



Therapeutic alternatives in chronic thromboembolic pulmonary hypertension: from pulmonary endarterectomy to balloon pulmonary angioplasty to medical therapy. State of the art from a multidisciplinary team

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease with a very complex pathophysiology differing from other causes of pulmonary hypertension (PH). It is an infrequent consequence of acute pulmonary embolism that is frequently misdiagnosed. Pathogenesis has been related to coagulation abnormalities, infection or inflammation, although these disturbances can be absent in many cases. The hallmarks of CTEPH are thrombotic occlusion of pulmonary vessels, variable degree of ventricular dysfunction and secondary microvascular arteriopathy. The definition of CTEPH also includes an increase in mean pulmonary arterial pressure of more than 25 mmHg with a normal pulmonary capillary wedge of less than 15 mmHg. It is classified as World Health Organization group 4 PH, and is the only type that can be surgically cured by pulmonary endarterectomy (PEA). This operation needs to be carried out by a team with strong expertise, from the diagnostic and decisional pathway to the operation itself. However, because the disease has a very heterogeneous phenotype in terms of anatomy, degree of PH and the lack of a standard patient profile, not all cases of CTEPH can be treated by PEA. As a result, PH-directed medical therapy traditionally used for the other types of PH has been proposed and is utilized in CTEPH patients. Since 2015, we have been witnessing the rebirth of balloon pulmonary angioplasty, a technique first performed in 2001 but has since fallen out fashion due to major complications. The refinement of such techniques has allowed its safe utilization as a salvage therapy in inoperable patients. In the present keynote lecture, we will describe these therapeutic approaches and results.

Keywords: Pulmonary hypertension; pulmonary endarterectomy; hypothermia; balloon angioplasty; vasodilator



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Introduction

As the name reflects, chronic thromboembolic pulmonary hypertension (CTEPH) is a type of pulmonary hypertension (PH) that is long lasting and evolving, secondary to peripheral venous clot embolization and subsequent intravascular thrombosis. It is classified as World Health Organization (WHO) group 4 PH. CTEPH is formally defined as (I) mean pulmonary artery pressure (mPAP) of 25 mmHg or higher and a pulmonary capillary wedge pressure of 15 mmHg or lower, (II) present after at least three months of effective anticoagulant therapy and (III) confirmation of organized thrombi in the pulmonary arteries by pulmonary angiography (1-3). However, two terms are currently used to describe symptomatic patients with chronic thromboembolic occlusions of pulmonary arteries according to the presence or absence of PH at rest: chronic thromboembolic pulmonary hypertension (CTEPH) and chronic thromboembolic disease (CTED), respectively (4). A change in the definition of PH to decrease the mPAP threshold from 25 to 21 mmHg and pulmonary vascular resistance (PVR) from three to two Wood units has been proposed (5).

In both cases, the natural history of the disease is very heterogeneous, as is the disease onset, anatomy and degree of hypertension. What is known is that the long-term prognosis is very poor, with progression to cardiac and pulmonary involvement, and if left untreated, can lead to compensatory mechanisms such as vascular remodeling. This can further exacerbate the degree of PH and right ventricular dysfunction, making the disease irreversible or less responsive to any proposed treatment (6,7). It is reasonable that early diagnosis is crucial to improve disease prognosis and the results of different therapies. Unfortunately, early diagnosis is not always feasible. Theoretically, patients with CTEPH should have had a previous episode of acute pulmonary embolism (PE), but it is estimated that fewer than 40% of patients have had an acute episode, which makes the differential diagnosis more difficult (8,9). This is due to the few or even lack of symptoms during the acute process, when thromboembolic fragments are of small caliber, in limited number and tend to obstruct distal arterial branches. Another reason that could explain the lack of a previous acute PE in some cases is that an “in situ” thrombosis of distal vessels can occur, particularly in patients who are prothrombotic. Moreover, the incidence of CTEPH after an acute PE is still not well identified, ranging from 0.6% to 3.2% (10). Regardless of

