

Chronic Thromboembolic Pulmonary Hypertension: Not So Infrequent After All

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Pulmonary hypertension (PH) after acute pulmonary emboli (PE) is an underrecognized condition that may have serious consequences. A recent study demonstrated that up to 43% of patients have residual PH on echocardiogram (ECHO) one year after an episode of acute PE and that 5% can develop severe PH over time.¹ These findings were confirmed by a prospective study demonstrating that 3.8% of 314 patients followed after an episode of acute PE developed severe PH within two years after the diagnosis of acute PE.² Considering that the incidence of acute thromboembolic disease is 0.5 to 1.0 per 1,000 people per year, 500 people to 1,500 people in Canada every year could end up with severe PH as a result of acute PE. Hence, the condition is much more frequent than previously estimated and should be recognized when encountered. The term chronic thromboembolic pulmonary hypertension (CTEPH) is used to describe residual PH after acute PE.

Pathophysiology

In the large majority of patients, acute PE is resolved by local fibrinolysis and complete restoration of the pulmonary arterial bed is established. However, for reasons that are unknown, the resolution of the PE does not always occur and the emboli evolve towards an organized clot within the pulmonary artery

wall. A residual organized clot can then lead to the development of PH, despite adequate anticoagulation, because of local phenomenon and not because of recurrent PE.³

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There is typically a honeymoon period between the acute PE and the occurrence of symptoms of PH. The honeymoon period can last from a few months to several years. The development of PH after this period is due to the development of a vasculopathy of the small pulmonary vessels, similar to that seen in idiopathic pulmonary arterial hypertension. Therefore, PH can progressively worsen despite adequate anticoagulation and will inevitably lead to right heart failure and death. If untreated, the prognosis is poor with a median survival of 12 months to 24 months and a five year survival of only 10% in patients with severe PH.⁴

Clinical presentation

Patients suffering from CTEPH typically present either with progressive dyspnea over months or years, or with an acute deterioration of their shortness of breath. Approximately half of the patients do not have any documented history of acute PE. Some patients do mention a past history of pneumonia or pleurisy that could be attributed to misdiagnosed PE. Some patients may also complain of:

- syncopal episodes during effort,
- angina,
- hemoptysis, or
- chest pain.

Rarely, patients can present with a paradoxical emboli due to a patent foramen ovale (Table 1). The diagnosis is rarely made during regular, long-term followup of patients presenting with acute PE.

Clinical examination may reveal signs of PH with a heart murmur secondary to tricuspid regurgitation, as well as a loud secondary heart sound and sternal heave. The tricuspid regurgitation murmur is holosystolic and can be best heard along the left lower sternal border. Occasionally, a systolic murmur can be heard in the pulmonary field suggestive of stenosis of the pulmonary artery branches. The chest x-ray can show an enlarged heart and filling of the aortopulmonary window secondary to pulmonary artery dilation. The ECG can show evidence of:

- right atrial enlargement,
- right ventricular hypertrophy and
- right-axis deviation.

Table 1

Mode of clinical presentation: Symptoms and approximate incidence

• Progressive dyspnea	50%
• Acute shortness of breath	50%
• Chest pain	20%
• Hemoptysis	10%
• Syncopal episodes	5%
• Stress angina	5%
• Paradoxical emboli	3%

Note: Patients often present with more than one symptom.

Table 2

Investigations for diagnosis of CTEPH

1. Ventilation perfusion (V/Q) scan and echocardiogram are required for the diagnosis of CTEPH
2. A normal V/Q scan can exclude a diagnosis of CTEPH
3. A normal contrast-enhanced CT scan or MRI scan does not rule out a diagnosis of CTEPH
4. A pulmonary angiogram and right heart catheterization confirms the diagnosis of CTEPH

CTEPH: Chronic thromboembolic pulmonary hypertension

Diagnosing CTEPH

The ECHO and ventilation-perfusion scan (V/Q) are the two initial non-invasive investigations to perform to establish the diagnosis of residual PH after acute PE (Table 2).

V/Q

The V/Q scan typically reveals ventilation-perfusion mismatch with one or more segmental perfusion defects and normal homogenous ventilation. It is important to emphasize that the V/Q scan does not differentiate between an acute PE and CTEPH. Perfusion scans also tend

to underestimate the severity of vessel obstruction in CTEPH. A normal V/Q scan does effectively rule out a diagnosis of CTEPH.

While both CT and MRI scans are useful to exclude alternate diagnoses and may be complementary to V/Q scan, these techniques should not be used to exclude the diagnosis of CTEPH. Indeed, a normal CT or MRI scan does not rule out a diagnosis of CTEPH.

ECHO

The trans-thoracic Doppler ECHO allows for an estimate of the severity of the PH and the degree of right ventricular dysfunction. ECHO also excludes other cardiac anomalies and can be used to demonstrate the presence of a right to left shunt through a reopening of the foramen ovale by intravenous injection of microbubbles in saline.

