Chapter 36

Hemostasis and blood coagulation

Events in hemostasis

- Vascular constriction → formation of platelet plug → formation of blood clot → growth of fibrous tissue into the blood clot

Vascular constriction

- Smooth muscle (myogenic spasm, autacoid factors, nervous reflex)
- Smaller vessels release vasoconstrictor *thromboxane A_2*
- Physical and chemical characteristics of platelets
    - Platelets (or thrombocytes)
    - Normal concentration 150.000 to 300.000 per micro liter of blood
    - Synthesizes prostaglandins cause vascular and other local tissue reactions, growth factor
    - Half life of 8-12 days
- Mechanism of platelet plug
    - Get in contact with collagen of ruptured vessel → swell, protrusions, sticky, *von Willebrand factor*
    - ADP and thromboxane A_2 activate other platelets → adherence → more and more → platelet plug
    - Fibrin threads constructing unyielding plug
- Clotting factors:
    - Factor I: fibrinogen
    - Factor II: prothrombin
    - Factor III: tissue factor
    - Factor IV: calcium
- Blood coagulation in ruptured vessel
    - Fibrinogen factor I; prothrombin factor II
- Fibrous organization or dissolution of the blood clot
    - Blot clot can become invaded by fibroblasts → form connective tissue throughout the clot
    - Or the clot can dissolved by enzymes

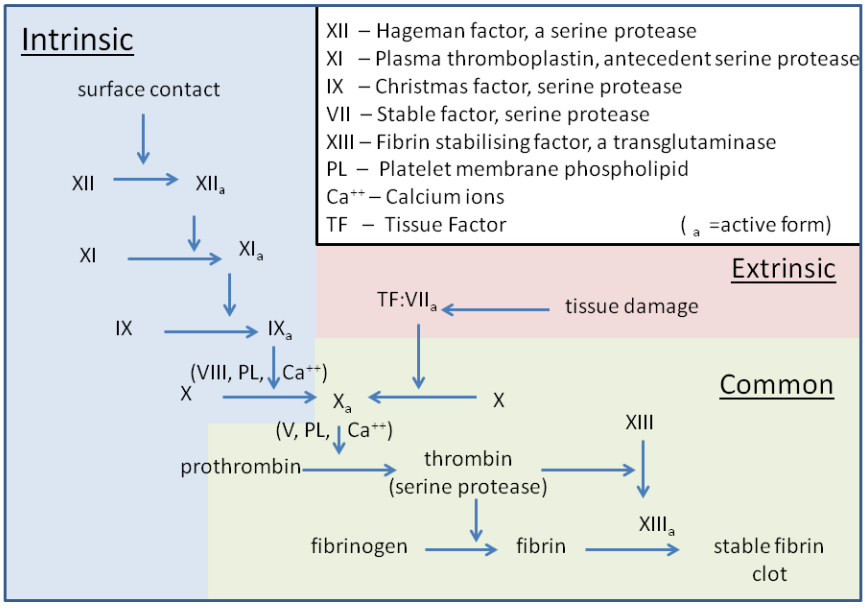
Mechanism of blood coagulation

- Procoagulants (promote, activated by rupture) and anticoagulants (inhibit) → coagulation depends on balance of both
- Conversion of prothrombin to thrombin
    - Tissue damage → forms prothrombin activator complex
      → Conversion of prothrombin to thrombin with Ca^{2+}
      → Causes polymerization of fibrinogen molecules into fibrin → enmesh platelets blood cells, plasma
        - Fibrin stabilizing factor (activated by thrombin, also released by platelets) increases strength of fibrin meshwork
    - Liver produces fibrinogen
    - Prothrombin
        - α 2-globulin
        - Splits into thrombin
        - Vitamin K “activates” prothrombin
        - Liver produces prothrombin → lack of vitamin K → no blood coagulation
    - *Prothrombin activator complex* is the *rate limiting factor* in blood coagulation
        - Formation of the complex (not the subsequent reactions)
    - Fibrinogen
        - Formed in liver
        - Not present in intestinal fluid, thus no clotting there
- Blood clot
    - Composed of a meshwork from fibrin fibers entrapping blood cells, platelets, and plasma

- Clot retraction
    - Serum fills spaces within clot, no clotting factors present
    - Platelets are necessary
        - Bind fibers together
        - Release pro-coagulants
            - Fibrin stabilizing factor, causes crosslinking
        - Release contractile proteins
            - Platelet thrombosthenin, actin, and myosin molecules → cause further contraction
    - Clot contract → expresses fluid called serum (lacks fibrinogen and other clotting factors)
    - Contraction accelerated by thrombin and Ca^{2+},
    - Edges of vessel come closer → closure
- Positive feedback of clot formation
    - Thrombin has positive feedback after a critical amount → more blood clotting more thrombin
- Initiation of coagulation: formation of prothrombin activator
    - Trauma to vascular wall and adjacent tissue
    - Trauma to the blood
    - Contact of blood with damaged endothelial cells or collagen (tissue elements outside of vessel)
    - Initiating clotting → leads to formation of prothrombin activator
    - Prothrombin formation
        - Extrinsic pathway for initiating clotting
            - Begins with damaged tissue which gets into contact with blood → release of *tissue factor (TF)* (or thromboplastin)
            - Tissue factor + blood coagulation factor VII + Ca^{2+} ions and with factor X they form→ activated factor Xa that combines with tissue factor to form
              → prothrombin activator → with Ca^{2+} ions splits prothrombin to form thrombin (positive feedback of thrombin → factor V, accelerating the process)
        - Intrinsic pathway for initiating clotting
            - Begins with trauma to the blood or exposure of the blood to collagen
              → Causes activation of factor XII to XIIa and release of platelets phospholipids
              → Activation of factor XI accelerated by prekallikrein and HMW
              → Activation of factor IX → IXa → together with VIIIa + platelets phospholipids and Factor 3 (from traumatized platelets) → activate factor X
                - Platelets are the clotting factor lacking in the disease *thrombocytopenia*
                - Factor VIII is missing in classic hemophilia (thus called antihemophilic factor)

              → Activated factor X with factor V and platelets or tissue phospholipids to form the complex called prothrombin activator → thrombin

The three pathways that makeup the classical blood coagulation pathway



- Steps following the activation of factor X are identical in both pathways
- Role of Ca^{2+} ions in the intrinsic and extrinsic pathway
  - Essential for any pathway (except first two steps, intrinsic pathway)
  - Without Ca^{2+} no blood clotting
  - If blood extracted one can inhibit clotting by Ca^{2+} deionization with citrate or oxalate ions
- Interaction between the extrinsic and intrinsic pathways – Summary of blood clotting initiation
  - Damage to blood vessel activates both pathways; converge by factor X
  - Both pathways act simultaneously
  - Intrinsic pathway is much slower
- Prevention of blood clotting in the normal vascular system – intravascular anticoagulants
  - Endothelial surface factors
    - Preventing clotting because of: smoothness of endothelial cell surface, layer of glycocalix on the endothelium (repels clotting factors and platelets), thrombomodulin bound to endothelial membrane
  - Antithrombin action of fibrin and antithrombin III
    - Anticoagulants remove thrombin from the blood like fibrin fibers, α-globulin called antithrombin III
      - Binds remaining thrombin, which is not yet bound
  - Heparin
    - Normally low concentration but together with antithrombin III increases by a hundredfold power of antithrombin III
    - produced in mast cells, abundant around liver and lung for preventing growing of blood clots
- Lysis of blood clots – plasmin
  - Plasmin (or fibrinolysin; porteolytic digestive enzyme) digests fibrin fibers and other factors
  - Activation of plasminogen (entrapped) to form plasmin, then lysis of clots
    - Small vessels are reopened by this mechanism of activating *tissue plasminogen activator* (t-PA)
    - Slow process

- Conditions that cause excessive bleeding in humans
  - Decreased prothrombin, factor VII, factor IX, factor X caused by *vitamin K deficiency*
    - Almost all blood clotting factors are formed by the liver
    - Liver diseases can cause severe bleeding because of the lack on clotting factors
    - Vitamin K is synthesized in the intestinal tract by bacteria (deficient when fat absorption lacks because of missing bile)
  - Hemophilia
    - 85% by factor VIII → hemophilia A
  - Thrombocytopenia
    - Low platelet count
    - Bleeding from small vessels
    - Bleeding will occur under 50000 platelets/µl
    - Idiopathic thrombocytopenia; cause unknown
- Thromboembolic conditions in the human being
  - Thrombi and emboli
    - Thrombus is a blot clot but immobile
    - Emboli is a blot clot floating through the vessels → cause obstruction called embolism
    - From vein and right heart mostly lung embolism
  - Cause of thromboembolic conditions
    - Rough vessel → initiate blood clotting → clots by flowing slowly
  - Use of t-PA in treating intravascular clots through catheter to activate plasmin
  - Femoral venous thrombosis and massive pulmonary embolism
    - Clot from leg → right heart → massive pulmonary embolism
  - Disseminated intravascular coagulation
    - Widespread clotting, many clots, from large tissue damage which release many tissue factors into blood → occlusion, lack of clotting factors

- Anticoagulants for clinical use
    - Heparin as an intravenous anticoagulant
    - Coumarins as an anticoagulant
    - Prevention of blood coagulation outside the body by silicon tanks, heparin, decrease Ca^{2+}
- Blood coagulation tests
    - Bleeding time by cutting
    - Clotting time by shake glass tube
    - Prothrombin time and international normalized ratio (INR)
        - Indicates concentration of prothrombin in the blood
        - Time required for coagulation
            - Prothrombin time, normal → 12 seconds
        - INR
            - Measurement for prothrombin time
            - International sensitivity index (ISI)
                - Indicated activity of tissue factor

$$INR = (PT_{test} / PT_{normal})^{ISI}$$

- Normal: 0.9 – 1.3
- High: (e.g. 4-5) high risk of bleeding
- Low: (e.g. 0.5) chance of having a clot

Extra material:

- Blood groups: 0 = 47% → A → B → AB
- RBC: red blood cell count
- MCV = mean corpuscular cell volume computed from hematocrit Ht and erythrocyte E count between 89-92 micro and macrocytosis
- MCH = average hemoglobin/ erythrocyte computed from hemoglobin and erythrocyte count
- MCHC = mean cell hemoglobin concentration HB/HTC

The cell and its functions

- 100 trillion cells
- Protoplasm
    - Water: 70-85%, no by fat cells,
    - Ions: K^+, Mg^{2+}, phosphate, sulfate, bicarbonate, Na^+, Cl^-, Ca^{2+}
    - Proteins: structural and functional
    - Lipids: phospholipids, cholesterol
    - Carbohydrates: nutrition
- Physical structure of the cell
    - Cell membrane (proteins, phospholipids)
        - Integral and peripheral cell membrane proteins
        - Glycocalix = carbohydrate coat → negative, connection, receptors, immune reaction
    - Cytoplasm and its organelles
        - Cytosol contains dissolved proteins, electrolytes, glucose
        - ER: distribution
            - Transport from ER to Golgi to cytoplasm
            - ER for glycogen breakdown, detoxifying
        - Ribosomes and granular ER: protein synthesizer
        - Agranular ER: smooth-ER synthesis of lipids,
        - Golgi Apparatus: transporting, form lysosomes, secretory vesicles

            - Produce hyaluronic acid and chondroitin sulfate for mucus, ground substance in interstitial spaces, forming new structures
        - Lysosomes: digest, damage, kill bacteria
        - Peroxisomes: self replication, contain oxidase, form H_2O_2, oxidizes alcohol
        - Mitochondria: outer and inner membrane, produce ATP, self replicating
    - Cell cytoskeleton filament and tubular structures
- Nucleus: chromosomes and DNA
- Nucleolus: mainly RNA and proteins (involved in synthesis of 40S and 60S ribosomal subunits)
- Nuclear membrane: lipid bilayer

Functional systems of the cell

- Ingestion by the Cell – Endocytosis
    - Pinocytosis: for macromolecules; engulf → form vesicle
    - Phagocytosis: for large particles; receptor attach to ligands on the particle
    - Lysosomes: digest vesicles with hydrolases
- Functional characteristics of ATP
    - Nucleotide, adenine, ribose and 3 phosphate radicals
    - Two phosphates bound by high energy phosphate bonds
    - Release energy → phosphoric acid radical splits away; ATP → ADP

Chapter 4

Transport of substances through cell membranes

The lipid barrier of the cell membrane, and cell membrane proteins

Ions	Extracellular fluid concentration mEq/L	Intracellular fluid concentration mEq/L
Na^+	142	10
K^+	4	140
Ca^{2+}	2.4	0.0001
Mg^{2+}	1.2	58
Cl^-	103	4

Diffusion

- Motion is heat
- Diffusion through cell membrane
    - Simple diffusion driven by kinetic energy through membrane, or by watery channels
    - Facilitated diffusion → with carrier protein
    - Diffusion of lipid soluble substance through the lipid bilayer
        - Determined by lipid solubility high for gases, alcohol
    - Diffusion of water and other lipid-insoluble molecules through protein channels
- Diffusion through protein pores and channels – selective permeability and gating of channels
    - Selective permeable, open or closed by gates by voltage or ligand
    - Selective permeability of protein channels
        - Size, charge, pore loop filter
    - Gating of protein channels
        - Voltage, ligand
    - open state versus closed state of gated channels
    - *Patch clamp method* for recording ion current flow through single channels
- Facilitated diffusion
    - Rate of diffusion cannot rise greater than max due to conformational change

- Factors that affect net rate of diffusion
    - Net diffusion rate is proportional to the concentration difference across membrane
    - Effect of membrane electrical potential on diffusion of ions the Nernst potential
      → Electrical and concentration gradient balance each other out
    - Effect of a pressure difference across the membrane → pressure increases diffusion increases
- Osmosis across selectively permeable membranes – net diffusion of water
    - Osmotic pressure
        - Importance of number of osmotic particles (molar concentration) in determining osmotic pressure
            - Small and large particles exert same pressure
        - Osmolality – the osmole
            - 1 gram for a solute which dissolves twice; 2 osmole
        - Relation of osmolality to osmotic pressure

Active transport of substances through membranes

- Primary active transport
    - Na^+-K^+ pump
        - Larger unit: 3 receptor sites for Na^+, 2 receptor sites for K^+, ATPase activity
        - Can run reverse and produce ATP from ADP
        - Is important for controlling cell volume
        - Causes electrical potential
    - Calcium pump
    - Hydrogen transport in gastric glands and distal kidneys
    - Energetic of primary active transport → could be quiet intensive to transport substance against gradient
- Secondary active transport – co-transport and counter-transport
    - Co-transport of glucose and amino acids along with sodium ions
        - Na^+ and glucose bind to carrier → conformation change → transport
    - Sodium counter-transport of calcium and hydrogen ions
        - Sodium binds to carrier → binding of substance on other side → energy change exchange
    - Active transport through cellular sheets
        - 2 parts: active transport and simple or facilitated diffusion

Chapter 5

Membrane potentials and action potentials

Basic physics of membrane potential

- Membrane potential caused by an ion concentration difference on two sides of the membrane
    - Diffusion potential: potential difference between inside and outside
- Relation of the diffusion potential to the concentration difference the Nernst potential
    - Nernst potential: diffusion potential level across a membrane that exactly opposes the net diffusion of a particular ion through the membrane
        - Nernst potential required to prevent additional net diffusion
        - Electromotive force (EMF) in millivolts

$$\text{EMF (mV)} = \pm 61 \times \log\left(\text{concentration}_{\text{inside}} / \text{concentration}_{\text{outside}}\right)$$

        - Just for one ion type
        - ± 0 potential outside

- *Goldmann-Hodgkin-Katz equation*

$$EMF\ (mV) = \pm 61 \times \log \left(c_{inside,ion1} \times p_{ion1} \times c_{inside,ion2} \times p_{ion2}\right) / \left(c_{outside,ion1} \times p_{ion1} \times c_{outside,ion2} \times p_{ion2}\right)$$

  - P: permeability to the membrane to each ion
  - Calculation of the diffusion potential when the membrane is permeable to several different ions
  - Depends on three factors: charge of each ion, permeability of membrane, concentrations

Measuring the membrane potential

Resting membrane potential of nerves

- Na^+-K^+ pump
  - K^+ → 2 inside
  - Na^+ → 3 outside
  - Maintaining negativity IC
  - Na^+: 140 to 14 (ratio of 0.1) and K^+: 4 outside to 140 inside (ratio of 35)
  - Electrogenic pump
- Leakage of potassium through the nerve membrane
  - 100 more permeable to potassium (important for resting membrane potential)
- Origin of the normal resting membrane potential
  - Contribution of the potassium diffusion potential alone is -94mv
  - Contribution of Na^+ diffusion through the nerve membrane (potassium higher contribution -86mv)
  - Contribution of the Na^+-K^+ pump: increasing resting potential more + transport outside to -90mv

Nerve action potential

- Resting state -90mv, membrane is polarized
- Depolarizing stage sodium flows inside, positive inside
- Repolarization stage sodium channels close and potassium channels opens, negative inside
- Voltage-gated sodium and potassium channels (+ pump + leak channel)
  - Resting state: activation gate is closed
  - Activation of sodium channel at -70 to -50mv → conformational change in activation gate → Increasing sodium permeability of membrane of 500 – 5.000 fold
  - Inactivation gate closes the sodium channel
    - Will not reopen until another repolarization
  - Voltage gated potassium channels activated when sodium channel become inactive

Roles of other ions during the action potential

- Anions: stay always inside, negative
- Calcium ions: calcium pump from inside to outside, outside 10.000 times greater
  - Voltage gated calcium channels,
  - Numerous in cardiac and smooth muscles
  - Slow, if Ca^+ low, Na^+ channels very sensitive
- Initiation of the action potential
  - Opening of sodium channels in positive feedback cycle (→ more and more)
  - Threshold for initiation of AP, when Na^+ influx is greater than K^+ efflux, (-65mV → threshold)

Propagation of the action potential

- Direction of propagation: there is no certain direction, until entire membrane is depolarized
- All or nothing principle: threshold must be greater than 1 (called safety factor)

Re-establishing sodium and potassium ionic gradients after action potentials are completed - importance of energy metabolism,

- Up to 50 million impulses until concentration differences too small → conduction ceases
- Na-K ATPase increases approximately to third power of sodium concentration inside

Plateau in some action potentials

- Slow calcium channels prolong plateau

Rhythmicity of some excitable tissues – repetitive discharge

- Heart, intestines, breathing,
- Re-excitation process necessary for spontaneous rhythmicity
    - Sodium calcium flow inward → membrane voltage in positive direction more permeable → Until AP is generated
    - Hyperpolarization delay of potassium outflow→ no self excitation

