Distal, small-vessel vasculopathy is generally considered a major contributor to the progression of pulmonary hypertension (PH) as chronic thromboembolic pulmonary hypertension (CTEPH) develops over time and is a major determinant of postoperative outcome after pulmonary endarterectomy (PEA). The pathogenesis and natural history of microvascular disease in CTEPH remain uncharacterized. Mechanisms for significant distal disease may involve the following processes: (1) predominant obstructions of “small” subsegmental elastic pulmonary arteries, (2) classical pulmonary arteriopathy of small muscular arteries and arterioles distal to nonobstructed vessels, (3) pulmonary arteriopathy of small muscular arteries and arterioles distal to totally or partially obstructed vessels. Patients in whom obstructed vessels are mainly subsegmental are considered poor surgical candidates. Distal pulmonary vasculopathy in both the occluded and nonoccluded pulmonary vascular bed is characterized by lesions considered typical for idiopathic pulmonary arterial hypertension, including plexiform lesions. The pathogenesis and time course of these vascular lesions remain unclear, but may involve endothelial and/or platelet production and release of mediators and/or altered pulmonary blood flow. The reciprocal contribution of large-vessel (operable) and small-vessel lesions in CTEPH is crucial for the indication and results of PEA. A combination of investigations is used to identify the extent of small-vessel disease, including right-heart catheterization, perfusion lung scan, multidetector spiral computed tomography, pulmonary angiography, and pulmonary arterial occlusion wave-form analysis. Preliminary evidence suggests that medical therapy may provide hemodynamic and clinical benefits for patients in whom PEA cannot be applied, in those who have persistent postoperative PH, or in selected patients with advanced preoperative hemodynamic changes.

Keywords: hypertension; pulmonary; pulmonary embolism.

Pulmonary endarterectomy (PEA) is the accepted treatment of choice for patients with chronic thromboembolic pulmonary hypertension (CTEPH). However, PEA can only relieve the portion of pulmonary vascular resistance (PVR) that is accessible and amenable to surgical intervention, and outcomes are poor in many cases where chronic thromboembolic obstructions lie in distal, subsegmental arteries (1–4). As a result, CTEPH is considered inoperable in 10 to 30% of cases—for instance, when a high PVR is present without evidence of proportional gross organized thromboembolic pathology on angiogram. Despite great advances in surgical success with PEA, postoperative pulmonary hypertension (PH) is seen in 10% of cases, and surgery cannot be considered curative in these cases (5). Indeed, nearly three-quarters of early postoperative and half of long-term deaths have been attributed to persistent PH, making this the main cause of post-PEA mortality (4).

The precise mechanisms and natural history of microvascular disease in CTEPH remain speculative (6, 7). Nevertheless, it is believed that a substantial component of persistent postoperative PH is related to distal pulmonary vasculopathy in small precapillary vessels both in the occluded and nonoccluded pulmonary vascular bed (2). Histopathologic studies of microvascular changes in CTEPH have identified vascular lesions similar to those seen in idiopathic pulmonary arterial hypertension (IPAH) and Eisenmenger’s syndrome (8–10). Although acute pulmonary embolism is generally accepted as the main initiating event in CTEPH, small-vessel arteriopathy is believed to appear and worsen later in the course of disease, and to contribute to the progression of hemodynamic and symptomatic decline (6, 7, 11). This can explain progressive PH and right ventricular dysfunction in the absence of recurrent pulmonary embolism (PE), as observed in patients with CTEPH (12).

Research to further characterize the natural history of small-vessel disease and to improve preoperative screening and identification of high-risk and inoperable patients may allow more targeted or earlier treatment, and could improve therapeutic outcome. This article describes the types, possible pathophysiology, and impact of microvascular disease in CTEPH, and suggests possible directions for future research.

