THROMBOEMBOLIC DISEASE: THE WHY’S AND HOW’S

Jonaki Manna, MD, FRCPC
Hematopathology
OVERVIEW

1. “Normal” thrombosis
2. Classification of all thrombotic diseases

3. Definitions and Epidemiology

4. Etiology/Risks -- Why does abnormal venous thromboembolism occur?

5. Pathophysiology -- How does it occur?

6. Diagnosing venous thromboembolism

7. Treatment principles
### Normal Clot Formation

1. **Primary clotting**
   - Platelet plug
   - Adhesion
   - Aggregation
   - Activation

2. **Secondary clotting**
   - Coagulation cascade
   - Negative feedback
The Clotting Cascade

Intrinsic

Extrinsic

Common

- Enzymes (proteases) = most of the factors
- Coenzymes = V & VIII
- Cofactors = Calcium, phospholipids
Coagulation Cascade

Surface Contact

XII → XIIa
XI → Xla
IX → IXa + VIIIa
X → Xa + Va

PROTHROMBIN (II) → THROMBIN (IIa)

FIBRINOGEN (Ia) → FIBRIN Clot

TISSUE FACTOR

TF: VII a

XIII → XIIIa

X-linked FIBRIN Clot
Negative Feedback Mechanisms

1. Anticoagulants
   a. Antithrombin: inhibits proteases
   b. TFPI: inhibits proteases, mainly VIIa/TF
   c. Thrombomodulin + Protein C & S: breakdown coenzymes (V & VIII)

2. Fibrinolysis
Plasminogen → Plasmin → Fibrin → FDPs, DDimers

- PAI
  - tPA
  +

Alpha 2 - PI
Fibrinogen → Thrombin → Fibrin mesh → Factor XIII → Crosslinked fibrin mesh

Other FDPs → Plasmin → D-dimer

DDimer
Classification of thrombotic diseases

1. VENOUS THROMBOEMBOLISM (VTE)

2. Arterial thrombosis – mainly due to atherosclerosis (cardiovascular block)

3. Capillary thrombosis – mainly due to microangiopathic hemolytic anemias (hematology block)
1. Superficial vein thrombosis (SVT)
   - From IV, catheters, etc
   - Complications rare

2. Migratory SVT
   - Harbinger of malignancy?

3. Deep vein thrombosis (DVT)

4. DVT complications:
   - Pulmonary embolism (PE)
   - Postphlebitic syndrome
Pulmonary Emboli

DVT
DVT/PE Epidemiology

- DVT is relatively common
  - Estimated incidence = ~ 70 /100,000 / yr
  - Higher incidence among inpatients
  - 1 in 20 will develop a DVT over a lifetime

- 50% DVT pt have occult PE
- 30% PE pt have demonstrable DVT
- 1-8% PE pt die

- 40% DVT pt develop postphlebitic syndrome
- 20% Recurrent DVT within 5 years

VTE is preventable and treatable
Etiology/Risks of VTE

- Acquired
- Hereditary
### Etiology/Risks of VTE

#### Acquired
- Immobility
- Age
- Pregnancy
- Obesity
- Trauma
- Surgery

#### Hereditary
- Factor V Leiden
- Prothrombin gene mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin -3 deficiency
- Increased Factor 8
- Increased Homocysteine

- Malignancy
- Meds – BCP
- Inflammation
- Hyperviscosity
- APLS
Pathophysiology: Virchow’s Triad

- **STASIS**
- **VASCULAR INJURY**
- **HYPERCOAG**

**THROMBOSIS**

- ↑ Clotting factors
- ↓ Anticoagulants
- ↓ Fibrinolysis
# Etiology/Risks of VTE

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Hereditary</th>
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<tbody>
<tr>
<td>Immobility</td>
<td>Factor V Leiden</td>
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<td>Meds – BCP</td>
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Pathophysiology: Virchow’s Triad

- STASIS
  - Surgery
  - Trauma
  - Malignancy
  - Inflammation
  - Homocysteine

- VASCULAR INJURY

- HYPERCOAG

THROMBOSIS
Pathophysiology: Virchow’s Triad

- STASIS
  - Immobility
  - Age
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  - Surgery
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THROMBOSIS
Pathophysiology: Virchow’s Triad

**STASIS**
- Immobility
- Age
- Pregnancy
- Obesity

**THROMBOSIS**

**VASCULAR INJURY**
- Surgery
- Trauma
- Malignancy
- Inflammation
- Homocysteine

**HYPERCOAG**
- Hereditary Thrombophilias
- Pregnancy
- Age
- Malignancy
- Hyperviscosity
- Meds -- BCP
Pathophysiology: Virchow’s Triad

1. Multiple mechanisms
   - Pregnancy
   - Age
   - Malignancy

2. Unknown mechanisms
   - Hyperhomocysteinemia
   - Antiphospholipid antibody syndrome (APLS)
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### Acquired Thrombophilias

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<th>Risk Factor</th>
<th>Odds Ratio of VTE</th>
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<tbody>
<tr>
<td>Immobilization</td>
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<tr>
<td>Hospitalization</td>
<td>11</td>
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<tr>
<td>Pregnancy</td>
<td>4</td>
</tr>
<tr>
<td>Post partum</td>
<td>14</td>
</tr>
<tr>
<td>Surgery</td>
<td>6</td>
</tr>
<tr>
<td>BCP</td>
<td>4</td>
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### Hereditary Thrombophilias

