Cardiovascular Physiology

Part 4

Lecture Outline

• General Functions
• Components
• Production & Function of Formed Elements
• RBC specialized functionality
  – Anemia
• Hemostasis
  – Platelets & Coagulation

General Functions

• Functions as:
  – a transport medium
  – a protective medium
  – a regulatory medium
  – a hydraulic medium

Components

• Whole blood is divided into
  – Formed elements (45%)
    • Erythrocytes
    • Leukocytes
    • Thrombocytes
  – Plasma (55%)
    • Extracellular matrix composed of
      – Water
      – Ions
      – Organic molecules
      – Trace elements and vitamins
      – gases

Gases
Nutrients
Chemical messengers
Heat
Wastes

Platelet activation
Coagulation
Adaptive Immunity
Non-specific defenses

pH
Temperature
Volume/Cell Count

Movement of tissues
Filtration force

Neutrophils
Eosinophils
Basophils
Lymphocytes
Monocytes

Amino acids
Proteins
Glucose
Lipids
Nitrogenous wastes

Albumins
Globulins
fibrinogens

CO₂
O₂
Production & Function of Blood Cells

• Production of blood cells is called hematopoiesis
  – Is initiated by week three of embryonic development
  – Rate is influenced by cytokines
    • EPO (erythropoietin)
      – Produced in the kidney
      – Targets bone marrow & increases production of erythrocytes
    • TPO (thrombopoietin)
      – Produced in the liver
      – Targets bone marrow & increases production of megakaryocytes
    • CSFs, IL’s, SCF (stem cell factor)
      – Produced by the endothelium and fibroblasts of bone marrow
        and by leukocytes
      – Targets all blood cell types & increases activity of hematopoietic
        stem cells

Production & Function of Blood Cells

• All blood cells differentiate from a pluripotent stem cell
  – The Hematopoietic stem cell is
    • Pluripotent because it is already partially differentiated… won’t produce anything else but
      blood cell types
  – This process occurs in bone marrow
    • Mainly in the epiphyses (ends) of long bones and
      in the flat bones (sternum, ribs, ilium)
Production & Function of Blood Cells

• Red Blood Cell Production
  – Low O₂ levels initiate synthesis of hypoxia-inducible factor-1 (HIF-1)
  – HIF-1 turns on EPO gene and synthesis of EPO is on!
  – Turns off as hypoxia is corrected due to the increase in O₂ carrying RBCs.
  – Today EPO is produced by recombinant DNA technology and other CSFs for WBCs
    • Benefits?
      – Cancer patients and
      – athletes! (illegally)

Production & Function of Blood Cells

• Colony-Stimulating Factors (CSFs)
  – Regulate wbc production and development = leukopoiesis
    • Rate must be able to be quickly amped up as a mature leukocyte no longer undergoes mitosis
      – Any additional wbcs must come from stem cell activity
    • Production of a specific type is controllable by the mature population of its type
      – This ensures the correct leukocyte production for the demand

Production & Function of Blood Cells

• Blood Cell Levels

<table>
<thead>
<tr>
<th></th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>40%-54%</td>
<td>37%-47%</td>
</tr>
<tr>
<td>Hemoglobin (g Hb/dL blood)</td>
<td>14-17</td>
<td>12-16</td>
</tr>
<tr>
<td>Red cell count (cell/µL)</td>
<td>4.5-6.5 \times 10^{6}</td>
<td>3.9-5.6 \times 10^{6}</td>
</tr>
<tr>
<td>Total white cell count (cell/µL)</td>
<td>4-11 \times 10^{3}</td>
<td>4-11 \times 10^{3}</td>
</tr>
<tr>
<td>Differential white cell count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>50%-70%</td>
<td>50%-70%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1%-4%</td>
<td>1%-4%</td>
</tr>
<tr>
<td>Basophils</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>20%-40%</td>
<td>20%-40%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>2%-8%</td>
<td>2%-8%</td>
</tr>
<tr>
<td>Platelets (per µL)</td>
<td>150-450 \times 10^{3}</td>
<td>150-450 \times 10^{3}</td>
</tr>
</tbody>
</table>

RBC Specialized Function

• Red Blood Cells
  – Specialized aspects:
    • Biconcave shape
      – Approx 7um in diameter
      – Due to cytoskeletal structure
      – Aids in movement through capillaries and allows them to maintain integrity even as osmotic pressures vary
        » Swelling vs. crenation (shrinking)
    • Anucleate condition in mature rbcs
      – Implications?
      – Life span?
RBC Specialized Function

• Red Blood Cells
  – Specialized aspects:
    • The last stage (immature form) of the production process is called a reticulocyte
      – Significant as a little bit of ER remains and is visible upon microscopic evaluation
        » The ratio of reticulocytes to erythrocytes is used to monitor production rates
    • Production and transport of hemoglobin (Hb) which accounts for 97% of the content of a mature rbc!
      – This comes to approximately 280 million hemoglobin molecules/cell!
      – Each Hb molecule carries 4 oxygen molecules
      – Increases the O₂ carrying capacity of blood by about 70 times!

