological findings in elastic pulmonary arteries, thereby allowing for an assessment of surgical accessibility (Fig. 4). It is often performed in conjunction with a diagnostic right heart catheterization, which is required to confirm the diagnosis of pulmonary hypertension (mean pulmonary arterial pressure \( \geq 25 \) mmHg), normal wedge pressure (\(< 15 \) mmHg) and to measure the cardiac output.

**SMALL VESSEL DISEASE AND SURGICAL OUTCOME**

A high PVR without parallel evidence of substantial proximal obstruction suggests significant distal vasculopathy and an unsuccessful postoperative outcome.\textsuperscript{10)} Moreover a high PVR after 100% oxygen (eliminating vasoactive component) and low central disease score may predict surgical mortality.

There are a couple of reports that assessed small vessel disease.

Fractional pulse pressure [(systolic–diastolic)/mean pulmonary arterial pressure] in CTEPH (1.23 \( \pm \) 0.21) is significantly higher than in PPH (0.93 \( \pm \) 0.22; \( p = 0.0017 \)) and low fractional pulse pressure is a significant predictor for mortality in patients with high pulmonary vascular resistance > 1100 dynes.sec.cm\(^{-5} \).\textsuperscript{22)} Kim used pulmonary arterial occlusion wave-form analysis to demonstrate that upstream resistance (Rup) is inversely correlated with both postoperative total pulmonary vascular index and mean pulmonary arterial pressure and all non survivors have Rup < 60%.\textsuperscript{23)}

Skoro-Sajer reported that 77.7% of CTEPH patients demonstrate acute pulmonary vascular reactivity of some degree by inhaled nitric oxide (NO). A decrease in the mean pulmonary arterial pressure > 10.4% under NO is a predictor of long-term survival after pulmonary endarterectomy.\textsuperscript{24)} NO acts predominantly on resistant vessels, i.e., arterioles, and it is likely that low vasoreactivity is caused by small vessel disease, thus resulting in a poor postsurgical outcome.

A recent study focused on the subpleural perfused area using capillary phase in pulmonary angiography, and found that no subpleural perfusion in any segments by pulmonary angiography with high PVR might be related to small vessel disease, thus resulting in a poor outcome after surgery (unpublished data).

**THERAPY FOR PULMONARY VASCULAR REMODELING**

Several reports suggest that medical therapy for PAH (sildenafil, bosentan) may provide hemodynamic and clinical benefits for inoperable patients and patients with persistent postoperative high PVR in CTEPH.\textsuperscript{18)} These medications are supposed to reverse pulmonary vascular remodeling as well as vasodilatation.

Recently, Ogawa reported the inhibition of mTOR to attenuate store-operated Ca\(^{2+} \) entry in cells from endarterectomized tissues of patients with CTEPH and also reduces PDGF-stimulated cell proliferation from CTEPH. They suggested that rapamycin may thus have some potential therapeutic benefit in CTEPH patients.\textsuperscript{25)}

**CONCLUSION**

Recent progress in imaging helps in making an accurate diagnosis of CTEPH or PAH and the identification of patients suitable to undergo surgery. However, it is difficult to accurately predict the surgical outcome, because of small vessel disease and the Japanese DVT-negative vasculopathy type. The assessment of the severity of vasculopathy distal to occluded thrombi is more difficult, although collateral bronchial arterial perfusion to the distal area has been analyzed by either CT\textsuperscript{26)} or MRI. Future research of small vessel disease and the elucidation of a possible immune mechanism in this disease is therefore required.

**REFERENCES**