Fluid Physiology

Body Fluids and Membrane Transport:

Body Fluids: Account for 50-70% of body weight.
- **Total Body Water:** (specific values in ~70kg human)
  - 1/3 Extracellular Fluid (14L)
    - 20% Plasma (3L)
    - 80% ISF (11L)
  - 2/3 Intracellular Fluid (28L)
- **Blood volume:** includes plasma volume and volume occupied by blood cells (blood cell volume/BV = hematocrit).
  - The hematocrit is normally about 45%.
- **Osmolality:** osmoles/kg H₂O
- **Osmolarity:** osmoles/L

Electrolyte Distribution:
- Ionic composition of plasma and ISF are similar (separated by highly permeable capillaries).
  - Plasma contains proteins, ISF does not.
- ECF and ICF differ markedly in ionic composition (separated by poorly permeable plasma membrane).
  - **Primary Cation:**
    - ECF = Na⁺
    - ICF = K⁺.
  - **Primary Anion:**
    - ECF = Cl⁻ and HCO₃⁻
    - ICF = phosphates and proteins.

Transport:
- **Permeability:**
  - **Flux:** Flux (J) across a membrane = number of molecules (or moles) crossing the unit area in the unit time.
    - \[ J = P (C_1 - C_2) = P \Delta C \]
    - \( P = \text{permeability} \)
    - \( P = \frac{D \beta}{X} \)
      - \( D = \text{diffusion coefficient} \)
      - \( \beta = \text{Partition coefficient} \)
      - \( \frac{\text{Solubility}_{\text{Lipid}}}{\text{Solubility}_{\text{Water}}} \)
      - \( X = \text{thickness of membrane} \)
  - **Solutes of small size (high D) and hydrophobic (lipid soluble \( \beta \) have a high permeability across lipid bilayer. But, most solutes of physiological interest are either large polar (hydrophilic- \( \beta \)) molecules or charged (ions, very hydrophilic), and have low permeability across lipid bilayer.
    - Note that simply diffusion is only effective over very short distances: 1micron = 5 seconds; 1cm = 14 hours
- **Transporters** (integral membrane proteins embedded in the lipid bilayer) mediate the movement of most solutes across the plasma cell membrane
  - **Channels:** \( \# \) rate of translocation (~1million ions/sec) and \( \# \) accessibility of binding sites.
    - contain a conducting pore that can be accessed by ions from either side of the membrane simultaneously.
      - **Selectivity:** structure and charge
      - **Gating:** open/closed determined by polarization (voltage gated), ligand gating, structural/mechanical gating, or constitutive activity (leak channels)
        - **Channel movement is always determined by the net driving force.**
  - **Carrier Proteins:** \( \# \) rate of translocation (~1000 ions/sec).
    - Contain 1+ binding site in ECF and in ICF that couples with conformation \( \Delta \) to facilitate movement in the direction of the driving force (facilitated, not active diffusion)
      - **3 steps:**
        - (1) Binding of solute
        - (2) Conformation \( \Delta \) of carrier protein
        - (3) Dissociation of solute
  - **Active Transport/Pumps:** couple the input of energy to translocation of solute (e.g. hydrolysis of ATP) Solute can be transported uphill by the carrier (active transport).
    - \( \text{Na}/\text{K} \) ATPase: 3 Na⁺ out of cell for 2 K⁺ in per ATP molecule.
    - Maintains \( \text{Na} \) and \( \text{K} \) and contributes to membrane potential and maintenance of cell volume.
Factors Influencing Membrane Transportation:
  • Δc: Differences of concentration
  • ΔΨ: Differences of electrical potential (influence of ionic charge, z)
  • Δp: Differences of hydrostatic pressure (important with regard to water flow)
    o Thermodynamics: \( \frac{\Delta \mu}{F} = 58 \log \frac{c^{\text{out}}}{c^{\text{in}}} + z_i \Delta \Psi \)
      ▪ \( \Delta \mu = \) electrochemical potential difference; \( z_i = \) valence; \( \Delta \Psi = \) electrical potential difference.
      ▪ The coefficient 58mV converts to 61mV at 37°C.
        ▪ \( \Delta \mu_i = 0 \) (thermodynamic equilibrium of species \( i \))
        ▪ \( \Delta \mu_i \neq 0 \) (absence of thermodynamic equilibrium of species \( i \))
    o Thermodynamic Equilibrium: equation reduces to Nernst: \( \Psi = \frac{(58/z_i) \log (c^{\text{out}}/c^{\text{in}})}{\mu} \) (\( \Delta \mu_i = 0 \))
      ▪ The value of \( \Delta \Psi \) at equilibrium is the “equilibrium potential” (\( E_{\text{Ni}} \) and \( E_{\text{K}} \)).
    o Water Flow: \( \Delta \mu_w = RT \ln (c^{\text{in}}/c^{\text{out}}) + \frac{v}{n} (p^{\text{out}}-p^{\text{in}}) \)
      ▪ \( z_w = 0 \), \( v \): no electrical force; \( v \): \( \mu_w = \) chemical not electrochemical potential; \( v = \) volume; hydrostatic pressure (p) of water is not negligible.
      ▪ \( \Delta \mu_w \neq 0 \) \( \implies \) water flow, where \( J_w \alpha \Delta \mu_w \).
        ▪ Flow can be due to hydrostatic pressure (filtration), concentration (osmosis), or both.
          ▪ Osmosis occurs from a region of high to a region of low water concentration and from a region of low to a region of high total solute concentration, or osmolality.
            ▪ If one of two baths separated by a membrane is pure water, the value of \( \Delta p \) that makes \( \Delta \mu_w \) equal to zero is called the osmotic pressure of the solution and is generally indicated by the symbol \( \pi \). (The component of osmotic pressure attributable to large protein molecules is generally referred to as colloid osmotic or oncotic pressure)
              ▪ van’t Hoff Equation: \( \Pi = RT \bar{C}_s \)
            ▪ Water moves from \( \uparrow \) \( \Downarrow \) hydrostatic pressure, and from \( \Downarrow \) \( \uparrow \) higher osmotic pressure. Movement of water into the solution builds up a hydrostatic pressure difference that opposes continuing flow. When \( \Delta p \) becomes equal to \( \Delta \pi \), flow =0.
              ▪ Transcapillary fluid flow: \( J_w \alpha (\Delta P - \Delta \Pi_{\text{osm}}) \)
o **Gibbs-Donnan Equilibria:** Presence of large molecules of protein or other highly charged solutes that cannot permeate biological membranes and, therefore, cannot equilibrate can yield states of partial equilibration. Permeant solutes and water can come to equilibrium, but their equilibrium concentrations, as well as equilibrium osmotic pressure and membrane electrical potential differences, will be influenced by the presence of the charged impermeant species.

