Circulatory system I: Blood

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Functions of Circulatory System

• Transportation of substances
  - respiration
  - nutrition
  - excretion
• Regulation
• Protection
Major components

- **Cardiovascular system**
  - heart
  - blood vessels
  - blood

- **Lymphatic system**
  - lymph nodes
  - lymph vessels
  - Lymphatic fluid, or lymph
Functions of blood

• Distribution
  - Oxygen
  - Metabolic wastes
  - Hormones

• Regulation
  - Body temperature
  - pH
  - Fluid volume (attributed most appropriately to kidney)

• Protection
  - Hemostasis to prevent blood loss
  - Immune components
Physical Characteristics of blood

- Viscosity varies with altitude
- Oxygen content of blood effects color
- pH = 7.35-7.45
- Temp = 38°C
- 8% of total body weight
- Average volumes
  - Females = 4-5L
  - Males = 5-6L
Hematocrit

10 ml

PLASMA - 55% of Total Blood Volume
91% Water
7% Blood Proteins (fibrinogen, albumin, globulin)
2% Nutrients (amino acids, sugars, lipids)
Hormones (erythropoietin, insulin, etc.)
Electrolytes (sodium, potassium, calcium, etc.)

5 ml

CELLULAR COMPONENTS - 45% of Total Blood Volume
Buffy Coat
White Blood Cells (7000-9000 per mm³ of blood)
Platelets (250,000 per mm³ of blood)

Red Blood Cells (RBCs)
About 5,000,000 per mm³ of blood
Plasma

- Water (90%) and dissolved solutes
  - Albumins
    - 60% of plasma proteins
    - Osmotic pressure regulation
    - Buffer
  - Globulins
    - 36% of plasma proteins
    - Alpha, beta globulins
      - lipid transport
    - Gamma
      - antibodies
  - Clotting proteins
    - Fibrinogen
    - Prothrombin
  - Nutrients, electrolytes, respiratory gases
Formed elements

• Erythrocytes
• Leukocytes
• Platelets
Hematopoietic stem cells and blood cell formation
Hemopoiesis

- Blood cell formation
  - Lymphocytes = lymphokines
  - Erythrocytes = erythropoietin
- Erythropoiesis

Decreased O2 detected in kidneys → Increased erythropoietin production → Increased plasma erythropoietin

Target cells = stem cells in red bone marrow → Increased production RBC’s → Increased O2
Erythrocytes

- Shape and structure
- How many?
  - $5.8 \times 10^3 / \text{mm}^3$ in males
- Lifespan
- Hemoglobin content
  - $280 \times 10^6$ per RBC
Erythrocyte fate

“old” RBC’s are engulfed by macrophage in liver, spleen, bone marrow

Cells are destroyed and hemoglobin is liberated and broken down

- Hemoglobin
- Bilirubin
- Heme
- Globin
- Ferritin, hemosidirin
- Iron + transferrin
- Bile
Leukocytes

- Agranular
  - Lymphocytes
  - Monocytes
- Granular
  - Basophils
  - Eosinophils
  - Neutrophils
Platelets

- Megakaryocytes
- Thrombocytes
- Life span – 5-9 days
- Role in blood clotting
Hemostasis

• Initiation
  – Endothelial damage exposes collagen fibers to blood

• Three responses
  – Vasoconstriction
  – Platelet plug formation
  – Production of fibrin web around the plug
Vasoconstriction

- Vascular spasms initiated by:
  - damaged smooth muscle in blood vessels
  - Chemicals released by endothelium and platelets
  - Reflexes due pain receptor stimulation
- Reduces blood loss especially in smaller blood vessels
Platelet plug formation

• Platelets become sticky
  - Negatively charged collagen fibers
    • Platelets stick directly to tissue at these sites
  - von Willebrand’s factor (VWF)
    • Protein leaking from damaged tissues to which platelets stick

• Thrombin activates platelets
  - Seratonin increases vascular spasms
  - ADP attracts additional platelets
  - Thromboxane A2 = platelet chemotaxis and vascular spasms
  - Localized by release of prostacyclin from endothelial cells
Production of fibrin web

• Clotting = positive feedback loop
• Prothrombin is activated and converts fibrinogen to fibrin
• Clot retracts and repair is initiated
Dissolution of clots

• After healing is complete, plasminogen is converted to plasmin to digest fibrin
  - Localized to clot by tissue plasminogen activator, released by endothelial cells, and thrombin

