Learning Objectives

By the end of this activity, the participant should be better able to:

- Identify risk factors and early signs of chronic thromboembolic pulmonary hypertension (CTEPH) among post-pulmonary embolism (PE) patients.
- Apply early screening and detection approaches for patients suspected of CTEPH.
- Discuss the role of primary care providers as part of the multi-professional healthcare team in the evaluation and management of the post-PE patient.

Outline

- Case presentation and CTEPH introduction
- Can we prevent CTEPH?
- Basics of CTEPH
- Surgical therapy
- Medical therapy
- Role of the PCP throughout this process

CTEPH: Practice Guidelines

SPECIAL ARTICLE
Diagnostic evaluation and management of chronic thromboembolic pulmonary hypertension: A clinical practice guideline


36 y/o Man with Chest Pain and Dyspnea

- Patient presents to the ED with chest pain and dyspnea that started earlier that day.
- History of DVT and was on warfarin but is homeless and ran out of medication 1 week ago.
- Reports severe stabbing chest pain diffusely and is asking for “Dilaudid.”
- Dyspnea with any movement; has a dry cough.
- Prior DVT unprovoked, he thinks he may have had a blood clot a few years ago after a surgery.

History

- Past Medical History
  - HTN
  - DVT (6 months ago)
- Past Surgical History
  - Cholecystectomy 2012
- Allergy
  - Daptomycin (unknown reaction)
- Family History
  - Estranged from family but mother has lupus and some unknown cancer, sister has had miscarriage
- Medications
  - Amlodipine (not taking)
  - Warfarin (not taking)
- Social History
  - Smoker
  - IV and inhalational heroin use
  - Denies EODH
  - Unemployed
  - Homeless (currently living on friend’s couch)
Physical Exam

<table>
<thead>
<tr>
<th>Temp</th>
<th>BP</th>
<th>HR</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/19 23:00</td>
<td>98.4/36.9</td>
<td>124/87</td>
<td>111 26</td>
</tr>
</tbody>
</table>

- General: NAD, alert & oriented × 4
- HEENT: OP clear, MMM, PERRL, EOMI
- Neck: no LAD, no thyromegaly
- CV: S1 and S2 normal, RRR, no m/r/g
- Lungs: CTA b/l, no W/R/R, on 2L NC
- Abdomen: s/nt/nd + bs, no HSM appreciated
- Skin: track marks on upper extremities
- Extremities: 2+ distal pulses, 1+ pitting edema to knee b/l
- Neuro: CN II-XII intact

Acute and Chronic Complications of PE

- Acute PE incidence 100 per 100,000 patient years\(^1\)
  - Increases with aging
- Incidence has increased over time
  - Aging population and increased sensitivity of testing
- Severity is widely variable\(^2\)
  - Mortality rate in shock approaches 50%
- Chronic Complications are common
  - PE recurrence in 40-50% at 10 years\(^3\)
  - Significant morbidity and mortality with development of PH

Risk Assessment in Acute PE

<table>
<thead>
<tr>
<th>Risk Parameters and Scoring</th>
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<tbody>
<tr>
<td>Early Mortality Risk</td>
</tr>
<tr>
<td>Shock or Hypoxemia</td>
</tr>
<tr>
<td>PE Class IV or V on EKG</td>
</tr>
<tr>
<td>Signs of RV dysfunction on imaging (TC)</td>
</tr>
<tr>
<td>Cardiac Laboratory Abnormalities(^8)</td>
</tr>
</tbody>
</table>

RV Dysfunction in Acute PE

- Obstruction of >30% of pulmonary vasculature correlates with RV dysfunction\(^1\)
- 100% negative predictive value for PE-related death with regards to RV dysfunction on TTE\(^2\)
- RV dysfunction associated with increased mortality\(^3\), though low specificity on TTE
- 24% ↑ risk of recurrent VTE with persistent RV dysfunction\(^4\)

Treatment of Acute PE

- Low Risk → Anticoagulation
  - ACCP recommend NOAC rather than warfarin
    - Less bleeding risk and greater convenience
  - Duration of anticoagulation remains unclear
    - Minimum 3 months, consider long term (24 months or more)
    - Unprovoked VTE has highest risk of recurrence

PE, pulmonary embolism; RV, right ventricular; TTE, transthoracic echocardiogram; VTE, venous thromboembolism
Treatment of Acute PE (cont.)

