New Frontiers in Percutaneous Therapy for Pulmonary Embolism

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Disclosures

• No relevant financial disclosures
Case

- 91 y female presented with severe dyspnea while on the commode
- Recent pelvic fracture
- UTI, mostly immobile
- BP 70-80 mmHg, HR 130s, RR 22-24, 10 Lt O2
- CT PE protocol: Large Bilateral clots, RV enlarged (RV:LV >1)
Options

Anticoagulation  Thrombolytics
Veno-Thromboembolism

• Venous thromboembolism (VTE) is responsible for the hospitalization of >250,000 Americans annually.
• It is a significant risk for morbidity and mortality.

Jaff MR Circ 2011;123:1788
Pulmonary embolism: A Public Health Problem

- **DVT**
  - 2 Million

- **PE**
  - 600,000

- **Death**
  - 100,000

- **Post-Thrombotic Syndrome**
  - 800,000

- **Silent PE**
  - 1 Million

- **Pulmonary Hypertension**
  - 30,000

**Estimated Cost of VTE Care** $2.5-14 Billion/year

Risk Stratification

Massive
- SBP<90mmHg
- Pulsesless
- HR<40/min

Sub-Massive
- SBP>90mmHg
- RV dysfunction
- ECG Changes
- Trop, BNP

Low Risk
- SBP>90mmHg
- RV normal
Why the concern?

International Cooperative Pulmonary Embolism Registry (ICOPER)

- 108 patients, the 90-day mortality rate for patients with acute PE and systolic blood pressure <90 mm Hg was 52.4%
- 14.7% in the remainder of the cohort.

Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET)

- 1001 patients with acute PE, in-hospital mortality was 8.1% for stable patients.
- 25% for those presenting with cardiogenic shock
- and 65% for those requiring cardiopulmonary resuscitation.

Kucher N. *Circ.* 2006;113:577  
Kasper W. *JACC.* 1997;30:1165
Pathophysiology of Acute Pulmonary Embolism

Piazza G. Circ 2010;122:1124
Algorithm for use of fibrinolytics to treat acute PE

Assess for evidence of increased severity that suggests potential for benefit of fibrinolysis

1. EVIDENCE OF SHOCK OR RESPIRATORY FAILURE:
   - Any hypotension (SBP<90 mm Hg)
   - Shock index >1.0
   - Respiratory distress (SaO2 <95% with Borg score>8, or altered mental status, or appearance of suffering)

2. EVIDENCE OF MODERATE TO SEVERE RV STRAIN:
   - RV dysfunction (RV hypokinesis or estimated RVSP>40 mm Hg)
   - Clearly elevated biomarker values (e.g., troponin above borderline value, BNP >100 pg/mL or pro-BNP>900 pg/mL)

No contraindications to fibrinolysis

Alteplase
100 mg over 2 h IV
Treatment with Thrombolytics

Figure 1. Right ventricular systolic pressures at diagnosis and 6 months after acute submassive pulmonary embolism. **Left Panel**, Patients initially treated with heparin and alteplase. **Right Panel**, Patients who received heparin alone. Plots for patients with a net increase in systolic pressure are highlighted in red. Reprinted from Kline et al. with permission of the publisher. Copyright © 2009, American College of Chest Physicians.

*ACC/AHA Guidelines 2011  Circulation 2006;113:577-82*
## Treatment of High Risk patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Intracranial Hemorrhage (Fibrinolysis Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICOPER</strong></td>
<td>9/304 (3%)</td>
</tr>
<tr>
<td>(Goldhaber SZ, et al. 1999)</td>
<td></td>
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<tr>
<td><strong>PEITHO</strong></td>
<td>10/506 (2%)</td>
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<td>(Meyer G, et al. 2014)</td>
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</table>
Endovascular Therapy

Goals
• Reduction in pulmonary artery pressure, RV strain, and pulmonary vascular resistance (PVR);
• increasing systemic perfusion; and
• facilitating RV recovery.

