Updates in the Diagnosis and Management of Acute and Chronic Pulmonary Embolism

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Changi General Hospital
Clinical Case

- 63yr. old IT engineer. Returned from Europe 2 days ago. C/O: SOBE, feeling dizzy, chest discomfort & Left leg discomfort of 2 days duration

- At A&E: BP 105/54mmHg, PR 108/min, SpO2 93% on RA. Creps at Rt. Lung base on auscultation. Left Calf: mild swelling noted.
Next Step?

• Is this PE with DVT?
  : massive vs. submassive
• Should we start empiric anticoagulation?

• What diagnostic strategies to consider?

• Current management options available
PE: How common is it?

About $6 \times 10^5$/yr are diagnosed in the USA: $5 \times 10^4 - 2 \times 10^5$/yr. die of it.  

(Arcasoy S, Chest ’99)

Singapore: DVT & PE incidence is 57 per $10^3$ & 15 per $10^3$  

(Moilna J. Ann. Acad. Med. ‘09)

Autopsy data: 74% of fatal PE were not diagnosed antemortem  

(Lau G. Ann Acad Med ’95)
Pulmonary Embolus

Venous Stasis: e.g. Immobility

Endothelial Damage: e.g. Surgery, Trauma

Hypercoagulable State: e.g. Cancer
Pulmonary Embolus
Differential Diagnosis

• Pneumonia
• Pulmonary Oedema
• Pneumothorax
• Aortic dissection
• AMI
Wells score

- Symptoms of DVT: 3 points
- No alternative diagnosis better explains the illness: 3 points
- Tachycardia with pulse > 100: 1.5 points
- Immobilization / surgery in the previous 4 weeks: 1.5 points
- Prior history of DVT or pulmonary embolism: 1.5 points
- Presence of haemoptysis: 1 point
- Presence of malignancy: 1 point

**Pulmonary Embolism Risk Score Interpretation**

- Score > 6: High probability
- Score >= 2 and <= 6: Moderate probability
- Score < 2: Low Probability
What about D-dimer?

• To be used in conjunction with clinical pre-test probability score

• When the clinical probability is low, D-dimer will assist in excluding PE.

  • Carrier M et al. Throm Haemost 2009; 101:886-92
Investigations to consider:

- CXR
- ECG
- ABG
- Troponins
- CT (pulmonary angiogram)
- V/Q scan
- Duplex U/S
- 2D Echo
CXR in PE
ECG in PE
Pt 1: Acute PE

Dilated pulmonary trunk

Multiple filling defects RPA
Pt 1: Acute PE

RV:LV > 1
Strain pattern
Pt 1: Acute PE

Distended LPA with thrombus
Algorithm for Mx. Of PE

1. Suspected PE without shock or hypotension
   - Assess clinical probability of PE
     - Clinical judgment or prediction rule
       - Low/intermediate clinical probability or PE unlikely
         - D-dimer
           - negative: No treatment
           - positive: CT angiography
             - no PE: No treatment
             - PE confirmed: Treatment
       - High clinical probability or PE likely
         - CT angiography
           - no PE: No treatment
           - PE confirmed: Treatment
Echocardiographic 4-chamber views of a patient with massive pulmonary embolism and right ventricular dysfunction in end-diastole (a); and in end-systole (b).
What Next for the patient?

• 2 D Echocardiogram
  • RV pressure overload and Dysfunction in Acute PE
  • Risk stratify
  • Look for signs of disturbed RV ejection pattern (60-60 sign) or McConnell sign.

