Management of Sub-Massive Pulmonary Embolus
The Controversy

Mitchell J Silver DO FACC
Director, Center for Critical Limb Care
Riverside Methodist Hospital
Columbus, Ohio
Associate Professor Cardiovascular Medicine
Ohio University Heritage College of Medicine
Athens, Ohio
Case # 1

- 60 year old female
- Presents with 1 hour of chest pain, diaphoresis
- PMH: Hypertension, Tobacco abuse, Brother MI age 58
- Physical Exam: BP 126/88  HR 96  Clear Lungs
- Killip Class 1
- EKG: 5 mm ST elevation Leads II, III, AVF
The Facts

• The mortality of an Inferior Wall STEMI treated with systemic thrombolysis is 3 – 5 %.

Topol E. Textbook of Int Card; 3rd ed
Case # 2

- 60 year old female, PMH: obesity, diabetes, borderline HTN
- Presents with Chest Pain, Dyspnea, 2 hour duration
- Returned from Europe via plane 2 days ago
- In Bed with “flu” since trip
- Physical exam: BP 106/60 HR 132 Dyspnea with talking
- CTA chest: Large Saddle PE
The Facts

• Approximately 20% of patients with PE die before diagnosis or on the first day after diagnosis.

• For those surviving more than one day, up to 11% may die in the first three months, even with “adequate” therapy.

PE Mortality (ICOPER)


All comers - Lytic and no Lytic

*62.5% from recurrent PE

52.4%

14.7%
Venous Thrombosis
A Leading Cause of Death in the US

- VTE kills 4 to 5 times more people annually than breast cancer\(^1,2\)
- Pulmonary embolism is the cause of death in ~200,000 patients per year in the US\(^1\)
- In-hospital case fatality rate of VTED\(^1\) = 12%
- PE: 1-year mortality rate of 39% in the elderly\(^3\)
- DVT: 1-year mortality rate of 21% in the elderly\(^3\)

PE may be the #1 preventable cause of death in hospitalized patients\(^4\)
Massive PE is *Bad*

- Hemodynamic instability
- Right heart strain marker of increased risk of death from PE
  - 13% in-hospital mortality right heart strain vs 0.9% without\(^1\)
  - 6-fold increase in-hospital death\(^2\)
- 44% in-hospital mortality with elevated cardiac troponin T\(^3\)

Results concluded from fatal pulmonary emboli recorded in general surgery, orthopedic, infectious disease, internal medicine, and oncology patients.

Submassive PE

- Is there a role for systemic thrombolysis for sub-massive PE?
- Should sub-massive PE be treated more aggressively?
What is the Dose of IV tPA?

- Guidelines Recommend:

- IV tpa **100 mg** over a 2 hour continuous infusion.....
A Major Disadvantage of Systemic Dosed “IV tPA” is: BLEEDING
# Thrombolysis Bleeding Risk: Controlled Trials

Adapted from Konstantinides

<table>
<thead>
<tr>
<th>Thrombolytic</th>
<th>Major</th>
<th>Intracranial / fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (vs. heparin)</td>
<td>37/82</td>
<td>1/82</td>
</tr>
<tr>
<td>UK vs. SK (no heparin group)</td>
<td>32/113</td>
<td>0/113</td>
</tr>
<tr>
<td></td>
<td>12/54</td>
<td>0/54</td>
</tr>
<tr>
<td>rtPA (vs. heparin)</td>
<td>0/33</td>
<td>0/33</td>
</tr>
<tr>
<td>rtPA (vs. heparin)</td>
<td>4/20</td>
<td>2/20</td>
</tr>
<tr>
<td>rtPA vs. UK (no heparin group)</td>
<td>7/34</td>
<td>1/34</td>
</tr>
<tr>
<td></td>
<td>8/29</td>
<td>1/29</td>
</tr>
<tr>
<td>2 rtPA regimens (no heparin group)</td>
<td>0/53</td>
<td>0/53</td>
</tr>
<tr>
<td>rtPA vs. UK (or vs. heparin)</td>
<td>—</td>
<td>6/312</td>
</tr>
<tr>
<td>rtPA (vs. heparin)</td>
<td>1/118</td>
<td>0/118</td>
</tr>
</tbody>
</table>

| Overall                        | 101/536 (19%) | 11/536 (2.0%) |

Adapted from Konstantinides
Thrombolysis Bleeding Risk: Registries/Retrospective Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Thrombolytic</th>
<th>Major</th>
<th>Intracranial / fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPPET 1997</td>
<td>registry</td>
<td>various</td>
<td>37/169</td>
<td>2/169</td>
</tr>
<tr>
<td>Meyer 1998</td>
<td>retrospective</td>
<td>rtPA</td>
<td>33/132</td>
<td>2/132</td>
</tr>
<tr>
<td>ICOPER 1999</td>
<td>registry</td>
<td>various</td>
<td>66/304</td>
<td>9/304 (3%)</td>
</tr>
<tr>
<td>Hamel 2001</td>
<td>registry</td>
<td>various</td>
<td>6/64</td>
<td>3/64</td>
</tr>
</tbody>
</table>