Basic Strategies
• Aspiration thrombectomy,
• Thrombus fragmentation, and
• Rheolytic thrombectomy.
• Pharmaco-mechanical with ultrasound assist

Jaff MR Circ 2011;123:1788
Endovascular Tools

Kuo WT. JVIR 2012;23:167
Thrombus Fragmentation

Rotating Pigtail

Balloon Angioplasty

Amplatzer Thrombectomy Catheter
Mechanical Thrombectomy
AngioVac® Suction

Inflated Balloon

Flow

Inflow
Catheter-Directed Thrombolysis

- In randomized trials, systemic PE thrombolysis is associated with a 13% risk of major bleeding and a 1.8% risk of intracranial hemorrhage \(^1\)
- In clinical practice, systemic PE thrombolysis is associated with a 20% risk of major bleeding and a 3% risk of intracranial hemorrhage \(^2\)
- In clinical practice, systemic thrombolysis is withheld in up to two thirds of patients with high-risk (massive) PE \(^3\)

\(^1\) Eur Heart J 2008; 29:2276-2315
\(^2\) Am J Cardiol. 2006;97:127-9
\(^3\) Circulation 2006;113:577-82
Back to our case

Pre Treatment Left

Post Treatment Left
• Pre Treatment Right

• Post Treatment Right
Local Lytic Therapy

Pre Intervention

Post Intervention
Right Ventricular Response
Ultrasound accelerated thrombolysis

Mechanism of Action

Ultrasound pulses

Fibrin separation

Active drug delivery by acoustic streaming

Ultrasound delivered in:
- High frequency (2.2 MHz)
- Low power (0.5 W per element)
- Pulses of varying waveforms

Fibrin without Ultrasound

Fibrin With Ultrasound

The ULTIMA Trial

A Prospective, Randomized, Controlled Study of Ultrasound Accelerated Thrombolysis for the Treatment of Acute Pulmonary Embolism
PE patients diagnosed by Chest CT (N = 363)

Screening failure: N = 304 (84%)
- No main pulmonary artery embolism at CT (N = 125)
- RV / LV ratio ≤ 1 at CT or echocardiography (N = 82)
- Active bleeding or increased risk of bleeding (N = 19)
- High-risk PE (N = 16)
- Major surgery or trauma within 10 days (N = 13)
- No symptoms or symptom duration > 14 days (N = 13)
- No patient consent (N = 12)
- Age > 80 years (N = 11)
- Life expectancy < 3 months (N = 6)
- Other reasons (N = 7)

Randomization (N = 59)

Data Safety Monitoring Board:
Randomization terminated if at least 25 patients per group with evaluable primary endpoint (RV/LV ratio) identified

Echocardiography Core Lab:
Blind assessment of echocardiograms

Received CDT + Heparin (N = 30)
- Primary endpoint evaluable (N = 25)
  FU 3 months (N = 27)

Received Heparin alone (N = 29)
- Primary endpoint evaluable (N = 28)
  FU 3 months (N = 26)
Primary endpoint: Reduction in RV/LV ratio (echo)

- **Baseline to 24 hrs**
  - CDT+Heparin: 0.30
  - Heparin: 0.03

- **Baseline to 90 days**
  - CDT+Heparin: 0.38
  - Heparin: 0.22

P-values:
- Baseline to 24 hrs: P<0.0001
- Baseline to 90 days: P=0.03
## Secondary endpoint analysis

<table>
<thead>
<tr>
<th>Clinical outcomes at 90 days</th>
<th>CDT+ Heparin (N = 30)</th>
<th>Heparin (N = 29)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 (0%)</td>
<td>1* (3%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3** (10%)</td>
<td>1§ (3%)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

* rehospitalization and death from advanced pancreatic cancer
** two patients with transient mild hemoptysis without medical intervention, one patient with groin hematoma requiring manual compression
§ one patient with transient anal bleeding following endoscopic removal of colon polyp
SEATTLE II

