Thrombo-Embolic Pulmonary HTN; Management Up To Date

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Updated clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension (PAH)
   - 1.1 Idiopathic PAH
   - 1.2 Heritable
     - 1.2.1 BMPR2
     - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
     - 1.2.3 Unknown
   - 1.3 Drugs and toxins induced
   - 1.4 Associated with (APAH):
     - 1.4.1 Connective tissue diseases
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart disease
     - 1.4.5 Scleroderma
     - 1.4.6 Chronic haemolytic anaemia
   - 1.5 Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   - 2.1 Systolic dysfunction
   - 2.2 Diastolic dysfunction
   - 2.3 Valvular disease

3. Pulmonary hypertension due to lung diseases and/or
   hypoxaemia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive
     and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension

5. PH with unclear and/or multifactorial mechanisms
   - 5.1 Haematological disorders: myeloproliferative
     disorders, splenectomy.
   - 5.2 Systemic disorders, sarcoidosis, pulmonary Langerhans
     cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   - 5.3 Metabolic disorders: glycojen storage disease, Gaucher
     disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis,
     chronic renal failure on dialysis

www.escardio.org/guidelines
European Heart Journal 2009;30:2493-2537
Definition of CTEPH

CTEPH is a syndrome of dyspnea, fatigue, and exercise intolerance caused by proximal thromboembolic obstruction and distal remodeling of the pulmonary circulation that leads to elevated PAP and progressive RV failure.
Incidence

1 in 25 patients with an initial episode of acute PE will subsequently develop CTEPH.

Based on the 2003 US Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample Database, the incidence is 3.4%, which represents 5000 cases of CTEPH in the United States in 2003.
Important note

- Up to 63% of patients with CTEPH are not previously aware of having had a PE and prior PE is not a criterion for diagnosis.
- So, the true incidence of this disorder may be higher.
- The true incidence of CTEPH is actually unknown.


Agenda

- Definition
- Incidence
- Pathogenesis
- Classification
- Prognosis
- Diagnosis
- Treatment strategies
Pathogenesis

Several mechanisms have been proposed:

- **Recurrence of embolism** after adequately treated pulmonary embolic events
- **In situ thrombus propagation** into branch pulmonary vessels
- **Failure to dissolve the initial embolus**


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Despite adequate treatment of PE after 1Y residual thrombus (R. Th) occurs in 50% of cases

- After 4 ws the **residual Th. becomes incorporated into the PA wall** at the main PA, lobar, segmental, or subsegmental levels.
- Over time, the initial **residual. Th is remodeled into connective and elastic tissue**, which contains endothelial and smooth muscle precursor cells → vessel narrowing.
- In some patients, **recanalization** of some of the PA branches occurs, with the formation of fibrous tissue called bands and webs.

In most cases, these changes do not result in CTEPH.
However, by a mechanism that is poorly understood, chronic thromboembolic obstruction may also lead to a small-vessel arteriolar vasculopathy (resembling PPH) characterized by excessive vascular and inflammatory cell proliferation around small precapillary arterioles in the pulmonary circulation.

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Classification

1. **Type 1 disease (25%)**: Fresh thrombus in the main or lobar PAs.
2. **Type 2 disease (40%)**: Intimal thickening, fibrosis and webbing with or without organized thrombus proximal to segmental arteries.
3. **Type 3 disease (30%)**: Intimal thickening, fibrosis and webbing with or without organized thrombus within distal segmental and subsegmental arteries only.
   - The most challenging surgical situation.
   - No occlusion of vessels can be seen initially. The endarterectomy plane must be raised individually in each segmental and subsegmental branch.
   - It may represent “burned out” disease, in which most of the proximal embolic material has been reabsorbed.
4. **Type 4 disease (<5%)**: Microscopic distal arteriolar vasculopathy without visible thromboembolic disease.
   - Unclassic, inoperable, & intrinsic small-vessel disease, although secondary thrombus may occur as a result of stasis.
   - Type 4 may be either a misdiagnosed WHO Group I PAH or due to to a previous (now resolved) thromboembolic vascular occlusion as a result of a high-flow or high-pressure state in previously unaffected vessels.