• Troponins & BNP
  • Risk stratify
Risk stratification using PESI and sPESI scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PESI</th>
<th>sPESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Points = age in years</td>
<td>If aged &gt;80 years old = 1 point</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10 points</td>
<td>-</td>
</tr>
<tr>
<td>Cancer</td>
<td>+30 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+10 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>+10 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Pulse rate ≥110 bpm</td>
<td>+20 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100 mmHg</td>
<td>+30 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Respiratory rate &gt;30 breaths/min</td>
<td>+20 points</td>
<td>-</td>
</tr>
<tr>
<td>Temperature &lt;36°C</td>
<td>+20 points</td>
<td>-</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60 points</td>
<td>-</td>
</tr>
<tr>
<td>Arterial oxyhaemoglobin saturation &lt;90%</td>
<td>+20 points</td>
<td>1 point</td>
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Risk stratification using PESI and sPESI scores

<table>
<thead>
<tr>
<th>Class I: ≤65 points</th>
<th>0 points = low risk</th>
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<tbody>
<tr>
<td>Very low 30-day mortality risk (0–1.6%)</td>
<td>Low 30-day mortality risk (1.0%)</td>
</tr>
<tr>
<td>Class II: 66–85 points</td>
<td>(95% CI 0–2.1%)</td>
</tr>
<tr>
<td>Low mortality risk (1.7–3.5%)</td>
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<table>
<thead>
<tr>
<th>Class III: 86–105 points</th>
<th>≥1 point(s) = not low risk</th>
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<tbody>
<tr>
<td>Moderate mortality risk (3.2–7.1%)</td>
<td>30-day mortality risk (10.9%)</td>
</tr>
<tr>
<td>Class IV: 106–125 points</td>
<td>(95% CI 8.5–13.2%)</td>
</tr>
<tr>
<td>High mortality risk (4.0–11.4%)</td>
<td></td>
</tr>
<tr>
<td>Class V: &gt;125 points</td>
<td></td>
</tr>
<tr>
<td>Very high mortality risk (10.0–24.5%)</td>
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## Risk stratification of PE

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Risk parameters and scores</th>
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<tbody>
<tr>
<td></td>
<td>Shock or hypotension</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
</tr>
<tr>
<td>Intermediate high</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate low</td>
<td>-</td>
</tr>
<tr>
<td>Low</td>
<td>-</td>
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Management of PE

• Stabilise patient first: Cardiorespiratory system

• **Assess haemodynamic status:**
  • Stable vs Unstable PE

  **Unstable:** BP<90mmHg for 15mins.,
  Needing Vasopressors
  Clinically in shock

  **Submassive:** Rt. Vent. Dysfunction(Echo evidence)
  (30 day mortality is high)
Treatment of PE

- Supportive measures: O2, inotropes
- Anticoagulants: UFH, LMWH, VKA, NOACs
- Thrombolytics: Streptokinase, r-tPA, Urokinase
  - Systemic vs Localised Delivery
- Catheter Embolectomy
- Surgical Embolectomy
ECS guidelines for traditional anticoagulant treatment in PE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Dose/regimen</th>
<th>Supporting data</th>
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<tbody>
<tr>
<td><strong>Traditional anticoagulants</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>UFH</td>
<td>Factor Xa and thrombin (indirect via AT)</td>
<td>Weight-adjusted s.c. bolus dose followed by i.v. infusion; overlapping with a VKA for at least 5 days and until INR &gt;2.0 for 2 consecutive days</td>
<td></td>
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<tr>
<td>LMWH</td>
<td>Factor Xa and thrombin (indirect via AT)</td>
<td>Weight-adjusted s.c. regimen; overlapping with a VKA for at least 5 days and until INR &gt;2.0 for 2 consecutive days</td>
<td>COLUMBUS</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Factor Xa (indirect via AT)</td>
<td>Weight-adjusted s.c. regimen (standard dose 7.5 mg) od; overlapping with a VKA for at least 5 days and until INR &gt;2.0 for 2 consecutive days</td>
<td>MATISSE DVT, MATISSE PE</td>
</tr>
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## ECS guidelines in the use of NOACs in PE

<table>
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<th>Acute treatment</th>
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<tr>
<td><strong>ESC recommendation</strong></td>
</tr>
<tr>
<td><strong>Novel OACs are recommended as alternatives to VKA/parenteral anticoagulation</strong></td>
</tr>
<tr>
<td>Rivaroxaban (15 mg bid for 3 weeks, followed by 20 mg od)</td>
</tr>
<tr>
<td>Dabigatran (150 mg bid, or 110 mg bid for patients ≥80 years of age or those under concomitant verapamil treatment) following acute-phase parenteral anticoagulation</td>
</tr>
<tr>
<td>Edoxaban(^d) following acute-phase parenteral anticoagulation</td>
</tr>
<tr>
<td>Thrombolytic therapy (for patients who do not have high risk of bleeding)</td>
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V/Q scan in PE

• Diagnostic in approx. 30-50% of PE patients.

