Pulmonary Embolism: To lyse or not to lyse?

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Disclosure

I have no relevant financial relationships or conflicts of interest to disclose

Objectives

- Describe the pathophysiology and clinical presentation of a pulmonary embolism (PE)
- Classify patients with PE based on presenting characteristics to determine risk of death and complication rate
- Discuss the risks and benefits of thrombolysis in the treatment of PE in patients within different risk stratifications
Pulmonary Embolism (PE)

Obstruction of the pulmonary artery or one of its branches by material (i.e., thrombus, tumor, air, fat) that originated elsewhere in the body

Epidemiology

- **Incidence**
  - 600,000 cases diagnosed annually in the US
- **Mortality**
  - More than 300,000 deaths each year
  - Rates as high as 2% on day 1 of diagnosis and 30% if left untreated

Virchow’s Triad

1. **Endothelial Injury**
2. **Thrombosis**
3. **Hypercoagulability**
4. **Abnormal Blood Flow**
Pathophysiology

Thrombus

Obesity
Age > 75
History of thrombus
Malignancy
Trauma
Prolonged immobility
Postop ≤ 1 month
Coagulable
Medications

Clinical Presentation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea at rest or with exertion</td>
<td>Tachypnea</td>
</tr>
<tr>
<td>Hyoxemia</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Cough/hemoptysis</td>
<td>Loud S2</td>
</tr>
<tr>
<td>Pleuritic pain</td>
<td>Crackles or decreased breath sounds</td>
</tr>
<tr>
<td>Syncope</td>
<td>Raised jugular vein pressure</td>
</tr>
</tbody>
</table>
Assessment of PE

- Massive
  - Hemodynamic instability
  - Symptomatic hypotension

- Submassive
  - Hemodynamic stability
  - Evidence of right ventricular dysfunction

- Stable
  - Hemodynamic stability
  - No evidence of RV dysfunction

Risk Stratification

- MASSIVE
  - High Risk
  - >15% mortality

- SUBMASSIVE
  - Intermediate Risk
  - 3-15% mortality

- STABLE
  - Low Risk
  - <1% mortality

CT: computerized tomography

Lancet 1999;353:1386-1389. CT: computerized tomography


Risk Stratification

High Risk
- >15% mortality

Intermediate Risk
- 3-15% mortality

Low Risk
- <1% mortality

Right Ventricular Dysfunction

**Electrocardiogram**
- T-wave inversion (leads V1-V4)
- New right bundle branch block

**Echocardiogram**
- RV dilatation, RV free wall motion hypokinesis
- Increased RV afterload
- Pulmonary hypertension as tricuspid regurgitation

**Biomarkers**
- Cardiac troponin T level > 0.07 ng/mL
- Pro-brain natriuretic peptide level ≥ 600 pg/mL

Considerations in Risk Stratification

- Clinical status
- Evidence of RV dysfunction
- Evidence of myocardial injury
- Residual deep vein thrombosis
- Oxygenation

Management Strategies

- Anticoagulation
- Thrombolysis
- Embolectomy
Anticoagulants

- Unfractionated heparin
- Low molecular weight heparins
- Vitamin K antagonist
- Factor Xa inhibitors
- Direct thrombin inhibitors

Coagulation Cascade

Thrombolyis

Selective for fibrin

Non-selective for fibrin
Thrombolytics

**Benefits**
- Rapid resolution of symptoms
- Stabilize cardiorespiratory function
- Reduce RV damage
- Improve exercise tolerance
- Avoid vasopressors and MV support

**Risks**
- Disabling or fatal hemorrhage (ICH)
- Blood transfusions
- Unnecessary intervention (surgery)
- Increased hospital length of stay?

