

# Chronic thromboembolic pulmonary hypertension and pulmonary endarterectomy: a rapid guide to diagnosis and management

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## Summary

**Chronic thromboembolic pulmonary hypertension (CTEPH) represents the only type of pulmonary hypertension surgically treatable and curable, in the majority of cases, avoiding the need of lung transplant. This life-saving conservative surgery is called pulmonary endarterectomy (PEA).**

To date, CTEPH is still under-diagnosed, and nowadays only few physicians are aware of the benefits of PEA. Clinical suspicion is the first step for diagnosis of CTEPH. Echocardiography, lung perfusion and ventilation scan, and right heart catheterization are useful for the diagnosis. Pulmonary angiogram, CT scan, and a multidisciplinary assessment are preliminary to surgical indication for PEA. PEA may have hemodynamically dramatic and immediate effects with a prompt restoration of normal values in most cases. Riociguat, a stimulator of soluble guanylate cyclase, is the only specific drug for non-operable CTEPH patients or those with persistent/recurrent disease after surgery.

**KEY WORDS:** chronic thromboembolic pulmonary hypertension, CTEPH, pulmonary endarterectomy, PEA, riociguat.

## Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is the only form of pulmonary arterial hypertension (PAH) potentially curable (1). It is due to the incomplete destruction of the thromboembolic material leftover from previous episodes of acute pulmonary embolism (PE). The elective care is the removal of the

obstruction by pulmonary endarterectomy (PEA), a surgical operation performed only in few centers in the world (Figure 1). The CTEPH is a complex disease due to the difficult diagnosis often late performed, the therapeutic indication to surgery possible only in experienced Centers, the drug therapy and the follow-up to be administered by devoted specialized physicians: therefore a multidisciplinary approach to the patient is essential to ensure excellent results (2). The prevalence of CTEPH in patients surviving an acute pulmonary embolism (ca. 80%) is calculated between 0.5-3.8%, as to say an incidence of 2,000 new cases/year in Italy (3). Nevertheless, the honeymoon asymptomatic period may last months, and even years.

The main feature of CTEPH is the lack of a pathognomonic clinical manifestation and the frequent absence of a venous thromboembolism history, so it is frequently under-diagnosed. When there is a suspicion of CTEPH, three objectives should to be achieved:

- to confirm the presence of pulmonary hypertension;
- to identify the etiology;
- to determine the appropriate treatment.

## The diagnostic work-up

### First level exams

The first level exams are the electrocardiogram (EKG), chest X-ray and echocardiography. EKG and chest X-ray tests are designed to highlight nonspecific signs of pulmonary hypertension

(PH), while echocardiography estimates the pressure in the pulmonary artery or the presence of intra-cardiac defects responsible for PH (4-8).

**The right heart catheterization is the only test to confirm the presence of PAH.**



Figure 1 - Pulmonary endarterectomy casts from a patient with complex and severe case of CTEPH (Pavia, 2014).

### Second level exams

Tests of the second level are the right heart catheterization and pulmonary ventilation-perfusion scan (9, 10).

The integrated analysis of vascular and parenchymal phases allow the radiologist to exclude thoracic rare diseases causing PH other than CTEPH.

The right heart catheterization is the only test that can confirm the presence of PH. The pulmonary ventilation-perfusion scan is important to differentiate the CTEPH from the idiopathic PAH by the presence of a mismatch between ventilation and perfusion lung (11, 12).

### Third-level exams

They are the pulmonary arteriography and the CT scan to identify the site and extension of the pulmonary arterial lesions. Pulmonary angiography is still considered the gold standard in the diagnosis of CTEPH to assess the accessibility of the surgical injury (13-16). The most common signs of CTEPH are the intimal irregularities, defects as pocket or intravascular networks, sudden reduction of the vascular dimension or amputation of the vase, frequently combined with bronchial artery dilation (Figure 2). In our center, this method has been replaced by chest CT thanks to the possibility of using devices 64 detectors and to the growing expertise of radiologists in using this method. Vascular phase confirms the thromboembolic etiology and allows to specify the localization and extension of embolic lesions, to identify the size and the thickness of the vessel wall and to identify the presence of atherosclerotic calcifications in the wall. The integrated analysis of vascular and parenchymal phases allows radiologist to exclude thoracic rare diseases causing PH with obstructive symptoms similar to CTEPH as the pulmonary artery sarcoma, the fibrosing mediastinitis and mediastinal neoplasms.