- **High Risk → Anticoagulation + Thrombolysis**
  - 30-50% reduction in mortality with systemic thrombolysis, ~3 fold increase in major bleeding
  - Catheter-directed thrombolysis and reperfusion
    - Appears efficacious, decreasing thrombus burden by >50%
    - Phase 3 trials are lacking and requires local expertise
- **Intermediate Risk → Anticoagulation + ?**

Chronic Complications of PE: CTEPH

What is Pulmonary Hypertension?

- Diagnosed by RHC with mPAP ≥25 mm Hg
  - Normal mPAP ≤20 mm Hg at rest
- Precapillary PH defined with PAWP ≤15 mm Hg
  - Normal ≤12 mm Hg
- PAH defined by PVR >3 Woods units
  - (PVR = ΔPressure/CO)
  - Normal PVR in some secondary PH

RHC, right heart catheterization; mPAP, mean pulmonary arterial pressure; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; CO, cardiac output.
Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension
2. PH due to left heart disease
3. PH due to chronic thromboembolic disease
4. PH due to left heart disease
5. Pulmonary hypertension associated with HIV infection
6. Pulmonary hypertension associated with ILD
7. Pulmonary hypertension associated with hemoglobinopathies
8. Pulmonary hypertension associated with myeloproliferative disorders
9. Pulmonary hypertension due to lung disease and/or hypoxia
10. Pulmonary hypertension due to disorders of the pulmonary vasculature

Group 4 Pulmonary Hypertension

- Chronic thromboembolic PH
- Estimated ~3% incidence after acute PE
- Obstruction + arteriopathy
- Treatment both surgical and medical

Can We Prevent CTEPH?

Six-Month Echocardiographic Study in Patients With Submassive Pulmonary Embolism and Right Ventricular Dysfunction: Comparison of Thrombolysis With Heparin


Identification of CTEPH

Table 6. Events after discharge and during follow-up

Table 7. Events after discharge and during follow-up

Thrombolysis to Prevent CTEPH

Incidence and Risk Factors of CTEPH in Patients After Acute PE

<table>
<thead>
<tr>
<th>Time from symptoms to diagnosis (days)</th>
<th>Unimproved R</th>
<th>EBC not contraindicated</th>
<th>Initial therapy</th>
<th>Death (1/3)</th>
<th>Deterioration (1/3)</th>
<th>Prognosis (1/3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>180-365</td>
<td>No</td>
<td>Low /Anticoagulation</td>
<td>Yes</td>
<td>30</td>
<td>1</td>
<td>Poor</td>
</tr>
<tr>
<td>180-365</td>
<td>Yes</td>
<td>Low /Anticoagulation</td>
<td>Yes</td>
<td>15</td>
<td>2</td>
<td>Poor</td>
</tr>
<tr>
<td>365-120</td>
<td>No</td>
<td>Low /Anticoagulation</td>
<td>Yes</td>
<td>7</td>
<td>1</td>
<td>Poor</td>
</tr>
<tr>
<td>365-120</td>
<td>Yes</td>
<td>Low /Anticoagulation</td>
<td>Yes</td>
<td>3</td>
<td>4</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Screen Appropriately

- Screening all patients 1 year after PE resulted in <1% diagnosis of CTEPH
- Targeted screening has better yield

Monitoring for PH Following PE: The INFORM Study

<table>
<thead>
<tr>
<th>Patients with subsequent diagnosis of pulmonary hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Graph showing incidence of PH following PE]</td>
</tr>
</tbody>
</table>

V/Q Scan vs. CT Angiography

- False positive V/Q in 15/149
  - PAH, PVOD, PH with parenchymal lung disease
- CT poor at identifying distal thromboembolic disease
Patient returns 6 months later, reports dyspnea when climbing 1 flight of stairs or ½ block on level ground.

