DISTURBANCES OF CIRCULATION
VPM 152 – General Pathology
Lisa Miller

PREFACE: In this portion of General Pathology normal hemostasis will be reviewed. The pathological processes which may be associated with abnormal hemostasis will be discussed. A good understanding of how fluids normally pass from tissue into the vascular system and back again is important for the study of disease, understanding the pathogenesis of disease, and treatment of disease processes.

Definition: Hemostasis - arrest bleeding, either by the physiological properties of vasoconstriction and coagulation or by surgical means.

Homeostasis - Normal fluid homeostasis encompasses maintenance of vessel wall integrity as well as intravascular pressure and osmolarity within certain physiologic ranges.

NOTES: "The metabolism of organs and cells depends on an intact circulation for continuous delivery of oxygen, nutrients, hormones, electrolytes, and water; and for the removal of metabolic waste and carbon dioxide. Delivery and elimination at the cellular level are controlled by exchanges between the intravascular space, interstitial space, cellular space, and lymphatic space."

'The survival of cells and tissues is exquisitely dependent on the oxygen provided in a normal blood supply and therefore on delivery of sufficient blood through a patent circulatory system.'

"The well-being of tissues requires normal fluid balance. Abnormalities in vascular permeability and hemostasis can result in cellular injury even if the blood supply is intact.”

REFERENCES:


BLOOD VESSELS - CHAPTER 10 (BENDITT & SCHWARTZ) In: ESSENTIAL PATHOLOGY, RUBIN AND FARBER, 1995, PP 245-275

**REVIEW ITEMS** - (some things you might want to think about)

**Important Items:**
1. Distribution of fluid is a carefully controlled homeostatic mechanism.
2. Deviations from normal may have profound pathological effects.
3. Normal functions require intact blood and lymph vessels.

**Capillary bed**
- Enormous volume
- Site where fluid exudes from circulating blood

**Endothelial Cells Synthesize and Secrete Glycoproteins**
FUNCTION of endothelial glycoproteins:
- Inhibit clotting
- Protect endothelial cells
When INJURY occurs to the endothelium
- Synthesis and release of glycoproteins impaired which results in problems with hemostasis and fluid transport

**Mechanisms for Substance to Transport Across Capillary Endothelium**
1. Direct diffusion (ions, water and small molecules)
   - Passive diffusion across vessel wall
2. Active transport
   - Occurs via special protein ion pumps embedded in plasma membranes at cell surface
3. Endocytosis and Exocytosis (discussed by Dr. Hanna)

**Expansion of Cell Junctions**
- Allows large molecules and excess fluids to pass into the interstitium

**Precapillary arterioles:**
- Contain small, innervated myocyte sheaths
- Contract to control blood flow (regulation of blood flow)

**Postcapillary Venules:**
- Sites of fluid exudation
- Susceptible to some toxins

**Capillaries:**
- Sites of fluid exudation

**Regional Differences in Capillary Permeability:**
- Dependant on the structural variation in the vascular wall
  - eg1: **Blood-Brain Barrier** - restricted transport
    - Tight intercellular junctions
    - Reinforced by astrocyte foot processes
  - eg2: **Bone Marrow Sinusoids**
    - Endothelium open to passage of soluble and particulate material

**Cyclic changes:**
- eg: Uterine Mucosal Capillary Endothelium - flattened and relatively structureless in sexually inactive females enlarged and filled with ribosomes with progesterone stimulation

**Blood Pressure:**
- **8 BP** (passage rates of low-molecular proteins)
  - Protein tracer molecules pass into tissue in massive amounts
  - Loss of barrier function in endothelium under high pressure
**EDEMA**

**TOTAL BODY WATER** - (65% of lean body weight) = plasma (5% lean body weight) + interstitial tissue fluid (15% lean body weight) + intracellular fluid (40% lean body weight) + transcellular fluid (5%).

**Edema** is the abnormal accumulation of excess fluid in interstitial tissue spaces or body cavities. Fluid is outside cells and outside vascular structures.

**Interstitium**: Space between tissue compartments  
-Binds most cellular and structural elements into discrete organs and tissues -  
(What remains after you remove the blood and lymphatic vessels, nerves and parenchymal cells from a tissue)

**Interstitium** = Extracellular Matrix (ECM) + Supporting cells  
Extracellular Matrix:  
Insoluble Components  
Collagen  
Elastic fibers  
Fibronectin  
Laminin  
Soluble Components  
Glycosaminoglycans  
Proteoglycans

**Interstitial Tissue Fluid**:  
Intermediary - all metabolic products pass to enter or leave cells  
-constant exchange both with plasma and with cellular fluids.  
**Endothelium + underlying basement membrane** allows the free passage of H$_2$O + ions and opposes the passage of plasma proteins.

**Starling’s law**: Hydrostatic pressure in the vascular system (aided slightly by perivascular osmotic pressure) moves fluid out of the system. Osmotic pressures of the plasma proteins, and to a lesser extent, tissue pressure around blood vessels are the forces that contain the fluid within the vascular system.
EDEMA: Abnormal accumulation of excess fluid in interstitial tissue spaces or in body cavities. Edema fluid is outside the vascular fluid compartment and outside the cellular fluid compartment. (ie: within interstitium)

Five Pathophysiological Mechanisms that underlie the development of edema
1. Decrease plasma colloidal-osmotic pressure
2. Increase blood hydrostatic pressure
3. Lymphatic obstruction
4. Increased vascular permeability
5. Sodium retention ([vascular hydrostatic psi, \ plasma colloid osmotic psi])

GROSS
Wet, gelatinous and heavy, organs are swollen, fluid weeps from cut surface
(In several species [horses and some breeds of cattle], fluids are slightly yellow)

HISTO Tissues are pale staining. Tissue spaces are distended by lightly staining eosinophilic fluid. Blood vessels maybe filled with erythrocytes (hyperemia). Lymphatics are dilated. The edema may be difficult to discern if the protein content is low. Collagen bundles of interstitial stroma are separated by an increase in intercellular space.