Special characteristics of signal transmission in nerve trunks

- Saltatory conduction in myelinated fibers from node to node
    - AP conducted from node to node→ saltatory conduction
    - Insulation allows repolarization with few ions

Excitation – the process of eliciting the action potential

- Acute subthreshold potentials
    - Acute local potentials that fail to elicit an AP
- *Refractory period* after an action potential, during which a new stimulus cannot be elicited
    - Because sodium channels become inactivated
    - Inactivation gates open → new AP can be generated
- *Absolute refractory period*
    - No 2nd AP can be generated even with a strong stimulus
- Calcium are stabilizers, slow down sodium channels
    - Membrane stabilizing factors can decrease excitability
        - E.g. high EC Ca^{2+} concentrations
    - Local anesthetics
        - AP strength / excitability ratio < 1.0 (“safety-factor”)
            - Nerve impulses fail to be propagated along anesthetized nerves
        - Procaine, tetracaine

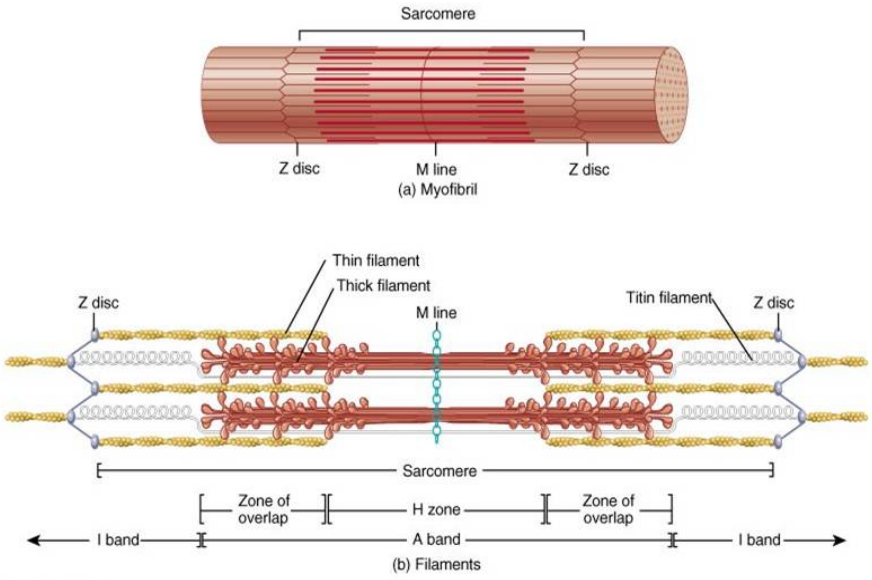
Chapter 6

Contraction of skeletal muscle

Physiologic anatomy of skeletal muscle

- Skeletal muscle fiber
    - Sarcolemma is a thin membrane enclosing a skeletal muscle fiber
        - Fuses at each end with a tendon fiber
    - Each muscle fiber consists of several hundred to thousand myofibrils
    - Myofibrils are composed of *actin* and *myosin* filaments
    - Each myofibril consists of about:
        - 1.500 myosin filaments → *A bands* (thick)
        - 3.000 actin filaments → *I bands* (attached to Z disk; “I” stands for “isotropic”)
        - Portion of myofibril located between two *Z discs* is a *sarcomere*
    - *Titin* filamentous molecules keep the myosin and actin filaments in place
        - Titin attaches to Z disc and to myosin filament

- Sarcoplasm is the intracellular fluid between myofibrils
  - Contains large amounts of K^+, Mg^{2+}, phosphate and enzymes
  - Large amount of mitochondria → ATP → contracting myofibrils
- Sarcoplasmic reticulum (SR) is a specialized endoplasmic reticulum of skeletal muscle
  - Numerous in fast twitch muscle fibers



General mechanism of muscle contraction

1) AP travels along a motor nerve to its endings on muscle fibers
2) Nerve secrete acetylcholine (Ach)
3) Ach opens channels and protein molecules float in the membrane
4) Channels are open → Na^+ influx (enters interior of muscle fiber membrane)
→ Depolarization → opens voltage-gated Na^+ channels → AP at membrane
5) Depolarization of muscle membrane causes → SR to releases Ca^{2+} ions
→ Ca^{2+} initiates attractive forces between actin and myosin filaments → contractile process
6) *Ca^{2+}-membrane-pump* transports Ca^{2+} back into SR

Molecular mechanism of muscle contraction

- Sliding filament mechanism of muscle contraction
  - Contraction occurs by a sliding filament mechanism
  - Ca^{2+} surrounds
- Molecular characteristics of the contractile filaments
  - Myosin: 6 chains → 2 heavy chains, 4 light chains
  - Two free heads at end of double helix, protruding arm and head together are called cross bridge
  - ATPase activity of the myosin head → cleaving ATP
  - Actin filaments are composed of → actin, troponin, and tropomyosin
  - Tropomyosin molecules: lie on top of active sites of actin strands, so that attraction cannot occur between actin and myosin
  - Troponin and its role in muscle contraction:
    - Three subunits' affinity for: actin, tropomyosin and Ca^{2+} ions
  - Interaction of 1 myosin, 2 actin filaments and Ca^{2+} ions for contraction
    - Active site of actin is covered by *troponin-tropomyosin complex*
      → Ca^{2+} ions inhibit the action of troponin-tropomyosin and pull them into a grove
    - Interaction between the activated actin filament and the myosin cross-bridges the walk along theory of contraction → when head attaches to active site
      → Intramolecular force causes heads to tilt forward and drag the actin filament along
      → Called *power stroke* → the higher the number of cross bridges the greater the contraction force

        - ATP as the source of energy for contraction – chemical events in the motion of the myosin heads
            - *Fenn effect* → the greater the amount of work performed the greater the amount of ATP that is cleaved

              1) Myosin head binds ATP → cleaves Pi → ADP and phosphate ion bound to head
              Conformation of the head → extends perpendicular (at right angle) to actin filament but not yet attached to the actin
              2) Troponin-tropomyosin complex binds Ca^{2+} ions → active sites on f-actin uncovered → myosin heads bind
              3) Bond causes conformation change of myosin head → head tilt toward arm of cross-bridge → *power stroke* (utilizes energy from ATP breakdown)
              4) Tilting causes release of ADP and Pi → new ATP binds → detachment of the head
              5) New ATP cleaved → new cycle → new power stroke

- Amount of actin and myosin filament overlap determines tension developed by the contracting muscle
    - Effect of muscle length on force of contraction in the whole intact muscle

Energetic of muscle contraction

- Work output during muscle contraction:

$$W = L \times D$$

  W: work
  L: load
  D: distance

- ATP; Sources of energy for muscle contraction
    - ATP is used for:
        - Walk along mechanism
        - Pumping Ca^{2+} ions into the SR
        - Pumping Na^{+} and K^{+} ions to maintain ionic environment
    - Phosphocreatine
        - 5-8 seconds of maximal muscle contraction
        - Phosphocreatine gets cleaved → ADP → ATP
    - Glycolysis
        - 1 minute of maximal contraction
        - Glycogen breakdown → pyruvic acid + lactic acid
        - Pyruvate → acetyl-coenzyme A → TCA → ATP
        - Anaerobic
    - Oxidative metabolism
        - 2-4 hours of maximal contraction from carbohydrates
        - > 4 hours energy from fats
        - Aerobic generation of ATP

Characteristics of whole muscle contraction

- Isometric muscle contraction
    - Muscle does not shorten during contraction
- Isotonic muscle contraction
    - Muscle shortens during contraction but with the same tension
- All muscle fibers innervated by 1 nerve are motor unit

Slow twitch fibers (type 1, red muscle)	Fast twitch fibers (type 2, white muscle)
Small fibers	Large fibers
Small nerves	Extensive SR
Extensive blood vessel system and supply	Large amount of glycolytic enzymes (glycolysis)
Numerous mitochondria (oxidative metabolism)	Less extensive blood supply (less oxidative metabolism)
Large amounts of myoglobin	Fewer mitochondria

- More innervation for exact muscle control
- Force summation
    - Muscle contractions of different forces by
        - Multiple fiber summation
        - Frequency summation
- Tetanization
    - Stimulation frequency → level at which it fuses to a continuous stimulation
    - Full contractile state due to calcium maintenance
- Staircase effect
    - Muscle contraction after a long period of rest → initial strength decreases
- Muscle hypertrophy
    - Total mass of muscle increases
    - Increase in actin and myosin filaments → enlargement of muscle fibers
- Muscle atrophy
    - Total mass of muscle decreases
    - Degradation of contractile proteins more rapid than replacement (through ATP-dependent ubiquitin-proteasome pathway)
- Rigor mortis
    - Rigidity results of ATP loss
    - Autolysis released from lysosomes

Chapter 7

Excitation of skeletal muscle: neuromuscular transmission and excitation - contraction coupling

Transmission of impulses from nerve endings to skeletal muscle fibers: the neuromuscular junction

- Skeletal muscle fibers → innervated by large, myelinated nerve fibers
- Each nerve ending makes a junction called *neuromuscular junction*, 1 junction /fiber
- Physiologic anatomy of the *neuromuscular junction* → the *motor end plate*
    - Nerve fiber forms branching nerve terminals called motor end plate
    - Synaptic gutter with folds called subneural clefts → increasing area for neurotransmitter action
- Secretion of acetylcholine by the nerve terminals
    - AP → Ca^{2+} channels open→ acetylcholine efflux
    - Effect of acetylcholine on the postsynaptic muscle fiber membrane to open ion channels
        - Acetylcholine gated channels → receptors → Na^{+} influx → creates an end plate potential → AP→ Contraction
    - Destruction of the released acetylcholine by *acetylcholinesterase*
    - End plate potential and excitation of the skeletal muscle fiber
        - Curare: nicotinic Ach receptor antagonist (in competition with acetylcholine)
        - Botulinum toxin: abolishes neurotransmitter release (of acetylcholine)

- Safety for transmission at the neuromuscular junction; fatigue of the junction
    - Three times higher stimulus than is needed for stimulating the muscle fiber
      → High safety factor; too much AP too little acetylcholine for end plate potential
      → Fatigue

Molecular biology of acetylcholine formation and release

- Vesicles (10.000 molecules) in motor neuron → transported via axoplasma → to end plate
- AP → opens Ca^{2+} channels→ Ca^{2+} influx → 125 vesicles fuse with membrane / AP
  → Reuptake by the membrane

Drugs that enhance of block transmission at the neuromuscular junction

- Drugs that stimulate the muscle fiber by Ach-like action
    - Methacholine, carbachol, nicotine
    - Same effect like acetylcholine, but acetylcholinesterase does not cleave them→ muscle spasm
- Drugs that stimulate the neuromuscular junction by inactivating Ach-esterase
    - Neostigmine, physostigmine, diisopropyl fluorophosphat
    - Inactivate acetylcholinesterase → muscle spasm
    - Can cause death → laryngeal spasm
- Drugs that block transmission at the neuromuscular junction
    - Curariform drugs
    - D-tubocurarine → blocks action of Ach on receptor → preventing sufficient increase in permeability

Myasthenia gravis

- Causes muscle paralysis
- Not enough transmission from nerve to muscle
- Autoimmune disease → antibodies → destruction of Ach receptors
- Paralysis of respiratory muscles → death
- Administration of neostigmine as treatment (anticholinesterase)

Muscle action potential – quantitative aspects of muscle potentials

- Resting membrane potential -80 to -90 mV
- AP duration 5 times longer than in large myelinated nerves
- Slow conduction (1/13 that of large myelinated nerves)

Spread of AP to the interior of the muscle fiber by way of *transverse tubules*

- AP spread along transverse tubules deep into muscle
- T tubules' AP cause release of Ca^{2+} inside the muscle fiber → direct vicinity of the myofibrils
  → Ca^{2+} cause contraction → process called *excitation-contraction coupling*

Excitation-contraction coupling

- Transverse tubule – sarcoplasmic reticulum system
    - T-tubules are extensions of cell membrane (like labyrinth through muscle)
    - Contain extracellular fluid
- Release of calcium ions by the sarcoplasmic reticulum (SR)
    - Store Ca^{2+};
    - AP running via the T tubules → triggers release of Ca^{2+} by SR
    - AP → activates dihydropyridine receptors (DHP-receptor) → opens Ca^{2+} release channels in SR
        - DHP-receptors also called ryanodine receptor channels
        - DHP-receptors are located in t tubule and are linked to Ca^{2+} release channels in SR
    - Ca^{2+} pump removes calcium ions from the myofibrillar fluid after contraction occurs
    - Calsequestrin → binds high quantities of Ca^{2+} within the T tubules

- Excitatory pulse of calcium ions
  - Ca^{2+} could increase 500 fold (but just 50 fold is needed)

Chapter 8

Excitation and Contraction of Smooth Muscle

Contraction of smooth muscle

- Small fibers, internal arrangement of muscle fibers is different
- Types of smooth muscle
  - Smooth muscle differs in:
    - Physical dimensions
    - Organization into bundles or sheets
    - Response to different types of stimuli
    - Characteristics of innervation
    - Function
  - Multi-unit smooth muscle
    - Separate fibers, independent, insulation, e.g.: ciliary muscle, iris muscle, piloerector muscle
  - Unitary smooth muscle, visceral, syncytial
    - Arranged in sheets or bundles, membranes connected, in blood vessels, contract together
- Contractile mechanism in smooth muscle
  - Chemical basis for smooth muscle contraction
    - No troponin
  - Physical basis for smooth muscle contraction
    - Actin attached to dens bodies (equivalent to Z discs), attached to cell membrane and to dens bodies from other smooth muscles, more actin is interspersed
    - Can contract to 80% of their length, actin pull myosin in one and another in opposite direction
  - Comparison of smooth muscle contraction and skeletal muscle contraction
    - Slow cycling of the myosin cross bridges
      - Cross-bridges are build much slower, attachment and force much higher, low ATPase activity of heads → slowing cycling
    - Low energy requirement to sustain smooth muscle contraction due to slow cycle,
    - One ATP is needed per cycle
    - Slowness of onset of contraction and relaxation of the total smooth muscle tissue
      - 0.2 - 30 seconds of contraction
    - Maximum force of contraction is often greater in smooth muscle than in skeletal muscle
      - Due to the prolonged myosin actin attachment
    - *Latch mechanism* facilitates prolonged holding of contractions of smooth muscle
      - Latch can maintain prolonged *tonic* contraction in smooth muscle for hours with little use of energy, for keeping it requirements is little nerve stimuli and less energy
    - *Stress relaxation* and *reverse stress relaxation* of smooth muscle → allow an organ to maintain the same amount of pressure despite volume change
- Regulation of contraction by Ca^{2+} ions
  - Calcium ions combine with calmodulin to cause activation of myosin kinase and phosphorylation of the myosin head
  - Calmodulin → regulatory protein, activates cross-bridges
    - Instead of troponin smooth muscle contain *calmodulin*
      1) Ca^{2+} ions bind with calmodulin
      2) → The *calmodulin-calcium complex* then joins with and activates
      → *Myosin light chain kinase* (MLCK)
      3) → One chain, the *regulatory chain*, becomes phosphorylated → myosin binds to actin
  - *Myosin phosphatase* is important in *cessation* of contraction
    - If Ca^{2+} falls under a certain level → the process reverses
    - Re-phosphorylation occurs by myosin phosphatase (determines time of relaxation)

- Possible mechanism for regulation of the latch phenomenon
  - ATP is not degraded, deactivation of enzymes allows maintained binding

Nervous and hormonal control of smooth muscle contraction

- Neuromuscular junctions of smooth muscle
  - Physiologic anatomy of smooth muscle neuromuscular junctions
    - Autonomic nerve fibers do not make direct contact with smooth muscle → *diffuse junctions* → secrete transmitter into matrix coating smooth muscle → diffuse to cells → nerve signal reaches only outer layer → conducting of AP via muscle mass
    - No end plates but they have *varicosities* along their axons (no Schwann cell covering)
    - Transmitters are *acetylcholine* and *norepinephrine*
    - Contact junctions in multi unit
  - Excitatory and inhibitory transmitter substances secreted at the smooth muscle neuromuscular junction
    - Acetylcholine is excitatory and norepinephrine is inhibitory (and vice versa)
    - Type of receptor determines whether smooth muscle inhibited or excited (not transmitter)
- Membrane potentials and action potentials in smooth muscle
  - Membrane potentials in smooth muscle at *resting state* is -50 mV to -60 mV
  - Action potentials in unitary smooth muscle
    - Action potentials of visceral smooth muscle two forms:
      1) *Spike potentials*
      2) *APs with plateaus*
    - Spike potential:
      - Occur in most types of unitary smooth muscle
      - Duration of 10 - 50 ms
      - Elicited by electrical, hormonal, neurotransmitter, or stretch stimulation
    - Action potentials with plateaus
      - Accounts for prolonged contraction in some types of smooth muscle
  - Calcium channels are important in generating smooth muscle action potentials
    - Sodium participates little in generating APs in most smooth muscle → Ca^{2+} is mainly responsible (Ca^{2+} channels open slower, remain open longer → plateau) → work also on smooth muscle contractility
  - *Slow wave potentials* in unitary smooth muscle can lead to spontaneous generation of action potentials → intestines
  - Excitation of visceral (unitary) smooth muscle by muscle *stretch* → cause decrease in negativity
  - *Depolarization of multi unit smooth muscle* without APs → transmitter → junctional potential
- Effect of local tissue factors and hormones to cause smooth muscle contraction without APs
  - Two ways: 1) local tissue chemical factors and 2) various hormones
  - Smooth muscle contraction in response to local tissue chemical factors
    - *Lack of* O_2 in the local tissues cause smooth muscle relaxation → vasodilatation
    - *Excess* CO_2 → vasodilation
    - *Increased* H^+ concentration → vasodilation
  - Effects of hormones on smooth muscle contraction
    - Hormone gated excitatory or inhibitory receptors
  - Mechanism of smooth muscle excitation or inhibition by hormones or local tissue factors
    - Hormones bind to receptors to activate or block them (ion in- or outflow)
    - Sometimes Ca^{2+} atoms go inside and cause contraction
    - Receptors at the outside are bound on the inside to cAMP or cGMP → second messengers (effect enzymes)
- Source of calcium ions that cause contraction through the cell membrane and from the sarcoplasmic reticulum (SR)
  - SR provides Ca^{2+} for skeletal muscle
  - Ca^{2+} mainly enters smooth muscle from extracellular space → time of diffusion → *latent period*
  - Role of the SR in smooth muscle → the more extensive the SR the faster the contraction (SR only slightly developed in smooth muscle)