the initial phenomenon, the fresh thrombi adhere to the pulmonary vascular wall and undergo fibrosis, giving rise to a plaster-like material that reduces or obstructs the lumen of the vessel (*Figure 1*). Furthermore, the pulmonary vascular bed not involved in the thromboembolic process tends to modify its vascular tone to regulate the overflow from the occluded areas. The protracted vasoconstriction leads to changes in the microarchitecture of the pulmonary vessel walls, similar to that of pulmonary venules in the context of post-capillary PH secondary to left ventricular heart disease in veno-occlusive disease. Vascular remodeling is also potentiated by a combination of defective angiogenesis, impaired fibrinolysis and endothelial dysfunction. In addition, substantial pre- and post-capillary broncho-pulmonary anastomoses lead to the transmission of systemic blood pressure to the pulmonary circulation (11,12). This complex pathophysiology explains why the statement “pulmonary endarterectomy (PEA) is curative” has been debunked. It is true that the ideal and curative treatment would be PEA, but its success depends on the degree of PH and how distal or accessible the disease is. As with any other major open heart operation, outcome also depends on the patient’s conditions and the center experience. This is the reason why not every patient with CTEPH has all the ideal characteristics to be a good candidate for PEA. In the literature, fewer than 60% of patients with a confirmed diagnosis of CTEPH have undergone PEA (13). Thus, the high percentage of patients considered inoperable has made the development of alternative therapies necessary to improve both the clinical conditions and the survival of patients suffering from this serious disease.

In the present keynote, we attempt to give a useful and introductory guide to the other extraordinary works published in this issue that discuss the main therapeutic options and its roles in the context of CTEPH: medical therapy, surgical therapy and interventional therapy. The synergistic work between the different specialists in the treating team is necessary to offer the treatment with the best risk-to-benefit ratio.

Pulmonary endarterectomy

Guidelines from both the American and European Society of Cardiology endorse PEA [also known as pulmonary thromboendarterectomy (PTE)] as a Class I recommendation with Level C evidence in patients affected by proximal and accessible CTEPH (14,15). Prior to the