TWO TYPES OF EDEMA:
1. INFLAMMATORY
2. NONINFLAMMATORY

NONINFLAMMATORY EDEMA
Mechanisms:
1. Decrease plasma colloidal-osmotic pressure
   eg: Hypoalbuminemia
   Definition: HYPOALBUMINEMIA - abnormal low concentration of albumin within blood
2. Increase hydrostatic pressure (impediment to venous blood flow)
   eg: right heart failure
3. Lymphatic obstruction
4. Sodium retention
Fluid Characteristics: "protein poor"

**Transude**
- low protein content < 30 g/L
- specific gravity below 1.017
- total nucleated cell count < 1.5 X 10^9/L

**INFLAMMATORY EDEMA**

**Mechanism:** Increased Vascular Permeability - Endothelial damage

**Fluid Characteristics:** "protein rich"

**Exudate**
- high concentration of protein > 30 g/L
- specific gravity > 1.025
- total nucleated cell count > 7.0 X 10^9/L

**LOCAL EDEMA**

**Mechanisms:** Local Increase in hydrostatic pressure
- Lymphatic obstruction
- Inflammation

**Etio:** impaired venous drainage or lymphatic blockade or inflammation

eg1: Improperly bandaged limb resulting in venous occlusion
eg2: Damage to lymphatics (surgery, neoplasm, or intravascular parasites)
eg3: Inflammation may also affect lymphatics (*lymphangitis*)

**GENERALIZED EDEMA**

**Mechanism:**
1. Increased hydrostatic pressure of blood
2. Decreased colloid osmotic pressure of plasma proteins
3. Sodium retention

**Etio:** Heart Failure – usually right heart failure
- Liver disease
- Chronic renal disease

**Location:** *Dependent edema*: Ventral abdominal subcutis
- Subcutis of the ventral cervical region
- Subcutaneous tissues of the limbs

**TERMINOLOGY used when describing Non-Inflammatory Edema:**

**PITTING EDEMA:**
When pressure is applied to an area of edema a depression or dent results as excessive interstitial fluid is forced to adjacent areas.

**ANASARCA:** Swelling of the subcutis due to severe generalized edema

**HYDROTHORAX:** Fluid in the thoracic cavity,
(Transude – noninflammatory fluid)

**HYDROPERICARDIUM:** Fluid (transude) in the sac around the heart
ASCITES -or- HYDROPERITONEUM: Fluid in the peritoneal cavity

LYMPHATIC BLOCKAGE
Pathogenesis: block lymphatic drainage 6 8 interstitium fluid
6 accumulation of lymph in tissue or in body cavities
[LYMPHANGIECTASIA: Dilatation of lymphatic vessels]
Etiology: Lymphatic damage due to: surgery, neoplasia, parasites, hereditary malformations

THORACIC DUCT OBSTRUCTIONS
Pathogenesis: Thoracic duct rupture 6 chylothorax
(Chyle - the milky fluid taken up by lacteals from food in the intestine, is composed of lymph and triglyceride droplets)
Etiology:
  Trauma
  Neoplasia
  Congenital defects
  Inflammation
  Idiopathic

Clinical Significance of Edema
Dependent upon:
  a. Extent - severity
  b. Location - ie. Site of accumulation
  c. Duration - tissues may become more firm and distorted due to an increase in fibrous connective tissue after prolonged edema.

PULMONARY EDEMA
Definition: Common cause of death in many disease processes
Sequence:
  1. Fluid accumulates in interstitium
  2. Fluid disrupts the basement membranes
     Endothelial cells
     Pneumonocytes
  3. Leads to fluid within alveoli
  4. Fluid drains via lymphatics
  5. Result dilated pleural lymphatics

Histo: Edema appears first perivascularly
  - Plasma exudes into alveoli
  - Dilated pleural lymphatics

GROSS: Lungs are heavy and wet; fluid may be present within bronchi and obvious on cut sections. The interlobular septa are often increased and contain clear fluid. Congestion often present (will be discussed in a later lecture).
Mechanisms of pulmonary edema: (2)

1. **Circulatory failure** - 8 hydrostatic psi of blood (pulmonary veins)
   - 6 Changes in pulmonary hemodynamics
   - 6 Slow exudation of fluid into alveoli
   - Most commonly cause of pulmonary edema

2. Damage to pulmonary capillary endothelium - *Inflammatory Edema*
   - Sudden, diffuse, direct - 8 vascular permeability
   - Usually peracute stage of inflammation
   - Followed by pneumonia - if animal survives

**CHRONIC PULMONARY EDEMA**
- Most commonly associated with cardiac failure
- 8 in the flow of lymph 6 dilation of pleural lymphatics
- Pleural fibrosis may occur
- Alveolar walls become thickened
- Hyperplastic pneumonocytes
- Collagen may be deposited in alveolar walls
  - 9 resiliency of pulmonary parenchyma