MICROVASCULAR DISEASE AND POSTOPERATIVE OUTCOME

CTEPH is currently classified intraoperatively according to the general scheme summarized in Table 1, which is based on extensive experience and postsurgery review (1, 13). As covered in detail elsewhere (14), the extent and type of microvascular disease in CTEPH have a strong influence on the likelihood of a successful outcome in PEA. Patients with CTEPH categories I and II who display significant and accessible organized thromboemboli in proximal pulmonary vessels are likely to benefit most from PEA. In general, only selected patients with type III CTEPH (with disease in distal segmental or subsegmental arteries) can be successfully operated on, and patients with type IV disease (isolated distal vasculopathy) have no indication for PEA (1, 13).

More pronounced microvascular disease contributes to a greater preoperative PVR, which has been shown to be associated with greater postoperative mortality (2). Pulmonary hypertension persists in patients with significant microvascular disease despite removal of proximal material. In the largest case series reported so far (n = 1,500), Jamieson and colleagues (4) established that persistent postoperative PH was the most important predictor of mortality after PEA surgery.

MECHANISMS FOR SMALL-VESSSEL DISTAL DISEASE

Mechanisms for distal small-vessel pulmonary disease seen in CTEPH can be broadly categorized into three processes (Table 2), which may occur alone or in combination: (1) obstructions
of small subsegmental elastic arteries, (2) classical pulmonary arteriopathy in small muscular arteries and arterioles distal to nonobstructed elastic pulmonary arteries, and (3) arteriopathy in small muscular arteries and arterioles distal to obstructed elastic pulmonary arteries.

Figure 1 shows obstructions of small, elastic, subsegmental arteries visualized by pulmonary angiography, and Figure 2A represents the histopathologic appearance of such lesions. In the large analysis of PEA data reported by Jamieson and coworkers (4), only a minority of patients showed distal vasculopathy restricted to subsegmental elastic arteries in the absence of significant proximal pathology (Table 1). On the basis of pathologic evidence, it is not clear if patients displaying such changes represent an extreme of the spectrum of CTEPH or if they should be considered as having IPAH with additional local subsegmental thrombosis. Patients of this type are considered poor candidates for surgical intervention due to the less accessible location of obstructed vessels. Although high PVR is not a contraindication to PEA, preoperative PVR has been consistently associated with operative mortality (2), and patients with additional risk factors, such as age or cardiopulmonary comorbidity, are considered to represent too high a risk for surgical candidacy.

Figure 2B shows the histopathologic appearance of classical pulmonary arteriopathy in small muscular arteries and arterioles distal to nonobstructed elastic vessels. Moser and Braunwald (15) were first to observe a “two-compartment pulmonary vascular bed” in CTEPH, describing small muscular pulmonary arteries distal to open elastic arteries that show marked structural changes of chronic PH; they also reported a relatively normal morphology in vascular elements distal to obliterated segments, which had not been exposed to high pressure and shear stress. In contrast, in a study with a series of lung biopsies and autopsies in over 30 patients with CTEPH, Moser and Bloor (8) showed that pulmonary hypertensive changes also occurred distally to open vessels as well as in small nonelastic arteries in lung regions distal to completely or partially obstructed vessels.

Figure 2C shows the histopathologic appearance of arteriopathy in areas distal to partially or totally obstructed elastic vessels (virtually identical to that observed distally to open vessels). Data from animal models with pulmonary artery ligation suggest that postobstructive arteriopathy may be related to development of precapillary bronchial-to-pulmonary vascular anastomoses, pulmonary arterial remodeling, and abnormal pulmonary artery vascular reactivity with pulmonary endothelial dysfunction (2, 16). Recent histopathologic evidence suggests that, in advanced CTEPH, such distal vasculopathy affects areas distal to obstructed pulmonary vessels more than areas distal to nonobstructed vessels (10).

