Thrombolysis

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Disclosures

- I have no financial disclosures to report.
Learning Objectives

- Understand the definition of thrombus and embolus.
- Understand the role of the natural clotting cascade.
- Understand the role of the natural fibrinolytic pathway.
- Understand the role of thrombolytic therapy patient care.
- Understand the difference between pharmacologic, mechanical, and pharmaco-mechanical thrombolysis.
Introduction

What is Thrombus?

- Before we start a discussion about thrombolysis, let’s first look into what thrombus is and what factors lead to its creation in both normal physiology as well as in pathologic states.

- A flow limiting platelet aggregation.

- A blood clot formed in situ within the vascular system of the body and impeding blood flow.
Coagulation System

- The formation of thrombus is a normal process, essential for maintaining life.

- The ability to produce clot is a complex orchestration of platelets, circulating proteins, and the damaged vascular wall.

- The a vascular wall is injured, initial formation of a hemostatic plug (primary hemostasis) involves platelet activation and adhesion.

- Simultaneously, degranulation of adhered platelets and locally exposed proteins activates an enzymatic cascade (secondary hemostasis) to ultimately form cross-linked fibrin strands that serve as the structural scaffold to strengthen the aggregated platelet plug.
Coagulation System

- The coagulation cascade generates fibrin through one of two pathways:
  - Tissue Factor (TF) Pathway
    - Extrinsic Pathway
    - Contact Activation Pathway
    - Intrinsic Pathway

- Of the two pathways, TF pathway is the main generator of thrombin.
Thrombosis

Extrinsic pathway

Vascular cell

Intrinsic pathway

Platelet

Platelet

FVII

TF

FXI_a

FX

Prothrombin

Thrombin

Fibrinogen

Fibrin

JEM
Coagulation System

- The TF pathway provides an immediate response to injury by rapid generation of thrombin ("thrombin burst").

- Whereas the TF pathway activates immediately, the contact activation pathway has a slower onset and is associated with coagulation involved in the setting of inflammation or hyperlipidemia.

- The coagulation cascade is normally kept in balance by inhibitory pathways that help down-regulate the cascade, turn off platelet aggregation, and stimulate fibrinolysis.
Thrombosis

- Derangements of the coagulation cascade result in either hypercoagulable or hemorrhagic states.

- Predisposing conditions for enhanced thrombus formation have been recognized for more than 100 years.

- Stasis of flow, vascular injury, and a hypercoagulable state were found to be among the most common causes of thrombus.
  - Virchow’s Triad
Thrombosis

Virchow’s triad

- Acute phase postop
- Cancer
- Thrombophilia
- Estrogen therapy
- Pregnancy and postpartum period
- Inflammatory bowel disease

- Surgery
- Trauma
- Indwelling catheter
- Atherosclerosis
- Heart valve disease or replacement

- Immobility or paralysis
- Heart failure
- Venous insufficiency or varicose veins
- Venous obstruction from tumour, obesity or pregnancy

Thrombosis

- Patients should be suspected of having a hypercoagulable condition when they present with:
  - Unprovoked venous thrombosis (i.e. no obvious inciting event)
  - Thrombosis is unusual locations (i.e. sagittal sinus, portal veins, renal veins)
  - Recurrent DVT
  - Spontaneous arterial thrombosis in the absence of underlying stenosis or embolization.

- Diagnostic evaluation includes a search for an occult malignancy
Thrombosis

- In general, thrombosis itself is not the pathology, but rather the presenting symptom.

- Most patients will have an identifiable underlying lesion or syndrome.

- Treatment of patients with acute arterial or venous thrombosis is directed toward both relief of the occlusion and diagnosis of the predisposing condition.
Thrombolysis

- Thrombosis of a blood vessel rarely occurs in the absence of one or more factors in Virchow’s Triad.

- Acute thrombosis is therefore the expression of one or more underlying problems.

- The goals of interventional treatment of thrombosis are to relieve the acute obstruction and unmask the underlying etiology.
Thrombolysis

- The human body has an endogenous mechanism for lysis of thrombus.

- The surgical approach to thrombus management is to open the vessel and pull or flush out the clot.

