Ultrasound Lysis of DVT and IVC Thrombosis

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Deep Vein Thrombosis (DVT)

• The precise number of people affected by DVT/PE is unknown.
• Estimates: as many as 900,000 people could be affected (1 to 2 per 1,000) each year in the United States.
• Estimates suggest that 60,000-100,000 Americans die of DVT/PE
  • 10 to 30% of people will die within one month of diagnosis.
  • Sudden death is the first symptom in about one-quarter (25%) of people who have a PE.
• Among people who have had a DVT, one-half will have long-term complications (post-thrombotic syndrome) such as swelling, pain, discoloration, and scaling in the affected limb.
• One-third (about 33%) of people with DVT/PE will have a recurrence within 10 years.
• Approximately 5 to 8% of the U.S. population has one of several genetic risk factors, also known as inherited thrombophilias in which a genetic defect can be identified that increases the risk for thrombosis.

CDC March 20, 2015
Deep Vein Thrombosis

- It is estimated that more than 250,000 patients are hospitalized annually with VTE\(^1\)
  - Of these, 30 percent die within 30 days, one fifth suffer sudden death due to PE, and about 30 percent develop recurrent VTE within 10 years\(^2\)

- Approximately 600,000 experience pulmonary embolism (PE)

- For up to 200,000 of those with PE, the blood clot in the lung proves fatal—killing more people than AIDS and breast cancer combined\(^3\)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th># of Annual Deaths(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>Up to 200,000</td>
</tr>
<tr>
<td>AIDS</td>
<td>18,017</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>40,870</td>
</tr>
</tbody>
</table>

3. American Heart Association Fact Sheet - 2008
Long-term Health Complications of DVT

- Post-thrombotic syndrome (PTS) may result in:
  - Chronic pain\(^1\)
  - Swelling\(^1\)
  - Skin ulceration secondary to post-phlebitis syndrome\(^1\)
- Chronic condition in 30% to 75% of DVT patients within 2 years\(^2\)
- Irreversible damage to veins & valves
- Significant and lasting impact on quality of life
- Nearly 90% of patients are unable to work due to leg symptoms 10 years after iliofemoral DVT\(^3\)

2. Parikh et al. JVIR 2008 19; 521-528
Long-term Health Complications of DVT

• PE: most preventable cause of in-hospital death\(^1\)
• 70%-80% of fatal PEs occur in nonsurgical patients\(^2\)
• Improved treatment might have a minimal impact on the number of deaths, more effective prevention of recurrent PE would represent the greatest opportunity to prevent fatal recurrent PE\(^1\)

1. Clinical Syndromes and Clinical Outcome in Patients With Pulmonary Embolism: Findings From the RIETE Registry - CHEST 2006 – Lobo et al
Venous thrombosis
Pathophysiology of Post Thrombotic Syndrome

A. Normal Blood Flow

B. Damage to Leg Veins

C. Valve Becomes Leaky, Allowing Fluid to Pass Through

D. Leg Pain, Swelling, and Redness

Blood Clot and Inflammation

Blood Clot

Pathophysiology of Post Thrombotic Syndrome (PTS)

- **DVT:**
  - obstructive/mechanical (thrombus) and inflammatory pathways.
  - Increased levels of inflammatory cytokines or adhesion molecules
    - Interleukin-6
    - Intercellular adhesion molecule-1

- **Valvular incompetence**
  - 17% at one week post DVT
  - 69% at one year post DVT

- **Venous reflux**
- **Venous hypertension**
- **Transudation of fluid and large molecules at the capillary level.**
- **Tissue edema and subcutaneous fibrosis**
- **Tissue hypoxia**
- **Venous ulceration**

Nicolaides et al. JVS 17(2):414-9; Araki et al. JVS 20(6):872; Wekkie et al. JVS 16(5):733-40
• Chronic condition developing in 30% to 70% of DVT patients within 2 years
• Damage to veins and valves is irreversible
• Enlarged veins may lead to insufficient valve closure
• Significant and lasting impact on quality of life
• Nearly 90% of patients are unable to work due to leg symptoms 10 years after iliofemoral DVT

Treatment of DVT:

- **Anticoagulation:**
  - Does not actively dissolve the clot.
  - Does not prevent long-term damage to the vein and valves
- **Catheter Directed Thrombolysis**
- **Pharmacomechanical thrombolysis**
- **Ultrasound assisted thrombolysis**
• Catheter Directed Thrombolysis
  • First intravascular instillation 1955-Tillet
  • Routinely used since 1980’s
  • Efficacy established 1991-Berridge
  • Very effective if the lytic agents can penetrate the clot
Pharmacomechanical Devices:
Ultrasound accelerated catheter directed thrombolysis
Is this a good idea?

- Watson, et al. Thrombolysis for acute deep vein thrombosis. Cochrane Library:
  - “Thrombolysis increases the patency of veins and reduces the incidence of PTS following proximal DVT by a third”.

