Mechanisms of Thrombosis

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Things You Should Know:
1. Arterial (and sometimes venous) Thrombosis and Atherosclerosis (Plaque Rupture) - I consolidated things she said throughout the lectures on Slides 2 & 30
2. Venous Thrombosis and Pulmonary Embolism - Slides 4, 5 & 8
3. Thrombosis and Cancer - Slide 9
4. Differentiating Pre-Mortem and Post-Mortem Clots: Slides 6 & 7
5. Virchow's Triad (especially inflammation and hypercoagulability): Slides 10-21, 25
Thrombosis

- Formation of a blood clot in an artery or vein of a living person
- Arterial thrombosis denies oxygen and nutrition to an area of the body
  - Thrombosis of an artery leading to the heart causes a myocardial infarction
  - Thrombosis of an artery leading to the brain causes a stroke
- Acute arterial thrombosis often results from the deposition of atherosclerotic material in the wall of an artery, which gradually narrows the channel, precipitating clot formation

Narrowing of channel leads to TURBULENCE which precipitates clot formation. Details on atheroscleroris-thrombosis relationship Slides 30-32.
Thrombosis

• Extends into vessel without blocking it completely - *mural thrombus*

• Blocks it completely - occlusive thrombus

• Extends along the blood vessel - propagative thrombus

After MI, clot may form at site of damage along wall of ventricle

common in patients with DEEP-VEIN THROMBOSIS can create a cast of the venous system
Thrombosis

- Venous thrombosis blocks return of deoxygenated blood to the heart
- Venous thrombosis is quite common in the lower extremities, but can also occur in the upper extremities
- Symptoms include swelling, bluish discoloration and pain.
- The most feared complication of venous thrombosis is pulmonary embolism

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**Getting blood from legs to heart is difficult - physical (muscle) inactivity can lead to stasis in veins in legs BUT after clot is formed, activity can break the clot leading to major complications (like pulmonary embolism)**

**Inflammation, trauma (SURGERY or CATHETERIZATION) in limbs increases the risk for thrombosis - a lot of patients in the hospital will have some degree of venous thrombosis.**
Pulmonary Emboli

Clot travels from venous circulation to pulmonary artery and death can occur RAPIDLY.
Differentiating clots Post-mortem Clot from Pre-Mortem Thrombus or Embolus
- Post-Mortem Clots: CURRANT-JELLY CLOT - soft, falls apart
- Pre-Mortem Thrombus / Embolus: LINES OF ZAHN - laminations, layers of cells deposited over time
- Healing of Embolus involves adhesion to wall and re-canalization through clot. At the very least, it is stabilized so that it doesn't break off.
Is it thrombus or post-mortem clot?

- Thrombus adheres to the vessel wall
- May be red, white, or mixed
- Is crumbly and layered

When Thrombus leads to quick death (i.e. via MI), it can be hard to tell pre-mortem from post-mortem clots. In these cases, pre-mortem clots may simply be mixed in with atherosclerotic plaque.
Small pulmonary emboli

Suggests that there was time for pieces to break off from a bigger embolus - evidence for scarring / healing gives a timeline - at least a few days

Normally vessels don't stand out in lung sections. Vessels with emboli are DISTENDED with a "pinkish-hyaline appearance" of clot instead of RBC filled lumen
Thrombosis and Cancer:
- Malignant cells probably make Pro-Coagulants (Tissue Factor)
- Example: Renal Cell Carcinoma has a tendency to invade in vessels leading to propagation of clots and tumor along vessels
What Causes Thrombosis?

Virchow’s Triad:

- Stasis
- Vascular Injury
- Hypercoagulability
**STASIS**

*Loss of laminar flow with turbulence and eddy currents*

- Turbulence around valves when there is low flow rate (STASIS)
- Endothelial gaps form and platelets aggregate
- Intrinsic system activated on exposed collagen in gaps
- Tissue factor released and extrinsic system activated
- Heparinoids lost, decreasing AT III reactivity
- Prostacyclin synthesis is decreased
Vascular Injury

endothelial cell

examples: catheterization, external trauma, surgery

Hope is that platelet plug forms around damaged site and that propagation eventually stops
Hypercoagulability

The coagulant/anticoagulant proteins and the cells each play a role

INFLAMMATION can be key driver for this (especially at local vascular beds)
Evolution of the Paradigm

Old:  Hypercoagulable State = Systemic Disorder

New:  Vascular Bed-Specific Disorders


- Vascular-Bed Specific Signals
- Vascular-Bed Specific Cell Subtypes
- Vascular-Bed Specific Transcriptional Regulation

How do we test vascular bed function?

- Sometimes - in these cases we can test blood
  - Local factors like inflammation may determine hypercoagulability
- Hard because lab test may not always pick up the local vascular-bed specific factors
Hypercoagulability is multifactorial

Lifestyle and environmental factors play critical roles
Hypercoagulability is multifactorial

This is different from hemorrhagic disorders which are often single gene defects
Hypercoagulability

- Gene defect
  - AT deficiency
  - Protein C/S deficiency

SYSTEMIC DISORDERS that are detectable by blood test

AT - Anti-Thrombin: inhibitor of coagulant factors
- Heterozygotes: develop clotting problems as young adults
- Homozygotes: develop problems as infants
Anti-Thrombin can be replaced

Vitamin K dependent factors (anti-coagulant system)
(1) Deficiency due to Mutation
(2) Deficiency due to Activated Protein C Resistance
- mutation in Factor V
- APC resistance/factor V Leiden