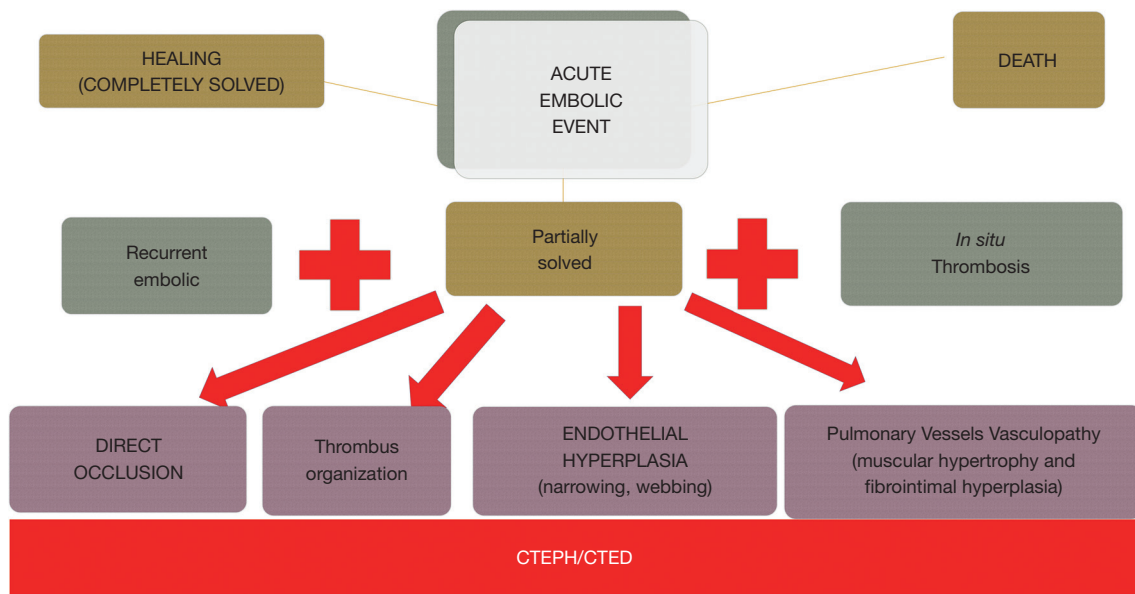


Figure 1 The natural history of the disease can be summarized as follows: once an acute pulmonary embolism has occurred, it can have a variable clinical expression, be asymptomatic or in the other extreme, lead to death of the patient. Although complete healing can certainly occur, in some cases, the fresh thrombus can also evolve towards the fibrotic organization, where further acute or thromboembolic events may even occur *in situ*. This situation would lead to evolution of the disease, in a variable time frame so-called the honeymoon period, which clinically corresponds to chronic thromboembolic pulmonary disease, giving rise in some cases to pulmonary hypertension, remodeling of the microcirculation and all the typical cardiopulmonary consequences of this disease. CTEPH, chronic thromboembolic pulmonary hypertension; CTED, chronic thromboembolic disease.

team discussion involving a PH cardiologist, radiologist, interventionist, cardiac surgeon and anesthesiologist, all patients must undergo echocardiography, ventilation-perfusion (VQ) scanning, right heart catheterization (RHC), CT pulmonary angiography and coronary angiography to meet the diagnostic criteria of CTEPH and to categorize the patient. At our center, every case of CTEPH is discussed and after a comprehensive evaluation of all data and images, risks and benefits are weighed alongside an extensive discussion with the patient, and a final therapeutic decision is made.

The reasons for not suggesting or contraindicating PEA as a first-line treatment are the associated high-risk comorbidities or surgically inaccessibility of certain thromboembolic lesions, even though one of the most important surgical advances has been the distal access of endarterectomy. Distal lesions in a context of associated pathologies and perhaps older age, used to be a strong deterrent for surgery. Thanks to increasing diagnostic and surgical experience, PEA can now be successfully performed in some patients with distal chronic thromboembolism (16,17).

Experienced centers should include expert cardiothoracic surgeons familiar with complex procedures requiring deep hypothermic circulatory arrest (DHCA), a case volume of >50 procedures per annum, ≥ 5 years of experience, an in-hospital mortality of <5%, the ability to perform distal endarterectomy and offer all three modalities of treatment. Also, PEA centers should be able to provide extracorporeal membrane oxygenation (ECMO) (18-20).

Although the European Respiratory Society task force did not delve into the technical aspects of the surgical operation, there is consensus that the procedure is performed through a median sternotomy on extracorporeal circulation. The safe completion of endarterectomy, especially for the removal of the most distal fibrotic thrombus, requires a bloodless field, which is obtained only with circulatory arrest (*Figure 2*). Organ protection during circulatory arrest is obtained by lowering the body temperature. As a result, experts advise that PEA should be performed under DHCA at 20 degrees limited to 20-minute intervals. One period is enough for the accomplishment on each side. Identification of the correct plane is crucial