• High probability V/Q: PPV = 85-90%

• Normal V/Q: NPV = 97%

Scotsman HD. (PIOPED II study). Radiology 2008; 246

• Note: Contrast Allergy, Pregnancy, CKD, Paraproteinaemias
NATURAL HISTORY OF ACUTE PULMONARY THROMBOEMBOLI

- Total resolution or resolution leaving minimal residua, with restoration of normal pulmonary hemodynamics and gas exchange within 30 days in ≥ 90% of patients

- Repeat catherization after acute PE shows R heart pressures return to near normal values in most people within 10-21 days

(Lang, *NEJM 2004*)
- **CTEPH** usually manifests only several years after the initial episode of PE 
  
  *(Fedullo, NEJM 2001)*

- Following an acute PE (N=223) a cumulative incidence of 3.8% symptomatic CTEPH at 2yrs. was noted.

  *(Pengo, NEJM 2004)*
This estimate ~ 4% within 2 year after a symptomatic episode of PE is a very conservative figure.

In multivariate model, these factors are associated with significant increased risk of CTEPH:

1. Younger age
2. Previous PE
3. A larger perfusion defect
4. Idiopathic PE at presentation (ie no risk factors)
PATHOPHYSIOLOGY OF CTEPH

- Inadequate thrombus resolution following one or more embolic events is believed to be inciting condition
- Embolic material become attached to pulmonary arterial wall at main, segmental levels
- With time, these become converted into connective and elastic tissue
- Recanalisation may occur, with formation of fibrous tissue (i.e bands and webs)
- This chronic obstructive disease → a small vessel arteriolar vasculopathy characterised by excessive smooth muscle cell proliferation around small arterioles (also seen in remaining non-obstructive vessels)
Combined obstructive and secondary vasculopathy cause progressive pulmonary hypertension

It’s unclear why acute emboli fail to resolve in a subset of patients who subsequently develop pulmonary hypertension…

- Identifiable hypercoagulable state is found only in a minority
- No abnormality in fibrinolytic pathway or within the pulmonary endothelium could account for incomplete thrombus dissolution so far

Variable progression and timing of patient presentation

1. Age
2. Previous physical health
3. Comorbid medical conditions
4. Residence at altitude

(Auger et al, Cardiol Clinics 2004)
If CTEPH is left untreated, poor prognosis

→ progressive pulmonary hypertension
→ R ventricular failure
→ ultimate death

Riedel et al (Chest, 1982) demonstrated 10 year survival rate in CTEPH at time of diagnosis

<table>
<thead>
<tr>
<th>mean PA pressure (mmHg)</th>
<th>10 year survival</th>
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<tr>
<td>31-40</td>
<td>50%</td>
</tr>
<tr>
<td>41-50</td>
<td>20%</td>
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CLINICAL PRESENTATIONS OF CTEPH

1. Exertional dysnoea
2. Decreased exercise tolerance
3. Non productive cough (exertional)
4. Hemoptysis
5. Atypical chest pain (pleuritic if infarcted lungs)
6. Exertional related presyncope, syncope
   → secondary to insufficient cardiac output
7. Peripheral edema in late course

❑ Nonspecific symptoms... delay diagnosis
Common masquerades:
- Physical deconditioning
- COPD / Asthma
- Coronary artery disease
- Valvular heart disease
- Psychogenic dyspnoea

PHYSICAL SIGNS OF CTEPH
- Signs of pulmonary hypertension
- High pitched, blowing pulmonary flow murmur over lung field

