Chapter 9

Chronic thromboembolic pulmonary hypertension

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SUMMARY: Chronic thromboembolic pulmonary hypertension (CTEPH) results from mechanical obstruction of (major) pulmonary vessels by non-resolving thromboemboli. If left untreated, the condition is fatal due to increased right ventricular afterload and right heart failure. Recent advances in the understanding of misguided thrombus resolution, small-vessel pulmonary arteriopathy and the identification of CTEPH risk factors have introduced novel disease concepts. In this chapter, we assemble the relevant literature into a picture of the old and new views of CTEPH evolution. Moreover, the role of established as well as experimental diagnostic tools is reviewed, with an emphasis on imaging techniques that allow visualisation of perfusion defects and differentiation between thromboembolic and non-thromboembolic pulmonary vascular disease. Finally, therapeutic options are discussed. Pulmonary endarterectomy (PEA) is the treatment of choice in patients with confirmed CTEPH. After successful PEA, patients are considered cured, since a vast majority nearly normalise their haemodynamic parameters and exercise capacity. Data on medical treatment of the condition and evidence-based knowledge are put into perspective with current clinical practice.

KEYWORDS: Chronic thromboembolism, diseases of pulmonary circulation, pathomechanisms, pulmonary heart disease, surgical and medical therapy

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Recent advances in the understanding of basic mechanisms and clinical course of chronic thromboembolic pulmonary hypertension (CTEPH) have shed new light on this enigmatic orphan condition and have challenged dogmatic views on the pathogenesis of this disease.

Traditionally, a strict line was drawn between the pathobiological processes underlying CTEPH and non-thromboembolic pre-capillary pulmonary arterial hypertension (PAH). In contrast to PAH, which is attributed to small-vessel arteriopathy and obliteration, CTEPH was thought to result from mechanical obstruction of the pulmonary vascular bed by organised fibrotic thromboemboli. However, current understanding of CTEPH is that of a dual vascular disorder, comprising a major-vessel thromboembolic vascular remodelling process and a small-vessel arteriopathy that is histologically indistinguishable from the pulmonary arteriopathy of PAH [1]. In agreement with this observation, no correlation could be found between the extent of

pulmonary arterial thromboembolic obstructions and pulmonary vascular resistance (PVR) [2]. One example of a condition that is associated with an overlap between classical ''major-vessel'' CTEPH and CTEPH ''small-vessel disease'' is splenectomy, which may lead to classical CTEPH but also to clinical presentations of PAH.

Moreover, the purely ''coagulatory'' concept of CTEPH as an uncontrolled thromboembolic state characterised by massive thrombosis and recurrent thromboembolic events has also been abandoned. A growing body of evidence suggests that in affected patients, minor or major thromboemboli do not resolve under conditions of concomitant inflammation, infection or malignancy, thereby leading to major vessel fibrosis and small-vessel remodelling [3–5].

In recent years, novel insights have affected our clinical routine. While the primary treatment remains surgical pulmonary endarterectomy (PEA), a recently published prospective CTEPH registry has illustrated that almost 40% of patients were not suitable for surgical removal of pulmonary thromboemboli [6]. Based on the concept that small-vessel arteriopathy is a major contributor to CTEPH evolution, vasodilator therapies may be useful alternatives for patients who are not suited for PEA. Although the BENEFiT (Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension) study [7], as the first multi-centre randomised controlled trial of the dual endothelin receptor antagonist (ERA) bosentan, failed to achieve the second co-primary end-point, the availability of novel vasodilators and adaptive study designs may open new perspectives on medical treatment of inoperable CTEPH patients. Uncontrolled reports of parenteral prostacyclins in severe patients have indicated a survival benefit [8, 9].

Definition

CTEPH is diagnosed if the following observations are made after at least 3 months of effective anticoagulation: 1) mean pulmonary arterial pressure (P_{pa}) exceeding 25 mmHg with a pulmonary capillary wedge pressure (P_{pcw}) equal to or less than 15 mmHg; and 2) one or more mismatched segmental or larger perfusion defects detected by ventilation/perfusion (V'/Q') lung scan/multidetector computed tomography pulmonary angiography (CPA)/conventional pulmonary angiography [10].

