Deep Venous Thrombosis

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Virchow’s Triad

Rudolph Virchow
1821 –1902
Stasis

- Bed Rest
- Travel
- Immobilization (cast)
- Obesity
- Limb Paralysis

Hypercoagulability

- Malignancy
Trousseau’s Syndrome

Armand Trousseau 1801-1867

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JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Genetic Link Between Cancer and Thrombosis

Guillem J. Roca and Paolo Marini

ABSTRACT

From the beginning of their lives, cancer cells evade a procoagulant activity in their microenvironment, which can extend systemically and become clinically evident as Trousseau’s syndrome, the well-known association between tumor and thrombosis. It is becoming clear that the genetic mechanisms responsible for neoplastic transformation activation of oncogenes such as Ras or Akt, and inactivation of tumor suppressor genes such as p53 or PTEN directly induce the expression of genes controlling hemostasis. Activation of blood coagulation results in a selective advantage for cancer cells, as fibrin provides a scaffold for anchorage and invasion, and coagulation proteins induce receptor-mediated intracellular signals promoting invasion growth. Targeting the tumor procoagulant activity can fight not only a dangerous tumor invasion effect, but also the core mechanisms of cancer onset and progression.
Hypercoagulability

- Malignancy
- Acquired or Inherited Disorders
  - Protein S and Protein C Deficiencies
  - Antithrombin III Deficiency
  - Factor V Leiden
  - Antiphospholipid Antibodies
- Trauma
- Pregnancy
- Estrogen
- Inflammatory States
  - Inflammatory bowel disease
  - SIRS
- Thrombophilia
- Cigarettes
Role of Risk Factors in the Modulation of Tissue Factor Activity and Blood Thrombogenicity

Antonis Sambois, MD, Julio Osende, MD, James Hothcock, PhD; Michael Degen, BS;
Yale Nemerson, MD, Valentina Fuster, MD, PhD; Jill Crandall, MD; Juan Jose Badimon, PhD

Background.—Several studies suggest a role for an increased circulating pool of tissue factor (TF) in atherothrombotic diseases. Furthermore, certain cardiovascular risk factors, such as diabetes, hyperlipidemia, and smoking, are associated with a higher incidence of thrombotic complications. We hypothesized that the observed increased blood thrombogenicity (BT) observed in patients with type 2 diabetes mellitus may be mediated via an increased circulating tissue factor activity. We have extended our study to smokers and hyperlipidemic subjects.

Methods and Results.—Poorly controlled patients with type 2 diabetes mellitus (n=35), smokers (n=10), and untreated hyperlipidemic subjects (n=10) were studied. Circulating TF was immunomagnetically removed from plasma, reisolated, and quantified by factor Xa (FXa) generation in the presence of factor VIIa. BT was assessed as thrombus formation in the rabbit mesenteric perfusion chamber. Patients with improvement in glycemic control showed a reduction in circulating TF (862±175 versus 243±74 pmol/L per min FXa, P<0.0001). A similar effect was observed in BT (15 445±1150 versus 12 072±596 µm/mg protein, P=0.01). Two hours after smoking 2 cigarettes, TF was increased (217±72 versus 283±106 pmol/L per min FXa, P=0.003). Hyperlipidemic subjects showed higher TF (217±65 versus 185±44 pmol/L per min FXa, P=0.035) than healthy volunteers.

Conclusion.—These findings suggest that high levels of circulating TF may be the mechanism of action responsible for the increased thrombotic complications associated with the presence of these cardiovascular risk factors. These observations strongly emphasize the usefulness of the management of the patients based on their global risk assessment.

(Circulation. 2003;107:975-977.)

