Innovative Endovascular Approach to Pulmonary Embolism by Ultrasound Enhanced Thrombolysis

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Conflict of Interest

• BTG
AC therapy prevents further clot growth

Studies\(^1-3\) found:
- LMWH as effective as UFH in reducing recurrent PE
- LMWH carries reduced bleeding risk compared to UFH

STANDARD OF CARE: usually UFH or LMWH, followed by oral warfarin
- However, AC therapy relies on endogenous t-PA to dissolve occluding clot\(^4\)
  - a process that typically occurs over several weeks or months
  - endogenous fibrinolysis may often be incomplete at the end

• Catheter-based thrombolysis

- Local administration of lytic agent
- Higher local drug concentration results in more rapid and complete thrombolysis
- Even distribution results in faster treatment of thrombus
Why do we treat these patients at all?

<table>
<thead>
<tr>
<th>Massive PE</th>
<th>Submassive PE</th>
<th>Minor/Nonmassive PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Moderate/intermediate risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>- Sustained hypotension (systolic BP &lt;90 mmHg for ≥15 min)</td>
<td>- Systemically normotensive (systolic BP ≥90 mmHg)</td>
<td>- Systemically normotensive (systolic BP ≥90 mmHg)</td>
</tr>
<tr>
<td>- Inotropic support</td>
<td>- RV dysfunction</td>
<td>- No RV dysfunction</td>
</tr>
<tr>
<td>- Pulselessness</td>
<td>- RV dysfunction</td>
<td>- No myocardial necrosis</td>
</tr>
<tr>
<td>- Persistent profound bradycardia (HR &lt;40 bpm with signs or symptoms of shock)</td>
<td>- Myocardial necrosis</td>
<td></td>
</tr>
</tbody>
</table>
Increased RV/LV Ratio and PE-Related Mortality

Rationale for thrombolysis in acute PE

REDUCE THROMBUS BURDEN (not achievable by AC alone)
- Reverse RV afterload / failure toward prevention of haemodynamic collapse
- Improve pulmonary reperfusion/capillary blood flow / gas exchange
- Restore systemic arterial perfusion pressure
- Decrease the risk of developing chronic pulmonary hypertension

100 mg t-PA infused over 2 hours
Indicated for management of acute massive PE in adults:
- For the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs.
- For the lysis of pulmonary emboli accompanied by unstable haemodynamics, e.g., failure to maintain blood pressure without supportive measures.

But the benefit of lysis came at the cost of major bleeds (including ICH)

<table>
<thead>
<tr>
<th></th>
<th>Tenecteplase (n=506)</th>
<th>Placebo (n=499)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes by day 7</td>
<td>12 (2.4%)</td>
<td>1 (0.2%)</td>
<td>0.003</td>
</tr>
<tr>
<td>- Haemorrhagic</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- Ischemic</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events (SAE)</td>
<td>29 (5.7%)</td>
<td>39 (7.8%)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

http://clinicaltrialresults.org/Slides/ACC%202013/Konstantinides_PEITHO_ACC%202013.pdf
Echocardiographic RV/LV ratio $\geq 0.9$ shown to be independent predictive factor of hospital mortality

- Registry of 1,416 patients
- Mortality rate:
  - 1.9% if RV/LV ratio < 0.9
  - 6.6% if RV/LV ratio $\geq 0.9$
Patients with RVD defined as RV/LV >0.9 have a greater chance of adverse events within 30 days.

- Retrospective analysis of 63 patients with chest CT
- Adverse event rate at 30 days:
  - 80.3% if RV/LV ratio > 0.9
  - 51.3% if RV/LV ratio ≤ 0.9

REDUCE THROMBUS BURDEN (not achievable by AC alone)

– Reverse RV afterload / failure toward prevention of hemodynamic collapse
– Improve pulmonary reperfusion/capillary blood flow / gas exchange
– Restore systemic arterial perfusion pressure
– Decrease the risk of developing chronic pulmonary hypertension

• Review of the clinical evidence for EKOS® for the treatment of PE

– ULTIMA trial
– SEATTLE II trial
– Meta-analysis of historical published data
– Recent single-center studies
EkoSonic® Endovascular System

**Features**
- 5.4 Fr catheter
- 106 and 135 cm working length
- 6, 12, 18, 24, 30, 40 and 50 cm treatment zones
EkoSonic® Endovascular System

– Mechanism of action

**How ultrasonic energy unlocks the clot**

– Ultrasonic energy causes fibrin strands to thin, exposing plasminogen receptor sites and fibrin strands to loosen

