Incidence and Treatment of PE – generated right heart strain in DVT patients

Prof. Ralf R. Kolvenbach MD,PhD,FEBVS
• PE patient population profile

Massive PE [High risk]
5% PE population
58% mortality @ 3 months

Submassive PE [Moderate / Intermediate risk]
40% PE population
21% mortality @ 3 months

Minor PE [Low risk]
55% PE population
Good prognosis
Low mortality rate

Patient risk stratification (per AHA Scientific Statement 2011)

<table>
<thead>
<tr>
<th>Massive PE</th>
<th>Submassive PE</th>
<th>Minor/Nonmassive PE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td><strong>Moderate/intermediate risk</strong></td>
<td><strong>Low risk</strong></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>- <strong>RV dysfunction</strong></td>
<td>- No RV dysfunction</td>
</tr>
<tr>
<td>- Pulselessness</td>
<td>- Myocardial necrosis</td>
<td>- No myocardial necrosis</td>
</tr>
<tr>
<td>- Persistent profound bradycardia (HR &lt;40 bpm with signs or symptoms of shock)</td>
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</tbody>
</table>

**RV dysfunction**
- RV/LV ratio > 0.9 or RV systolic dysfunction on echo
- RV/LV ratio > 0.9 on CT
- Elevation of BNP (>90 pg/mL)
- Elevation of NTpro-BNP (>500 pg/mL)
- ECG changes:
  - new complete or incomplete RBBB
  - anteroseptal ST elevation or depression
  - anteroseptal T-wave inversion

The presence of RV hypokinesis was associated with a 57% higher mortality rate at 3 months even though most of the patients (88.9%) were haemodynamically stable.

An RV:LV >0.9 was shown to be an independent predictor of mortality.

Mortality risk increased with stepwise increase in RV:LV.

PE pts with RV enlargement had a significantly higher chance of adverse events within 30 days.

The significance of RV dysfunction.

The significance of RV dysfunction

- PE pts with RVD which wasn’t resolved prior to discharge were 8-times more likely to have a recurrent VTE and had 4-times the mortality rate than patients whose RVD was resolved prior to discharge.

- Patients that presented with acute PE and elevated RV pressures treated with heparin alone have worsening elevated RV Pressures, as well as dyspnea at rest or exercise intolerance at six months.
• Adoption of IV thrombolysis hampered by elevated risk of severe bleeds

– 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
Adverse outcomes associated with RVD

Echocardiographic RV/LV ratio ≥ 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 ≥ 0.9
- Adverse outcomes associated with RVD

PE-related mortality risk increases with stepwise increase in RV/LV Ratio

- Retrospective analysis of 120 patients with haemodynamically stable PE based on chest CT

- PE-related mortality at 3 months:
  - 17% if RV/LV ≥ 1.5
  - 8% if 1.0 ≤ RV/LV < 1.5
  - 0% if RV/LV < 1.0

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
• Adverse outcomes associated with RVD

Presence of RV hypokinesis associated with 57% increase in mortality rate at 3 months

Prospective study of 2,454 consecutive PE patients at 52 hospitals in 7 countries

Mortality rate at 3 months:
- 21% with hypokinesis
- 15% with no hypokinesis
• Adverse outcomes with unresolved RVD

PE patients with RVD unresolved exhibit 4x increased incidence of mortality compared to those with RVD resolved at discharge

- Retrospective analysis of 301 patients with first episode PE with mean f/u at 3.1 years

- Mortality rate at f/u:
  - 10.2% if RVD unresolved at d/c
  - 2.3% if RVD resolved at d/c

Grifoni et al. Arch Intern Med 2006; 166:2151-2156
Catheter Directed Thrombolysis: The Magic Bullet for Submassive Pulmonary Embolism?
• 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
• Standard PE therapy

ANTICOAGULATION (AC) – HEPARIN
– 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

• IV thrombolysis with t-PA

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
• 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
**Fibrin Separation**

Non-cavitational ultrasound separates fibrin without fragmentation of emboli

**Active Drug Delivery**

Drug is actively driven into clot by “Acoustic Streaming”

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• 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

• EkoSonic® Endovascular System

Placement in the left and right pulmonary arteries for the treatment of bilateral PE
• Greater RVD reduction with EKOS® with tPA + heparin than with heparin alone