If the ECHO demonstrates PH and the V/Q scan demonstrates a ventilation-perfusion mismatch with segmental perfusion defects and a normal ventilation pattern, the diagnosis is established and patients should be sent to a specialist. The diagnosis will then be confirmed by a right heart catheterization and a pulmonary angiogram.

Further evaluating CTEPH

Pulmonary angiography and right heart catheterization confirm the diagnosis of CTEPH and determine the possibility of pulmonary endarterectomy according to the

location of the obstruction and the correlation between the burden of disease and the severity of the pulmonary vascular resistance.

The standard definition of PH is defined by most experts as a mean pulmonary arterial pressure of ≥ 25 mmHg with a concomitant pulmonary capillary wedge pressure of ≤ 15 mmHg.

Angiography

Ideal angiographic technique is required for the pulmonary angiogram, showing the entire arterial tree of each lung captured in the same frame. Angiography must include serial pictures from the injection of dye into the pulmonary artery throughout the venous return in the pulmonary veins, including parenchymography to show the non-perfused areas of the lung. The right and left pulmonary arterial trees are studied in anterior and lateral views.

The angiography interpretation in CTEPH is more difficult than in acute PE, where the obstruction appears as a discrete intraluminal defect.

CT scan

A high-resolution helical CT scan can show obstruction or a reduction in the diameter of the arterial lumen when compared to the external diameter of the pulmonary artery. Proximal lesions on the right or left pulmonary arterial trunks are well characterized, whereas the distal lesions downstream from the first branches are rarely well visualized. Hence, a normal CT scan does not exclude the diagnosis of chronic pulmonary thromboembolic disease and does not preclude the possibility of pulmonary endarterectomy. All patients presenting with pulmonary arterial hypertension and segmental perfusion defect on the ventilation-perfusion

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Figure 1. The intra-luminal material resulting from the organized clot is composed of fibrous tissue, inseparable from the intima without any fresh thrombus.

scan must have a pulmonary angiogram to determine the feasibility of pulmonary endarterectomy.

CT scanning is essential to exclude rare conditions that can mimic CTEPH. These conditions include:

- fibrous mediastinitis,
- sarcoma of the pulmonary artery,
- tumour emboli into the pulmonary artery,
- hydatid emboli, or
- pulmonary arteritis (*i.e.*, Behcet's arteritis or Takayasu's arteritis).

A CT scan also delineates arteromatous calcifications of the pulmonary artery that can increase the technical difficulty of the endarterectomy in long-standing disease.

Treatment

Pulmonary endarterectomy is the treatment of choice for CTEPH and whenever possible, near-normal cardiopulmonary function can be

restored postoperatively with anticoagulation as the only therapy in the long term. Pulmonary endarterectomy is performed on cardiopulmonary bypass with a period of circulatory arrest at 18 C to remove the obstructive material from each lobar and segmental branches of the pulmonary artery, in total 20 branches to 30 branches. This is the only way to reduce the pulmonary vascular resistance by at least 50%. The intra-luminal material is, at this stage, composed of fibrous tissue inseparable from the intima and therefore, inaccessible to:

- thrombectomy,
- thrombolysis, or
- dilatation (Figure 1).

Patients who are not candidates for pulmonary endarterectomy should be followed prospectively in a PH clinic. Medical treatment with endothelin-receptor antagonists or other pulmonary vascular vasodilators can be started, but their efficacy has not yet been demonstrated in randomized trials for patients with CTEPH.

Eventually, patients who are not candidates for pulmonary endarterectomy can potentially be assessed for lung transplantation, based on their clinical condition.

Results of pulmonary endarterectomy

The results of pulmonary endarterectomy are directly related to the technical feasibility of a patient's anatomy and to the experience of the surgeon. Good-to-excellent results are achieved in almost all cases where the hemodynamic compromise corresponds to the degree of vascular obliteration. Most centers report an operative mortality ranging between 5% and 10% when the pulmonary vascular resistance is below 1000 Dyn-sec.cm⁻⁵.^{5,6}

After surgery, considerable diminution of the pulmonary resistance is observed along with a significant improvement in the functional state of the patient. In the long-term, most patients return to the New York Heart Association's class I or II and can resume a normal life. The only treatment required is adequate anticoagulation for the rest of their life. Survival at 10 years and at 15 years time after the surgery is 70% to 80%.^{7,8} Recurrence of PH has not been reported if the surgery achieved normalization of the pulmonary artery pressures and the patient remains adequately anticoagulated.

Conclusions

The incidence of CTEPH is higher than previously estimated and could involve 500 people to 1,500 people every year in Canada.


Approximately half of the patients presenting with CTEPH do not have a documented

history of acute PE. Typically, their PH will progress over time, despite adequate anticoagulation and in the absence of recurrent PE.

The diagnosis is made by V/Q scan and ECHO. A normal contrast-enhanced CT or MRI scan does not rule out a diagnosis of CTEPH.

Pulmonary endarterectomy is the treatment of choice for CTEPH. However, this is a complex procedure requiring considerable expertise and results depend on:

- the experience of the surgical team,
- the anatomical location of the obstruction and
- the severity of the disease.

Therefore, the surgery should only be performed in highly specialized centers. 

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