RBC Specialized Function

• Red Blood Cells
  – Hemoglobin (Hb)
    • A quaternary protein (2 alpha & 2 beta units)
    • Hb exhibits plasticity in its shape
      – When O₂ binding sites are fully loaded it is in its “tense” configuration
        » Holds onto O₂ with more tenacity
        » Where does this happen?
      – When O₂ binding sites are less than fully loaded it enters a “relaxed” configuration
        » Makes binding and releasing O₂ easier
        » Where does this happen?

RBC Specialized Function

• Red Blood Cells
  – Hemoglobin (Hb)
    • A quaternary protein (2 alpha & 2 beta units)
    • Hb exhibits plasticity in its shape
      – When O₂ binding sites are fully loaded it is in its “tense” configuration
        » Holds onto O₂ with more tenacity
        » Where does this happen?
      – When O₂ binding sites are less than fully loaded it enters a “relaxed” configuration
        » Makes binding and releasing O₂ easier
        » Where does this happen?

RBC Specialized Function

Anemia

• Reduction in O₂ carrying capacity in blood because of low Hb content.
• RBC damage and loss from
  – Blood loss
  – Hemolytic anemia – cells bursting, may be
    • Hereditary such as
      – Sickle cell anemia
      – Spherocytosis
    • Acquired
      – Parasitic issue – malaria, dengue fever
      – Drugs
      – autoimmune issues
• Reduced capacity for RBC production
  – Aplastic anemia – cells don’t form correctly
  – Loss/lack of iron (needed for Hb synthesis)
  – Deficiency in folic acid (needed for DNA production)
  – Deficiency of Vit B₁₂ (needed for DNA production)
    • May be a result of lack of intrinsic factor – needed for B₁₂ absorption
    – Low EPO production

Dietary Iron

Intestinal Cells

Transported in plasma attached to the protein transferrin (Fe-transferrin)

Incorporated into hemoglobin in bone marrow by RBCs

Hb is broken down into the heme and globin components

Heme is further separated into Fe and biliverdin

Biliverdin converted to bilirubin and excreted in urine and feces

Old RBCs are phagocytosed in liver and spleen

Excess iron stored as ferritin and hemosiderin

RBCs circulate for ~120 days “holding” the iron in hemoglobin

small % lost in blood

some lost in sweat & urine
RBC Specialized Function
Polycythemia

- Too many RBCs (and WBCs too)
  - May be due to stem cell dysfunction
  - May be relative polycythemia
    - The hematocrit is high but volume is normal
    - Dehydration reduces plasma volume and therefore increases relative cell count.

- Why is polycythemia bad?

Hemostasis
Platelet Plug Formation

- Platelets stick to damaged vessel
  - Release cytokines which initiate further vasoconstriction and additional platelet adhesion
  - Sets up a cascading effect
  - Leads to a loose plug being formed
- The damaged vessel at the same time with collagen exposed and tissue factor released starts the coagulation cascade

<table>
<thead>
<tr>
<th>TABLE 16-4</th>
<th>Factors Involved in Platelet Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEMICAL FACTOR</td>
<td>SOURCE</td>
</tr>
<tr>
<td>Collagen</td>
<td>Subendothelial extracellular matrix</td>
</tr>
<tr>
<td>von Willebrand factor (vWF)</td>
<td>Endothelium, megakaryocytes</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Secretory vesicles of platelets</td>
</tr>
<tr>
<td>Adenosine diphosphate (ADP)</td>
<td>Platelet mitochondria</td>
</tr>
<tr>
<td>Platelet-activating factor (PAF)</td>
<td>Platelets, neutrophils, monocytes</td>
</tr>
<tr>
<td>Thromboxane A2</td>
<td>Phagocytic granules in platelet membranes</td>
</tr>
<tr>
<td>Platelet-derived growth factor (PDGF)</td>
<td>Platelets</td>
</tr>
</tbody>
</table>