Reminder: Pulmonary edema will be discussed again with pulmonary congestion

**EDEMA OF THE BRAIN**

**Synonym:** Cerebral Edema

**Causes:**
- Trauma to the calvarium
- Obstruction of venous outflow
- Intracranial infections
  - (meningitis, brain abscess, and encephalitis)

**Gross:** Brain heavier than normal
- Sulci are narrow
- Gyri are swollen and become flattened

**Cerebral Coning** - herniation of the caudal cerebral cortex through the tentorium cerebelli

**Cerebellar coning** - herniation of the cerebellum through the foramen magnum

**Histo:** Expansion of perivascular spaces (Virchow-Robin)
REVIEW OF PATHOPHYSIOLOGY OF EDEMA

Figure 4-2, (page 121). Sequence of events leading to systemic edema due to primary heart failure, primary renal failure, or reduced plasma osmotic pressure (as in malnutrition, diminished hepatic protein synthesis, or loss of protein owing to the nephrotic syndrome). ADH, antidiuretic hormone; GFR, glomerular filtration rate. Downloaded from: Robbins & Cotran Pathologic Basis of Disease.

DEHYDRATION

Definition: Deficiency of water resulting from imbalance between the uptake and loss of water from the body. It is the opposite of edema.

Causes: Uncontrolled diarrhoea
           Vomiting
           Renal Failure
           Diabetes
           Heat-stroke
           Water Deprivation

Mechanism: A decrease in the total body water results in water deficit shared among plasma, intracellular, and interstitial fluid compartments. Hypovolemic shock accompanies severe dehydration as plasma water is drawn into the interstitium. Renal perfusion is reduced.

Pathological Findings:
- Folds of skin pulled out from the body hesitate before returning to their normal position, "tenting"
- Eyes are sunken
- Mucous membranes and subcutaneous tissues are dry and sticky
HYPEREMIA AND CONGESTION

TERMINOLOGY

HYPEREMIA: An excessive amount of blood in an organ (refers to both volume and flow)
1E implication - active, arteriolar-mediated engorgement of vascular bed

CONGESTION: An excessive amount of blood (refers to volume)
1E implication - passive, venous engorgement
AKA Passive Hyperemia

NOTES:
-Both indicate a local increase in blood volume in a particular tissue.
-Congestion within capillary beds is closely related to edema formation. Therefore, congestion and edema frequently are observed together.

HEMORRHAGE VS HYPEREMIA:
Hemorrhage - blood outside vessel wall
ie: extravascular
Hyperemia - blood inside of vessel wall
ie: intravascular

ETIOLOGY of HYPEREMIA:
1. Too much blood via the arterioles - Active Hyperemia – red
2. Too little blood is being removed by the venules - Passive Hyperemia – blue

TYPES of Hyperemia:
1. Physiologic Hyperemia:
   eg1: 8 blood flow to the stomach and intestines during digestion
   eg2: 8 blood flow in the muscles of athletes during exercise
   eg3: neurovascular Hyperemia
2. Pathologic Hyperemia
   -manifestation of some alteration in blood flow (NOT THE CAUSE)
   -result of an underlying pathologic process

3 factors used in defining the types of pathological Hyperemia
1. Duration
2. Extent
3. Mechanisms

1. DURATION: acute/chronic
   Acute: implies abrupt onset with rapid development
   Chronic: slowly developing and/or present for a long time
2. EXTENT: localized/generalized
   Local: change confined to a discrete area (localized or limited)
   Generalized: indicates a systemic change or generalized within an organ
3. MECHANISMS: active/passive
   Active: due to increased arteriolar flow
   Passive: due to impaired venous drainage

EXAMPLES:
1. Acute Local Active Hyperemia:
   Engorgement of the vascular bed due to increased arteriolar blood flow into an area
   -cardinal sign of inflammation =
   "Hyperemia of Inflammation"

2. Acute Local Passive Hyperemia:
   Local obstruction to venous drainage
   - Passive engorgement of the drainage area
   - Blood backs up into the microvascular bed
   - Local venous engorgement results

3. Chronic Local Passive Hyperemia:
   Differs from #2 by the time frame required
   Example - A slowly developing tumour or abscess enlarges and eventually compresses adjacent veins can produce passive hyperemia.

   Another example - A chronic inflammatory lesion that progresses to fibrosis and can lead to venous outflow obstruction.
   eg. Hepatic CIRRHOSIS

4. Chronic Generalized Passive HYPEREMIA
   NOTE: Generalized passive hyperemias (congestions) are most often associated with pathology of either the heart or lungs (there are exceptions)

   Ā - CONGESTIVE HEART FAILURE
   ⊕ Chronic Generalized Passive Hyperemia

   LUNG - certain types of primary pulmonary disease
   ⊕ Progressive loss of the pulmonary vascular bed
   ⊕ Pulmonary hypertension 8 psi within pulmonary arteries
   ⊕ Right heart failure (secondary to primary pulmonary disease)

   DEFINITION: COR PULMONALE: the syndrome of right heart failure resulting from primary pulmonary disease
APPEARANCE OF HYPEREMIA

GROSS: Cut surfaces of hyperemic or congested tissues are hemorrhagic and wet.
Excessively bloody - blood oozes on cut section.
Wet - Due to edematous tissue.
Red colour associated with acute local active hyperemia.
Dark brown colour is associated with congestion (passive hyperemia).

