CATHETER-DIRECTED TREATMENT OF PULMONARY EMBOLISM: Where are we in 2015?

Critical Care Medicine San Francisco

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DISCLOSURES

- Consultant, AngioDynamics (AngioVac)

CASE 1: Acute chest pain
PEA arrest in ambulance, now hypotensive requiring pressor support

CASE 2: Acute dyspnea
Hemodynamically stable, O2 92% 10L HFNC.
RV volume severe ↑, severe ftnt ↓, PASP > 60
Troponin 0.06
OUTLINE

- What are catheter-directed therapies for PE?
- Why consider CDT for PE?
- What data exists for CDT in 2015?

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- Why consider CDT for PE?
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The Simple: Drip Thrombolysis

The Simple (2): Ultrasound-Accelerated Thrombolysis (EKOS)
The Advanced: Fragmentation

Rotating Pigtail Catheter
Angioplasty Balloon
Trerotola Device

BEFORE CDT

AFTER CDT
The Exotic?: Aspiration Embolectomy

22F coil-reinforced cannula

Designed with a balloon actuated, expandable funnel shaped distal tip

OUTLINE

• What are catheter-directed therapies for PE?

• Why consider CDT for PE?

• What data exists in 2015?
Not all PE are the same...

• 530,000 symptomatic PE annually in U.S.
• 300,000 deaths from PE annually in U.S.

• Acute PE with hemodynamic shock: 30-60% mortality
  – Most deaths within 1 hour of presentation

Heit JA et al. Blood 2005; 106:267a
Wood KE. Chest 2002; 121:877-885

Case 1: Massive PE

GOAL OF THERAPY:
Save this patient’s life!

PEA arrest in ambulance, now hypotensive requiring pressor support

Massive PE: ACCP Guidelines

3.6.1.1. In patients with acute PE associated with hypotension (eg, systolic BP <90 mm Hg) who do not have a high risk of bleeding, we suggest systematically administered thrombolytic therapy over no such therapy (Grade 2C).
Massive PE -> Why consider CDT?

1. Contraindication to IV tPA in up to 50% of patients
2. Insufficient time for IV tPA (2 hr infusion)
3. Improved tPA admixture with thrombus = improved thrombolysis?


Complications from Systemic Thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Major Hemorrhage</th>
<th>Intra-Cerebral Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute PE</td>
<td>21.7%</td>
<td>3%</td>
</tr>
<tr>
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<td>19.2%</td>
<td>5%</td>
</tr>
<tr>
<td>Acute PE</td>
<td>11.5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Kearon C et al. CHEST 2012; 141(2) (Suppl):e419S-e494S.

Hemodynamically stable, O2 92% 10L HFNC. RV volume severe ↑, severe ftn ↓, PASP > 60
Troponin 0.06

CASE 2: Submassive PE

Massive PE: ACCP Guidelines

February 2012

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

5.1. In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (e.g., within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).
Not all PE are the same...

- 530,000 symptomatic PE annually in U.S.
- 300,000 deaths from PE annually in U.S.

**Acute PE, hemodynamically stable:**
- Right ventricular dysfunction on echo: ↑ Mortality
- Elevated troponin: ↑ Mortality
- Elevated BNP: ↑ Risk adverse in-hospital outcome

Heit JA et al. Blood 2005; 106:267a
Wood KE. Chest 2002; 121:877-886
Sapioff EJ. N Engl J Med 2003; 349:2648-54

CASE 2: Submassive PE

**GOAL OF THERAPY:** Prevent death

Hemodynamically stable, O2 92% 10L HFNC.
RV volume severe ↑, severe fn ↓, PASP > 60
Troponin 0.06

Submassive PE -> Why CDT instead of systemic thrombolysis?