CT-confirmed PE
- Symptoms ≤ 14 days
- Massive or submassive
- Meets all inclusion and no exclusion criteria

RV enlargement as documented by initial CT
- RV:LV ratio ≥ 0.9

Ultrasound-facilitated fibrinolysis
- t-PA 1 mg/hr for 24 hours (1 device)
- t-PA 1 mg/hr for 12 hours (2 devices)
- TOTAL t-PA Dose = 24 mg

Follow-up at 48 ± 6 hours after start of the procedure
- CT measurement of RV:LV ratio
- Echocardiogram to estimate PA systolic pressure

Study Sites = 21
Total Trial Population = 150
### Baseline Characteristics

<table>
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<tr>
<th>Patient Demographics</th>
<th>N = 150</th>
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<tbody>
<tr>
<td>Mean age $\pm$ SD, years</td>
<td>59 ± 16.1</td>
</tr>
<tr>
<td>Mean BMI $\pm$ SD, kg/m$^2$</td>
<td>35.6 ± 9.1</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>77 (51.3)</td>
</tr>
<tr>
<td>Race/Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>119 (79.3)</td>
</tr>
<tr>
<td>African American</td>
<td>22 (14.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Co-morbid Conditions, n (%)</td>
<td>N = 150</td>
</tr>
<tr>
<td>Concomitant use of antiplatelet agents</td>
<td>52 (34.7)</td>
</tr>
<tr>
<td>Immobility within 30 days of PE</td>
<td>45 (30)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>42 (28)</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>30 (20)</td>
</tr>
<tr>
<td>Previous PE</td>
<td>15 (10)</td>
</tr>
</tbody>
</table>
Outcomes: RV/LV Ratio

- Pre-Procedure: 1.55
- 48 Hours: 1.13

p < 0.0001
## Clinical Outcomes

<table>
<thead>
<tr>
<th>Clinical outcomes*</th>
<th>( N = 150 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean length of stay ± SD, days</td>
<td>8.8 ± 5</td>
</tr>
<tr>
<td>In-hospital death, n (%)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>30-day mortality**, n (%)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Serious adverse events due to device, n (%)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Serious adverse events due to t-PA, n (%)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>IVC filter placed, n (%)</td>
<td>24 (16)</td>
</tr>
<tr>
<td>Major bleeding within 30 days**, n (%)</td>
<td>17 (11.4)</td>
</tr>
<tr>
<td>GUSTO moderate**</td>
<td>16 (10.7)</td>
</tr>
<tr>
<td>GUSTO severe**</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Intracranial hemorrhage, n (%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*All death, serious adverse, and bleeding events were adjudicated by an independent safety monitor.

**\( N = 149 \) (1 patient lost to follow-up)
Conclusions

• Ultrasound-facilitated catheter-directed low-dose fibrinolysis for acute PE improves RV function and decreases pulmonary hypertension and angiographic obstruction.

• By minimizing the risk of intracranial bleed, ultrasound-facilitated catheter-directed low-dose fibrinolysis represents a potential “game-changer” in treatment of high-risk PE patients.
I am Young.. Case of 15 y Girl
Sequence of Events

- Day 0 - admit and CTA
- Day 1 - CDT
- Day 2 - Reangio; further therapy if needed.
- Day 3 - PCU
- Day 4 - Discharge on oral anticoagulation

Bed Rest, 5-7 Days
Heparin/Warfarin

Early Ambulation,
Discharge on Newer
anticoagulants
Is it time to Change our Practice?

**Systemic Thrombolysis**
- Requires high drug doses
- Not locally targeted
- Associated with high levels of bleeding complications

**Endovascular (Catheter-Directed) Targeted Therapy**
- Long treatment times, but targeted and tailored
- Low bleeding complications
- **TO BE DONE IN SURGICAL CENTRES ONLY**
- Efficacious, safe (SEATTLE II)
- ?Cost Effective
Thanks!

From first hospital visit (7\12) to first marathon (1\13)
Thank you, Dr. B., for saving my life and making this all possible.