Clinical Perspective Physiology/Hemostasis

Ebaa M Alzayadneh, PhD

Associate Professor of Physiology

Causes of Excessive Bleeding

- Any clotting factor deficiency

  Most commonly:

- Hepatocellular disease

- Vitamin K deficiency

- Hemophilia

- Low platelet count (thrombocytopenia)

Vitamin K Deficiency

- **Essential to carboxylate glutamic acid in five important clotting factors:**
  - prothrombin and factors VII, IX, X, and protein C (1972)

- **In this process vitamin K is oxidized and inactivated**

- **Vitamin K epoxide reductase complex 1 (VKOR c1) reduces vitamin K and reactivates it**

Vitamin K

- Produced in the intestine by bacteria

- Fat-soluble: malabsorption of fats can lead to deficiency

- Lack of bile production or delivery can cause fat malabsorption and vitamin K deficiency

- In patients with liver or biliary disease, vitamin K can be injected 4-8 hours before surgery

Hemophilia

- **Hemophilia A – Deficiency of factor VIII**
  - 85% of hemophilia cases
  - 1 / 10,000 males

- **Hemophilia B – Deficiency of factor IX**
  - 15% of cases
  - About 1 / 60,000 males

- **Both impair Intrinsic Pathway activation**

- **Both genes are on the X chromosome (males only get one copy)**

- **Clinically: Bleeding after minor trauma**

Factor VIII Deficiency

- **Factor VIII has a partener…Von willbrand factor**

- **Deficiency of factor VIII causes hemophilia A**

  → **treat bleeding with factor VIII replacement**

- **Deficiency of Von willbrand factor causes von Willebrand disease (resembles decreased platelet function)**

Thrombocytopenia

- **Low numbers of platelets**

- **Bleeding from small venules or capillaries**

- **Petechaiae, thrombocytopenic purpura**

- **Often idiopathic**

    < 50,000 platelets / μL – usually modest bleeding
    < 10,000 platelets / μL – life-threatening

- **Treated with platelet infusions**
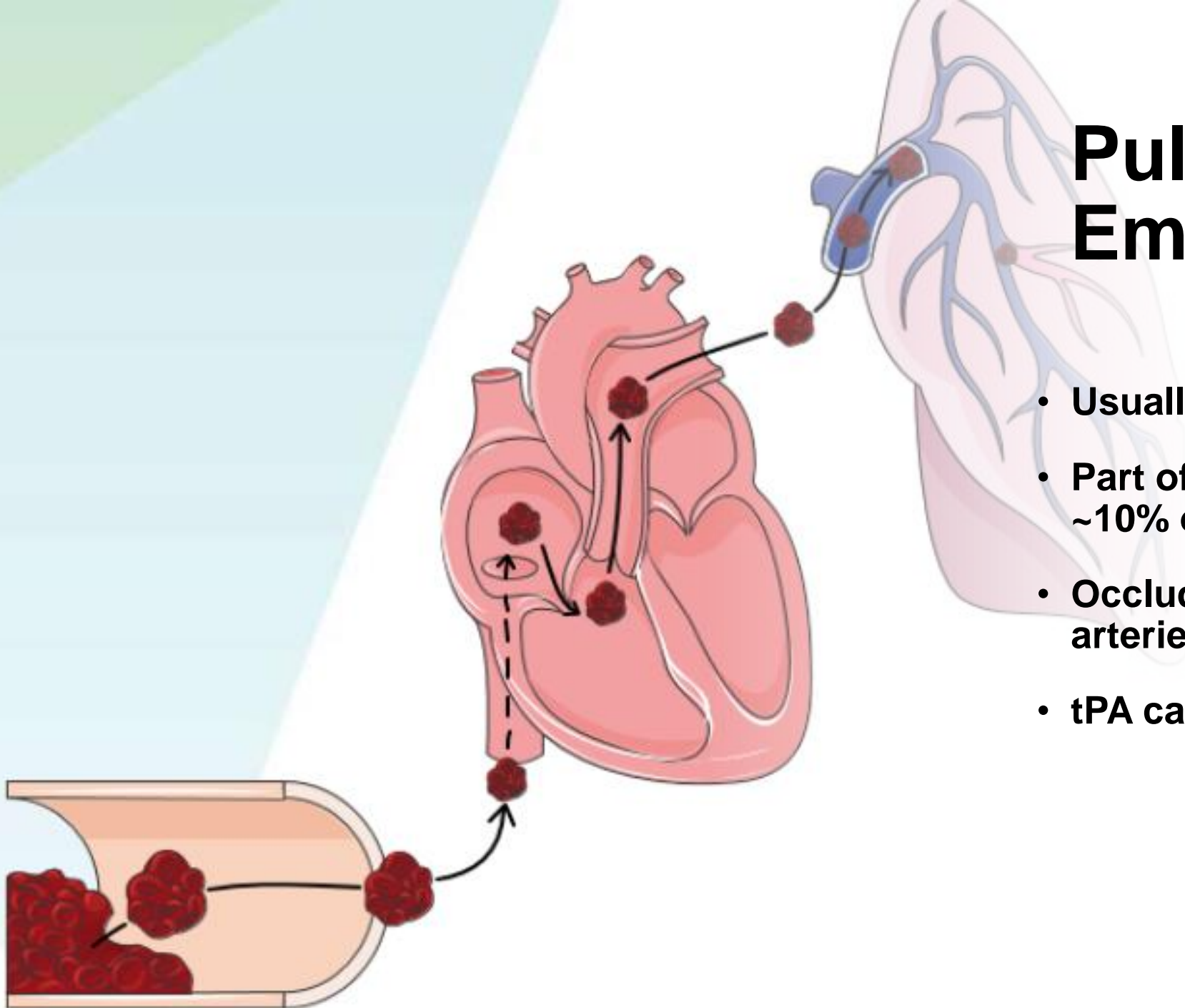   **→ effective for 1 – 4 days each time**