Endothelial Injury

- Trauma
- Surgery
- Vascular catheters
Pathophysiology of DVT

- Clots form in valve cusps of calf deep veins
- 15-20% of these clots will propagate proximally
- Approximately 50% of deep vein clots will lyse and recanalize within 3 months

Diagnosis of DVT

- Clinical Assessment
- Laboratory Studies
- Imaging Techniques

Table 1 | Clinical model for predicting pretest probability for DVT

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Active cancer (treatment ongoing or within previous 6 months or palliation)</td>
</tr>
<tr>
<td>1</td>
<td>Paralysis, paresis or recent plantar immobilization of the lower extremities</td>
</tr>
<tr>
<td>1</td>
<td>Recently bedridden &gt; 3 days or major surgery within 4 weeks</td>
</tr>
<tr>
<td>1</td>
<td>Localized tenderness along the distribution of the deep venous system</td>
</tr>
<tr>
<td>1</td>
<td>Edema, leg swollen</td>
</tr>
<tr>
<td>1</td>
<td>Calf swelling 3 cm &gt; asymptomatic side (measured 30 cm below malleolar)</td>
</tr>
<tr>
<td>1</td>
<td>Pitting edema confined to the symptomatic leg</td>
</tr>
<tr>
<td>1</td>
<td>Collateral superficial veins (not varicose)</td>
</tr>
<tr>
<td>-1</td>
<td>Alternative diagnosis as likely or greater than that of DVT</td>
</tr>
</tbody>
</table>

PRETEST PROBABILITY: X

Score = Pretest Probability

NOTE: In patients with symptoms in both legs, the more symptomatic leg is used.

PRETEST PROBABILITY CALCULATED AS FOLLOWS:

Total Points

<table>
<thead>
<tr>
<th>Points</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3</td>
<td>HIGH</td>
</tr>
<tr>
<td>1-2</td>
<td>MODERATE</td>
</tr>
<tr>
<td>≤ 0</td>
<td>LOW</td>
</tr>
</tbody>
</table>
Homans’ Sign

• Homans’ Sign: Present in less than 1/3 of the cases

Predictive Value of the Wells’ Criteria

• High Probability Group  76%
• Moderate Probability Group  21%
• Low Probability Group    10%

DVT Laboratory Studies

- D-dimer
- Hypercoaguability Screen
  - Protein S
  - Protein C
  - Antithrombin III
  - Factor V Leiden
  - Phospholipid Antibodies
  - Platelet count
Ways to Measure D-dimers

- Rapid ELISA test (most commonly used)
- Latex Agglutination
- Whole-Blood Agglutination (SimpliRED)

Basic Principle

- A negative D-dimer excludes DVT in patients with low risk factors
- A positive D-dimer is an indication for an imaging study
- MOST surgical patients will have positive D-dimers related to surgery
Imaging Studies

- Venography
- Compression Ultrasound
  - Noninvasive
  - Easily repeatable
  - accurate

Ultrasonography

- Should be the initial imaging study
- Full compressibility of the popliteal and femoral veins excludes proximal DVT
- Sensitivity/Specificity for proximal DVT = 97/98%

Ultrasound

- DVT Sensitivity/Specificity for calf veins = 70/60%
- Proximal extension rare (2%) after 1 week
- Non-extending calf vein DVT rarely responsible for PE
- Therefore, if 2 ultrasounds 1 week apart are negative, no therapy required


Initial Rx of DVT

- Once daily LMWH (150-200 U/KG as effective as twice daily LMWH (100 U/kg)
- LMWH as effective as continuous iv unfractionated heparin with PTT 1.5 X control
Unfractionated Heparin

- Narrow Rxic window
- Bleeding rate 7-30%
- Risk of HIT
- IV bolus 80 U/kg followed by 18 U/kg/hr iv drip
- PTT to be kept at 1.5 X control

LMWH

- Once daily dose
- No need to monitor PTT
- Low risk of HIT
- Much lower cost

Fibrinolysis

- Fibrinolytic Drugs
  - Streptokinase
  - Urokinase
  - Rt-PA
- Urokinase and Plasminogen Activators equal in terms of efficacy and complications

Systemic Fibrinolysis vs Heparin

<table>
<thead>
<tr>
<th>Events</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Clot Lysis</td>
<td>2.71</td>
<td>1.84-3.99</td>
</tr>
<tr>
<td>Post Thrombotic Syndrome</td>
<td>0.66</td>
<td>0.47-0.94</td>
</tr>
<tr>
<td>Total Bleeding</td>
<td>1.73</td>
<td>1.04-2.99</td>
</tr>
<tr>
<td>Leg ulceration</td>
<td>0.53</td>
<td>0.12-2.43</td>
</tr>
<tr>
<td>Normal venous function</td>
<td>0.43</td>
<td>0.06-3.17</td>
</tr>
<tr>
<td>Death</td>
<td>1.33</td>
<td>0.34-5.24</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>1.41</td>
<td>0.37-5.40</td>
</tr>
</tbody>
</table>