- Smooth muscle contraction is dependent on extracellular calcium ion concentration
- *Calcium pumps* remove IC Ca^{2+} → EC fluid (or SR if present) → causes smooth muscle relaxation (takes longer)

Chapter 9

Physiology of cardiac muscle

Physiologic anatomy of cardiac muscle

- Striated, actin myosin
- Cardiac muscle as a syncytium
  - Intercalated discs → "cell borders", joined by gap junctions, AP conducts, atrial and ventricular syncytium → atria contracts first

Action potentials in cardiac muscle

- What causes the long action potential and the plateau
  - AP in skeletal muscle caused by fast sodium channels
  - AP in cardiac muscle caused by
    - *Fast sodium channels* and *slow calcium channels* → prolonged period of depolarization → causes *plateau*; Ca^{2+} initiates contractile process;
    - AP → potassium permeability decreases 5 fold → decreases K^{+} efflux → prevents MP to return to RMP → results in plateau
    - Slow calcium channels → open slower and remain open longer
- Velocity of signal conduction in cardiac muscle slower than nerve or skeletal muscle AP
- Refractory period of cardiac muscle: atrial refractory period shorter; refractory period and relative refractory period (excitation is possible but would be weaker)

Excitation – contraction coupling – function of calcium ions and the transverse tubules

- SR in cardiac muscle less developed, T tubules have greater diameter and store Ca^{2+},
- AP → release of Ca^{2+} in cell→ Ca^{2+} activates release of more Ca^{2+} from SR → contraction
- Moderate Ca^{2+} change in extracellular fluid do not change force of skeletal muscle contraction, but excess of Ca^{2+} → more acetylcholine release → higher frequency of contraction
- Contraction force depends on the concentration of Ca^{2+}; calcium pump transports Ca^{2+} back into the SR and T tubules
- In skeletal muscle Ca^{2+} is stored in SR so not dependent on extracellular Ca^{2+} concentration

The heart as a pump and function of the heart valves

Cardiac cycle

- Diastole and systole
  - Diastole: relaxation (heart filling)
  - Systole: contraction (heart ejection)
  - Effect of heart rate on duration of cardiac cycle
    - Fast heart rate decreases the diastole from 0,6 seconds to 0,35 seconds, not enough time for complete filling
- Relationship of the electrocardiogram to the cardiac cycle
  - P wave: depolarization of atria → contraction → rise pressure
  - QRS wave: depolarization of ventricles → rising pressure → systole
  - T wave: repolarization of ventricles → end of ventricular contraction
- Function of the atria as primer pumps
  - 80% of venous blood directly into ventricle; atria increases ventricular pump by 20%, fail of atrial work not noticed in resting because heart ejects 300% more blood than is needed

    - Pressure changes in the atria – a, c, and v waves
        - a → atria contraction
        - c → AV valves bulge in atria due to increasing pressure in the ventricles
        - v → atrial filling
- Function of the ventricles as pumps
    - Filling of the ventricles during diastole
        - Rapid filling during the first 1/3 of diastole, 2/3 less filling; 3/3 atria contract 20% of filling
    - Emptying of the ventricles during systole
        - Period of isovolumic (isometric) contraction (tension increases but no shortening of muscle)
            - Contraction → pressure rises→ AV valves close→ pressure increases→ aortic and pulmonary valves open
        - Period of ejection
            - 70% of blood empty in the first 1/3; period of rapid and slow ejection
            - Semilunar valves open by left ventricular pressure above 80 mmHg and right ventricular pressure slightly above 8mmHg
        - Period of isovolumic (isometric) relaxation
            - End of systole, between closure of semilunar valves and opening of AV valves
            - Right and left intraventricular pressures decrease rapidly
            - Elevated pressure in distended large arteries → push blood back → closes aortic and pulmonary valves
        - End-diastolic volume, end-systolic volume, and stroke volume output
            - End diastolic volume when ventricle is filled → 120ml
            - Stroke volume output → 70ml
            - Remaining 50ml are then the end systolic volume
            - By increasing end diastolic volume (filling) and decreasing end systolic volume → increase stroke volume
- Function of the valves
    - Atrioventricular valves
        - AV valves prevent backflow from ventricles to atria
        - Aortic and pulmonary valves prevent backflow from arteries into ventricles
        - Act passive by pressure
    - Function of the papillary muscles
        - Prevent valve bulging too far backward toward atria
    - Aortic and pulmonary valves
        - Smaller → higher velocity of ejection, have fibrous tissue to withstand extra physical stresses
    - Aortic pressure curve
        - Entry of blood increases pressure
        - *Incisura* in aortic pressure curve → due to backward flow in aorta, pressure falls slightly
        - Pressure curve in right ventricle, pulmonary artery and aorta similar

Relation of heart sounds to heart pumping: valve opening is soundless

Work output of the heart

- Up to 150ml blood can easily flow into ventricle → above, pressure rises
- Systolic pressure rises fast by low ventricular volume more than 150ml → because actin myosin is not aligned optimal
- Concepts of preload (tension of muscle at contraction start → end diastolic volume pressure) and afterload (load at which muscle exerts its contractile force → pressure in the aorta)

Chemical energy required for cardiac contraction: oxygen utilization by the heart

- Heart efficiency 25%
- 90% of energy from fatty acids

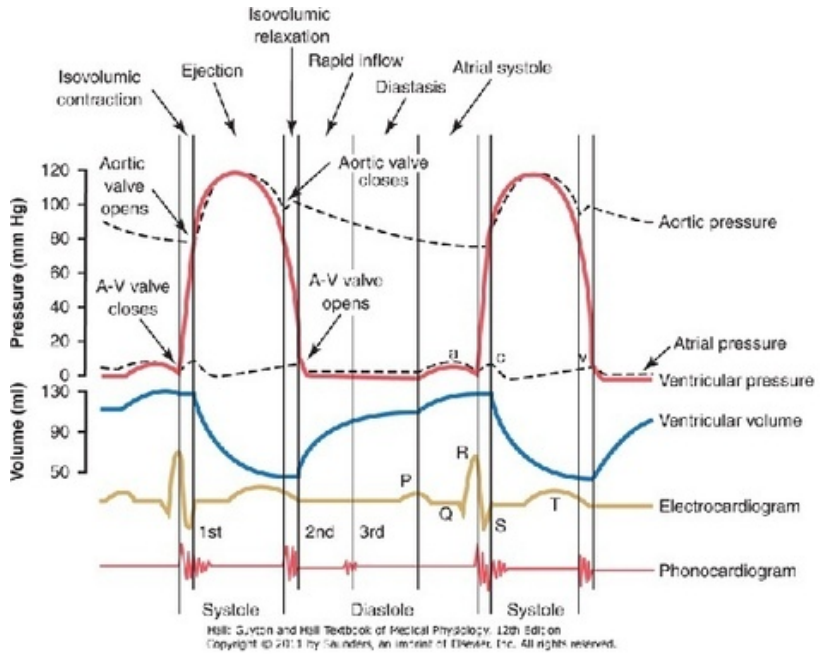
Regulation of heart pumping

- Intrinsic regulation of heart pumping – the frank-staring mechanism
    - Heart pumps that amount which reaches it
    - The greater the heart is stretched during filling → the greater the force of contraction → the greater the blood flow
    - Explanation for the frank starling mechanism
        - More stretch → more tension→ actin myosin more optimal aligned
        - Stretch of right atrial wall directly increases the heart rate
    - Ventricular function curves
    - Control of the heart by the sympathetic and parasympathetic nerves
        - Mechanism of excitation of the heart by the sympathetic nerves
            - Increases *force* of heart contraction, heart *rate* → cardiac output up to 2 or 3 times
        - Parasympathetic vagal stimulation of the heart
            - Strong stimulation can stop the heart
            - Decreases mainly heart rate because it innervates mostly the atrium and does not affect force
- Effect of potassium ions and calcium ions in heart function
    - Effect of potassium ions
        - Excess potassium extracellular → heart dilated, slows heart rate
        - Decreases resting potential → less negative → AP weaker → heart weaker
    - Effect of calcium ions
        - Opposite effect, fast heart rate, excess
        - But decrease Ca^{2+} cause similar to potassium excess
- Effect of temperature on heart function
    - Temperature increases permeability of cardiac muscle membrane to ions that control heart rate → acceleration of self excitation
    - Moderate increase
- Increasing of the arterial pressure up to 160 mmHg did not affect the cardiac output

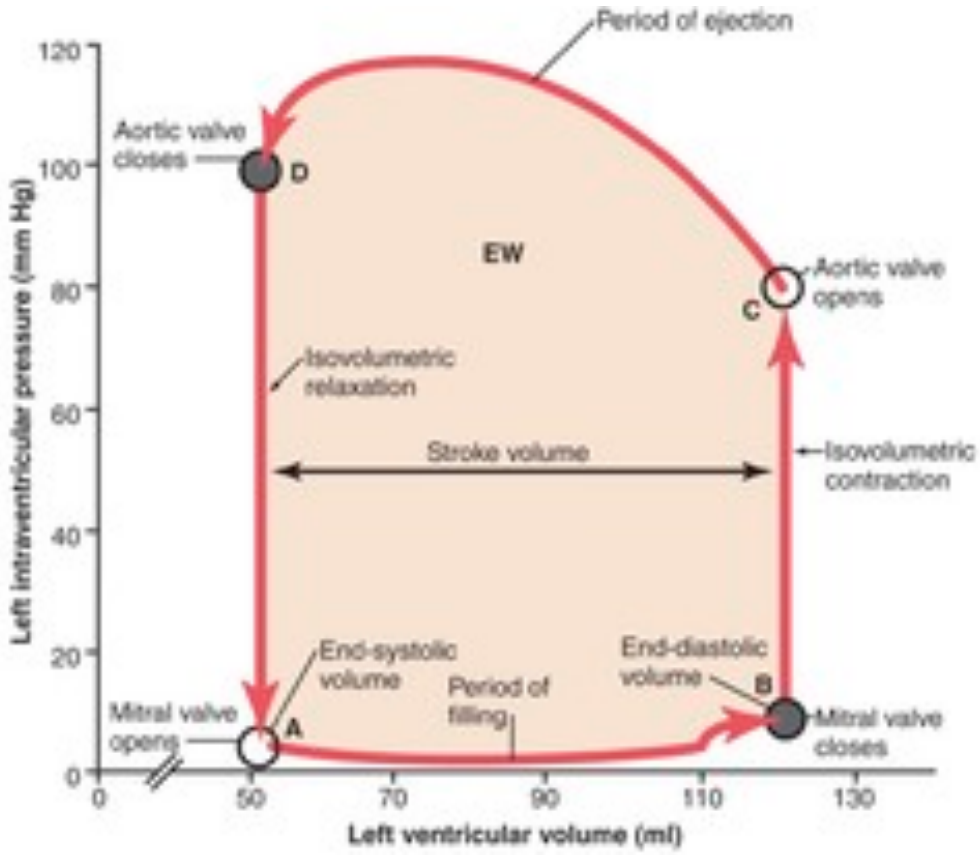
Extra material:

- Pericardium limits heart filling
- Right ventricle more compliant
- Vagus nerve: Ach muscarinic
- Sympathetic: norepinephrine beta receptors

Cardiac cycle



- Events of cardiac cycle
    - R wave: AV valve closes
    - R-S wave: isovolumic contraction
    - S wave (end): aortic valve opens
    - S-T wave: ejection
    - T wave (end): isovolumic relaxation
    - T wave (stops): AV valve opens, rapid filling of ventricles
- Volumes
    - End-diastolic volume (end-filling volume): 110 – 120 ml (max. 150-180 ml)
    - Stroke volume output (amount ejected from ventricles): 70 ml
    - End-systolic volume (volume remaining in ventricles): 40 – 50 ml (strong contraction 10 -20 ml)
    - Ejection fraction (fraction of end-diastolic volume ejected): 60 %



Volume pressure diagram

- AB: period of filling
- BC: isovolumetric contraction
- CD: period of ejection
- DA: isovolumetric relaxation

Chapter 10

Rhythmical excitation of the heart

Specialized excitatory and conductive system of the heart

- Sinus node (sinoatrial node, SA node)
    - Specialized cardiac muscle
    - In superior posterolateral wall of right atrium
    - Directly connected with atrial muscle fibers
    - No contractile muscle element

- Automatic electrical rhythmicity of the sinus fibers
  - Mechanism of sinus nodal rhythmicity
    - Resting potential is -55 mV to -60 mV → cell membrane more leaky towards sodium and calcium ions
    - Cardiac muscle has (1) fast sodium channels; (2) slow sodium calcium channels; (3) potassium channels
    - Opening of fast sodium channels → rapid influx → rise in resting potential
      - At level of -55mv fast sodium channels become inactivated → any time the membrane potential remains less negative than about -55mv
        → Inactivation gates on the inside of the cell membrane that close fast sodium channels become closed and remain so
    - Plateau slow sodium calcium channels → potassium channels open and return to negativity
      - Only the slow sodium calcium channels can open → cause action potential → slower AP
  - Self excitation of sinus nodal fibers
    - Sodium tend to leak inside
    - Between two heartbeats sodium influx rises to resting potential → threshold of -40 mv → sodium calcium channels become activated → AP
    - Inherent leakiness of the sinus nodal fibers to sodium and calcium ions cause their self-excitation
    - Depolarization not all the time because → sodium calcium channels become inactivated 100-150 ms after opening and potassium channels open → bring back resting potential → hyperpolarization
    - Hyperpolarization does not maintain forever → because potassium channels close and normal leaking of sodium and calcium ions overbalance outward flux of potassium
- Internodal pathways and transmission of the cardiac impulse through the atria
  - Anterior, middle, and posterior internodal pathways
- Atrioventricular node and delay of impulse conduction from the atria to the ventricles
  - Delay in AV node and adjacent conductive fibers allows the atria to empty their blood into the ventricles before ventricular contraction begins
  - AV node in posterior wall of the right atrium, immediately behind the tricuspid valve
  - Total delay in AV node and AV bundle system is 0,13 seconds; and 0,16 seconds before the excitatory signal finally reaches the contracting muscle of the ventricles
  - Cause of slow conduction → diminished numbers of gap junctions between successive cells in conducting pathway
- Rapid transmission in the ventricular purkinje system
  - From *AV node* through *AV bundle* into the *ventricles*, much faster than muscle and AV nodal fibers 1,5 to 4 m/sec → instantaneous transmission of cardiac impulse throughout ventricular muscle → due to many gap junctions, just few myofibrils
  - One way conduction through the AV bundle
    - Barrier acts as an insulator
  - Distribution of the purkinje fibers in the ventricles – left and right bundle branches
    - Divide, to apexes, turn to base and become continuous with cardiac muscle fibers
- Transmission of the cardiac impulse in the ventricular muscle
  - From endocardium to epicardial surface need 0,03 s → separation of fibrous septa take time
- Summary of the spread of the cardiac impulse through the heart
  - Middle velocity in atria → slow in AV system → fast in purkinje fibers → slower in ventricles

Control of excitation and conduction in the heart

- Sinus node as the pacemaker of the heart
  - Sinus rate 70 – 80 times per minute other below
  - Sinus node discharge again before AV or purkinje cells can excite themselves → SA → pacemaker

    - Abnormal pacemakers – ectopic pacemaker
        - If any part of conducting system develops faster conducting then SA node
        - If SA node signal is blocked → AV node becomes pacemaker
        - Stokes Adam syndrome: delay in discharge, 5-20 seconds to repolarize
- Role of the purkinje system in causing synchronous contraction of the ventricular muscle
- Control of heart rhythmicity and impulse conducting by the cardiac nerves: sympathetic and parasympathetic nerves
    - *Parasympathetic* fibers mainly to SA and AV
    - *Sympathetic* to ventricular muscle but also to all other areas
    - Parasympathetic vagal stimulation can slow or even block cardiac rhythm and conduction → *ventricular escape*
        - Ach → decreases sinus rhythm, decreases the excitability of the AV junctional fibers between the atrial musculature and the AV node
        - Ventricular escape is when purkinje fibers develop rhythm of its own due to stop of signal conduction from AV node
    - Mechanism of the vagal effects
        - Acetylcholine causes release of potassium and makes the fiber much less excitable in lowering resting potential → hyperpolarization
        - In SA node decreases resting potential to -65 to -70mv→ slow down excitation
    - Effect of sympathetic stimulation on cardiac rhythm and conduction
        - Increases the sinus nodal discharge → increase rate of conduction
    - Mechanism of sympathetic effect
        - Increases hear rate
        - Increases rate of conduction
        - Increases force of contraction
        - Releases hormone *norepinephrine* → stimulates beta 1 adrenergic receptors → increase permeability to calcium and sodium ions → accelerating the self excitation in rising the resting potential
        - In AV node and AV bundles → increases sodium, calcium permeability → AP travels easier
        - Increase contractile strength due to higher permeability of Ca^{2+}

Chapter 11

The normal electrocardiogram

Characteristics of the normal electrocardiogram

- Depolarization waves
    - P wave: when atria depolarize before atrial contraction begins
    - QRS complex: when ventricles depolarize before contraction begins
- Repolarization wave
    - T wave: caused by potentials when ventricles recover
- Depolarization waves vs. repolarization waves
    - Electrodes measure the difference in charge between each other
    - Relation of the monophasic action potential of ventricular muscle to the QRS and T waves in the standard electrocardiogram
        - No potential is recorded in the electrocardiogram when the ventricular muscle is either completely polarized or completely depolarized
        - Only when muscle is partly polarized and partly depolarized → we get a current flow
- Relationship of atrial and ventricular contraction to the waves of the electrocardiogram
    - Ventricles stay contracted until the end of T wave
    - Atrial T wave, repolarization wave, is obscured by the much larger QRS complex
- Voltage and time calibration of the electrocardiogram
    - 10 lines are 1 mV
    - Vertical → is time calibration, 25mm = 1s

- Normal voltages in the electrocardiogram
  - Depend on the placement of the electrodes
  - P-Q or P-R interval (Q is often absent)
    - Interval between the beginning of electrical excitation of the atria and the beginning of excitation of the ventricles → 0.16 s
  - Q-T interval
    - Contraction of ventricles → 0.35 s
- Rate of heartbeat as determined from the electrocardiogram → calculated from time between 2 beats 1 second → 60 beats/m