HISTO:
acute - associated with capillaries engorged with blood usually some edema
chronic -
\[\begin{align*}
\&\text{engorgement by poorly oxygenated venous blood} \\
\&\text{Degree of chronic local hypoxia} \\
\&\text{Degeneration, Atrophy or even Necrosis of parenchymal cells}
\end{align*}\]

LUNG
Cause: Can be acute or chronic. If acute see diffuse pulmonary congestion and edema (for review see page 6). Chronic failure of left ventricle impedes the flow of blood from the lungs to the heart \[\pi\] chronic passive congestion \[\pi\] 8 psi in alveolar capillaries and alveolar capillaries become engorged with blood.

4 consequences - of chronic pulmonary congestion (hyperemia)

1. Microhemorrhages
   Small capillaries rupture \[\pi\] intra-alveolar hemorrhages \[\pi\] extravascular red cells are phagocytized by alveolar macrophages \[\pi\] hemosiderin pigment "heart failure cells"
2. Pulmonary Edema (see lectures on edema- page 6)
   causes interference with gaseous exchange
3. \[\psi\] fibrosis of interstitium (fibroblasts secrete excess collagen)
4. \[\psi\] 8 psi pulmonary arteries \[\pi\] Pulmonary Hypertension

LIVER
Causes: Right Heart Failure, Pulmonary Hypertension
Gross: - mottled appearance - "nutmeg liver"
[Dark red appearance of the zones around the central veins (zone3) and yellow-brown appearance of less affected parenchyma around the portal areas]

- Overall 8 in hepatic size (acute)
- Due to 8 volume and mass of added blood
- Chronic, low-grade hypoxia and 8 psi pressure \[\pi\] atrophy and death of central hepatocytes
HISTO:
- Acute: central vein and sinusoids are distended with erythrocytes
  " Central hepatocyte degeneration and/or necrosis (zone 3)
  " Midzonal hepatocyte fatty change (zone 2)
  " Periportal hepatocytes may be normal (zone 1)

- Chronic: Hemosiderin-filled fixed macrophages
  (Kupffer cells) - due to erythrocyte phagocytosis
  - 8 blood psi of central veins \( \geq \) fibrous connective tissue
  - Dilation of sinusoids \( \geq \) pressure atrophy and necrosis of
centrilobular hepatocytes, dilated centrally located lymphatics

- "Cardiac Cirrhosis" - chronic centrilobular (zone 3) fibrosis

HEMORRHAGE

HEMORRHAGE: Escape of blood from the cardiovascular system (extravasation).
Discharge of blood from the vascular compartment to the exterior of the body or
enclosed within a tissue. Capillary bleeding can occur under conditions of chronic
congestion.

CAUSES OF HEMORRHAGE: (Multiple)

- Trauma 6 subcutaneous or intramuscular hemorrhage
- Septicemia, viremia or toxic conditions 6 widespread petechiae and ecchymoses
- Coagulation Disorders 6 haemorrhage
- Thrombocytopenia (decreased numbers of platelets)

SIGNIFICANCE of HEMORRHAGE - Dependent upon...
1. SITE/location
   - 2 critical sites:
     CNS and HEART

   eg1: Subdural hematomas

   eg2: Cardiac tamponade - specific syndrome of acute
cardiac failure which is caused by massive fluid
accumulation within the pericardium usually blood
- (hemopericardium) which results in acute right
heart failure (RHF).
2. RATE

3. TOTAL BLOOD VOLUME LOST
hemorrhagic shock

TERMINOLOGY:

HEMORRHAGE BY RHEXIS: Hemorrhage due to a substantial rent or tear present in the blood vessel (or heart) \[\text{moderate flow of blood out of vascular system}\]

HEMORRHAGE BY DIAPEDESIS: Hemorrhage due to a small defect or red blood cells passing through the wall in hyperemia of inflammation

HEMATOMA: Accumulation of blood in tissue. Forms an extravascular clot (three-dimensional).

HEMOPERICARDIUM: Blood in the pericardial space.

HEMOTHORAX: Blood in the pleural space.

HEMOPERITONEUM: Blood in the peritoneal cavity.

HEMARHTHROSIS: Blood in a joint space.

HEMOPTYSIS: Coughing up of blood clots from the trachea and bronchi.

EPISTAXIS: Bleeding from the nose.

EXTRAVASATION: Escape of blood from a vessel into tissue [also used as extensive hemorrhage within the substance of a tissue].

PETECHIAL HEMORRHAGES: (PETECHIAE): minute, pin-point foci of haemorrhage up to 1-2 mm in size

HEMORRHAGIC DIATHESIS: Increased tendency to hemorrhage from usually insignificant injuries. Seen in a wide variety of clinical disorders. (A predisposition for abnormal bleeding).
PURPURA: Hemorrhages • 3mm. May be associated with diseases which cause petechiae, vascular inflammation or vascular damage. Often scattered on many body surfaces.

ECCHYMOTIC HEMORRHAGES: (ECCHYMOSES):
Larger than petechiae and usually blotchy or irregular areas up to >1-2 cm in size often seen with trauma and other problems. (eg: subcutaneous hematomas / bruises)

PAINT BRUSH HEMORRHAGES: Hemorrhages which look as though a paint brush dipped in red paint was hastily applied to the tissue [most commonly found on serosal or mucosal surfaces].

