The aftermath of acute pulmonary embolism: approach to persistent functional limitations

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Essential aspects of the follow-up after an acute pulmonary embolism: an illustrated review

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ABSTRACT

Care for patients with acute pulmonary embolism (PE) involves more than determination of the duration of anticoagulant therapy. After choosing the optimal initial management strategy based on modern risk stratification schemes, patients require focused attention aimed at prevention of major bleeding, identification of underlying (malignant) disease, prevention of cardiovascular disease and monitoring for long-term complications. The most frequent complication of PE is the so-called 'post-PE syndrome', a phenomenon of permanent functional limitations after PE occurring in up to 50% of patients. The post-PE syndrome is caused by persistent deconditioning, anxiety, and/or ventilatory or circulatory impairment as a result of acute PE. The most severe and most feared presentation of the post-PE syndrome is chronic thromboembolic pulmonary hypertension (CTEPH), a deadly disease if it remains untreated. While CTEPH may be successfully treated with pulmonary endarterectomy, balloon pulmonary angioplasty and/or pulmonary hypertension drugs, the major challenge is to diagnose CTEPH at an early stage. Poor awareness for the post-PE syndrome and in particular for CTEPH, high prevalence of persistent symptoms after PE and inefficient application of diagnostic tests in clinical practice all contribute to an unacceptable diagnostic delay and underdiagnosis. Its consequences are dire: increased mortality in patients with CTEPH, and excess health care costs, higher prevalence of depression, more unemployment and poorer quality of life in patients with post-PE syndrome in general. In this review, we provide an overview of the incidence and impact of the post-PE syndrome, and illustrate the clinical presentation, optimal diagnostic strategy as well as therapeutic options.

List of abbreviations

BPA = balloon pulmonary angioplasty
CO = carbon monoxide
COPD = chronic obstructive pulmonary disease
CPET = cardiopulmonary exercise test
CTED = chronic thromboembolic disease
CTEPH = chronic thromboembolic pulmonary hypertension
CTPA = computed tomography pulmonary angiography
DVT = deep vein thrombosis
ECG = electrocardiography
i.v. = intravenous
IQR = interquartile range
LV = left ventricle
NYHA = New York Heart Association
PA = pulmonary artery
PE = pulmonary embolism
PEA = pulmonary endarterectomy
PFT = pulmonary function test
PH = pulmonary hypertension
PVR = pulmonary vascular resistance
QoL = quality of life
RHC = right heart catheterization
RV = right ventricle
TRPG = tricuspid regurgitation peak gradient
TRV = tricuspid regurgitation velocity
VTE = venous thromboembolism
V/Q scan = ventilation/perfusion scan

Capsule 1

ESSENTIAL ASPECTS OF OPTIMAL CARE AFTER ACUTE PE

1 DIAGNOSIS[1]

- Risk stratification based on hemodynamic status
- Initial treatment (reperfusion, parenteral or oral anticoagulation)
- Optimal setting for initial treatment (critical care unit, regular ward, home treatment)

2 DISCHARGE

- Provide relevant medical background information
- Instruction on handling potential complications
- Target modifiable risk factors for bleeding and VTE

3 INITIAL WEEKS[2]

- Screen for cancer, antiphospholipid syndrome or genetic thrombophilia in selected patients
- Monitor the clinical course
- Target modifiable risk factors for bleeding and VTE

4 3-MONTH FOLLOW-UP

- Determine duration of anticoagulation: weighing risk of recurrence versus risk of bleeding[3]
- Determine optimal anticoagulation drug class and dosing (if decided to continue)
- Evaluate the presence of and/or risk factors for CTEPH
- Target modifiable risk factors for cardiovascular disease