Epidemiology and prognosis

The exact incidence and prevalence of CTEPH are unknown. Current data derived from registries suggest that CTEPH occurs at an incidence of 3–30 cases per million in the general population. Classical estimates of disease prevalence refer to the number of CTEPH cases per survived pulmonary thromboembolic event [11–18] and report cumulative incidences between 0.1% and 9.1%. A significant number of patients develop CTEPH after asymptomatic or mildly symptomatic venous thromboembolic events, or in the absence of any clinically apparent venous thromboembolism (VTE) [19]. If left untreated, 3-year survival after CTEPH diagnosis has been reported as 78–85% in affected patients from Japan [20] and 70% in inoperable *versus* 76% in operable patients within the UK ($p=0.023$) [21]. For comparison, contemporarily treated patients with idiopathic, familial or anorexigen-associated PAH face a 3-year survival of 69.6% [9].

Pathophysiology

CTEPH evolution is triggered by thrombotic obstruction of the pulmonary vascular tree by single or repetitive thromboembolic events arising from sites of venous thrombosis. Typically, it appears that thrombi fail to resolve and undergo a fibrotic organisation process with concomitant positive vascular remodelling in the major vessel compartment, and a negative vascular remodelling process in the resistance arteries. Progressive rarefication of the pulmonary vascular bed leads to a gradual rise in PVR, increased right ventricular (RV) afterload and right heart failure.

Although CTEPH is understood as a thromboembolic disorder, neither classical plasmatic risk factors for VTE nor defects in the fibrinolytic system have been identified in affected patients. For example, a deficiency of antithrombin, protein C and protein S, the G20210 mutation of prothrombin and hyperhomocysteinaemia are not associated with CTEPH. Furthermore, the factor V R506Q mutation (factor V Leiden) is not found to be more common in CTEPH patients [22]. However, in a recent retrospective study, factor V Leiden was significantly more common in CTEPH patients than in those with other forms of PH and the prothrombin mutation occurred more often in CTEPH patients, although the difference was not statistically significant [23]. Only lupus anticoagulant/antiphospholipid antibodies and the coagulation factor VIII, both well-known prothrombotic risk factors for VTE, have been found in a significant proportion of CTEPH patients in a majority of studies [3, 5, 10, 22–24].

No functional defects in the pulmonary vascular fibrinolytic system [25, 26] or gene polymorphisms [27] were found. Neither alterations in plasma levels of type 1 plasminogen activator inhibitor nor tissue-type plasminogen activator could be linked with CTEPH [28].

In recent years, attentive studies of large cohorts with pulmonary hypertension (PH) have demonstrated a clear association between distinct medical conditions and the occurrence of CTEPH. These have generated novel pathomechanistic hypotheses and set the stage for innovative experimental research. Our current understanding is that populations at increased risk for CTEPH are those with a history of splenectomy [3, 5, 29, 30], carriers of ventriculo-atrial shunts for the treatment of hydrocephalus or carriers of pacemakers with a history of device infection [3, 5], patients with inflammatory bowel disease [3], patients undergoing thyroid hormone replacement [5], patients with circulating antiphospholipid antibodies [5, 22, 24], patients who have survived cancers [5], individuals with non-0 blood types [5, 31], individuals with elevated plasma coagulation factor VIII [31], and carriers of the fibrinogen Aα Thr312Ala polymorphism (table 1) [27].

A large European prospective registry containing clinical and epidemiological data of 679 newly diagnosed CTEPH cases was closed in January 2009 [6]. In an ongoing project, registry data are analysed with respect to CTEPH risk factors. Results are expected later this year and will add a significant puzzle piece to our current knowledge on CTEPH risk factors.

Patients with ventriculo-artrial shunts and a history of device infection are at increased risk for CTEPH [3, 5]. It is well known that *Staphylococcus aureus* or *Staphylococcus epidermidis* are responsible for up to one-half of these infections [34], leading to thrombosis and device failure [35]. Molecular analysis of PEA specimens harvested from patients with CTEPH associated with ventriculo-artrial shunt infection uncovered staphylococcal DNA in a majority of samples [4]. In a

Table 1. Overview of risk factors for chronic thromboembolic pulmonary hypertension (CTEPH)