• Factor XII leads to:
  - kallikrein formation
  - catalyzes plasminogen to plasmin
  - plasmin digests fibrin

• Anticoagulants
  - heparin = inactivates thrombin
  - dicoumarin, warfarin = inhibit Vitamin K activity
    • Vitamin K needed by liver for normal formation of clotting factors, such as prothrombin
Spasm in damaged smooth muscle

Injury

Platelet aggregation and adhesion

1. VASCULAR PHASE

2. PLATELET PHASE

COMMON PATHWAY

Prothrombin

Fibrinogen

Fibrin

Plasminogen

Plasmin

EXTRANSC PATHWAY

Tissue thromboplastin

Clotting factor VII

Clotting factors VIII, IX, X, XI, XII

Ca²⁺

Platelet factors

Tissue factors

INTRINSIC PATHWAY

Platelet thromboplastin

Thrombin

3. COAGULATION PHASE

Activation of clotting system and clot formation

4. CLOT RETRACTION

Contraction of blood clot

5. CLOT DESTRUCTION

Enzymatic destruction of clot
Disorders

• DIC
  - Clots block blood vessels, remaining blood does not clot = severe bleeding
• Thrombocytopenia
  - Deficiency in number of platelets
• Hemophilia
  - Hereditary bleeding disorders
  - Deficiency of blood factors that effect ability to clot
• Liver impairment
  - Decreased production of coagulants
  - Decreased production of blood proteins = ascites
Disseminated Intravascular Coagulopathy

- Balance of Coagulation +
- Precipitating Event (e.g., infection or sepsis)
- Tissue Factor Release
- Coagulation Cascade
- Excess Thrombin
- Conversion of Plasminogen to Plasmin
  - Microvascular Clotting
  - Macrovacular Clotting
  - Thrombocytopenia
  - Consumption of Clotting Factors
  - Excess Clotting
- Ischemia
- Impaired Organ Perfusion
  - End-Organ Damage
- Fibrinolysis with Excess FDPs
  - Excess Bleeding
  - Shock
  - Hypotension
  - Increased Vascular Permeability
# ABO Blood Groups

<table>
<thead>
<tr>
<th>Blood Type</th>
<th>Antigens</th>
<th>Antibodies</th>
<th>Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>Anti-B</td>
<td>Type A, O</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Anti-A</td>
<td>Type B, O</td>
</tr>
<tr>
<td>AB</td>
<td>A &amp; B</td>
<td>None</td>
<td>Type AB, A, B, O</td>
</tr>
<tr>
<td>O</td>
<td>None</td>
<td>Anti-A, Anti-B</td>
<td>Type O</td>
</tr>
</tbody>
</table>

Type O is the universal donor: Type AB is the universal recipient
Rh Factor

• Identified by D-antigen on surface of RBC’s
  - 46 additional antigens have been identified
• Classification
  - Rh positive = dominant
  - Rh negative = recessive
• Implications in pregnancy
  - Rh⁻ mother and Rh⁺ fetus

Hemolytic Disease of the Newborn or Erythroblastosis fetalis

Symptoms: enlarged liver, edema, jaundice, anemia
Development of HDN
Typing and cross-matching

- Two step process to determine blood group compatibility
  - Typing
    - Determination of ABO blood group
    - Determination of Rh factor
  - Crossmatching
    - Serum from recipient mixed with donor erythrocytes
- Agglutination signifies incompatibility
- Must be performed within 3 days of transfusion
Not as simple as ABO

- Genotyping vs serology
- 29 known blood groups determined by 200 antigens
  - 31 genes code for surface antigens
  - Minor blood groups (those other than ABO)
- Acute or delayed hemolytic reactions in people with multiple transfusions
- Weak or partial D antigens
  - \( \approx 40\% \) pregnant women may receive RhoGam inappropriately

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Disorders

- **Erythrocytes**
- **Anemias**
  - Hemorrhagic
  - Hemolytic
  - Aplastic
  - Iron deficiency
  - Pernicious
- **Hemoglobinopathies**
  - Sickle-cell
  - Thalassemias
- **Polycythemia**

- **Leukocytes**
- **Leukemias**
  - Acute
    - Lymphoblastic
    - Myelocytic
  - Chronic
    - Lymphoblastic
    - Myelocytic
Sickle cell anemia

- Single amino acid substitution causes hemoglobin to clump together and cells to sickle under low oxygen tension.
- Heterozygous advantage in malaria endemic area.
Thalassemia syndromes

