Hemodynamic Disorders, Thromboembolic Disease, and Shock
Normal Fluid Homeostasis

- Vessel wall integrity
- Intravascular pressure
- Osmolarity
- Maintaining blood as a liquid
- Appropriate clot formation during injury
Factors Affecting Fluid Transit Across Capillary Walls
Edema

Increased fluid in interstitial spaces
Body Water

- Intracellular
- Interstitial
- Plasma
Pathophysiologic Categories of Edema

- Increased hydrostatic pressure
- Reduced plasma osmotic pressure
- Lymphatic obstruction
- Sodium and water retention
- Inflammation
Increased Hydrostatic Pressure

- Impaired venous return
  - CHF
  - Constrictive pericarditis
  - Ascites (cirrhosis)
  - Venous obstruction
    - Thrombosis
    - External pressure
    - Lower extremity inactivity

- Arterial dilation
  - Heat
  - Neurohormonal regulation
Edema: morphology

• Better appreciated grossly than microscopically
• Subcutaneous
  – Localized
  – Generalized (anasarca)
• Pulmonary
• Brain
Clinical Correlation

• Subcutaneous edema
  – Signals underlying disease
  – Can impair wound healing

• Pulmonary edema
  – Impairs ventilatory function
  – Can lead to death
  – Increased susceptibility for bacterial infection

• Brain edema
  – Can be rapidly fatal and lead to herniation
Hyperemia and Congestion
Hyperemia vs. Congestion

• Hyperemia
  – Increased inflow of blood
  – Active process
  – Bright red discoloration of tissue

• Congestion
  – Decreased outflow of blood
  – Passive process
  – Often associated with edema
  – Blue-red discoloration
Hyperemia and Congestion

NORMAL

Arteriole

Venule

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HYPEREMIA
erythema

Increased inflow

(e.g., exercise, inflammation)

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CONGESTION
cyanosis/hypoxia

Decreased outflow

(e.g., local obstruction, congestive heart failure)

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Congestion

- Commonly occurs with edema
- Chronic passive congestion can lead to tissue hypoxia and cell death
- Capillary rupture at the site of congestion can lead to hemorrhage
Congestion of the Liver
Hemorrhage

Extravasation of blood due to vessel rupture
Patterns of Hemorrhage

- Hematoma: accumulation of blood within a tissue
- Petechiae: 1-2 mm hemorrhages in skin, or mucus membranes, or serosal surfaces
- Purpura: slightly larger >3 mm than petechiae
- Ecchymoses: Larger 1-2 cm subcutaneous hematoma
- Hemothorax, hemopericardium, hemoperitoneum, hemarthrosis
Clinical Significance of Hemorrhage

- Depends on volume and rate of bleeding
- >20% may lead to hypovolemic shock
- Site of hemorrhage is important
- Iron deficiency anemia can develop in chronic blood loss
Hemorrhage
Hemostasis and Thrombosis
Stages of normal hemostasis

- Vasoconstriction
- Primary hemostasis
  - platelet plug formation
- Secondary hemostasis
  - Fibrin deposition and polymerization to strengthen plug
  - Coagulation cascade
- Antithrombotic mechanisms to limit formation of thrombotic plug (fibrinolysis)
Vasoconstriction

A. VASOCONSTRICTION

Endothelium  Basement membrane  Arteriole smooth muscle

Endothelin release causes vasoconstriction  Reflex vasoconstriction  ECM (collagen)

Site of injury

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Primary Hemostasis

1. Platelet adhesion
2. Shape change
3. Granule release (ADP, TXA$_2$)
4. Recruitment
5. Aggregation (hemostatic plug)

Endothelium, Basement membrane, Collagen

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Secondary Hemostasis
Anti-thrombotic Counter-Regulation

D. THROMBUS AND ANTITHROMBOTIC EVENTS

Release of:
- t-PA (fibrinolysis)
- thrombomodulin (blocks coagulation cascade)

Trapped neutrophil
Trapped red blood cells
Polymerized fibrin

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Factors in Normal Hemostasis

• Direct players
  – Endothelium
  – Platelets
  – Coagulation cascade
Pro- and Anti-coagulant Activities of Endothelial Cells
Capillary Endothelium

• Anti-thrombotic properties
  – Anti-platelet effects
    • Prevention of platelet aggregation to underlying extracellular matrix
  – Anti-coagulant effects
    • Heparin-like molecules
    • Thrombomodulin
    • Tissue factor pathway inhibitor
  – Fibrinolytic effects
    • t-PA
Capillary Endothelium