- **Macroscopic Electroneutrality:** Although existence of an electrical potential difference across a membrane requires an excess of electrical charge at one surface and a deficit at the other, from a macroscopic point of view this discrepancy is usually very small.

<table>
<thead>
<tr>
<th>Initial</th>
<th>Equilibrium</th>
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<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5Na⁺</td>
<td>10Na⁺</td>
</tr>
<tr>
<td>10Cl⁻</td>
<td>4Cl⁻</td>
</tr>
<tr>
<td>5 Protein</td>
<td>5 Protein</td>
</tr>
</tbody>
</table>

Permeant ions will move until they are all at equilibrium, and the electrochemical potential difference across the membrane will be zero for each permeant ion. At equilibrium: \([Na^+]_1[Cl^-]_1 = [Na^+]_2[Cl^-]_2 \rightarrow [5+x][x] = [10-x][10-x] \rightarrow \) where \(x = 4\); restriction of protein movement has resulted in a concentration difference (and osmotic pressure difference) across the membrane, with \(\pi_1/\pi_2 = Na_1 + Cl_1 + \text{Protein}_1)/(Na_2 + Cl_2) \rightarrow (9 + 4 + 5)/(6 + 6) = 1.5\) times as many solute particles on side 1 as on side 2. The tendency of the Gibbs-Donnan effect to induce an osmotic pressure difference across membranes is usually compensated for by the action of membrane ion pumps that maintain ions at levels at which osmotic equilibration can occur without cell swelling.

**Rule:** The region containing the impermeant solute has higher osmotic pressure and a negative electrical pressure.

- **Coupling Solute-Solvent Flow** *(Solvent Drag/Electroosmosis):* Flowing solvent will tend to carry along all solute species.