- Heterogenous group of Mendelian disorders
- Deficient synthesis of $\beta$ chain ($\beta$-thalassemia) or $\alpha$ chain ($\alpha$-thalassemia)
- Decreased amount of Hb in cell
- Aggregation of most abundant chains in cell results in RBC destruction in spleen
- Severe disease in homozygous individuals
  - Transfusion dependent
Leukemias

- Acute lymphoblastic leukemia
- Acute myelocytic leukemia
- Normal blood
- Acute lymphoblastic leukemia
Leukemia

• Acute myeloblastic leukemia
  - Predominately in adults 15-39 yo
  - Heterogenous: increased production of myeloblasts in bone marrow that would differentiate cells in myeloid image
  - Difficult to treat
    • usually opt for bone marrow transplant
    • Only 15% of patients treated with chemo remain dz free after 5 years

• Acute lymphoblastic leukemia
  - Predominately in children & young adults
  - More common in Caucasian children
  - > 90% of children achieve complete remission
  - Immature cells in bone marrow that would develop into lymphoctes
Circulatory System II: The Heart

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Pathway of blood through the heart
Pulmonary and Systemic Circulations

• Pulmonary circulation:
  - Path of blood from right ventricle through the lungs and back to the heart.

• Systemic circulation:
  - Oxygen-rich blood pumped to all organ systems to supply nutrients.

• Rate of blood flow through systemic circulation = flow rate through pulmonary circulation.
Cardiac muscle

• Striated, involuntary

• Intercalated discs
  - Gap junctions and desmosomes
  - Functional syncytium
  - Spontaneous depolarization
Energy requirements

• Aerobic respiration
  - Increased # mitochondria
  - Cannot function without oxygen for extended time periods

• Myoglobin
  - Protein which releases oxygen when muscle contracts

• Enhanced ability to switch metabolic pathways to utilize available nutrients
Action potential in myocardial cells

- Rmp of myocardial cells = -90mV
- Steps:
  - Influx of Na\(^+\) into cell initiates positive feedback loop
  - Voltage regulated Na\(^+\) channels open and reverse membrane potentially to ~ +30mV
  - Ca\(^{++}\) enter cell from ECF, then from SR
  - Voltage regulated Ca\(^{++}\) (slow Ca\(^{++}\) channels) open in myocardial cells allowing for the slow infusion of Ca\(^{++}\) = plateau phase
  - K\(^+\) channels open, K\(^+\) moves out and cell repolarizes
  - Na\(^+\)K\(^+\)ATPase pump & Ca\(^{+2}\) ATPase pump restores ions to their proper locations
Plateau phase

• Prolonging of depolarization due to influx of Ca++ into myocardial cells

• Result:
  – Action potential $\geq 200\text{ms} = \text{sustained contraction for blood ejection}$

• Rapid return of Ca++ to SR and ECF during repolarization
Pacemaker potential

- Slow spontaneous depolarization of the SA node during diastole

- Steps
  - rmp of SA node = -60mV
  - spontaneous diffusion of Ca\(^{++}\) through slow calcium ion channels = -40mV
  - threshold depolarization opens fast Ca\(^{++}\) channels = rapid diffusion into cell
  - voltage-regulated Na\(^{+}\) channels open
  - influx of Na\(^{+}\) as a/p begins
  - repolarization by opening K\(^{+}\) channels and outflow of K\(^{+}\)
  - new pacemaker potential begins when rmp reestablished at end of diastole
Definitions

- **cardiac cycle** = one contraction & one relaxation of heart
- **Systole**
- **diastole**
- **EDV** = total blood volume in ventricles at end of diastole
- **ESV** = total blood volume in ventricles at end of systole
- **stroke volume** = amount of blood ejected by heart per beat
- **cardiac output** = amount of blood ejected by heart per minute
- **heart sounds:**
  - **Lub** = closing of AV valves during isovolumetric contraction
  - **Dub** = closing of SLV
Pressure changes during cardiac cycle

- **Step #1: Isovolumetric contraction**
  - AV close (intraventricular pressure at onset of contraction)
  - SLV closed
  - No blood ejected or added

- **Step #2: Ejection phase**
  - increased pressure in ventricles push SLV’s open
  - 120mm Hg in L ventricle and aorta

- **Step #3: Back pressure**
  - causes SLV to close and aortic pressure goes to 80 mm Hg
  - pressure in ventricles = 0