142/669 (21.2%)  16/669 (2.4%)

Adapted from Konstantinides
Pharmacology 101
The Larger the Dose – The Higher the Risk
What about Efficacy?
Meta-Analysis of 13 randomized trials of thrombolytic therapy vs anticoagulation alone.

No significant reduction in recurrent PE or death with thrombolytic therapy.

Alteplase treatment was associated with a significantly higher rate of hemorrhage than anticoagulation alone.

Neither recurrent PE nor death was significantly different in the alteplase versus placebo groups.
Thrombolytic Therapy for Pulmonary Embolism

Meta-analysis of 8 randomized trials (679 pts); stable pts with acute PE who received thrombolysis followed by heparin were compared to those who received heparin alone. No statistically significant differences between Rx groups in terms of:

- **Mortality:** OR 0.89; 95% CI 0.45-1.78
- **Recurrent PE:** OR 0.63; 95% CI 0.33-1.20

Dong et al. *Cochrane Database Syst Rev* 2006; CD004437
Thrombolytic Therapy for Pulmonary Embolism

- 256 pts. Randomized. Sub-Massive PE
- Systemic tPA vs anticoagulation
- Primary endpoint
  - In-hospital death or clinical deterioration requiring treatment escalation
    - Risk of In-hospital death similar
    - 3.4% tPA vs 2.2% anticoagulation
    - Primary endpoint was reached, but driven by less treatment escalation with tPA not death.

Konstantinides NEJM 2002
PEITHO Trial – ACC 2013

- Randomized double blind
- 1006 patients
- Evaluated efficacy and safety of single IV bolus TNK vs anticoagulation in normotensive PE patients

- Primary endpoint:
  - Death from any cause
  - Circulatory collapse
Results:

- “It’s a wash”......
- The benefits of TNK equals risks from bleeding

- Primary endpoint decreased by 56% with TNK
- Major bleeding significant with TNK (6.3 vs 1.5 %)
  - 10 hemorrhagic strokes with TNK
  - 1 hemorrhagic stroke with anticoagulation alone
Systemic Thrombolysis – Real World

- Systemic thrombolysis has absolute and relative contraindications.
- Up to 2/3 of patients with PE do not receive therapy due to contraindications.
- In patients without contraindications, up to 20% major hemorrhagic complications and 3 – 5% of intracranial bleeds have been reported.

Goldhaber ICOPER 1999
Fiumara Am J Card 2006
So Why Interventional Therapy for PE?

- Total dose of thrombolytic agent much less
- Catheter directed therapy much more efficient
- More rapidly restores systemic perfusion
- Access to IVC allows placement of IVC filters to prevent recurrent PE
EKOS - Ultrasound Accelerated Catheter-Directed Lysis
Ultrasound Accelerated Thrombolysis

EKOS EkoSonic® Mach 4e Endovascular System

- Infusion side-hole catheter with a multi-element ultrasound core
- 12 cm nominal treatment zone length typically used for PE therapy
EKOS Technology

Microsonic energy breaks the fibrin strands making the thrombus more permeable to the thrombolytic drug.
Ultrasound Accelerated Thrombolysis

Mechanism of Action

Ultrasound pulses

Fibrin separation

Active drug delivery by acoustic streaming

Ultrasound is delivered at a basic frequency of 2.2 MHz. The pulse frequency, pulse amplitude and pulse width vary in a randomized fashion.

Fibrin without Ultrasound

Fibrin With Ultrasound

EKOS Technology

Pre EKOS PA 75/30

Post EKOS PA 33/15
ULTIMA Trial
Ultrasound Assisted Thrombolysis

• Randomized, controlled study comparing EKOS EkoSonic Ultrasound Accelerated thrombolysis to anticoagulation in the treatment of Sub-Massive PE
• 59 pts  30 EKOS  29 Anticoagulation
• tPA dose = 20 mg
• All pts RV/LV end diastolic ratio > 1

Kucher  ACC March 2013
ULTIMA Trial
Ultrasound Assisted Thrombolysis

• Results:
  • RV/LV ratio improvement at 24 hours
    – EKOS improved by an average of 23%
    – Anticoagulation improved by an average of 3%
  • RV/LV ratio improvement at 90 days also significantly improved with EKOS (p<.0001)
  • NO serious bleeding in either group.

