Clinical Controversy: tPA Use in Cardiac Arrest
OSHP Annual Meeting
April 2015

Sarah A. Day, Pharm.D., BCPS
Clinical Pharmacist, Critical Care
OhioHealth Doctors Hospital
Objectives

• Review current literature regarding the use of tPA in cardiac arrest secondary to suspected pulmonary embolism (PE)
• Discuss outcomes, risks, benefits, and optimal dosing strategy of tPA in cardiac arrest
Disclosure

- No potential conflicts of interest to disclose
Situation
OhioHealth

- 11 hospitals and many care sites
- 5 central Ohio hospitals
  - OhioHealth Riverside Methodist Hospital – Neuroscience Center
  - OhioHealth Grant Medical Center – Level 1 Trauma Center

The Instigating Request

• Pulmonologist/Intensivist request for tPA to be readily available during in-hospital cardiac arrest due to suspected PE
• Request brought forth to pharmacy and system committees for discussion
• Disagreement among physicians regarding appropriateness and utility
Background
Morbidity and Mortality

• In-Hospital Cardiac Arrest
  – Each year 209,000 people are treated for in-hospital cardiac arrest
  – 25.5% survived to hospital discharge in 2013
Morbidity and Mortality

• PE as a cause of cardiac arrest
  – Up to 25% present initially as sudden death
    • 1 day survival after PE 64% vs. DVT 97% and lower at 7 days 59%
  – Varying mortality rates reported
  – PEA most common initial rhythm

• Complications
  – Chronic thromboembolic pulmonary hypertension
  – Post-thrombotic syndrome
  – Increased risk of VTE recurrence
  – Neurological sequela after arrest

DVT = Deep Venous Thrombosis, PEA = Pulseless Electrical Activity, VTE = Venous Thromboembolism

Pathophysiology of PE

Anatomical obstruction and neuromoral effects

\[ \uparrow \text{RV after load} \]

RV dilatation/dysfunction

\[ \downarrow \text{RV output and septal shift towards LV} \]

\[ \downarrow \text{LV pre load} \]

\[ \downarrow \text{LV output} \]

\[ \downarrow \text{Systemic perfusion} \]

\[ \uparrow \text{Natriuretic peptides (BNP and NT-proBNP)} \]

\[ \uparrow \text{RV wall stress} \]

\[ \uparrow \text{Oxygen demand and } \downarrow \text{oxygen reserve of RV} \]

\[ \uparrow \text{Troponin I or T} \]

\[ \downarrow \text{Coronary perfusion} \]

Systemic blood hypotension

LV = Left ventricle, RV = Right ventricle

tPA

- FDA approved for acute massive PE for lysis
  - Hypotension (SBP < 90 mmHg) with low bleeding risk
  - 100 mg IV given over 2 hours

Guyatt GH et al. Chest 2012 Feb;141(2 Suppl):7S-47S.

SBP = Systolic Blood Pressure
Current Guideline Recommendations

2012 CHEST Guidelines
• In acute PE with hypotension (SBP < 90 mmHg) without a high bleeding risk, systemic therapy is recommended (Grade 2C)
• Short infusion time (e.g. 2 hours) recommended over long infusion time (e.g. 24 hours) (Grade 2C)

2010 ACLS Guidelines
• Routine fibrinolytic therapy is not recommended (Class III, LOE A)
• It is reasonable to administer fibrinolytics in cardiac arrest due to presumed or known PE (Class IIa, LOE B)


LOE = Level of Evidence
Efficacy and Safety of Low Dose rt-tPA

- 100 mg/2 hours (n = 53) vs. 50 mg/2 hours (n = 65)

  **Efficacy**
  - RV dysfunction on ECHO: RVED/LVED, RVWM, estimated SPAP
  - Lung perfusion defects on ventilation perfusion scans
  - PA obstruction on CT angiograms

  **Safety**
  - Death
  - Bleeding
  - VTE recurrence


RVED/LVED = RV and LV End-Diastolic Diameter Ratio, RVWM = RV Wall Movements, SPAP = Systolic Pulmonary Artery Pressure, PA = Pulmonary Artery
Efficacy and Safety of Low Dose rt-tPA

A

RVED/LVED ratio

- 100mg (n=45)
- 50mg (n=52)

0 24h 14d

B

Lung perfusion defects score

- 100mg (n=37)
- 50mg (n=42)

0 24h 14d

C

Lung artery obstruction score

- 100mg (n=48)
- 50mg (n=55)

0 24h 14d

P > 0.05 rt-PA 50mg vs. 100mg

RVED/LVED = RV and LV End-Diastolic Diameter Ratio, RVWM = RV Wall Movements, SPAP = Systolic Pulmonary Artery Pressure, PA = Pulmonary Artery