– Thrombus permeability and lytic penetration are dramatically increased

– Ultrasound pressure waves force lytic agent deep into the clot and keep it there

**Braatan et al. Thromb Haemost 1997;78:1063-8.**

**Francis et al. Ultrasound in Medicine and Biology, 1995;21(5):419-24.**

**Soltani et al. Physics in Medicine and Biology, 2008;53:6837-47.**
• EkoSonic® Endovascular System

Placement in the left and right pulmonary arteries for the treatment of bilateral PE
The Seattle Protocol

CT-confirmed PE
- Symptoms ≤14 days **AND**
- Massive or submassive PE **AND**
- RV/LV diameter ratio ≥0.9

Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis
- tPA 1 mg/h for 24 h (1 device) **OR**
- tPA 1 mg/h for 12 h (2 devices)

TOTAL tPA Dose = 24 mg

Outcomes
- 25% decrease in CT-measured RV/LV diameter ratio over 48 h
- 30% decrease in pulmonary arterial systolic pressure by the end of the procedure
- 30% decrease in pulmonary artery angiographic obstruction over 48 h
- No intracranial hemorrhage

Modified Miller Score

Obstruction Score according CT scan
No Perfusion Scoring, too subjective

Transthoracic Cardiac Echo
end-diastolic right ventricular area on the apical four-chamber image. A ratio of end-diastolic right ventricle area to end-diastolic left ventricle area greater or equal to 0.6 indicated right ventricle dilatation

PA Pressure Measurements
Modified Miller Score  Arterial Obstruction  Right PA

9 Segments:

3 Upper Lobe
2 Middle
4 Lower
Modified Miller Score
Arterial Obstruction left  PA

7 Segmental Arteries

2 Upper Lobe
2 Lingula
3 Lower Lobe

Obstruction 1 Segment = 1 Point

Maximum:  16
SEATTLE II examined EKOS® benefit in a clinical trial setting in the US

Patients
Acute Massive and Submassive PE with RV/LV ratio ≥ 0.9
(n = 150; 22 centers)

Objectives
Evaluate ultrasound-facilitated, catheter-directed low-dose fibrinolysis:
- **Efficacy** - as measured by reduction in RV/LV ratio
- **Safety** - as measured by major bleeding within 72 hours

- Ultrasound-facilitated fibrinolysis using EKOS®
  - If unilateral PE: tPA 1 mg/hr using one device for **24 hours**
  - If bilateral PE: tPA 1 mg/hr per device (using two simultaneously) for **12 hours**
- Follow up at 48 +/- 6 hours
  - CT measurement of RV/LV ratio
  - Echocardiogram to estimate PA systolic pressure

## The SEATTLE II Study

### Patient characteristics and treatment details

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total enrollment</td>
<td>150*</td>
<td>100%</td>
</tr>
<tr>
<td>Massive / Submassive PE</td>
<td>31  / 119</td>
<td>21% / 79%</td>
</tr>
<tr>
<td>History of previous DVT</td>
<td>30</td>
<td>20%</td>
</tr>
<tr>
<td>History of previous PE</td>
<td>15</td>
<td>10%</td>
</tr>
<tr>
<td>Concomitant use of antiplatelet agents</td>
<td>51</td>
<td>34%</td>
</tr>
<tr>
<td>Unilateral / Bilateral PE</td>
<td>20  / 130</td>
<td>13% / 87%</td>
</tr>
<tr>
<td>Total rtPA dose</td>
<td>23.7 ± 2.9 mg</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes 1 patient died prior to treatment

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Reduced RV/LV ratio and Modified Miller Score at 48 hours post-EKOS®

25% decrease in RV/LV ratio over 48 hours

<table>
<thead>
<tr>
<th></th>
<th>Pre-Procedure</th>
<th>48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/LV Ratio</td>
<td>1.55</td>
<td>1.13</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
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</table>

Rapidly relieved pulmonary artery obstruction

<table>
<thead>
<tr>
<th></th>
<th>Pre-Procedure</th>
<th>48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Modified Miller Score</td>
<td>22.5</td>
<td>15.8</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Reduced pulmonary artery pressure immediately post-procedure

Massive and Submassive PE

• Modified Treatment Protocol

20 mg rtPA in 1 PA  or

10 mg rtPA in each PA

Duration: 2 h
Main Differences to Seattle Protocol

- Duration max 2 hours
- 10 mg rTPA per PA
- Maximum Dosage 20 mg rTPA
- No Heparin during Lysis
- If necessary 1 Catheter in each PA
- Endovascular Treatment of DVT as soon as possible

- Miller Score only no Perfusion Index
Pulmonary angiography with a digital subtraction system (GE and Siemens workstation was performed in all patients with a standard Seldinger femoral approach).