• Pro-thrombotic properties
  – Platelet effects
    • von Willebrand factor (vWF)
  – Procoagulant effects
    • Tissue factor
  – Anti-fibrinolytics
Platelets

- Platelet adhesion
  - vWF- glycoprotein Ib
- Secretion of granule contents
- Aggregation
  - Primary hemostatic plug (platelets)
  - Secondary hemostatic plug (platelets and fibrin)
Platelet Adhesion and Aggregation
Coagulation Cascade

• Series of enzymatic reactions in the plasma
• Conversion of proenzymes into active enzymes
• Culminates in the formation of thrombin, which then converts soluble fibrinogen into fibrin
Coagulation Cascade

• Reactions are assembled on a phospholipid complex (i.e. surface of platelets)
• Requires calcium
• Intrinsic and extrinsic pathways
  – Factor XII (Hageman factor) activates intrinsic pathway
  – Tissue factor activate extrinsic pathway
  – Interconnections exist
Coagulation Cascade

The diagram illustrates the coagulation cascade, separated into Intrinsic Pathway and Extrinsic Pathway. Key components include factors X, IX, Xa, II, VII, X, and protective mechanisms. Calcium ions (Ca²⁺) and thrombin are central to the process. The diagram highlights the interactions and activation steps leading to fibrin formation and cross-linking.
Control of the Coagulation Cascade

• Anti-thrombins
  – Anti-thrombin III
  – Proteins C and S
  – Tissue factor pathway inhibitor

• Fibrinolytic cascade
  – Plasmin
  – T-PA
  – Fibrin split products (D-dimer)
The Fibrinolytic System
Thrombosis

Inappropriate activation of a normal hemostatic process
Virchow Triad
Endothelial Injury: Causes

- Myocardial infarction
- Valvular disease
- Hypertension
- High blood cholesterol
- Bacterial endotoxins
- Cigarette smoke
Alterations in Normal Blood Flow: Stasis and Turbulence

• Disrupt laminar flow and bring platelets into contact with the endothelium
• Prevent dilution of clotting factors by preventing fresh inflow of blood
• Permit the build up of thrombi by retarding inflow of clotting factor inhibitors
• Promote endothelial cell activation
Stasis and Turbulence: Causes

- Ulcerated atherosclerotic plaques
- Aortic aneurysms
- Myocardial infarctions
- Inactivity
Hypercoagulability

• Any alteration of the coagulation pathways that predisposes to thrombosis
• Inherited
• Acquired
Inherited Hypercoagulability

- Factor V gene mutation (Factor V Leiden)
- Prothrombin gene mutations
- Inherited deficiencies of anticoagulants such as Protein C and S
- Should be considered in patients under the age of 50 who present with thrombosis in the absence of any acquired predisposition
Acquired Hypercoagulability

- Prolonged bed rest or immobilization
- Myocardial infarction
- Atrial fibrillation
- Tissue damage (fracture, burns, surgery)
- Cancer
- Obesity
- Oral contraceptives
- Pregnancy
Heparin Induced Thrombocytopenia

- Affects 3-5% of the population
- Occurs with unfractionated heparin
- Induces circulating antibodies that bind heparin AND platelet membrane proteins
- Antibodies activate platelets
- Low-molecular-weight heparin circumvents the problem
Anti-phospholipid Antibody Syndrome

- High titers of antibodies against phospholipids (cardiolipin)
- Tends to occur in patients with lupus
- Recurrent arterial and venous thrombosis, repeated miscarriages, cardiac valvular vegetations, thrombocytopenia
- Interfere with *in-vitro* lab tests for coagulability
- Lead to hypercoagulability *in-vivo*
Morphology of Thrombi
Cardiac and Aortic Thrombi

• Lines of Zahn
  – Laminations due to alternating platelets/fibrin and red cells

• Mural thrombi
  – Applied to the wall of cardiac chambers or the aorta
Mural Thrombus in the Heart
Thrombus in a Dilated Abdominal Aortic Aneurysm
Arterial Thrombi

- Coronary arteries
- Cerebral
- Femoral
- Usually superimposed on atherosclerotic plaques
Venous Thrombi

• Generally due to stasis
• Creates a long cast of the vein lumen
• 90% of cases occur in lower extremities
• Can also occur in upper extremities, the periprosthetic plexus, ovarian and periuterine veins, dural sinuses, portal vein, or hepatic vein
Potential Outcomes of Venous Thrombosis
Clinical Correlation of Thrombi

• Cause obstruction of arteries and veins
• Possible sources of emboli
Venous Thrombosis (Phlebothrombosis)

