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Treating the "Untreatable". Recent advances in chronic thromboembolic pulmonary hypertension

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Take-home message:
Main treatment for CTEPH is Pulmonary Endarterectomy, a complex surgical procedure, that is performed in roughly half of all CTEPH patients. Refinements of Medical Treatments and Balloon Pulmonary Angioplasty have emerged as effective treatment strategies for the remaining patients who had no options in the past.

Chronic thromboembolic pulmonary hypertension (CTEPH) is thought to result from incomplete resolution of pulmonary thromboemboli that undergo organisation into fibrous tissue within pulmonary arterial branches, filling pulmonary arterial lumina with collagenous obstructions. The treatment of choice is pulmonary endarterectomy (PEA) with low post-operative mortality and good long-term survival in expert hands. Patients ineligible for PEA or who have recurrent or persistent pulmonary hypertension after surgery have been previously the "Untreatable". Modern CTEPH management has now a solution for those previous no-option patients: balloon pulmonary angioplasty (BPA), and targeted medical therapies. Riociguat has been approved for inoperable CTEPH, and persistent-recurrent PH after PEA, and SC Treprostinil has been efficacious in a randomized controlled trial of very severe CTEPH. Observational studies report that BPA improves haemodynamic, symptoms and functional capacity in patients with CTEPH, but controlled trials with long-term follow-up are needed. Complications include haemoptysis, wire injury, vessel dissection, vessel rupture, reperfusion pulmonary oedema, pulmonary parenchymal bleeding and haemorrhagic pleural effusions. This review summarises available evidence for PEA, BPA, and medical therapy, patient selection, peri-procedural imaging and technical refinements achieved by CTEPH teams, and discusses future management of CTEPH.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease of the pulmonary vasculature which is classified as a distinct entity (Group 4) of pulmonary hypertension (PH) (1). CTEPH is believed to develop when a pulmonary embolism does not resolve and transforms into fibrous tissue that occludes major pulmonary arteries. A concomitant small-vessel arteriopathy plays an important role in the development of persistent PH after surgical pulmonary endarterectomy (PEA) and survival.

Early diagnosis and treatment by a multidisciplinary team are essential. Screening is based on ventilation/perfusion lung scanning, and diagnosis is made by imaging typical CTEPH lesions with angiography, best by invasive digital subtraction angiography or direct injection. Computed tomography is emerging to provide

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similar quality images as invasive angiography in the future, including parenchymal lung images as well as images of the heart and the great vessels for differential diagnoses. The CTEPH team should then address the question whether the gold-standard treatment PEA as a potentially curative intervention is feasible with an in-hospital mortality rate <5%. About 40-50% of patients with CTEPH is no surgical candidates or cannot undergo surgery at an acceptably low in-hospital mortality rate, and 17–31% of patients after PEA experience persistent/recurrent PH. Modern CTEPH management has now a solution for those previous no-option patients: balloon pulmonary angioplasty can be performed, and targeted medical therapies can be given.

Pulmonary Endarterectomy – An old technique newly stimulated

PEA remains the gold standard treatment with the option of potential cure with mortality rates as low as 2% in specialised centers *(Table 1)* (1, 2). Elligibility for PEA should be determined by a CTEPH team consisting of surgeons, PH specialists, radiologists and interventionists. Tradionally, PEA was limited to patients with proximal disease and localisation of most proximal clot has been the main determinant of PEA eligibility (2, 3). Experienced centers have advanced their skills to allow surgical treatment for patients with more distal disease (4). Moreover, there is a growing understanding that PEA may lead to RV afterload reduction even in patients with high PVR and distal disease, in combination with other treatments (2).

Peri-procedural complications include stroke, bleeding, arrhythmia, pericardial and pleural effusions and post-operative reperfusion pulmonary edema (5). Reperfusion edema occurs in 5–20% of patients, especially in patients with high pre-operative pulmonary pressure (2, 6, 7). When supportive treatment with mechanical ventilation, diuresis and drugs approved for PAH are not enough, ECMO may be indicated (2, 8, 9). ECMO both intra and post-operative has become standard of care in centers performing high-risk PEA (2, 8, 9).