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**Thistlethwaite et al. Semin Thorac Cardiovasc Surg. 2006; 18: 257-264.**

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Prognosis

Traditionally, it has been presumed to be very poor; death due to right-sided HF in patients with undiagnosed or untreated CTEPH is correlated with PAP at diagnosis.

- 70% with a mean PAP ≥ 40 mm Hg,
- 90% with a mean PAP ≥ 50 mm Hg.

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When to suspect?

- Patients presenting with **unexplained dyspnea, exercise intolerance**, or clinical evidence of **right-sided HF**, with or without prior history of symptomatic VTE, should be evaluated for CTEPH

  \[(Class \ I; \ Level \ of \ Evidence \ C)\]

- It is reasonable to evaluate patients with an echocardiogram **6 weeks after an acute PE** to screen for persistent PH that may predict the development of CTEPH

  \[(Class \ IIa; \ Level \ of \ Evidence \ C)\]

Aims of Diagnostic Evaluation for CTEPH

1. To establish the presence and severity of PH and resultant cardiac dysfunction
2. To determine its cause (if CTEPH)
3. To determine to what degree it will be correctable surgically.
Diagnostic workup

- History, physical examination,
- **Chest roentgenogram (PA, lateral):** Late
  - Hilar fullness caused by enlarged central PAs
  - Clear or oligemic lung fields
  - RV enlargement.
  - Peripheral lung opacities suggestive of scarring from previous infarction
- **ECG**
- **Pulmonary function testing:** to exclude COPD or IPF
  - 20% of pts will have a mild to moderate restrictive defect that is caused by parenchymal scarring
- **Arterial blood gases:**
  - PaO2 normal despite high PAP and may decrease with exercise
- **Echocardiography:** Useful for screening but insufficient for diagnosis of PH.

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**Arbitrary criteria for detecting the presence of PH based on tricuspid regurgitation peak velocity and Doppler-calculated PA systolic pressure at rest**

- **Echocardiographic diagnosis: PH unlikely**
  - Tricuspid regurgitation velocity ≤ 2.8 m/sec, PA systolic pressure ≤ 36 mmHg and no additional echocardiographic variables suggestive of PH.
- **Echocardiographic diagnosis: PH possible**
  - Tricuspid regurgitation velocity ≤ 2.8 m/sec, PA systolic pressure ≤ 36 mmHg but presence of additional echocardiographic variables suggestive of PH.
  - Tricuspid regurgitation velocity 2.9-3.4 m/sec, PA systolic pressure 37-50 mmHg with without additional echocardiographic variables suggestive of PH.
- **Echocardiographic diagnosis: PH likely**
  - Tricuspid regurgitation velocity >3.4 m/sec, PA systolic pressure > 50 mmHg with without additional echocardiographic variables suggestive of PH.
- **Exercise Doppler echocardiography is not recommended for screening of PH**

*Assuming a normal right atrial pressure of 5 mmHg and on additional echocardiographic variables suggestive of PH.
• **V/Q scan:**
  - Important, lobar, segmental or subsegmental defects.
  - Can under estimate defect size & partial thrombus recanalization.
  - Although it can differentiate between CTEPH and IPAH, it does not help in identifying other causes of PH, such as unsuspected shunts, large-vessel pulmonary arteritis, and primary pulmonary vascular tumors.

• **Cardiac cath:** to do
  - **Rt cardiac cath:** to
    - **Confirm PH** (Resting systolic PAP > 40 mmHg + mean systolic PAP > 25 mmHg + PVR > 3 wood units at rest ie. 234 dynes.cm⁻²)
    - **Exclude Lt HF by PCWP** < 15 mmHg (remember when PVR > 600 dynes.cm⁻², PCWP can be > 15 mmHg dt Bernhium effect)
    - **Measurement of oxygen saturations** in the IVC, SVC, right-sided chambers, and PA may document previously undetected left-to-right shunting.
    - **Measure filling pressures** in both Rt and Lt sides.
    - **Response to vasodilator challenge**, such as administration of inhaled nitric oxide, may be tested
  - **CA:** for pts > 50Ys
  - **Pulmonary angiography:** defer to the expert surgical center
  - **Pulmonary angioscopy:** when diagnosis of CTEPH is equivocal, but uncommonly performed.
Selective Pulmonary Arteriography

- Only in specialized centers due to some concerns in pts with severe PH.
- “gold standard” test for definition of pulmonary vascular anatomy.
- Confirms diagnosis, operative feasibility and plan.
- Biplane imaging is preferred.
- Thrombi appear as:
  - Unusual filling defects,
  - Pouches,
  - Webs, or bands
  - Completely thrombosed vessels that may resemble congenital absence of a vessel.
  - Organized material along a vascular wall produces a scalloped or serrated luminal edge.

