CLINICAL INVESTIGATION

New developments in the treatment of chronic thromboembolic pulmonary hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by pulmonary arterial obstructions that typically result from non-resolving fibrotic organized pulmonary thromboemboli, causing elevated pulmonary vascular resistance, progressive pulmonary hypertension and, eventually, right heart failure. In more than 50% of patients, particularly those with a history of venous thromboembolism, CTEPH is a 'surgical disorder' meaning that the treatment of choice is a pulmonary endarterectomy, which restores pulmonary hemodynamics in a great majority of patients. However, in a recent registry, 36.4% of patients in major European expert centers were classified as non-operable, mainly due to surgically inaccessible thrombi or unacceptably high risk for surgery in general. Because of the observation of a secondary pulmonary vascular disease in some patients, pulmonary arterial hypertension (PAH)-targeted pharmacotherapies have been widely used in CTEPH patients – in up to 40% of patients in Europe – regardless of their operability status. However, the only randomized controlled trial that was powered to detect a difference between PAH-targeted drugs and placebo in CTEPH demonstrated that despite a moderate effect on hemodynamics, no improvement in 6-min walking distance was achieved. These data illustrate the great need for further trials of PAH-targeted drugs in CTEPH, or (mechanical) treatments to salvage the right ventricle.

Keywords: chronic thromboembolic pulmonary hypertension • drug therapy

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by pulmonary vascular obstructions that are typically originating from non-resolving pulmonary thromboemboli, causing fibrotic vascular stenoses and occlusions, elevated pulmonary vascular resistance (PVR), progressive pulmonary hypertension (PH) and, eventually, right heart failure. Hemodynamics [1,2], and in particular PVR [3,4], appear to be predictors of outcome, at baseline and after pulmonary endarterectomy (PEA), in parallel with CTEPH subsets [5]. CTEPH most commonly occurs in a population of typically 50 to 60-year-olds of either sex [6], and is labeled as group 4 of the current WHO diagnostic classification system for PH [7]. Current registry data suggest that CTEPH occurs at an incidence of 3–30 per million in the general population. Although CTEPH does not show the classical risk profile of venous thromboembolism, the disease has been demonstrated to emerge as a complication of symptomatic pulmonary embolism (PE) with a cumulative incidence of 0.1–9.1% within 2 or more years of the event [6, 8–16]. These numbers do not take into account that at least 25% of cases may originate from asymptomatic PE [17–19].

There remain many uncertainties surrounding CTEPH [17]: the incidence and prevalence of this disease are not well characterized; CTEPH pathogenesis

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is poorly understood; diagnostic and treatment approaches, for example, PEA, have not been standardized; and operative techniques have not been taught to enough dedicated surgeons in the USA (~0.8 PEAs per million), and in European countries (~2.2 PEAs per million). An international, prospective, observational registry was set up in 2007 to resolve these uncertainties, including 679 newly diagnosed (≤6 months) consecutive patients with CTEPH. According to the registry data, diagnosis was confirmed by all of the following: right heart catheterization, (ventilation–)perfusion scintigraphy of the lungs, computed tomography and/or pulmonary angiography in the majority of patients. CTEPH is a potentially correctable cause of PH, and vascular reopening by PEA is the treatment of choice [3,20]. The disease is diagnosed 14.1 months (median) after first symptoms. In the registry, 63% (427 patients) were considered operable, and 37% (247 patients) were non-operable. Approximately 60% of all patients effectively underwent surgery. A history of acute PE was reported for 74.8% patients. PEA mortality rate was 4.7%. A key finding in the registry was that at CTEPH diagnosis, 38% of all patients initiated at least one pulmonary arterial hypertension (PAH)-targeted therapy, including phosphodiesterase type V inhibitor, endothelin-receptor antagonist or prostacyclin analogue, regardless of their operability status [19].

