



Chronic thromboembolic pulmonary hypertension: early recognition leads to optimal therapy and drastically decreases mortality!

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Introduction & definitions

In their article of *Annals of Translational Medicine*, Ignatov *et al.* describe their results regarding their early experience with pulmonary endarterectomy (PEA) in Bulgaria for chronic thromboembolic pulmonary hypertension (CTEPH) (1). While acute pulmonary embolism (APE) is a widely recognized entity, CTEPH is much more difficult to diagnose (1,2). The symptoms of CTEPH are attributed to obstruction of pulmonary arteries by chronic organized fibrotic clots (3).

These patients typically suffer from initial APE, initially respond to un-fractionated heparin or fibrinolysis. In some cases of CTEPH, there is no initial APE. Direct oral anticoagulants (apixaban, endoxaban, rivaroxaban or dabigatran) can be also used as a first-line therapy in patient with systolic blood pressure higher than 90 mmHg (4), but despite 3 months of anticoagulation remain dyspneic at rest. The patients' computed tomography (CT) scans show lung thrombosis, transthoracic doppler echocardiograms reveal repercussions of pulmonary hypertension (PH),

and ventilation/perfusion scintigraphy show mismatched perfusion defects (5). Diagnostic criteria include at least 3 months of effective anticoagulation before confirming diagnosis with right heart catheterisation showing pre-capillary PH, which is defined as mean pulmonary arterial pressure (mPAP) ≥ 20 mmHg (5). The frequency of CTEPH is only 3% after an episode of APE (1,6).

Pathophysiology

Regarding pathophysiology, occluded pulmonary arteries cannot create bypass vessels (7). On the contrary, systemic vessels can generate bronchial-to-pulmonary artery anastomoses to supply the ischemic lung region (7). Anastomoses between the enlarged bronchial arteries and pulmonary arteries contribute to the development of microvasculopathy (8). As a result, massive life threatening hemoptysis have been reported in 4% of the CTEPH, necessitating arterial embolization (9). Inflammatory conditions and especially infection are also associated with CTEPH (10).

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Table 1 Multimodal approach of CTEPH

Items	PEA	BPA	Medical therapy Riociguat	Medical therapy prostanoind treprostinil
Indication	Treatment of choice for CTEPH In segmental and subsegmental arteries in experienced centers	Non operable patients Distal arteries	Contraindication to PEA & BPA Microcirculation Pre-treatment for BPA (→ increased effectiveness and safety)	Refractory cases of CTEPH
Complications	Lung re-perfusion injury Haemoptysis Residual pulmonary hypertension leading to right ventricle failure	Frequent lung injuries with declining incidence Further decrease in lung injury incidence with Riociguat Bleeding possible (gelatin embolization > coil embolization)	–	–
Multimodal approach	Treat every part of the lung vessels: PEA for proximal arteries, BPA for distal arteries and pulmonary hypertension drugs for microcirculation Medical treatment before or after surgical or interventional therapy is common practice, but evidence is scarce			

CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; BPA, balloon pulmonary angioplasty.

Diagnosis

When a patient remains dyspneic at rest 3 months after an episode of APE and effective anticoagulation, it becomes urgent to rule out CTEPH as delay in diagnosis is related to higher mortality (11). The key for diagnosing CTEPH is computed tomography pulmonary angiography (CTPA) after ventilation/perfusion V/Q scintigraphy which is still used as first step to rule out CTEPH (12). What is really important is the thickness of the reconstruction slices, which should be less than 1 mm (13). Several types of signs are sought out, including first signs of PH—enlarged arteries, dilated right ventricle (RV)—along with signs of chronic pulmonary embolism (PE)—eccentric thickening and occlusions—and finally signs of lung perfusion abnormalities like bronchial artery hypertrophy (14). Recently, a reproducible sign of abnormal pulmonary venous filling, the “pulmonary vein sign” was added to this list of signs with a high sensitivity and specificity (15). Right heart catheterization remains necessary to accurately measure the mPAP and pulmonary artery wedge pressure (5).

An interesting non-ionizing technique is lung perfusion magnetic resonance imaging (MRI), offering a high sensitivity equivalent to perfusion scintigraphy especially in case of acute kidney injury (16).