- **Step #4: Isovolumetric relaxation**
  - all valves remain closed until pressure in ventricles exceeds pressure in aorta

- **Step #5: Atrial contraction**
  - Initial movement of blood into the ventricles is passive
  - Contraction forces final amount of atrial blood into ventricles
Cardiac Cycle
Heart Sounds

- **Closing of the AV and semilunar valves.**
- **Lub (first sound):**
  - Produced by closing of the AV valves during isovolumetric contraction.
- **Dub (second sound):**
  - Produced by closing of the semilunar valves when pressure in the ventricles falls below pressure in the arteries.
Heart Murmurs

- Abnormal heart sounds due to abnormal patterns of blood flow in the heart.
  - Defective heart valves:
    - Valves become damaged by antibodies made in response to an infection, or congenital defects.
  - Mitral stenosis:
    - Mitral valve becomes thickened and calcified.
    - Impairs blood flow from left atrium to left ventricle.
    - Accumulation of blood in left ventricle may cause pulmonary HTN.
  - Incompetent valves:
    - Damage to papillary muscles.
      - Valves do not close properly.
      - Murmurs produced as blood regurgitates through valve flaps.
Heart Murmurs

• Septal defects:
  - Usually congenital.
    • Holes in septum between the left and right sides of the heart.
    • May occur either in interatrial or interventricular septum.
  - Blood passes from left to right.
Electrical activity of heart

• Ectopic pacemaker
  - pacemaker in tissues other than SA node
  - rmp of most myocardial cells = -90mV

• Components of conduction system
  - sinoatrial node
  - atrioventricular node
  - bundle of His
  - R/L bundle branches
  - Purkinje fibers
Impulse conduction

- 0.8-1.0 m/sec across the atria
- Slow at AV node
- 5 m/sec over Purkinje fibers
- Long refractory period = no summation

Components of left bundle branch

Conduction System of the Heart

- SA Node
- Bachmann's Bundle
- Atrial Internodal Tracts
- AV Node
- Bundle of His
- Right Bundle Branch
- Left Bundle Branch
  - Anterosuperior Fascicle
  - Inferoposterior Fascicle
  - Septal Fascicle Fibers
  - Purkinje Fibers
EKG

- Electrolytes
- Uses 12 electrodes to obtain different “views” of 3-D heart
- Measures electrical activity of myocardial cells
  - Duration: fractions of a second
  - Amplitude: mV
  - Configuration: shape and appearance of wave
- Three distinct waves
  - P = atrial depolarization
  - QRS = depolarization of ventricles + repolarization of the atria
  - T = repolarization of ventricles
ECG Leads

• Bipolar leads:
  - Record voltage between electrodes placed on wrists and legs.
  - Right leg is ground.

• Unipolar leads:
  - Voltage is recorded between a single “exploratory electrode” placed on body and an electrode built into the electrocardiograph.
  - Placed on right arm, left arm, left leg, and chest.
    • Allow to view the changing pattern of electrical activity from different perspectives.
Reading an EKG

- Horizontal axis measures time
  - One small square (1x1mm) = 0.04 seconds
  - One big square (5x5mm) = 0.2 seconds
- Vertical axis measures voltage
  - One small square = 0.1mV
  - One big square = 0.5mV
Intervals and segments

• **PR interval**
  - P wave and straight line connecting it with QRS complex
  - Measure amount of time from beginning of atrial depolarization to beginning of ventricular depolarization

• **ST segment**
  - Straight line connecting the end of QRS complex and start of T-wave
  - End of ventricular depolarization to beginning of ventricular repolarization

• **QT interval**
  - QRS complex + ST segment + T wave
  - Beginning of ventricular depolarization to end of ventricular repolarization
EKG

Normal EKG

Atrial flutter

Note: saw-toothed appearance

Atrial fibrillation

Note: irregular, undulating baseline

Second degree AV block

Note: progressive prolongation of P-R interval until a QRS is dropped
Cardiac Arrhythmias

- **Bradycardia**: HR < 60 bpm
  - athletes bradycardia: normal HR between 40 and 60 bpm
- **Tachycardia**: HR > 100 bpm
  - sinus tachycardia: normal
  - ventricular tachycardia: abnormally fast ectopic pacemakers
- **Flutter**
  - rapid, coordinated
- **Fibrillation**
  - rapid, uncoordinated

Both result in decreased filling time and decreased MAP.
Cardiac output

- \( CO \text{ (ml/min)} = SV \text{ (ml/bt)} \times HR \text{ (bts/min)} \)