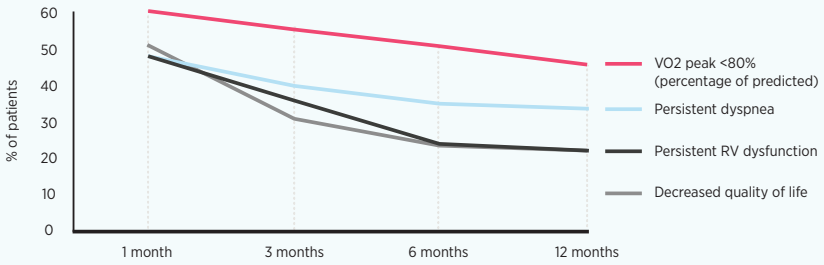
5 LONG-TERM FOLLOW-UP

- Evaluate the anticoagulant treatment periodically (e.g. risk factors for bleeding)
- Monitor long-term complications (e.g. post-PE syndrome)

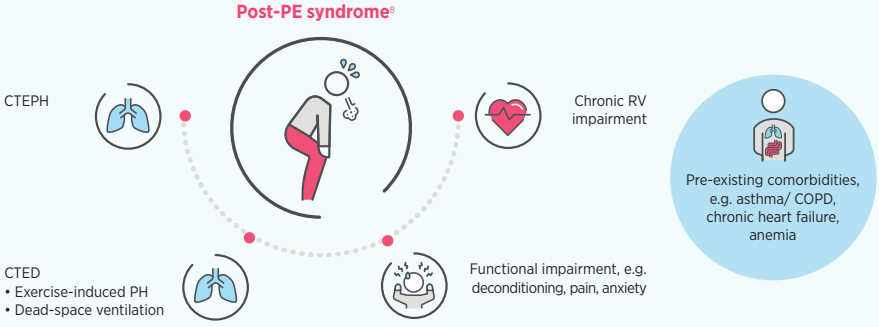
Capsule 2

CONSEQUENCES OF PULMONARY EMBOLISM

1 INCOMPLETE PHYSICAL RECOVERY AFTER PE IS COMMON[4-7]



2 UNDERLYING CAUSES OF PERSISTENT SYMPTOMS AFTER PE



3 IMPACT OF POST-PE SYNDROME ON A PATIENT'S DAILY LIFE

⬇ Quality of life, to be measured by:
- quality of life questionnaires (particularly the PEmb-QoI)

⬇ Functional status, to be measured by:
- CPET: reduced VO2 peak, low O2 pulse (VO2/HR), cardiovascular limitation, inefficient ventilation due to increased dead-space ventilation and arterial hypoxemia
- PFT: reduced diffusion capacity; alternatively restrictive or obstructive comorbidities
- Post-VTE Functional Status (PVFS) Scale[9]

⬆ Depressive disorders, to be measured by:
- e.g. Hospital Anxiety and Depression Scale (HADS)

⬆ Unemployment

⬆ Healthcare costs

⬆ Mortality in case of untreated CTEPH

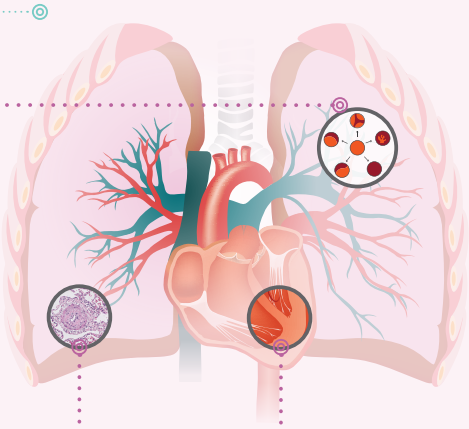
Capsule 3

PATHOPHYSIOLOGY OF CTEPH

1 INITIAL TRIGGER[10,11]

Persistent obstruction of proximal pulmonary arteries by organized thrombi

- Incomplete thrombus resolution may be caused by inflammation/infection and resistance to physiological fibrinolysis or reduced endogenous fibrinolytic potential
- Residual thrombi progressively evolve into a fibrotic mass, which is highly adherent to the pulmonary vascular wall in contrast to a fresh thrombus
- On CTPA or pulmonary angiography, those chronic thrombi are visible as bands, webs, stenoses and occlusions