RESOLUTION OF HEMORRHAGE

Resorption - Small amount of hemorrhage can be resorbed.

Organization - Generally larger amounts of hemorrhage pHagocytosis
Erythrocytes are degraded and phagocytosed by macrophages.

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Bilirubin</th>
<th>Hemosiderin</th>
</tr>
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<tbody>
<tr>
<td>Red-blue</td>
<td>Blue-green</td>
<td>Golden-brown</td>
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Organizing Hematoma - Mass of fibrin and red cells pHagocytose and degrade both the fibrin and red cells Hemosiderin hematoidin formation

HEMOSTASIS & THROMBOSIS

NOTE: Normal hemostasis is the result of a well-regulated process which maintains blood in a fluid, clot-free state within a normal vessel. Rapid clot formation (hemostatic plug) will occur at vessel injury. The pathological form of hemostasis is thrombosis where a clot (thrombus) forms within a vessel which is not injured. Can be considered an inappropriate activation of normal hemostatic processes.

3 general components required for hemostasis and thrombosis
1. Vascular wall – endothelial cells primarily
2. Platelets
3. Coagulation Cascade
NORMAL HEMOSTASIS

Sequence of events following vascular injury
1. Arteriolar vasoconstriction (transient effect)
   Reflex neurogenic mechanism
   Local secretion of endothelin
2. Primary hemostasis – PLATELET
   - Damage to the endothelium exposes platelets to the subendothelial extracellular matrix (ECM).
   - Platelets adhere to the ECM and become activated (Activation)
     a. Shape Change
     b. Release granules
     c. Recruit other platelets to site (Aggregation)
   - Form a HEMOSTATIC plug
3. Secondary Hemostasis - COAGULATION
   a. Tissue factor, a membrane-bound procoagulant factor synthesized by endothelium is exposed at the site of injury. It acts in conjunction with the material secreted by platelets to activate the coagulation cascade.
   b. Phospholipid complex expression
   c. Thrombin activation
     a. Formation of thrombin induces more platelet recruitment and granule release
     d. Fibrin Polymerization – resulting in local fibrin admixed with platelets – form plug to prevent further hemorrhage.
4. Antithrombotic Counter-Regulation
   a. Release of components to limit the size of hemostatic plug

ENDOTHELIAL FACTORS

Injury to the endothelium is the major initiating event for thrombosis and coagulation. Modulate many aspects of normal hemostasis

Antithrombotic (Anticoagulant) Properties of Endothelial Cells

Antiplatelet
1. Barrier to subendothelial collagen - prevent platelets and plasma factors from exposure
2. Prostacyclin - PGI$_2$ and Nitric Oxide - inhibit platelet adhesion and aggregation
3. Express adenosine diphosphatase to degrade ADP (ADP promotes platelet aggregation)

Anticoagulant properties
1. Membrane associated, heparin-like molecules
2. Thrombomodulin - specific thrombin receptor
   - Binds to thrombin making it an anticoagulant which can activate protein C
   - Requires protein S - synthesized by endothelial cells
4. Plasminogen activators which promote fibrinolytic activity to clear fibrin deposits from endothelium

Prothrombotic (Procoagulant) Properties of Endothelial cells

Endothelial cells may be activated by infectious agents, hemodynamic factors, plasma mediators and cytokines or injured indirectly.
1. Synthesize, store, and release von Willebrand factor (vWF) - essential cofactor for platelet binding to collagen and other surfaces. Stored in Weibel-Palade bodies.
2. Endothelial cells are also induced by cytokines (eg: TNF, or IL-1) or bacterial endotoxin - to secrete tissue factor (Factor VII) which activates the extrinsic clotting pathway.
3. Endothelial cells bind IXa and Xa and increase their catalytic activities
4. Secrete plasminogen activator inhibitors - to depress fibrinolysis
PLATELETS

NOTES: 1. Play a central role in normal hemostasis
2. Circulate as round, smooth discs with glycoprotein receptors
   Contain two types of granules
   A. Alpha (α) granules - P-selectin on membrane
      1. Fibrinogen
      2. Fibronectin
      3. Coagulation factors V and VIII
      4. Platelet factor 4
      5. Platelet derived growth factor
      6. Transforming growth factor β
   B. Dense granules (delta granules)
      1. ADP and ATP
      2. Ionized calcium
      3. Histamine
      4. Serotonin
      5. Epinephrine

Platelet Response

Vascular injury Y exposes Extracellular Matrix (ECM)
   Normally hidden by intact endothelium
   Composed of - Collagen, proteoglycans, fibronectin, others
Platelets + ECM Y 3 reactions
1. Adhesion and shape change
   Mediated via interactions with vWF - acts as bridge for platelets and ECM
2. Secretion (release reaction) of both granule types
   Release of dense granules is very important because calcium is required for coagulation cascade.
   ADP is a very important mediator of platelet aggregation
   Leads to surface expression of a phospholipid complex
      Needed binding site for calcium and coagulation factors.
3. Aggregation
   Thromboxane A2 (TxA2) secreted by platelets (necessary for aggregation)
   ADP + TxA2 start reaction which leads to enlarging platelet aggregation
   1° hemostatic plug
   Activates coagulation generated thrombin increasing aggregation
   Platelet contraction - fused mass of platelets, fibrin formed cements mass
   2° hemostatic plug