Assessments from the European CTEPH Registry suggest that time from symptoms to diagnosis and to surgery were 12 to 22 months and 12 to 116 days, respectively. A wide variation in non-operability was observed between countries (from 12.0 to 60.9%). Low-volume centers performing up to ten PEAs per year reported a higher percentage of non-operable patients (47%) than intermediate centers performing 11 to 50 PEAs per year (32%) or high-volume centers performing over 50 PEAs per year (34%), suggesting that center expertise is likely to impact on the decision to operate. In contrast to the US center at the University of California at San Diego, CA, USA, who operate on the vast majority of patients, about 40% of the European CTEPH population is classified as non-operable [21,22]. In ~10–20% of patients, PH persists or recurs after PEA, being the most important determinant of post-operative poor outcome [20,23,24]. All these data suggest that there is a need for non-surgical treatment options in CTEPH.

Pathogenesis, risk factors & vascular biology

Today, CTEPH is viewed as a complex 'dual' vascular disorder. While elevations in mean pulmonary artery pressure (PAP) and total pulmonary resistance are correlated with the degree of pulmonary vascular obstruction in patients with PE [25], no such correlation was detectable for patients with CTEPH, suggesting that PH in CTEPH is not solely based on the obstruction of proximal pulmonary arteries, but is also due to the remodeling of small distal arteries.

All available evidence today indicates that CTEPH is primarily caused by pulmonary thromboembolism, as opposed to primary pulmonary vascular *in situ* thrombosis [26]. One of the key factors for the differential diagnosis between CTEPH and idiopathic PAH is a clinical history of acute venous thromboembolism. However, a purely mechanistic view of CTEPH as a disease caused by obliteration of central pulmonary arteries by pulmonary emboli is too simplistic. We speculate that PE may be followed by a misguided pulmonary vascular remodeling process that is triggered by conditions such as high pressure and shear stress due to obstructed major vessel-dependent pulmonary vascular territories ('PH begets PH'), infection [27], immune phenomena [28], inflammation [29] and malignancy [30]. Both plasmatic factors (hypercoagulation [31–33], uncleavable fibrin [34,35] and abnormal circulating cells ['sticky' red blood cells, high platelet and erythrocyte counts and progenitor cells [36,37]]), and a predominantly 'negative' vascular remodeling process (fibrotic vessel shrinkage) enhance major vessel and small vessel obliteration. Endothelial dysfunction and endothelial mesenchymal transition may play an additional role, as well as many of the mechanisms of pulmonary vascular remodeling that have been identified in classical pulmonary arteriopathy. Recently, the role of the calcineurin pathway as a disease mediator [38] has shed new light and interest on a potential role for tacrolimus and sirolimus [39] in preventing occlusive vascular fibrosis. However, these pathways, as well as infection or the role of thrombus-borne vascular precursor cells, are still poorly understood in their relation to thrombus persistence, and are not ready to be translated into clinical practice.

Therapeutic options for CTEPH

Conventional treatments

The decision of how to treat each patient is complex and requires a multidisciplinary team of cardiologists, pulmonologists, radiologists and surgeons to estimate both surgical risk and the degree of hemodynamic improvement to be expected after surgery [20]. All patients with CTEPH receive lifelong anticoagulant medication to prevent recurrent thromboembolic events, and a 3-month period of watchful waiting should have elapsed before a full diagnostic workup and any decision is made regarding choice of

treatment [19].

The primary treatment for suitable cases of CTEPH is PEA. Management of CTEPH patients should be reserved for expert centers with internists, cardiologists, pulmonologists, thoracic surgeons who specialize in PEA, and anesthesiologists who are ready to take on the challenges of reperfusion pulmonary edema and post-operative PH. PEA is performed under hypothermia and total circulatory arrest, and involves the removal of obstructive material from each pulmonary artery, and its lobar and segmental branches (Figure 1). Today, PEA is yielding excellent results in well-selected patients, with near normalization of hemodynamics and symptoms. Postoperative mortality rates are 4.4 to 16% [3,18,20, 40–43].