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

- Ultrasound energy causes fibrin strands to thin and loosen, exposing plasminogen receptor sites
- Thrombus permeability and thrombolytic penetration are dramatically increased
- Ultrasonic pressure waves force drug deep into the clot and keep it there
- Drug acts faster, clearing clot sooner with reduced bleeding complications

\[
\begin{align*}
48\% \text{ more } t\text{-PA in one hour,} \\
84\% \text{ more } t\text{-PA in two hours} \\
89\% \text{ more } t\text{-PA in 4 hours} \\
\text{versus} \\
\text{thrombus not exposed to ultrasound}^{1}
\end{align*}
\]

Mechanism of Action

• Ultrasound pressure waves pass through the thrombus all the way to the vessel walls and behind venous valves¹

• Ultrasound energy causes the fibrin strands to thin, exposing plasminogen receptor sites. The thrombus becomes more permeable and allows the lytic to penetrate deeper²

What it does

Simultaneously delivers low energy, high frequency (2.2 Mhz) ultrasound and drug along the entire treatment zone of the infusion catheter (6-50cm.) Time to clot lysis is dramatically reduced.
How it works

• Reversibly changes fibrin structure
  • Unwinds fibrin stands

• Enhances transport into fibrin bundles
  - Ultrasound creates a pressure wave that drives drug into the permeable clot
  - Constant infusion of fresh drug

• Enhanced clot dissolution, not disruption
The EkoSonic® Endovascular System

5.2 fr side-hole drug delivery catheter

MicroSonic™ Core
• Fits through a 6F sheath
• Central lumen accommodates a 0.035 in. guidewire and, later, the microsonic device (MSD)
• Coolant flows through central lumen and out the distal end hole
• Thermocouples monitor temperature
• Drug flows through drug lumen and out the side holes
Hospital infusion pump used to:

- Infuse lytic through the drug port
- Infuse Heparinized Saline or Normal Saline through the Coolant port
• RPM™ generates ultrasound pulses of varying waveforms

• Intermittent bursts of high and low intensities, number of pulses and delay between clusters of pulses increases clot permeability

• Simultaneous ultrasound pressure wave drives the lytic into the clot and keeps it there

*Rapid Pulse Modulation (RPM)* demonstrated greater clot permeability and drug penetration, resulting in accelerated dissolution

Thrombus exposed to ultrasound absorbed 48% more t-PA in one hour, 84% more t-PA in two hours and 89% more t-PA in 4 hours than thrombus not exposed to microsonic pressure.³

DVT Clinical Site Results

National Venous Registry (N=287):
- Complete clot lysis: 31%
- Partial clot lysis: 52%
- No clot lysis: 17%

Cleveland Clinic Foundation Retrospective Data (N=80):
- Complete clot lysis: 38%
- Partial clot lysis: 45%
- No clot lysis: 18%

EKOS (N=53):
- Complete clot lysis: 70%
- Partial clot lysis: 21%
- No clot lysis: 9%

Average Infusion Times:
- National Venous Registry: 53.4 hrs.
- Cleveland Clinic Foundation Retrospective Data: 36.8 hrs.
- EKOS: 24.7 hrs.
UltraSonic Accelerated Thrombolysis

More Complete.

<table>
<thead>
<tr>
<th>Percent of Patients with Complete Lysis at Final Angiogram</th>
</tr>
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<tbody>
<tr>
<td><strong>EKOS</strong>&lt;sup&gt;17&lt;/sup&gt; Microsonic Accelerated Thrombolysis</td>
</tr>
<tr>
<td><strong>EKOS standalone therapy</strong></td>
</tr>
<tr>
<td><strong>NVR</strong>&lt;sup&gt;18&lt;/sup&gt; National Venous Registry</td>
</tr>
<tr>
<td>Inclusive of post-adjunctive therapy</td>
</tr>
<tr>
<td>31%</td>
</tr>
</tbody>
</table>


UltraSonic Accelerated Thrombolysis

Faster...
Rapid Pulse Modulation 4X+

<table>
<thead>
<tr>
<th>Time To Final Angiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKOS&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>with Rapid Pulse Modulation</td>
</tr>
<tr>
<td>12 Hours 80% Complete Lysis</td>
</tr>
<tr>
<td>(Estimate based on In vitro data)</td>
</tr>
<tr>
<td>EKOS&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Microsonic Accelerated Thrombolysis</td>
</tr>
<tr>
<td>22 Hours 70% Complete Lysis</td>
</tr>
<tr>
<td>EKOS standalone therapy</td>
</tr>
<tr>
<td>NVR&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>National Venous Registry</td>
</tr>
<tr>
<td>Inclusive of post-adjunctive therapy</td>
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<tr>
<td>53.4 Hours 31% Complete Lysis</td>
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</tbody>
</table>

<sup>9</sup>Data on File


UltraSonic Accelerated Thrombolysis

Safer.

<table>
<thead>
<tr>
<th>Bleeding Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EKOS</strong>\textsuperscript{12} Microsonic Accelerated Thrombolysis</td>
</tr>
<tr>
<td><strong>Warfarin</strong>\textsuperscript{3}</td>
</tr>
<tr>
<td><strong>NVR</strong>\textsuperscript{14} National Venous Registry</td>
</tr>
</tbody>
</table>


# UltraSonic Accelerated Thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Urokinase</th>
<th>Alteplase (t-PA)</th>
<th>Reteplase (r-PA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKOS (n=14)</td>
<td>EKOS (n=9)</td>
<td>EKOS (n=22)</td>
<td></td>
</tr>
<tr>
<td>CDT (n=38)</td>
<td>CDT (n=32)</td>
<td>CDT (n=12)</td>
<td></td>
</tr>
<tr>
<td><strong>Median Drug Dose</strong></td>
<td>2.02 MU</td>
<td>14.0 mg</td>
<td>6.9 U</td>
</tr>
<tr>
<td><strong>Median Infusion Time</strong></td>
<td>19.3 hr</td>
<td>18.0 hr</td>
<td>24.0 hr</td>
</tr>
</tbody>
</table>


In conclusion:

• Acute iliofemoral and femoral DVT probably should be treated with clot removal

• Ultrasound accelerated thrombolysis appears to be a very effective tool to do so.
Inferior Vena Cava Thrombosis

- Bilateral iliofemoral thrombosis based on a hypoplastic inferior vena cava (Phlebology. 2015 May;30(4):293-5)
- Inferior vena cava thrombosis after an orthotopic liver transplant (Exp Clin Transplant. 2015 Feb;13(1):96-9)
Thank You
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