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<td>Goldhaber et al. Lancet 1999; 353:1386-89.</td>
<td>21.7%</td>
<td>3%</td>
</tr>
<tr>
<td>Fiumara et al. Am J Cardiol 2006; 97:127-129.</td>
<td>19.2%</td>
<td>5%</td>
</tr>
<tr>
<td>Meyer et al. N Engl J Med. 370;15:1402-1411</td>
<td>11.5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Systemic Thrombolysis for Submassive PE

**PEITHO Trial (2014)**

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism
Gar Mess, M. N ENGL J MED 2014; 370:15:1402-1411

**Multicenter double-blinded RCT of systemic lysis (TNK) versus placebo + heparin in acute HD stable PE with RV strain and troponin elevation (n=1086)**

**Primary outcome:** Death or hemodynamic decompensation (or collapse) within 7 days after randomization

5/9/2015
Submassive PE -> But why CDT?

PEITHO Trial (2014)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treated (n=505)</th>
<th>Placebo (n=506)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>6 (2.2)</td>
<td>11 (3.8)</td>
<td>0.48 (0.23-1.00)</td>
<td>0.07</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>6 (2.2)</td>
<td>9 (3.0)</td>
<td>0.63 (0.33-1.25)</td>
<td>0.40</td>
</tr>
<tr>
<td>Hemorrhagic decompenlation</td>
<td>6 (2.2)</td>
<td>10 (3.3)</td>
<td>0.63 (0.34-1.14)</td>
<td>0.10</td>
</tr>
<tr>
<td>Time between randomization and death</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>1.00 (0.26-3.70)</td>
<td>0.99</td>
</tr>
<tr>
<td>Recurrent pulmonary embolism between randomization and day 1</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1.00 (0.26-3.70)</td>
<td>0.99</td>
</tr>
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</table>

Submassive PE: ACCP Guidelines

February 2012 Supplement

Arterial Thrombotic Therapy for VTE Disease

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

5.6.1.2. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1C).

5.6.1.3. In selected patients with acute PE not associated with hypotension and with a low risk of bleeding 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).
CASE 2: Submassive PE

GOAL OF THERAPY: Prevent death AND...

Hemodynamically stable, O2 92%, 10L HFNC. RV volume severe ↑, severe ftn ↓, PASP > 60. Troponin 0.06

What is the natural history of survivors of submassive PE?

DIVIDED PATIENTS:
Group 1: RV-A and PASP ≤ 30 mmHg
Group 2: RV-B or PASP > 30 mmHg

44%

RVSP ≥ 40 mmHg: 35% @ entry -> 7% @ 6 months
RVSP INCREASED in 27% of patients
46% of these patients with NYHA ≥ 3 or exercise intolerance at 6 months
CASE 2: Submassive PE

GOAL OF THERAPY:
Prevent death and limit long-term cardiopulmonary morbidity?

RV volume severe ↑, severe ftn ↓, PASP > 60 Troponin 0.06

Submassive PE -> But why CDT?

TOPCOAT Trial (2014)

Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial

Multicenter double-blinded RCT of tenecteplase versus placebo + anticoagulation in acute HD stable PE with RV strain on basis of RV hypokinesis or elevated troponin or BNP (n=83)

End-point: Composite of survival without need for life-supporting interventions in hospital/follow-up and good functional capacity at 90 days (normal RV FTN, NYHA < 3, adequate 6-minute walk test tolerance)

59% reduction in composite outcome 37% placebo versus 15% tenecteplase 1 patient (2.5%) who received TNK suffered fatal ICH at 5 days.

"The main drivers of this effect were the composite endpoint of impaired functional capacity and a low self-assessment of physical wellness from the SF-36 measured 3 months after PE diagnosis."

OUTLINE

- What are catheter-directed therapies for PE?
- Why consider CDT for PE?
- What data exists for CDT in 2015?
CDT for Massive PE

- Meta-analysis of global data
- 594 patients treated with “modern” CDT
- All hemodynamically unstable

The pooled clinical success rate from CDT was 86.5% [82.1% - 90.2%].