Methods for recording electrocardiograms

- Records for electrocardiographs

Flow of current around the heart during the cardiac cycle

- Recording electrical potentials from a partially depolarized mass of syncytial cardiac muscle
- Flow of electrical currents in the chest around the heart
  - Heart suspended in conductive medium
  - Electric current flows from the depolarized area → to the polarized area
  - The average current flow occurs with negativity toward the base of the heart and with positivity toward the apex

Electrocardiographic leads

- Three bipolar limb leads
  - Bipolar: 2 electrodes on each side of a heart
  - Lead 1: right arm → negative; left arm → positive
  - Lead 2: right arm → negative; left leg → positive
  - Lead 3: left arm → negative; left leg → positive
  - Einthoven's triangle → arms and leg form triangle around heart
  - Einthoven's law
    - 3rd lead can be calculated by summing up the other 2 leads
    - Lead I = -0,2 to 0,3 is → +0,5
  - Normal electrocardiograms recorded from the 3 standard bipolar limb leads
- Chest leads
  - The closer to the apex the more positive the curve,
- Augmented unipolar limb leads
  - 2 limbs to negative terminal and 1 to positive

Chapter 12

Electrocardiographic interpretation of cardiac muscle and coronary blood flow abnormalities: vectorial analysis

Principles of vectorial analysis of electrocardiograms

- Use of vectors to represent electrical potentials
  - Arrowhead in positive direction, length proportional to voltage of potential
  - Resultant vector in the heart at any given instant
    - From base to apex → instantaneous mean vector
- Direction of a vector is denoted in terms of degrees
  - Mean QRS vector is +59 degrees
- Axis for each standard bipolar lead and each unipolar lead
  - Axis of: lead 1 = 0 degree; lead 2 = 60 degrees; lead 3 = 120 degrees

Vectorial analysis of potentials recorded in different leads

- When the vector of the heart is in a direction, almost perpendicular to the axis of the lead, the voltage recorded in the electrocardiogram of this lead is very low

    - Conversely when the heart vector has almost exactly the same axis as the lead axis essential the entire voltage of the vector will be recorded
- Vectorial analysis of potentials in the 3 standard bipolar leads

Vectorial analysis of the normal electrocardiogram

- Vectors that occur at successive intervals during depolarization of the ventricles – the QRS complex
    - Depolarization spreads from:
        - Left endocardial surface of septum → both endocardial surfaces → spread around remainder of ventricles → through ventricular muscle to outside of heart
    - Positive arrow recording above the 0 line
    - Vector becomes 0 when whole heart is depolarized
- Electrocardiogram during repolarization – the T wave
    - The greatest portion of ventricular muscle mass to repolarize first is the entire outer surface of the ventricles
        - Especially near the apex of the heart → caused by high blood pressure → slow repolarization in septum and endocardium
    - Repolarizing vector towards apex → greatest when half of heart is depolarized and half is polarized
- Depolarization of the atria – the P wave
    - Repolarization of the atria – the atrial T wave
        - The area in the atria that also becomes repolarized first is the sinus nodal region → the area that had originally become depolarized first (slow no purkinje fibers)
        - Vector is inverted and opposite to ventricular depolarization →←, ventricle →→
        - Is covered by QRS and is negative
- Vector-cardiogram
    - Vector change in length and direction

Mean electrical axis of the ventricular QRS – and Its significance

- Mean electrical axis of the ventricles is 59 degrees
- Determining the electrical axis from standard lead electrocardiograms
    - Electrical axis of the heart is usually estimated from the standard bipolar limb lead electrocardiograms
- Abnormal ventricular conditions that cause axis deviation
    - Between 20 to 100 degrees in normal heart → due to variations in purkinje fibers
    - Change in the position of the heart in the chest
        - To the left → end of deep expiration; position of organs press against diaphragm; obesity
        - To the right → inspiration, standing, tall and skinny
    - Hypertrophy of one ventricle: more muscle → greater electrical potential shift towards it
    - Vectorial analysis of *left axis deviation* resulting from *hypertrophy* (aortic valvular stenosis, aortic valvular regurgitation) of the left ventricle
    - Vectorial analysis of right axis deviation resulting from hypertrophy of the right ventricle due to congenital pulmonary valve stenosis or tetralogy of Fallot
    - Bundle branch block causes axis deviation: one fiber is faster polarized than the other
    - Vectorial analysis of left axis deviation in left bundle branch block: arrow went to the left side due to slower innervation and longer depolarization
    - Vectorial analysis of right axis deviation in right bundle block → vector points to side of block

Chapter 13

Cardiac arrhythmias and their electrocardiographic interpretation

Abnormal sinus rhythms

- Tachycardia (fast heart rate)
    - Faster than 100 beats
    - Due to increased temperature (18 beats per 1°)
        - Sympathetic stimulation, toxic, weak heart, blood loss,

- Bradycardia (slow heart rate)
    - Slower than 60 beats
    - Due to stimulation of vagus parasympathetic part, carotid sinus syndrome (sensitive)
- Sinus arrhythmia
    - ± 5% during quiet respiration; ± 30% in deep respiration → due to spill over from medullary respiratory center into adjacent vasomotor center

Abnormal rhythms that result from block of heart signals within the intercardiac conduction pathways

- Sinoatrial block: sudden cessation of P waves with standstill of the atria→ ventricle pick up new rhythm
- Atrioventricular block: ischemia of the A-V node or AV bundle
    - Compression of AV bundle by scar tissue block conduction
    - Inflammation of AV node or AV bundle
    - Extreme stimulation of vagus nerve
- Incomplete atrioventricular heart block:
    - Prolonged P-R or P-Q interval first degree block → more than 0,2 s; (normal P-Q → 0,16 s; increase with faster beat)
    - Second degree block: no QRST wave, dropped beats of the ventricle → conduction to slow to go through AV bundle
    - Third degree block, complete AV block: ventricles establish their own rhythm from AV bundle → P wave becomes dissociated from QRS-T complex
    - Stokes Adam's syndrome – ventricular escape: sometimes ventricles start their own beat 5-30sec later because conduction stops from atria, periodic fainting (treatment: pacemaker to right ventricle)
- Incomplete intraventricular block – electrical alternans
        - Blockage in purkinje system

Premature contractions (extrasystole, premature beat, ectopic beat) → before normal contraction

- Causes of premature contraction
    - Abnormal random impulses due to ischemia, plaques which irritate fibers, toxic irritation of AV node, catheterization
- Premature atrial contractions
    - P wave occur too soon, reason: no sleep, coffee, smoking
    - Too early contraction → ventricles are not filled properly → lack of or weak pulse
- A-V nodal or A-V bundle premature contraction
    - Signal of P wave and QRS over each other → signal travels in both directions
- Premature ventricular contraction
    - QRS is long→ high voltage no neutralization; T wave opposite
    - Vector analysis of the origin of an ectopic premature ventricular contraction
    - Disorders of cardiac repolarization – the long QT syndromes

Paroxysmal tachycardia

- Rapid rhythmical excitations that spread in all directions
- Atrial paroxysmal tachycardia
    - Abnormal p wave
    - A-V nodal paroxysmal tachycardia, normal QRST missing P

- Ventricular paroxysmal tachycardia
    - Severe: caused by ischemia can leads to ventricular fibrillation
    - May be caused by digitalis

Ventricular fibrillation

- Stop immediately, self excitation in ventricle which goes around in circles → no coordinated contraction
- Caused by electrical shock, ischemia of conducting system

- Phenomenon of re-entry – circular movements as the basis for ventricular fibrillation
    - When cardiac muscle is not in refractory phase any more, excitation occurs again and again
    - Due to long pathway in dilated hearts; decreased rate of conduction frequency from block in purkinje fibers, ischemia of muscle, high potassium; shortened refractory period
- Chain reaction mechanism of fibrillation
    - Many circuits, signals divide, other pathways, excitation inhabitation, slower more time for relaxation
- Electrocardiogram in ventricular fibrillation → just irregular fluctuation
- Electroshock, defibrillation of the ventricles → current excites all fibers at the same time so they go into refractory time together
- Hand pumping of the heart (cardiopulmonary resuscitation) as an aid to defibrillation
    - No nutrition → hand pumping → nutrition → defibrillation

Atrial fibrillation

- Due to enlargement, long pathways and slow conduction
- Pumping characteristics of the atria during atrial fibrillation
    - Decrease of heart work by 30%, not lethal
- Electrocardiogram in atrial fibrillation → normal line and normal QRST but no P wave
- Irregularity of ventricular rhythm during atrial fibrillation
- Electroshock treatment of atrial fibrillation

Atrial flutter

- 200-300 atrial beats, in circuit, three P waves, one QRST wave

Cardiac arrest

- Deep anesthesia → hypoxia

Chapter 14

Overview of the circulation

Biophysics of pressure, flow, and resistance

Physical characteristics of the circulation

- Functional parts of the circulation
    - Arteries transport blood under high pressure
    - Arterioles control blood flow
    - Capillaries are nutrients exchanger
    - Venules→ veins
- Volumes of blood in the different parts of the circulation
    - 84% → systemic circulation (64% veins, 13% arteries, 7% arterioles);
    - 16% → heart (7%) and pulmonary circulation (9%)
- Cross-sectional areas and velocities of blood flow
    - Velocity of blood flow is inversely proportional to vascular cross-sectional area (F: volume; A: area)

$$v = F / A$$

- Pressure in the various portions of the circulation
    - Same amount of blood flows each minute through lungs and body
    - Aorta, large arteries, small arteries → around 100mmHg
    - Capillaries → 35-10 mmHg (mean 17mmHg)

- Pulmonary → 25-8 mmHg (mean 16mmHg)

Basic principles of circulatory function

- Rate of blood flow to each tissue of the body is precisely controlled in relation to the tissue nutrient needs
  - Oxygen and nutrients act directly on local blood vessels → dilation or constriction; nerve control
- The cardiac output is controlled mainly by the sum of all the local tissue flows
- Arterial pressure regulation is generally independent of either local blood flow control or cardiac output control

Interrelationships of pressure, flow, and resistance

- Blood flow determined by (1) pressure difference between ends of vessel and (2) by vascular resistance
- Ohm's law:

$$F = \Delta P / R$$

→ Blood flow directly proportional to pressure difference but inversely proportional to resistance

$$\Delta P = F \times R \; ; \; R = \Delta P / F$$

100 mmHg at start and end → no flow

- Blood flow
  - Normal → 5 l/min → cardiac output (CO)
  - Methods for measuring blood flow by flowmeters
  - Electromagnetic flowmeter
    - Blood vessel in electric field, between two poles of strong magnet → flow creates electrical signal
  - Ultrasonic Doppler flowmeter
    - *Doppler effect* → reflected waves have a lower frequency because of moving away
  - Laminar flow of blood in vessels or streamline flow → each blood layer remains at the same distance
  - Parabolic velocity profile during laminar flow
    - Flow in center much greater called parabolic profile for velocity of blood flow → due to blood adjacent to vessel wall slow because of adherence→ layer slip over each other
  - Turbulent flow of blood under some conditions
    - Flow crosswise, whorls, called *eddy currents* increase resistance
    - Turbulences increase proportionally to velocity, density of blood, diameter of vessel; inversely proportional to the viscosity
    - Reynold's number:

$$Re = (v \times d \times \rho) / \eta$$

v: velocity; d: diameter; ρ:density; η: viscosity

Reynold's number > 200-400 → turbulent flow

(Turbulences occur in large vessel almost never in small vessels)

- Blood pressure
  - Force exerted by the blood against any unit area of the vessel wall, vessel pressure will push mercury → 100 mmHg high
- Resistance to blood flow
  - Must be calculated
    - By the measurement of blood flow and pressure difference between two points in the vessel
  - Total peripheral vascular resistance and total pulmonary vascular resistance
    - Total peripheral resistance is → 1 (flow 100/100 pressure difference)
    - Total pulmonary vascular resistance is → 0.14 PRU (one seventh)
  - Conductance of blood in a vessel and its relation to resistance
    - Measure of the blood flow through a vessel for a given pressure difference; reciprocal of resistance; conductance → 1/resistance
  - Very slight changes in diameter of a vessel can change its conductance tremendously
    - Conductance of vessel increases in proportion to the 4^{th} power of the diameter
    - Poiseuille's law:

$$\text{Flow} = (\pi \times \Delta p \times r^4) / (8 \times \eta \times l)$$

  - Importance of the vessel diameter → 4^{th} power law; in determining arteriolar resistance
    - 4 times vessel diameter = 256 increase in flow
    - 2/3 of total systemic resistance is arteriolar resistance
  - Resistance to blood flow in series and parallel vascular circuits
    - Series = R1+R2+R3…
    - Parallel = total resistance far less than resistance of a single vessel
      - Each it's own resistance, but increasing one resistance increases the total resistance
      - More parallel vessels → decrease in resistance
      - Removing kidney → increase resistance
  - Effect of blood hematocrit and blood viscosity on vascular resistance and blood flow
    - The bigger the viscosity the lower the blood flow → due to red blood cells friction
    - Hematocrit: normal at 40 and blood plasma
    - When hematocrit rises → viscosity also rises; (normal 3 times of water)
- Effects of pressure on vascular resistance and tissue blood flow
  - Blood flow auto-regulation → ability of each tissue to adjust its vascular resistance
  - Increasing pressure does not affect flow so greatly because the resistance increases
  - Pressure, flow relationship in passive vascular beds
    - In passive blood vessels increase pressure increases flow and decrease resistance due to dilation
    - Inhibition of sympathetic activity greatly dilates the vessel and can increase the blood flow two fold or more

Chapter 15 Vascular distensibility and functions of the arterial and venous systems

Vascular distensibility

- All vessels are distensible
- Units of vascular distensibility
  - Dispensability is expressed as the fractional increase in volume for each millimeter of mercury rise in pressure

Dispensability = increase in volume / increase in pressure x original volume

- Differences in distensibility of the arteries and the veins
    - Veins → 8 times more distensible than arteries
    - Pulmonary arteries more distensible than systemic arteries
- Vascular compliance:

Vascular compliance = Increase in volume / Increase in pressure

    - Total quantity of blood that can be stored for each mmHg pressure rise; same formula without original vol.
    - Compliance is equal to distensibility times volume
    - Systemic veins are 24 times more compliant than corresponding artery
- Volume-pressure curves of the atrial and venous circulations
    - Volume rises → pressure in arteries rises strongly → but in veins just slightly
- Effect of sympathetic stimulation or sympathetic inhibition on the volume-pressure relations of the arterial and venous systems
    - Sympathetic stimulation can maintain pressure by constriction (even during blood loss)
- Delayed compliance, stress relaxation of vessel
    - Adding of volume → the pressure adjusts and falls slowly; and vice versa,
    - Pressure increases first but is ultimately lowered

Arterial pressure pulsations

- Pulse pressure is the difference between systole and diastole → 40mmHg
    - Two factors affect pulse pressure: (1) stroke volume output (2) the compliance of atrial tree

Pulse pressure = stroke volume / arterial compliance

    - Rise in pressure due to less compliance in arteriosclerosis
- Abnormal pressure pulse contours
    - By aortic valve stenosis reduces aortic pressure pulse due to diminished blood flow
    - Patent ductus arteriosus (PDA): causes diastolic pressure to fall low
- Transmission of pressure pulses to the peripheral arteries
    - The greater the compliance of each artery the slower the velocity of the transmission
    - Damping of the pressure pulse in the smaller arteries, arterioles and capillaries
        - Only when aortic pulsation is extremely large or arterioles are greatly dilated pulsations can be observed in capillaries due to (1) resistance to blood movement in vessel and (2) compliance of the vessel
- Clinical methods for measuring systolic and diastolic pressures
    - Auscultatory method
        - Korotkoff sound: pulsation sound against cuff resistance → turbulence
        - Cuff pressure higher than arterial pressure → no blood flow → pressure release → first sound after passing of systolic pressure → below diastolic pressure no more turbulences → no sound
    - Normal arterial pressure as measured by the ausculatory method → rises in age, less compliant
    - Mean arterial pressure: closer to diastole, determine pressure → 60% of mean

Veins and their functions

- Venous pressures – right atrial pressure (central venous pressure) and peripheral venous pressures
    - Central venous pressure in right atrium
        - Determined by ability to pump blood out; tendency of return
        - Right heart pumps strongly, severe hemorrhage → lowers pressure
        - Increase in venous return: increased blood volume, increased venous pressure, dilation of arterioles which allows rapid flow of blood from arteries into veins
        - Normal is about 0mmHg increase strongly by massive blood transfusion, heart failure; decrease by hemorrhage or high vigor
    - Venous resistance and peripheral venous pressure
        - Normal venous resistance is almost 0mmHg, sometime depressed by surrounding tissue so they usually have resistance
        - Effect of high right atrial pressure on peripheral venous pressure
            - Venous pressure rises
        - Effect of intra-abdominal pressure on venous pressures of the leg
            - Femoral vein has to adapt to intrabdominal pressure to prevent that all blood will flow back to heart in laying person
    - Effect of gravitational pressure on venous pressure
        - Standing person, pressure in right atrium is 0 but in feet 90mmHg due to the weight of the blood
        - 35mmHg in hand: 6mmHg do to compression and 29mmHg do to weight
        - In head is non-collapsible chamber pressure is -10mmHg
        - Effect of the gravitational factor on arterial and other pressures → 100mmHg by heart but 190mmHg in feet
    - Venous valves and the venous pump: their effects on venous pressure
        - Valves and muscles causing muscle pump of venous blood towards heart, during walking is 20mmHg, by standing 90mmHg, legs swell 20%, blood fluid loss while standing
        - Venous valve incompetence causes varicose veins
            - → Veins get dilated and the valves do not close → varicose veins
        - Reference level of pressure measurement is by tricuspid valve no gravity affected
- Blood reservoir function of the veins
    - 60% stored in veins, by blood loss veins constrict and body could function properly
    - Specific blood reservoirs
        - Spleen can contract and release 100ml, (same effect in liver, abdominal veins, venous plexus beneath the skin, heart, and lungs)
    - The spleen as a reservoir for storing red blood cells
        - In venous sinuses and pulp (contains many red blood cells), sinus could swell and store blood

Chapter 16

The microcirculation and lymphatic system: capillary fluid exchange, interstitial fluid, and lymph flow

Structure of the microcirculation and capillary system

- By beginning of each capillary is smooth muscle called precapillary sphincter
- Structure of the capillary wall
    - Diameter 4-9micrometer, unicellular wall, thin membrane
- Pores in the capillary membrane
    - Intercellular cleft, caveolae
- Special types of pores occur in the capillaries of certain organs
    - In brain are tight junctions only for water, oxygen; liver has wide clefts for all substances; gastrointestinal are middle wide; glomerular capillaries in kidney called fenestrae, numerous and small, but no proteins can pass