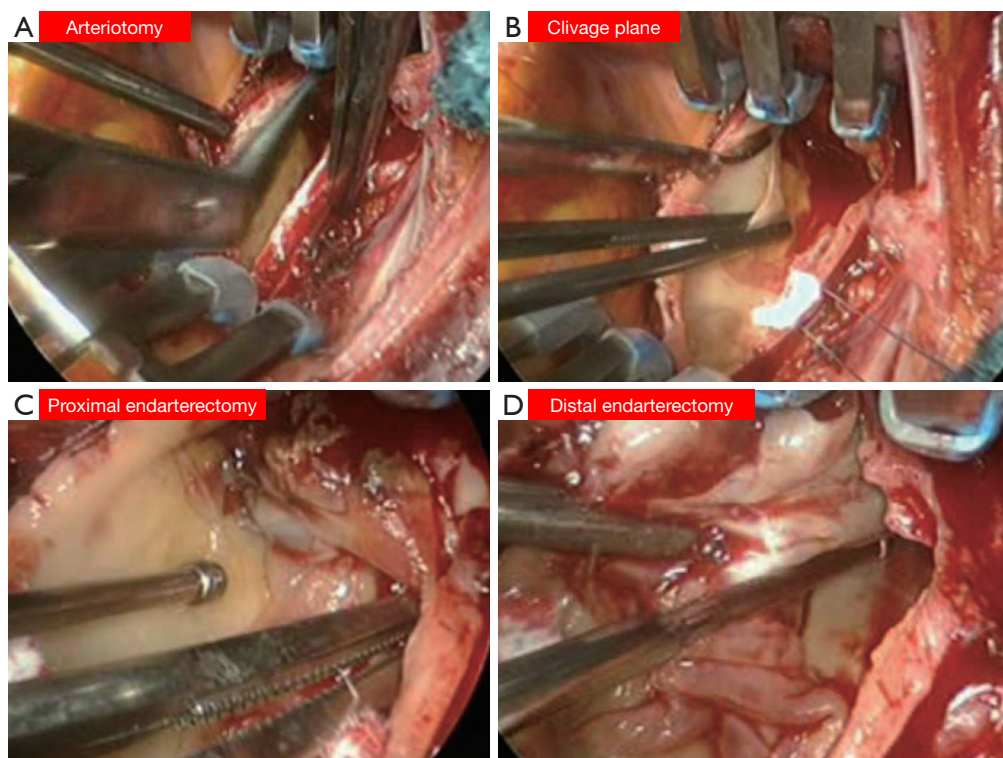


Figure 2 Leading experts in PEA suggest performing the surgery in hypothermic circulatory arrest, in order to ensure a complete, safe and effective endarterectomy. A crucial moment of the intervention is the recognition of the cleavage plane (B) after correct exposure and arteriotomy (A). The cleavage plane is not always recognizable at the proximal level when fibrosis is present in segmental or distal branches. Naturally, a cleavage plane that is too deep or too superficial would result in an extreme permeability of the vessel with the risk of parenchymal hemorrhage in the first case or a failure to resolve pulmonary hypertension in the second case. It is possible to extract up to the distal branches (D) using precise instruments, such as Jamiesson aspirators, following the cleavage plane (C) and maintaining a progressive and delicate traction of the fibrotic thrombus. PEA, pulmonary endarterectomy.

to prevent perforation of the pulmonary artery (*Figure 3*) (21-23). The International CTEPH Registry reported a <5% incidence of postoperative mortality from seventeen centers, although a larger patient series from a single center reported <2.2% mortality rate (24,25).

PEA is the most effective treatment for CTEPH as recently reported in a meta-analysis (26). The longest complete follow up from the UK National Series demonstrated a 72% survival rate at ten years, with almost 50% of deaths not related to CTEPH. From a functional point of view, a group from Pavia, Italy reported the longest follow up for functional class, with 74% of patients in class NYHA II at four years after surgery (27).

There is no current definition of success after PEA surgery, and results of PEA are determined by patient-specific characteristics. Although patients should expect to survive the operation without cognitive dysfunction or major

morbidity, residual PH following PEA is not rare. This is one of the main indications for ECMO in the early postoperative phase, particularly when severe. In the long term, true recurrence is rare and patients are mostly affected by residual PH. As residual PH predicts CTEPH-related deaths, medical therapy as well as balloon pulmonary angioplasty (BPA) in this setting have an important role (28,29).

Medical treatment: pulmonary vasodilators

Basic therapies for CTEPH include lifelong anticoagulation, diuretics and oxygen in hypoxic patients. Regarding anticoagulation, vitamin K inhibitors (VKI) are the mainstay. Novel oral anti-coagulants (NOAC) are increasingly used, but more evidence is needed regarding its efficacy, safety and interactions.

