Overview of Circulation

Cardiovascular System Overview

- The plumbing: circulation systems in the body
- The wiring: cardiac electrophysiology
- The pump: the heart as a pump
- The flow: blood and hemodynamics
- The control: brain/hormonal/local, feedback
Cardiovascular System Regulation

- Goal: adequate flow
- Process: pump and flow
- Regulation: parallel circuit with valves
  - Sensors?
  - Feedback?

Role of the Circulation System

- Transport of Nutrients: $O_2$, $H_2O$, glucose, ions, heat, etc.
- Removal of wastes and byproducts: $CO_2$, pH, urea, nitrates
- Immune system: homeostasis, response to invasion
- Endocrine system: hormone delivery, control and regulation
Function of Circulation System

- Components
  - Propulsion organ (heart)
  - Arterial system
  - Capillaries
  - Venous system
- Movement of blood (roles vary across species)
  - Heart
  - Elastic recoil
  - Venous squeezing (movement and muscles)
  - Paristaltic contractions (smooth muscle)
  - Valves or septa control flow (present in all CV systems)

Open Systems

- Blood empties into body space
- Bathes tissues directly, blood in small chambers
- Low pressure system (4-10 mm Hg)
- Typically limited regulation and low oxygen transport (with exceptions)
- Built in Lymph system
- Insects bypass lungs and transport oxygen directly so open circulation does not carry oxygen
Closed Systems

- Blood stays in vessels, higher pressure than open system
- Separated systemic and pulmonary systems
- Central, peripheral, and microcirculation
- Capillaries provide transport
- Lymph system
- Ultrafiltration occurs (kidneys)
- Lungs have low pressure and hence no filtration
- Many regulation points so wide range of transport rates

List the advantages and disadvantages of closed and open circulatory systems.
What situations would favor one system over the other?
Roles of Blood

• Capture, transport, and release nutrients e.g., O$_2$, glucose, minerals
• Store and transmit heat
• Buffer acid/base balance
• Transport water in and out of regions
• Provide substrate and components of the immune system (lymphocytes)
Functional characteristics of Blood

- Composition: RBC, WBC, platelets (40% of volume), plasma proteins, transported substances.
- Production of blood cells (regulation and control)
- Response to injury: coagulation, clotting, self-preserving (regulation and control)
- Hemodynamics (regulation and control)

*Note: all these system have regulation and control components so as to maintain homeostasis.*

Red Blood Cells (Erythrocytes)

- Function
  - carry oxygen from the lungs to the tissue (increases capacity by 40-50 times!)
  - some buffering of acid/base
- Physical Details
  - 8 µm diameter, 2 µm thick disks
  - deformable
- Amount
  - 5 x 10^6 cell/ml
  - hematocrit (% by volume) = 40-45%
How to Characterize a Physiologic Mechanism (a template)

• Goal: what is the overall purpose of the system (e.g., to control blood pressure, to regulate RBC production)
• Process Steps: the set of steps that produce something (e.g., RBC production)
• Points of Regulation: where can we alter the process?
• Sensor types and locations: the measurement system(s)
• Feedback mechanisms: how do sensors communicate with points of regulation to alter the process?
**Production and (possible) Regulation of Erythrocytes**

**Sensor types:**
- RBC concentration?
- stem cell concentration?
- oxygen concentration (hypoxia)?

**Sensor locations:**
- bone marrow?
- brain?
- kidney?
- liver?
- heart?

**Possible regulation points:**
- stem cell production?
- cell differentiation and division?
- maturation of RBCs?
- RBC lifetime?

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**Actual Regulation of Erythrocyte Production**

**Regulation point:**
- maturation of RBCs
- regulated by EPO concentration

**Sensor type:**
- blood \( [O_2] \) levels

**Sensor location:**
- kidneys

**Feedback:**
- kidneys sense drop in \([O_2]\), produce EPO, stimulate RBC maturation, increase \([O_2]\).
• If you were to artificially increase the amount of RBC in your body (hematocrit), how would you do it?
• Why would you want more RBC?

Response to Altitude

• Drop in arterial $O_2$ leads to increase in ventilation
  – first 65% above normal
  – later, 300-400% above normal as negative feedback reduced
• Drop in $O_2$ saturation leads initially to rise in heart rate to bring more blood to the tissues
• To increase hematocrit, blood volume decreases (dehydration) initially and only slowly recovers (2 months). Too high hematocrit increase blood viscosity and reduced cardiac output.
• Concentration of 2,3 diphosphoglycerate (DPG) increase and shifts $O_2$ dissociation curve.
• Increased ventilation causes loss of $CO_2$ and alkalosis. Leads to shift in acid/base balance.
• Increase in erythrocyte concentration (sustained): 4-5 fold production in first few days of exposure. Not complete even after a year at (high) altitude.
Homeostasis of Blood

• Response to damage
  – Block off damaged area, reduce pressure (vasoconstriction)
  – Make a patch (platelet aggregation and coagulation)
  – Restore pressure (vasodilation)
  – Restore tissue (cell division and growth)
  – Remove patch (clot retraction/dissolving)

Homeostasis and Tissue Repair

• Vascular Spasm: lasts minutes to hours, CNS mediated
• Platelet plug: within seconds, bind to injured tissue, form plug adequate for small incisions.
• Coagulation: (clotting) complex series of reactions that result in the formation of a fibrinous plug that stops blood loss.
• Clot retraction: platelets interact with fibrin to pull clot together and squeeze out plasma; role unclear but perhaps to promote vessel closure.
• Tissue repair, clot removal by plasmin
Platelet Aggregation

- Example of positive feedback: what stops it?
  - Selective adhesion of platelets to vessels

Coagulation

Intrinsic pathway:
- Collagen or other activators
- Active X
  - Ca²⁺
  - Active XI

Extrinsic pathway:
- Tissue factor (II) and active VII
  - Positive feedback
  - Active IX
  - Ca²⁺, PL
  - Active X
  - Ca²⁺, V, PL
  - Thrombin
  - Fibrinogen
  - Fibrin
  - Active XIII
  - Cross-linked fibrin
Coagulation

• Key steps:
  – initiation of coagulation cascade
  – conversion of soluble fibrinogin into fibrin monomers by thrombin
  – conversion of fibrin monomers into strands and linking into a mesh by activated stabilizing factor
  – clot includes plasmin, which cause eventual dissolving
• Calcium is key ingredient
• Two initiation pathways:
  – extrinsic (tissue trauma)
  – intrinsic (blood trauma)

Regulation of Coagulation

• Physical/mechanical
  – New endothelial cells coat the vessels, reduce stimulus
• Remove pro-coagulants
  – Restored blood flow washes pro-coagulants away (perhaps most important factor)
  – Pro-coagulant substances removed by the liver, spleen, and bone marrow
• Inactivate Thrombin
  – Heparin: secreted by mast cells in lung and liver
  – Thrombin (pro-coagulant) absorbed by fibrin threads
  – Blood protein antithrombin III binds and eventually inactivates thrombin
• Calcium
  – Citrate: removes calcium from the blood for blood doning. (tingling lips during apheresis)
Removal of Clots (thrombus, embolus)

- Goal: produce plasmin, which dissolves clot (digests fibrin and other clotting factors)
- Process Steps: complex, see Berne and Levy or Silverthorn
- Points of regulation:
  - urokinase: released from kidneys, activates plasminogen
  - streptokinase and tissue plasminogen activator (TPA) exogenous drugs that activate plasminogen
- Feedback:
  - complex and multilayered
  - e.g., thrombin production eventually activates plasminogen

Why is it a good idea to apply compression to a cut?