  - **Reflection Coefficient** \((\sigma)\):
    - \(\sigma = 1\) = reflection = impermeant
    - \(\sigma = 0\) = no reflection = permeant (solute/solvent permeance is equivalent).
    - When \(\sigma < 1\), equilibrium is not reached until solute and water movements have made solute concentrations and hydrostatic pressures equal on opposite sides of the membrane.

  - **Reciprocal Interaction:** just as solvent flow influences solute flow, so also will solute flow influence solvent flow.

    - \(J_{\text{solute}} = (1 - \sigma_{\text{solute}})C_{\text{solute}}J_{\text{solvent}}\)
      - If \(\sigma = 1\), \(J_{\text{solute}} = 0\) (complete reflection)
      - If \(\sigma = 0\), \(J_{\text{solute}} = 1\) (no reflection)

  Positive osmotic pressure difference moves \(H_2O\) toward region of higher [solute]. Higher osmotic pressure is \(\therefore\) counteracted by solvent drag. Complete reflection is osmotically preferable.

- **Effective osmotic pressure** \((\Delta\pi_{\text{eff}})\): \(\Delta\pi_{\text{eff,i}} = \sigma_i RT\Delta c_i\)

- **Iso-osmotic Flow:**

  - **Active Solute Transport**
    - Cell
    - Interstitium
    - Capillary
    - \(\sigma_s = 3\); \(\therefore\) \(H_2O\)
    - Follows solute by effective osmotic pressure
    - \(\uparrow\) hydrostatic pressure
    - Leaky barrier with \(\uparrow\) hydraulic conductivity

  Solute is actively transported out of the cell (1) into the interstitium (2) and passively transported out of (2) into capillaries (3). Membrane (a), representing the cell basolateral membrane, has a high value of \(\sigma\), whereas \(\sigma\) of membrane (b), representing the capillary wall, is near zero. Active transport of solute raises the solute concentration in compartment (2) above that in (1), and the resulting effective osmotic pressure (with respect to membrane a) causes a volume flow from (1 to 2). The elevated solute
concentration in (2) does not, however, induce volume flow from (3 to 2), because the effective osmotic pressure difference across membrane ‘b’ is nearly zero, because σ is nearly zero. Since compartment (2) is closed, volume flow from (1 to 2) leads to an increase in hydrostatic pressure in (2) and this pressure in turn causes a volume flow from (2 to 3) across the leaky barrier, which has a high hydraulic conductivity. The net result could be a brisk volume flow from (1 to 3) even with a small osmotic pressure difference between these two compartments. This model is expanded to the concept that the osmotic pressure between the lumen and ISF of the kidney and of the small intestine is much more effective at moving water than the smaller osmotic pressure difference between ISF and capillaries that may result from solute deposit in ISF. This is NOT active transport per se, but instead internal osmotic and hydrostatic pressure gradients effect on transepithelial \( H_2O \) flow.

**Fluid Movement:**
- The process of movement of water from a solution in which its activity (concentration) is higher to one in which its activity is lower is called **osmosis**. The osmolality of an aqueous solution is defined as the number of osmoles of solute (i.e., moles of solute particles) dissolved in 1 kilogram of water.
- **Colligative properties** (depend on the number of solute particles per unit volume, rather than the size, molecular weight, or chemical nature of the particles) include vapor pressure, freezing point and boiling point. Osmolality (in osmols/kg) of any solution is given by its freezing point depression divided by 1.86. Osmolality of most body fluids is very near 285 m-osm/kg. (For convenience the normal osmolality is often said to be about 300 m-osm/kg.) Osmolality, expressed in m-osm/kg, can be calculated approximately by doubling the serum Na⁺ concentration, expressed in m-Eq/L.
  - **Isotonic:** Cells maintain normal volume
  - **Hypertonic:** Solution causes shrinkage
  - **Hypotonic:** Solution causes swelling.
    - \( H_2O \) crosses cell membranes readily [from regions of \( \downarrow \) → \( \uparrow \) osmolality (or osmotic pressure)]. RBCs in solutions of \( \downarrow \) osmolality swell → **hemolysis**.

