Clinical and Hemodynamic Insight into the Mechanisms of Initiation of Venous Thrombosis

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“Clinical and Hemodynamic Insight into the Mechanisms of Initiation of Venous Thrombosis”

• FINANCIAL DISCLOSURE:
No relevant financial relationship exists
Venous Thrombosis Initiation: Importance

• Definitions:
  – provoked/unprovoked
  – Assumption of known factor
  – Assumption of different mechanisms
Venous Thrombosis Initiation: Classic concepts

- Arterial vs. venous thrombosis
- “Virchow” triad
- Valve as the site of thrombus initiation
Venous Thrombosis Initiation: 
Arterial vs. Venous

Different initiation mechanisms
Venous Thrombosis Initiation: Arterial vs. Venous

A 'Trojan Horse' strategy for the prevention of vascular thrombosis

K Ouriel. Thrombi—beware of red cells bearing gifts
Venous Thrombosis Initiation: Classic concepts

“Virchow” triad

Virchow’s hypothesis if factors attributed to PE:

- interrupted blood-flow
- irritation of the vessel and its vicinity
- blood-coagulation
- All caused by thrombus in the vein

Venous Thrombosis Initiation

Role of venous valves
Venous Thrombosis Initiation: Importance

• Prevention
  – effectiveness
  – recurrences
  – mechanical vs. pharmaceutical
DVT prevention: compression therapy

Dynamic - IPC  Static – GCS

Suggested mechanism of action – increasing blood flow
IPC: Tissue deformation and hemodynamics

Static compression in prevention of DVT

- Compression stockings decrease deep vein diameter and flow
Venous Thrombosis Initiation: Clinical Questions

– Recurrent issue – incidence
– Recurrence – link to other diseases
– Primary CVD and DVT
Clinical perspective: recurrent VTE

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madeley Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators.

Aspirin for Preventing the Recurrence of Venous Thromboembolism

Cecilia Becattini, M.D., Ph.D., Giancarlo Agnelli, M.D., Alessandro Schenone, M.D., Sabine Eichinger, M.D., Eugenio Bucherini, M.D., Mauro Silingardi, M.D., Marina Bianchi, M.D., Marco Moia, M.D., Walter Ageno, M.D., Maria Rita Vandelli, M.D., Elvira Grandone, M.D., and Paolo Prandoni, M.D., Ph.D., for the WARPASA Investigators.

Annual Risk 9%

Annual Risk 11.2%
**Table 5. Cause of Death Among 37895 Patients With Venous Thromboembolism**

<table>
<thead>
<tr>
<th>Cause of Death (Immediate)</th>
<th>n (%)</th>
<th>Venous Thromboembolism Cohort (95% Confidence Interval)*</th>
<th>Comparison Cohort (95% Confidence Interval)</th>
<th>Mortality Rate Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases of the circulatory system</td>
<td>27989 (36)</td>
<td>34.0 (33.6–34.4)</td>
<td>12.5 (12.4–12.6)</td>
<td>3.16 (3.11–3.20)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>9602 (12)</td>
<td>11.7 (11.4–11.9)</td>
<td>0.3 (0.3–0.3)</td>
<td>32.32 (30.77–33.95)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1702 (2)</td>
<td>2.1 (2.0–2.2)</td>
<td>1.2 (1.2–1.2)</td>
<td>2.01 (1.91–2.12)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1952 (2)</td>
<td>2.4 (2.3–2.5)</td>
<td>1.6 (1.5–1.6)</td>
<td>1.81 (1.72–1.90)</td>
</tr>
<tr>
<td>Diseases of the respiratory system</td>
<td>11645 (15)</td>
<td>14.2 (13.9–14.4)</td>
<td>8.0 (7.9–8.0)</td>
<td>2.10 (2.06–2.15)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>2541 (3)</td>
<td>3.1 (3.0–3.2)</td>
<td>1.4 (1.4–1.4)</td>
<td>2.55 (2.44–2.66)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6048 (8)</td>
<td>7.4 (7.2–7.5)</td>
<td>4.8 (4.8–4.9)</td>
<td>1.86 (1.81–1.91)</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>5524 (7)</td>
<td>6.7 (6.5–6.9)</td>
<td>3.0 (3.0–3.0)</td>
<td>2.46 (2.39–2.53)</td>
</tr>
</tbody>
</table>

*Cause of death was missing for 11773 venous thromboembolism patients (15%).