Efficacy and Safety of Low Dose rt-tPA

- **Safety (100 mg/2 hour vs. 50 mg/2 hour)**
  - Death
    - 3 (6) vs. 1 (2), $p = 0.472$
    - Due to bleeding: 1 (2) vs. 0 (0)
  - Bleeding
    - Overall: 17 (32) vs. 11 (17), $p = 0.54$
    - Major: 5 (10) vs. 2 (3)
    - Minor: 12 (22) vs. 9 (14)
  - VTE recurrence
    - 2 (4) vs. 1 (2), $p = 0.858$

# Single Bolus Dose vs. Placebo or 2 Hour Infusion

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Levine et al.</th>
<th>Sors et al.</th>
<th>Goldhaber et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine if short course regimen can achieve thrombolysis by relative improvement &gt;50% from baseline perfusion scan</td>
<td>Compare extent of PE resolution as determined by TPR over first hour of treatment to show a 10% reduction between groups</td>
<td>Bolus rt-tPA will result in fewer bleeding complications compared to 100mg/2 hours (18→2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Measures</strong></td>
<td>Lung perfusion scans (baseline, 24 hrs, 7 days)</td>
<td>Lung perfusion scans (baseline, 20-28 hrs)</td>
<td>Major vs. Important bleeding</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>Heparin x24 hours (all patients)</td>
<td>Bolus: Alteplase 0.6 mg/KG over 15 minutes, maximum dose 50 mg (n=36)</td>
<td>Bolus: rt-tPA 0.6 mg/KG over 15 minutes, maximum dose 50 mg (n=61)</td>
</tr>
<tr>
<td></td>
<td>rt-tPA 0.6 mg/KG IBW over 2 minutes (n=33)</td>
<td>Infusion: Alteplase 100 mg over 2 hours (n=17)</td>
<td>Infusion: rt-tPA 100 mg over 2 hours (n=29)</td>
</tr>
<tr>
<td></td>
<td>Saline placebo (n=25)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TPR = Total Pulmonary Resistance
# Single Bolus Dose vs. Placebo or 2 Hour Infusion

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Levine et al.</th>
<th>Sors et al.</th>
<th>Goldhaber et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine if short course regimen can achieve thrombolysis by relative improvement &gt;50% from baseline perfusion scan</td>
<td>Compare extent of PE resolution as determined by TPR over first hour of treatment to show a 10% reduction between groups</td>
<td>Bolus rt-tPA will result in fewer bleeding complications compared to 100mg/2 hours (18 → 2%)</td>
<td></td>
</tr>
</tbody>
</table>

| Results | 24 hrs: 34.4% rt-tPA vs. 12% placebo (p=0.026) 7 days: 59.4% vs. 56% | 1 hr: Bolus group TPR 29±17% decrease from baseline vs. 36±16% (p=0.19) | Major bleeding: 2 (3) vs. 2 (7.4), p=0.58 Important bleeding: 6 (10) vs. 4 (14.8), p=0.49 |

| Mortality | rt-tPA, 1 vs. placebo, 0 | No deaths | Bolus, 5 vs. infusion, 1 |

| Adverse Events | No major bleeds Minor bleeding: 15 vs. 1 | Major bleeding: 3 (8) vs. 1 (6) Other bleeding: 1 (3) vs. 4 (24) | Death, recurrent VTE, Major or Other Important bleeding: 10 (17) vs. 7 (26), p=0.38 |

| Summary | Bolus rt-tPA while fully heparinized significantly increased proportion with >50% improvement at 24 h | Bolus rt-tPA did not show a greater efficacy compared to 100mg/2 hr | A significant difference in bleeding complications was not detected between groups |

Data presented as number (%), mean±SD


ICH = Intracranial Hemorrhage
rt-tPA during CPR in Fulminant PE: Case Series

- 6 patients, ages 28 – 76 years
- Regimen: 50 mg bolus x2
  - Heparin: 5 (83)
- Average CPR duration: 47 minutes
- Mortality: 2 (33)
- Adverse Events
  - Hemorrhage at injection site: 2 (33)
  - GI bleed: 1 (17)


GI = Gastrointestinal
Major Bleeding Complications in CPR and Thrombolytic Therapy

• Retrospective chart review (n = 66) to determine impact of:
  – Thrombolysis during or after CPR
  – Thrombolysis in prolonged CPR (> 10 minutes) on incidence of major bleeding complications
  – Thrombolysis on outcome

• Regimen
  – rt-tPA 0.6 – 1 mg/KG x1, maximum dose 100 mg
  – Heparin initiated after ROSC in patients without bleeding complications

Janata K et al. Resuscitation 2003;57:49-55.