Flow of blood in the capillaries – vasomotion (periodic stop and flow of blood)

- Regulation of vasomotion
    - Concentration of oxygen
- Average function of the capillary system

Exchange of water, nutrients, and other substances between the blood and interstitial fluid

- Diffusion through the capillary membrane
    - Lipid soluble substances can diffuse directly through the cell membranes of the capillary endothelium like oxygen, CO_2
    - Water soluble, non-lipid soluble substances diffuse through intercellular pores in the capillary membrane like water, sodium, chloride, and glucose
    - Effect of molecular size on passage through the pores
        - Pores 6-7 nanometers
        - Approx. 20 nanometer for molecules larger than water → NaCl → Urea → Glucose→ etc.
    - Effect of concentration difference on net rate of diffusion through the capillary membrane
        - Net rate diffusion proportional to concentration difference between two sides, difference is sufficient to be very little

Interstitium and interstitial fluid – space and fluid between cells

- Contains collagen and proteoglycans filaments
- Gel in the interstitium
    - Tissue gel: fluid + proteoglycans, fluid diffuses through the gel
- Free fluid in the interstitium is slight but in edema this areas become huge

Fluid filtration across capillaries is determined by hydrostatic and colloid osmotic pressures, as well as capillary filtration coefficient

- Hydrostatic and colloid osmotic forces determine fluid movement through the capillary membrane
    - Four *starling forces* determine whether fluid diffuses or not
    - Capillary hydrostatic pressure → force fluid out
        - Micropipette method for measuring capillary pressure → pressure is highly variable depending on tissue and condition 25mmHg
        - Isogravimetric method for indirectly measuring functional capillary pressure → 17mm Hg
    - Interstitial fluid hydrostatic pressure → forces fluid inward when positive; but when negative force fluid outward
        - Loose connective tissue has -2mmHg (slightly less than atmospheric pressure)
        - Interstitial fluid pressures in tightly encased tissues although positive still negative in relation to capsular pressure
        - The true interstitial fluid pressure in loose subcutaneous tissue is slightly sub-atmospheric
            - -3mm Hg
        - Pumping of the lymphatic system is the basic cause for the negative interstitial fluid pressure
            - Lymphatic system removes excess fluid, proteins, and debris from tissue space
    - *Capillary plasma colloid osmotic pressure* → cause osmosis of fluid inward
        - 28mmHg and Donnan effect (extra pressure by cations held in place by proteins)
            - 80% due to albumin
        - Proteins in the plasma cause colloid osmotic pressure→ colloid means that a protein solution resembles a colloidal solution despite the fact that it is actually a molecular solution
    - *Interstitial fluid colloid osmotic pressure* → cause osmosis of fluid outward
        - Average is 8mmHg, total amount higher in interstitial fluid but percentage smaller
    - If sum of these forces is *positive*→ fluid filtration and if *negative* → fluid absorption into capillaries → filtration = net filtration pressure x capillary filtration coefficient

- Net filtration pressure:

$$NFP = P_c - P_{if} - \pi_p + \pi_{if}$$

P_c: capillary pressure; P_{if}: Interstitial fluid pressure; π_p: plasma colloid osmotic pressure; π_{if}: interstitial fluid colloid osmotic pressure

- Exchange of fluid volume through the capillary membrane
  - Pressure is at the beginning of capillaries greater (by 15-25mmHg) so fluid leaks out at the arteriolar end and at the venous end it is reabsorbed
  - Analysis of the forces causing filtration at the arterial end of the capillary
    - Summation of force at the arterial end is net filtration pressure of 13mm Hg → fluid outward
  - Analysis of reabsorption at the venous end of the capillary
    - Difference between total inward force 28mmHg and total outward force 21mmHg → is 7mm Hg; is the net reabsorption pressure; absorption of 9/10
- Starling equilibrium for capillary exchange
  - Near equilibrium between the total inward force 28mmHg and outward force 28,3mmHg → more filtration outward → removed by lymph
  - Filtration coefficient
    - Imbalance of filtration of 6,67 ml/minute/mm Hg → called whole body capillary filtration coefficient
  - Effect of abnormal imbalance of force at the capillary membrane
    - 20mmHg rise in blood pressure (0,3mmHg → 20,3mmHg) results in 68 times increase in filtration pressure → too much for the lymphatic system → edema develops

Lymphatic system

- Terminal lymphatic capillaries and their permeability
  - 2-3 liters each day, lymph vessels have valves formed by endothelial cells which prevent backflow
- Formation of lymph
  - Same composition as interstitial fluid; liver and intestinal lymph have highest protein concentration
- Rate of lymph flow
  - 120ml/h
  - Effect of interstitial fluid pressure on lymph flow → any factor which increases interstitial fluid pressure increases lymph flow → like elevated capillary hydrostatic pressure, decreased plasma colloid osmotic pressure
  - Increased interstitial fluid colloid osmotic pressure, increased permeability of the capillaries → increases flow into interstitial space→ increases interstitial pressure
  - A rise above atmospheric pressure can't increase lymph flow any more (due to lymph compression)

- Lymphatic pump increases lymph flow
  - Smooth muscle can create a pressure of 50-100mmHg
  - Pumping caused by external intermittent compression of the lymphatics
  - Other factors cause lymph pump: skeletal muscle, movement, pulsation, compression, exercise
- Lymphatic capillary pump
  - Anchoring filaments compression causes lymph to flow, when interstitial fluid rises
- Role of the lymphatic system in controlling interstitial fluid protein concentration, interstitial fluid volume, and interstitial fluid pressure
  - Proteins into interstitial space → accumulate → interstitial pressure rises → rate of lymph flow increases

Chapter 17

Local and humoral control of tissue blood flow

Local control of in response to tissue needs

- Needs oxygen, nutrients, removal CO_2, removal hydrogen ions, hormones
- Variations in blood flow in different tissues and organs → huge variations
- Importance of blood flow control by the local tissues → every organ is saturated but nothing above it

Mechanisms of blood flow control

- Acute control of local blood flow
    - 8 times more metabolism → 4 times more blood flow
    - Acute local blood flow regulation when oxygen availability changes → blood flow increases if oxygen saturation falls
    - Vasodilation theory for acute local blood flow regulation – possible special role of adenosine
        - No nutrients → release of vasodilation substances (CO_2, adenosine, histamine, K^+, H^+)
        - Decrease oxygen in heart → degradation of ATP → release of adenosine → vasodilation
    - Oxygen lack theory for local blood flow control
        - Smooth muscle need for oxygen → when oxygen is in excess, smooth muscle contract and decrease blood flow
    - Possible role of other nutrients besides oxygen in control of local blood flow
    - Special examples of acute metabolic control of local blood flow
        - Reactive hyperemia → when occlusion lasts for 1 hour blood flow increases many times after removal of occlusion to restore the needs
        - Active hyperemia → increase exercise → rising blood flow
    - Auto-regulation of blood flow, when the arterial pressure changes from normal – metabolic and myogenic mechanisms
        - Metabolic theory
            - Pressure rises → blood flow rises → oxygen level rises too much → vasoconstriction
        - Myogenic theory
            - Stretch of blood vessel → constriction of smooth muscle
    - Special mechanisms for acute blood flow control in specific tissues
        - Kidney: tubuloglomerular feedback, macula densa, fluid in early tubule
        - Brain: CO_2 and H^+ strong vasodilators
        - Skin: body temperature
    - Control of tissue blood flow by endothelial-derived relaxing or constricting factors
        - Nitric oxide (NO) - a vasodilator released from healthy endothelial cells
            - O_2 + arginine via nitric oxide synthase (NOS) → NO half life of 6 minutes → activates soluble guanylate cyclase in smooth muscle cause → cGTP → cGMP and protein kinase
            - Blood flow → friction of blood on epithelial cells → NO release→ dilation of blood vessels
            - NO synthesis is trigger also by vasoconstrictor substances → protection against excessive constriction
        - Endothelin
            - Powerful vasoconstrictor released from damaged endothelium
            - Usually when vessel is injured
- Long term blood flow regulation
    - 100-150mmHg → blood flow increases about 100% → 2 minutes later decreases to 10-15%
        - Long term the original blood flow reestablishes
        - Important when needs of a tissue change
    - Mechanism of long term regulation – change in tissue vascularity
        - Role of oxygen in long term regulation
            - Retrolental fibroplasias → oxygen tent → capillaries decrease → normal air → excess of vessel growth

    - Importance of vascular endothelial growth factor in formation of new blood vessels
        - Three factors vascular endothelial growth factor (VEGF), fibroblast growth factor, angiogenin → formed by deficiency of O_2 or nutrients
        - Angiogenesis explains the manner in which metabolic factors in local tissues can cause growth of new vessels
        - Steroid hormones cause dissolution of vascular cells which are not needed
            - E.g. angiostatin, endostatin
        - Vascularity is determined by maximum blood flow need, not by average need
            - Heavy exercise→ excess blood flow→ VEGF formed→ increase vascularity
            - New vessels stay constricted until lack of oxygen
- Development of collateral circulation – a phenomenon of long-term local blood flow regulation
    - Follows the usual principle of both acute and long term local blood flow control, acute being rapid dilation followed chronically by growth and enlargement of new vessels over a period of weeks and months – by the age of 60 years

Humoral control of the circulation – control by substances secreted or absorbed into the body fluids

- Vasoconstrictor agents
    - Norepinephrine and epinephrine
        - Norepinephrine: powerful vasoconstrictor
        - Epinephrine: less powerful; in small amounts also vasodilation
        - Also released as hormones provide direct nerve stimulation and indirect effects of these hormones in blood
    - Angiotensin II
        - Vasoconstrictor, constrict powerful small arterioles, increases resistance and arterial pressure
    - Vasopressin or antidiuretic hormone (ADH)
        - More powerful, formed by hypothalamus, increase water reabsorption of renal tubules
- Vasodilator agents
    - Bradykinin
        - Arteriolar dilation, increased capillary permeability
    - Histamine
        - From mast cells released in damaged tissue, increase capillary porosity, causing edema
- Vascular control by ions and other chemical factors
    - Ca^{2+} → vasoconstriction→ stimulate smooth muscle
    - K^+ → vasodilation→ inhibit smooth muscles
    - Mg^{2+} → powerful vasodilation→ inhibit smooth muscles
    - H^+ → decrease in pH→ dilation of arterioles; slight opposite
    - Anion → vasodilation
    - CO_2 → vasodilation in brain widespread vasodilation
- Most vasodilators or vasoconstrictors have little effect on long term blood flow unless they alter metabolic rate of the tissue

Chapter 18

Nervous regulation of the circulation and rapid control of arterial pressure

Nervous regulation of the circulation

- Autonomic nervous system
    - Sympathetic nervous system
    - Sympathetic innervation of the blood vessels
        - All vessel except the capillaries (aorta, vena cava) are innervated, innervation allows increase of resistance and decrease of blood flow
    - Sympathetic nerve fibers to the heart
    - Parasympathetic control of heart function, especially heart rate – decrease of heart rate and contractility – minor role in regulation of vascular function

- Sympathetic vasoconstrictor system and its control by the central nervous system
  - Many vasoconstrictor fibers, sympathetic effect strongest in kidney, intestines, spleen, skin
  - Vasomotor center in the brain and its control of the vasoconstrictor system
    - In medulla and pons, parasympathetic to heart and sympathetic to all vessels
    - (1) Vasoconstrictor area, sends sympathetic neurons to all levels of spinal cord
    - (2) Vasodilator area, lower medulla, fibers project upward to vasoconstrictor area to inhibit them → vasodilation
    - (3) Sensory area located bilaterally in the tractus solitarius in posterolateral portions of the medulla and lower pons → receive signals from circulatory system by vagus and glossopharyngeal nerve → reflex control in contact with vasodilator and vasoconstrictor area
  - Continuous partial constriction of the blood vessels is normally caused by sympathetic vasoconstrictor tone
    - 0,5 – 2 signals/s: called sympathetic vasoconstrictor tone → vasomotor tone is maintained
    - Spinal anesthesia drop of 50% of blood pressure
    - Control of heart activity by the vasomotor center
      - From vasomotor center, heart rate and strength of heart contraction increases when vasoconstriction occurs and ordinarily decreases when vasoconstriction is in inhibit
    - Control of the vasomotor center by higher nervous centers
      - Small neurons in reticular formation can excite or inhibit vasomotor center
      - Hypothalamus can exert powerful excitatory or inhibitory effects on vasomotor center
      - Also cerebral cortex, motor cortex,
    - Norepinephrine – the sympathetic vasoconstrictor transmitter substance
      - Acts directly on alpha adrenergic receptors of vascular smooth muscle
    - Adrenal medullae and their relation to the sympathetic vasoconstrictor system
      - Nerve signal to vessels and medulla → medulla secrets epinephrine (vasodilator via beta adrenergic receptors) and norepinephrine in blood
- Emotional fainting – vasovagal syncope
- Vasodilation center for muscle anticipation

Role of the nervous system in rapid control of arterial pressure

- Three major steps to increase arterial pressure
  - (1) Arterioles constricted → higher resistance → higher pressure
  - (2) Veins strongly constricted → more blood in heart chamber → greater heart beat → higher pressure
  - (3) Sympathetic stimulation of heart → higher cardiac output
- Rapidity of nervous control of atrial pressure
  - Nervous control of arterial pressure is the fastest

- Increase in arterial pressure during muscle exercise and other types of stress
  - Heavy exercise → arterial pressure rises about 30-40% → doubles blood flow
  - In fight or flight situations → pressure can rise as 75-100 mmHg in a few seconds
- Reflex mechanisms for maintaining normal arterial pressure
  - Baroreceptor arterial pressure control system – baroreceptor reflexes
    - Rise in pressure → stretches receptors → signals to brain → ANS reduces pressure
    - Physiologic anatomy of the baroreceptors and their innervation
      - In wall of artery, abundant in carotid artery and aortic arch, glossopharyngeal, Hering's nerve
    - Response of the baroreceptors to arterial pressure
      - Send signals above 60 - 180mmHg in carotid, aortic starts at 90mmHg
      - Most effective where it is most needed around 100mmHg

        - Circulatory reflex initiated by the baroreceptors
            - Baroreceptor signals → tractus solitarius → inhibit vasoconstrictor center of medulla and excite vagal parasympathetic center → vasodilation, decreased heart rate and strength
            - Low pressure opposite effect
        - Function of the baroreceptors during changes in body posture
            - Pressure decreases → baroreceptor signals inhibit → rise in pressure
        - Pressure buffer function of the baroreceptor
            - Baroreceptor nerves called buffer nerves, pressure buffer system
            - Extreme variability of pressure in absence of baroreceptors
            - React strongest if pressure changes rapidly
        - Control of arterial pressure by the carotid and aortic chemoreceptors – effect of oxygen lack on arterial pressure
            - Cells sensitive to oxygen lack, CO_2 excess, hydrogen ion excess
            - Nerves pass with Hering's nerves to vasomotorcenter of brain stem
            - Becomes important under 80mmHg
        - Atrial and pulmonary artery reflexes regulate arterial pressure
            - Atria and pulmonary arteries have stretch receptors called low pressure receptors
            - Can detect excess volume and pressure in low pressure areas
        - Atrial reflexes that activate the kidneys – the volume reflex
            - Stretch atria → signal hypothalamus → decrease ADH → glomerular kidney pressure rises → more filtration
        - Atrial reflex control of heart rate (the Bainbridge reflex)
            - More volume → stretch SN and atria stretch receptors → increase heart rate
- Central nervous system ischemic response (reduce blood flow) – control of arterial pressure by the brains vasomotor center in response to diminished brain blood flow
    - Arterial pressure elevation in response to cerebral ischemia is known as the central nervous system ischemic response → one of the most powerful of all the activators of the sympathetic vasoconstrictor system
    - Importance of the CNS ischemic response as a regulator of arterial pressure
        - Emergency pressure control system work under 60mmHg → most activated at 15-20mmHg
    - Cushing reaction to increase pressure around the brain
        - Helps protect the vital centers of the brain from loss of nutrition; if ever the cerebrospinal fluid pressure rises high enough to compress cerebral arteries → ischemia
          → arterial pressure must be above cerebral pressure

Special features of nervous control of arterial pressure

- Role of the skeletal nerves and skeletal muscles in increasing cardiac output and arterial pressure
    - Abdominal compression reflex
        - Baro- or chemoreceptor signal→ abdominal compression reflex in order to squeeze the blood out the veins (paralyzed people more hypertension)
    - Increased cardiac output and arterial pressure caused by skeletal muscle contraction during exercise
        - Cause more blood flow into the heart
- Respiratory waves in the arterial pressure
    - Pressure rises and falls 4-6mmHg
    - Respiratory signals in medulla spill over, by inspiring pressure in thorax become negative → blood vessels expand → less blood to left side → decreasing cardiac output
    - Expiration → increase
    - Pressure changes cause vascular and atrial stretch response
- Arterial pressure vasomotor waves – oscillation of pressure reflex control systems
    - Mayer waves due to → reflex oscillation of one or more nervous pressure control mechanisms some of which are the following

        - Oscillation of the baroreceptor and chemoreceptor reflexes
            - High pressure excites the baroreceptors → inhibits sympathetic nervous system → lowers pressure → decreased pressure reduced baroreceptor signal → vasomotor center become active → elevating pressure
        - Oscillation of the CNS ischemic response
            - Any reflex can oscillate if response is very strong

Chapter 19

Role of the kidneys in long-term control of arterial pressure and in hypertension:

The integrated system for arterial pressure regulation

- Long-term pressure is closely related to body fluid volume

Renal body fluid system for arterial pressure control

- Rising pressure causes more fluid excretion
- Quantitation of pressure diuresis as a basis for arterial pressure control
    - Pressure diuresis, at 100mmHg normal at 200mmHg (6-8 times higher)
    - Also excretion of sodium called pressure natriuresis
    - An experiment demonstrating the renal body fluid system for arterial pressure control → kidney extremely capable of regulating blood pressure
    - Arterial pressure control by the renal body fluid mechanism – near infinite feedback gain feature
        - Return of arterial pressure always back to the equilibrium (water and salt intake equals loss) point is the near infinite feedback gain principle for control of pressure by renal body fluid mechanism
    - Two determinants for the long term arterial pressure level
        - (1) Degree of pressure shift of the renal output curve for water and salt and
        - (2) The level of water and salt intake
            - → If one of those factors is changed there will be establish a new pressure
    - The chronic renal output curve is much steeper than the acute curve
        - Chronic: 6 times more → but pressure elevates just slightly
        - Acute: rises immensly → but will adapt
        - Salt insensitive → people's pressure do not change due to salt intake
        - Salt sensitive→ salt intake leads to huge changes due to damage to kidney
    - Failure of increased total peripheral resistance to elevate the long term level of arterial pressure if fluid intake and renal function do not change

