



# Residual pulmonary hypertension after pulmonary thromboendarterectomy: incidence, pathogenesis and therapeutic options

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Submitted Aug 02, 2021. Accepted for publication Aug 26, 2021.

doi: 10.21037/acs-2021-pte-11

View this article at: <https://dx.doi.org/10.21037/acs-2021-pte-11>

Pulmonary endarterectomy (PEA) remains the gold standard to treat and potentially cure chronic thromboembolic pulmonary hypertension (CTEPH), despite advances in medical and interventional management of CTEPH in the last ten years (1). There is no clear definition of a successful PEA (2). The outcomes after PEA are multifaceted, and should take the different dimensions of the disease into account: besides procedure survival, should the success of PEA be evaluated according to clearance of pulmonary vessels, hemodynamic evolution or symptom improvement? This question is unsolved and the correlation between these endpoints is quite loose. Indeed, a surgeon may achieve a significant flow restoration without reaching a normalization of hemodynamics, especially if pulmonary microvascular disease (PMD) is present. Conversely, an uncompleted revascularization may lead to dramatic clinical improvement, particularly if the dead space ventilation can be improved. Some patients may also present with a significant improvement in hemodynamics with persistence of substantial perfusion defects. However, due to the difficulty and lack of standardization for evaluation of vascular obstruction and the subjectivity and challenge to quantitatively assess clinical improvement, achievement of normal or nearly normal hemodynamics [mean pulmonary artery pressure (mPAP) and/or pulmonary vascular resistance (PVR)] has been pragmatically considered as the best hallmark for PEA success. This point of view has led to present PEA as a potentially curative treatment for CTEPH and the concept of residual pulmonary hypertension (PH)

after PEA.

The reported incidence of residual PH after PEA varies according to definition and timing. A recent meta-analysis of 25 studies concerning 4,686 patients who underwent PEA has found an incidence of residual PH of 25% (3). The reduction in mPAP and the improvement of PVR were 21 mmHg and 7 WU after PEA, respectively. Although most of the studies used a mPAP cut-off value of 25 mmHg to define residual PH, some studies used a cut-off value of 30 mmHg or a combination of mPAP and PVR; notably, no studies used the recently proposed value of 21 mmHg to define PH (4).

The clinical significance of residual PH after PEA has been investigated by Cannon *et al.* (5). They found that a mPAP higher than 30 mmHg was a threshold above which treatment was frequently initiated, presumably because of clinical deterioration. Moreover, the same authors found that a mPAP >38 mmHg with a PVR >425 dyne/sec/cm<sup>-5</sup> were associated with a higher risk of death due to CTEPH.

The etiology of persistent PH after PEA is attributed to PMD, failure to remove fibrotic material from the pulmonary vascular tree or both. Recurrence of CTEPH after a previous period of improvement may also occur, due to recurrent thrombo-embolic events or evolution of an underlying PMD. The following predictors of residual PH have been reported: high preoperative PVR, distal surgical material and associated medical conditions (splenectomy, ventriculo-atrial shunt, permanent central intravenous lines, inflammatory bowel disease and osteomyelitis).

PMD is the rationale for medical treatment of residual PH after PEA. Few randomized controlled trials have been published and they concerned mixed populations of patients with inoperable CTEPH and residual PH after PEA. Bosentan, an antagonist of the endothelin-1 receptor, was evaluated in the BENEFiT study (6). In the subgroup of patients with residual PH, there was no significant improvement in terms of hemodynamics or exercise capacity after 16 weeks of treatment (6). Riociguat, a stimulator of soluble guanylate cyclase, was also investigated in patients with residual PH in the CHEST study (7). The study was positive with a significant improvement of six-minute walk distance after 16 weeks in patients with inoperable CTEPH or residual PH, although the improvement in six-minute walk distance was less pronounced in the subgroup with residual PH (54 and 26 meters, respectively). Based on this study, riociguat was the first drug approved for residual PH after PEA.

Persistence of endoluminal fibrotic material may be mechanically treated with a reoperative PEA or balloon pulmonary angioplasty (BPA). Reoperative PEA may be proposed in very selected cases if proximal disease remains substantial. However, due to the previous endarterectomy which has already removed the inner layer of the vessel walls, it remains a highly challenging surgery with poor outcomes and an in-hospital mortality of 40% (8). BPA, a percutaneous technique aiming to reopen pulmonary arteries lumen by pushing back fibrotic materials against the vessel walls, has also been proposed for treatment of residual PH. Retrospective studies for BPA after PEA have shown improvements in hemodynamics, exercise capacity and symptoms after BPA (9,10). A recent Japanese series that compared 25 patients with residual PH treated by BPA with inoperable CTEPH patients treated only with BPA showed that patients with residual PH after PEA displayed a higher rate of complications, mainly severe hemoptysis (11). Interestingly, it has been recently shown in a cohort of patients from the UK, that patients treated with BPA after PEA were less likely to respond to BPA (12). The difficulties encountered with BPA after PEA could be due to several factors: involvement of more distal lesions under the form of occlusive residual “tails” and hard fibrotic obstructions which has been associated with elastic recoil, resulting in re-occlusion after dilation. Moreover, the weakening of the pulmonary artery wall in combination with high pressure may lead to aneurysmal dilation, making the BPA procedure more difficult, and therefore reducing the rate of vascular clearance compared with non-operated patients (10).

Interestingly, most BPA studies have recruited patients who have been medically treated; however, the timeframe of both treatments remains to be clarified. Despite this, whatever the treatment options (medical therapy, BPA, redo PEA or a combination), long term anticoagulation remains the cornerstone of the treatment to preclude CTEPH recurrence (2).

Residual PH after PEA is therefore far more complex than a residual pressure. It is not only a matter of definition, but also has direct implications concerning the best therapeutic approach and treatment targets. An area of research is now open to clarify what a successful PEA is and what to do if PEA fails.

### Acknowledgments

*Funding:* None.

### Footnote

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

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**Cite this article as:** Godinas L, Verbelen T, Delcroix M. Residual pulmonary hypertension after pulmonary thromboendarterectomy: incidence, pathogenesis and therapeutic options. *Ann Cardiothorac Surg* 2022;11(2):163-165. doi: 10.21037/acs-2021-pte-11