2 COURSE OF THE DISEASE[10,12]

Small-vessel disease plays an important role in disease progression:

Nonoccluded pulmonary arteries are affected due to abnormal shear stress

Maintaining perfusion of the capillary bed is essential:
1. hypertrophy of bronchial arteries
2. anastomoses between these high-pressure systemic arteries and pulmonary vasculature distally from occlusions

Anastomoses could, in turn, increase shear stress and induce microvasculopathy, mainly in areas obstructed by organized thrombi

Molecular processes: not fully understood

Increased pulmonary vascular resistance is associated with chronic to finally irreversible RV dysfunction:

The RV is severely and progressively affected because of chronically increased RV afterload

1. Adaptive RV wall thickening (decreased wall stress + improved pumping capability)

↓

2. Sustained RV overload → maladaptive RV wall thickening (increased wall stress + decreased pumping capability)

↓

3. Imbalance between increased oxygen demand & decreased supply to the coronary arteries → ischemia, necrosis and fibrosis of the RV wall

Capsule 4

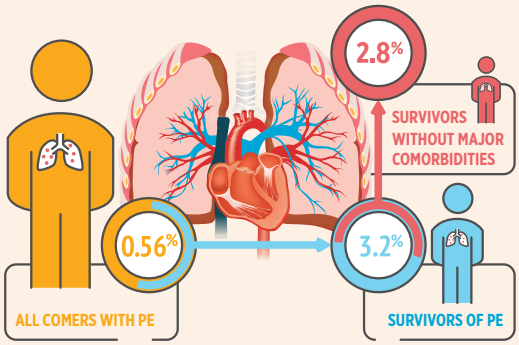
EPIDEMIOLOGY OF CTEPH

1 CTEPH INCIDENCE*

25% of CTEPH patients have no history of symptomatic PE or DVT[14]

Signs of CTEPH are often present on CTPA or echocardiography at the time of index PE[15]

Sometimes long duration between diagnosis of PE and first CTEPH symptoms (honeymoon period)



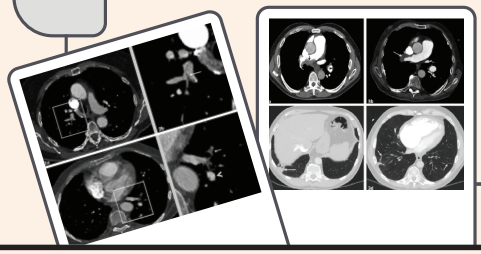
2 RISK FACTORS AND PREDISPOSING CONDITIONS OF CTEPH[1]

Findings at the time of the acute PE event

- Recurrent PE or DVT
- Central pulmonary arterial thrombi on CTPA
- Unprovoked PE
- Diagnostic delay of PE
- Echocardiographic signs of PH/RV dysfunction
- CTPA findings suggestive of CTEPH

Concomitant chronic diseases and conditions

- Hypothyroidism treated with thyroid hormones
- Infected chronic i.v. lines or pacemakers
- Ventriculo-atrial shunts
- History of splenectomy
- Non-O blood group
- Thrombophilic disorders, particularly antiphospholipid antibody syndrome and high coagulation factor VIII levels
- Inflammatory bowel disease
- Chronic osteomyelitis
- Myeloproliferative disorders
- Malignancy



* Numbers in the figure are based on a meta-analysis including 16 independent studies. Arrows indicate that the group of 'Survivors of PE' (blue) is a subset of 'All comers with PE' (yellow), whereas 'Survivors without major comorbidities' (red) is a subset of 'Survivors of PE'.[13]

Capsule 5

CLINICAL PRESENTATION AND DIAGNOSIS OF CTEPH

1 CLINICAL PRESENTATION

Symptoms - non-specific and often absent in early CTEPH:

- Predominant: exertional dyspnea and functional limitations;
- Other: fatigue, edema, syncope, chest pain, hemoptysis

Clinical signs – may become evident at later stages of disease when the right ventricle (RV) fails:

- Palpable RV heave
- Closely split second heart sound with accentuation of its pulmonic component
- Tricuspid regurgitation murmur
- Jugular venous distension
- Peripheral edema
- Hepatomegaly and ascites

2 CURRENT DIAGNOSTIC ALGORITHM[16]

Clinical suspicion of CTEPH

↓

Echocardiography
After 3 months of adequate anticoagulant treatment

Intermediate/high probability of PH

↓

Ventilation/perfusion lung scan

normal

↓

CTEPH ruled out

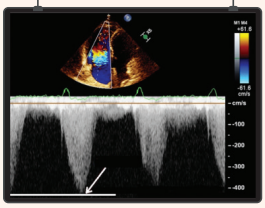
≥1 mismatched perfusion defect

↓

Right heart catheterization
and pulmonary angiography
(by conventional digital subtraction angiography, multidetector CT or MRA)

Peak tricuspid regurgitation velocity (TRV) (m/s)	Presence of other echocardiographic signs of pulmonary hypertension*	Echocardiographic probability of pulmonary hypertension
≤ 2.8 or not measurable	No	Low
≤ 2.8 or not measurable	Yes	Intermediate
2.9 - 3.4	No	
2.9 - 3.4	Yes	High
> 3.4	Not required	

TRV is calculated from a tricuspid jet on echocardiogram (arrow) and used to estimate PA pressures.



*Adapted with permission[22]**

Diagnostic criteria of CTEPH:

- ≥1 mismatched segmental perfusion defect demonstrated by ventilation/perfusion scanning after ≥3 months of adequate therapeutic anticoagulation
- Mean pulmonary artery pressure ≥ 25 mmHg at rest measured by invasive right heart catheterization
- Pulmonary capillary wedge pressure ≤ 15 mmHg

* According to the '2015 ESC/ERS Guidelines for the diagnosis and treatment of PH'[16]

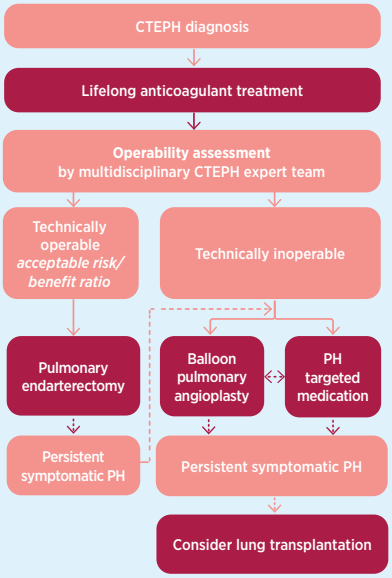
Capsule 6

TREATMENT AND PROGNOSIS OF CTEPH

1 AIMS OF TREATMENT

- To restore normal flow distribution within the pulmonary vasculature
- To unload the right ventricle
- To prevent or treat small-vessel disease
- To prevent recurrent VTE
- To reduce functional limitations and improve quality of life

2 TREATMENT ALGORITHM[16]



3 OUTCOMES FOR EACH TREATMENT STRATEGY

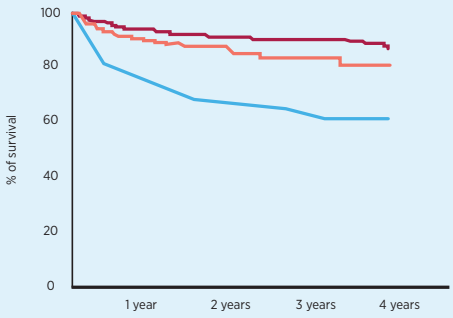
1. Lifelong anticoagulant treatment
→ Best experience is with vitamin K antagonists, unclear whether DOACs are as effective and safe