ROSC = Return of Spontaneous Circulation
Major Bleeding Complications in CPR and Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No rt-tPA (n = 30)</th>
<th>rt-tPA (n = 36)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding</td>
<td>3 (10)</td>
<td>9 (25)</td>
<td>0.15</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3 (10)</td>
<td>9 (25)</td>
<td>0.15</td>
</tr>
<tr>
<td>ROSC</td>
<td>13 (43)</td>
<td>24 (67)</td>
<td>0.06</td>
</tr>
<tr>
<td>Survival 24 hours</td>
<td>7 (23)</td>
<td>19 (53)</td>
<td>0.01</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>2 (7)</td>
<td>7 (19)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>CPR &gt; 10 min. (n = 52)</th>
<th>CPR &lt; 10 min. (n = 14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>10 (19)</td>
<td>2 (14)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

ROSC = Return of Spontaneous Circulation

Data presented as number (%)
Thrombolytic Therapy after Initially Unsuccessful CPR

- Prospective study to determine whether thrombolytic therapy is safe and effective after unsuccessful CPR out of hospital
- Control group (CPR only, n = 50) vs. rt-PA (n = 40)
  - Heparin bolus 5,000 units + 50 mg rt-PA after 15 minutes of unsuccessful resuscitation
  - Repeated following 30 minutes if no ROSC
- Primary end point: Protocol safety, ROSC, and cardiac ICU admission

Thrombolytic Therapy after Initially Unsuccessful CPR

No CPR-related bleeding complications were observed.

Outcomes in rt-PA-treated patients and controls

ICU=cardiac intensive care unit; ROSC=return of spontaneous circulation; rt-PA=recombinant tissue-type plasminogen activator. *p=0.026. †p=0.009.
tPA in Cardiac Arrest with PEA

- Double blind, placebo-controlled, RCT to evaluate effect of t-PA during CPR with undifferentiated PEA not responsive to initial therapy
- Placebo vs. t-PA 100 mg IV over 15 minutes during CPR
- Primary outcome: survival to hospital discharge
- Secondary outcomes: ROSC, hospital length of stay, hemorrhage (major or minor), neurologic outcome


RCT = Randomized Controlled Trial
## tPA in Cardiac Arrest with PEA

<table>
<thead>
<tr>
<th></th>
<th>t-PA (n=117)</th>
<th>Placebo (n=116)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival to Discharge</td>
<td>1 (0.9)</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>ROSC</td>
<td>25 (21.4)</td>
<td>27 (23.3)</td>
<td>0.85</td>
</tr>
<tr>
<td>Major Hemorrhage</td>
<td>2 (1.7)</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>Minor Hemorrhage</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
<td>0.99</td>
</tr>
<tr>
<td>Median Hospital Length of Stay, days</td>
<td>0.4</td>
<td>0.5</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Data presented as number (%)

tPA in Cardiac Arrest with PEA

• Autopsy results (n = 42)
  – Cardiovascular cause, n = 25 (59.5)
  – Hemorrhage, n = 4 (9.5)
  – PE, n = 1 (2.4)
  – Miscellaneous, n = 12 (28.6)
Assessment
Summary

• Cardiac arrest caused by PE has a very high mortality rate
• Lower doses (e.g. 50 mg) appear as efficacious as 100 mg IV over 2 hours but do not have less bleeding risk
• May increase likelihood of ROSC and survival to discharge with tPA compared to no tPA
• Low mortality due to tPA complications alone
• Increased risk of bleeding, primarily minor
• Logistical barriers
• Less drug = Less $$$
Decisions, decisions, decisions

**Risks**
- Emergent situation
- High risk medication
- Increased risk of bleeding
- Lack of strong data and clinical guidelines to support use

**Benefits**
- May increase likelihood of achieving ROSC and survival to discharge
- May improve long-term neurological function
- Multiple small studies and case reports to support use

Recommendation
Recommendation

- In patients experiencing cardiac arrest with a suspected or known PE, bolus dose thrombolytic therapy with tPA may be used
- 0.6 mg/KG IV push (maximum dose 50 mg) x1 given over 15 minutes
Current State

• At the requesting hospital, tPA is readily available in critical care satellite pharmacy and central pharmacy
• Must be administered by a physician
• Pharmacy to monitor usage and report back to committees
Unanswered Questions

- Who is the MOST appropriate patient for fibrinolytic therapy during cardiac arrest?
- Can these patients be identified earlier?
- What role does catheter directed thrombolysis play, if any?
- Should heparin and fibrinolytic be given simultaneously or is it one or the other? What is the optimal regimen?
BELIEVE IN WE™ OhioHealth

A FAITH-BASED, NOT-FOR-PROFIT HEALTHCARE SYSTEM

RIVERSIDE METHODIST HOSPITAL + GRANT MEDICAL CENTER + DOCTORS HOSPITAL
GRADY MEMORIAL HOSPITAL + DUBLIN METHODIST HOSPITAL + HARDIN MEMORIAL HOSPITAL
MARION GENERAL HOSPITAL + REHABILITATION HOSPITAL + O’BLENESS HOSPITAL + MEDCENTRAL MANSFIELD HOSPITAL
MEDCENTRAL SHELBY HOSPITAL + WESTERVILLE MEDICAL CAMPUS + HEALTH AND SURGERY CENTERS
PRIMARY AND SPECIALTY CARE + URGENT CARE + WELLNESS + HOSPICE
HOME CARE + 28,000 PHYSICIANS, ASSOCIATES & VOLUNTEERS