Risk factor [ref.]	OR (95% CI)
Infected ventriculo-artrial shunt/pacemaker [3, 5]	13.0 (2.5–129), 76.4 (7.7–10351)
Splenectomy [3, 5]	13.0 (2.7–127), 17.9 (1.6–2438)
Recurrent VTE [5]	14.5 (5.4–43.1)
Thyroid disease [5]	6.1 (2.7–15.1)
Previous VTE [5]	4.5 (2.4–9.1)
Antiphospholipid antibodies [5]	4.2 (1.6–12.2)
Survived cancer [5]	3.8 (1.5–10.4)
Inflammatory bowel disease [5]	3.2 (0.7–16.0)
Blood groups non-O [5]	2.1 (1.1–3.9)
Fibrinogen Aα Thr312Ala polymorphism [27]	1.7 (1.1–2.5)
HLA-B*5201 [32, 33]#	2.1 (1.3–3.6), 2.5 (1.6–3.9)¶
HLA-DPB1*0202 [32, 33]#	3.4 (1.7–6.7), 5.1 (2.5–10.2)¶
IKBL-p*03 [33]#	2.3 (1.5–3.7)¶

VTE: venous thromboembolism; HLA: human leukocyte antigen; IKBL: inhibitor of nuclear factor-κB-like. #: studies conducted in Japan; ¶: odds ratio for VTE-negative CTEPH.

murine model of stagnant-flow venous thrombosis, infection with *S. aureus* delayed thrombus resolution and led to an upregulation of profibrotic genes, including transforming growth factor (TGF)-β and connective tissue growth factor [4]. Moreover, experimental work in recent years suggests that thrombus angiogenesis, a key driver of thrombus resolution, may be impaired in CTEPH [36–40].

Small-vessel pulmonary vascular remodelling mainly affects unobstructed pulmonary vascular areas and is histologically indistinguishable from other forms of PH [1]. There is a broad individual range with respect to the degree of secondary small-vessel arteriopathy, which is clearly independent from thrombus burden [2], but may be related to the duration of the disease. It is still unclear whether it is individual susceptibility or thrombus composition, or both factors together, that determine the degree of small-vessel disease. Mutations in the bone morphogenetic protein receptor type II gene (*BMPR2*) that have been linked to the development of pulmonary vascular disease in familial or heritable PAH [41, 42] could not be related to CTEPH [43]. Interestingly, CTEPH patients with typical predisposing medical conditions, such as a history of splenectomy, ventriculo-artrial shunt, inflammatory bowel disease or osteomyelitis, face an adverse outcome when compared with other CTEPH patients [5]. This finding has been attributed to more severe small-vessel disease, although the exact mechanisms remain unclear.

The current pathomechanistic model of misguided thrombus resolution in pulmonary arteries of CTEPH patients is summarised in figure 1. Taken together, the initial trigger for CTEPH evolution is thought to be a thromboembolic event that may or may not be symptomatic. Concomitant inflammatory processes may cause fibrotic transformation of thrombus tissue. The potent fibrinolytic system of the lungs [44] fails to remove thrombus that is transformed into collagenous tissue. Fibrous obstructions grow by further *in situ* apposition of thrombotic material that is due to local imbalances of haemostasis [45]. Less obstructed resistance vessels undergo remodelling processes, *i.e.* small-vessel arteriopathy.

Clinical presentation

Like patients with other forms of PH, CTEPH patients suffer from symptoms of progressive right heart failure. However, unless a significant degree of heart failure is present, the clinical manifestation of which is unremarkable. At early stages, typical complaints are exertional dyspnoea, fatigue and rapid exhaustion. At more advanced stages, signs and symptoms of overt right heart failure, such as resting dyspnoea and fluid retention, are predominant. Physical findings in earlier stages are subtle and may include a prominent pulmonary component of S2, left parasternal heave and a systolic murmur, if tricuspid regurgitation is present. At later stages, physical examination may reveal distended neck veins, leg oedema, ascites, hepatomegaly and acrocyanosis. A typical but rare clinical finding is bruits over peripheral lung fields [46]. This acoustic phenomenon is thought to occur in approximately 10% of CTEPH patients and has been attributed to turbulent flow in partially occluded pulmonary vessels [47].

Despite similarities in clinical presentation, the course of CTEPH is clearly different from PAH. There is a significant difference with respect to age at disease onset. On average, CTEPH patients are 7 years older when the disease is diagnosed, with a vast majority of patients presenting between their sixth and seventh decades [5]. In contrast to a progressive course of disease in PAH, CTEPH progresses episodically. A thromboembolic event that may be symptomatic or not is typically followed by a so-called honeymoon period that is characterised by an absence of symptoms or by mild symptoms. Episodes of desaturation and deterioration occur, interrupting apparent health.

Diagnosis

In contrast to other subtypes of pre-capillary PH, CTEPH is amenable to surgery. Patients subjected to successful PEA regain a near-normal functional capacity with normal haemodynamics [48].