**Contraindications to Lysis**

<table>
<thead>
<tr>
<th>ABSOLUTE</th>
<th>RELATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of intracranial hemorrhage</td>
<td>Recent internal bleeding</td>
</tr>
<tr>
<td>Known intracranial neoplasm, AV malformation or aneurysm</td>
<td>Recent surgery or organ biopsy</td>
</tr>
<tr>
<td>Significant head trauma</td>
<td>Recent trauma, including cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>Active internal bleeding</td>
<td>Venipuncture at noncompressible site</td>
</tr>
<tr>
<td>Known bleeding diathesis</td>
<td>Uncontrolled hypertension</td>
</tr>
<tr>
<td>Intracerebral or intraspinal surgery within 3 months</td>
<td>Diabetic retinopathy</td>
</tr>
<tr>
<td>Cerebrovascular accident within 2 months</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td></td>
</tr>
</tbody>
</table>

**Risk Factors Associated with Bleeding**
- Age > 70 years
- Recent invasive procedure
- Elevated diastolic blood pressure

RV: right ventricular
MV: mechanical ventilation
ICH: intracranial hemorrhage
AV: arteriovenous
ICH: intracranial hemorrhage
FDA Approved Thrombolytics

<table>
<thead>
<tr>
<th></th>
<th>Streptokinase</th>
<th>Urokinase</th>
<th>Alteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigenicity</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Fibrin Specificity</td>
<td>Non-selective</td>
<td>Non-selective</td>
<td>Fibrin-specific</td>
</tr>
<tr>
<td>Half-life</td>
<td>23 min</td>
<td>20 min</td>
<td>7 min</td>
</tr>
<tr>
<td>Dosing for PE:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial Maintenance</td>
<td>250,000 units over 30 min</td>
<td>100,000 units/hr over 24 hrs</td>
<td>4400 units/kg over 12 hrs</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 mg over 15 min</td>
<td>90 mg over 2 hrs</td>
<td></td>
</tr>
</tbody>
</table>

Alternative Thrombolytic Agents
In Comparison to Alteplase

- **Reteplase**
  - Faster onset
  - Longer half-life

- **Tenecteplase**
  - Longer half-life
  - Enhanced relative fibrin specificity

- **Desmoteplase**
  - Longer half-life
  - Enhanced fibrin specificity
  - Twice as potent

Thrombolysis in Massive PE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thrombolyte</th>
<th>Increased</th>
<th>Decreased</th>
<th>All (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent PE or death</td>
<td>12/28 (43)</td>
<td>6/28 (21)</td>
<td>1/28 (3)</td>
<td>8/28 (29)</td>
</tr>
<tr>
<td>Death</td>
<td>6/28 (21)</td>
<td>12/28 (43)</td>
<td>1/28 (3)</td>
<td>8/28 (29)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1/28 (3)</td>
<td>3/28 (11)</td>
<td>4/28 (14)</td>
<td>8/28 (29)</td>
</tr>
</tbody>
</table>

Risk vs Benefit

- Mortality
- Sensitivity
- Necrosis

Circulation 2004;110:744-749
Who Should Receive Anticoagulation Alone?

Stable

- Hemodynamic stability
- No evidence of RV dysfunction

Who Should Receive Lysis?

Massive

- Hemodynamic instability
- Symptomatic hypotension

What We Do Know

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

5.6.1.1. In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).
The Controversy Begins

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

5.6.1.3. In selected patients with acute PE not associated with hypotension and with a low bleeding risk whose initial clinical presentation, or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension, we suggest administration of thrombolytic therapy (Grade 2C).

MAPPETT-3

- **Patients**
  - N=256
  - Acute PE and pulmonary HTN or RVD without arterial hypotension or shock

- **Intervention**
  - UFH + alteplase or UFH alone

- **Primary Endpoint**
  - In-hospital death or clinical deterioration requiring escalation of treatment

- **Results**
  - Alteplase group 11% vs. UFH alone group 24.6%; p=0.006

- **Safety**
  - Major bleeding: Alteplase group 0.8% vs. UFH alone group 3.6%; p=0.29

PEITHO

- **Patients**
  - N=1006
  - Acute PE with RVD and myocardial injury without arterial hypotension or shock

- **Intervention**
  - UFH + Tenecteplase or UFH alone

- **Primary Endpoint**
  - Death from any cause or hemodynamic decompensation within 7 days

- **Results**
  - Tenecteplase group 2.6% vs. UFH alone group 5.6%; P=0.02

- **Safety**
  - Major bleeding: Tenecteplase group 6.3% vs. UFH alone group 1.2%; p<0.001
### MAPPETT-3 vs. PEITHO

