**Anatomy of veins & arteries:** three layers

1. Tunica intima: inner layer
   - Endothelial layer – lining
     → Key in clottinb
   - Connective tissue – support
   - Internal elastic lamina – stretch
2. Tunica media: thicker in arteries
   - Connective tissue – support
   - External elastic lamina – stretch
   - Vascular smooth muscle – myogenic tone
3. Tunica adventitia: thicker in veins
   - Connective tissue – support
   - Nerves – regulation
   - Capillaries – nutrients for larger vessels

**Definitions**

- Hemostasis: regulation of fluid blood
  - Permit hemostatic blood clot at site of vascular injury
- Thrombosis: formation of clot in blood vessel
  - Pathogenic when it becomes too large or moves to new location
- Embolus: intravascular substance in wrong location
  - Substance from elsewhere
  - Travels in bloodstream

**Systemic blood vessels**

**Resistance vessels (arteries)**

- RESIST increase in BP
- Vessels stretched during cardiac ejection
- Elastic to distend & recover
- Dynamic to regulate blood pressure
  → Myogenic tone/reactivity: sustained & regulated vascular smooth muscle contraction in response to stretch/pressure
  → Convert high-pressure pulsatile to low-pressure non-pulsatile flow

**Capacitance vessels (veins)**

- Readily distend increasing CAPACITY w/ ↑pressure
- Accommodate increased blood volume
- No myogenic contractibility

**Hemostasis:** stop bleeding

- Retain blood in damaged vessel
  → Blood state change (liquid → solid)
- Three stages:
  1. Vasoconstriction
  2. Platelet plug formation
  3. Blood coagulation

**Thrombogenesis:** injury leads to transient vasoconstriction (limit blood loss)

**Triggers:**

- Injury to vascular smooth muscle
- Endothelial damage chemical release
- Platelet chemical release
- Local pain receptor reflex

**Role of platelets**: 3 functions after injury

1. Adhesion – to endothelium
2. Secretion – activating/regulating factors
3. Aggregation – accumulation at site of injury

**Role of endothelium**

- HOMEOSTATIS: "slippery" surface allows smooth blood flow
  → Has anticoagulant & antiplatelet adhesion properties
- Injury damages endothelium
  → Results in procoagulant/prothrombotic conditions
  - Adhesion of platelets to endothelium clot formation
  - Tissue factors synthesis regulates clotting cascade
  - Localized inhibitor secretion regulates clot formation
    - Limit FIBRINOLYSIS
    - Enhance THROMBOSIS

**Thrombogenesis steps**

1. Primary homeostasis → hemostatic plug formation
2. Coagulation cascade → secondary plug (stable clot)
3. Permanent plug formation

**Thrombogenesis** (continued – steps of clot formation)

**Primary hemostasis – short lived**

1. Platelet adherence to damaged endothelium to underlying exposed collagen
   - → Von Willibrand factor strengthens this interaction (platelet glycoprotein receptors & collagen)
2. Results in platelet activation
   - → Thromboxane: positive feedback on activation & local vasoconstriction
3. Release platelet secretory granules
4. Platelet recruitment to site of injury
5. Platelet morphological change: spherical → stellate (extending pseudopods over damaged surface)
6. Hemostatic plug formation
   - → Crosslinked fibrinogen w/ glycoprotein receptors
   - → Platelet aggregation
   - → SOFT PLUG could shear under blood flow

**Factors maintain localized formation of clot:** prevents spread

- Antithrombin: degrades/inhibits serine proteins in coagulation cascade IXa, Xa, Xia
- Protein C: vitamin K dependent anticoagulant degrades Va and VIIIa
- Tissue factor pathway inhibitor: limits tissue factor & downstream activation
- Plasmin: cleaves fibrin → degraded products unable to clot
- Prostacyclin: decreases free calcium levels available for pathway cascades

**Coagulation cascade:** enzymatic cascade

→ Intrinsic pathway
→ Extrinsic pathway
→ Common pathway

- Proenzyme → active enzyme
  - V & VIII = glycoproteins (not enzymes)
- Thrombin formation: essential coagulation factor
  - Fibrinogen → fibrin
- Platelets + fibrin → secondary plug
  - Proinflammatory effects

**Secondary hemostasis –** consolidation of platelet plug

- Tissue factor (factor III or thromboplastin)
  - Membrane-bound procoagulant glycoprotein
  - Exposed at site of injury
  - Prothrombin → thrombin
- **Permanent plug formation –** prevent further hemorrhage
  - Polymerized fibrin
  - Aggregated platelets