**Muscle Anatomy and Molecular Mechanisms:**
**Structure:**
- **Sliding Filament Theory:** During muscle contraction, thick and thin filaments slide past one another and do not themselves shorten.
  - Cross-bridges project from the thick filaments, and in a cyclic and repetitive process, attach to and advance along thin filaments. The hydrolysis of ATP generates the force of contraction.

Note: Cardiac muscle has banding pattern (a la striated skeletal muscle) but cells are mono- or bi-nucleated. Conversely, smooth muscle has no banding (structure is not as regimentally organized). Shortening of muscle is accomplished by sliding of thin filaments further into the array of thick filaments. The A-band contains thick myosin filaments; the I-band (bisected by the Z-line) includes regions of thin (actin containing) filaments that are outside the A-band; the H-zone is that part of the A-band in which there is no overlap of thin and thick filaments. During muscle shortening, the greater overlap of thin and thick filaments causes a decrease in the width of both the I-bands and H-bands. Decrease in sarcomere length occurs without a change of thick or thin filament length. Thick Filaments are bipolar, creating a mirror image, allowing “contra-motion.” Titin serves as an elastic connection between the thick filaments and Z-lines. Nebulin lies flat along thin filaments, and is a “ruler” determining TF length.

**Excitation-Contraction Coupling:**
- Regulation of muscle activity is under the control of the muscle plasma membrane (sarcolemma).
  - Depolarization of the sarcolemma leads to an AP propagating over the surface of the muscle cell. The electrical signal is carried deep into the cell via surface invaginations, transverse tubules (t-tubules). The propagated AP is carried via **voltage dependent Na⁺ channels**.
    - Without t-tubules, muscle cells are too thick for complete propagation.
    - t-tubules are “hotspots” for conduction, but Ca²⁺ is the trigger of contraction
      - The t-tubular membrane is in close apposition to the SR.
        - When depolarization begins, the sarcoplasmic reticulum releases Ca²⁺. When depolarization ends, Ca²⁺ release stops, Ca²⁺ is returned to SR, and muscle relaxes. Ca²⁺ is the trigger of contraction.
        - Contraction is triggered within milliseconds of the action potential
• depolarization of the t-tubule affects an **L-type Ca\(^{2+}\) channel** (dihydropyridine receptor [DHPR]) in the t-tubule membrane that is physically coupled to a Ca\(^{2+}\) channel in the membrane of the SR (the ryanodine receptor RyR1).
  o **In skeletal muscle**, the L-type Ca\(^{2+}\) channel undergoes a conformational change acting as a voltage sensor. This change triggers opening of the SR Ca\(^{2+}\) channel (RyR1).
  o **In cardiac muscle**, influx of Ca\(^{2+}\) from the ECF (extra-cellular fluid) through the cardiac DHPR is the trigger for Ca\(^{2+}\) release through the SR ryanodine receptor (type RyR2).
  - Ca\(^{2+}\) is resequpered into the SR by active transport by the Ca\(^{2+}\)-ATPase pump in the SR membrane.
  - Large amounts of Ca\(^{2+}\) can be stored in the SR, because much of it is bound to a high-capacity, low-affinity Ca\(^{2+}\)-binding protein (*calsequestrin*), which buffers the ion. The removal and lowering of the sarcoplasmic free Ca\(^{2+}\) cause relaxation. Injection of Ca\(^{2+}\) into a muscle is sufficient to initiate contraction in all muscles. The cross-bridge cycle is modulated by changes in the sarcoplasmic concentration of Ca\(^{2+}\).

**Crossbridge-Thin Filament Interactions:**
  o **Myosin**: the primary component of thick filaments. Rod-like tail (shaft of thick filament) and two globular heads (form crossbridges). Aggregate in a bipolar orientation, allowing crossbridges to move in direction of H-zone. Composed of two heavy chains and four light chains (two types – one molecule of each is present on each myosin head). Crossbridges emerge from thick filaments in a helical fashion at \(\sim143\,\text{Å}\) intervals.
  o **Actin**: the primary component of thin filaments. A globular protein that associates to form a double-stranded helix; it is actin to which myosin crossbridge attaches.