- Interventionalists employ both pharmacologic and mechanical tools when dealing with thrombus.
Thrombolytic Pathway

- Prothrombin activator
- Prothrombin → Thrombin
- Crosslinked polymer fibrin
- Ca²⁺ → Fibrin
- Fibrinogen
- Plasminogen activator
- Plasminogen → Plasmin
- Fibrin degradation products → Clearance
Pharmacologic Thrombolysis

- The native thrombolytic system can be enhanced by the administration of drugs that ultimately activate plasminogen.

- Although peripheral infusion of these drugs can accomplish this to some extent, catheter-directed drug delivery into the thrombus is the core principle of the IR approach to thrombolysis.
  - The thrombolytic infusion is performed over many hours and up to several days.
Pharmacologic Thrombolytic Agents

- **Streptokinase** (derived from streptococcal bacteria) was the first thrombolytic drug available.
  - Forms complexes with free plasminogen, and later plasmin, that in turn convert plasminogen to plasmin.
  - Although inexpensive, it works slowly; so infusions are long.
  - Up to 14% of patients have allergic reactions because of sensitivity to streptococci.

- **Urokinase** is a non-antigenic substance produced by human renal tissue.
  - A direct plasminogen activator with little fibrin specificity; lysis is faster (24-48 hr) than streptokinase and has fewer bleeding complications.
  - Taken off the market in 1999 because of safety concerns stemming from manufacturing issues.
Recombinant tissue plasminogen activator alteplase (t-PA) and a derivative—reteplase (r-PA)—both have increased activity in the presence of fibrin.

- t-PA greater than r-PA
- Theoretically, these agents are more thrombus-specific than urokinase or streptokinase.
- Duration of activity is usually short, in the range of 12-36 hr.

Many additional agents have been studied, but few have reached clinical practice.

- The dosages of each agent vary based on the vascular bed, the volume of thrombus, and the method of delivery.
# Pharmacologic Thrombolytic Agents

<table>
<thead>
<tr>
<th>Name</th>
<th>Origin</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-generation fibrinolytic agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urokinase</td>
<td>Human urine and kidney tissue culture</td>
<td>Effective at thrombolysis; no immunogenicity</td>
<td>No fibrin specific; expensive</td>
<td>State Food and Drug Administration (SFDA) approved, 1994</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>β-Hemolytic streptococcus</td>
<td>Effective at thrombolysis</td>
<td>Immunogenic; inaction for organized embolus</td>
<td>SFDA approved, 1999</td>
</tr>
<tr>
<td><strong>Second-generation fibrinolytic agents</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tissue plasminogen activator (t-PA)</td>
<td>Vascular endothelial cells</td>
<td>Fibrin selective; no immunogenicity</td>
<td>Short half-life; high doses</td>
<td>Listed in the U.S., 1987</td>
</tr>
<tr>
<td>Single chain urokinase plasminogen activator (Scu-PA)</td>
<td>Renal cells</td>
<td>Fibrin selective</td>
<td>Short half-life</td>
<td>Not approved for clinical use</td>
</tr>
<tr>
<td><strong>Third-generation fibrinolytic agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reteplase</td>
<td>t-PA mutant</td>
<td>Fibrin selective <em>in vivo</em>; long half-life</td>
<td>Low fibrin affinity <em>in vitro</em></td>
<td>On the market in Germany, 1996</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>t-PA mutant</td>
<td>High fibrin selectivity</td>
<td>Hemorrhagic side effects</td>
<td>Listed in the U.S., 2000</td>
</tr>
<tr>
<td>Lanoteplase</td>
<td>t-PA mutant</td>
<td>Fibrin specificity</td>
<td>High rate of cerebral hemorrhage</td>
<td>Listed in the U.S., 2000</td>
</tr>
<tr>
<td>Montepase</td>
<td>t-PA mutant</td>
<td>Long half-life</td>
<td></td>
<td>On the market in Japan, 1998</td>
</tr>
<tr>
<td><strong>Fourth-generation fibrinolytic agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasminogen activator inhibitors (PAI)</td>
<td>Plasma</td>
<td>Low molecular weight; reduce plasma PAI-1 activity levels</td>
<td></td>
<td>Not approved for clinical use</td>
</tr>
</tbody>
</table>
Pharmacologic Thrombolysis

- All thrombolytic agents ultimately result in dissolution and fragmentation of thrombus.

- The fresher the thrombus, the faster and more complete the thrombolysis.