*Per 1000 person-years.

†See description of the crude and adjusted model in Table 3 or in the text.
Catheter-Directed Thrombolysis

Residual rates of reflux and obstruction and their correlation to post-thrombotic syndrome in a randomized study on catheter-directed thrombolysis for deep vein thrombosis

Ylva Haig, MD, Tone Enden, MD, PhD, Carl-Erik Slagsvold, MD, PhD, Leiv Sandvik, MSc, PhD, Per Morten Sandset, MD, PhD, and Nils Einar Kløw, MD, PhD, Oslo, Norway

- 189 patients from CoVenT trial
- who completed 24-month follow up
- Ultrasound and APG at 6 and 24 months
- PTS definition: Villalta score >4
Residual rates of reflux and obstruction and their correlation to post-thrombotic syndrome in a randomized study on catheter-directed thrombolysis for deep vein thrombosis

Ylva Haig, MD, a, b, c Tone Enden, MD, PhD, a, b, c Carl-Erik Slagsvold, MD, PhD, c Leiv Sandvik, MSc, PhD, d Per Morten Sandset, MD, PhD, b, c and Nils Einar Klow, MD, PhD, a, c Oslo, Norway

Table IV. Distribution of venous reflux in venous segments

<table>
<thead>
<tr>
<th></th>
<th>CDT group (n = 90)</th>
<th>Control group (n = 99)</th>
<th>PTS (n = 92)</th>
<th>No PTS (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% (95% CI)</td>
<td>No.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>At 24 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep reflux</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral vein</td>
<td>53</td>
<td>60.2 (49.8-69.9)a</td>
<td>70</td>
<td>75.3 (65.6-83.0)a</td>
</tr>
<tr>
<td>Popliteal vein</td>
<td>53</td>
<td>58.9 (48.6-68.5)a</td>
<td>69</td>
<td>72.6 (62.9-80.6)a</td>
</tr>
<tr>
<td>Femoral and popliteal</td>
<td>44</td>
<td>50.0 (39.8-60.2)</td>
<td>58</td>
<td>62.4 (52.2-71.6)</td>
</tr>
<tr>
<td>Superficial reflux</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater saphenous vein</td>
<td>22</td>
<td>24.7 (16.9-34.7)</td>
<td>28</td>
<td>29.2 (21.0-39.0)</td>
</tr>
<tr>
<td>Lesser saphenous vein</td>
<td>10</td>
<td>11.4 (6.1-19.9)</td>
<td>14</td>
<td>14.9 (9.0-23.6)</td>
</tr>
</tbody>
</table>

\[ \text{RR} = 1.53 \]

CDT, Catheter-directed thrombolysis; CI, confidence interval; PTS, post-thrombotic syndrome.
Chi-square test.

\(^a\) P value < .05.
\(^b\) P value < .001.
prospective cohort of patients suspected for DVT
August 2013-December 2014

Suspected first-time acute unprovoked DVT (n=760)

venous duplex

confirmed DVT

confirmed DVT

frequency matching by age and gender (1:4)

no DVT

DVT group

Control group

Provoked DVT
Recurrent DVT
Prevalence of reflux in general population

<table>
<thead>
<tr>
<th>Reflux location</th>
<th>Current study</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DVT group</td>
<td>Control group</td>
</tr>
<tr>
<td>Any venous segment</td>
<td>66.7</td>
<td>29.0</td>
</tr>
<tr>
<td>Superficial veins</td>
<td>43.7</td>
<td>14.4</td>
</tr>
<tr>
<td>Deep veins</td>
<td>36.8</td>
<td>21.6</td>
</tr>
<tr>
<td>Combined deep+superficial</td>
<td>13.8</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Edinburgh Vein Study, 1998 ¹
San-Diego Population Study, 2003 ²
Bohn Vein Study, 2008 ³

<table>
<thead>
<tr>
<th></th>
<th>Affected/symptomatic leg</th>
<th>Unaffected/asymptomatic leg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DVT group</td>
<td>Control group</td>
</tr>
<tr>
<td>OR</td>
<td>2.01</td>
<td>3.47</td>
</tr>
<tr>
<td>[1.11-3.62]</td>
<td>[2.04-5.88]</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.027</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>%</td>
<td>23.0%</td>
<td>36.8%</td>
</tr>
</tbody>
</table>
Superficial Reflux