**RELEVANCE OF HISTOPATHOLOGIC FINDINGS IN CTEPH**

Moser and Bloor (8) conducted the first comprehensive and systematic analysis of histopathology of small pulmonary arteries of patients with an established diagnosis of CTEPH, and concluded that, in general, patients with CTEPH displayed a full range of distal histopathologic changes indicating advanced vessel remodeling, including plexiform lesions typical of all forms of pulmonary arterial hypertension (PAH). In fact, smooth muscular hypertrophy, intimal proliferation-fibrosis, and plexogenic lesions are characteristically seen in IPAH (17–19) as well as in PAH associated with congenital or acquired conditions (20, 21). It was thus proposed that such lesions most likely represent the nonspecific effect of chronic PH on exposed (nonoccluded) areas of the vasculature.

Plexogenic lesions are now regarded as a hallmark of obstructive intimal remodeling associated with severe PAH. In a study of lungs removed at autopsy or explantation (15 cases of IPAH, 11 of PAH),

| TABLE 1. POSTOPERATIVE PULMONARY CLASSIFICATION OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION |
|---------------------------------|-------------------------------|
| Type   | Patients Undergoing PEA (%) | Features                                      |
| I      | 34                            | Central organized clot (main/lobar pulmonary arteries) |
| II     | 49                            | Intimal thickening and fibrosis proximal to the segmental arteries |
| III    | 12                            | Disease within distal segmental and subsegmental arteries only |
| IV     | 1 – 2                         | PAH with hypertensive distal vasculopathy without visible thromboembolic disease |

*Definition of abbreviations: PAH = pulmonary arterial hypertension; PEA = pulmonary endarterectomy.

*Data from Reference 1.

**TABLE 2. POSSIBLE MECHANISMS CONTRIBUTING TO DISTAL INOPERABLE MICROVASCULAR DISEASE IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Vascular Pathology</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Predominant obstructions of “small” subsegmental elastic pulmonary arteries</td>
<td>Occlusions of small arteries with stenoses, webs, and bands; Similarity/overlap with IPAH</td>
</tr>
<tr>
<td>2</td>
<td>Classical pulmonary arteriopathy of small muscular arteries and arterioles distal to nonobstructed elastic pulmonary arteries</td>
<td>Intimal proliferation and/or increased media thickness, plexiform lesions; Endothelial dysfunction possibly related to increased pressure and flow</td>
</tr>
<tr>
<td>3</td>
<td>Pulmonary arteriopathy of small muscular arteries and arterioles distal to partially or totally obstructed elastic pulmonary arteries</td>
<td>Endothelial dysfunction possibly related to poor perfusion and/or bronchial-to-pulmonary vascular anastomoses</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: IPAH = idiopathic pulmonary arterial hypertension.*
22 cases of CTEPH, 8 cases of Eisenmenger’s syndrome, and 3 cases of PH due to other causes), Yi and coworkers (10) demonstrated prominent obstructive intimal thickening and formation of plexiform lesions. The pattern of lesions in CTEPH was similar to that seen in Takayasu’s arteritis (Figure 3A). Lesions were seen primarily at the level of small arteries and arterioles in IPAH (Figure 3B). This latter finding supports the proposed natural history of the disease whereby endothelial damage is initiated at these locations, followed by intimal and medial proliferation and luminal obstruction in the damaged arteries (10, 22). In contrast, similar vessels in lungs mainly from patients with severe CTEPH (and hence, with more pronounced small-vessel involvement) showed significantly less intimal thickening than in IPAH (Figure 3B). This may be due to relatively nonuniform distribution of small-vessel pathology in CTEPH compared with IPAH. The scleroderma pattern was intermediate between IPAH and CTEPH (10).

As shown in Figure 3C, patterns of intimal thickening were mirrored in the occurrence of well-formed plexiform lesions, where lesions were generally associated with vessels of smaller diameter in IPAH (mean ± SEM, 79 ± 6.1 μm) compared with CTEPH (149.5 ± 11.4 μm) and significantly smaller versus those in Eisenmenger’s syndrome (209 ± 17.6 μm) (10). Overall, Yi and coworkers concluded that the degree and distribution of arteriopathy in CTEPH differ from that seen in IPAH, but it is questionable whether CTEPH could be differentiated from IPAH on the basis of histopathologic evidence alone.