Emerging Diagnostic Techniques

- Multidetector CT angiography with 3-D reconstruction,
- MRI
  - Although MRI and CT imaging are frequently used as primary imaging techniques in selected patients before pulmonary endarterectomy, conventional angiography remains the “gold standard”
  - Importantly, a relatively normal CT angiogram can be observed in CTEPH despite significant abnormalities on ventilation-perfusion scintigraphy.
Left Selective Vs CT Angiogram

Right Selective Vs 3D MR Pulmonary Angiogram
High-resolution CT in a patient with CTEPH

Perfusion scintigraphy

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High-resolution CT and

Idiopathic pulmonary arterial hypertension

Pulmonary Venoocclusive disease

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CT, in combination with MR, represents the future for diagnosis and management of patients with CTEPH. Both techniques detect postembolic obstructions at the lobar and segmental levels, although **at the subsegmental level the spatial resolution of CT is superior to MR.**

Not every patient with PH has CTEPH; imaging must identify patients with CTEPH, but it must also provide alternative diagnoses when other causes of PH are present.
Diagnostic algorithm

Symptoms / signs / history suggestive of PH

Non invasive assessment compatible with PH?

Yes

Consider common causes of PAH

Group 2
Left heart disease?

History, Symptoms, Signs ECG, Chest X Ray TTE, PHT, HRCT

Group 3
Lung diseases and/or hypoxia

Group 2 or 3: diagnosis confirmed

Yes

PH 'proportionate' to severity

Treat underlying disease & check for progression

No

Perform VIQ scan

Search for Other causes And/or Re-check

www.escardio.org/guidelines

European Heart Journal 2009;30:2493-2537

Continue’d

Segmental perfusion defects

Consider Group 4 CTEPH

Yes

Consider other uncommon causes

No

Perform RHC (PAH probability)

Specific tests

Specific tests

Yes

mPAP ≥ 25 mmHg

PWP ≤ 15 mmHg

Search for other causes

No

No

www.escardio.org/guidelines

European Heart Journal 2009;30:2493-2537
Differential Diagnosis

<table>
<thead>
<tr>
<th>Conditions Mimicking CTEPH</th>
<th>Techniques Used for Diagnostic Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosing mediastinitis causing obstruction of the pulmonary veins and arteries</td>
<td>Chest X-ray is rarely helpful. <strong>CT shows mediastinal soft tissue</strong> obliterating fat planes and encasing and compressing vascular structures.</td>
</tr>
</tbody>
</table>
| Pulmonary artery sarcoma | - Echocardiography, CT angiography, and MR have difficulty distinguishing sarcoma from central thrombus. Sarcoma may involve the pulmonary valve and extend retrogradely into the RV infundibulum, unlike thrombus.  
- **Contrast-enhanced MR may show tumor enhancement, whereas thrombus will not.** |
| Large-vessel arteritis (or Takayasu's arteritis) | - Pulmonary angiography, angioscopy, and aortography may not be helpful.  
- **Cross-sectional CT or MR may identify concentric inflammatory mural thickening.** |

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Updated Treatment Strategies For CTEPH

**Pulmonary Endarterectomy**

The treatment of choice for documented cases

**Medical Therapy**

- **Warfarin**: Life long targeting INR 2-3

**WHO Group I medical therapy drugs:**
- ET1 antagonist (Bosentan)
- Prostanoids (epoprostenol by IV infusion, Treprostinil subcut., iloprost inhaled, Beraprost orally)
- Phosphodiesterase-5 inhibitors (theophylline)

AHA Recommendations for CTEPH

1. **Pulmonary endarterectomy:**
   - Patients with objectively proven CTEPH should be promptly evaluated for pulmonary endarterectomy, even if symptoms are mild (*Class I; Level of Evidence B*).