50% with first unprovoked VTE have a Hereditary Disorder

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<th>Loss of Anticoagulant Function</th>
<th>Gain of Factor Function</th>
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<td>Factor V Leiden</td>
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<tr>
<td>Protein C Deficiency</td>
<td>Prothrombin Gene</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>Elevated Factor VIII</td>
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Hereditary Thrombophilias

- Hereditary Disorders of the Fibrinolytic Pathway are rare

- Hyperhomocysteinemia → Vascular damage?
## Epidemiology of Hereditary Thrombophilias

<table>
<thead>
<tr>
<th>Hereditary Disorder</th>
<th>Prevalence: % General Population</th>
<th>Prevalence: % Thrombosis Patients</th>
<th>Relative Risk Of VTE</th>
</tr>
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<tbody>
<tr>
<td>Protein C Deficiency</td>
<td>0.3</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>0.3</td>
<td>1-2</td>
<td>9</td>
</tr>
<tr>
<td>Antithrombin Deficiency</td>
<td>0.02</td>
<td>1</td>
<td>9</td>
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<tr>
<td>Factor V Leiden</td>
<td>5</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>2</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>High Factor VIII</td>
<td>11</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>5</td>
<td>10</td>
<td>3</td>
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Accumulative Risks

1. Hereditary + Hereditary  
   (eg. Factor V leiden and Protein C deficiency)

2. Acquired + Acquired  
   (eg. Pregnancy and immobilization)

3. Acquired + Hereditary  
   (eg. BCP + Factor V leiden)

4. > 2 Risk Factors → “Supra-Additive”
Combined Genetic Defects
Protein C Deficiency + Factor V Leiden

Thrombosis
Free Survival

Combined Genetic + Acquired Risks
Factor V Leiden + BCP or HRT
Supra-Additive Effect

Thrombosis Threshold

BCP
Factor V Leiden
Age
Immobilization

Thrombosis Potential

Age

Factor V Leiden
1. Mechanisms = Virchow’s Triad

2. DVT Complications:
   a. PE
Pulmonary Emboli

DVT
VTE Pathophysiology

1. Mechanisms = Virchow’s Triad

2. DVT Complications:

- PE
- Postphlebitic Syndrome:
  - Chronic venous insufficiency
  - Venous Hypertension
  - Edema
  - Hypoxia
  - Inflammation
1. “Normal” thrombosis
2. Classification of all thrombotic diseases
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4. Etiology/Risks -- Why does abnormal venous thromboembolism occur?
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7. Treatment principles
Diagnosing VTE

1. Clinical Aspects
   - DVT
   - PE
   - Postphlebitic syndrome

2. Radiologic Tests
   - Ultrasonography (doppler vs. compression)
   - Spiral CT (vs. V/Q scan and angiography)

3. Lab Tests
   - DDimers
   - Etiologic testing
Clinical Aspects

1. **DVT**
   - Swelling, painful,
   - Red, warm

2. **PE**
   - Typical: SOB, chest pain, hemoptysis
   - Atypical: Abdominal pain, syncope, fever, cough, seizure

3. **Postphlebitic Syndrome**
   - Swelling, pain,
   - Ulcers, rash
1. Ultrasonography
   - High sensitivity and specificity for *proximal* DVT but not for *distal* DVT
   - Compression US +/- Doppler US in symptomatic pt

2. Spiral CT
   - Higher accuracy and less radiation than V/Q scan
   - Non-invasive unlike angiography
Lab Testing

1. DDimers
   - High sensitivity
   - Low specificity

2. Etiologic testing
   - What?
   - When?
Lab Testing

1. DDimers

- High sensitivity: If negative, excludes VTE.
- Low specificity: If positive, can be due to thrombosis, infection, trauma, surgery, etc.

2. Etiologic testing

- What?
  - Acquired: Lupus inhibitor, antiphospholipid antibodies

- When?
  - Age, family history, recurrent, in ‘odd’ vessels
  - ~ 50% of pt with unprovoked VTE have underlying hereditary problem.
Approach To Diagnosis

Mod to High clinical suspicion
In order for radiologic and lab testing
To be of value

Determining Pretest probability
- Prevalence
- Clinical signs and symptoms
Pre test probability

Post Test Likelihood

Likelihood Ratio

Post Test Likelihood

- Likelihood Ratio

+ Likelihood Ratio

+ Post Test Likelihood
Treatment Principles

• Goal? = - To prevent further clot formation

• How? = - Heparin + Coumadin (Warfarin)
  - ~ 5 day overlap

Why?

- Heparin acts more rapidly (increases AT-3 activity) but is given IV
- Coumadin is PO but acts slower and has a potential, transient procoagulant state (inhibits vitamin K dependent factors + Pr C & S).
Treatment Principles

- **Goal?** = To prevent further clot formation
- **How?** = Heparin + Coumadin (Warfarin)
  - ~ 5 day overlap
- **Monitor?** = Heparin with PTT (~ 50 to 75)
  - Coumadin with INR (~ 2.0 to 3.0)
- **How Long?** = Typically 6 months on coumadin
  - 3 months (with transient risk factor)
  - Indefinite (eg. recurrent DVT)
1. Understand ‘normal’ clotting
2. Understand ‘abnormals’ = VTE

- Relatively common: Especially inpatients
- Etiology/Risks: Acquired + Hereditary
- Pathophysiology: Virchow’s Triad + Complications
- Diagnosis: Clinical + Radiologic + Lab
- Treatment: Heparin + Coumadin
?? QUESTIONS ??
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