- Chronic organized thrombus that has become fibrotic and endothelialized is less likely to be successfully thrombolysed.
  - The inability to cross the thrombus with a guidewire is a rough predictor of unsuccessful thrombolysis.

- Mechanical disruption of the thrombus accelerates thrombolysis by exposing a larger surface area to the agent, leading to enhanced local activation of plasminogen.
Pharmacologic Thrombolysis

- Thrombolytic agents do not prevent formation of new thrombus or platelet aggregation.

- The smaller the vessel and the slower the flow, the more important it is that the patient be anticoagulated during the procedure.
  - However, bleeding complications increase with anticoagulation.
  - The dose of heparin varies with the thrombolytic agent.
  - Smaller doses of heparin (~500 units/hr) are often used with t-PA and r-PA to offset the higher rates of bleeding complications with these agents.
Pharmacologic Thrombolysis

- **Indications**
  - Arterial occlusion with viable extremity or organ
  - Thrombotic occlusion of dialysis access
  - Conversion of thrombotic occlusion to stenosis before angioplasty or stent
  - Acute thrombotic stroke
    - Anterior circulation <6 hr
    - Posterior circulation 12-24 hr
  - Extensive DVT
  - Massive PE
  - Central Venous Catheter malfunction

- **Contraindications**
  - Irreversible limb or organ ischemia
  - Active hemorrhage
  - Recent major surgery
  - Recent intra-ocular surgery/bleeding
  - Craniotomy within 2 months
  - Brain tumor (primary or mets)
  - Stroke within 6 months
  - History of spontaneous intracranial hemorrhage
  - Uncooperative or demented patients
Pharmacologic Thrombolysis

- Success of a thrombolytic procedure can be defined as technical, hemodynamic, or clinical.
  - Technical success is restoration of antegrade flow with <5% residual thrombus.
  - Hemodynamic success is the return of the patient to the pre-occlusive vascular status.
  - Clinical success is the relief of acute symptoms with return to baseline functional level.
Pharmacologic Thrombolysis

- Thrombolytic agents cannot distinguish between “good” thrombus, such as at an arterial access site, and “bad” thrombus at a stenosis.
- Already bleeding patients bleed more during thrombolysis.
- Pre-existing lesions (e.g. vascular brain mets) that already have a tendency to bleed are more likely to bleed during thrombolysis.
- Limbs or organs that are irreversibly ischemic should be undergo thrombolysis because reperfusion of dead tissue may lead to severe metabolic disturbances.
- Vessels opened during thrombolysis that have no runoff do not stay open.
Pharmacologic Thrombolysis

- **Drip Infusion**
  - The essential feature is to span the entire length of the thrombus with a catheter.
    - Most catheters are designed with multiple side-holes between two radio-opaque markers to facilitate positioning.
    - The catheter should be positioned so that the proximal side-hole is just above the top of the thrombus; otherwise, the distal clot will thrombolysle leaving an obstructing proximal plug.
  - Dosage is controversial, with passionate advocates for all regimens, but in general complications are fewer and results satisfactory using modest doses.
  - Infusions usually require 12-48 hrs depending on the drug, so patients must be monitored in a controlled setting.
Pharmacologic Thrombolysis

- When concurrent anticoagulation is used, the aPTT should be followed during treatment.
- Serial hematocrit and fibrinogen levels are followed (usually every 6 hrs). There are suggestions that fibrinogen levels have little correlation with outcomes.
- Infuse with high pressure mechanical pumps.
- Secure catheter at insertion site.
- Periodic neurologic checks with frequent monitoring of access site for bleeding.
- Strict bedrest with limb immobilization
- Foley catheters should be placed.
- Minimize blood draws
# Pharmacologic Thrombolysis

<table>
<thead>
<tr>
<th>Complication</th>
<th>Streptokinase</th>
<th>Urokinase</th>
<th>t-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access-site Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>20-40%</td>
<td>20-40%</td>
<td>20-40%</td>
</tr>
<tr>
<td>(Access Site Hematoma)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>10-20%</td>
<td>5%</td>
<td>5-15%</td>
</tr>
<tr>
<td>(Requiring transfusion or operative therapy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial Bleed</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5-3%</td>
</tr>
<tr>
<td>Distal Embolization</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Failed Procedure</td>
<td>30-40%</td>
<td>5-10%</td>
<td>5-10%</td>
</tr>
</tbody>
</table>
Mechanical Thrombectomy

- Catheter-based mechanical devices can pulverize and/or remove thrombus without the use of a thrombolytic agent.