The functional significance of plexogenic lesions in CTEPH remains unclear. No studies have so far established a firm relationship between the extent or type of small-vessel lesions and either the course of disease or treatment outcome in PH of different origins. Moser and Bloor (8) demonstrated that patients with plexiform lesions in small pulmonary arteries showed functional and hemodynamic improvements after PEA that paralleled those in patients without them. In addition, the profile of hypertensive lesions seen in CTEPH does not appear to relate to preoperative hemodynamic values, symptom duration, or patient
POSSIBLE PATHOGENETIC MECHANISMS

The pathogenesis of microvascular disease in CTEPH has yet to be characterized, but may share some mechanisms with PAH. In terms of the thrombotic pathology, abnormalities in the clotting cascade, endothelial cells, or platelets may contribute to a prothrombotic environment, particularly in nonoccluded areas. There is biological evidence that intravascular coagulation is a continuous process in a number of forms of PH (2, 28), although it is not known whether this results from genetic predisposing factors or endothelial/platelet dysfunction secondary to pulmonary vascular injury (29, 30). Studies of plasminogen activator-inhibitor 1 (PAI-1) alterations have provided some evidence of a molecular basis for the promotion of in situ thrombosis and stabilization of vascular thrombi in CTEPH (30, 31). However, the bulk of current evidence to date does not indicate a significant role for traditional prothrombotic factors such as antithrombin, protein S, or protein C deficiencies, or altered fibrinolytic pathways in CTEPH pathogenesis (2, 30, 32). It is suggested that the core of the pathologic process in CTEPH is not only related to thrombus formation but that it is also linked to disturbed thrombus resolution (28, 33).

Endothelial dysfunction may occur in small muscular arteries distal to nonobstructed pulmonary elastic vessels, but the degree and mechanisms of endothelial dysfunction as a contributor to PH in these areas are unclear (2, 7, 10). Endothelium actively participates at a number of points in the thrombotic process (28). As covered in detail elsewhere (30), humoral markers that have so far been linked with CTEPH include antithrombin and protein C—known risk factors for venous thromboembolism (34)—elevated factor VIII (29, 35), and monocyte chemotactic protein 1 (36). Of these, only antithrombin antibodies are considered as a possible specific marker for CTEPH (2). The release of humoral mediators from endothelial cells may be stimulated by the disturbed blood flow (proximal obstruction, bronchial-to-pulmonary circulation anastomoses) in the vascular bed distal to obstructed vessels in some, as yet, unknown way.

Finally, studies indicate that impairment of nitric oxide function and endothelin-mediated vascular remodeling are possible contributory mechanisms to altered small-vessel morphology in areas distal to occluded vessels in CTEPH as well as in severe PH (16, 37, 38). Reesink and colleagues (39) identified relationships between endothelin-1 and hemodynamic parameters in CTEPH, suggesting a possible role of this mediator in the pathobiology of small-vessel disease.

CLINICAL, HEMODYNAMIC, AND IMAGING FINDINGS INDICATING MICROVASCULAR DISEASE

At least 40% of the proximal pulmonary vascular bed is obstructed in the majority of patients with CTEPH and, in addition to the effect of recurrent thromboembolism or in situ thrombosis, a number of lines of clinical evidence indicate that progressive worsening is contributed by remodeling in the small distal pulmonary arteries in the open vascular bed: (1) a combination of the extent of central obstruction visible on pulmonary angiography and the degree of PH (2), (2) progressive PH in the absence of recurrent thromboemboli (9), (3) evidence of redistribution of pulmonary blood flow from nonoccluded to newly endarterectomized areas after PEA (vascular steal phenomenon) (8), and (4) persistent PH despite successful PEA in approximately 10 to 30% of patients (2). Clinical consequences of microvascular disease include poor surgical candidacy or outcome, response to treatments developed for PAH, and the need for appropriate methods of detection and assessment.