- \( HR = \text{beats per minute (mean = 70 in adults)} \)
- \( SV = \text{volume of blood pumped per beat by each ventricle (mean = 70-80)} \)
- \( \text{average CO per minute} \)

- \( \text{Cardiac Reserve} = \text{maximal CO-resting CO} \)
  - Nonathletes = 20-25 L/min (4-5x > normal)
  - Athletes = 35L/min (7x > normal)
Regulation of heart rate

- Autonomic innervation of SA node
  - Sympathetic = positive chronotropic effect
    - Increased rate of depolarization
  - Parasympathetic = negative chronotropic effect
    - Decreased rate of depolarization

- Other autonomic influences
  - Sympathetic = increased contraction strength
  - Increased stimulus by vagus nerve = decreased heart rate in athletes
    - Usually exercise decreases vagus nerve inhibition of SA node = increased HR
Cardiac control centers

- Medulla oblongata
  - Receives input from
    - baroreceptor reflex
      - Aorta & carotid arteries
  - higher brain centers
Regulation of stroke volume

- **EDV**
  - preload

- **TPR** = frictional resistance to blood flow in arteries
  - Afterload imposed on ventricle after contraction has started
  - higher TPR = higher blood pressure = decrease SV
  - Intraventricular pressure must be higher than aortic pressure for ejection to occur

- **Contractility**
  - strength of ventricular contraction
  - increased contractility = increased SV
  - Increased EDV = increased contractility (why?)
Intrinsic control of contractility

- Starling law
  - Increased EDV = increased contraction strength = increased SV

- Heart adjustment to increased TPR
  - Incr TPR = decr SV of ventricle = incr ESV = incr EDV for next cycle = incr contraction strength = incr blood ejected
Extrinsic control of contractility

• Sympathoadrenal system
  • NE and Epi
    - increase contraction strength
  - Two effects
    • positive *inotropic* effect on contractility
      - increased contraction strength
    • positive *chronotropic* effect on HR
      - increased HR

• Thyroxine
  - Slow sustained increase in heart rate
  - Potentiates effect of NE and Epi
Pathology

- Angina pectoris
- Cardiomegaly
- Left ventricular hypertrophy
- Tetralogy of Fallot
- Transposition of the great vessels
Angina Pectoris

- Myocardial ischemia results in chest pain
- Duration: approximately 3-5 minutes
- Usually transient and alleviated with restored blood flow
- Reversible if temporary
Myocardial infarction

- Reduction of blood flow through a coronary artery leads to ischemia and necrosis
- Leading cardiovascular cause of death in US and Western Europe
Bypass surgery
Cardiomegaly

- Enlargement of heart
- May be secondary to right or left hypertrophy
- Also seen in Chaga’s disease
Left ventricular hypertrophy

- May be acquired or congenital
- Disproportionate thickening of left ventricle
- May be inherited as a non-sex linked autosomal dominant trait
- Results eventually in heart failure
Congestive heart failure
CO inadequate for blood flow requirements of body

- **left ventricular heart failure**
  - pulmonary edema (MI, valvular stenosis)

- **right ventricular heart failure**
  - congestion and edema in systemic circulation

- **electrolyte disturbances**
  - excessive plasma K⁺ (decreased RMP)
  - decrease Ca⁺⁺ (decreased coupling)
  - excessive K⁺ + decrease Ca⁺⁺ (heart stops in diastole)
  - decrease K⁺ + increase Ca⁺⁺ (heart stops in systole)

- **Compensatory mechanisms**
  - activation of sympathoadrenal system
  - **outcome:** dilation and hypertrophy of ventricles
Tetralogy of Fallot

- Complex of four cardiac defects: ventricular septal defect, pulmonary stenosis, right ventricular hypertrophy, and dextroposition of the aorta
- Allows unoxygenated blood to mix with oxygenated because blood is shunted left to right
- 10% of congenital heart disease, equally prevalent in both sexes
Transposition of the great vessels

- Great arteries are reversed
- Results: two noncommunicating systems
  - one pulmonary
  - one systemic
- Usually occurs with patent ductus
- more common in males
Circulatory System

III: Blood vessels

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Blood vessels

- Three layers
  - tunica externa
  - tunica media
  - tunica intima
- Arteries
- Capillaries
- Veins
Arteries

• Blood away from heart
• large
  - elastic recoil
• smaller arteries/arterioles
  - greatest resistance to blood flow in arterial system
  - less recoil
Capillaries