Pre- and post-operative PVR, pulmonary vasoreactivity, as well as age, comorbidities and functional status are factors assisting in the prediction of post-operative outcomes (10, 11, 12).

Persistent/recurrent PH after PEA is a major determinant of poor prognosis and functional capacity for CTEPH patients undergoing PEA (7, 13). According to the European registry, 16.7% of patients are diagnosed with persistent/recurrent PH after PEA (14). The ability to predict which patients are prone to develop such condition is of major practical importance. A concomitant secondary microvasculopathy in addition to major pulmonary artery obstruction has been suggested as one of the mechanisms leading to persistent/recurrent PH after PEA (2). Recently *Gerges et al.* have confirmed the role of preoperative pulmonary artery pres-

TABLE 1. Reported effects of PEA, BPA and medical treatments in CTEPH

Treatment	Source	Year of publication	Number of patients	Change in 6MWD (*)	Change in PVR (*)	Change in mPAP (*)	Peripro-cedural mortality
PEA	Italian registry (39)	2016	554	41%	–71%	–48%	8.50%
	French reference center (40)	2018	150	29%	–60%	–41%	2.90%
	San Diego Health center (41)	2012	500	–	–64%	–43%	2.20%
	United Kingdom National Cohort (42)	2016	880	36%	–62%	–43%	2.4%**
	German registry – Bad Nauheim (43)	2017	236	–	–	–	2.50%
	European CTEPH registry (6)	2011	386	–	–66%	–	4.60%
BPA	French reference center (29)	2019	184	11%	–45%	–28%	2.20%
	Hannover & Bad Nauheim (44)	2017	56	9%	–26%	–18%	1.80%
	Japanese multicenter registry (36)	2017	308	35%	–66%	–48%	2.60%
Riociguat	CHEST 1 (19)	2013	261	13%	–31%	–9%	–
Bosentan	BENEFiT (21)	2008	157	0%	–24%	–5%	–
Macitentan	MERIT–1 (23)	2017	80	10%	–16%	–4%	–
Treprostinil SC	CTREPH (25)	2019	105	15%	–34%	–7%	–
Oral combinations***	(45)	2018	117	13%	–41%	–13%	–

*for PEA – change is from pre procedure to post, BPA: baseline to completion of treatments, medications – change after 4–6 months of treatment. **30 day mortality rate for second half of the cohort. ***(ERAs+ PDE–5i/Riociguat). PEA: pulmonary endarterectomy, BPA: balloon pulmonary angioplasty, SC: subcutan, 6MWD: 6 minute walk distance, PVR: pulmonary vascular resistance, mPAP: mean pulmonary artery pressure

sure waveform analysis to predict secondary microvasculopathy and outcomes prior to PEA (15).

Advances in Medical Treatments for CTEPH

The initial step in the management of CTEPH is appropriate anticoagulation. Current guidelines suggest that effective anticoagulation over at least 3 months should precede a CTEPH diagnosis. 3 months is the minimal guideline-recommended treatment duration for acute pulmonary embolism. Furthermore, guidelines advise to continue lifelong anticoagulation to prevent recurrent thrombosis. While there are no large randomized trials regarding the preferable type of anticoagulation for CTEPH patients, recent registries point to beneficial effects of Vitamin K antagonists as compared with DOACs (16), despite greater safety of direct oral anticoagulants (DOACs) (17). Post-PEA functional and hemodynamic outcomes appeared unaffected by anticoagulant choice. Bleeding events were similar, but recurrent VTE rates were higher in patients receiving DOACs (16).

Medical treatment for CTEPH patients is required in many patients, particularly in those who are no candidates for PEA because of distal location of vascular disease, or because they carry an unfavorable risk-benefit ratio for major surgery. Furthermore, medical treatments are considered for patients with severe hemodynamic compromise prior to PEA or balloon pulmonary angioplasty (BPA), and after mechanical interventions in those with persistent/recurrent PH (18).

Riociguat was the first drug with clinical effectiveness to be approved for the treatment of inoperable CTEPH, or persistent/recurrent PH after PEA (19, 20). The drug is a stimulator of soluble guanylate cyclase (sGC) with both a direct effect and an indirect effect by sensitizing GC receptors to endogenous nitric oxide (NO). Improved exercise capacity (EC) and PVR were shown in the CHEST-1 and CHEST-2 trials (19).