- Superficial and deep veins of the leg
- Local congestion with swelling, pain, tenderness or may be asymptomatic
- Deep thrombi more likely to embolize
- Major danger is pulmonary embolism
Clinical Settings of DVT

- Cardiac failure
- Trauma, surgery, burns
- Pregnancy and post-partum states
- Disseminated cancer
- Advanced age, immobilization, bed rest
Arterial and Cardiac Thrombosis

• Atherosclerosis is major initiator
• Mural thrombi
• Valve disease
• Arterial thrombi can also embolize
  – brain, kidneys, spleen
Disseminated Intravascular Coagulation

- Sudden or insidious onset of widespread thrombi in the microcirculation
- Diffuse circulatory insufficiency
- Rapid consumption of platelets and fibrin
- Activation of fibrinolytic mechanisms can of all into a bleeding disorder
- Potential complication of any condition associated with widespread activation of thrombin
Embolism

Detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.
Pulmonary Thromboembolism

- 200,000 deaths per year in United States
- Most originate from deep leg vein thrombi
- Carried through the circulation, pass through the right side of the heart, and into the pulmonary vasculature
Pulmonary Thromboembolism

• Can occlude:
  – Main pulmonary artery
  – Bifurcation of the pulmonary artery (saddle embolus)
  – Pass into smaller arterioles

• Can be clinically silent, or result in sudden death, pulmonary hemorrhage, or cause pulmonary hypertension
Pulmonary Thromboembolus
Systemic Thromboembolism

- Refers to emboli traveling within the arterial circulation
- Most arise from intracardiac mural thrombi
- Remainder originates from thrombi associated with ulcerated atherosclerotic plaques
- Lower extremities (75%), brain (10%), intestines, kidneys, and spleen
Other types of Emboli

• Bone marrow/fat emboli
• Air embolism
• Amniotic fluid embolism
Bone Marrow Embolus
Infarction

An area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage of a particular issue.
Infarction

• Nearly all infarcts result from thrombotic or embolic events
• Almost all result from arterial occlusion
• Other mechanisms
  – Local vasospasm
  – Hemorrhage within an atherosclerotic plaque
  – Extrinsic compression of a vessel
Examples of Infarcts
Morphologic Characteristics of Infarcts

- Can be red in color due to hemorrhage, or pale due to lack of blood supply
- Wedge shaped
- Coagulative necrosis
  - Most replaced by scar tissue
- Inflammation incited by necrotic tissue
Depressed Cortical Scar from an Old Kidney Infarct
Factors that Influence Development of an Infarct

- Nature of the vascular supply
- Rate of development of the occlusion
- Vulnerability to hypoxia
- Oxygen content of blood
Shock

Systemic hypoperfusion due to a reduction either in cardiac output or in the effective circulating blood volume
Shock

• Cardiogenic
  – Myocardial pump failure

• Hypovolemic
  – Loss of blood, fluid loss

• Septic
  – systemic microbial infection
Septic Shock

- 25 to 50% mortality rate
- #1 cause of death in intensive care units
- Spread and expansion of an initially localized infection into the bloodstream
Septic Shock

- Most caused by gram-negative bacilli that produce endotoxin
- Bacterial wall component (LPS) activates immune cells, complement, and results in a cytokine cascade
Effects of Septic Shock

- Systemic vasodilatation (hypotension)
- Diminished myocardial contractility
- Widespread endothelial injury and activation
- Activation of the coagulation system, leading to DIC
- Multi-organ system failure
Stages of Shock

• Nonprogressive stage
  – Reflex compensatory mechanisms are activated to maintain perfusion of vital organs
  – Tachycardia, peripheral vasoconstriction, renal conservation of fluid
Stages of Shock

• Progressive stage
  – Tissue hypoperfusion and onset of worsening circulatory and metabolic imbalances
  – Lactic acidosis
  – Blunting a vasomotor response
  – Confusion, decrease in urine output
Stages of Shock

• Irreversible stage
  – Severe tissue injury
  – Survival not possible
  – Myocardial contractile function worsens
  – Renal shutdown
  – Ischemic bowel
Morphology Of Shock

• Brain
  – Ischemic encephalopathy

• Heart
  – Widespread coagulation necrosis, subendocardial hemorrhage

• Kidneys
  – Acute tubular necrosis

• Lungs
  – Diffuse alveolar damage

• Gastrointestinal tract
  – Mucosal hemorrhage and necrosis

• Liver
  – Central hemorrhagic necrosis