Ileo-Femoral Thrombosis

Images courtesy of Dr. Mark Wilson, Chief of Radiology, San Francisco General Hospital

Percutaneous Mechanical Thrombectomy

- Review of 281 patients in 16 retrospective case series
- No randomized trials available
- 82-100% success rate for partial and complete clot lysis
- No deaths, <1% PE
- 7.5% of patients bled requiring transfusion

Conclusion

- Mechanical thrombectomy appears safe and feasible
- No evidence to support routine use


Vena Cava Filters

TYPES OF IVC FILTERS

STAINLESS-STEEL OVER-WIRE GREENFIELD
BIRD’S NEST FILTER
GUNTER TULIP FILTER*
OPT EASE *
RECOVERY FILTER *
OPTION FILTER*

( * Retrievable filters )

Slide courtesy of Dr. Mark Wilson
INDICATIONS FOR IVC FILTER PLACEMENT

1. PATIENTS WITH EVIDENCE OF PE OR ILIOFEMORAL DVT WITH ONE OR MORE OF THE FOLLOWING:
   > CONTRAINDICATION TO ANTICOAGULATION
   > COMPLICATION OF ANTICOAGULATION
   > FAILURE OF ANTICOAGULATION
   (ACUTE PE OF ENLARGING DVT)

2. MASSIVE ACUTE PE IN A PATIENT WITH ON GOING DVT WHO IS THEREFORE AT RISK FOR ADDITIONAL PE

3. FREE-FLOATING ILIOFEMORAL OR IVC THROMBUS

4. DVT IN THE SETTING OF SEVERE CARDIOPULMONARY DISEASE

5. POOR COMPLIANCE WITH ANTICOAGULATION REGIMEN
RELATIVE
INDICATIONS FOR IVC FILTER PLACEMENT

1. PROPHYLACTIC IVC FILTER PLACEMENT IN TRAUMA PATIENTS.

2. “HIGH-RISK” PATIENTS
   >LONG-TERM IMMOBILIZATION
   >PRE-OPERATIVELY PRIOR TO IMMOBILIZATION
   >HYPERCOAGULABLE PATIENTS WITH OR WITHOUT DVT (e.g., MALIGNANCY)

PREPIC Study

## Filter vs No Filter Results
### Day 12

<table>
<thead>
<tr>
<th>Significant Outcome</th>
<th>Filter/No Filter</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>1.1/4.8%</td>
<td>1.87</td>
<td>1.1-3.20</td>
</tr>
</tbody>
</table>


## Filter vs No Filter Results
### 2 Year Follow-up

<table>
<thead>
<tr>
<th>Significant Outcome</th>
<th>Filter/No Filter</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent DVT</td>
<td>20.8/11.6%</td>
<td>1.87</td>
<td>1.1-3.20</td>
</tr>
</tbody>
</table>

Filter vs No Filter Results
8 Year Follow-up

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Filter / No Filter</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sxtic PE</td>
<td>9 (6.2%) / 24 (15.1%)</td>
<td>0.008</td>
</tr>
<tr>
<td>DVT</td>
<td>57 (35.7%) / 41 (27.5%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Post Thrombotic Syndrome</td>
<td>70% / 70%</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>103 (51%) / 98 (49%)</td>
<td></td>
</tr>
</tbody>
</table>


Conclusions

- PE prevention mainly required short term initially following acute proximal DVT
- We need a randomized trial with retrievable filters
- In DVT w/o PE, doubtful whether filters + anticoagulation are useful

DVT Prophylaxis

THROMBOEMBOLISM AFTER TRAUMA

AN ANALYSIS OF 1602 EPISODES FROM THE ACS NATIONAL TRAUMA DATA BANK
Annals of Surgery 2004;240:490-6

M. Margaret Knudson, Danagra G. Ikossi, Linda Khaw, Diane Morabito, Larisa S. Speetzen

The University of California, San Francisco
RESULTS

- 450,375 patients included
- 84% blunt injuries
- 31% ISS>10
- 998 pts: DVT (0.36%)
- 522 pts: PE (0.13%)
- 82 pts: both DVT/PE
- PE mortality: 18.7%