- Proximity to tissues
- Regulation of blood flow to organs
  - sphincter
  - resistance
- Three types
  - Continuous
    - Tight junctions
    - Intercellular clefts
    - Skin and muscle
  - Fenestrated
    - Oval pores
    - Kidneys
  - Discontinuous
    - Sinusoids
    - Liver, bone marrow, lymphoid organs
Veins

- Low pressure
- Capacitance vessels
  - Contain 65% of blood supply
- Valves
Definition

• **Blood Flow**
  - Volume of blood flowing through vessel, organ, or circulatory system (=CO)
  - Varies within body organs

• **Blood Pressure**
  - Force per unit area exerted on vessel wall by blood

• **Resistance**
  - Opposition to flow of blood through vessels
  - TPR = sum of all vascular resistance within systemic circulation
Vascular resistance to blood flow

- Flow of blood depends on pressure difference at both ends of the blood vessels
- Change in pressure ($\Delta P$) = $P_1 - P_2 = 100 - 0 = 100$ mm Hg
- Blood flow
  - directly proportional to $\Delta P$
  - inversely proportional to frictional resistance
  - resistance depends on:
    - 1. Length of the vessel
    - 2. Viscosity of blood
    - 3. $r^4$

$$\text{Resistance} = \frac{Lv}{r^4}$$

Resistance has a greater influence on blood flow to individual organs than the difference in pressure.
Systemic blood pressure

- Blood flow opposed by resistance results in blood pressure
- Highest pressure closest to pump
  - Arterial (≈ 120 mm Hg)
    - Elasticity
    - Blood volume
  - Capillary (≈ 40 to 20 mmHg)
    - Permeable
  - Venous (≈ 20 to 10 mm Hg)
Pulse pressure and MAP

• Pulse
  - reflection of heart rate
  - produced by pulse pressure
• pulse pressure = systolic-diastolic
  - increase in TPR and HR = pulse pressure decrease
  - increase in CO = pulse pressure increases
• MAP = diastolic + 1/3 pulse pressure
Factors effecting venous return

• Total blood volume
• venous pressure
  - 10mm Hg in venules to 0 mm Hg in vena cavae
  - Movement from high pressure to low
• Compliance: veins more compliant than arteries
  - capacitance vessels = veins (average 2mm Hg)
  - resistance vessels = arteries (90-100 mm Hg)
• other factors
  - difference in pressure
  - skeletal muscle pumps
  - respiratory pump
  - sympathetic nerves stimulate smooth muscle contractions in walls of veins
Regulators of blood flow

• **Major regulators of blood flow through an organ**
  - MAP
  - Vascular resistance

• **Maintenance of blood pressure**
  - Diversion of blood flow
    • vasodilate in one organ = vasoconstrict in other areas + increase cardiac output to compensate
    • example: exercise = vasodilation to skeletal muscle, vasoconstriction of blood vessels in viscera and skin
Blood pressure

• Arterial blood pressure raised by:
  - vasoconstriction of arterioles
  - increasing cardiac output

• Three most important factors:
  - HR
  - SV
  - TPR

• Regulation
  - kidneys
    • blood volume
  - sympathoadrenal system
    • constriction of renal blood vessels = decrease urinary output
Vasomotor Center

- Cluster of sympathetic neurons in medulla
- Regulate blood vessel diameter
- Vasomotor tone
  - Continuous stimulation of smooth muscle by sympathetic fibers
- Work in conjunction with cardiovascular center to integrate bp by changing CO and bv diameter
- Function
  - Incr activity = generalized vasoconstriction - increased bp
  - Decr activity = relaxation = decreased bp
Baroreceptor reflex

- **Location**
  - aortic arch and carotid sinus

- **Stimulated by increase or decrease in blood pressure**
  - greater sensitivity to decrease or to sudden change

- **Mechanisms**
  - stand up from lying position = drop in blood pressure = stimulation of baroreceptors = signaling decreases = sympathetic activity overtakes parasympathetic = increased HR and vasoconstriction = increased blood pressure
  - an increase in blood pressure initiates the baroreceptor reflex = decrease in HR and vasodilation
    - massaging carotid artery

Chemoreceptors in same location respond to changes in pH and CO2 levels. More info in respiratory system.
Renal blood volume regulation

- 98-99% $H_2O$ reabsorbed in kidneys
- Hormonal control
  - ADH
  - Aldosterone
  - Renin-Angiotensin system
  - ANF
Antidiuretic hormone