THROMBOCYTOPENIA

Definition: Drop below 100 X 10^9 platelets/L
Most species bleed < 50 X 10^9 platelets/L
dogs < 30 X 10^9 platelets/L
Diagnosis: history of bleeding
low platelet counts
increased mucosal bleeding times
Mechanisms:
Deficient formation of platelets
   (eg: estrogen toxicoses)
Excessive utilization
   (eg: consumptive coagulopathies)
Premature destruction

Causes:
Thrombocytopenia - decreased number of platelets
platelet production
neoplasms
estrogen therapy
platelet destruction
antiplatelet antibodies
viral diseases
drug toxicity
Thrombocytopenia - defective function of platelets
Adhesion – von Willebrand’s disease
Aggregation
Afibrinogenemia
Granule Factors – Chediak-Higashi Syndrome
BLOOD COAGULATION - COAGULATION CASCADE

NOTES:
A clot is formed by an enzymatic cascade = series of zymogen activations in which an activated form of one coagulation factor catalyses the activation of the next.

Reaction Complex is composed of an enzyme - activated coagulation factor + a substrate - proenzyme -coagulation factor which are assembled on a phospholipid complex and held together by calcium ions.

Coagulation -the formation of fibrin - is initiated when activated factor X (Xₐ) cleaves the circulating protein prothrombin into two fragments. The active fragment is thrombin, a proteolytic enzyme that converts plasma fibrinogen to fibrin. The generation of thrombin is probably the most important factor in the progression and stabilization of the thrombus. Thrombin can be generated at the site of injury by either the intrinsic or extrinsic coagulation pathway.

The coagulation cascade is usually divided into extrinsic and intrinsic pathways which converge where factor X is activated. However, this division is an artifact of in vitro testing. Several interconnections occur between the two pathways.

Coagulation must be restricted to the site of vascular injury to prevent extensive clotting away from the site of vascular damage. - controlled by anticoagulants
1. Antithrombins (e.g., Antithrombin III)
2. Proteins C and S
3. Plasminogen-plasmin system
4. Tissue factor pathway inhibitor

INTRINSIC PATHWAY: Although all factors of the intrinsic system are present in normal plasma. The cascade is activated by contact with subendothelial collagen.


COMMON PATHWAY: Activated factor X is produced by proteolysis of Factor X, which occurs at the terminus of both intrinsic and extrinsic coagulation pathways.
Xₐ is a prothrombinase complex that converts prothrombin to thrombin.
-Calciu and platelet phospholipids are also necessary for factor Xₐ to be active.
-Prothrombin is a zymogen for thrombin
-Thrombin cleaves peptides from fibrinogen
-Fibrin is stabilized by enzyme factor XIII

Reminder: Platelet phospholipid becomes available on platelet surfaces during platelet activation
COAGULATION DISORDERS

In general, large hematomas suggest a coagulation disorder whereas chronic bleeding from a mucosal surface may indicate a platelet deficiency or abnormality.

INHERITED DEFICIENCIES OF COAGULATION - numerous - see a clinical pathology text.

ACQUIRED DEFICIENCIES OF COAGULATION

Accompany many severe diseases
- Transitory depression of factor synthesis
- Excessive utilization or consumption of factors
- Acquired disorders may be general or specific
  - Severe trauma or deep burns
  - Snake venoms and plant toxins
- Liver failure
  - Site of synthesis of many coagulation factors.
  - Acute destruction of hepatocytes or chronic liver disease may result in bleeding tendencies

PREVENTION OF COAGULATION/FIBRINOLYTIC SYSTEM

Thromboresistance of endothelium
- Antithrombin III and heparin inhibit thrombin action

Fibrinolysis
- Plasmin from plasminogen
- Plasminogen activator from endothelium
- Exogenous substances activate plasminogen
  - PLASMINOGEN (in plasma)
  - PLASMINOGEN ACTIVATOR
  - PLASMIN
  - FIBRIN
    - BREAKDOWN PRODUCTS
      - (FIBRIN DEGRADATION PRODUCTS)

THROMBOSIS and INFARCTION

PATHOGENESIS: - 3 primary influences - Virchow’s triad

1. **Endothelial injury**
   - Dominant influence = can lead to thrombosis by itself
     - eg: inflammation of heart valves
     - Expose of subendothelial ECM
     - Platelet adherence
     - Release of tissue factor
     - Depletion of prostacyclin
     - Primary and secondary hemostatic plug formation

2. **Alterations in normal blood flow** - turbulence or stasis
   - Normal blood flow is laminar - cellular elements in the middle, surrounded by plasma.
   - Disrupt normal laminar flow
     - Allows platelets to contact endothelium
     - Prevents dilution of activated clotting factors by fresh-flowing blood
     - Allows the build up of thrombi (slows the inflow of anticoagulants)
     - Promotes endothelial cell activation
3. **Hypercoaguability**

**Definition:** any alteration of the coagulation pathways that predisposes to thrombosis

- **Coagulation factors**
- **Inhibitory factors**

**Terminology and Morphology**

**Thrombosis:** Formation, development or presence of a solid mass within the blood vessels or heart. Adherent to the vascular endothelium and must be differentiated from a simple (post mortem) blood clot.

**Thrombus:** An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causes vascular obstruction at the point of its formation or embolism.

**Thrombi:** Pleural of thrombus ie: several aggregations within the blood vascular system.

- Thrombi may develop anywhere in cardiovascular system
  - Cardiac chambers
  - Valves
  - Arteries (usually endothelial injury)
  - Veins (often a result of stasis)
  - Capillaries

Arterial thrombi are attached and grow away from the heart.