### RV/LV Ratio Significantly Improved at 24 Hours

<table>
<thead>
<tr>
<th>RV/LV Ratio</th>
<th>Baseline</th>
<th>24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKOS® with tPA + Heparin</td>
<td>1.28</td>
<td>0.99</td>
</tr>
<tr>
<td>Heparin</td>
<td>1.20</td>
<td>1.17</td>
</tr>
</tbody>
</table>

- P < 0.001
- P = 0.31

### Reduction in RV/LV Ratio Significantly Greater at 24 Hours and Improved at 90 Days

<table>
<thead>
<tr>
<th>Reduction in RV/LV Ratio</th>
<th>Baseline to 24 hrs</th>
<th>Baseline to 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKOS® with tPA + Heparin</td>
<td>0.30</td>
<td>0.35</td>
</tr>
<tr>
<td>Heparin</td>
<td>0.03</td>
<td>0.24</td>
</tr>
</tbody>
</table>

- P < 0.001
- P = 0.07

*Kucher et al. Circulation. 2014;129:479-486*
• Reduced pulmonary artery pressure immediately post-procedure

• 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


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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></td>
<td>23.7 ± 2.9 mg</td>
</tr>
</tbody>
</table>

* Denotes 1 patient died prior to treatment

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

- Reduced pulmonary artery pressure immediately post-procedure
• Zero cases of intracranial hemorrhage reported in the study

<table>
<thead>
<tr>
<th>Clinical outcomes*</th>
<th>N = 150</th>
</tr>
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<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)


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- Metaanalysis showed consistent recovery of hemodynamics among patients treated using EKOS®

Single center experience showed CTA evidence of RVD resolution

- Single center retrospective single arm study
- 24 patients with high risk (n=5) or intermediate risk (n=19) PE treated with EKOS®
- Mean rtPA dose was 33.5±15.5 mg over 19.7 hours

<table>
<thead>
<tr>
<th></th>
<th>Pre-EKOS®</th>
<th>Post-EKOS®</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/LV ratio</td>
<td>1.33 ± 0.24</td>
<td>1.00 ± 0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Modified Miller Score</td>
<td>17.8 ± 5.3</td>
<td>8.7 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- No deaths or systemic bleeding complications, including intracranial haemorrhage; 4 access site bleeds requiring transfusion

• Modified Treatment Protocol

Initial Injection 5 mg rtPA

20 mg rtPA in 1 PA or

10 mg rtPA in each PA

Duration: 2 h
Sub Massive PE
59 years old female patient

Left Iliac vein Thrombosis

RV / LV Ratio: 1,4

Ekos, Venous Aspiration Thrombectomy
Massive PE

87 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
<table>
<thead>
<tr>
<th>Massive PE:</th>
<th>8  Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submassive PE:</td>
<td>15 Patients</td>
</tr>
<tr>
<td>Duration of Symptoms:</td>
<td>2,2 (0 -6) Days</td>
</tr>
</tbody>
</table>

- 23 Patients
- Intention to treat: 22
- Resuscitations: 2
- 1 PA Catheter: 12
- 2 PA Catheters: 9
- Mortality: 1
- Rejected: 1
- Ven.Thrombectomy: 4
- Major AE (incl. Bleeding): 0
- V Cava Filter: 1
Modified Protocol

• Only 2 (8.6%) patients treated in ICU

• 91% treated in Intermediate Care Unit or Recovery Room

• No Bleeding Complications

• No Access Site Complications
50 % Thrombus Resolution in half of all patients yet significant drop in PA pressure.

Sometimes Less is More in high risk patients!

- PA Pressure
  Before
  After
• Summary

- RV dysfunction in PE patients predicts poor outcomes:
  - Mortality
  - Adverse events
  - VTE recurrence
- Anticoagulant therapy does not actively resolve the existing thrombus
- IV thrombolysis is not used broadly:
  - Clinical data show improvement in hemodynamics,
  - but it carries an elevated risk of severe bleeding, including ICH
• Summary

- Consistent EKOS® results among the various published studies:
  - Restoration of hemodynamics as evidenced by a reduced RV/LV ratio and decreased PA pressure
  - Resolution of pulmonary artery obstruction
  - Favorable outcomes with low dose thrombolysis (20-24 mg tPA based on the clinical trials)
  - No reports of intracranial hemorrhage in published clinical studies
RV dysfunction in PE patients predicts poor outcomes:
- Mortality
- Adverse events
- VTE recurrence

IV thrombolysis is not used broadly:
- Clinical data show improvement in haemodynamics,
- but it carries an elevated risk of severe bleeding, including ICH

Clinical data establish the evidence for EKOS® in massive and submassive (intermediate risk) PE

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