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MAPPETT-3</th>
<th>PEITHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Size</td>
<td>N=256</td>
<td>N=1006</td>
</tr>
<tr>
<td>Onset of Symptoms to Randomization</td>
<td>≤4 days</td>
<td>≤15 days</td>
</tr>
<tr>
<td>Thrombolytic Agent</td>
<td>Alteplase</td>
<td>Tenecteplase</td>
</tr>
<tr>
<td>Right Ventricular Dysfunction (%)</td>
<td>31%</td>
<td>51%</td>
</tr>
<tr>
<td>Anticoagulation Prior to Enrollment (%)</td>
<td>Unknown</td>
<td>30%</td>
</tr>
<tr>
<td>UFH Dosing</td>
<td>5000 unit, 1000 unit/hr</td>
<td>80 units/kg, 18 units/kg/hr</td>
</tr>
<tr>
<td>UFH Protocol</td>
<td>Targeted aPTT 2-2.5 x ULN</td>
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<td>Targeted aPTT 2-2.5 x ULN</td>
<td>Targeted aPTT 2-2.5 x ULN</td>
</tr>
<tr>
<td>Composite Endpoint (TG vs. CG)</td>
<td>11% vs. 24.6%; p&lt;0.006</td>
<td>2.6% vs. 5.6%; p&lt;0.02</td>
</tr>
<tr>
<td>Mortality (TG vs. CG)</td>
<td>2.1% vs. 3.4%; p=NS</td>
<td>1.1% vs. 1.8%; p=NS</td>
</tr>
<tr>
<td>Major Bleeding (%)</td>
<td>0.8% vs. 3.6%; p=NS</td>
<td>6.3% vs. 1.2%; p&lt;0.001</td>
</tr>
<tr>
<td>Intracranial Hemorrhage (%)</td>
<td>None</td>
<td>2% vs. 0.2%; p=0.003</td>
</tr>
</tbody>
</table>

### MOPETT

- **Patients**
  - N=121
  - Symptomatic "moderate" PE

- **Intervention**
  - AC + low-dose alteplase or AC alone

- **Primary Endpoint**
  - Pulmonary hypertension and composite of pHTN and recurrent PE at 28 months

- **Results**
  - pHTN: Alteplase group 16% vs. AC alone 57%; p<0.001
  - Composite: Alteplase group 10% vs. AC alone 63%; p<0.001

- **Safety**
  - No bleeding

### Controversies with Lysis

- Mortality and composite primary endpoints
- Dosing strategies
- Optimal administration techniques
- Safety of thrombolytics
Mortality and Composite Primary Endpoints

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Massive PE</th>
<th>Submassive PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NO reduction in composite endpoint of PE or death with lysis</td>
<td>• Significant reduction in composite endpoint of PE or death with lysis</td>
<td>• Significant reduction in composite endpoint of death or escalation of treatment</td>
</tr>
<tr>
<td>• No difference in mortality</td>
<td>• No difference in mortality</td>
<td>• No difference in mortality</td>
</tr>
<tr>
<td>• No difference in major bleeding</td>
<td>• No difference in major bleeding</td>
<td>• Major bleeding? MAPPETT-3 vs. PEITHO</td>
</tr>
</tbody>
</table>

Dosing Strategies

• What is the safest and most effective dose?
  – Weight-based vs. fixed dose alteplase?
  – Acute ischemic stroke and myocardial infarction dosing

• Low-dose alteplase vs. standard dosing
  – Improvement in RV function in both groups
  – No difference in mortality
  – Higher risk of bleeding in standard dosing group

Optimal Administration Techniques

• Continuous infusion vs. bolus dosing
  – Guidelines are inconsistent
  – Large bolus may be resistant to antifibrinolytic effects of platelet activator inhibitor-1

• Concurrent anticoagulation
  – UFH recommended when administering thrombolytics
  – Achievement of therapeutic anticoagulation in first 24 hours decreases recurrence of PE and mortality
    • Should UFH be withheld during thrombolytic therapy?
Safety of Thrombolytics