Venous thrombi are attached and grow in the direction of blood flow (to heart).

**Arterial and venous thrombi differ!**

**Arterial:** Generally due to endothelial injury, initial thrombus is composed of aggregated platelets and RBC's and is soft, friable and red. As arterial thrombi grow, flow patterns adjacent to the thrombi cause fibrin to be deposited and the platelet mass that persists is transformed into a fibrin mass. Fibrin strands polymerize between the separating and degenerating platelets. The alternating lines of yellow platelets and fibrin separating RBC's forms the *lines of Zahn.*

**Venous:** A venous thrombi is composed of fibrin strands with entrapped RBC's, since the dominant mechanism of formation is coagulation.
Morphological Differentiation of Thrombi Vs Post Mortem Clots

<table>
<thead>
<tr>
<th>Arterial Thrombus</th>
<th>Venous Thrombus</th>
<th>Post Mortem Clot</th>
<th>Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grey, pale, white</td>
<td>Red</td>
<td>Yellow = chicken fat</td>
<td>Colour</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Lamination</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Attachment</td>
</tr>
<tr>
<td>Small - may be mural</td>
<td>often fill lumen</td>
<td>fill lumen</td>
<td>Size and location</td>
</tr>
</tbody>
</table>

**BLOOD CLOT:** Clotted blood within a blood vessel (usually not associated with a pathological condition - usually post mortem clot). [NOTE: the distinction between a thrombus and a blood clot is difficult, since the two are clearly related].

**CHICKEN-FAT CLOT:** Common blood clot seen at necropsy in horses 6 plasma clot that develops because of spontaneous erythrocyte ROULEAUX formation and the rapid sedimentation rate of red cells in equine blood. A chicken-fat clot is a gelatinous, post-mortem clot with relatively few red cells.

**OUTCOME OF THROMBI:**

1. **Lysis** of thrombus (due to potent thrombo-lytic/fibrinolytic activity of blood)
2. **Propagation** of a thrombus (8 in size)
   - may eventually obstruct the vessel
3. **Embolization** - possible
4. **Organization** - The presence of a thrombus stimulates reaction which will result in inflammation and fibrosis. Smooth muscle cells and fibroblasts will proliferate and invade. The thrombus will become firm and grey-white.
   and
5. **Recanalization** - New lumina, lined by endothelial cells form to allow blood flow through the damaged vasculature

**Frame 13223**
Recanalization of Thrombus
EMBOLISM: Passage through the venous or arterial circulations of any material capable of lodging in a blood vessel and thereby obstructing the lumen. The usual embolism is a thromboembolus. -or- Sudden blocking of an artery by a clot or foreign material which has been brought to its site of lodgement by the blood current.

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

EMBOLI: Pleural of embolus, ie: several emboli become dislodged and travel downstream of the blood current.

THROMBOEMBOLUS: A thrombus formed in one location that detaches from the vessel wall and travels to a distant site. (99% of all emboli arise from a thrombus).

THROMBOEMBOLISM: Obstruction of a blood vessel with thrombotic material carried by the blood stream from the site of origin to plug another vessel.

EMBOLISM: Varies in composition - most are primarily fibrin (thrombi)

Etiology:
1. Parasites
   A. Dirofilaria immitis
   B. Nematode larvae
      i) Ascarid larvae
      ii) Strongyle larvae
2. Fibrocartilaginous emboli
   A. Spinal cord infarcts
   B. Origin intervertebral disk material
   C. Necrotizing myelopathy
3. Fat
   A. Bone fractures
   B. Prolonged surgery
   C. Osteomyelitis
   D. Hyperlipidemia
      i) "Lipid glomerulopathy"
4. Systemic infections
   Any disease that causes widespread damage to endothelium
      i) Bacterial diseases
      ii) Viral diseases
         eg: hog cholera (swine fever)
5. Other
   Air bubbles
   Hair
   Tumour cell clusters
   Amnionic fluid
DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

“DIC, the sudden or insidious onset of widespread fibrin thrombi in the microcirculation. Although these thrombi are not usually visible on gross inspection, they are readily apparent microscopically and can cause diffuse circulatory insufficiency, particularly in the brain, lungs, heart, and kidneys. With the development of the multiple thrombi, there is a rapid concurrent consumption of platelets and coagulation proteins (hence the synonym consumption coagulopathy); at the same time, fibrinolytic mechanisms are activated, and as a result an initially thrombotic disorder can evolve into a serious bleeding disorder. It should be emphasized that DIC is not a primary disease but rather a potential complication of any condition associated with widespread activation of thrombin.” Robbins and Cotran p 135

Some Causes:
- Severe burns
- Widespread metastatic tumours
- Systemic viral disease
- Heatstroke
- Shock (toxemias, specticemias, etc)
- Severe pneumonia (dogs)
- Congestive heart failure (dogs)
- Heartworm disease (dogs)

INFARCTION

DEFINITION: Area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage in a particular tissue.