Although PEA remains the treatment of choice for

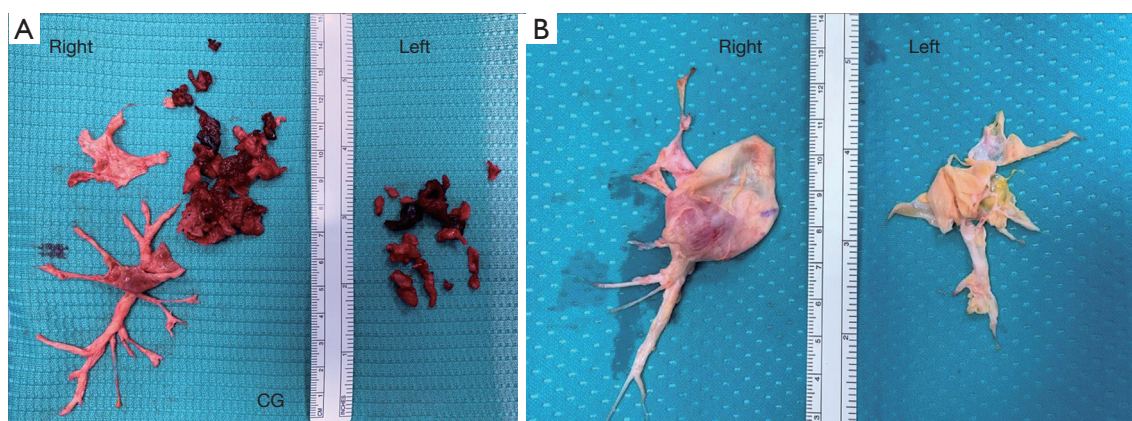


Figure 3 These two pictures represent the macroscopic differences between a fresh thrombus (A) and chronic fibrotic material (B) removed by pulmonary endarterectomy. In *Figure 2A*, there is a combination of both, with apposition of a fresh thrombus upstream to a fibrotic thrombus characteristic of CTEPH. A case like this might be very confounding, as the clinical condition of the patient was rapidly worsening, mimicking an acute high-risk pulmonary embolism. CTEPH, chronic thromboembolic pulmonary hypertension.

most patients with CTEPH, around 40% of patients in the International CTEPH Registry were considered inoperable due to concerns for inaccessible vascular obstruction, mPAP out of proportion to morphological lesions and significant prohibitive comorbidities (30). Inoperable patients and patients with residual persistent or recurrent PH after PEA should be treated with PH-specific medications to improve symptoms and hemodynamics (31).

In 2014, a soluble guanylate- cyclase stimulator (sGC), riociguat, which targets the nitric oxide pathway with a pulmonary vasodilatory effect, received approval for insurance reimbursement in the context of inoperable or persistent/recurrent CTEPH. This was based on the findings of a multi-center randomized controlled trial (RCT), CHEST-1 (28). Riociguat is an effective pulmonary vasodilator and is associated with a low risk of serious adverse events. It has been reported that sequential treatment with riociguat and BPA results in significant improvements in terms of mPAP and PVR among patients with inoperable CTEPH. Currently, Riociguat is also being tested in RCTs for its efficacy and safety as bridging therapy for patients scheduled to undergo PEA.

Currently, sildenafil, a phosphodiesterase type 5 inhibitor (PDE5i) is not approved for use in CTEPH, as studies regarding its efficacy have insufficient power (32).

Recently, the MERIT-1 trial showed that macitentan [an endothelin receptor antagonist (ERA)] improved PVR ($P=0.041$), six-minute walk distance ($P=0.033$) and n-terminal pro-brain natriuretic peptide ($P=0.040$) in

patients with inoperable CTEPH, providing evidence of combination drug therapy (33). The use of medical therapy as a bridge to PEA is still controversial, even though there is consensus about the microvascular component of the PH. Medical therapy before surgery is felt to delay referral without demonstrable clinical benefit. In the international registry, pre-treatment, even independently, predicted worse outcome (hazard ratio 2.62; $P=0.0072$) (24). However pulmonary vasodilators while attending the operation is common in the clinical practice, and its efficacy is currently being studied in the ongoing riociguat RCTs.