2. Pulmonary endarterectomy (PEA)[17-24]
operability is dependent on surgical accessibility of thrombi, presence of comorbidity and patient preference
→ Mean pulmonary artery (PA) pressure: (near-)normalization in most patients
→ Pulmonary vascular resistance (PVR): decrease from 700-800 to ~250 dyn·s·cm^{-5}
→ RV: immediate recovery of RV dimensions, RV systolic function restores in the majority within 1-3 years
→ NYHA functional status: improvement from class III/IV to II/I in ~80%
→ Quality of life: significant improvement

3. Balloon pulmonary angioplasty (BPA)[25-28]
a median of 4 sessions are performed per patient
→ Mean PA pressure after final BPA session: (near-)normalization in most patients
→ PVR: mean reduction of 47-68%
→ NYHA functional status: improvement from class III/IV to II/I in ~90%
→ Quality of life: significant improvement

4. PH targeted medication[29]
→ 6-minute walk distance: increase from mean 351 ± 78 m to 409 ± 96 m at 1 year
→ Quality of life: significant improvement

4 ESTIMATES OF SURVIVAL[30-32]



Legend:

Patients treated with PEA

Non-operated patients treated with PH targeted medication and/or BPA in the modern management era

Historical control patients treated for CTEPH between 1964 and 1979

Capsule 7

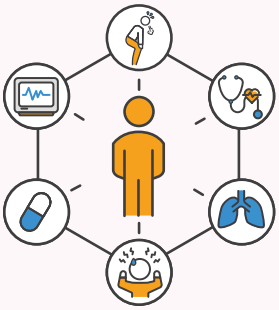
CURRENT CLINICAL PRACTICE PATTERNS AFTER PE

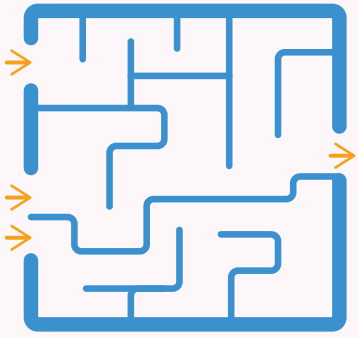
1 FOLLOW-UP AFTER PE

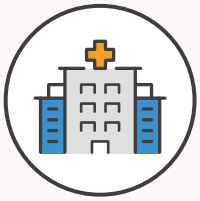
- Large practice variation
- Guidelines do not provide clear recommendations regarding diagnosis, treatment and prevention of the post-PE syndrome
- No tools available for assessing patient-relevant functional outcomes
- Timely CTEPH diagnosis is challenging because of non-specific presentation and diagnostic misclassification

2 DIAGNOSING CTEPH

- Considerable diagnostic delay of median 14 months (IQR 7.5-33)[33,34]
  - → higher pulmonary pressures at diagnosis
  - → higher risk of all-cause mortality
- History of recurrent VTE associated with a longer delay
- Insufficient healthcare utilization:
  - Only 61% of PE patients with post-PE syndrome are subjected to targeted diagnostic tests for CTEPH[35]
  - Before CTEPH is diagnosed, on average patients consult 4 different physicians for 13 consultations[36]
  - Diagnostic results suggestive of CTEPH are not always recognized
  - The recommended diagnostic algorithm for CTEPH is often not followed







3 HOW TO IMPROVE PATIENT OUTCOMES?

- Better physician and patient education
- Higher awareness for CTEPH/post-PE syndrome
- Validation and implementation of follow-up algorithms aimed at early CTEPH diagnosis
- Clear guideline recommendations for optimal follow-up after acute PE