RISK FACTOR ANALYSIS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock on admission (BP &lt; 90 mHg)</td>
<td>1.95</td>
</tr>
<tr>
<td>Age ≥ 40 yrs.</td>
<td>2.29</td>
</tr>
<tr>
<td>Head injury (AIS ≥ 3)</td>
<td>2.59</td>
</tr>
<tr>
<td>Pelvic fracture</td>
<td>2.93</td>
</tr>
<tr>
<td>Lower extremity fracture</td>
<td>3.16</td>
</tr>
<tr>
<td>Spinal cord injury with paralysis</td>
<td>3.39</td>
</tr>
</tbody>
</table>

  p < .0001 for all factors
### RISK FACTOR ANALYSIS (CONT')

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgical procedure</td>
<td>4.32</td>
</tr>
<tr>
<td>Venous injury</td>
<td>7.93</td>
</tr>
<tr>
<td>Ventilator days &gt; 3</td>
<td>10.62</td>
</tr>
</tbody>
</table>

* p < .0001 for all factors

### MULTIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head injury (AIS ≥ 3)</td>
<td>1.24</td>
</tr>
<tr>
<td>Major operative procedure</td>
<td>1.53</td>
</tr>
<tr>
<td>Lower extremity fracture (AIS ≥ 3)</td>
<td>1.92</td>
</tr>
<tr>
<td>Age ≥ 40 years</td>
<td>2.01</td>
</tr>
<tr>
<td>Venous injury</td>
<td>3.56</td>
</tr>
<tr>
<td>Ventilator days &gt; 3</td>
<td>8.08</td>
</tr>
</tbody>
</table>

* p ≤ 0.0125 for all factors
Spinal cord injuries

- Highest risk trauma patients
- DVT rates: 80%
- PE rates: 5%
- PE-most common cause of death

PROPOSED ALGORITHM

Injured Patient

High Risk Factor
(OR for VTE = 2-3)
- Age ≥ 40
- Pelvic fx
- Lower extremity fx
- Shock
- Spinal cord injury
- Head trauma (AIS ≥ 3)

Contraindication for heparin?
No
LMWH*
*Prophylactic dose
Yes
Mechanical compression

CONTRAINDICATION FOR HEPARIN?
No
Yes
LMWH* and mechanical compression
Mechanical compression and serial CFD OR temporary IVC filter

VERY High Risk Factor
(OR for VTE = 4-10)
- Major operative procedure
- Venous injury
- Ventilator days > 3
- 2 or more high risk factors

Mechanical compression
Serial CFD
Temporary IVC filter
### DVT PROPHYLAXIS: PATIENT CHARGES- SFGH

<table>
<thead>
<tr>
<th>Service</th>
<th>Avg. 2 Week Charge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential Compression Devices</td>
<td>$679</td>
</tr>
<tr>
<td>- stockings, sleeves, pump</td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>$3,220</td>
</tr>
<tr>
<td>- 30mg/twice daily</td>
<td></td>
</tr>
<tr>
<td>IVC Tulip (insertion/removal)</td>
<td>$10,400*</td>
</tr>
<tr>
<td>- filter and procedure charges</td>
<td></td>
</tr>
<tr>
<td>Serial CFD Scanning</td>
<td>$1,700*</td>
</tr>
<tr>
<td>- scan/tech charges</td>
<td></td>
</tr>
</tbody>
</table>

*Does not include professional fees*

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Summary

- Fondaparinux: safe and effective in trauma
- VTE protocol prospectively applied: successfully identified patients at risk
- Further multi-center studies are warranted

Factor Xa Inhibitors
Summary

- LMWH Rx of choice for DVT
- Factor Xa Inhibitors likely to replace Coumadin for chronic anticoagulation in the near future
- Catheter directed thrombolysis likely to have increasing role in management of DVT
- Removable caval filters may expand indications and reduce complications of Caval filters for prevention of PE.