The first goal of the diagnostic evaluation of PH in general is to rule out CTEPH, because once this diagnosis is made the patient should proceed to evaluation for PEA [44]. Medical treatments for CTEPH are empirical at this stage, and not supported by evidence. Lung transplantation remains a last resort for CTEPH patients [18]. Optimal medical therapy (OMT) for CTEPH comprises anticoagulation, diuretics and oxygen to correct hypoxemia to a minimum of 92% oxygen saturation, and has contributed to long-term outcomes similar to those after surgery, ranging from 70–80% at 3 years, at least in retrospective surveys [45,46]. Whether these observations also reflect the impact of PAH-specific treatments remains elusive.

Targeted medical treatments

CTEPH is understood as a dual vascular disorder, affecting the major vessel compartment (note the definition of CTEPH as chronic major vessel thromboembolic PH in the original description of Moser *et al.* [47]), and the compartment of pulmonary resistance vessels measuring 200 µm and less. While major vessel disease is the result of a 'positive', that is, 'outwards directed' vascular remodeling process of thrombus resolution, small vessel disease represents a classical pulmonary arteriopathy as seen in PAH characterized by a 'negative', that is, 'inwards directed' vascular remodeling pattern. Whether these lesions result from the general hemodynamic effect of chronic PH on exposed non-occluded areas of the vasculature [48] or from thrombus organization is unknown. However, the observation of a vascular pathology in CTEPH that appears similar to PAH is laying the ground for medical therapies for PH, targeting the three main pathways involved in the abnormal proliferation and contraction of smooth muscle cells of pulmonary vessels in patients with CTEPH (i.e., the endothelin, prostacyclin and nitric oxide pathways). PAH-targeted treatments in CTEPH may be useful:

- In patients with predominantly distal disease that is not surgically accessible;
- When surgery is contraindicated because of significant co-morbidity;
- In patients who are at high risk because of extremely poor hemodynamics and general condition before PEA (bridging to PEA) [49–51];
- In patients with persistent or recurrent PH after PEA.

Calcium-channel blockers have not been a realistic option for treating CTEPH because true hemodynamic responders are rare [52], and responders are mainly observed among operable patients [4]. Apart from numerous uncontrolled trials using bosentan, an endothelin-receptor antagonists, iloprost, sildenafil, a phosphodiesterase-5 inhibitor, and treprostinil [49–51, 53–60], three randomized, controlled trials have involved patients with CTEPH. Inhaled iloprost [61], sildenafil [62] and bosentan [63] have been tested, with only the latter trial carrying the statistical power to demonstrate a difference between study drug and control. There exists a strong rationale that the endothelin pathway may be important in CTEPH: endothelin is a potent endogenous vasoconstrictor and both endothelin-1 and the G-protein-coupled endothelin receptors on endothelial cells and smooth muscle cells are upregulated in CTEPH [64]. Endothelin-dependent pulmonary vascular remodeling has been

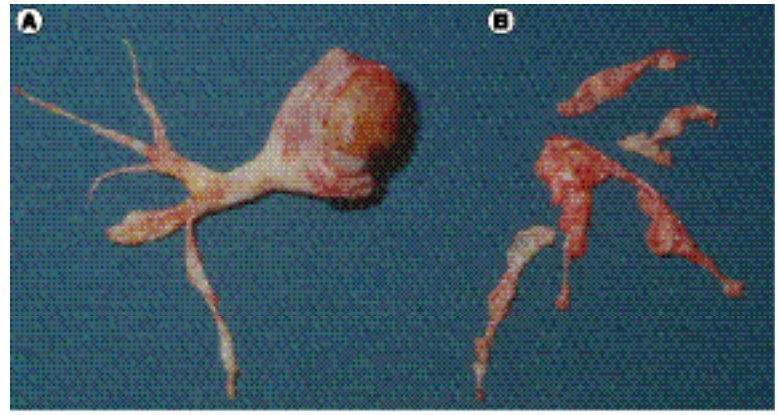

Figure 1. Material removed by pulmonary endarterectomy from the (A) left and (B) right pulmonary artery. The specimen is an example of type I disease [3].