Capsule 8

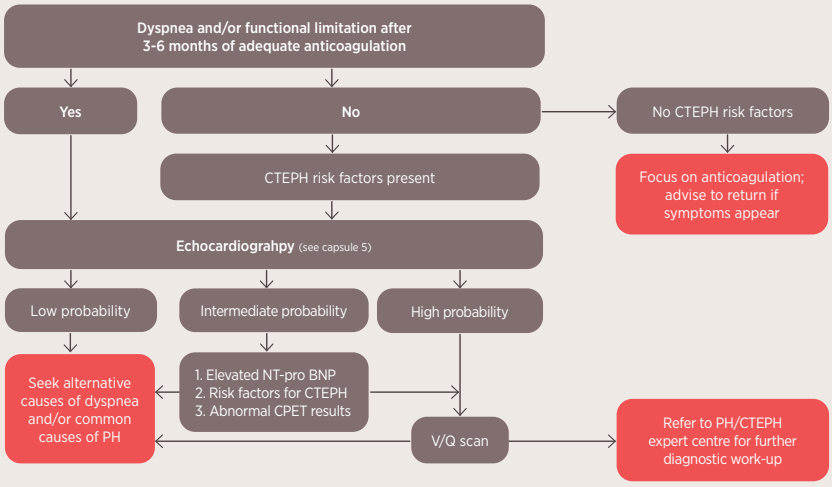
STRATEGIES FOR EARLIER CTEPH DIAGNOSIS

1 FOLLOW-UP AFTER PE[37]

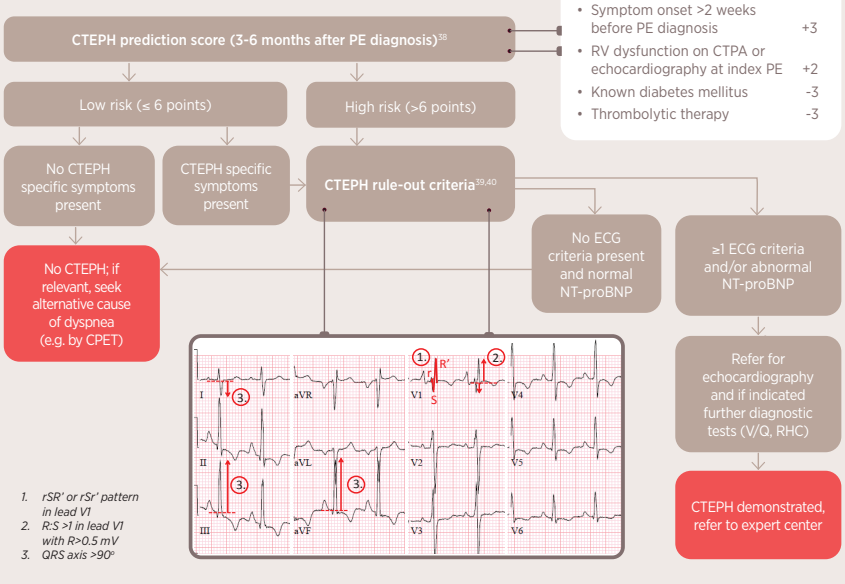
	Advantages	Disadvantages
 Transthoracic echocardiography	• non-invasive test • imaging of structural as well as functional changes	• lack of precision in estimating PA pressure, leading to both false positives and false negatives • not cost-effective if performed as routine screening test in all patients
 V/Q scan	• very high sensitivity	• poor specificity • not cost-effective if performed as routine screening test in all patients • radiation exposure
 Algorithms of sequential diagnostic tests	• optimal use of healthcare resources	• not (yet) formally validated in outcome studies

2 SUGGESTED SCREENING ALGORITHMS

1. European Society of Cardiology 2019 suggests echocardiography in patients with risk factors for and/or symptoms of CTEPH *(adapted with permission[1])*



2. The InShape II algorithm aims to limit the number of required echocardiograms and is currently being evaluated in a prospective, multicenter outcome study in consecutive acute PE patients (NCT02555137)



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