In rigor, bridges bind actin tightly at an angle. No ATP – crossbridges maximally attached and highly flexed (4\(^{5}\)). In relaxation (no Ca\(^{2+}\), but ATP present), crossbridges all detached from actin, and are at 90\(^{0}\) angles to filament. The mass of the thin filament relative to that of the thick filament is greatest during rigor, is reduced in contracting muscle and is even less in resting muscle. During contraction, crossbridges move, attach to and detach from actin in an asynchronous manner, which is thought to provide for gradual shortening and to prevent slippage of the filaments under tension.

**Lymn-Taylor Muscle Contraction:**
  o Myosin is an ATPase, contained in the globular head (S-1). Interaction of actin and myosin can account for the ATPase activity.

1. ATP binds to the myosin crossbridge (M) and causes it to dissociate from actin (A) and to assume a ~90\(^{0}\) position with respect to the thick filament axis; 2. hydrolysis of ATP further energizes the crossbridge; 3. in the presence of Ca\(^{2+}\) the energized crossbridge binds to actin; 4. the attached crossbridge changes its configuration and pulls the thin filament toward the center of the sarcomere. This step is associated with the displacement of products of hydrolysis. Binding of ATP to the crossbridge dissociates it from actin (1) so that it can begin another cycle.
**Ca\(^{2+}\) Regulation of Actin-Myosin Interactions:**

- Regulation of the actomyosin interaction in skeletal and cardiac muscle is governed by complexes of troponin and tropomyosin.
  - Purified actomyosin splits ATP in the absence of Ca\(^{2+}\). Thus the troponin-tropomyosin complex confers calcium dependency. The complex acts by inhibiting the actomyosin ATPase in the absence of calcium (troponin, specifically, binds calcium).
  - Troponin is a complex of three protein subunits:
    - **Troponin-I**: inhibits ATPase activity of actomyosin
    - **Troponin-C**: binds calcium, releasing inhibition
    - **Troponin-T**: links TN-I and TN-C to tropomyosin
  - Tropomyosin normally binds actin. In the absence of calcium, it blocks actin’s myosin binding site, providing steric hinderence. In the presence of calcium, Ca\(^{2+}\) binds TN-C, and the bond between TN-I and actin is broken, and tropomyosin can move to its equilibrium position. Therefore troponin induces a conformation change in tropomyosin, exposing the myosin binding site on actin.
  - Tropomyosin and Troponin bind only actin, and not myosin.
    - **One troponin binds one tropomyosin, and this complex binds seven (7) actin monomers (~400 Å interval).**
  - Calcium (via troponin) induces a change in the position of tropomyosin on the thin filament that exposes the myosin binding site on actin. When cross-bridges attach to the filament (active state or rigor state) they nudge the tropomyosin molecule (TM) even further away from the myosin binding site. Dotted circle represents position of tropomyosin during the relaxed state where it blocks myosin docking.

<table>
<thead>
<tr>
<th>Muscle Activity</th>
<th>Without Calcium</th>
<th>With Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Muscle</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Homogenized Muscle</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>A + M (no Tm/TN)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>A + M + TN</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>A + M + Tm</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>A + M + Tm + TN-T</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>A + M + Tm + TN-T + TN-I</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>A + M + Tm + TN-T + TN-I + TN-C</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

**Calcium binding is the key in removing the inhibitory effects of TN-I.**

- Since tropomyosin lies along the entire length of the thin filament, the troponin effect is mediated by tropomyosin.
- **Mechanism:** Calcium activation causes movement of tropomyosin from a peripheral inhibitory position on the filament surface toward a more central location. This uncovers myosin binding sites on the actin that were sterically blocked by tropomyosin such that myosin cannot enter into a crossbridge-ATPase cycle. The binding of calcium to troponin, therefore, apparently causes it to move the tropomyosin and expose the S-1 binding sites on actin so that contraction can occur.