Arterial pressure = cardiac output x total resistance

        - Peripheral resistance increase except in kidneys → more salt and water loss → decreased blood volume → return to equilibrium
        - But peripheral resistance also increase intrarenal vascular resistance (is the determining factor) → alters function of kidney to higher pressure level
    - Increased fluid volume can elevate arterial pressure by increasing cardiac output or total peripheral resistance
        - (1) Increased extracellular fluid volume → (2) increases the blood volume → (3) increases the mean circulatory filling pressure → (4) increases venous return of blood to the heart → (5) increases cardiac output → (6) increases arterial pressure → (7) increases renal excretion
        - Increased cardiac output → autoregulation, too much perfusion → increases total peripheral resistance → increases pressure

- Importance of salt NaCl in the renal body fluid schema for arterial pressure regulation
    - Salt excretion is more difficult, if there is n accumulation → increases blood volume
        - Increase osmolality → more salt activates thirst center in brain → more fluid intake → increase in volume
        - Increase osmolality → increase in ADH levels → reabsorption of water
    - Salt is the determining factor for extracellular fluid volume
- Chronic hypertension is caused by impaired renal fluid excretion
    - More than 90-135 mmHg
    - Lethal due to:
        - Excess work of heart → heart attack
        - Damage of major blood vessels in brain → stoke in brain
        - High pressure damages kidneys
    - Experimental volume loading hypertension caused by reduced renal mass along with simultaneous increase in salt intake
    - Sequential changes in circulatory function during the development of volume-loading hypertension
        - We can divide volume loading hypertension into 2 separate sequential stages:
            - (1) First stage results from increased fluid volume→ causing increased cardiac output → hypertension
            - (2) Second stage has high blood pressure and high total peripheral resistance but return of cardiac output towards normal
        - → Total peripheral resistance occur after hypertension has develop and is *secondary* to hypertension and not the cause
        - Higher pressure → more perfusion → higher resistance
    - Volume-loading hypertension in patients who have no kidneys but are being maintained on artificial kidney → keep volume normal
    - Hypertension caused by primary aldosteronism
        - Excess aldosterone → increases rate of absorption of salt and water → increased volume

The rennin-angiotensin system: its role in arterial pressure control

- Renin: *enzyme* (not a vasoactive substance), released by kidney when pressure falls to low → increases arterial pressure
- Components of the renin-angiotensin system
    - Decreased arterial pressure → initiate intrarenal functions → release of renin → up to 1h in blood → forms renin substrate *angiotensinogen* → forms *angiotensin I* → in lung conversion to *angiotensin II* → rise in blood pressure
    - Angiotensin II is a powerful vasoconstrictor and decrease excretion of both salt and water (fast inactivation by angiotensinase)
    - Rapidity and intensity of the vasoconstrictor pressure response to the renin-angiotensin system
        - Needs 20 minutes to act
        - Powerful, but no fast changes
    - Effect of *angiotensin II* in the kidneys to cause renal retention of salt and water – an important means for long-term control of arterial pressure
        - (1) Angiotensin II acts directly on the kidneys to cause salt and water retention
        - (2) Angiotensin II causes the adrenal glands to secrete aldosterone, and the aldosterone in turn increase salt and water reabsorption by the kidney tubules
        - Mechanisms of the direct renal effects of angiotensin II cause → renal retention of salt and water → constriction of renal arterioles → less blood flow → cause reabsorption of fluid from tubules and increase reabsorption of sodium and water in tubules
        - Stimulation of aldosterone secretion by angiotensin II, and the effect of aldosterone to increase salt and water retention by the kidneys → stimulates aldosterone → increase sodium reabsorption by the kidney tubules → increases volume

    - Role of the renin-angiotensin system in maintaining a normal arterial pressure despite large variations in salt intake
        - Increased salt → increase extracellular fluid → increased pressure → decrease renin and angiotensin → decreased absorption of salt and water → return extracellular fluid and pressure to normal
- Types of hypertension in which angiotensin is involved: hypertension caused by a renin-secreting tumor or by infusion of angiotensin II
    - Tumor in JG cells → excess in renin and angiotensin II
    - *One kidney Goldblatt hypertension*
        - Occluding one kidney's renal artery to a certain percent
        - Other kidney was removed
            - Systemic pressure rises
            - Distal renal arterial pressure falls
            - Rises back to normal but systemic pressure is strongly increased
    - *Two kidney Goldblatt hypertension*
        - Both kidneys become salt and water absorber if just one kidney is occluded because renin goes into the circulation and affects the other kidney
    - Hypertension caused by diseased kidneys that secrete renin chronically
    - Other types of hypertension caused by combinations of volume loading and vasoconstriction
        - Hypertension in the upper part of the body caused by *coarctation of the aorta*
            - Occlusion in aorta before renal artery→ pressure normal in lower body but elevated in upper body
        - Nearly complete long term auto regulation → regulation with need of tissue, not with pressure
        - Hypertension in preeclampsia → hypertension after birth for mother
        - Neurogenic hypertension → stress response sympathetic innervation
        - Acute neurogenic hypertension → caused by sectioning the baroreceptor nerves
        - Genetic causes of hypertension → cause excessive salt and water reabsorption
- Primary (essential) hypertension
    - Cardiac output increased due to more supply of fat tissue
    - Sympathetic nerve activity, especially in the kidneys is increased in overweight patients
    - Angiotensin II and aldosterone levels are increased 2 to 3 times in many obese people
    - The renal-pressure natriuresis mechanism is impaired, and the kidney will not excrete adequate amounts of salt and water → unless the arterial pressure is high or kidney function is improved
    - Graphical analysis of arterial pressure control in essential hypertension
    - Treatment of essential hypertension by admission of
        - Vasodilator drugs → increase renal blood flow and natriuretic or diuretic drugs that decrease reabsorption of salt and water

Summary of the integrated, multifaceted systems for arterial pressure regulation

- Rapidly acting pressure control mechanisms, acting within seconds or minutes
    - Baroreceptor reflex; CNS ischemic mechanism; chemoreceptor mechanism
- Pressure control mechanism that act after many minutes
    - Renin-angiotensin vasoconstriction; stress relaxation of vasculature (to high pressure stretch of vessels); shift of fluid in and out
- Long term mechanism for arterial pressure regulation

Chapter 20

Cardiac output, venous return, and their regulation

- Venous return = cardiac output (CO)

Normal values for cardiac output at rest and during activity

- CO:
    - Metabolism, activity, age, size → affect CO
    - 5l/min
        - Decreases from 10 to 80 years

Control of cardiac output by venous return – role of the *frank-starling* mechanism of the heart

- Primary by venous return → more blood→ more stretch → more power
- SA node stretch called → *Bain-bridge reflex* → to brain and back to heart
    - Heart becomes limiting factor if venous return exceeds
- CO regulation is the sum of blood flow regulation in all the local tissues of the body – tissue metabolism regulates most local blood flow
    - O_2 consumption and cardiac output rise parallel
    - Effect of total peripheral resistance on the long term cardiac output level
        - Peripheral resistance rises but cardiac output falls

$$CO = P/R$$

- The heart has limits for the cardiac output that it can achieve
    - In normal heart can pump 2,5 times normal output 13 L
    - Factors that cause a hyper-effective heart
        - Effect of nervous excitation to increase heart pumping
            - Nervous excitation could rise CO to 25 L/m by contractility (strength of contraction) and beats/m
        - Increased pumping effectiveness caused by heart hypertrophy
            - Size of muscle growth up to 30-40 L/m
    - Factors that cause a hypo-effective heart
        - Increased arterial pressure against which the heart must pump (hypertension)
        - Nerve inhibition
        - Abnormal heart rhythm
        - Coronary artery block, valvular heart disease
        - Congenital heart disease
        - Inflammation
        - Cardiac hypoxia
- Role of the nervous system in controlling cardiac output
    - Importance of the nervous system in maintaining arterial pressure when peripheral blood vessels are dilated and venous return and cardiac output increase
        - Effect of the nervous system to increase the arterial pressure during exercise
            - Autonomic nervous system (ANS) → excites circulatory activity, venous constriction, increase in heart rate → increase of pressure because you need to compensate dilation of muscle vessels

Pathologically high or low cardiac outputs

- High cardiac output, caused by
    - Reduced total peripheral resistance
    - Beriberi
    - Arterio-venous fistula, shunt connection (artery → vein)

    - Hyperthyroidism
    - Anemia (less oxygen or red blood cells)
- Low cardiac output, caused by
    - Cardiac factors
        - Due to blockage and myocardial infarction
        - Severe valvular heart disease
        - Myocarditis
        - Cardiac tamponade
    - Decrease in cardiac output caused by non-cardiac peripheral factors – decreased venous return
        - Decreased blood volume
        - Acute venous dilation
        - Obstruction of large veins
        - Decreased tissue mass (especially decreased skeletal muscle mass)
        - Decreased metabolic rate
        - Hypothyroidism
        - If body suffers from malnutritional supply → called cardiac shock
- A more quantitative analysis of cardiac output regulation
- Cardiac output curves used in the quantitative analysis
    - Effect of external pressure outside the heart on cardiac output curves
        - Factors that alter external pressure and increase cardiac output (due to increase external pressure)
        - Respiration; breathing against negative pressure to left; against positive to right; opening thoracic cage to right; cardiac tamponade → fluid in pericardial cavity shift to right
    - Combinations of different patterns of cardiac output curves
- Venous return curves
    - Factors which affect venous return to heart: right atrial pressure; degree of filling of the systemic circulation; resistance to blood flow between peripheral vessels and blood flow
    - Normal venous return curve
        - The higher the right atrial pressure the smaller the venous return
        - Right atrial pressure up to 7mmHg → venous return decreases to 0 → called *mean systemic filling pressure*
        - Plateau in the venous return curve at negative atrial pressures caused by collapse of the large veins
            - Negative pressure in right atrium sucks the walls of the veins together
    - Mean circulatory filling pressure and mean systemic filling pressure and their effect on venous return
        - If heart stops pressure is everywhere equal → called mean circulatory filling pressure
        - Effect of blood volume on mean circulatory filling pressure
            - More volume, more pressure, linear rising
        - Effect of sympathetic nervous stimulation of the circulation on mean circulatory filling pressure
            - Increases mean circulatory filling pressure
        - Mean systemic filling pressure (pressure after blood flow stops) and its relation to mean circulatory filling pressure → both are about the same value without lungs
        - Effect on the venous return curve of changes in mean systemic filing pressure
            - The greater the system is filled, the easier is it for the blood to return into the right heart
        - Pressure gradient for venous return – when this is 0 → there is no venous return
            - The bigger the difference between mean systemic filling pressure and right atrial pressure the greater the venous return
    - Resistance to venous return
        - 2/3 by veins and 1/3 by arteries (increase resistance much more because of lack of distensibility)
        - Effect of resistance to venous return on the venous return curve
            - The higher the resistance the less the venous return

- Analysis of cardiac output and right atrial pressure using simultaneous cardiac output and venous curves
    - Systemic pressure = right heart pressure; input = output
    - Effect of increased blood volume on cardiac output; higher CO and right atrial pressure
    - Further compensatory effects initiated in response to increased blood volume
        - More fluid uptake from tissue; tissue resistance increases → more venous return → veins dilate
    - Effect of sympathetic stimulation on cardiac output
    - Effect of opening a large arterio-venous fistula

Methods for measuring cardiac output

- Pulsatile output of the heart as measured by an electromagnetic or ultrasonic flowmeter
- Measurement of cardiac output using the oxygen Fick principle

CO (L/min) = 0_2 absorbed by the lungs (ml/min) / arterio-venous O_2 difference (ml/L of blood)

    - 5 = 200/40
- Indicator dilution method for measuring cardiac output

Chapter 25

The body fluid compartments: extracellular and intracellular fluids

Edema

Fluid intake and output are balanced during steady-state conditions

- Daily intake of water
    - Ingestion: 2.100ml water
    - Metabolism, oxidation of stuffs: 200ml
- Daily loss of body water
    - Insensible water loss: respiratory and via skin 700ml
    - Fluid loss in sweat: normal 100ml (up to 1-2 L)
    - Water loss in feces: 100ml
    - Water loss via kidney, urine: 1.400ml

Body fluid compartments

- Intracellular fluid compartment
    - All cells are one large compartment 40% of body weight
    - 28 L
- Extracellular fluid compartment
    - 3/4 are interstitial fluid and plasma 1/4
    - 11 L and 3 L

Blood volume

- 60% of blood is plasma
- 40% red blood cells
- Hematocrit: packed red cell volume

Constituents of extracellular and intracellular fluids

- Ionic compensation of plasma and interstitial fluid is similar
    - Higher protein concentration in plasma, Donnan effect on plasma side

- Intracellular fluid constituents
    - Many proteins, K^+, phosphate, Mg^{2+}

Measurement of fluid volumes in the different body fluid compartments – the indicator-dilution principle

Volume = volume a x concentration a / concentration b

- No loss, stay in compartment

Determination of volumes of specific body fluid compartments

- Measurement of total body water → heavy water
- Measurement of extracellular fluid volume: inulin
- Calculation of intracellular volume: can not be measured directly (ICV = TBW – ECV)
- Measurement of plasma volume: albumin
- Calculation of interstitial fluid volume: cannot be measured directly EFV-PV
- Measurement of blood volume: plasma and hematocrit

Regulation of fluid exchange and osmotic equilibrium between intracellular and extracellular fluid

Basic principle of osmosis and osmotic pressure

- Osmosis is the net diffusion of water across a selectively permeable membrane from a region of high water concentration to one that has a lower water concentration
- Relation between moles and osmoles → osmole refers to: number of particles in solution
- Osmolality (osmoles/kg water) and osmolarity (osmoles/L of solution) about the same
- Calculation of the osmolarity and osmotic pressure of a solution
    - 0,9% NaCl → 9g/L; 58,5g/mol →0.154mol/L
- Osmolarity of the body fluids
- Correct osmolar activity of the body fluids → cations and anions exert attraction on each other → decrease in osmotic activity

Osmotic equilibrium is maintained between intracellular and extracellular fluids

- Small changes in concentration of impermeant solutes extracellular can cause large changes in cell volume
- Isotonic (same outside and inside), hypotonic (water diffuse into the cell), and hypertonic (causes cells to shrink greater then 0.9) fluids
- Isosmotic (same osmolarity as cell), hyperosmotic, and hypo-osmotic fluids
- Osmotic equilibrium between intracellular and extracellular fluids is rapidly attained

Volume and osmolality of extracellular and intracellular fluids in abnormal states

- Water moves rapidly across cell membranes; cell membranes are almost completely impermeable to many solutes
- Effect of adding saline solution to the extracellular fluid
    - Calculation of fluid shifts and osmolarities after infusion of hypertonic saline
        - Adding 2 L of a hypertonic sodium chloride solution causes more than a 5 L increase in extracellular fluid volume while decreasing intracellular fluid volume by 3 L

Glucose and other solutions administered for nutritive purposes → slow uptake for maintaining the equilibrium

Clinical abnormalities of fluid volume regulation: Hyponatremia and hypernatremia

- If plasma sodium concentration:
    - Is reduced → hyponatremia
    - Is elevated → hypernatremia

- Causes of hyponatremia: excess water or loss of sodium
    - Loss of sodium in dehydration, diarrhea, vomiting, sodium wasting kidneys, Addison's disease: fail of aldosteron (sodium reuptake), excessive ADH
- Consequences of hyponatremia: cell swelling
    - Brain cell edema, severe by 115-120 mmol/L
- Causes of hypernatremia: water loss or excess sodium
    - No ADH, dehydration, nephrogenic diabetes insipidus, excessive aldosterone
    - Diabetes insipidus = highly diluted urine
- Consequences of hypernatremia: cell shrinking
    - Could happen in patients who are not thirsty

Edema: excess fluid in the tissues

- Intracellular edema
    - Due to: hyponatremia → water follows salt and salt is in cell, depression of metabolism in tissue (ion pumps depressed), lack of nutrition, inflammation of the tissue
- Extracellular edema
    - Due to: abnormal leakage of fluid from the plasma to the interstitial spaces and failure of lymphatics, increase capillary filtration
    - Factors that can increase capillary filtration: increased capillary hydrostatic pressure, plasma colloid osmotic pressure, filtration coefficient
- Lymphedema – failure of the lymph vessels to return fluid and protein to the blood
    - Due to worm (filariasis) or after cancer
- Summary of causes of extracellular edema
    - Increased capillary pressure: due to excessive kidney retention of salt and water, high venous pressure and venous constriction, decreased arteriolar resistance
    - Decreased plasma proteins: loss in urine, damage to skin, failure to produce proteins
    - Increased capillary permeability: histamine, lack of vitamin C, burns, ischemia
    - Blockage of lymph return: cancer, infections like worm, surgery,
    - Caused by heart failure:
        - Heart weak → fail of pumping blood from arteries into veins → venous pressure rises → increase filtration
        - Arterial pressure decreases → kidney retain salt and water → rise capillary hydrostatic pressure
        - Pulmonary edema if left heart is to weak pressure rises in lung and causes edema; fails to pump blood from veins into arteries
    - Caused by decreased kidney excretion of salt and water → sodium and water leaks in interstitial fluid
    - Caused by decreased plasma proteins → kidney failure when membrane becomes leaky to plasma proteins, cirrhosis of liver
- Safety factors that normally prevent edema
    - Safety factor caused by low compliance of the interstitium in the negative pressure range
        - A bit *negative*, when pressure is *positive* → the compliance of the tissue is lost and edema occurs → safety factor -3mmHg
        - Importance of interstitial gel in preventing fluid accumulation in the interstitium
            - Gel prevents easy flowing of fluid, compliance very low in low pressure,
            - Pitting edema (interstitium swells), non pitting edema (tissue cell swells)
        - Importance of the proteoglycans filaments as a spacer for the cells and in preventing rapid flow of fluid in the tissues
            - Keep fluids in space, exchange of nutrients
    - Increased lymph flow as a safety factor against edema
        - Flow can increase up to 50 times, bring proteins back to blood, 7 mmHg safety factor
    - Wash-down of the interstitial fluid protein as a safety against edema
        - Lymph flow increases and interstitial pressure decreases

- Summary of safety factors that prevent edema
    - Low tissue compliance in negative pressure 3 mmHg; increased lymph flow 7 mmHg; proteins washed out 7 mmHg→ total is 17 mmHg; capillary pressure could double before edema occur

