Hemostasis

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• Required reading / viewing
  – http://www.youtube.com/watch?v=HFNWGCx_Eu4
  – Assigned text: pages 73-78

What is hemostasis?
• A process which causes bleeding to stop
• The process of keeping blood within a damaged vessel
• Why is hemostasis important?
  – Hemorrhage results in:
    • Loss of blood - fluid, protein components, oxygen carrying
    • Tissue dysfunction – hypovolemia, hypoproteinemia, anemia
  – Major traumatic episodes
  – Continual minor ‘trauma’ of every-day life
Forms of hemorrhage

- Petechia and purpura
  - Petechia = < 3 mm ‘pin point’ hemorrhage into tissue
  - Purpura = small ‘3-10 mm’ hemorrhage into tissue
- Hematomas
  - Aural
  - Subdural

- Bruise
  - Confluence = >10 mm hemorrhage into tissue

Hemoperitoneum / hemothorax – bleeding into cavities
Hematoma – hemorrhage forms a mass-like swelling – can occur in many different locations e.g. brain, subcutaneous

Outline of lecture

- Normal hemostasis
- Abnormal hemostasis
  - Insufficient hemostasis
  - Excessive hemostasis

Normal hemostasis I: overview

- Trauma resulting in hemorrhage
  - Thrombus
    - Hemostatic mechanisms
    - Fibrinolytic mechanisms
Normal hemostasis II: overview

- Integrated response to vessel injury that involves the vessel itself, as well as cellular (thrombocytes) and protein components (clotting factors) in blood

Normal hemostasis III: vasoconstriction = vasospasm

- Short lived effect – 20-30 minutes
- Limits blood loss
- More vasoconstriction with blunt versus sharp object trauma
- Mediated by-
  - pain reflex
  - release of vasoconstrictor substances e.g. serotonin form platelets

Normal hemostasis IV: platelets are derived from the bone marrow

- Platelets are fragments of cytoplasm of megakaryocytes
- Platelets are produced in the bone marrow and released into blood
- Megakaryocytes are not normally present in blood
Normal hemostasis V: platelet plug formation [primary hemostasis]

- Endothelial cells release NO and PGI2 which inhibit platelet aggregation
- Platelets bind to exposed subendothelial basement membrane

Normal hemostasis VI: platelet plug stabilization [secondary hemostasis]

- Platelet plug is stabilized by fibrin deposition

Normal hemostasis VII: mechanism of fibrin deposition [clotting cascade]

- Many clotting proteins are proteases e.g. XII, XI, IX, X
- Produced in liver
- Vitamin K is required for correct maturation of many clotting proteins
- "Cell injury pathway is most important for hemostasis"
Abnormal hemostasis

Non-traumatic causes of hemorrhage

- **Diseases involving thrombocytes**
  - Depletion = thrombocytopenia
  - Immune-mediated thrombocytopenia
  - Abnormal thromocyte function
- **Diseases involving coagulation cascade**
  - Genetic defects
  - Acquired disease – warfarin as a poison
- **Diseases of blood vessels**
  - Direct damage to vessel walls by immune system or infectious agents
  - Secondary depletion of hemostatic mechanisms – disseminated intra-vascular coagulopathy (DIC)

Diseases of thrombocytes I: Immune-mediated thrombocytopenia

- Thrombocytopenia = decreased number of thrombocytes in blood
- Example of type II immune-mediated hypersensitivity
- Antibodies are directed against platelet surface proteins, for example,
  - Glycoprotein IIb/IIIa – fibrinogen receptor (see prior figures)
  - Glycoprotein Ib/IX complex
- Binding of antibodies (=opsonization) results in phagocytosis of thrombocytes in liver and spleen by macrophages
- Half-life of platelets reduced in humans from 7-10 days to a matter of minutes
Von Willebrand's disease
- Von Willebrand's factor [vWF] is a blood glycoprotein required for thrombocyte adhesion
- Genetic defects of vWF are a common cause of coagulation defects in humans and some breeds of dog.

Diseases of thrombocytes II: Decreased binding to basement membrane

Diseases of thrombocytes III: Diseases that secondarily affect thrombocytes
All these conditions can cause thrombocytopenia
- Bone marrow neoplasia e.g. leukemia
- Radiation poisoning
- Chemical bone marrow poisoning e.g. bracken fern, chemotherapy

Disease of blood vessels I: Endotheliotropic infectious agents
- Agents replicate in capillary endothelial cells
- Damage endothelial cells resulting in petechiations
- May results in secondary thrombocytopenia
- Many disease examples:
  - endotheliotropic adenoviral infections
  - endotheliotropic ricketsial infections e.g. Rocky Mountain Spotted fever of dogs and man
Disease of blood vessels II: Type-III immune hypersensitivity

- Antigen – antibody complexes form and circulate in blood stream
- Deposit in blood vessel walls and initiate inflammatory response
- Damage to blood vessels initiates hemostatic response. This may lead to depletion of thrombocytes.

Diseases involving coagulation cascade I: Single gene defects

Hemophilia A/B
- X-linked recessive inheritance
- Leads to deficiency of factor VIII/IX
- No petechiations – why?
- Easy bruising
- Bleeding into joints
- Trauma results in severe hemorrhage
Warfarin poisoning = anti-coagulant rodenticide
- Used as a rodenticide
- Poisoning common in dogs
- Interferes with action of vitamin K in maturation [post-translational modification] of many clotting factors

End-stage liver disease [cirrhosis]
- Clotting factors are produced in the liver
- Deficiency of multiple factors occurs with advanced liver disease
- Many potential causes of underlying disease – what disease processes can result in cirrhosis?

The hypercoagulable state: characterized by increased tendency to form thrombi
Causes of hypercoagulability

- Blood vessel wall disease
  - Atherosclerosis of coronary and brain arteries
  - Vasculitis = inflammation of blood vessels
- Aberrant coagulation cascade regulation
  - Genetic disease of fibrinolytic system – very rare
  - Anti-phospholipid antibodies e.g. lupus
  - Septicemia
  - Some drugs – possibly hormone replacement therapy
- Other
  - Immobilization – economy class syndrome, bed rest

Consequences of hypercoagulability

Vascular thrombosis → Consumption coagulopathy = disseminated intravascular coagulopathy (DIC)
- Ischemic
- Infarction
- Embolism

Coagulation modifying interventions are used therapeutically and in humans

Fibrinolytic drugs
- Used in acute managements of some stroke and heart attack patients
- Tissue plasminogen activator

Coronary artery thrombus
Example questions

• What does the term consumption coagulopathy mean?
• Where are clotting factor proteins produced?
• What feature of the clotting protein system enables a rapid response to thrombogenic stimuli?
• Why can bone marrow injury be associated with increased tendency to bleed?
• What other signs might you expect in an animal or person with bone marrow disease?