- Devices use impellers, fluid jets, brushes, baskets, lasers, and ultrasound to break thrombus into fragments small enough to be aspirated through a catheter or released into the circulation.

- The goal of these devices is the rapid restoration of blood flow by rapid reduction of the volume of thrombus.
Mechanical Thrombectomy

- Devices vary in sheath requirements and their ability to be advanced over a guidewire.

- These devices can be used to declot surgical dialysis access or bypasses, as well as native arteries or veins.

- Fresh thrombus responds best, particularly within small-diameter surgical grafts.

- A common limitation is an inability to completely clear thrombus in large-diameter vessels.
Mechanical Thrombectomy
CAT5 vs. New CAT8 Aspiration

Indigo CAT5

Indigo CAT8
CAT8 XTORQ with SEP
Mechanical Thrombectomy

- The complications of mechanical thrombectomy are somewhat device-dependent and include:
  - Embolization
  - Hemolysis
  - Volume Overload
Pharmacomechanical Thrombolysis

- The simultaneous use of a device that disrupts thrombus with a thrombolytic agent.

- This approach takes advantage of the best of both thrombolysis and mechanical thrombectomy.

- Any device that breaks up thrombus can be combined with a thrombolytic agent to decrease overall treatment times and improve efficacy.
Pharmacomechanical Thrombolysis

- Fundamental concept is to fragment the thrombus to expose more surface area to the thrombolytic agent and triggering additive endogenous lytic pathways.

- Two major devices:
  - AngioJet Catheter—Power Pulse Spray
    - Can be set to deliver the thrombolytic into the clot under pressure.
    - After a short dwell time, the lysed thrombus is aspirated using the usual operating mode for the device.
  - EKOS Infusion System
    - Mechanical thrombus disruption is accomplished by local delivery of high-frequency low-power ultrasound from within the infusion catheter along with the agent to accelerate catheter-directed thrombolysis.
Pharmacomechanical Thrombolysis

- Results using this combination therapy are promising, with rapid restoration of flow and often reduced overall doses of thrombolytic agents.
Pulmonary Embolism (PE)

Annual incidence
- United States: 69 per 100,000/year\(^1\)
  - Over 600,000 cases annually\(^2\)
  - 1-2 PE episodes per 1000 people, up to 10 per 1000 in the elderly population\(^3-6\)

Venous thromboembolism\(^3\)
- PE commonly originates from lower limb deep vein thrombosis (DVT)
- 79% of patients presenting with PE have evidence of DVT
- PE occurs in up to 50% of patients with proximal DVT
PE: A silent and fatal epidemic

- PE causes or contributes to 15% of all hospital deaths\textsuperscript{1,2}
- More people die each year from PE than highway fatalities, breast cancer and AIDS combined\textsuperscript{3}

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th># of deaths/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE\textsuperscript{4,5}</td>
<td>Up to 200,000</td>
</tr>
<tr>
<td>Highway fatalities\textsuperscript{6}</td>
<td>42,116</td>
</tr>
<tr>
<td>Breast Cancer\textsuperscript{7}</td>
<td>40,200</td>
</tr>
<tr>
<td>AIDS\textsuperscript{8}</td>
<td>14,499</td>
</tr>
</tbody>
</table>
## PE risk stratification

### 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>- RV dysfunction</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>
<td></td>
<td></td>
</tr>
</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
PE patient population profile

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

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

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

Why treat intermediate risk PE patients aggressively?

Various studies report presence of right ventricular dysfunction (RVD) as a predictor of poor clinical outcomes:

1. Mortality
2. Adverse events
3. VTE recurrence
Adverse outcomes associated with RVD

- 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 $\geq 0.9$
Adverse outcomes associated with RVD

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

- Retrospective analysis of 120 patients with hemodynamically 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
Adverse outcomes associated with RVD

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

Fremont et al. CHEST 2008;133:358-362
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
Adverse outcomes with unresolved RVD

PE patients with RVD unresolved exhibit 8x increased incidence of recurrent VTE 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

Incidence of VTE at 4 years:

- 0.4 if RVD unresolved
- 0.05 if RVD resolved
ANTICOAGULATION (AC) – HEPARIN
- AC therapy prevents further clot growth
- Studies\textsuperscript{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\textsuperscript{4}
  - a process that typically occurs over several weeks or months
  - endogenous fibrinolysis may often be incomplete at the end
Rationale for thrombolysis in acute PE

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
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 hemodynamics, e.g., failure to maintain blood pressure without supportive measures.
Recent RCT examined benefit of IV thrombolysis in intermediate risk PE

**PEITHO Trial**

**Primary Objective:**
Investigate clinical benefits (efficacy) of thrombolysis with tenecteplase over placebo in **normotensive patients with acute intermediate-risk PE** (both treatment arms receive standard heparin anticoagulation)

**Secondary Objective:**
To assess the safety of tenecteplase in patients with intermediate-risk PE
IV thrombolysis reduced the risk of hemodynamic collapse

<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 cause mortality within 7 days</td>
<td>6 (1.2%)</td>
<td>9 (1.8%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hemodynamic collapse within 7 days</td>
<td>8 (1.6%)</td>
<td>25 (5.0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>- Need for CPR</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>- Hypotension / BP drop</td>
<td>8</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>- Catecholamines</td>
<td>3</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>- Resulted in death</td>
<td>1</td>
<td>6</td>
<td></td>
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</tbody>
</table>

http://clinicaltrialresults.org/Slides/ACC%202013/Konstantinides_PEITHO_ACC%202013.pdf
But the benefit of lysis came at the cost of major bleeds (including ICH)

<table>
<thead>
<tr>
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<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></td>
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<tr>
<td>Hemorrhagic</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>
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 hemorrhage¹
- In clinical practice, systemic PE thrombolysis is associated with a 20% risk of major bleeding and a 3% risk of intracranial hemorrhage²
- In clinical practice, systemic thrombolysis is withheld in up to two thirds of patients with high-risk (massive) PE³
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
Acoustic Pulse Thrombolysis™
Mechanism of action

Fibrin Separation
Non-cavitational ultrasound separates fibrin without fragmentation of emboli

Active Drug Delivery
Drug is actively driven into clot by “Acoustic Streaming”

Fibrin without Ultrasound
Fibrin With Ultrasound

Acoustic streaming drives lytic into clot


EKOS® Acoustic Pulse Thrombolysis™ is a minimally invasive system for dissolving thrombus.
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
ULTIMA study compared EKOS® to heparin in intermediate risk PE therapy

The first RCT for an advanced catheter-based modality

Primary Objective:
Determine whether fixed low-dose catheter-directed ultrasound accelerated thrombolysis is superior to heparin alone in reversal of RV dilatation in submassive / intermediate risk PE
RCT compared EKOS® to heparin for the treatment of intermediate risk PE

Patients: Acute PE with RV/LV ratio ≥ 1.0

Randomization

30 patients

Unfractionated heparin
+ Ultrasound-assisted CDT using EKOS®

29 patients

Unfractionated heparin

Infusion Protocol
- rtPA 1mg/h; saline coolant 35ml/h
- Patients monitored in the intermediate or ICU
- After five hours, rtPA reduced to 0.5mg/h
- At 15 (+/- 1) hours, rtPA infusion, saline coolant and ultrasound discontinued
- EkoSonic® devices removed in the intermediate or ICU

- IV bolus: 80 IU/kg
- Infusion: 18 IU/kg/hour
Greater RVD reduction with EKOS with tPA + heparin than with heparin alone
More improved echo findings from EKOS® with tPA + heparin than heparin alone

No statistical difference in safety outcomes with EKOS® with tPA + heparin than heparin alone

<table>
<thead>
<tr>
<th>Clinical outcomes at 90 days</th>
<th>EKOS® with tPA + Heparin N = 30</th>
<th>Heparin N = 29</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>1*</td>
<td>0.49</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3**</td>
<td>1</td>
<td>0.61</td>
</tr>
</tbody>
</table>

* Rehospitalization and death from advanced pancreatic cancer
** Two patients with transient mild hemoptysis without medical intervention, one patient with groin hematoma requiring manual compression
† One patient with transient anal bleeding following endoscopic removal of colon polyp