demonstrated in a canine model of CTEPH [65]. A recent meta-analysis has emphasized a positive effect of bosentan on hemodynamics and exercise capacity in patients with CTEPH, illustrating that uncontrolled trials are subjected to significant bias in non-operable CTEPH [66]. The BENEFIT study [63] randomized 157 patients with non-operable CTEPH over 16 weeks, and tested the hypothesis that the combined end point 6-min walking distance (6-MWD) and PVR would be improved in the study drug group. Although PVR was reduced by 24% compared with placebo ($p < 0.0001$), in concordance with a significant effect on cardiac output and pro-brain natriuretic peptide, there was no significant benefit on 6-MWD [63]. Based on these data, bosentan did not receive market approval for treatment of CTEPH. Mechanisms of disease that account for the difference between BREATHE-1 and BENEFIT remain obscure, but may be related to the magnitude of the bosentan effect in CTEPH versus PAH, which each represent very different patient populations.

Given the urgent clinical need for medical treatments for CTEPH in a growing population of off-label treated patients, randomized controlled trials are needed, possibly separating patients who have previously undergone PEA from those never classified as operable. Two randomized controlled trials in CTEPH are ongoing. Bayer's trial 11349 (long-term extension, multicenter, multi-international study to evaluate the safety and tolerability of oral BAY63–2521 [1, 1.5, 2.0 and 2.5 mg three-times a day] in patients with CTEPH, [CHEST-2]) and the academic CTREPH trial (efficacy and tolerability of subcutaneously administered treprostinil sodium in patients with severe [inoperable] CTEPH NCT01416636) are currently under way. Due to the lack of evidence, all ongoing trials except CTREPH strictly enroll only patients who are treatment-naive.

Future perspective

There appears to be a disconnection between significant hemodynamic benefits of bosentan, and an improvement in the 6-MWD test. This may be because of differing mechanisms of exercise limitation (gas exchange issues, lung dead space issues pertinent to CTEPH, hypoxemia, deconditioning and muscle weakness, a limited study duration of 16 weeks, etc.), or simply because of an insufficient primary treatment effect that created statistical but not biological significance.

A near goal is the revelation of data from the European CTEPH registry, which is expected to put into perspective surgery and optimal medical therapy, in a prospective database format. In the absence of prospective randomized controlled trials investigating this area, the registry information will be crucial. In addition, prospective follow-up data of patients diagnosed with CTEPH will be provided.

Over the next 5–10 years from the point at which this review was written, it is to be expected that in Europe, the surgical knowledge will be spread and through effective educational efforts patients will have a wider access to PEA in well-defined expert centers, under standardized protocols.

Whether burgeoning non-pharmacologic treatments such as percutaneous balloon dilatation of proximal lesions [67] employing drug-eluting balloons will add to the armamentarium of treatments for CTEPH is speculative today. However, a desperate elderly CTEPH population may be the driver for treatment innovations.

By contrast, primary prevention of CTEPH by aggressive anticoagulation or targeted antiproliferative and antibiotic treatments will remain experimental, even years from today.

Financial & competing interests disclosure

Executive summary

Background

- Pulmonary endarterectomy is the treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH).

Pathogenesis, risk factors & vascular biology

- Recent data confirm that venous thromboembolism is a risk factor for CTEPH, yet the precise incidence after pulmonary embolism remains unproven.

Therapeutic options for CTEPH

- Surgery is the prime treatment modality for CTEPH.
- PAH-specific drug therapy may be indicated in selected CTEPH patients such as patients who are not candidates for surgery or patients with residual pulmonary hypertension after pulmonary endarterectomy (class of recommendation IIb, level of evidence C).
- Despite a lack of evidence, the European Registry has demonstrated that in real life more than 50% of non-operable patients and almost one third of operable patients receive off-label treatments. Endothelin-receptor antagonists are the most commonly used PAH-targeted drugs (37.7%), followed by phosphodiesterase type 5 inhibitors (19.4%), combined therapy (7.7%) and prostanoids (4.5%) [19].

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