**Our Patient Gets RHC**

HEMODYNAMIC DATA:

<table>
<thead>
<tr>
<th>Pressure (mm Hg)</th>
<th>O₂ Saturations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AORTA: 132/87 (105)</td>
<td>94%</td>
</tr>
<tr>
<td>LV: 143/0</td>
<td></td>
</tr>
<tr>
<td>PCW: Poor quality tracing despite multiple attempts</td>
<td></td>
</tr>
<tr>
<td>PA: 84/29 (49)</td>
<td>57.8%</td>
</tr>
<tr>
<td>RV: 86/13</td>
<td></td>
</tr>
<tr>
<td>RA: 15</td>
<td></td>
</tr>
</tbody>
</table>

CARDIAC OUTPUT (L/MIN) by Thermodilution: 4.5; by Estimated Fick: 4.8

CARDIAC INDEX (L/MIN/M²) by Thermodilution: 1.8; by Estimated Fick: 1.9

RESISTANCE (WOOD units = dynes-sec/cm⁵)

PULMONARY VASCULAR RESISTANCE (NL 20–130)

Thermodilution: 824

Estimated Fick: 771

LV, left ventricle; PCW, pulmonary capillary wedge; PA, pulmonary artery; RV, right ventricle; RA, right atrium.

**The Basics of CTEPH**

**CTEPH**

By T. O. Right and (B) left pulmonary angiograms from a patient with acute pulmonary hypertension secondary to thromboembolic disease.


**Pathogenesis of CTEPH**

Risk Factors for CTEPH

- Recurrent PE
- Proximal disease
- Antiphospholipid syndrome
- Hemostatic Factors
  - Elevated Factor VIII, vW factor
- Splenectomy
  - Erythrocytosis and thrombocytosis
- Non-O blood group


Therapies for CTEPH

- Pulmonary Endarterectomy
  - Performed through median sternotomy
  - Circulatory arrest for ~20 minutes at a time
  - Unilateral endarterectomy at each arrest
  - Can be successful to subsegmental branches
  - Jamieson Classification:
    - Type I – Acute or subacute proximally
    - Type II – Chronic disease proximally
    - Type III – Segmental and subsegmental only

Pulmonary Endarterectomy

Fig 1. Embolic thrombus removed from the patient described in Fig 2. The figure is in high definition for high quality.

Outcomes of PEA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 500)</th>
<th>Group 2 (n = 500)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVR (dyn/cm²)</td>
<td>Preoperative 86.0 ± 46.2</td>
<td>79.0 ± 36.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Postoperative 29.3 ± 24.2</td>
<td>33.4 ± 14.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>Preoperative 3.0 ± 1.3</td>
<td>4.3 ± 1.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Postoperative 5.4 ± 1.5</td>
<td>5.6 ± 1.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>Preoperative 46.0 ± 12.2</td>
<td>45.5 ± 11.6</td>
<td>0.384</td>
</tr>
<tr>
<td></td>
<td>Postoperative 28.7 ± 10.1</td>
<td>26.0 ± 8.4</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

PEA: pulmonary endarterectomy

Outcomes of PEA

10-15% of patients develop recurrent CTEPH from residual small vessel disease


Our Patient is Referred to Cleveland Clinic for PTE Evaluation

ADMISSION DIAGNOSIS: CTEPH (chronic thromboembolic pulmonary hypertension)
History of Pneumonia

- 55-year-old man with a medical history significant for COPD and emphysema
- CTA: Multiple filling defects in bilateral pulmonary arteries
- Right heart catheterization: pulmonary hypertension
- Hypoxemia