The BENEFiT trial, (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial with the Endothelin receptor antagonists (ERA) Bosentan did not meet the primary combined endpoint of 6MWD and decrease in PVR (21). Positive results where demonstrated for the use of bosentan as bridging therapy before PEA (22). The MERIT-1 trial, examining the effect of macitentan in inoperable CTEPH showed improved PVR and 6MWD, however no change in WHO-FC (23). Actelion-Janssen has withdrawn their application for approval of macitentan for the treatment of CTEPH.

A significant advancement in medical treatment of CTEPH was made in the CTREPH trial, examining the effect and the safety of subcutaneous (SC) treprostinil for severe CTEPH (18, 24). Treprostinil treatment was evaluated for both inoperable CTEPH and persistent/recurrent PH after PEA. To ensure blinding of the study a high dose of the drug (uptitrated to 30 ng/kg/min) was compared with a low dose peaking at 5 ng/kg/min. About 30% of patients were treated concomitantly with other PH related oral medications, such as riociguat, ERAs and PDE5 inhibitors. The study demonstrated significant changes in 6MWD, hemodynamics and most significantly, WHO-FC (18, 25). SC treprostinil, although not officially approved for the treatment of CTEPH, is used for patients who require medical treatment and can either not tolerate riociguat or are high-risk patients, defined by a low 6MWD and unfavorable hemodynamic criteria such as a PVR > 800 and dynes.s.cm–5 and mPAP ≥40 mmHg (18).

Balloon pulmonary angioplasty – a new technique changing CTEPH

BPA treatment, first introduced in 2001 (26), is a percutaneous balloon intervention breaking intraluminal webs and bands without dissecting medial vessel layers. The procedure has been improved and refined over the years with better results and safety profiles, using a sequential approach with 4-7 sessions (27, 28). Mainly developed in Japan, the procedure is now introduced and offered to European centers with favourable results (2, 29, 30, 31, 32). Current guidelines recommend BPA for patients with either inoperable disease or those with unfavourable risk-benefit ratio for PEA (1). However, more and more centers are now offering this option to patients with persistent or recurrent PH after PEA surgery and in specific cases as combined treatments, prior to, during or after PEA (33, 34).

In Japan BPA is preferred over PEA surgery. More and more data are collected regarding safety and effectiveness (30), for example in the Euroeopan BPA Registry (NCT03245268). In a recent Japanese study, BPA alone or in combination with PEA has been shown to improve prognosis when compared to patients treated with PEA alone or medical treatment alone (30). Survival of inoperable patients diagnosed in the BPA era is better than previous (35).

BPA protocols vary from one center to the other, but repeat sessions are required. The main imaging assessment used to assess the patients is pulmonary angiography, however CT scans, with 3D reconstructions and OCTs have provided important anatomic insights (2, 28). Routine use of OCT or IVUS during BPA has not been recommended.

According to a recent Japanese registry mPAP is reduced by about 20 mmHg to levels below 25 mmHg, with significant reduction in the need for other PH related medications and supplemental oxygen (36). The French BPA experience has documented improved hemodynamics as well as improved 6MWD and NYHA functional class after 5.2 ± 2.4 BPA sessions. mPAP

has decreased by 26% and PVR by 43% when compared to baseline values 29. BPA has also been shown to improve comorbidities such as metabolic function and renal function in parallel to improvement in pulmonary hemodynamics (37).
Complication rates have been drastically reduced in recent years with the use of balloons that have a smaller diameter than the lumen of the target vessel, tapered balloons, soft wires, and a stepwise approach (2). Complications, including bleeding, wire-induced pulmonary artery perforation and reperfusion edema occur in up to 10% of sessions however 30-day mortality is as low as 1-2% (2, 36, 28, 38, 29).