**Ca\(^{2+}\) Regulation in Smooth Muscle:**

- ATPase activity is slower in smooth muscle.
- Activity is regulated by myosin light-chain subunits, indirectly influenced by Ca\(^{2+}\) concentration.
  - The ATPase of smooth muscle myosin is activated by phosphorylation of specific myosin light chains by MLCK. MLCK is in turn regulated by Ca\(^{2+}\)-Calmodulin. When Ca\(^{2+}\) levels are low, myosin is dephosphorylated by endogenous kinases (see smooth muscle section)
  - **There is no Troponin or Tropomyosin in smooth muscle**
<table>
<thead>
<tr>
<th>Muscle Type</th>
<th>Structure/Organization</th>
<th>ATPase Activity</th>
<th>Crossbridge Cycling Time</th>
<th>Contraction Velocity</th>
<th>Ca²⁺ Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal (Fast)</td>
<td>Sarcomeric</td>
<td>High</td>
<td>Fast</td>
<td>Fast</td>
<td>Troponin/Tropomyosin</td>
</tr>
<tr>
<td>Skeletal (Slow)</td>
<td>Sarcomeric Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Troponin/Tropomyosin</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Sarcomeric Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Troponin/Tropomyosin</td>
</tr>
<tr>
<td>Smooth</td>
<td>Non-Sarcomeric</td>
<td>Low</td>
<td>Slow</td>
<td>Slow</td>
<td>Calcium-Calmodulin</td>
</tr>
</tbody>
</table>

**Smooth Muscle Characteristics and Regulation:**

**Characteristics:**
- **Greater Contraction Length**: Smooth muscle can contract 200-300x length (skeletal muscle can only contract 20-30x length).
- **Side Polar Conformation**: Side polar conformation with all cross-bridges on one side allows more efficient sliding.
- **Slow Contraction Velocity**: Decreased contraction velocity and decreased cross-bridge formation rate provides for more economic use of ATP (decreased actinomyosin ATPase rate); due to a different myosin isoform from skeletal muscle.
  - **Compromised speed for strength**
- **Neutral Tonic Activity**: Never fully contracted (tetanic) nor relaxed (off), due to the Ca/Calmodulin regulatory mechanism.
- **Comparable Force Generation** to skeletal muscle.
- **Long thin filaments**: Longer thin filaments than skeletal muscle, and TF are attached to dense bodies and are therefore not restricted by collisions with Z-bands during contraction.
- **Degree of tension of smooth muscle depends on the level of myosin phosphorylation**.

**Regulation:**
- **Agonist**: (i.e. E/NE → α receptor) → ↑ Rho•GTP → ↑ Rho-kinase activity → ↑ myosin phosphatase phosphorylation → ↓ myosin phosphatase activity → ↑ myosin light chain phosphorylation → ↑ contractility.
- **Antagonist**: (i.e. NO → cGMP) → ↑ PKG activity → ↓ Rho-kinase activity → ↓ myosin phosphatase phosphorylation, → ↑ myosin phosphatase activity → ↓ light chain phosphorylation → ↓ contractility
  - **OR**: E/NE → β receptors → ↑ cAMP → ↑ PKA activity → phosphorylation of myosin light chain kinase (MLCK) → inhibition of MLCK → no phosphorylation of MLC → no contraction
- **Latch-State**: Tonic contraction due to slow cycling or non-cycling of crossbridge attachments (“latched” on actin in a rigor-like state). **Tension maintained without energy expenditure.**

**Muscle Mechanics:**

**Isometric Contraction**: Muscle can develop tension, but cannot shorten because it is fixed at both ends.
- **Tetanic versus Twitch Contractions**: A single depolarization will yield an isometric twitch.
**Latent Period:** The time of activation: (1) AP sweeps through membrane, (2) Ca\(^{2+}\) release and diffusion from SR, (3) TN-C – Ca\(^{2+}\) binding, (4) Tm changes conformation to expose myosin binding site.

**Refractory Period:** Considerably shorter than mechanical event. Therefore muscle can be restimulated before relaxation is complete.

**Mechanical Summation:** Second stimulation before complete relaxation yield higher peak tension of contraction.

**Tetanic Contraction:** Smooth, sustained contraction at maximum tension capability for a given length (peak tension strength ~3-4x individual twitch) resulting from high frequency (fusion frequency) of stimulation. During fused tetanus, sarcoplasmic levels are constant. Calcium concentrations in a twitch are similar to that of tetanic contraction (maximal), thus calcium does not limit twitch contraction. Instead, the time of an action potential/twitch is not sufficiently long to fully extend the series elastic component (SEC).