Fluids in the potential spaces of the body

- Fluid is exchanged between the capillaries and the potential spaces
- Lymphatic vessels drain protein from the potential spaces
- Edema fluid in the potential spaces is called effusion

Chapter 26

Urine Formation by the kidneys

Glomerular filtration, renal blood flow and their control

- Excretion of metabolic waste products, foreign chemicals, drugs, and hormone metabolites
    - Urea from amino acids, creatinine, bilirubin, toxins
- Regulation of water and electrolyte balances
- Regulation of arterial pressure – long and short time (remember hormones, renin)
- Regulation of acid-base balance – are only organs who can excrete acids
- Regulation of erythrocyte production – hypoxia → erythropoietin → synthesis
- Regulation of 1,25 dihydroxyvitamin D3 production → calcitrol for Ca^{2+} and phosphate regulation
- Glucose synthesis → glucose in times of starving

Physiologic anatomy of the kidneys

- General organization of the kidneys and urinary tract
- Renal blood supply
    - 1.100 ml/min, glomerulus, peritubular capillaries
    - By regulation in afferent and efferent arterioles the kidneys can regulate hydrostatic pressure
- Nephrons are the functional unit of the kidney
    - 1 million, glomeruli 60 mmHg,
- Regional differences in nephrons structure: cortical and juxtamedullary nephrons

Micturition

- Bladder empties when it is filled

Physiologic anatomy of the bladder

- innervation of the bladder → stretch activates emptying

Transport of urine from the kidney through the ureters and into the bladder

- Peristaltic contractions at renal calyces enhanced by parasympathetics
- Pain sensation in the ureters, and the uretrorenal reflex → well supplied with pain fibers
    - Rapid rise of pressure from 400 ml filling in bladder,

Micturition reflex

- Micturition reflexes become more frequent by filling and contract detrusor muscle tighter
    - Is a single complete cycle of (1) progressive and rapid increase of pressure, (2) a period of sustained pressure, and (3) return of the pressure to the basal tone of the bladder
- Facilitation or inhibition of micturition by the brain
    - Voluntary urination: contraction of abdominal muscle → increase in pressure in the bladder → allows extra urine to enter bladder neck and posterior urethra → stretching the walls → micturition reflex → inhibit external sphincter
    - Atonic bladder and incontinence caused by destruction of sensory nerve fibers → no stretch reflex → losing bladder control → overflow incontinence

- Automatic bladder caused by spinal cord damage above the sacral region → micturition reflex can still occur

Urine formation results from glomerular filtration, tubular reabsorption, and tubular secretion

Urinary excretion = glomerular filtration – reabsorption of substances from the renal tubules into the blood + secretion of substances from the blood into the renal tubules

- Fluid free of proteins from glomerular capillaries into → Bowman's capsule → into tubules reabsorption of water and solutes or secretion of other substances from peritubular capillaries into tubules
- Possibilities: filtration only (creatinine); filtration and reabsorption (sodium); filtration and complete reabsorption (amino acids); filtration and secretion (organic acids and bases)
- Filtration, reabsorption and secretion of different substances
  - GFR → from 180 L/Day to 198 L/Day would rise urine volume 13 times
- Why are large amounts of solutes filtrated and then reabsorbed by the kidneys
  - High GFR → fast rid of waste products, allows kidney to precisely and rapidly control volume and composition of the body fluids

Glomerular filtration – the first step in urine formation

- Composition of the glomerular filtrate
  - Like plasma but without proteins, no compounds bind to proteins, no calcium
- GFR is about 20% of the renal plasma flow
  - GFR dependant of hydrostatic and colloid factors, capillary filtration coefficient
  - Filtration fraction = GFR/renal plasma flow → amount that is filtered from total renal flow
- Glomerular capillary membrane
  - 3 layers including podocytes, fenestrae, negative charges against proteins
  - Filterability of solutes is inversely related to their size
  - Negatively charged large molecules are filtrated less easily than positively charged molecules of equal molecular size (fail=minimal change nephropathy)

Determinants of the GFR

GFR = net filtration coefficient x net filtration pressure

  - Forces + filtration: glomerular hydrostatic pressure, Bowman's colloid pressure → 0
  - Force – filtration: Bowman's hydrostatic pressure, glomerular capillary colloid osmotic pressure → 10mmHg net filtration
- Increased glomerular capillary filtration coefficient increases GFR
  - GFR / net filtration = coefficient; 125/10= 12,5; lowering by disease diabetes, hypertension
- Increased Bowman's capsule hydrostatic pressure decreases GFR→ rises when ureter is occluded
- Increased glomerular capillary colloid osmotic pressure decreases GFR (not hydrostatic pressure)
  - Affected by arterial plasma colloid osmotic pressure, fraction of plasma filtered by the glomerular capillaries
  - Increasing filtration fraction also concentrates plasma proteins → rises glomerular colloid osmotic pressure
  - With constant glomerular hydrostatic pressure → greater rate of blood flow into glomerulus tends to increase GFR
  - Changes in renal blood flow can influence GFR independently of changes in glomerular hydrostatic pressure → more blood increase GFR
- Increased glomerular capillary hydrostatic pressure increased GFR (table 316)
  - Determined by arterial pressure, afferent arteriolar resistance, efferent arteriolar resistance
  - Occlusion of afferent artery → reduces hydrostatic pressure and decreases GFR
  - Occlusion of efferent artery pressure → increases resistance of outflow → GFR increases slightly but too much decreases GFR → is biphasic

Renal blood flow

- 22% to both kidneys of blood in order to provide them with enough plasma to maintain homeostasis
- Renal blood flow and oxygen consumption → because of active sodium reabsorption
- Determinants of renal blood flow
    - Renal arterial pressure – renal venous pressure / total renal vascular resistance
    - Can keep pressure independent
- Blood flow in the vasa recta of the renal medulla is very low compared with flow in renal cortex

Physiologic control of glomerular filtration and renal blood flow

- Sympathetic nervous system activation decreases GFR
    - All renal vessel innervated but only strong impulses have an effect
- Hormonal and autacoids control of renal circulation
    - Norepinephrine, epinephrine, and endothelin → constrict renal blood vessels and decrease GFR
    - Angiotensin II preferentially constricts efferent arterioles in most physiologic conditions maintain GFR by constriction of efferent arteriole, prevents decrease of GFR
    - Endothelial-derived nitric oxide → decreases renal vascular resistance and increases GFR
    - Prostaglandins and bradykinin tend to increase GFR → vasodilators

Autoregulation of GFR and renal blood flow

- Constant GFR = autoregulation, in range of 75 – 160 mmHg
- Importance of GFR autoregulation in preventing extreme changes in renal excretion
    - GFR 180 L/Day and reabsorption 178,5 L/Day
    - Additional adaptive mechanisms in renal tubules that cause them to increase their reabsorption rate when GFR rises called glomerulotubular balance
- Tubuloglomerular feedback and autoregulation of GFR
    - Changes in sodium receive macula densa → regulation via arteriolar resistance
    - Juxtaglomerular complex includes macula densa cells and juxtaglomerular cells in walls of efferent and afferent arterioles
    - Decreased macula densa sodium chloride causes dilation of afferent arterioles and increased renin release
        - Decrease GFR → slow flow so increased sodium reabsorption → reducing concentration at macula densa → decrease resistance in afferent arterioles to blood flow and increases renin (juxtaglomerular cells) → angiotensin I → angiotensin II → constrict efferent arteriole → increasing glomerular hydrostatic pressure → rise in GFR
        - *Angiotensin II blocker* to treat hypertension (but pay attention that GFR is not reduced)
- Myogenic autoregulation of renal blood flow and GFR → increase pressure increase contraction
- Glucose and amino acids reabsorbed together with sodium → increase GFR less sodium by macula densa

Chapter 27

Urine formation by the kidneys

Tubular reabsorption and secretion

Renal tubular reabsorption and secretion

- Tubular reabsorption is quantitatively large and highly selective

Filtration = glomerular filtration rate x plasma concentration

Tubular reabsorption includes passive and active mechanisms

- Substance through tubular epithelial membrane into renal interstitial fluid → through peritubular capillary membrane back into blood
- Active transport
    - Sodium-potassium ATPase pump
    - Solutes can be transported through epithelial cells or between cells
        - Transcellular and paracellular pathway
    - Primary active transport through the tubular membrane is linked to hydrolysis of ATP
        - Sodium diffuse from tubule into cell because of negative charge (Na-K pump) and because of electric gradient → in interstitial fluid by active transport against concentration gradient via Na^+-K^+ pump → into peritubular capillaries by ultrafiltration due to hydrostatic and colloid osmotic pressure gradients
    - Secondary active reabsorption through the tubular membrane
        - Co transport: one substance like sodium with concentration gradient takes glucose against its gradient with in the cell, energy released from Na^+
    - Secondary active secretion into tubules
        - Counter transport: 2 substances against each other downhill and uphill movement, sodium hydrogen exchanger
    - Pinocytosis – an active transport mechanism for reabsorption of proteins
    - Transport maximum for substances that are actively reabsorbed
        - Transport maximum: exceeding of capacity
        - Appearance of glucose in the urine at the threshold occurs before the transport maximum is reached
    - Substances that are actively transported but do not exhibit a transport maximum
        - Some others need no transport carrier but are dependent on other things like electrochemical gradient, permeability of membrane, time
- Passive water reabsorption by osmosis is coupled mainly to sodium reabsorption
    - Water follows solutes, diffuses by tight junctions,
- Reabsorption of chloride, urea, and other solutes by passive diffusion

Reabsorption and secretion along different parts of the nephrons

- Proximal tubular reabsorption
    - 65% reabsorption of water and sodium; also amino acids, glucose $HCO3^-$,
    - Proximal tubules have a higher capacity for active and passive reabsorption
        - Many mitochondria for active transport, increased surface for solute uptake
        - First sodium reabsorbed by co transport with glucose, amino acids later with chloride ions
    - Concentrations of solutes along the proximal tubule
        - Concentration of sodium relatively constant
        - Amino acids, glucose decrease strongly
        - Creatinine-urea concentration rises slightly
    - Secretion of organic acids and bases by the proximal tubule
        - Fast removal of toxins, drugs
- Solute and water transport in the loop of Henle
    - Descending part: high permeable to water 20% moderate to solutes, hyperosmotic
    - Ascending limb: impermeable to water → concentration of urine
    - Thick segment: active absorption of Na^+, Cl^-, K^+, 25%, Na^+-K^+ pump, 1 Na^+ 2 Cl^- co-transporter, counter transport sodium up, hydrogen out, fluid becomes very dilute due to impermeability to water
- Distal tubule
    - First part, macula densa, solute uptake but impermeable to water → diluting segment, hypoosmotic
    - 5% of sodium with chloride, chloride channels, thiazide diuretics inhibit Na+-Cl^- co transporter
- Late distal tubule and cortical collecting tubule
    - Principal cells reabsorb sodium and secrete potassium
        - Na^+-K^+ pump, potassium in cell and then concentration gradient in tubule
        - Potassium-sparing diuretics act on principal cells → prevent sodium absorption
    - Intercalated cells secrete hydrogen and reabsorb bicarbonate and potassium ions

    - Summary: almost no reuptake of urea; reabsorption of sodium controlled by aldosterone and secretion of potassium; acid, base regulation due to secretion of hydrogen ions; ADH for water uptake
- Medullary collecting duct
    - Final processor, ADH controls water, urea is reabsorbed (for concentrate urine), secretion of hydrogen ions → acid base balance
- Summary of concentrations of different solutes in the different tubular segments
    - Ratio of water and solute reabsorption, < 1 → more solutes in ratio than water is absorbed → dilution
    - Inulin is not secreted or reabsorbed → measure ratio of water loss

Regulation of tubular reabsorption

- Glomerulotubular balance – the ability of the tubules to increase reabsorption rate in response to increase tubular load
- Peritubular capillary and renal interstitial fluid physical forces
    - Normal values for physical forces and reabsorption rate

Reabsorption = K^+ x net re-absorptive force

    - Due to huge colloid osmotic pressure in capillary from proteins
        - Same forces as usually; 12,4 ml/min/mmHg x 10 ml = 124 ml/min
    - Regulation of peritubular capillary physical forces
        - Peritubular capillary hydrostatic pressure is influenced by the arterial pressure and resistance of the afferent and efferent arterioles
        - Colloid osmotic pressure of peritubular capillaries is determined by the systemic plasma colloid osmotic pressure, pressure increases by higher filtration fraction = increase GFR / or decrease renal plasma flow → more filtration concentrates proteins in glomerulus
        - Reabsorption decreases = by decreasing efferent and afferent resistance or by increasing arterial pressure
        - Reabsorption increases = by increasing colloid peritubular capillary pressure, increase filtration fraction, higher arterial plasma colloid pressure
    - Renal interstitial hydrostatic and colloid osmotic pressures
        - Back-leak due to increases interstitial hydrostatic pressure reduces reabsorption
- Effect of arterial pressure on urine output – pressure natriuresis and pressure diuresis
    - Increased arterial pressure → increases urinary outflow
    - Reduced angiotensin II → reduced water and sodium reabsorption
- Hormonal control of tubular reabsorption
    - Need of independent control of each solute
    - Aldosterone increase sodium reabsorption and stimulates potassium secretion
        - Aldosterone acts on principal cells → stimulates Na^+-K^+ pump → increases sodium absorption and potassium secretion, increases sodium permeability
        - Stimulated by exes of potassium and angiotensin II
    - Angiotensin II increases sodium and water reabsorption
        - Stimulation of aldosterone; constrict efferent arterioles; directly stimulates sodium absorption stimulation of Na^+-K^+ pump, sodium hydrogen exchange, sodium-bicarbonate co transporter
        - Without retention of metabolic waste products
    - ADH increases water reabsorption
        - ADH binds to V2 receptors in late distal tubules → formation of cAMP → protein kinase → aquaporins 2

    - Atrial natriuretic peptide decreases sodium and water reabsorption
        - Atria cells because of stretch secrete → atria natriuretic peptide (ANP) → inhibit water and sodium uptake, inhibit renin → increase urine excretion
    - Parathyroid hormone increases calcium reabsorption and (phosphate, magnesium)
- Sympathetic nervous system activation, increases sodium reabsorption
    - Constriction renal arterioles; decrease sodium and water excretion by acting on alpha adrenergic receptors

Use of clearance methods to quantify kidney function

- Renal clearance of a substance is the volume of plasma that is completely cleared of the substance by the kidneys per unit time

Clearance rate of a substance x plasma concentration of substance = urine concentration of that substance x urine flow rate
c = u x v/p

- Creatinine not 100% correct because little amount is secreted
- If substance is completely cleared from plasma

Chapter 31

Diuretics, kidney diseases

Diuretics and their mechanism of action

- Diuretics: substance which favors increase output of urine
- Decreasing sodium reabsorption → sodium and water loss natriuresis and diuresis
- Osmotic diuretics decrease water reabsorption by increasing osmotic pressure of tubular fluid
- Loop diuretics decrease active sodium-chloride-potassium reabsorption in the thick ascending loop of Henle
    - Block co transporter, most powerful
- Thiazide diuretics inhibit sodium-chloride reabsorption in the early distal tubule
    - Block sodium-chloride co transporter
- Carbonic anhydrase inhibitors block sodium bicarbonate reabsorption in the proximal tubules
- Competitive inhibitors of aldosterone decrease sodium reabsorption from and potassium secretion into the cortical collecting tubule
- Diuretics that block sodium channels in the collecting tubules decrease sodium reabsorption

Chapter 28

Urine concentration and dilution

Regulation of extracellular fluid osmolarity and sodium concentration

Kidneys excrete excess water by forming dilute urine

- Ability to regulate water excretion independently of solute excretion
- Antidiuretic hormone controls urine concentration
    - ADH secretion determines if kidney excrete dilute or concentrated urine
- Renal mechanisms for excreting dilute urine
    - Vary between 50-1.400 mOsm/L
    - Tubular fluid remains isosmotic in the proximal tubule
    - Tubular fluid is diluted in the ascending loop of Henle → regardless of ADH fluid leaving early distal tubular segment is hypo-osmotic
    - Tubular fluid in distal and collecting tubules is further diluted in the absence of ADH

Kidneys conserve water by excreting concentrated urine

- Body must excrete 600 mOsm/Day → minimal urine excretion is 0,5 L/Day

- Urine specific gravity → the more concentrated the urine thy higher the urine specific gravity
- Requirements for excreting concentrated urine – high ADH levels and hyperosmotic renal medulla
    - Interstitium hyperosmotic due to: countercurrent mechanism
- Countercurrent mechanism produces a hyperosmotic renal medullary interstitium
    - Normal are 300 mOsm/L in plasma and interstitial fluid
    - In kidney medulla 1.200-1.400 mOsm/L
        - Active transport of solutes of the thick ascending limb of Henle into medullary interstitium, from collecting ducts, urea from collecting ducts, not so much water diffusion
    - Special characteristics of loop of Henle that cause solutes to be trapped in the renal medulla → because they take sodium up but no water
    - Steps involved in causing hyperosmotic renal medullary interstitium
        - Repetitive reabsorption of sodium chloride by the thick ascending loop of Henle and continued inflow of new sodium chloride from the proximal tubule into the loop of Henle is called countercurrent multiplier → sodium chloride reabsorbed from the ascending loop of Henle keeps adding to the newly arrived sodium chloride multiplying concentration
- Role of distal tubule and collecting ducts in excreting concentrated urine
    - Large amounts of water are reabsorbed into the cortex helps to preserve the high medullary interstitial fluid osmolarity
- Urea contributes to hyperosmotic renal medullary interstitium and formation of concentrated urine
    - Urea 40-50% to renal medullary interstitium
    - Water is reabsorbed → concentration of urea increases → concentration gradient and urea transporters cause medulla to diffuse into interstitial space
    - Recirculation of urea from collecting duct to loop of Henle contributes to hyperosmotic renal medulla
        - Excretion of urea determined by concentration in plasma and GFR
        - Urea leaves in proximal tubule, thin descending and ascending limb of Henle and in medullary collecting duct but only if ADH is present in large amounts
        - Diffuses in interstitium several times in order to form a hyperosmotic renal medulla
- Countercurrent exchange in the vasa recta preserves hyperosmolarity of the renal medulla
    - Low blood flow in medulla helps to minimize solute loss from medullary interstitium; vasa recta serve as countercurrent exchangers minimizing washout of solutes from the medullary interstitium
    - Maintain medullary hyperosmolarity
    - Water diffuses faster in proximal vasa recta so at distal slope blood flow is slow
    - Increased medullary blood flow reduces urine concentrating ability
        - Vasodilators wash out solutes and reducing urine concentration
- Summary of urine concentrating mechanism and changes in osmolarity in different segments of the tubules
    - Proximal tubule water and solutes→ 300 mOsm
    - Descending loop of Henle → osmolarity increases, more water uptake when ADH is high water absorption 1.200 mOsm
    - Thin ascending loop of Henle → dilution, decreases due to solute uptake
    - Thick ascending loop of Henle → dilution 100 mOsm impermeable to water but high uptake of solutes
    - Early distal tubule → dilution, 50 mOsm
    - Late distal tubule and cortical collecting tubules → concentration depends highly on ADH
    - Inner medullary collecting ducts → concentration depend highly on ADH
    - Hyperosmotic medullary interstitium is required for maximal urine concentration ability