Future perspectives for CTEPH management

Despite all advances, there are still several challenges in CTEPH management that have to be faced. First, diagnosis remains hard and best accomplished if one thinks about CTEPH in the setting of major acute pulmonary embolism. Machine learning algorithms are being developed to identify CTEPH cases as they present under the clinical picture of acute PE in emergency rooms. Once diagnosed, the next step is the CTEPH team decision. Multidisciplinary teams face challenges which are case-loads, logistics, and cost. Patient management is shifting from the simple question of PEA or no PEA to multimodality treatment choices *(Figure 1)*. Patients who were labelled inoperable may be found operable upon a second assessment (5). Patients who are inoperable or have persistent / recurrent PH post-surgery may benefit from a multitude of interventions including BPA, oral medical treatment in different combinations and SC Treprostinil in severe cases (18). Treatment is increasingly individualised according to anatomical disease location, response to different treatments, personal preferences and treatment availabilities.
Refined BPA is a safe and effective treatment option for patients with distal disease, patients with comorbidities, as well as patients with recurrent/persistent PH after surgery (14, 33, 34). Randomized studies will have to compare the role of BPA with PEA in suitable patients.

Conflicts of Interest

IML has relationships with drug companies including AOPOrphan Pharmaceuticals AG, Actelion-Janssen, MSD, Medtronic, and Ferrer. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards. Table 1 – Reported effects of PEA, BPA and medical treatments in CTEPH.

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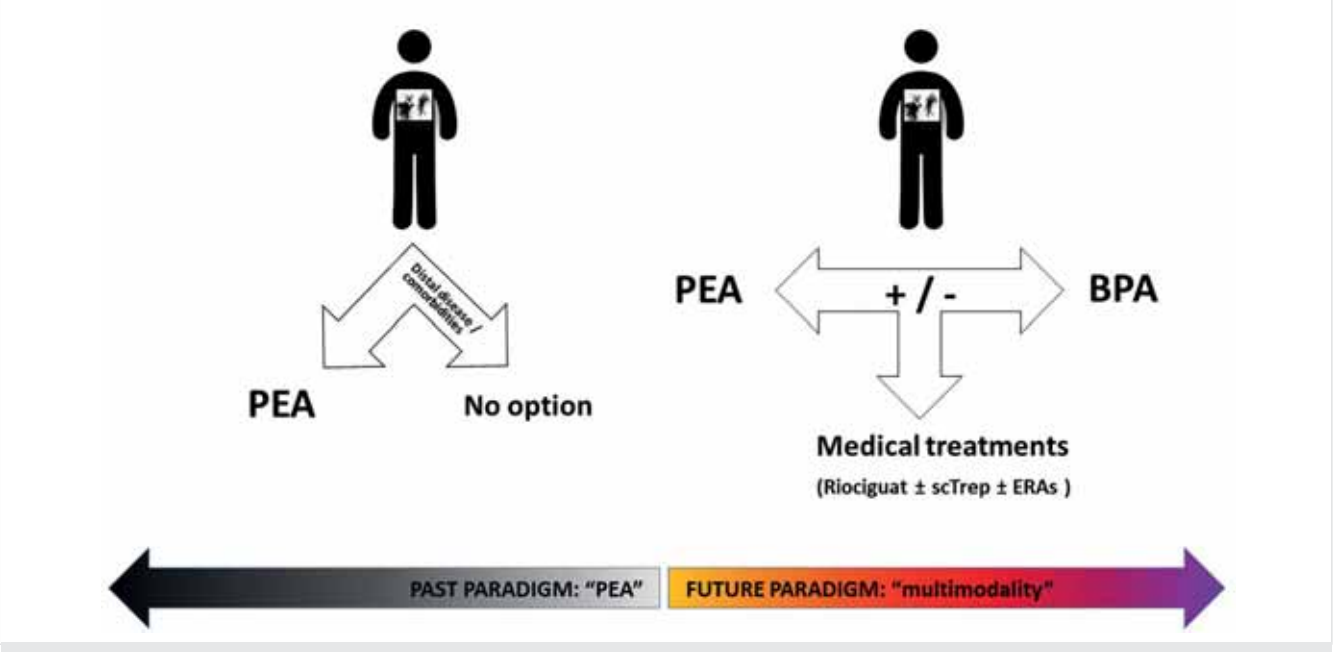

FIGURE 1. Treatment paradigm shift – from an era where PEA was the only treatment to an era where both mechanical and medical treatments are combined

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