- **Source**
  - Posterior pituitary

- **Stimulus**
  - plasma osmolality

- **Pathway**

  - Increased plasma osmolality
  - Osmoreceptor stimulation
  - Increased thirst
  - Increased ADH release
  - Increased water reabsorption
  - Decrease urine excreted
  - Increased water uptake
Aldosterone

• Source
  - Adrenal cortex

• Mechanism
  - stimulates reabsorption of NaCl by kidneys
  - increase in blood volume without changing plasma osmolality

• Stimulus
  - decrease in blood volume and pressure
  - Activation of renin-angiotensin system
Renin-angiotensin system

• **Pathway**
  - Decrease blood flow & pressure in the renal artery
  - JGA releases renin into circulation
  - Angiotensinogen in plasma
  - Angiotensin I

• **Lung capillaries**
  - Angiotensin II

• **Effects**
  - Increase blood pressure
  - Vasoconstriction

• **Two mechanisms:**
  - 1. Stimulate thirst centers in hypothalamus
  - 2. Aldosterone secretion
Atrial naturitic factor

- **Stimulus**
  - increased blood volume

- **Actions**
  - salt & water excretion
  - vasodilation
  - decrease aldosterone secretion
Atrial stretch receptors

• Location

• Stimulation
  - Increased venous return to the heart

• Results in:
  - reflex tachycardia
  - inhibition of ADH secretion
  - increased ANF secretion
Additional influences on blood volume

- **Epinephrine and norepinephrine**
  - Source: Adrenal medulla
  - Stimulus: fight or flight
  - Effect: Generalized vasoconstriction, vasodilation in skeletal and cardiac muscle

- **Endothelium derived factors**
  - Endothelin
    - stimulus: Low blood flow
    - Effect: vasoconstriction
  - PDGF
    - Effect: vasoconstriction
Additional influences on blood volume

- **Nitric Oxide**
  - Stimulus: increased blood flow, chemical signals
  - Effect: vasodilation

- **Inflammatory Chemicals**
  - Stimulus: inflammatory response
  - Effect: vasodilation, increased vascular permeability

- **Alcohol**
  - Effect: inhibits ADH, increased vasodilation = decrease bp
Extrinsic regulation of blood flow

• **Endocrine**
  - **Angiotensin II**: vasoconstriction of smooth muscle in blood vessels

• **Autonomic nervous system**
  • **Sympathetic**
    - Alpha ($\alpha$) adrenergic stimulation
      - vasoconstriction of arterioles in viscera & skin
    - Beta ($\beta$) adrenergic stimulation
      - vasodilation of blood vessels to skeletal muscle
  • cholinergic sympathetic fibers
    - vasodilation of blood vessels in skeletal muscle
  - **Parasympathetic**
    • cholinergic parasympathetic fibers
Intrinsic regulation of blood flow

- **Myogenic control mechanisms**
  - direct response to pressure changes
  - *Goal:* to keep blood flow constant in spite of changes
    - decrease in arterial pressure results in vasodilation of cerebral vessels
    - increase in blood pressure leads to vasoconstriction

- **Metabolic control mechanisms**
  - local vasodilation due to local chemical conditions
    - decreased [O] due to increased metabolic rate
    - increased [CO₂]
    - decreased pH in tissues
    - release of adenosine or K⁺ from tissue cells
  - active hyperemia
    - increased shunting to organs with increased metabolic rate
  - reactive hyperemia
    - local vasodilation after blood supply has been temporarily blocked
Coronary circulation & aerobic requirements

• Aerobic requirements
  - capillary bed: 10 μm
  - Myoglobin
    • releases oxygen during systole
    • stores during diastole
  - increase in blood flow during exercise
    • from 80 ml/min/100g to 400 ml/min/100g

• Coronary blood flow
  - high vascular resistance
  - intrinsic metabolic control mechanisms during exercise
    • Cardiac cells use 65% of oxygen carried to them in blood
    • Vasodilation with incr $CO_2$ and decr $O_2$
Regulation of blood flow through skeletal muscles

- Blood flow dependent on type of fiber and activity
- Sympathetic innervation
  - Alpha (a) receptors
    - Vasoconstriction
    - Protects against excessive demands for blood on heart
    - Maintains blood pressure by decreasing flow of blood to viscera and skin
  - Beta (b) receptors
    - Vasodilation
    - Increases blood flow to exercising muscle
- Cholinergic innervation
  - vasodilation
Circulatory changes during exercise