ULTIMA confirmed that a fixed-dose, ultrasound-assisted catheter-directed thrombolysis EKOS® regimen was superior to anticoagulation alone in improving RV dysfunction at 24 hours without an increase in bleeding complications.
SEATTLE II examined EKOS® benefit in a clinical trial setting in the US

**Patients**

Acute Massive and Submassive PE with RV/LV ratio \( \geq 0.9 \)
\( n = 150; 22 \) 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
Endpoints

Primary Efficacy
- Change in core lab-measured RV/LV ratio from baseline to 48 hours as assessed by chest CT

Secondary Efficacy
- Change in invasively measured PA systolic pressure from baseline to device removal and as estimated on 48-hour echocardiogram

Primary Safety
- Adjudicated major bleeding within 72 hours of the start of the procedure

### The SEATTLE II Study

**Patient characteristics and treatment details**

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

* Denotes 1 patient died prior to treatment

---

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

25% decrease in RV/LV ratio over 48 hours

Rapidly relieved pulmonary artery obstruction

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>
</thead>
<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)
Zero cases of intracranial hemorrhage reported in the study

Minimized risk of intracranial hemorrhage

<table>
<thead>
<tr>
<th>Study</th>
<th>Intracranial Hemorrhage (Fibrinolysis Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICOPER</strong></td>
<td>9/304 (3%)</td>
</tr>
<tr>
<td>(Goldhaber SZ, et al. 1999)</td>
<td></td>
</tr>
<tr>
<td><strong>PEITHO</strong></td>
<td>10/506 (2%)</td>
</tr>
<tr>
<td>(Meyer G, et al. 2014)</td>
<td></td>
</tr>
<tr>
<td><strong>SEATTLE II</strong></td>
<td>0/150 (0%)</td>
</tr>
</tbody>
</table>

CONCLUSION

Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute PE improves RV function and decreases pulmonary hypertension and angiographic obstruction. By minimizing the risk of intracranial bleed, it represents a potential “game-changer” in the treatment of high-risk PE patients.

Metaanalysis showed consistent recovery of hemodynamics among patients treated using EKOS®
Metaanalysis demonstrated a favorable safety profile among patients treated using EKOS®

<table>
<thead>
<tr>
<th>First author and year of publication</th>
<th>No. of patients</th>
<th>Patients with high-risk PE</th>
<th>Total rt-PA dose (mg)</th>
<th>Total thrombolysis duration (h)</th>
<th>Bleeding complications</th>
<th>Mortality at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minor</td>
<td>Major</td>
</tr>
<tr>
<td>Chamsuddin et al. (2008)²⁶</td>
<td>10</td>
<td>NA</td>
<td>21.8</td>
<td>24.8 ± 8.4</td>
<td>2 (20)</td>
<td>0 (0)³</td>
</tr>
<tr>
<td>Lin et al. (2009)²⁵</td>
<td>11</td>
<td>2 (18)</td>
<td>17.2 ± 2.4</td>
<td>17.4 ± 5.2</td>
<td>0 (0)</td>
<td>0 (0)³</td>
</tr>
<tr>
<td>Engelhardt et al. (2011)²⁹</td>
<td>24</td>
<td>5 (21)</td>
<td>33.5 ± 15.5</td>
<td>19.7 ± 8.1</td>
<td>2 (8)</td>
<td>4 (17)²</td>
</tr>
<tr>
<td>Quintana et al. (2013)²⁷</td>
<td>10</td>
<td>2 (20)</td>
<td>18 (7 – 38)²</td>
<td>20.8 (12 – 49)²</td>
<td>2 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Kennedy et al. (2013)²⁸</td>
<td>60</td>
<td>12 (20)</td>
<td>35.1 ± 11.1</td>
<td>19.6 ± 6.0</td>
<td>1 (2)</td>
<td>1 (2)³</td>
</tr>
<tr>
<td>Engelberger et al. (2013)²¹</td>
<td>52</td>
<td>14 (27)</td>
<td>21.0 ± 5.7</td>
<td>15.2 ± 1.7</td>
<td>11 (21)</td>
<td>2 (4)²</td>
</tr>
<tr>
<td>Kucher et al. (2013)³⁰</td>
<td>30</td>
<td>0 (0)</td>
<td>20.8 ± 3.0</td>
<td>15.0 ± 1.0</td>
<td>3 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total¹</td>
<td>197</td>
<td>35 (18)</td>
<td>26.9m</td>
<td>17.8m</td>
<td>21 (10.7)</td>
<td>7 (3.6)</td>
</tr>
</tbody>
</table>

Single-center experience showed CTA evidence of RVD resolution

Case study 1

Pre-treatment:
RV/LV = 1.64

Post-treatment:
RV/LV = 1.10
Single-center experience showed CTA evidence of RVD resolution

Case study 2

Pre-treatment
RV/LV = 1.40

Post-treatment
RV/LV = 0.91
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
DVT in the U.S.

