Pathology C 601
Hemodynamic Derangements

Assignment page.

Reading:

Robbins: Chapter 4

Clinical Lab Source:
- Protime (PT) Know about INR
- Activated partial thromboplastin time (APTT)
- Activated coagulation time (ACT)
- Fibrin Split Products (FSP)
- Fibrinogen
- D-dimer

Wheater: Part 1: Thrombosis, embolism and infarction

Laboratory assignment: C601/C602 Histopathology manual, hemodynamic unit.

Case studies: There is no online case for this unit. Instead, there are several “paper cases.” Work through all of these with the members of your autopsy group and be prepared to discuss them during our laboratory time.
Hemodynamic Disorders
Thrombosis and Shock

I. Body water, where is it and what keeps it there?

A. Intracellular

B. Extracellular (intercellular)

1. Interstitial, between the cells, but “outside” of the vascular system
   - lymph fluid while it is between the cells, but not yet collected by the
   lymphatic vessels

2. Intravascular
   - water making up the blood and
   - lymphatic fluid when it is within the lymph vessels

C. Oncotic pressure

D. Hydrostatic pressure
   - local
   - generalized -CHF
   - lymphatic obstruction

Ref: Robbins, Pathologic Basis of Disease, 6th Ed.
E. Constant leakage and retrieval by lymph vessels. As long as everything is working right, the balance is maintained and the water goes merrily around and around.

But things don’t always go as planned. Disorders described here are a daily events in every hospital. The leading causes of death in the “civilized” world revolves around excessive and/or inappropriate blood clotting.

- Myocardial infarction (MI)
- Pulmonary embolus (PE)
- “Stroke” (CVA)

II. Too much water in the intercellular (between the cells) space. **EDEMA**
A. TRANSUDATE vs EXUDATE  (How do you tell which is which)

B. Inflammatory edema “injury water” “Tumor of inflammation”

C. Non-inflammatory edema

1. Water in the tissues themselves
   - Anasarca
   - “Pre-sacral” edema
   - periorbital edema

2. Water filling up hollow (or potential) spaces
   - hydrothorax
   - hydropericardium
   - hydroperitoneum

3. “Third space” concept

4. Cerebral edema, a special situation
III. Hyperemia and congestion

A. Active

B. Passive
   - acute
   - chronic (nutmeg liver for example)

IV. Hemorrhage, hemostasis and thrombosis

A. There are three essential elements for blood clotting to work as it should.

1. Platelets

2. Vessels

3. Proteins (no I am not going to ask you to produce the clotting sequence)
A. Vasoconstriction

Endothelium  Basement membrane  Arteriole smooth muscle

Endothelin release causes vasoconstriction  Reflex vasoconstriction  ECM (collagen)

B. Primary Hemostasis

1. Platelet adhesion (ADP, TXA₂)
2. Shape change
3. Granule release (vWF)
4. Recruitment
5. Aggregation (hemostatic plug)

Endothelium  Basement membrane  Collagen

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C. Secondary Hemostasis

1. Tissue factor
2. Phospholipid complex expression
3. Thrombin activation
4. Fibrin polymerization

Fibrin

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D. Thrombus and Antithrombotic Events

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

Trapped neutrophil  Trapped red blood cells  Polymerized fibrin

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 Favor Thrombosis

Extrinsic coagulation sequence

Platelet adhesion: Held together by fibrinogen

Exposure of membrane-bound tissue factor

INHIBIT THROMBOSIS

Inactivates thrombin and factors Xa and IXa

Proteolysis of factors Va and Villa

Active protein C  Protein C

Fibrinolytic cascade

Thrombomodulin  Heparin-like molecule  Thrombin receptor

Tissue factor pathway inhibitor

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B. Hemorrhage

- what does it look like?

- volume?

- location?