### Drug therapy

Medical therapy is not able to heal the CTEPH. The most important drugs are anticoagulants to prevent re-



Figure 2 - CT scan in a case of CTEPH with proximal defect: combined intimal irregularities of the pulmonary artery main branch and bronchial artery dilatation.

current VTE and pulmonary circulation selective vasodilators. The curable treatment is the PEA. If some patients are inoperable or have persistent or recurrent CTEPH after surgery, a specific drug therapy could be used: Riociguat (17), a stimulator of soluble guanylate cyclase (sGC). To date, Riociguat is the only drug designed for PAH having a specific indication for CTEPH not operable or persistent/recurrent after surgery thanks to the results of ad hoc RCT. Other specific drugs for PAH failed to reach the primary end-point in placebo-controlled trial (18). Only a small percentage of patients with CTEPH is not candidates to PEA (19) for the presence of lesions located exclusively at a very distal level or associated with other parenchymal lung diseases (e.g. severe pulmonary emphysema). In these cases the surgical alternative if indicated, is represented by bilateral lung transplantation.

Riociguat is the only drug for PAH having a specific indication for CTEPH.

### Surgical treatment (PEA)

The indications for PEA (pulmonary endarterectomy) are:

- clinical: patient with functional class WHO II, III, IV. The clinical spectrum in which the EAP is indicated is therefore broad, ranging from moderately symptomatic forms in young patients at high risk cases in elderly patients with early multiple organ dysfunction;
- hemodynamic: the presence of  $PVR > 300 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$  or a value of mean pulmonary artery pressure at rest  $> 25 \text{ mmHg}$  at the right heart catheterization;
- anatomical: the location and extent of the disease within the pulmonary arterial circulation are the main determinants operability, although the accessibility of the lesions is strongly influenced by the experience of the surgeon.

The interdisciplinary collaboration is important for operability judgement: advanced age, associated comorbidities, severe right ventricular failure and a long duration of the disease should not be considered as absolute exclusion criteria. A careful evaluation of the indication for PEA is a key factor in the management of patients with CTEPH. Otherwise, the non-appropriate assignment of some patient to surgery may be fatal. It is therefore essential referring the patient to an experienced center both for PEA and lung transplantation (20, 21).

The operative mortality of PEA intervention has undergone a significant decrease from 22% of the first published series in the second half of the 80s to the current 2-5% after overcoming the learning curve plateau (22). It is therefore considered obsolete the belief that PEA may be associated

The hemodynamic changes after PEA may be dramatic immediately into the operating room.

with high morbidity and mortality, such as having to reserve intervention for the sickest patients. The functional improvement strictly depends on the hemodynamic changes after PEA.

The hemodynamic changes after PEA may be dramatic immediately into the operating room, with a regular return to normal values in most cases (23, 24). Within the first few days post-surgery there was also an initial recovery of cardiac function, with a clear reduction of right ventricular dilatation. One year after it documents the reverse remodeling of the right ventricle, with the disappearance of ventricular hypertrophy and the recovery of a normal kinesis (24). The functional improvement of patients instead occurs more gradually and is linked to the age of the patient or to the duration of the disease.

Currently 90% of patients referred to a referral Centre for CTEPH is judged operable, thanks to an optimal selection of patients referred by the peripheral centers, and to the experience that has allowed to operate patients with distal disease, removing patients from the waiting list for lung transplantation (25). The age of patients has increased over the years. Age, however, does not affect the outcome of surgery in standardization hemodynamics and survival in the medium and long term.

**Currently 90% of patients referred to a CTEPH Centre is judged operable.**

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