Quantifying renal urine concentration and dilution free water and osmolar clearances

Disorders of urinary concentration ability

- Nephrogenic diabetes insipidus → no respond to ADH

Control of extracellular fluid osmolarity and sodium concentration

- Estimating plasma osmolarity from plasma sodium concentration
    - 94% of solute in extracellular compartment is sodium

Plasma osmolarity = 2.1 x Na^+ concentration

    - Osmorecetor ADH system and thirst mechanism regulate the concentration of sodium and osmolarity of extracellular fluid

Osmoreceptor ADH feedback system

- Water deficit → extracellular osmolarity rises causes osmoreceptor cells to shrink → signals to pituitary gland → release ADH → in blood and increases water permeability of later tubules
- ADH synthesis in supraoptic and paraventricular nuclei of the hypothalamus and ADH release from posterior pituitary
    - Hypothalamus contains two types of magnocellular neurons that synthesize ADH in the supraoptic and paraventricular nuclei of the hypothalamus
    - Ca^{2+} influx due to AP → change of membrane → release
- Stimulation of ADH release by decreased arterial pressure and or decreased blood volume
    - ADH also released by baroreceptor reflex (decreased blood pressure), cardiopulmonary reflex (decreased blood volume)
- Quantitative importance of osmolarity and cardiovascular reflexes in stimulating ADH secretion
    - ADH secretion is affected mainly by changes in plasma osmolarity
- Other stimuli for ADH secretion

Importance of thirst in controlling extracellular fluid osmolarity and sodium concentration

- Central nervous system centers for thirst
    - 3^{rd} ventricle and others called thirst center, respond to hypertonic salt solutions, osmoreceptors
- Stimuli for thirst
    - Increased extracellular fluid osmolarity → which causes intracellular dehydration in the thirst centers
    - Decrease in extracellular fluid volume and arterial pressure also stimulates thirst
    - Angiotensin II
    - Dryness of mouth and mucous membranes of esophagus
- Threshold for osmolar stimulus of drinking
    - Even 2 mEq/L activates threshold for drinking
- Integrated responses of osmoreceptor-ADH and thirst mechanism in controlling extracellular fluid osmolarity and sodium concentration
    - ADH and thirst mechanism more relevant then aldosterone

Salt appetite mechanism for controlling extracellular fluid sodium concentration and volume

- Primary stimuli that increases salt appetite are those associated with sodium deficits and decreased blood volume or decreased blood pressure

Chapter 29

Renal regulation of potassium, calcium, phosphate, and magnesium

Integration of renal mechanisms for control of blood volume and extracellular fluid volume

Regulation of extracellular fluid potassium concentration and potassium excretion

- Potassium must keep stable, cell could store or excrete potassium → first line of defense, main regulator kidney
- Regulation of internal potassium distribution
    - Most of excess potassium moves quickly into cells
    - Insulin stimulates potassium uptake into cells
    - Aldosterone increases potassium uptake into cells → stimulated by excess potassium
    - β-adrenergic stimulation increases cellular uptake of potassium like epinephrine
    - Acid-base abnormalities can cause changes in potassium distribution → hydrogen ion reduce activity of Na^+-K^+ pump
    - Cell lysis causes increased extracellular potassium concentration
    - Strenuous exercise can cause hyperkalemia by releasing potassium from skeletal muscle
    - Increased extracellular fluid osmolarity causes redistribution of potassium from the cells to extracellular fluid → water out→ cell K concentration rises→ K^+ follows water
- Overview of renal potassium excretion
    - Determined by GFR, reabsorption, secretion
    - GFR constant, 65% in proximal tubule and 30% in thick a Henle
    - Daily variations in potassium excretion are caused mainly by changes in potassium secretion in distal and collecting tubules
        - Principal cell of late distal tubules secrete the excess K^+ but could also reabsorb in hypokalemia
- Potassium secretion by principal cells of late distal and cortical collecting tubules
    - Principal cells: uptake from interstitium by Na^+-K^+ pump → passive diffusion by concentration gradient into tubule by channels
    - Control of potassium secretion by principal cells are Na^+-K^+ pump and electrochemical gradient and permeability
    - Intercalated cells can reabsorbed potassium during potassium depletion against hydrogen
- Summary of factors that regulate potassium secretion: plasma potassium concentration, aldosterone, tubular flow rate, and hydrogen ion concentration
    - Increased extracellular fluid potassium concentration stimulates potassium secretion
        - By activation of Na^+-K^+ pump and diffusion; increased extracellular K^+ increases K^+ gradient from renal interstitium fluid to interior of epithelial cell reduces back leakage of K^+ from inside cells through basolateral membrane; increase K^+ stimulates aldosterone
    - Aldosterone stimulates potassium secretion of principal cells, increase also permeability
    - Increased extracellular potassium ion concentration stimulates aldosterone secretion → small changes in K^+ cause large changes in aldosterone
    - Blockage of aldosterone feedback system greatly impairs control of potassium concentration
        - Addison disease: no aldosterone,
    - Increased distal tubular flow rate stimulates potassium secretion
        - If K^+ is secreted into tubule→ concentration increases→ reducing diffusion → but with increase tubular flow K^+ is flushed away so increase in flow = increase in K^+ secretion
        - High Na^+ decreases aldosterone→ decrease K secretion but increases also fluid flow which counterbalance and increase K secretion
    - Acute acidosis decreases potassium secretion by reducing Na^+-K^+ pump
        - But chronic acidosis leads to loss of potassium because inhibit Na^+ c reabsorption → increase fluid flow→ increase K^+ secretion
    - Beneficial effects of a diet high in potassium and low in sodium content

Control of renal calcium excretion and extracellular calcium ion concentration

- PTH regulates plasma calcium concentration by bone reabsorption, activation of vitamin D, and directly increasing renal tubular calcium absorption
- Control of calcium excretion by the kidneys
    - Is filtered and reabsorbed but not secreted
    - Just 50% can be filtered and 99% of this is reabsorbed (65 proximal, 30 Henle)
    - Proximal tubular calcium reabsorption: dissolved and between cells just 20% transcellular first by diffusion then by active calcium ATPase pump and Na^+-Cl^- countertransport
    - Loop of Henle and distal tubule calcium reabsorption mainly by paracellular, transcellular by PTH stimulation
    - Factors that regulate tubular calcium reabsorption
        - In proximal tubule independent of PTH like Na^+ and water
        - Increased plasma phosphate stimulates PTH, acidosis, low blood pressure, low extracellular fluid volume
- Regulation of renal phosphate excretion
    - Max amount of phosphate reabsorption, if not present all is absorbed
    - Proximal tubule absorb 80%, 10% excreted
    - PTH increases tubular phosphate reabsorption is decreased and more phosphate is excreted

Control of renal magnesium excretion and extracellular magnesium ion concentration

- 50% in bones, 50% in cells just 1% free, kidneys just excrete 10-15%,
- Primary reabsorption is by loop of Henle
- Magnesium excretion due to: increased mg extracellular concentration, extracellular volume expansion, increased extracellular calcium concentration

Integration of renal mechanisms for control of extracellular fluid

- Sodium intake and excretion are precisely matched under steady-state conditions
- Sodium excretion is controlled by altering glomerular filtration or tubular sodium reabsorption

Importance of pressure natriuresis and pressure diuresis in maintaining body sodium and fluid balance

- Pressure diuresis: increased blood pressure increased urinary excretion
- Pressure natriuresis: increased blood pressure increased sodium excretion
- Pressure natriuresis and diuresis are key components of a renal-body fluid feedback for regulating body fluid volumes and arterial pressure
    - Increase fluid → accumulation of fluid in body → increase blood volume and extracellular volume → rising mean circulatory filling pressure → raises pressure gradient for venous return → elevates cardiac output → rises arterial pressure → rise in urinary secretion
- Precision of blood volume and extracellular fluid volume regulation

Distribution of extracellular fluid between the interstitial spaces and vascular system

- Extracellular fluid and blood volume controlled together
- Accumulation in interstitium → increased capillary hydrostatic pressure; decreased plasma colloid pressure; increased permeability; obstruction of lymph vessels

Nervous and hormonal factors increase the effectiveness of renal-body fluid feedback control

- Sympathetic nervous system control of renal excretion: arterial baroreceptor and low-pressure stretch receptor reflexes
    - Blood loss → constriction renal arterioles → decrease GFR; increased tubular reabsorption of sodium water; stimulation of renin
- Role of angiotensin II in controlling renal excretion → retain sodium and water
    - Importance of changes in angiotensin II in altering pressure natriuresis
        - Inability to suppress angiotensin II formation when there is excess sodium reduces the slope of pressure natriuresis and makes arterial pressure very salt sensitive

    - Excessive angiotensin II does not usually cause large increases in extracellular fluid volume because increased arterial pressure counterbalances angiotensin-mediated sodium retention (if there is no heart and kidney failure)
- Role of aldosterone in controlling renal excretion
    - Absorption of water, sodium
    - Excretion of potassium
    - During chronic over-secretion of aldosterone, the kidneys escape from sodium retention as arterial pressure rises and excrete more sodium
- Role of ADH in controlling renal water excretion
    - Excess ADH secretion usually causes only small increases in extracellular fluid volume but large decreases in sodium concentration
        - High ADH do not cause major increases of either body fluid volume or arterial pressure
        - High ADH can cause severe reductions in extracellular sodium ion concentration
            - Because excess water dilutes sodium and sodium is excreted due to high pressure
- Role of atrial natriuretic peptide in controlling renal excretion
    - ANP from right atrium → increase in GFR and decrease in sodium reabsorption, loss of water

Integrated responses to changes in sodium intake

- High sodium intake suppresses antinatriuretic systems and activates natriuretic systems
    - Increase in extracellular fluid
    - Activation of low-pressure receptors reflexes that originate from stretch receptors in right atrium and pulmonary vessels → decrease tubular sodium reabsorption
    - Suppression of angiotensin II formation by increased arterial pressure → decrease sodium reabsorption
    - Stimulation of natriuretic systems ANP → increased sodium excretion
    - Small increases in arterial pressure → pressure natriuresis

Conditions that cause large increases in blood volume and extracellular fluid volume

- Increased blood volume and extracellular fluid volume caused by heart diseases → reduce CO → reduce pressure → sodium retaining → maybe pulmonary edema
- Increased blood volume caused by increased capacity of circulation

Conditions that cause large increases in extracellular fluid volume but with normal blood volume

- By leakage of fluid and protein into interstitium
- Nephritic syndrome – loss of plasma proteins in urine and sodium retention by the kidneys
    - Glomerular capillaries filter is damaged → loss of plasma → low colloid osmotic pressure → water in interstitium → edema
- Liver cirrhosis – decreased synthesis of plasma proteins by the liver and sodium retention by the kidneys

Chapter 30

Acid-Base Regulation

H^+ concentration is precisely regulated

- Enzymes influenced by H^+ concentration

Acids and bases – their definitions and meanings

- Molecules that can release H^+ are acids
- Base: molecule that accepts H^+, like hemoglobin
- Strong and weak acids and bases
    - Strong acids release quickly H^+ like HCL in solution
    - Strong base takes up H^+ quickly
- Normal H^+ concentration and pH of body fluids and changes that occur in acidosis and alkalosis
    - Normal pH is 7,4; low pH = high H+ concentration

- Acidosis and alkalosis, venous blood 7,35 due to more CO_2
- Defending against changes in H^+ concentration: buffers, lungs and kidneys
- Chemical acid base buffer systems oft he body fluids which immediately combine with acid or base to prevent excessive changes in H+ concentration
- Respiratory center regulate removal of CO_2
- Kidneys can excrete acidic or alkali urine
- → Buffer system keep H^+ locked; respiratory eliminate CO_2 and therefore H_2CO_3 → finally kidneys eliminate excess acid or base
- Buffering of H^+ in the body fluids
- Buffer is substance which binds reversely H^+
- Bicarbonate buffer system
- Contains weak acid H_2CO_3 and bicarbonate salt $NaHCO_3$
  - $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^- + Na^+$
- CO_2 decrease inhibits respiration and decreases rate of CO_2 expiration
- Henderson Hasselbach equation

$$pH = 6,1 + \log HCO_3^- / 0,03 \times pCO_2$$

- Metabolic alkalosis → increase in $H_2CO_3^-$
- Bicarbonate buffer system is he most important extracellular buffer
- Phosphate buffer system
- Important for renal tubular fluid (because it becomes greatly concentrated there, and more on optimal operating pH) and intracellular fluid (same here)
- $H_2PO_4^-$ and HPO_4^{2-}
- pK of 6,8 operates near optimal buffer power
- Proteins are important intracellular buffers
- Diffusion of elements oft he bicarbonate buffer system causes the pH in intracellular fluid to change when there are changes in extracellular
- Most buffering is inside the cell
- Respiratory regulation of acid-base balance
- 2nd line of defense against acid base disturbance is control of extracellular fluid CO_2
- Increase ventilation in CO_2 reduces H^+ concentration
- Pulmonary expiration of CO_2 balances metabolic formation of CO_2, increased ventilation decreased pCO_2
- Increasing alveolar ventilation decreases extracellular fluid H^+ concentration and raises pH
  - CO_2 increases→ H_2CO_3 and H+ increase → lowering pH
  - pH can change a lot from respiration
- Increased H^+ concentration stimulates alveolar ventilation
  - Respiratory compensation for an increase in pH is not nearly as effective as the response to a marked reduction in pH
  - Feedback control of H^+ concentration by the respiratory system
    - Increase H^+ → increase ventilation → lower pCO_2
  - Efficiency of respiratory control of H^+ concentration
    - If pH falls respiration can return a little bit but not to previous value
  - Buffering power oft he respiratory system
    - Stronger then chemical buffer the physiologic buffer respiration
  - Impairment of lung function can cause respiratory acidosis
- Renal control of acid base balance
- Continuous secretion of H^+ and HCO_3^-; more H^+ pH rises
- Losing HCO_3^- is like adding H^+
- Nonvolatile acids can not be excreted by lungs
- All bicarbonate is reabsorbed
- Kidneys regulate extracellular fluid H^+ concentration through three mechanisms: (1) secretion of H^+;

(2) reabsorption of filtered HCO_3^-; production of HCO_3^-

- Secretion of H^+ and reabsorption of HCO_3^- by the renal tubules
- Except in thin limb, 90% in proximal,
- H^+ is secreted by secondary active transport in early tubular segment with Na
    - Every H^+ in tubular HCO_3^- enters blood
- Filtered HCO_3^- is reabsorbed by interaction with H^+ in the tubules
- HCO_3^- is titrated against H^+ in the tubules
- Primary active secretion of H^+ in the intercalated cells of late distal and collecting tubules

Combination of excess H^+ with phosphate and ammonia buffers in the tubule generates new HCO_3^-

- Excess H^+ kidney absorb and generate new HCO_3^-
- Phosphate buffer system carries excess H^+ into the urine and generates new HCO_3^-
    - More effective in tubular fluid
    - H^+ plus other buffer 1 additional HCO_3^-
- Excretion of excess H^+ and generation of new HCO_3^- by the ammonia buffer system
    - For each NH_4^+ excreted new HCO_3^- in blood added
    - Chronic acidosis → dominant mechanism is NH_4^+

Quantifying renal acid-base excretion

- Regulation of renal tubular H^+ secretion
    - The most important stimuli for increasing H^+ secretion by the tubules in acidosis are (1) an increase in pCO_2 of the extracellular fluid in respiratory acidosis and (2) an increase in H^+ concentration of the extracellular fluid decrease pH respiratory or metabolic acidosis
    - Increase H^+ secretion: increase pCO_2; high H^+; angiotensin II, aldosterone, hypokalemia; decrease in extracellular fluid volume

Renal correction of acidosis – increased excretion of H^+ and addition of HCO_3^- to the extracellular fluid

- Respiratory acid-base disorders are initiated by increase or decrease in pCO_2
- Metabolic disorders are initiated by increase or decrease in HCO_3^-

Renal correction of alkalosis – decreased tubular secretion of H^+ and increased excretion of HCO_3^-

Clinical causes of acid- base disorders

- Respiratory acidosis results from decreased ventilation and increased pCO_2
    - Caused by abnormal function of the lungs, hypoventilation
- Respiratory alkalosis result from increased ventilation and decreased pCO_2
    - High altitudes,
- Metabolic acidosis result from decreased extracellular fluid HCO_3^- concentration
    - Caused by diarrhea loss of kali;
- Metabolic alkalosis results from increased extracellular fluid HCO_3^- concentration
    - Cause by vomiting loss of acid;
- Sodium bicarbonate increase HCO_3^- against acidosis
- Ammonium chloride → cause HCL

Lectures

- Consomic animals → backcrossing linking the phenotype to a gene
- Transgenic animals → carrying a foreign gen
- Knock out animals → deactivate gen

Lecture 5

- Cell surface receptors→ peptide hormones, catecholamines
- Agonist imitate but productive; antagonist same but inactive
- Activates by PKA → CREB = cAMP response element binding protein→ CREB Binding Protein
- β1 in myocardium accelerator
- β2 dilation in lungs and vessels
- α receptor vasoconstriction
- Ca^{2+} as second messenger transported out or in mitochondria
- Ligand activated receptor → phosphorylated by GRK BARK → docking of arrestin → inactivation
- Acetylcholine mostly used by parasympathetic nervous system equal to cholinergic
    - Postganglionic sympathetic adrenergic mostly α norepinephrine
- All preganglionic fibers sympathetic and parasympathetic are cholinergic
    - Parasympathetic postganglionic also cholinergic
    - Sympathetic postganlionic adrenergic (exception sweat glands, piloerrector)
- Acetylcholine receptors: nicotine (between pre and postganglions); muscarinic parasympathetic postganglionic;
- Adrenergic receptors: α and β receptors