<table>
<thead>
<tr>
<th></th>
<th>Affected/symptomatic leg</th>
<th>Unaffected/asymptomatic leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT group</td>
<td>27.6%</td>
<td>28.7%</td>
</tr>
<tr>
<td>Control group</td>
<td>9.8%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

OR = 3.52 [1.95-6.34]  
OR = 4.44 [2.43-8.08]  

P < .0001
Combined deep+superficial reflux

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT group</td>
<td>13.8%</td>
</tr>
<tr>
<td>Control group</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

OR = 2.01
[1.11-3.62]
Primary venous insufficiency increases risk of deep vein thrombosis

Maxim E. Shaydakov, MD, PhD, Anthony J. Comerota, MD, FACC, FACS, and Fedor Lurie, MD, PhD,


Prevalence of preexistent reflux

65.5%  P<.000001

29.0%

OR = 4.65 [2.82-7.65]
Systemic nature of changes in Primary CVD

- Similar or identical pathological changes in varicose veins and “normal veins” of the same and contralateral extremity

- Identical collagen changes (Type I > Type III), SMC and fibroblast changes in veins and skin.

Venous Thrombosis Initiation: Hemodynamic perspective

- Issue of “stasis”
- Normal Valves – Hamer-Malone hypothesis
- Abnormal valves – reflux
- Abnormal valves – prograde flow
Flow separation at the valve cusp and re-attachment at the valve sinus create a vortex behind valve cusp.

Pressure created by this vortex ($P_i$) is equal to the pressure created by flow through valve ($P_0$) during the equilibrium phase.

Change in flow velocity leads to $P_i > P_0$, and the valve starts closing.
Venous Valve

Role in the circulation

Flow from a tributary
Venous Valve

Role in the circulation

Flow from a tributary
Venous Valve
Role in the circulation

Flow from a tributary
Venous Valve
Role in the circulation

Gravity and Venous Flow

Supine

Standing
Normal Valve
Normal Valve
Valve vortex is different from annular vortex – streamlines are not closed, and there is continuous exchange of material between the vortex and the mainstream.

Secondary Vortex

- Has opposite direction
- At low velocities particles do not migrate in/out the vortex (plasma only)
- At high velocities particles are trapped in the secondary vortex and slowly move in circular orbits
Venous Valve

Hamer-Malone hypothesis

Relative Oxygen Tension, $P/P_A$

<table>
<thead>
<tr>
<th>Subject</th>
<th>Position</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human saphenous vein (10 min) n=2</td>
<td>B</td>
<td>0.998</td>
<td>0.985</td>
<td>0.684</td>
</tr>
<tr>
<td>Dog femoral vein (10 min) n=4</td>
<td>B</td>
<td>0.998</td>
<td>0.993</td>
<td>0.833</td>
</tr>
<tr>
<td>Dog femoral vein (90 min) n=4</td>
<td>D</td>
<td>0.999</td>
<td>0.361</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Original data from
Venous Valve

Flow optimization

Venous Valve: maximal opening
Prograde flow through a normal valve

18 cm/sec  13 cm/sec  7 cm/sec
Abnormal outflow downstream from the valve.

Impact of altered venous hemodynamic conditions on the formation of platelet layers in thromboemboli.

Valve dysfunction resulted in reversed vortex
Reflux vs. “venous hypertension”
Reflux
Reflux

Refluxing flow jet is most frequently asymmetrical, directed towards the wall.
Shear rate in asymmetric reflux

**Normal flow**

\[ d = 8 \cdot 10^{-3} \text{ m} \]
\[ \nu_{\text{max}} = 0.3 \text{ ms}^{-1} \]
\[ Y = \frac{8\nu}{d} = 300 \text{ s}^{-1} \]

**Reflux**

\[ h = 10^{-4} \text{ m} \]
\[ \nu_{\text{max}} = 0.8 \text{ ms}^{-1} \]
\[ Y = \frac{\nu}{h} = 8 \cdot 10^{-3} \text{ s}^{-1} \]
Conclusions:

Venous thrombus initiation:

• Clinically important (primary and secondary VTE prevention)

• Several potential mechanisms related to:
  – Changes in venous wall (primary disease)
  – Flow in the normal valve (secondary vortices)
  – Reflux (Increased shear rate)
  – Antegrade flow through abnormal valve
Thank You