- duration (in other words did you have time to accommodate)

1. What does it look like? Skin

   - petechiae, little bitsy specks, often called a “rash” (platelet abnormality)

   - purpura

   - ecchymosis

2. Accumulation = hematoma (a blood “body” or “tumor”)

3. In a hollow or potential space

   - hemopericardium

   - hemothorax
- hemarthrosis

- hemoperitoneum

4. Location

- vital structures, CNS

- can you even see it, GI loss

- expected, but is too much, menstrual

5. Volume, much harder to assess than you might think.

6. Duration

- The longer it takes, the lower it can go.

- Sudden massive loss is a disaster.

7. Genetic causes

- family history

8. Acquired deficiency (can this be for real?)
- habits and coexisting diseases
- medications (Do really mean aspirin is a medication?)
C. Thrombosis

1. How does a thrombus differ from a blood clot? You know, philosophically.

2. Three major factors in increased coagulability

   - endothelial damage

   - stasis (alterations in normal blood flow, ie slowing and pooling)

   - abnormalities of proteins
     - too many clotting factors

   - too little inhibition (AT III, Protein C and S)
3. Venous thrombosis

- location

- stasis (get ‘um up)

- factor activation with slowed flow

4. Arterial thrombosis

- endothelial damage

- platelet adherence

5. Morphologic characteristics

- laminar assembly

- lines of Zahn

- mural thrombus

6. What happens now?
- resolution

- propagation

- organization and “recanalization”

- embolization (actually, lots of things can be emboli)

  - pulmonary embolization (PE)

  - “saddle embolus” a really big one

- air

- bone chips and marrow

- bullets

- amniotic fluid

- These are all space occupying substances, moving along in the more or less intact circulatory system.
7. The disastrous “melt down” - Disseminated Intravascular Coagulation (DIC)

1. Never on its own

2. Remove or correct the offending circumstance

3. Obstetrical disaster most commonly

4. Sepsis

5. Shock

V. Infarction: an area of *ischemic* necrosis *within* a tissue or an organ, resulting from occlusion of the arterial supply or venous drainage. (Please know this definition.)

A. Most are arterial thrombosis, but not all.

B. Anemic (white)

1. “End artery” supply system.

2. No blood, the tissue dies and there is no hemorrhage into the dead meat.

- organs?
C. Hemorrhagic (red)

1. Venous occlusion generally
   - often previous congestion

2. “Looser” tissues

3. Overlapping or “dual circulation systems
   - lung
   - gastrointestinal

4. Bleeding into the area of ischemic necrosis

D. Other complicating factors

1. “bland” (sterile)

2. “septic” (infected area of necrosis)

E. What features make an infarction likely to develop?

1. What kind of vascular supply does this organ have?
2. Rate of development of the occlusion. Again, is there time to develop collateral channels?

3. Vulnerability of the organ
   - Skeletal muscle
   - CNS
   - Heart

4. Outcome or significance?

VI. Shock: widespread hypoperfusion of tissues due to reduction in blood volume or cardiac output, or even redistribution of blood, resulting in an inadequate effective circulatory volume.

   A. TISSUE HYPOXIA AND ACIDOSIS

   B. Downward spiral that may not turn around

   C. Basic patterns

      1. Hypovolemic or hemorrhagic

      2. Cardiogenic
3. Septic, more common than many people think.

- Intensive care units, catheters, really sick folks
- gram negative bugs
  - endotoxins
- rarely gram positive or fungi

4. Anaphylactic - type 1 hypersensitivity

5. Neurogenic

- anaesthetic disasters
- spinal cord injuries

D. Stages

1. Non-progressive; compensatory mechanisms activated and vital organs spared
2. Progressive: going down the spiral with acidosis and further deterioration

3. Irreversible: enough ischemic injury so that survival is not possible

E. Vulnerable organs

1. CNS

2. Kidneys - tubular damage - no urine output

3. GI - hemorrhagic enteropathy

4. Adrenals - they get wrung dry

5. Heart - subendocardial hemorrhages - generalized dysfunction of pump

F. Clinical course and outcome

1. Depends on age, general state of health and type of precipitating condition

   - cardiogenic and septic very poor prognosis in elderly

   - young people with hypovolemia actually do pretty well

2. Clinical appearance
- cardiogenic or hypovolemic

  - ashen grey with weak and thready pulse

  - cold and clammy

  - mottled areas of skin coloration

- septic

  - with septic may be flushed and even seem warm because of peripheral vascular dilation
Hemodynamic Case Studies

Case 1:

HISTORY: This 25-year-old male motorcycle racer was admitted to the hospital with a comminuted fracture of the left femur. He reported no significant past medical history nor was he taking drugs of any kind.