  • Gene prevalence about 7% in Caucasians

  • Not Blacks or Asians

  • Up to 10% in some European populations
Protein C circulates in blood as zymogens

Leftover thrombin (from a triggered clot formation event) travels to healthy endothelium, binds to Thrombomodulin and activates Protein C (see next slide)

diagram:
- Protein C (PC)
- EPCR (Endothelial Protein C Receptor)
- TM (Thrombomodulin)
- IIa (Factor IIa)
- APC (Activated Protein C)

endothelial protein C receptor
endothelial cell
Thrombin on an Endothelial Surface has Anti-coagulant Activity

(1) Pro-Coagulant Activity generates Thrombin (COAGULANT)

(2) Thrombin binds to Thrombomodulin on a healthy cell (ANTI-COAGULANT) and activates Protein C (APC)

(3) APC binds to Protein S to inactivate Pro-Coagulants V and VIII

-Mutations affecting this pathway:
- Mutations in Protein C and S
- Mutations in Factor V that prevents its cleavage by APC / PS complex
- Mutation in Prothrombin

-Inflammation causes shedding of Thrombomodulin (TM) - inflammation promotes thrombosis
Hypercoagulability

Prothrombin G20210A Mutation

- Prevalence 1-2% in Caucasians
- Results in elevated prothrombin level
- Synergistic with FV Leiden
# Relative Risk of Thrombosis

Testing for people with family histories of thrombosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td>4</td>
</tr>
<tr>
<td>Factor V Leiden, <em>heterozygous</em></td>
<td>5-7</td>
</tr>
<tr>
<td>FV Leiden, <em>hetero + OC</em></td>
<td>30-35</td>
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<tr>
<td>FV Leiden, <em>homozygous</em></td>
<td>80</td>
</tr>
<tr>
<td>FV Leiden, <em>homo + OC</em></td>
<td>&gt;100</td>
</tr>
<tr>
<td>Prothrombin 20210AT, <em>heterozygous</em></td>
<td>3</td>
</tr>
<tr>
<td>Prothrombin 20210AT, <em>hetero + OC</em></td>
<td>16</td>
</tr>
</tbody>
</table>

*Synergistic*

*With age, risk of thrombosis increases dramatically*
“Anti-phospholipid” antibodies aka “Lupus Anticoagulants”

- Mildly prolong clotting assays, especially aPTT, by interfering with coagulation complex assembly on phospholipid surface
“Anti-phospholipid” Antibodies

• Are usually associated with thrombosis, not hemorrhage
• May be associated with autoimmune disease or may be primary
• Syndrome of recurrent fetal loss
Inflammation can also Promote a Hypercoagulable State

• “Activates” endothelial cells
  – Enhances TF expression
  – Reduces TM and heparan sulfate expression
  – Enhances expression of endothelial adhesion molecules
Impaired Fibrinolysis can Lead to Thrombosis

- Small clots probably form all the time in the vasculature and are lysed by the fibrinolytic system
tPA Release Initiates Fibrinolysis

Blood Flow

Endothelium

Plasminogen

Plasmin

Fibrinogen

Fibrin degradation products

Fibrin clot

tPA

Endothelium

tissue plasminogen activator
tPA and THROMBOSIS

• Deep vein thrombosis and pulmonary emboli occur in patients with depressed endothelial tPA stores

• Many factors lead to decreased endothelial synthesis of tPA including:
  – Obesity
  – Sedentary life style
  – Smoking
  – Birth Control Pills
PAI-1 AND THROMBOSIS

- Vascular smooth muscle and fat cells (and maybe others, too) synthesize an inhibitor of tPA called plasminogen activator inhibitor 1 (PAI-1)
- Some patients have elevated PAI-1
  - Inflammation
  - Hyperhomocysteinemia
  - Obesity
- PAI-1 levels are associated with thromboembolic disease
Thrombosis is Associated with Atherosclerosis

- Thrombosis can occur on atherosclerotic plaques - especially if a plaque ruptures
- Deposition of fibrin and activation of platelets intravascularly is associated with development of atherosclerotic lesions
- Sites of vascular injury – including turbulence – are sites of plaque development

When you’re on the wards, the answer is always PLAQUE RUPTURE:
- Plaques are inflexible and won’t distend / contract normally in response to systolic / diastolic pressure - inevitably they will break
- Pro-coagulant (Tissue Factor) in necrotic center of plaque is exposed when plaque ruptures. Precipitates a major clot and OFTEN a HEART ATTACK
Atherosclerosis starts young

PLAQUE RUPTURE - the precipitating event

MYOCARDIAL INFARCT

CEREBRAL INFARCT

GANGRENE OF EXTREMITIES

ABDOMINAL AORTIC ANEURYSM

CALCIFICATION
Complicated lesion: hemorrhage, ulceration, thrombosis

FIBROUS PLAQUE

FATTY STREAK

CLINICAL HORIZON

Age in Years

0 10 20 30 40 50 60 70
Atherosclerosis thickens the vessel wall and reduces the lumen size.
Thrombus from an aortic aneurysm

an impressive clot - vessel walls balloon due to atherosclerosis. dead tissue precipitates clot formation
Vegetations on Aortic Valve
Mechanical Heart Valve – a good source of emboli
What do we normally do for someone with a prosthetic heart valve?

ANTICOAGULANTS for life!
Bottom Line

- Thromboembolism is **multifactorial**, and risk factors accumulate (or even multiply)
- Thromboembolism can affect any organ/tissue
- Many aspects of modern lifestyle promote thrombosis and atherosclerotic vascular disease

"Go out there and jog, and avoid a pulmonary embolism"