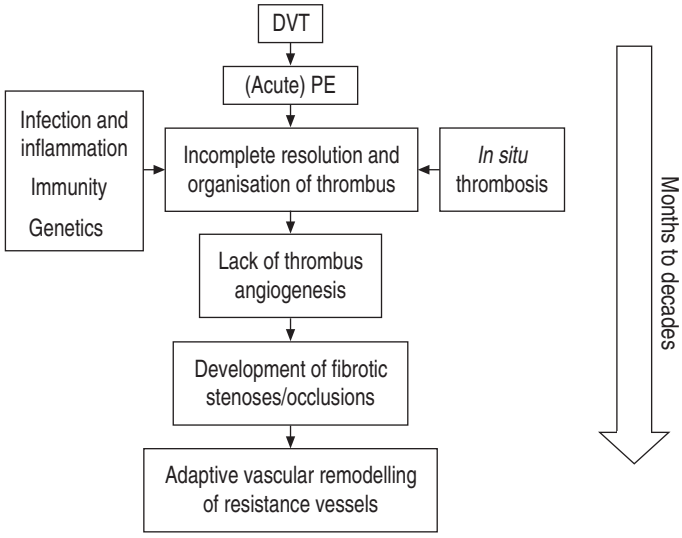

Figure 1. Pathophysiological concept of chronic thromboembolic pulmonary hypertension. DVT: deep vein thrombosis, PE: pulmonary embolism.

Therefore, the main goal of the diagnostic work-up of patients with an established diagnosis of pre-capillary PH is to test for the presence of thrombotic obstructions in major pulmonary arteries. Careful diagnostic work-up is crucial for the choice of optimal treatment. If CTEPH is suspected, patients should be referred to specialised expert centres with an experienced team of PH specialists, radiologists, anaesthetists and surgeons.

Imaging has become central to the diagnosis of CTEPH [49] and is guiding surgical accessibility of the obstructions. While visualisation of thrombus site and burden may serve as a surgical road map, the determination of operability is complex and hardly standardised. Major determinants of operability are thrombus localisation, PVR, relationship between haemodynamic compromise and thrombus burden, status of the lung parenchyma, previous cardiothoracic surgeries, comorbid conditions, unilateral *versus* bilateral disease, the response to nitric oxide (NO) during acute vasoreactivity testing [50], upstream resistance [51], and plasma levels of biomarkers, *e.g.* asymmetric dimethylarginine [5] or heart-type fatty acid-binding protein [52].

In PEA centres, available imaging techniques are used in a complementary fashion. Traditionally, V'/Q' scanning and pulmonary angiography have been key tools for the assessment of CTEPH. An attractive logistic approach is to combine invasive diagnostic techniques, *i.e.* right heart catheter and pulmonary angiography, in a one-stop shop. In the light of technological advances, multidetector CTA and magnetic resonance angiography may supersede traditional imaging techniques. However, in current European practice, all imaging modalities are employed [6] to distinguish CTEPH from chronic obstructive pulmonary disease (COPD) with left subacute pulmonary embolism, cardiomyopathy, idiopathic PAH (IPAH) of the elderly or pulmonary veno-occlusive disease (PVOD).

Right heart catheterisation

The diagnosis of pre-capillary PH is made by right heart catheterisation (RHC). Advanced techniques relying on invasive haemodynamic assessment have proven useful for quantification of concomitant pulmonary vascular disease, which is a strong predictor of adverse surgical outcome in patients with CTEPH [50, 51]. Secondary vascular disease is escaping current imaging algorithms because of their still-limited spatial resolution [47]. Analysis of pulmonary arterial occlusion pressure waveforms may be used for partitioning PVR, thus estimating the upstream contribution of resistance to total PVR. Pre-operative assessment of upstream resistance in 26 CTEPH patients predicted post-operative total pulmonary resistance index as well as mean P_{pa} [51]. In a more recent study, our group demonstrated that acute vasoreactivity testing with inhaled NO may unmask the functional status of the pulmonary microvasculature and, thereby, predict surgical outcome [5].

Ventilation/perfusion scanning

V'/Q' scanning is the key imaging tool in the diagnostic work-up of patients with pre-capillary PH. A normal ventilation/perfusion scintigram virtually rules out CTEPH [53–56], with few

exceptions [57], while in established pre-capillary PH the presence of one or more mismatched segmental or larger perfusion defects generally indicates CTEPH [55]. In clinical practice, an abnormal perfusion study alone is diagnostic for CTEPH, if pulmonary parenchymal disease is absent.