The series elastic component (2-3% of muscle length) represents the elements that support active tension [thin filaments, crossbridges (also function as the contractile element), Z-bands, etc.], and the parallel elastic component represents titin. When the muscle contracts, there is no external shortening (fixed at both ends in an isometric contraction), small internal changes in length cause the SEC components to elongate until their tension can support the applied force. As tension is applied, the forces pull the z-bands toward each other, but when the muscle is fixed, it cannot shorten (equal and opposite forces). This action-reaction mechanism is coupled at every sarcomeric junction. When the SEC is maximally extended, the tension represents the maximum contractile force: **tetanic contraction**. Therefore, in a single twitch, the contractile component is activated to briefly for the developed tension to reach full tetanic tension. Furthermore, twitch tension is less than tetanic tension, in part, because during a twitch, not all of the crossbridges have had time to attach to thin filaments. If SEC is replaced by a rigid object, tetanic levels are reached immediately (therefore the SEC allows modulation of tension).

**Effects of Length on Striated Muscle Tension:**

- **Passive Relationship:** Elasticity is found in active (contracting) muscle and in passive (resting) muscle. Titin serves the role of passive elasticity, by keeping the thin filament centered with respect to thin filaments and Zlines.
  - The SEC only develops tension when the muscle is activated.
  - When a relaxed muscle is stretched, the Z-lines move away from each other (length increases) and Titin develops tension (of recoil).
  - **When resting muscle is rapidly stretched, muscle tension rises. However, the initial tension response decreases exponentially with time to a lower stable value (stress relaxation).**
    - Titin is therefore visco-elastic.
  - Smooth muscle has greatest stretch relaxation, and cardiac muscle the least.

- **Active Relationship:** The maximum isometric force a muscle can generate is a function of length. At a given length, the **total tension developed is the sum of active and passive tensions.**
  - The length at which maximum active tetanic tension can be developed is the rest length \(L_0/L_{max}\). At rest length, there is optimal thick filament crossbridge interaction with thin filaments (without Zband obstruction).
  - At longer lengths, fewer crossbridges overlap. At shorter lengths, Z-bands collide (reducing active tension by providing a force opposing shortening).
Smooth Muscle: (see smooth muscle section): Smooth muscle can develop 50% of its maximum tension at lengths \(0.6L_{\text{max}}\) where active force development of skeletal/cardiac muscle is negligible. Smooth muscle can operate over wide ranges of lengths (down to \(0.3L_{\text{max}}\)).

Isotonic Contraction: Muscle shortens while carrying a load, and during the action, tension is approximately equal to the load (if lifted at a constant velocity).

- Following a stimulus, crossbridges pull on thin filaments, extending SEC until tension in the muscle equals the weight of the load. Further pulling by the crossbridges causes the load to be lifted.
  - **Preload**: The passive (resting) tension in muscle. Determined by tension in Titin
  - **Afterload**: The load lifted.

After stimulation (A) crossbridges, which go through attachment, pulling, detachment cycles with actin, cause *stretch of elastic elements that bear active tension*. Elastic elements are elongated (A to B) until the **tension equals the weight of the load** (B). Tension greater than the load causes it to be lifted. During shortening (C), if the load is lifted at constant velocity, the tension in the muscle will equal the weight of the load.

- **Influence of Load on Shortening Profile**:
  - (1): *Latent period \(\alpha\) load* (takes time to build isometric tension to a level equal to the load).
  - (2): *Amount of Shortening \(1/\alpha\) load*.
  - (3): *Maximum velocity of shortening \(1/\alpha\) load*.
Energy Supply:

- ATP is the primary source of energy for muscle contraction. ATP is buffered by creatine phosphate (PCr) (held in equilibrium with ATP by the transphosphorylating enzyme creatine phosphokinase (CPK). Phosphocreatine stores are limited. If O₂ supply is limited, ATP is produced from anaerobic glycolysis. Equilibrium constant for CPK reaction is ~20, and therefore ATP will be regenerated from PCr until concentration is depleted.

Hemodynamics and the Cardiovascular System:

Heart Overview:

- The heart is composed of two pumps in series. One is low pressure (pulmonary circulation) and one is high pressure (systemic circulation).
  - **Systole**: Ventricular Contraction. Ejection of blood into arteries at relatively high pressures.
  - **Diastole**: Ventricular Relaxation. Recoil of arterial walls propels blood toward the capillaries and back into the heart (acting as a compression chamber).
    - Blood pressure is pulsatile in the aorta and large arteries. Small arteries and arterioles dampen the pressure of pulsation, and it is nearly absent in capillaries.