Thrombi and Emboli

- **An abnormal clot is a thrombus**

- **When it floats it's an embolus**

- **Caused by…**
  - **Endothelial roughening (e.g. atherosclerosis)**
  - **Slow flow (e.g. prolonged air travel)**

- **Treatment…**
  - **tPA**
  - **Embolectomy**

Pulmonary Embolus

- **Usually from deep leg veins**

- **Part of thrombus disengages ~10% of the time**

- **Occludes pulmonary arteries—potentially fatal**

- **tPA can be life-saving**

Disseminated Intravascular Coagulation (DIC)

- Occurs in the setting of massive tissue damage or sepsis

- Wide-spread coagulation in small vessels, circulatory shock

- Manifested as bleeding from multiple sites because of depletion of clotting factors

Clinically Useful Anticoagulants

Heparin

- **Binds, potentiates antithrombin III**
- **Works rapidly, generally used acutely**

Coumarins

- **Inhibit VKOR c1**
- **Deplete active vitamin K → deplete active prothrombin, factors VII, IX, X**
- **Slower acting (days); used chronically**
- **Over-anticoagulation – Treat with FFP and vitamin K**

In vitro Anti-coagulation

- **Siliconized containers prevent activation of factor XII and platelets**

- **Heparin – used in blood collection, heart-lung and kidney machines**

- **Calcium chelators (citrate, EDTA) used in blood collection, blood storage**

Blood Coagulation Tests

Bleeding	Bleeding Time (from small cut) • normally 1 - 6 minutes • Largely reflects platelet function
Clotting	Clotting time • Invert tube every 30 seconds • Normally 6 – 10 minutes • Not reproducible, generally not used

Bleeding time

- A **bleeding time** is used to evaluate the second phase of hemostasis, which involves adherence of the platelets to the injured vessel, platelet activation and aggregation (formation of a plug).

✓ The time measures how long it takes for a platelet plug to form.

✓ It increases when the platelets count is low (thrombocytopenia), platelet function is abnormal or with the use of aspirin .

- Disadvantages: Insensitive, Invasive & operator dependent.
- Advantages: good test to evaluate the platelet's function and structural abnormalities.

The Duke method

1. Clean the tip of the finger or the ear lobe with alcohol.
2. Puncture the skin with a special lancet. The wound should be 3–4 mm deep.
3. Wipe the blood drop by a filter paper every 30 seconds
4. Repeat until no more blood is absorbed by the filter paper. Which indicates a platelet plug has formed

5. Multiply the number of blood drops by 30 seconds
   - Or divide the number of spots of blood by 2 and that will give you the bleeding time in minutes.