Notes: -50% of all human deaths result from myocardial or cerebral infarction due to cardiovascular disease
- Pulmonary infarction, intestinal infarction, renal infarction common in domestic animals
- Most infarcts are the results of thrombotic or embolic events or vascular occlusion due to twisting of a vessel

GROSS: wedge-shaped: The base of the wedge is at the periphery. The occluded
- Margins may be irregular
- Early - ill defined and hyperemic
- 48 hours most become paler
- Kidney infarcts are usually white (ischemic, pale)
- Pulmonary infarcts are usually red

PALE (WHITE) INFARCT: Lacks blood, also called anemic infarct. (Usually has a red zone at periphery because of capillaries at the border of infarct undergo dissolution and blood seeps into the area of necrosis). Occurs with arterial occlusions in solid organs (heart, kidney).
RED INFARCT: Filled with blood. Characterized by coagulation necrosis and erythrocytes from adjacent arteries and veins. Seen with venous occlusions or within loose tissue that allow blood to collect in the infarcted zone of organs with dual blood supply (lung, liver) or extensive collateral circulation (brain, small intestine). The latter results because blood flows from the unobstructed vascular channels into the necrotic area.

MICRO: -Ischemic coagulation necrosis of all parenchyma tissues
-Infarcts arising from septic emboli may convert to an abscess

REPAIR: Scar tissue - fibrous connective tissue
Forms an indentation on the organ surface

SEQUELLA: dependent upon
1. Degree/severity of injury to vascular supply
2. Size of artery affected
3. Degree of vascular occlusion
4. Collateral blood supply available
5. Vulnerability of cells to ischemia
6. O₂ carrying capacity of RBC's at time of infarct

SEPTIC INFARCT: When the necrotic tissue of an infarct is seeded by pyogenic bacteria the tissue becomes a good growth medium for these pathogenic organisms

VENOUS OBSTRUCTION:
Significance:
- may cause slowly developing stasis with engorgement of the tributary venous system (chronic passive hyperemia)
- Serious if anterior or posterior vena cava obstructed
- common cause of shock

Acute Blockage of the Portal Vein:
Result: Infarction of intestine
Sequelae: shock and death w/o surgery
Example: Gastric torsion in dogs 6obstruction of the portal venous system 6severe venous congestion 6vascular stasis 6ischemia 6loss of endothelial integrity 6hemorrhages 6shock

Blockage of the pulmonary artery:
Etiology: Pneumonia
Congenital heart disease
Bronchiectasis
Parasite infestations
Hyperadrenalcorticism
Renal amyloidosis
Result:
- If sudden and large artery - death
- If incomplete and smaller arteries
  6 Anastomoses develop between pulmonary arteries and bronchial arteries

Blockage of the posterior vena cava:
  Etiology:  Hepatic abscesses in ruminants
             Dirofilariasis in dogs - overwhelming infections
  Pathogenesis:
  1. Acute, complete occlusion 6 death
  2. Collateral circulation could develop
     (azygous vein)

SHOCK

Shock is the final common pathway for many potentially lethal clinical events which include microbial sepsis, severe hemorrhage, extensive trauma or burns, myocardial infarction, and mass pulmonary embolism. Whatever the cause the result is a decreased perfusion due to either decreased cardiac output or blood volume. The end result is hypotension which results in impaired tissue perfusion and cellular hypoxia.

Definition:
A syndrome resulting from a disproportion between the amount of blood volume present and the volume of the circulatory system. In other words, an acute generalized failure of the capillary bed. -or- A condition of profound hemodynamic and metabolic disturbance characterized by failure of the circulatory system to maintain adequate perfusion of vital organs.

Fundamental Disturbance:  The blood volume is too small to fill the vascular system resulting in peripheral circulatory failure and cell damage due to hypoxia from inadequate tissue perfusion. Either not enough volume or blood flow is impaired.

Three general categories of shock
  1. Cardiogenic
  2. Hypovolemic
  3. Septic Shock

Note:  Neurogenic and Anaphylactic shock both result in widespread vasodilation

Pathogenesis of Septic Shock
~ 70% of septic shock are caused by endotoxin-producing gram-negative bacilli reason for the term endotoxic shock. Endotoxins are bacterial wall lipopolysaccharides (LPSs). These are released when bacterial cell walls are degraded. LPS consists of a toxic fatty acid (lipid A) core surrounded by a complex polysaccharide coat which is unique to the particular bacteria. Similar molecules can also be found on gram + bacteria and fungi.

LPS injected into the blood stream can result in shock. LPS + LPS binding protein together bind to a cell surface receptor. This reaction can directly activate endothelial cells (makes them prothrombotic), WBC’s to release cytokines, activate complement mediated reactions (we’ll review in inflammation).
The brain and heart are the most susceptible organs. (NOTE: amount of $O_2$ removed during blood flow varies average is approximately 25%, myocardium removes 75%)

**Stages of shock** include nonprogressive, progressive and **Irreversible shock**. The latter is defined as a refractory state of circulatory control with inability to control the clinical disease.

Shock is characterized by failure of multiple organ systems.

**Lesions:**
- Pulmonary edema (cattle/horses - prominent shock organ)
- Liver Congestion: (dogs - prominent shock organ)
- Kidneys: Acute tubular necrosis
- Heart: Subendocardial hemorrhage and necrosis
- Zonal lesions deep in myocardium
- Brain – Neuronal cell death
- Adrenal glands:
  - Cortical cell lipid depletion
  - Degranulation of adrenalin-producing cells
  - Hemorrhagic with foci of necrosis
- Gastrointestinal tract:
  - Hyperemia of mucosa with erosions are possible
- Skeletal muscle: Pallor (peripheral vasoconstriction)
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