Approximately **600,000** new cases are diagnosed in the US each year.

Source: Sirweb.org
Venous Thrombosis Complications

Approximately one-third develop pulmonary embolism (PE)
Venous Thrombosis Complications

- **Symptomatic Pulmonary Embolism (PE)**
  - Death from DVT-associated massive pulmonary embolism (PE) causes as many as 300,000 deaths annually in the United States\(^1\)
  - Leading cause of preventable hospital deaths\(^2\)
  - Major pulmonary embolism is often undiagnosed antemortem. Approximately 70% of major pulmonary embolism diagnosed at autopsy had been overlooked\(^3\)
Venous Thrombosis Complications

- Post Thrombotic Syndrome (PTS)
  - *Up to 47% of DVT patients develop PTS*

- **Socioeconomic Factors**
  - 33% with PTS develop ulcers\(^1\)
  - 500,000 with leg ulcers yearly\(^1\)
  - $200M / year to treat ulcers\(^1\)
  - 33% nursing home admissions\(^2\)
  - $140,000 per patient over 10 years\(^3\)
  - Two million work days lost per year\(^4\)
Venous Thrombosis Complications

Post Thrombotic Syndrome (PTS)
- Swelling
- Pain
- Dermatitis
- Varicose veins
- Ulceration Fibrosis with atrophy
- Lymphedema
- Venous Claudication

Courtesy of Dr. Ali Amin
Deep Venous Thrombosis

Risk of Acute Leg Complications & Pulmonary Emboli

Risk of Post Thrombotic Syndrome

Iliofemoral Deep Venous Thrombosis

High Risk

Femoral-Popliteal Deep Venous Thrombosis

Low Risk

Calf Deep Venous Thrombosis
Traditional Therapy

Advantages

- Easily administered without specialized skills
- Low cost of medications / appliances
- Accepted as standard of care

Limitations

- Slow to resolve symptoms
- May require long-term patient management
- May fail to restore normal vein function
- Relies on the patient’s fibrinolytic system for thrombolysis
  - Veins have limited capacity to dissolve thrombus
Traditional Therapy

- Prevents clot propagation
- Reduces risk of pulmonary embolism
- May provide moderate symptomatic relief

But does not

- Resolve clot
- Reduce risk of venous valvular damage
- Prevent venous hypertension
- Prevent occurrence or severity of Post Thrombotic Syndrome
- Rapidly resolve symptoms
Traditional Therapy

- Randomized trials have shown, that despite use of anticoagulation and support stockings:
  - 25-47% of DVT patients develop PTS within 2 years
  - DVT Patients with PTS experience significantly poorer quality of life

- Annual economic burden of chronic venous disease remains:
  - PTS – $261 mil
  - Venous ulcer – $153 mil
Proactive Endovascular Treatment

- Pharmacomechanical Thrombectomy (PMT)
  - Endovascular intervention
  - Delivery of mechanical catheter to affected site
  - Thrombolytic drug power-infused into clot
  - Mechanical thrombectomy breaks apart and removes clot
Proactive Endovascular Treatment

Pharmacomechanical Thrombectomy (PMT)

- **Advantages**
  - Minimally invasive
  - Removes thrombus
  - Can reduce procedure time/length of ICU stay
  - May provide rapid symptomatic relief
  - Potential for reduced lytic dosage

- **Limitations**
  - Specialized skills required
  - Higher cost of disposables
  - Effectiveness may be reduced in long-standing chronic thrombus
AngioJet® Ultra Thrombectomy
AngioJet® Thrombectomy in Veins

- AngioJet® Thrombectomy Catheter.
- High velocity saline jets create a localized low pressure zone at the catheter tip (Bernoulli principle) for thrombus aspiration, break-up, and removal of venous thrombus.