   - Normal value: is less than 5 minutes

Clotting time

- It measures the time required for a blood sample to coagulate in vitro. Clotting time depends on the **availability of coagulation factors.**

- Many techniques are used the one we use in our lab depends on using non-hepranized capillary tubes

- Clotting time is prolonged in conditions like hemophilia, vitamin K deficiency, liver diseases, and warfarin overdose.
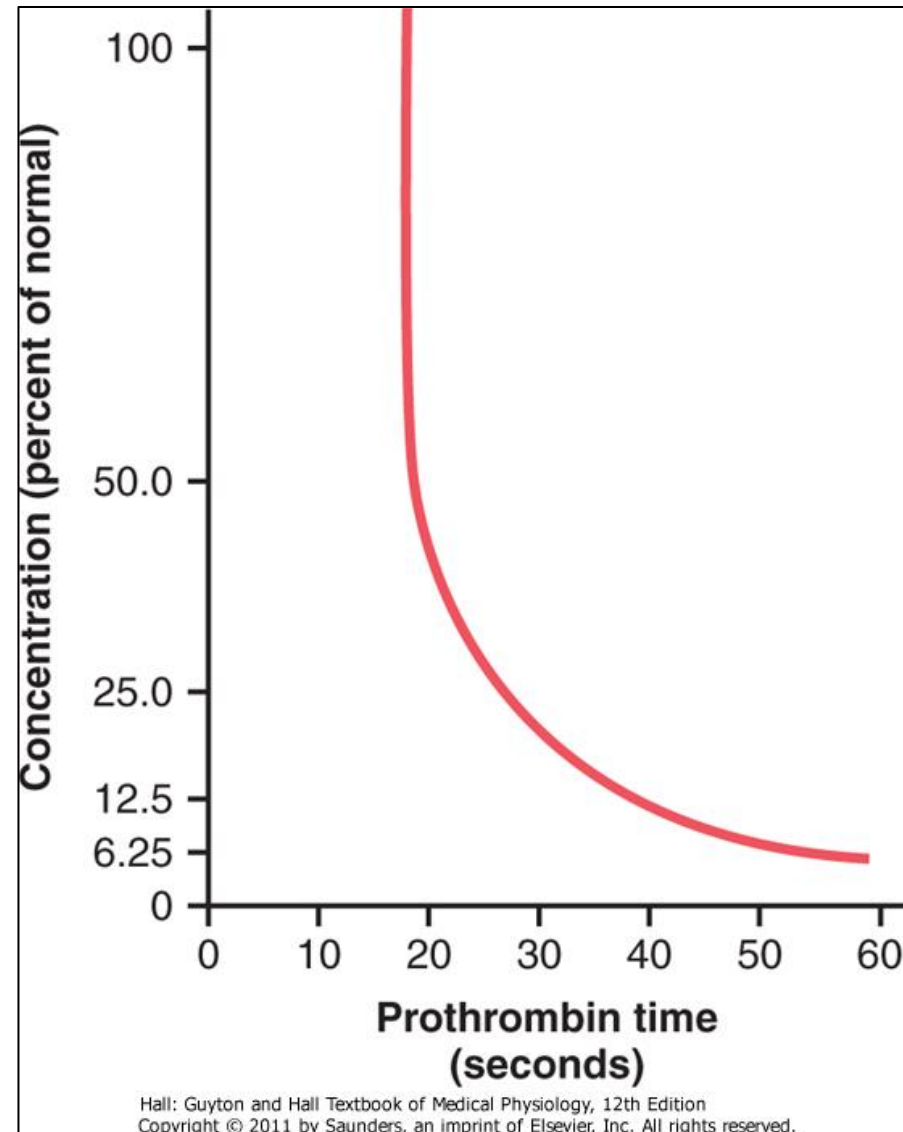
Prothrombin Time

- **Add excess calcium and tissue factor to oxylated blood, measure time to clot**

- **Assesses Extrinsic and Common Pathways**

- **Usually about 12 seconds**

- **Tissue factor batches have to be standardized (activity expressed as "International Sensitivity Index (ISI)")**

Prothrombin Concentration and Function

International Normalized Ratio (INR)

$$INR = \left(\frac{PT_{test}}{PT_{normal}} \right)^{ISI}$$

- **Normal INR: 0.9 – 1.3**

- **Therapeutic range: 2.0 - 3.0**

Tests of Other Clotting Factors

- Mix the patient's plasma with a large excess of all needed components except the factor being tested

- Compare time to coagulation with that for pooled plasma of healthy volunteers