It is suggested that in case of residual PH after PEA, initiation of medical therapy with pulmonary vasodilators, specifically with riociguat, might be consider when mPAP rises up to 30 mmHg (26). The 2018 World Symposium on Pulmonary Hypertension (WSPH) treatment algorithm recommended medical therapy and consideration of BPA or redo-PEA in patients with persistent symptomatic PH following PEA (15).

Interventional approach: balloon pulmonary angioplasty

BPA has had a recent renaissance thanks to technical refinements from Japan (34-36). BPA was first reported in 2001 but was not included in the therapeutic armamentarium of CTEPH due to high, potentially lethal, complications rates. BPA has been demonstrated to improve hemodynamic parameters. It also yields other

positive effects, like cardiac function, quality of life and exercise capacity, not only in CTEPH patients, but also in chronic thromboembolic disease (CTED) cases (37). BPA is indicated in cases of inoperable CTEPH, after a multidisciplinary discussion and weighing of risks and benefits of PEA. The European Society of Cardiology and the European Respiratory Society have a Class I recommendation with Level IIb for the use of BPA in the guidelines for the treatment of PH (14,38).

Several articles in the current issue are dedicated to the technical aspects of BPA. The main message is that BPA requires multiple sessions and dilatations in order to obtain optimal results safely. Reperfusion edema is considered one of the major and frequent complications, even as the rate of complications has decreased significantly since the first reports in 2001. The incidence varies in each report, depending on how each complication is defined and counted (37,39).

BPA may also have a role in patients with residual PH after PEA. Cases series report an improvement in hemodynamics and exercise capacity following BPA, with the same rate of complications as non-operable CTEPH. Most of these patients were treated with PH-targeting drugs prior to BPA (29,40,41).

There is not enough information to make a statement about the role of BPA as bridging therapy prior to PEA and this area warrants more research (42).

Multidisciplinary therapeutic approach

CTEPH patients used to have a wide phenotypical heterogeneity due to the pathophysiology and natural course of the disease. They might have mixed lesions with proximal, segmental occlusions, stenosis and webs, etc., with different degrees of PH. Thus, the current treatment paradigm includes a multimodal management approach, which involves employing a combination of PEA for proximal lesions, BPA for very distal lesions and targeted pharmacological therapy for microvasculopathy. Due to the lack of guidance regarding multimodal therapeutic management of CTEPH, patient selection and treatment is individualized and customized, based on the expertise of the multidisciplinary team.

Recent cohorts have, however, demonstrated that in general, revascularization of targeted vessels, including with PEA and BPA, have similar long-term results in terms of survival and CTEPH-related deaths compared with medical therapy alone (43).

Conclusions

CTEPH is a rare, or at least under-recognized type of PH resulting from thrombotic occlusion (embolic or not embolic) of the pulmonary arteries at different levels. As it is not easy to recognize, it is the duty of PH experts to familiarize the medical community with the disease as soon as possible in order allow for early referral to a PH expert center.

Expert centers must be constituted by a multidisciplinary team, offering a complete diagnostic pathway and the best customized treatment. Multimodal treatment must inevitably include expert radiologists and PH cardiologist in order to make the correct diagnosis, medically treat inoperable patients and those with residual PH after PEA, and categorize the disease in terms of anatomy, degree of PH etc. Similarly, an expert team composed of surgeons, anesthesiologists and interventionist must be able to offer the best results of PEA or BPA after carefully weighing the risks and the benefits. The lack of all these components would inevitably result in the failure of the diagnostic and therapeutic process.

The aim of the present issue is to practically summarize CTEPH to every physician interested in the subject and highlight the priceless contribution of the outstanding authors who developed all aspects related to CTEPH, pulmonary endarterectomy and all therapeutic alternatives.

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Footnote

Conflicts of Interest: The authors declare no conflicts of interest.

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