AngioJet thrombectomy catheters are the only percutaneous mechanical devices indicated for thrombus removal in peripheral veins…

- upper extremity veins ≥ 3mm in diameter
- Iliofemoral and other lower extremity veins ≥ 3mm in diameter

Refer to each catheter IFU for further details.
AngioJet® Power Pulse® Delivery Combination Therapy

- Single-Catheter Option for Combination Therapy

- DUAL FUNCTIONALITY

Power Pulse Delivery INFUSION of physician-specified fluid (PSF)

Mechanical Thrombectomy Thrombus REMOVAL
AngioJet® Power Pulse® Delivery Combination Therapy

- Pharmacomechanical (PMT) is a combination of drugs and mechanical thrombectomy to remove thrombus.

- **Best of both treatments:**
  - PMT or “combination therapy” allows medication to soften the clot – followed by mechanical action to remove the clot.
AngioJet® Power Pulse® Delivery Combination Therapy

- **Deliver**
  - Lytic, power infused directly into thrombus

- **Wait**
  - Allowing drug to lyse thrombus
  - Convert AngioJet System to thrombectomy function

- **Remove**
  - Mechanical thrombectomy removes fibrin-cleaved thrombus
The AngioJet® Ultra Power Pulse® Delivery Kit is intended for the control and selective infusion of physician-specified fluids, including thrombolytic agents, into the peripheral vascular system using Power Pulse enabled Thrombectomy Sets and the AngioJet Ultra System.

The Ultra Power Pulse Kit enables The AngioJet Ultra Thrombectomy Set to deliver a pulsed infusion of physician specified fluid to a local treatment area. The Power Pulse Kit includes a Y-set with vented bag spikes bonded to PVC tubing. Each upper arm of the Y-set tubing contains a tubing clamp one white and one red.
CASE STUDY

- Acute DVT left lower extremity swelling

48-year-old woman with a history of metastatic cervical cancer with new left lower swelling. The patient has known intracranial aneurysm in addition to an enhancing pelvic mass.

Pre-treatment

Thrombectomy treatment with Solent® Omni catheter

Stent placement following AngioJet® Treatment

Post treatment venogram

Source: Reginald Baker, MD – Baptist Cardiac and Vascular Institute, Miami, Florida – Procedure Date: November

This literature is produced by Bayer and is intended for physician education only. The case study presents one case; results may not be typical.
CASE STUDY

- **Thrombectomy of Subclavian DVT**

22 yr old female; left subclavian. Presented with left arm pain, numbness and swelling. Access via cephalic vein with wire down the basilic vein and positioned in distal arm veins.

Pre-treatment:

- 22 yr old female; left subclavian. Presented with left arm pain, numbness and swelling. Access via cephalic vein with wire down the basilic vein and positioned in distal arm veins.

Post Power Pulse® Delivery & AngioJet® Thrombectomy:

- Thrombectomy of Subclavian DVT Console:

  - Thrombectomy, post Power Pulse® Delivery, was 109 seconds.

- Physician preference using Power Pulse® Delivery with 75ml of a 20 mg/100ml TPA solution. 60 minute dwell time followed by AngioJet® Thrombectomy with 90 cm catheter.
CASE STUDY

- Thrombectomy in May-Thurner Syndrome DVT

Pre-procedure venogram

1 Pass AngioJet® Solent® Proxi Catheter
(patient has not had any lytics)

Collection bag after 1st pass (no lytics)

IVC/Iliac and Proximal Common Femoral

Distal Iliac and Common Femoral

Clot from single pass of Distal Iliac and Common Femoral
(Patient was not given lytics prior to procedure.)
Summary

Interventional therapies for DVT treatment

- Early invasive treatment can be more successful and have lasting benefit
  - Improved patient outcomes
  - Shorten treatment time / Patient's time in hospital
- Variety of techniques with early intervention and for restoring venous flow
  - Benefits with early thrombus removal
- Post-Thrombotic Syndrome is preventable
References

- Geering et al. CMAJ 2012; 184(3):305-310
- Chunilal et al. JAMA 2003;290:2849–58
- http://www.sirweb.org/patients/deep-vein-thrombosis/
- Society of Interventional Radiology. Fact Sheet. March 2005
References

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- *Circulation* 2006;113:577-82
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- Postthrombotic Syndrome; Patricia E. Thorpe, MD, FSIR; October 2007; Endovascular Today