PHYSICAL FINDINGS: The patient was conscious and in pain. BP-90/50 mm Hg; pulse rate=120/min.

LABORATORY RESULTS: values obtained on admission samples were all within normal ranges.

CLINICAL COURSE: The course of his recovery was unremarkable
until the second hospital day when he developed a temperature of 39.5°C, cough, dyspnea, confusion and a scattering of petechiae over his chest and upper arms. These signs and symptoms became progressively worse until day 8 when they began to subside. By day 13 he had returned to normal. He was discharged on day 20 and completed an uneventful recovery from the fracture.

1. The disease exemplified in this case as a complication of severe fracture is what?
2. If the patient's urine had been examined during hospitalization, it very likely would have been found to contain what?

3. Other diseases or forms of injury in which this same clinical complication might be found?

4. Had our man died, we might have found the following at autopsy. What does this microscopic photo show?

Case2:

HISTORY: This 6-month-old boy, according to the mother, has a painful left knee. He bled from his umbilical stump at birth and his maternal grandfather had had a "bleeding problem" all his life.

PHYSICAL FINDINGS: The left knee was swollen, red-blue, and had limited movement.

LABORATORY RESULTS:
  hemoglobin: 14.5 g/dl
  platelets: 200,000 /cu mm
  prothrombin time: 12 sec (normal 11-13)
PTT (activated): 150 sec (normal 30-45)  
blooding time:  5 min (normal less than 8)

CLINICAL COURSE: A diagnosis of hemorrhysis was made and the left knee immobilized. The following laboratory tests are then obtained:
   platelets: 190,000 /cu mm  
   PTT (activated):  140 sec with the addition of an equal amount of a normal patient's serum: 36 sec

1. Based on the evidence presented, the MOST LIKELY diagnosis is?

2. Do you think there is anything significant about the follow-up (second) value for platelets?

3. If the partial thromboplastin time (PTT) is so far off, why are the bleeding time and Protime (PT) not prolonged?

Here, this might help:

![Diagram of blood coagulation pathway]

Case 3:
HISTORY: This 52-year-old woman, with longstanding history of smoking, complained that her left foot had been cold, blue and pulseless for 2 days. A month previously she had been hospitalized with pneumonia but improved with antibiotic therapy. Several hours before admission she noted weakness of her right arm.

PHYSICAL FINDINGS: Gangrene of all left toes; multiple petechial skin hemorrhages on trunk and extremities; moderate paresis of the left upper extremity with sensory loss.

LABORATORY RESULTS:
- hemoglobin: 10.4 g/dl
- WBC: 2,500/cu mm
- platelets: 25,000/cu mm
- prothrombin time: 25 sec (normal 11-14 sec)
- partial thromboplastin time: 48 sec (normal 27-39 sec)
- fibrinogen: 90 mg/dl (normal 170-410 mg/dl)

CHEST X-RAY

![Normal chest film](image1.png)  ![Our patient](image2.png)
CLINICAL COURSE: She was treated with antibiotics and heparin. On the 6th hospital day she developed cyanosis and respiratory distress and died the next day. Autopsy findings included a mass in the apex of the left lung, consolidation of pneumonia distal to the mass, and enlarged mediastinal lymph nodes, containing “gritty” neoplastic tissue.

1. The most likely cause of the paresis of the right upper extremity was?

2. The cause of the left foot gangrene was most likely?

3. Why the enlarged mediastinal lymph nodes at autopsy?