- Total PEA was performed on right heart catheter and CTEPH protocol scans were on placebo
- 75% open in place - created 5 years ago by patient
- Recent pulmonary embolism 3 months ago
- Patient with smoking history and left at the highest risk

- Right heart catheterization: pulmonary hypertension
- Fresh pathology for evaluation of pulmonary vascular disease

- CTEPH

Riociguat for the Treatment of CTEPH

- Phase 3, randomized, placebo-controlled trial
- 261 patients with inoperable CTEPH
- 66% women, 71% white, 22% Asian
- 95% functional class II-III
- 2:1 riociguat:placebo
- Up to 2.5 mg riociguat TID × 16 weeks


Our Patient: Operative Findings

- Large amount of chronic scarring and organizing thrombus throughout both pulmonary arterial trees
- Were able to open up all lobar and segmental vessels
- Pulmonary pressures were not substantially different post-operatively, but PVR decreased over two-fold

Riociguat for the Treatment of CTEPH

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Balloon Pulmonary Angioplasty

Medical Therapy Versus Balloon Angioplasty for CTEPH: A Systematic Review and Meta-Analysis

- **Functional Class**
  - Study name, description of study ° Statistics for each study ° Forest plot, and ES (J)
  - Pulmonary hypertension 0.00 (95 % CI, 0.00 - 0.00)
  - Pulmonary vascular disease 0.00 (95 % CI, 0.00 - 0.00)
  - Secondary endpoint 0.00 (95 % CI, 0.00 - 0.00)

- **Mean PA Pressure**
  - Study name, description of study ° Statistics for each study ° Forest plot, and ES (J)
  - Pulmonary hypertension 0.00 (95 % CI, 0.00 - 0.00)
  - Pulmonary vascular disease 0.00 (95 % CI, 0.00 - 0.00)
  - Secondary endpoint 0.00 (95 % CI, 0.00 - 0.00)

- **Pulmonary Vascular Resistance**
  - Study name, description of study ° Statistics for each study ° Forest plot, and ES (J)
  - Pulmonary hypertension 0.00 (95 % CI, 0.00 - 0.00)
  - Pulmonary vascular disease 0.00 (95 % CI, 0.00 - 0.00)
  - Secondary endpoint 0.00 (95 % CI, 0.00 - 0.00)

- **6-Minute Walk Distance**
  - Study name, description of study ° Statistics for each study ° Forest plot, and ES (J)
  - Pulmonary hypertension 0.00 (95 % CI, 0.00 - 0.00)
  - Pulmonary vascular disease 0.00 (95 % CI, 0.00 - 0.00)
  - Secondary endpoint 0.00 (95 % CI, 0.00 - 0**.

Our Patient Returns to University of Illinois at Chicago

Hospital Course
- Maintained on anticoagulation with rivaroxaban and on sildenafil for persistent PH
- A 6MWT revealed mild desaturation on exertion, qualifying him for 3L of oxygen on exertion
- Patient remained stable with no acute issues
- Social work was consulted regarding homelessness
- Sister agreed to take patient to her residence in Wyoming following discharge
- On discharge, patient was well appearing and hemodynamically stable
- The pharmacy was able to provide him with a supply of medication prior to discharge
The Role of the PCP in Evaluation and Management of the Post-PE Patient

- CTEPH needs to be on your radar
  - Minority of post-PE patients, but carries serious morbidity and mortality consequences
- Screen when appropriate
  - Identify key risk factors
  - Recognize symptoms and signs
- Refer probable or likely subjects
  - RHC will be necessary to confirm, but early referral is key
- Maintain communication with multi-professional team
  - Surgical treatment associated with 10-15% recurrence rate
  - Medical therapies require routine monitoring

Conclusions

- Differentiating acute and chronic thromboembolic disease is important
  - Though it can be difficult
- CTEPH is a rare complication but identifying risk factors is essential
- All CTEPH patients should be evaluated for PEA
- Medical therapy has been shown to improve morbidity of CTEPH
- The PCP is important in each step of this process