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
- **Post-Thrombotic Syndrome**: 800,000
- **Death**: 100,000
- **Silent PE**: 1 Million
- **Pulmonary Hypertension**: 30,000

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

Risk Stratification

Massive
- SBP<90mmHg
- P 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

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

Jaff MR Circ 2011;123:1788
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$^{145}$ 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>
</tr>
<tr>
<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
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

Dilated RV

Post Intervention
Ultrasound accelerated thrombolysis

**Mechanism of Action**
- Fibrin separation
- Active drug delivery by acoustic streaming

Ultrasound pulses

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)

CDT+Heparin

Baseline to 24 hrs: 0.30
Baseline to 90 days: 0.38

P<0.0001

Heparin

Baseline to 24 hrs: 0.03
Baseline to 90 days: 0.22

P=0.03
Systolic RV dysfunction

Baseline
24 hrs
90 days

P<0.0001Δ

P=0.003**

**Two-sided exact Mantel-Haenzel test
Δ Wilcoxon rank sum test
## 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</td>
<td>1*</td>
<td>0.49</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3**</td>
<td>1§</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
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>
<thead>
<tr>
<th>Patient Demographics</th>
<th>N = 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, years</td>
<td>59 ± 16.1</td>
</tr>
<tr>
<td>Mean BMI ± SD, kg/m²</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-Procedural RV/LV Ratio: 1.55
- 48 Hours RV/LV Ratio: 1.13

$p < 0.0001$
Outcomes: PA Systolic Pressure

Mean PA Systolic Pressure (mmHg)

- Pre-Procedural: 51.4 mmHg, p < 0.0001
- Post-Procedural: 37.5 mmHg
- 48 Hours: 36.9 mmHg

Comparison: Pre-Procedural vs. Post-Procedural, p < 0.0001
Outcomes: Modified Miller Score

Mean Modified Miller Score

Pre-Procedure: 22.5
48 Hours: 15.8

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
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.