→ vascular bruits from turbulent flow across large, narrowed pulmonary vessels (not present in 1º pulm arterial HTN)
Chronic thromboembolic disease  Chest radiograph in a patient with chronic thromboembolic disease shows enlarged, irregular central pulmonary arteries with left lower lobe oligemia. Courtesy of Peter F Fedullo, MD.
2. **Pulmonary function tests**
   - To exclude other obstructive airway or parenchymal lung disease
   - Unremarkable in CTEPH (20% mild-mod restrictive defect secondary to parenchymal scarring)

3. **ABG**
   - Resting ABG reveals relatively normal PaO2
   - With exercise, reduced PaO2 and increased dead-space ventilation

4. **Echocardiography**
   - Enlarged R heart chamber, abnormal RV systolic function
   - Paradoxical (L ward displacement) interventricular septal motion
   - Abnormal L ventricle diastolic function
   - Doppler estimation of PA pressure and Tricuspid regurg
   - Contrast echo to detect any communication (eg. patent foramen ovale)
   - During exercise: increased R heart size and PA pressure
Once pulmonary hypertension established, need to distinguish between major-vessel obstruction or small vessel pulmonary vascular disease

5. Radioisotope V/Q lung scan

- In CTEPH: ≥ 1 segmental or large perfusion defects (if recanalised → gray zones/ relative hypoperfusion)
- In 1º pulmonary arterial HTN: normal or mottled subsegmental perfusion pattern

Fig. 1—A. A perfusion scan in a patient with CTEPH demonstrating multiple, bilateral, segmental perfusion defects. B. A patient with PPH with a "mottled" perfusion scan without any segmental perfusion defects.
6. **Helical CT with contrast**

- Mosaic perfusion of lung parenchyma
- Central pulmonary vessel enlargement, variation in size of segmental level vessels
- Mediastinal collateral vessels
- Organised thrombus lining pulmonary vessels in an eccentric fashion
7. **R and L heart catheterizations**
   - For quantification of severity of pulmonary hypertension and assessment of cardiac function
   - For assessment of coronary artery status, important for preop assessment and concurrent CABG

8. **Pulmonary angiography**
   - To define pulmonary vasculature and determine thromboembolic location and surgical accessibility
   - Typical angiographic patterns of chronic disease
     - Pouch defects
     - Pulmonary artery webs or bands
     - Intimal irregularities
     - Abrupt narrowing of major pulm vessels
     - Obstruction of main, lobar, segmental pulm arteries
Management of CTEPH

CTEPH assessment (Life-Long Anticoagulation)

Operable
- Pulmonary Endarterectomy

Non-Operable
- Medical Therapy
- Lung Transplant

PTPA
Fig. 3—Angiographic findings of chronic thromboembolic disease: pouches in the right upper lobe and interlobar artery (black arrows), a band with post-stenotic dilatation (white arrow), and rapid tapering of the left descending pulmonary artery.
PULMONARY ENDARTERECTOMY
REASONS FOR:

1. Hemodynamic goal
   - To prevent R ventricular compromise from pulm HTN
2. Improve respiratory function
   - To reduce a large ventilated but unperfused dead space
3. Prophylactic goal
   - To prevent retrograde extension of clot
   - To prevent secondary vasculopathic changes

RECOMMENDED FOR:

- All symptomatics with evidence of hemodynamic or ventilatory impairment at rest or with exercise
- Asymptomatics with significant thromboembolic changes on angiogram
RESULTS OF PULMONARY ENDARterectomy

✔ Reduction in pulmonary pressure/resistance to normal levels and immediate improvement in pulm blood flow and cardiac output
✔ Improvement in functional status
✔ Echo: R vent geometry rapidly reverts toward normal, RA and RVH & dilatation regress, Tricuspid valve function return to normal within days
✔ Survival after endarterectomy: 75% at 6 year

😊 Peri-mortality rates 4.4% (from UCSD experience, Cardiol Clin 2004)
Pt 1: Acute PE

- Multiple filling defects RPA
- Distended LPA with thrombus
Pt 2: Chronic PE

Non-enhancing small RUL PA branches

Compare enhancing vessels on the (L)
Pt 2: Chronic PE

Chronically truncated RUL PA
Non enhancing