• increased total blood flow (CO)
• metabolic vasodilation of bv to muscles
• diversion of blood
  – increased to heart, no change to brain
• effects of endurance training
  • lowers HR
    – vagus nerve inhibits SA node
  • increases SV
    – Blood volume increased up to 500ml in 8 days of training
• higher CO
Cerebral circulation

• Autoregulation
  - constant blood flow under changing conditions

• Metabolic regulation
  - Decr in MAP=cerebral arteries dilate
  - Incr in MAP=cerebral arteries constrict

• Ischemia due to increase intracranial pressure=brain regulates own blood flow
  - Syncope <60mmHg
  - Cerebral edema>160 mmHg
Cerebral Circulation and $CO_2$ levels

Myogenic regulation: extreme pH sensitivity

- increased [CO$_2$] due to hypoventilation
  - cerebral arteries dilate
- decreased [CO$_2$] due to hyperventilation
  - cerebral arteries constrict

- Why?
  - Increased blood flow moves the $CO_2$ and H$^+$ quickly away from the tissues!
Cutaneous blood flow

- Thermoregulation
- Arteriovenous anastamoses
  - cold = cutaneous vasoconstriction
  - increased temperature = vasodilation of cutaneous arterioles
- exercise
  - why is exercising on a hot, humid day problematic?
Blood volume

- **TBW**
  - 2/3 intracellular
  - 1/3 extracellular
    - 80% interstitial, 20% in plasma

- **Determinants of distribution**
  - blood pressure: out into tissues
  - osmotic pressure: back into vessels
Fluid exchange: capillaries & tissues

- Filtration
- Osmotic pressure

25 mmHg

37 mmHg

17 mm Hg
Hypertension

- **Essential**
  - cause unknown
    - increased aldosterone
      - increased blood volume
    - chronic high stress
    - chronic elevated blood pressure
      - arteriosclerosis
  - dangers
    - damage
      - increased afterload
  - treatment

- **Secondary**
Circulatory shock

- **Hypovolemic shock**
  - Definition: circulatory shock due to low blood volume
  - Symptoms:
    - Low blood pressure and rapid pulse
    - Cold, clammy skin
    - Decreased urinary output

- **Septic shock**
  - Definition: hypotension due to sepsis
  - Symptoms:
    - Vasodilation
    - Decrease in blood pressure
Circulatory shock

- **anaphylactic shock**
  - severe allergic reaction
  - Result = vasodilation and decreased TPR

- **neurogenic shock**
  - spinal anesthesia, upper spinal cord damage
  - Result = decreased sympathetic tone

- **cardiogenic shock**
  - cardiac failure, decreased perfusion
  - Result = decreased CO and inadequate tissue perfusion
Atherosclerosis: Plaquing of arteries

Thrombus $\rightarrow$ arteriosclerosis $\rightarrow$ decrease lumen size $\rightarrow$
$\rightarrow$ damage to endothelium $\rightarrow$ macrophage digest
lipids in tunica intima $\rightarrow$ foamy cells $\rightarrow$ CT matrix
proteins secreted by smooth muscle cells $\rightarrow$ proliferation
of altered endothelial cells $\rightarrow$ plaquing
Atherosclerosis

• Most common form of arteriosclerosis (hardening of the arteries).

• Mechanism of plaque production:
  - Begins as a result of damage to endothelial cell wall.
    • HTN, smoking, high cholesterol, and diabetes.
  - Cytokines are secreted by endothelium; platelets, macrophages, and lymphocytes.
    • Attract more monocytes and lymphocytes.
Atherosclerosis (continued)

- Monocytes become macrophages.
  - Engulf lipids and transform into foam cells.

- Smooth muscle cells synthesize connective tissue proteins.
  - Smooth muscle cells migrate to tunica interna, and proliferate forming fibrous plaques.
Atheroma

- Usually caused by atheromatous plaques
- May regress with medications which lower LDL cholesterol and raise HDL cholesterol
- Clinical symptom: angina pectoris
Abdominal aortic aneurysm

- Abnormal dilation of arterial wall in abdomen
- Four times more common in men
- 95% caused by arteriosclerosis
- Other causes include cystic medial necrosis, trauma, syphilis, other infections
Edema

- High arterial pressure
- venous obstruction
- plasma protein leakage
- myxedema
- liver disease
- lymphatic obstruction