Pulmonary angiography

Pulmonary angiography is the established gold standard for CTEPH diagnosis and mandatory in the diagnostic work-up of affected patients. Allowing for the visualisation of thromboembolic obstructions, pulmonary angiography is the key data source for the assessment of operability [58, 59]. Major drawbacks of this technique are its invasive nature and limited availability, which results in limited expertise, especially in low-volume centres. Expert centre-specific experience with other imaging modalities (*e.g.* magnetic resonance) may obviate the need for invasive angiography in selected cases.

Ancillary diagnostic tools

Recently, SCHEIDL *et al.* [60] demonstrated that capillary to end-tidal carbon dioxide gradients may be helpful in the differentiation between CTEPH and non-thromboembolic PH. In a retrospective analysis of 16 CTEPH and 21 PAH patients, capillary to end-tidal carbon dioxide gradients were significantly increased in CTEPH compared with PAH, at rest and during exercise. Of course, this study is limited by its retrospective nature and small size.

Intravascular optical coherence tomography (OCT) is a catheter-based modality that acquires images at a resolution of less than 10 μm, enabling visualisation of blood vessel wall microstructure *in vivo* at a high level of detail. The technique has been widely used in patients with coronary artery disease [61]. In a very recent report from Japan, OCT was used to guide percutaneous transluminal pulmonary angioplasty in patients with CTEPH [62].

Treatment

PEA is the treatment of choice in patients with confirmed CTEPH. After successful PEA, patients are considered cured, since a vast majority nearly normalise their haemodynamic parameters and exercise capacity [63–65]. Surgical success not only depends on patient suitability, but also on the experience of the surgical team and available resources. PEA suitability is multifaceted, varies from centre to centre and cannot be based on uniform criteria [48].

A key issue in the pre-operative assessment of CTEPH patients is the degree of concomitant small-vessel arteriopathy and its contribution to PVR. Overall, patients with thromboembolic obstructions in the main, lobar or proximal segmental pulmonary arteries represent the target population for PEA, while those with more distal obstructions, or even lacking visible thromboembolic obstructions, are thought to be poor candidates for surgery [66]. Other criteria for PEA, except surgical accessibility of thrombi in the main, lobar or segmental pulmonary arteries, are a confirmed diagnosis of CTEPH in New York Heart Association (NYHA) functional class II–IV, a pre-operative PVR greater than 300 dyn·s·cm^{-5}, absence of severe comorbidities and patient consent [65].

In a contemporary registry [6], 63.3% of patients were considered operable and 36.7% inoperable. Inoperability was due to surgical inaccessibility of the occlusions in almost half of patients, imbalance between PVR and the amount of accessible occlusions in 10.1%, PVR greater than 1,500 dyn·s·cm^{-5} in 2.5%, advanced age in 2.0%, comorbidities in 13.4% and other reasons in 22.7% of patients.

In fact, patients who do not undergo surgery or suffer from persistent or recurrent PH after PEA face an adverse outcome. In a vast majority of cases, out-of-proportion small-vessel arteriopathy that is indistinguishable from histological changes found in PAH lungs precludes affected

individuals from surgical therapy. Despite a strong rationale to administer vasodilator drugs in affected patients, current evidence from randomised controlled trials does not support the use of PAH-targeted pharmacotherapy. Still, compassionate use may be justified in cases considered inoperable, as a therapeutic bridge to PEA, in patients with persistent or recurrent PH after PEA, or even when surgery is contra-indicated due to comorbid conditions. Supportive medical treatment used for CTEPH patients includes oral anticoagulants, diuretics, digitalis and oxygen supplementation. Oral anticoagulants reduce the risk of recurrent thromboembolic events and lifelong anticoagulation is recommended [47].

Pulmonary endarterectomy

PEA in CTEPH has not been assessed in randomised controlled trials, which are considered unethical in the absence of adequate alternative treatments. However, the outcome after successful PEA with respect to survival, functional status, haemodynamic parameters, RV function and pulmonary gas exchange is favourable for most patients [53, 67–70].