2. **Indefinite therapeutic anticoagulation**
   - Patients with objectively proven CTEPH should receive indefinite therapeutic anticoagulation in the absence of contraindications (*Class I; Level of Evidence C*).

3. **PAH (WHO Group I)-specific medical therapy**
   - **may be considered for**
     - patients with CTEPH who are not surgical candidates (because of comorbidities or patient choice)
     - or who have residual pulmonary hypertension after operation not amenable to repeat pulmonary endarterectomy at an experienced center (*Class IIb; Level of Evidence B*).
   - **should not be used in**
     - lieu of pulmonary endarterectomy or delay evaluation for pulmonary endarterectomy for patients with objectively proven CTEPH who are or may be surgical candidates at an experienced center (*Class III; Level of Evidence B*).
ESC Recommendations for a PH Referral Centre

- Required to provide care by a **multiprofessional team** (cardiology and respiratory medicine physicians, clinical nurse specialist, radiologists, psychological and social work support, appropriate on-call expertise) I C
- Required to have **direct links and quick referral patterns to other services** (such as CTD service, family planning service, PEA service, lung transplantation service, adult congenital heart disease service) I C
- Should **follow at least 50 patients** with PAH or CTEPH and should **receive at least two new referrals per month** with documented PAH or CTEPH IIa C
- Should perform **at least 20 vasoreactivity tests** in PAH patients per year IIa C
- Should **participate in collaborative clinical research in PAH**, which includes phase II and phase III clinical trials


Pulmonary Endarterectomy

- **Treatment of choice** for all documented cases including:
  - Mild cases
  - No upper limit for PVR, RV dysfunction TR (don’t exclude pts based on the severity of hemodynamic or echo findings as these pts get the best benefit if done in experienced centers)
  - Advanced age (>80), renal insufficiency, hepatic dysfunction are not absolute contraindications although they affect the risk.
- **Contraindications**:
  - Severe underlying parenchymal lung disease is a contraindication (Surgery improved hemodynamics but not symptoms or lung disease progression).
  - PH with little or no visible evidence of CTEPH.

**Pulmonary Endarterectomy: Short-Term Outcome**

- Improves:
  - Pulmonary pressures and resistance often normalize and are accompanied by improvements in pulmonary blood flow and cardiac output.
  - NYHA class from 91% class III, IV to 91% class I or II one year post operative.
  - RV geometry rapidly returns to normal.
  - TR rapidly returns to normal.

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Before Surgery  
3 m after pulmonary thromboendarterectomy

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**Pulmonary Endarterectomy: Short-Term Outcome**

- **Perioperative mortality:** ranges from 0-24% according to center experience and disease classification. Reported as 4.7% in the largest recently reported series.

- **Perioperative morbidity:**
  - Average duration of surgery was 6.7 hours (range 3.5 to 13.1 hours)
  - Severe reperfusion injury manifesting as pulmonary edema:
    - is the most frequent complication after pulmonary endarterectomy, occurring in ≈5% to 15% of patients.
    - Majority recover after a short period of ventilatory support and aggressive diuresis.
    - Minority require prolonged periods of ventilatory support, whereas extreme cases require veno-venous extracorporeal support for oxygenation and blood carbon dioxide removal.
  - Neurological complications from circulatory arrest have mostly been eliminated by
    - shorter circulatory arrest periods
    - use of a direct cooling jacket placed around the head, which provides even cooling to the surface of the cranium.
  - Pulmonary hemorrhage: rare (3.8%).
  - Perioperative wound infection: rate of only 2.4%.