CDT for Massive PE

- “Clinical success”
  - Stabilization of hemodynamics
  - Resolution of hypoxia
  - Survival from massive PE

<table>
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<tr>
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<th>Major Complications</th>
<th>Cerebral Hemorrhage</th>
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<tr>
<td>Modern CDT</td>
<td></td>
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<tr>
<td>Meta-Analysis 2009</td>
<td>2.4% [1.9% to 4.3%]</td>
<td>&lt;0.2%</td>
</tr>
<tr>
<td>n = 594 (all HD unstable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic tPA</td>
<td>21.7% (66/304)</td>
<td>3% (9/304)</td>
</tr>
<tr>
<td>ICOPER 1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 304 (≤1/3rd HD unstable)</td>
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</table>
ULTIMA Trial (2014)

Randomized, Controlled Trial of Ultrasound-Accelerated Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism
Silas Kallans, Peter Bechgaard, Oliver I. Miller, Christina Keating, Jon Byron Wenzelof, Thomas Hutton, Uthita Talal, Jon Haacktke, Ralf Miller, Devra Biro, Maria Gelf, Philipp Lange, Ralf Thomas, Bullova, Sebastian Rehly, Astrid Barut, Dari Breslau, Benjamin Grotte, Klaus Eifaz and Ines Hamann

Multicenter RCT comparing ultrasound-accelerated catheter-directed thrombolysis + anticoagulation versus anticoagulation alone in the treatment of acute PE with RV/LV ≥ 1.0 by echocardiography (n=59)

Primary outcome: Change in RV/LV ratio from baseline to 24 hours.

CDT for Submassive PE

ULTIMA Trial (2014)

Multicenter single-arm trial of ultrasound-accelerated thrombolysis + anticoagulation for massive and submassive PE (RV/LV > 0.9 by CT) (n=150)

- 21% of patients had massive PE

End-point: RV/LV ratio and PA pressure (echo) at 48 hours
CDT for Massive and Submassive PE

Seattle II Trial (presented at ACC 2014, publication pending)

PERFECT Registry – Kuo WT et al CHEST. 2015 Apr 9

- Multicenter registry (7 sites) evaluating results of CDT for acute PE in 101 consecutive patients receiving CDT
  - Massive PE n = 28
  - Submassive PE n = 73

- Technique
  - Massive PE: immediate mechanical or pharmacomechanical thrombectomy +/- subsequent infusion thrombolysis
  - Submassive PE: infusion thrombolysis only
    - If thrombolytic infusion, therapeutic anticoagulation suspended with low-dose heparin (300-500 U/hr) only through sheath
    - 64% standard infusion catheters, 36% USAT
  - IVC filter placed in 64%

CDT for Massive and Submassive PE

PERFECT Registry – Kuo WT et al CHEST. 2015 Apr 9

- CLINICAL SUCCESS (meet all 3)
  - Stabilization of hemodynamics – prevention/resolution hemodynamics shock with no need for pressor support
  - Improvement in PA HTN and/or R heart strain
  - Survival to hospital discharge

- RESULTS
  - Massive PE: 85.7% (24/28) clinical success (4 deaths from PE)
  - Submassive PE: 97.3% (71/73) clinical success (2 deaths from PE)
  - Mean PA 51.17 +/- 14.06 mmHg > 37.23 +/- 15.81 mmHg (improved in 84.8% of 92 patients where measured)
  - RV strain improved in 89.1% of 64 patients with f/u echo

- COMPLICATIONS
  - No major hemorrhage, ICH, or procedure-related complications

Conclusions:

- Risk stratification of acute pulmonary embolism is critical to determining prognosis and guiding therapy
- Patients with massive PE have high mortality rates and should receive systemic thrombolytic therapy if possible
  - CDT should be strongly considered if systemic thrombolytic contraindication, failure, or insufficient time to work
Conclusions:

- Patients with **submassive PE** have increased mortality rates and some may have significant intermediate term cardiopulmonary morbidity
  
  - Given the **risk of ICH with systemic thrombolysis**, this therapy should be used with **caution in this population**
  
  - CDT **MAY** confer the benefits of systemic thrombolysis with significantly lower risk of ICH
    
    - Current data are promising but insufficient