Copyright © 2019 Pearson Education, Inc.
Hemostasis
Coagulation Cascade

- This coagulation forms a more permanent clot!
- Two pathways to achieve this
  - Intrinsic Pathway
    - Exposed collagen activates the initiating factor of the cascade event = factor XII
  - Extrinsic Pathway
    - Damaged tissues release tissue factor (factor III or tissue thromboplastin)

Table of Factors involved with the coagulation cascade

<table>
<thead>
<tr>
<th>Number and/or name</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>I = fibrinogen</td>
<td>Forms clot (fibrin)</td>
</tr>
<tr>
<td>II = prothrombin</td>
<td>Its active form (IIa) activates I, V, VII, VIII, XI, XIII, protein C, platelets</td>
</tr>
<tr>
<td>III* = Tissue factor</td>
<td>Co-factor of VIIa (formerly known as factor III)</td>
</tr>
<tr>
<td>IV* = Calcium</td>
<td>Required for coagulation factors to bind to phospholid (formerly known as factor IV)</td>
</tr>
<tr>
<td>V = procoacteitin, labile factor</td>
<td>Co-factor of X with which it forms the prothrombinase complex</td>
</tr>
<tr>
<td>VI = Unassigned – old name of Factor Va</td>
<td></td>
</tr>
<tr>
<td>VII = stable factor</td>
<td>Name: Pro Convertin - Activates IX, X</td>
</tr>
<tr>
<td>VIII = Anti Hemophilic factor A</td>
<td>Co-factor of IX with which it forms the tenase complex</td>
</tr>
<tr>
<td>IX = Anti Hemophilic Factor B or Christmas factor</td>
<td>Activates X: forms tenase complex with factor VIII</td>
</tr>
<tr>
<td>X = Stuart-Prower factor</td>
<td>Activates II: forms prothrombinase complex with factor V</td>
</tr>
<tr>
<td>XI = plasma thromboplastin antecedent</td>
<td>Activates IX</td>
</tr>
<tr>
<td>XII = Hageman factor</td>
<td>Activates factor XI and prekallikrein</td>
</tr>
<tr>
<td>XIII = fibrin-stabilizing factor</td>
<td>Crosslinks fibrin</td>
</tr>
</tbody>
</table>

Table of other factors involved with hemostasis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>prekallikrein</td>
<td>Activates XII and prekallikrein; degrades HMWK</td>
</tr>
<tr>
<td>high-molecular-weight kinogen</td>
<td>Supports reciprocal activation of XII, XI, and prekallikrein</td>
</tr>
<tr>
<td>fibronectin</td>
<td>Mediates cell adhesion</td>
</tr>
<tr>
<td>antithrombin III</td>
<td>Inhibits II, Xa, and other proteases;</td>
</tr>
<tr>
<td>heparin cofactor II</td>
<td>Inhibits IIa, cofactor for heparin and dermatan sulfate</td>
</tr>
<tr>
<td>protein C</td>
<td>Inactivates Va and VIIa</td>
</tr>
<tr>
<td>protein S</td>
<td>Cofactor for activated protein C</td>
</tr>
<tr>
<td>protein Z</td>
<td>Mediates thrombin adhesion to phospholipids and stimulates degradation of factor X by ZPI</td>
</tr>
<tr>
<td>Proteins Z-related protease inhibitor</td>
<td>Degradates factors X (in presence of protein Z) and XI</td>
</tr>
<tr>
<td>plasminogen</td>
<td>Converts to plasmin, lyses fibrin and other proteins</td>
</tr>
<tr>
<td>alpha 2-antiplasmin</td>
<td>Inhibits plasmin</td>
</tr>
<tr>
<td>tissue plasminogen activator (tPA)</td>
<td>Activates plasminogen</td>
</tr>
<tr>
<td>urokinase</td>
<td>Activates plasminogen</td>
</tr>
<tr>
<td>plasminogen activator inhibitor-1</td>
<td>Inactivates IPA &amp; urokinase (endothelial PAI)</td>
</tr>
<tr>
<td>plasminogen activator inhibitor-2</td>
<td>Inactivates IPA &amp; urokinase (placental PAI)</td>
</tr>
<tr>
<td>cancer procoagulant</td>
<td>Pathological factor X activator linked to thrombosis in cancer</td>
</tr>
</tbody>
</table>
Summary

• Blood as a transport, regulative, hydraulic and protective medium
• Production of RBCs involves a recycling aspect (Fe conservation)
• Hemostasis involves
  – Vascular spasm
  – Platelet plug formation
  – Coagulation
  – Functionally a positive feedback system