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**Post-operative Hemodynamic Results of Pulmonary Endarterectomy**

- Results From a Single-Center Cohort of 1100 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>PTE Patients</th>
<th>PTE-CABG Patients</th>
<th>PTE-Valve Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean decrease in PAS, mm Hg</td>
<td>29±20</td>
<td>29±20</td>
<td>29±18</td>
<td>25±20</td>
</tr>
<tr>
<td>Mean decrease in PAD, mm Hg</td>
<td>10±10</td>
<td>10±10</td>
<td>8±10</td>
<td>8±7</td>
</tr>
<tr>
<td>Mean decrease in PVR, dynes·cm⁻²</td>
<td>563±394</td>
<td>567±392</td>
<td>539±412</td>
<td>488±382</td>
</tr>
<tr>
<td>Mean decrease in CO, L/min</td>
<td>1.5±1.6</td>
<td>1.5±1.6</td>
<td>1.5±1.6</td>
<td>1.2±1.3</td>
</tr>
<tr>
<td>Mean decrease in tricuspid regurgitant velocity, m/s</td>
<td>1.1±0.8</td>
<td>1.1±0.8</td>
<td>1.1±0.7</td>
<td>0.3±0.9</td>
</tr>
</tbody>
</table>

PTE indicates: pulmonary endarterectomy; PTE-CABG: pulmonary endarterectomy plus coronary artery bypass graft; PTE-Valve: pulmonary endarterectomy plus valve repair; PAS, pulmonary artery systolic pressure; PAD, pulmonary artery diastolic pressure; PVR, pulmonary vascular resistance; CO, cardiac output.

Data are shown as mean±standard deviation.

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R&M Solutions
Post-operative Hemodynamic Results of Pulmonary Endarterectomy

- Results From a Single-Center Cohort of 1100 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=1100, 100%)</th>
<th>Type 1 (n=430, 39.1%)</th>
<th>Type 2 (n=424, 38.5%)</th>
<th>Type 3 (n=223, 20.3%)</th>
<th>Type 4 (n=23, 2.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVR, dyne·s·cm⁻³⁻¹</td>
<td>859±440</td>
<td>924±450</td>
<td>800±417</td>
<td>963±454</td>
<td>885±412</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.9±1.3</td>
<td>3.7±1.4</td>
<td>4.1±1.3</td>
<td>4.0±1.5</td>
<td>3.8±1.2</td>
</tr>
<tr>
<td>Systolic PA pressure, mm Hg</td>
<td>54±1.5</td>
<td>55±1.5</td>
<td>55±1.5</td>
<td>52±1.4</td>
<td>45±1.1</td>
</tr>
<tr>
<td>Mean PA pressure, mm Hg</td>
<td>76±19</td>
<td>77±19</td>
<td>75±20</td>
<td>76±16</td>
<td>78±18</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>52±4.7</td>
<td>16±3.9</td>
<td>22±4.7</td>
<td>6±3.3</td>
<td>4±1.7</td>
</tr>
</tbody>
</table>

PVR indicates pulmonary vascular resistance; CO, cardiac output; and PA, pulmonary artery. Data are shown as mean±standard deviation or number (percentage). Top numbers are preoperative values and bottom numbers are postoperative values obtained immediately before removal of the Swan-Ganz catheter.

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Pulmonary Endarterectomy: Long-Term Outcome

- Questionnaires were mailed to 420 patients who were more than 1 yr post-PTE; 308 responded
  - mean age, 56 yr [range, 19–89 yr];
  - mean years since PTE, 3.3 [range, 1–16]).

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Pulmonary Endarterectomy: Long-Term Outcome

- 93% of the patients were found to be in NYHA class I or II, compared with ≈95% in NYHA class III or IV before surgery.
- Of the population desiring employment, 62% of patients who were unemployed before the operation returned to work.
- Patients who had undergone pulmonary endarterectomy scored several quality-of-life components slightly lower than healthy individuals but significantly higher than the patients before their operations.

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Pulmonary Endarterectomy: Long-Term Outcome

75% at 6 ys

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Although guidelines make recommendations for management, optimal medical decisions must incorporate other factors, including

- **patient wishes**, 
- **quality of life**, 
- **life expectancy** based on age and comorbidities.
Take Home Messages

- CTEPH is considered recently as a challenging type of PH that has been previously underdiagnosed and undertreated.
- It has a poor prognosis if not properly treated.
- Recent advances in diagnostic approaches improved identification of these patients for proper management.

Take Home Messages (cont.)

- Pulmonary endarterectomy is the gold standard for treatment if proved surgically feasible with excellent short and long-term outcomes.
- Treatment should be conducted in experienced centers for best outcomes.
THANK YOU