In a contemporary European registry comprising 386 PEA cases [48], in-hospital mortality due to peri-operative complications was as low as 4.7%. In patients evaluated within 1 year after surgery, median PVR had decreased from 698 to 235 dyn·s·cm^{-5} and median 6-minute walking distance (6MWD) had increased from 362 to 459 m. NYHA functional class had improved in most patients, progressing from class III–IV to class I–II. Interestingly, PVR at the end of intensive care was an independent predictor of in-hospital death and death at 1 year. The 6MWD at diagnosis was also an independent predictor of death at 1 year. Survivors had a higher 6MWD and a lower PVR at diagnosis than non-survivors. Mortality rates, in-hospital and at 1 year, increased with increasing values of PVR at diagnosis to reach 10.6% and 12.8%, respectively, for those patients with a PVR exceeding 1,200 dyn·s·cm^{-5}. Moreover, the mortality rate tended to be higher in patients without a history of pulmonary embolism, it increased with increasing NYHA functional class at diagnosis and with duration of circulatory arrest. Centre expertise defined by number of PEAs performed per year tended to confer a lower risk for mortality after PEA [71, 72]. Single-centre experience reports survival rates of 90.3% at 5 years if a post-operative mean P_{pa} under 30 mmHg is achieved [73].

Medical treatment

So far, only one double-blind, randomised, placebo-controlled, adequately powered vasodilator trial has been completed in patients with inoperable CTEPH: the BENEFiT study investigated bosentan effects in inoperable CTEPH [7]. A total of 157 patients were enrolled and randomised in a 1:1 fashion to receive bosentan or placebo for 16 weeks. Patients could only be included if CTEPH had been judged inoperable because of surgically inaccessible thrombotic material, or persistence/recurrence of PH after PEA in the absence of recurrent thromboembolism. PVR, which directly reflects disease pathology, and the 6-minute walk test (6MWT), a measure of exercise capacity, were chosen as co-primary end-points. Although a significant treatment effect of bosentan over placebo on PVR (-24.1% of baseline, 95% CI -31.5- -16.0%) could be demonstrated, there was only a minor effect on the second co-primary end-point (6MWD +2.2 m, 95% CI -22.5– +28.8 m).

A subgroup of patients enrolled in the AIR (Aerosolized Iloprost Randomized) study, a prospective, randomised, placebo-controlled trial, suffered from CTEPH [74]. The study failed to demonstrate beneficial effects of inhaled iloprost in this population.

Despite disappointing study results, a significant proportion of real-world CTEPH patients are on specific vasodilator treatment. Of the 679 patients studied in the European prospective registry [6], 37.9% initiated at least one PAH-targeted therapy (28.3% of operable and 53.8% of inoperable patients), including phosphodiesterase type-5 inhibitors (PDE-5 I), ERAs and prostacyclin analogues. Cautious use of PAH-targeted therapies is, however, endorsed by current guidelines [75], since

pre-operative treatment may induce unnecessary delay to a potentially curative surgical intervention [48, 76].

In the near future, patients may benefit from adaptive trial designs and new vasodilator compounds. Currently, the effects of vasodilators, such as riociguat (CHEST trial) [77] and treprostinil sodium (CTREPH trial), are being tested in a multi-national, placebo-controlled, randomised fashion.

Future perspectives

Successful PEA is still the only curative therapy for patients with CTEPH and will remain the treatment of choice. However, the assessment and quantification of concomitant small-vessel arteriopathy that may preclude an adequate relief from PH after PEA in 10–20% of patients, and increased operative mortality remains a black box in the diagnostic work-up of CTEPH patients. Innovative techniques for the evaluation of the distal pulmonary vascular bed have been introduced. One of the future efforts to be undertaken is the establishment of standardised approaches with clear-cut differentiation between surgical candidates and those who are not suitable for surgery. Recent reports of successful percutaneous transluminal pulmonary angioplasty [63] may widen therapeutic opportunities possibly even further with the availability of drug-eluting balloons, and even set the stage for staged hybrid procedures with adjuvant medical therapy.

At present, none of the vasodilator compounds approved for the treatment of nonthromboembolic PH have proven effective in inoperable CTEPH. Despite its outcome, the BENEFiT trial reinforced the principle of vasodilation as a future direction in CTEPH research.

Statement of Interest

D. Bonderman has received speaker's fees from Actelion, GSK, Bayer, Pfizer and AOP Orphan Pharma, and has sat on advisory boards for Actelion, United Therapeutics and Bayer. I.M. Lang has received speaker's fees and/or educational grants from Actelion, GSK, United Therapeutics, Bayer and AOP Orphan Pharma, has sat on advisory boards for Actelion, GSK, Pfizer, Lilly, Servier and AstraZeneca, and received a fellowship grant from the US Tobacco Research fund in 1991.

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