Treatment options (see Table 1)

PEA

PEA is the treatment of choice for CTEPH. With the progress of the surgical technique, PEA can be realized in segmental and subsegmental arteries and, in experienced centers (defined as center performing more than 50 PEAs per year), without an increase in mortality (17). However, numerous complications can arise during or after PEA including lung reperfusion injury, hemoptysis and residual PH which can lead to RV failure (17). These complications can be amended in intensive care units (ICU) (17).

Balloon pulmonary angioplasty (BPA)

BPA is a very recent technique, however, throughout the years, experience has made this technique more reliable and efficient with a reported reduction of mean pulmonary pressure of 25 % and increase of cardiac output of 10% after BPA (18). Lung injury is a frequent complication of BPA, but the incidence is declining (18). The use of Riociguat (soluble guanylate cyclase stimulator) further reduce the incidence of lung injury after BPA (19). Another complication that may occur is bleeding. In this case, gelatin

embolisation is preferred to coil embolisation because gelatin is absorbed within weeks after which patency of the artery is restored (20).

A recent French study shows the existence of a learning curve and that “high volume” experience can drastically reduce the incidence of lung injury (21).

Medical therapy

Medical therapy is reserved for patient who cannot be treated by PEA or BPA. The first medical treatment is Riociguat, an oral stimulator of soluble guanylate cyclase. Riociguat showed efficacy and safety in the randomized controlled study called CHEST-1 (22). Prostanoid treprostinil is also used as medical treatment for refractory cases of CTEPH (23). Pre-treatment with medical therapy is crucial to improve effectiveness and safety of BPA (22,23).

Multimodal approach (see Table 1)

A multimodal approach might be necessary to treat the entire vascularisation of the lungs—PEA for proximal arteries, BPA for distal arteries and PH drugs for the microcirculation (24). In daily practice, a multimodal approach with medical treatment before/after surgical or interventional therapy is commonplace. Nevertheless, evidence base regarding this common practice is scarce (24).

What can we say and learn from the experience of Ignatov's center?

Not all patients with CTEPH can be treated by PEA as less experienced centers can only care for central CTEPH, for example (5). Ignatov says that the incidence of CTEPH is approximately 150 per year in Bulgaria (1). Only two thirds would need PEA which means it is possible that 100 cases of CTEPH that could undergo PEA (1). According to literature, and as stated by Ignatov, international experience demonstrates that “large volume” centers offer better results in terms of morbidity and mortality, as well as improved functional status (3).

A recent consensus was reached that an expert center should perform at least 50 PEAs per year for a population of 40–50 million adults, the center must have ≥ 5 years' experience with mortality rates consistently below 5%. Additionally, surgeons should be able to perform segmental and subsegmental endarterectomy and the center should also offer BPA and medical therapy for inoperable patients

(3,25). The population in Bulgaria is only around 6 million, which is significantly lower than the 40–50 millions required in the recent consensus, and since only 2/3 of the CTEPH presenting at the experienced center are suitable for PEA, these numbers are also too low to be considered a reference center for PEAs. Currently the mortality rate is 18 % in Ignatov's centre which is too high. The question is, then, to know if the neighboring countries of Bulgaria would agree to send their CTEPHs to Ignatov's centre to reach a global population of 40–50 millions as in the consensus for the center to become a reference hospital (3,25). This remains a huge challenge.

A multidisciplinary team discussion including a PH cardiologist or a pneumologist, radiologist interventionist, cardiac surgeon and an anesthesiologist is paramount and is also the key to success and offer a better patient's selection (26).

Conclusions

There has been significant advances in the diagnosis of CTEPH in the recent years. While the ventilation/perfusion scintigraphy (V'/Q' scintigraphy) remains the cornerstone to exclude CTEPH, perfusion CT scans using spectral imaging and reconstruction slides of less than 1mm is an accurate and adequate reference exam. Right heart catheterization is mandatory to accurately measure the PH and confirm the diagnosis. PEA remains the cornerstone therapy. BPA and medical treatments are used for non-operable patients and as additional therapy post-PEA. A multimodal approach including the association of PEA, BPA and medical therapy is improving the safety and long-term outcomes of CTEPH patients. Knowing the very low incidence (50 PEAs for 40–50 millions inhabitants per year), “large volume” centers are necessary to improve quality and decrease mortality below 5%. In this context, it remains to be seen if the Ignatov's center in Bulgaria (6 millions inhabitants) will be able to take on the challenge and bring the mortality down from 18% to less than 5%. Let's hope that with the help of the neighboring populations, Ignatov's center can achieve this goal in the future.

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Footnote

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