Risk and outcome assessments need standardization for surgical intervention in CTEPH and, as addressed elsewhere (14), evidence indicates that a more thorough preoperative appraisal of distal disease is vital for optimizing outcome. For example, preoperative PVR is a crucial factor to consider in assessing PEA candidacy as it can be used to identify high-risk patients (2). It is generally accepted that a high PVR without parallel evidence of substantial proximal obstructive changes suggests significant distal vasculopathy and greater chance of an unsuccessful postoperative outcome (4). Because persistent PH has some degree of reversibility, it has been suggested that advanced vasculopathy can be avoided in some patients by earlier diagnosis of CTEPH and PEA intervention. However, this would require a standardized system for preoperative classification of surgical candidates that takes the degree and type of microvascular disease into account.

We therefore need to shift current focus from assessments of the obvious large-vessel component of CTEPH to the equally relevant small-vessel contribution. A number of techniques may be useful in achieving this (Table 3) (14, 40). In particular, the pulmonary artery occlusion technique may become increasingly useful for the partitioning of PVR into an arterial segment and arteriole-venous segment, and for the determination of an effective pulmonary precapillary pressure (41, 42). This could help in defining mortality risk based on upstream versus downstream vascular resistance due to distal disease (43). However, further experience and validation are required to standardize this method.
Pulmonary V/Q scintigraphy is an important first step in spotting any imbalance between the magnitude of perfusion defects and PVR, although it can underestimate the actual degree of vascular obstruction. Traditional pulmonary angiography is the current “gold standard” diagnostic imaging technique for CTEPH as it allows visualization of proximal as well as distal pathology in elastic pulmonary arteries, allowing an assessment of surgical accessibility. However, multidetector spiral computed tomography in combination with traditional angiography is likely to represent the future standard for imaging as it allows clear detection of obstructions right down to the subsegmental level (40) as well as of the thickness of proximal pulmonary artery wall (which is an important technical detail for planning surgery). The comparison between the increase of the PVR (as assessed by right-heart catheterization) and the extent and location of obstructions along the elastic pulmonary arterial tree can give an estimate of the existing small-vessel vasculopathy in areas distal to open arteries. In contrast, the assessment of the degree of vasculopathy in areas distal to occluded vessels is currently an unresolved challenge.

**FUTURE RESEARCH AIMS**

An important future aim in research on the natural history of CTEPH is to characterize the time course over which hypertensive microvascular changes develop. We need to ascertain whether specific types of small-artery lesions predominate at certain locations or under certain conditions and we need to establish why the same pathologic changes occur in areas that are affected by high pressure as in those that are not.

Microvascular disease in CTEPH also presents a number of challenges to overall disease management. Identification of poor surgical candidacy and/or likelihood of poor surgical outcomes is vital in optimizing PEA outcome, as is the recognition of screening methods for early detection. Further research on how multidisciplinary care can be applied and how potential pharmacotherapies can be best used, alongside or as an alternative to surgical intervention, is vital (44, 45). For instance, preliminary evidence suggests that medical therapy may provide hemodynamic and clinical status benefits for patients in whom PEA cannot be applied, in those who have persistent postoperative PH, or in selected patients with unstable preoperative hemodynamics or other conditions causing unacceptable risk from PEA intervention (44, 46, 47). However, the precise role of medical therapies in the global treatment strategy of CTEPH has yet to be fully clarified, including type of medications, doses, and timing for initiation.

**CONCLUSIONS**

Pulmonary microvascular disease associated with CTEPH is an important consideration in optimizing patient care and subsequent clinical outcome. Its pathogenesis remains unclear, and further research is required to define mechanisms related to persistent postoperative PH and its association with known operative CTEPH subtypes. Common, agreed-upon criteria for nonoperability due to distal disease are required and, based on future studies, will likely need to be stratified according to the type of microvascular pathology present (2). This requires that definitive inclusion criteria be incorporated in clinical trials. Further formal randomized trials will be valuable in helping to define better the role of medical therapy in CTEPH, particularly in patients with significant microvascular disease.

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