The right and the left pulmonary arteries were selectively catheterized.

Angiograms were obtained at a rate of five frames per second after injection of 35-40 mL of 300 mg I/mL Ultravist at a flow rate of 15-20 mL/sec.

A minimum of two selective angiograms (anteroposterior and oblique projections) was obtained per lung.

Measurement of the mean pulmonary arterial pressure was obtained in 50 patients before angiography and before removal of catheter.

Embolism was diagnosed on selective pulmonary angiography if an intraluminal filling defect or a cutoff in a vessel measuring at least 2 mm in diameter was seen.
Massive PE: 21 Patients
Submassive PE: 29 Patients
Duration of Symptoms: 1,8 (0 - 6) Days

- 50 Patients
- Intention to treat 61
- Resuscitations: 3
- 1 PA Catheter: 19
- 2 PA Catheters: 31
- Mortality: 2
- Rejected: 11
- Ven. Asp. Thrombectomy: 14
- Major AE (incl. Bleeding): 1
- V Cava Filter: 1

Thrombectomy was performed after PA Lysis
Sub Massive PE

- 59 years old female patient
- Left Iliac vein Thrombosis
- RV / LV Ratio: 1,4
- EKOS, Venous Aspiration Thrombectomy
Massive PE

- 85 year old female Patient
- DVT: Left Iliac Vein, Femoral Vein
- Massive PE
- CARDIO – Pulmonary Arrest
- EKOS bilateral PA Catheters
- RV / LV Ratio: 1,5
- Discharged after 9 days
- RV / LV Ratio: 0,9
Anticoagulation

- IV unfractionated Heparin aPTT 60-80 sec
- No Heparin during Lysis
- Post intervention full heparinization
- Coumadine or NOAC for 6 months
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>61</td>
<td>(19 - 86)</td>
</tr>
<tr>
<td>Body mass index kg/m</td>
<td>2.24 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>(60%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>29</td>
<td>(58%)</td>
</tr>
<tr>
<td>Antiplatelet medications</td>
<td>18</td>
<td>(36%)</td>
</tr>
<tr>
<td>Immobility within 30 days of PE</td>
<td>29</td>
<td>(58%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19</td>
<td>(38%)</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>16</td>
<td>(32%)</td>
</tr>
<tr>
<td>Active tobacco use</td>
<td>18</td>
<td>(36%)</td>
</tr>
<tr>
<td>Active infection within 30 days of PE</td>
<td>6</td>
<td>(12%)</td>
</tr>
<tr>
<td>Atherosclerotic cardiovascular disease</td>
<td>21</td>
<td>(42%)</td>
</tr>
<tr>
<td>Previous PE</td>
<td>12</td>
<td>(24%)</td>
</tr>
</tbody>
</table>
Modified Protocol - Preliminary Results

- Only 8 patients (16%) treated in ICU
- 84% treated in Intermediate Care Unit or Recovery Room
- Only 1 minor Bleeding Complications
RV / LV Ratio n = 50
More than 50% complete Thrombus Resolution in half of all patients yet significant drop in PA pressure.

Significant improvement of RV/LV Ratio
Seattle II
Major Bleeding within 30 days: 15 patients (10%)
(only 1 severe)
Intracranial Hemorrhage: 0

Modified Protocol:
Major Bleeding: 1 Patient (2%)
unclear, requiring 2-U PRBCs

No Difference between Massive and Submassive PE
Mortality

• No patient died after discharge (Mean Follow up 13 months)
• 3 Patients were treated with CPR

3 → 2 died during CPR → 1 Lysis could be completed
Advantages of a modified Protocol

• Less logistical efforts required, because of fast track protocol

• No Intensive Care resources necessary. Lower dependency unit is sufficient.

• No Heparin during ultra sound assisted lysis further reduces risk of bleeding complications

• Faster hospital discharge possible
Conclusion

• Ultrasound-facilitated low-dose fibrinolysis for acute PE improves RV function and decreases pulmonary hypertension.
• By minimizing the risk of intracranial bleed, it represents a potential “game-changer” in the treatment of high-risk PE patients.
• The modified protocol further reduces the risk of bleeding.
• Less ICU capacity is required.
• Results are comparable to Seattle Protocol
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