<table>
<thead>
<tr>
<th>Major Bleeding</th>
<th>Intracranial Hemorrhage</th>
<th>Minor Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICOPER</td>
<td>21.7% vs. 8.8%</td>
<td>ICOPER</td>
</tr>
<tr>
<td>Wan et al.</td>
<td>0% vs. 0%</td>
<td>Wan et al.</td>
</tr>
<tr>
<td>MAPPET-3</td>
<td>0.8% vs. 1.6%</td>
<td>MAPPET-3</td>
</tr>
<tr>
<td>PEITHO</td>
<td>6.9% vs. 1.2%</td>
<td>PEITHO</td>
</tr>
</tbody>
</table>

ICOPER 21.7% vs. 8.8%
Wan et al. 0% vs. 0%
MAPPET-3 0.8% vs. 1.6%
PEITHO 6.9% vs. 1.2%

Intracranial Hemorrhage

<table>
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<tr>
<th>Intracranial Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICOPER</td>
</tr>
<tr>
<td>Wan et al.</td>
</tr>
<tr>
<td>MAPPET-3</td>
</tr>
<tr>
<td>PEITHO</td>
</tr>
</tbody>
</table>

ICOPER 3% vs. 0.3%
Wan et al. 0.5% vs. 0.3%
MAPPET-3 0% vs. 0%
PEITHO 2% vs. 0.2%

Catheter-Directed Thrombolysis (CDT)

- Low-dose “local” thrombolysis and thrombus fragmentation or aspiration
- An alternative advanced therapy when full-dose thrombolysis has failed or is contraindicated

Local Thrombolysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>Primary Endpoint</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULTIMA</td>
<td>N=59</td>
<td>Acute symptomatic PE with RV to LV ratio &gt;1 (intermediate risk)</td>
<td>UFH alone vs. 10-20 mg alteplase via EKOS plus UFH</td>
<td>Reduction of RV/LV ratio at 24 hours EKOS group 0.3±0.2 vs. UFH alone 0.03±0.16; p&lt;0.001</td>
<td>Minor bleeding EKOS 10% vs. UFH alone 3%; p=0.61 - No major bleeding</td>
</tr>
</tbody>
</table>
**Systemic vs. Catheter-directed**

**Systemic**
- Easily accessible
- Ease of administration
- Greater familiarity
- More supportive literature

**Catheter-directed**
- Lower dose
- Locally administered
- Administration that requires trained personnel
- Availability of special devices
- Logistics of device placement

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**Guideline Recommendations**

<table>
<thead>
<tr>
<th>Category</th>
<th>American College of Cardiology Task Force</th>
<th>European Society of Cardiology</th>
<th>Endovascular Society of North America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for thrombolysis</td>
<td>Administration of fibrinolytic for all patients</td>
<td>Recommended to high-risk patients</td>
<td>Recommended in high-risk patients</td>
</tr>
<tr>
<td>Thrombolysis indication</td>
<td>Low-dose recombinant tissue plasminogen activator (t-PA)</td>
<td>Recommended in high-risk patients</td>
<td>Recommended in high-risk patients</td>
</tr>
<tr>
<td>Thrombolysis indication</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Thrombolysis indication</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Administration site</td>
<td>Peripheral vein (S)</td>
<td>Peripheral vein (S)</td>
<td>Peripheral vein (S)</td>
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<tr>
<td>Dose of fibrinolytic</td>
<td>100 mg/kg over 2 h (S)</td>
<td>100 mg/kg over 2 h (S)</td>
<td>100 mg/kg over 2 h (S)</td>
</tr>
<tr>
<td>Dose of fibrinolytic</td>
<td>No specific recommendation (S)</td>
<td>No specific recommendation (S)</td>
<td>No specific recommendation (S)</td>
</tr>
<tr>
<td>Dose of fibrinolytic</td>
<td>No specific recommendation (S)</td>
<td>No specific recommendation (S)</td>
<td>No specific recommendation (S)</td>
</tr>
</tbody>
</table>

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**Embolectomy**

- Considered when:
  - Patients have contraindications to thrombolysis when hemodynamically unstable
  - Thrombolysis has been unsuccessful and hypotension persists

- Mortality approximately 20%
Summary

- Pulmonary embolism is the most common preventable cause of death in hospitalized patients.
- Certain risk factors are independent predictors of increased mortality in this patient population.
- The use of thrombolytic agents in patients who present with submassive PE is extremely controversial.
- Patients with submassive PE must be closely monitored and evaluated for the need for thrombolysis and a risk versus benefit analysis should be performed.

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