BALANCE between activators and inhibitors prevents PATHOLOGICAL CLOTTING

**Virchow's triad:** vessel quality, blood flow & blood composition

**Endothelial injury:** disturbs homeostatic procoagulation balance

→ Mainly involves ARTERIES (high blood flow rate)
  - Surgery, trauma
  - PmHx (previous embolism)
  - MI, atherosclerosis, vasculitis

**Hypercoagulation:** altered coagulation pathway

- Predisposition to thrombosis
  - Primary: genetic (V & prothrombin mutated genes)
  - Secondary: acquired

**Blood flow**

- Turbulence: blood flow is chaotic (non-linear, not smooth)
  - ARTERIES & HEART; worse in large/branching vessels
  - Pockets of STASIS → damage to ENDOTHELIUM
- Stasis: disturbance/low blood flow (stagnant)
  - Retention in extremities/viscera
  - VENOUS THROMBOSIS
  - Risk factors: age; immobility; stroke; paralysis; spinal cord injury; viscous blood (↑ RBC & WBC); CHF; COPD; obesity
- Altered BLOOD FLOW → promotes endothelium procoagulation (low flow = buildup of activation factors)
  - Normal flow: platelets to center; plasma to endothelium
  - Disrupted laminar flow: more platelet interaction w/ luminal lining

**Thrombosis**: systemic risk as clots can develop anywhere with circulation

Secondary (acquired) hypercoagulation:
- HIGH RISK: bed rest, immobilization, injury, heart valves, surgery, heparin, antiphospholipid Ab syndrome
- LOW RISK: cardiomyopathy, nephrotic syndrome, oral contraceptive, sickle cell anemia, smoking

**Outcomes**
- Propagation: accumulation clots towards heart
  - Retrograde in arteries (slows blood flow → clot dam)
  - Anterograde in veins (tail of clot points with blood flow)
- Embolization: dislodged & transit
- Dissolution: normal clot removal/restore circulation
- Organization & recanalization → limited restoration of blood flow
  - Ingrowth smooth muscle, fibroblasts, epithelium = new "capillary" formation

**Common sites**:
- Coronary → myocardial infarction
- Cerebral → stroke
- Deep veins → pulmonary embolism

**Composition of thrombi**
- Arterial: platelet aggregates → white thrombi
- Venous: fibrin & RBCs → red thrombi

**Ischemic stroke:** lack of $O_2$ to tissues

**Causes**
- Local thrombus formation
- Embolitic occlusion
  - Cranial arteries
  - Cardiac embolism (Afib)

**Risk factors**
- Age
- Gender
- Family hx
- Hypertension
- Atrial fibrillation
- Diabetes
- High cholesterol (dyslipidemia)
- Smoking
- Alcohol

**Symptoms**
- Weakness
- Difficult/slurred speech
- Vision problems
- Headache, dizziness

3 HR THERAPEUTIC WINDOW FOR EFFECTIVE MEDICAL INTERVENTION (limit ischemic tissue damage)

**Pulmonary embolism:** blockade of pulmonary artery

**Sx:**
- Sputum production
- Difficulty/RAPID breathing
- Chest pain on inspiration
- Low blood $O_2$ sat/cyanosis
- Tachycardia, dizziness, syncope

**Dx:**
- Spiral CT scan
- V/Q scan
- Imaging
- EKG

- <u>Hemodynamic changes:</u> ↑ pulmonary vascular resistance & ↑ right ventricular afterload → ↓ CO
- <u>Impaired gas exchange:</u> no perfusion distal to site of occlusion → V/Q mismatch → dead space
- **<u>HYPOXIA</u>**

**Deep vein thrombosis:** thrombus in deep vein; generally occlusive; 95% cause in PE

**Risk factor DVT = pulmonary embolism**
- Clotting disorder
- Hormone/CA therapy
- Injury to big/deep vein
- Reduced blood flow rate (bedrest)
- Pregnancy/peri-pardem
- Venous catheter
- Age (>60 years)
- Smoking
- Obesity

**Sx**
- Swelling
- Pain
- Discoloration
- Edema
- Tenderness
- Warmth
- HOMAN'S TEST- pain dorsoflexion of foot

**Well's criteria for diagnosis** (score -2 → 9)
1 point each for:
- Tenderness along vein system
- Swelling of entire leg/limb
- >3cm difference in calf circumference
- Pitting edema
- Swollen/visible superficial veins
- Risk factors (cancer, immobility, paralysis, surgery, illness)

SUBTRACT 2 pts for possible alternative diagnosis

→ High DVT risk = > 3
→ Moderate = 1-2
→ Low DVT risk = < 0