Kucher  ACC March 2013
SEATTLE 2 TRIAL

- 150 Patients who had proximal pulmonary embolism, with submassive or massive pulmonary embolism (21%).
- Right ventricular enlargement on chest CT defined as a right ventricular (RV) to left ventricular (LV) ratio of at least 0.9.

Piazza G. ACC 2014
SEATTLE 2 TRIAL

- Patients underwent ultrasound-facilitated fibrinolysis for either unilateral or bilateral pulmonary embolism.
- Mean total dose 24 mg tPA.
- At 48 hours, measured the change in RV:LV diameter ratio with CT scan – and measured pulmonary artery systolic pressures using echocardiography.

Piazza G.  ACC 2014
SEATTLE 2 TRIAL

- The procedure itself was able to be completed successfully 98% of the time.
- 86% of patients had bilateral disease.
- The RV:LV ratio decreased by 30% from the start of the procedure to when the 48-hour CT scan was performed.

Piazza G.  ACC 2014
SEATTLE 2 TRIAL

- Pulmonary artery systolic pressures decreased by 30% from the start of the procedure to the completion of the procedure.
- Submassive and massive pulmonary embolism patients showed no difference in response.
- The pulmonary artery angiographic obstruction score (the modified Miller index) also decreased by 30% from before the procedure to after.

Piazza G.  ACC 2014
SEATTLE 2 TRIAL

- Intracranial hemorrhage rate = 0 with catheter based therapy.

- Systemic fibrinolysis and full-dose tPA (100 mg over 2 hours) showed a 2.5%-3% rate of intracranial hemorrhage.

Piazza G. ACC 2014
Should We Treat Submassive PE More Aggressively?
Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism

- 200 patients with submassive PE
- All treated with anticoagulation
- 21/200 received thrombolysis due to worsening clinical status
- Baseline RVSP measured in all patients
- 6 month F/U of RVSP, NYHA class, and 6 min walk test

Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism

- RVSP was higher than baseline in 27% who received anticoagulation alone at 6 months.
- 46% of these pts had a NYHA class > 3 and poor 6 minute walking distance at 6 months.
- The RVSP at follow-up was not higher than at the time of diagnosis in any of the thrombolytic patients.

- Six months after experiencing submassive PE, a significant proportion of patients had echocardiographic and functional evidence of pulmonary hypertension.

Should We be More Aggressive in Patients with Sub-Massive PE?

- 209 consecutive patients with PE
  - Shock or cardiac arrest: 13%
  - Hypotension without shock: 9%
  - Normotensive without RVD: 47%
  - Normotensive with RVD: 31%

- 10% who were normotensive with RVD deteriorated, and 50% died.

Grifoni S. Circulation 2000:101;2817-2822
Environment = Treatment Choice
Conclusion

- Ultra Sound Accelerated Thrombolysis should be considered in the appropriate patient with submassive PE.
RMH Experience
Low Dose Catheter Directed Thrombolysis and Removable IVC filter

- **N = 98 patients in last 3 years**
  - High risk markers, echo, troponin, BNP
  - Take from ER if saddle and evaluate in cath lab
  - Ultrasound guided access of vein
  - Single bolus TNK into PA
  - Pulm pressures evaluated after IVC filter placement

- **Evaluated all patients under the age of 80**
  - 97% 30-day survival (2 deaths; Both pts brought to lab with CPR)
  - 1 pt went on to surgical embolectomy at 3 months
  - On going evaluation of functional status and PA pressures
  - 88% IVC filter removal rate
So Why Interventional Therapy for PE?

- Total dose of thrombolytic agent much less
- Catheter directed therapy much more efficient
- Thrombectomy (when needed) more rapidly unloads RV and restores perfusion to lungs
- More rapidly restores systemic perfusion
- Access to IVC allows placement of IVC filters to prevent recurrent PE
Systemic IV tPA for Submassive Pulmonary Embolus: *Con*
Acknowledgement

• Yes, we do have limited prospective, randomized data for endovascular management of sub-massive PE

• But,
  – Evolving device technology
  – Evolving pharmacology/drug therapy
  – Maturing operator experience and skill set
Acknowledgement

- This presentation on management of PE was outside of current published guidelines and is academic only in content.

- We may be seeing a transition from how we treat pulmonary embolism that is similar to what we saw with STEMI. First using systemic fibrinolysis for STEMI and then with greater experience in the cath lab, moving to an interventional approach.