Hemodynamics:

- Compliance (C) = \( \frac{\Delta V \text{ (volume)}}{\Delta P \text{ (pressure)}} \)
- \( Q \text{ (flow)} = \frac{(P_A - P_B)}{R} \text{ (frictional resistance)} \)
- \( P = \frac{F}{A} \)
- \( \rho (h \cdot A) \cdot g = \rho g h \)
- \( E_T = E_P + E_K + E_g + E_R \rightarrow E_K = \frac{1}{2} \rho v^2; \ E_g = \rho gh; \ E_P = \text{lateral (static) pressure}; \ E_R = \text{energy lost to resistance (friction)} \)

- **Resistance**:
  - Poiseuille’s Law: \( Q = \frac{\Delta P \pi r^4}{8\eta L} \rightarrow R = \frac{8\eta L}{\pi r^4} \)
    - As the resistance is inversely proportional to the 4th power of the radius, changes in vessel radius are predominant in controlling flow through vascular beds.
  - **Fluid Velocity**:
    - \( V = \frac{Q}{A} \)
    - Primarily dependent upon diameter of vessel and its influence on lateral pressure.
    - Because of conservation of mass, flow at any given point of a rigid tube
is constant. If area is reduced in a segment of tube, velocity in that segment will be greater than in wider segments (in tubes, $A = \pi r^2$ and the velocity will be inversely proportional to the square of the radius). $E_K \uparrow$, $E_R \uparrow$, and $E_F \downarrow$.

- **Resistance in Parallel and in Series:**
  - **Parallel:** Adds: $R_T = R_1 + R_2 + R_3$ …
  - **Series:** Adds One-over: $R_T = 1/R_1 + 1/R_2 + 1/R_3$ …
    - Flow through vessels in series must be the same, but each of those in parallel only receives a portion of total flow.
    - Total Peripheral Resistance is determined by the sum of the resistances of each segment of the circuit (from aorta $\rightarrow$ SVC/IVC). Each segment contributes resistance based upon the local individual resistances of vessels.
      - $TPR = (P_A - P_{RA}) / Cardiac Output$. – Right atrial pressure is nearly zero. Thus…
        - $TPR = P_A / Cardiac Output$

- **Streamline (laminar) and Turbulent Flow:**
  - Velocity is distributed parabolically in vessels (fastest in center and ~zero along walls).
  - Becomes turbulent (fluid flows in a random pattern forming eddy currents that mix fluid and increase resistance especially after passing through constrictions.
  - **Reynolds Number ($R_e$):** $R_e = \frac{(Density)(Diameter)(Velocity)}{Viscosity} \leftrightarrow [(Density)(Diameter)(Velocity) / Viscosity]
    - $R_e = >3,000 = turbulent flow$
    - $R_e = 2,000-3,000 = transitional flow$
    - $R_e = <2,000 = laminar flow$
      - turbulence produces bruits and sounds of Korotkoff (murmurs).
      - lowering of blood viscosity in anemia may lead to turbulent flow and murmurs.

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**Electrophysiology of the Heart:**

**Autorhythmicity:** Specific cells located in pacemaker regions spontaneously excite themselves at regular intervals (specialized muscle cells)

- **Pacemaker Cells (nodal):**
  - Initiate APs that are later conducted to entire heart
  - Poorly developed contractile capability.
  - Slow conduction velocity.

**Conduction:**

- **Conduction Cells (purkinje fibers)**
  - Rapid conduction of activity through ventricular walls.
  - Poor contractile power.
  - Poor ability of spontaneously activity.

**Contractility:**

- **Contractile Tissue (atrial and ventricular)**
  - High degree of contractile power.
  - No tendency for spontaneous activity.

**Pacemaker Potentials:**

- *SA node and AV node contain spontaneously activated pacemaker cells* (purkinje cells contain limited spontaneous activity as well).
- **Pacemaker potentials** differ from non-pacemaker cardiac potentials.
  - Primary difference is the slow membrane depolarization in diastole that culminates in the generation of an AP. Membrane is NEVER completely at rest, and are always poised for depolarization.
  - Slow depolarization occurring between discharges is called the pacemaker potential.
    - **Lower (less negative) MRP** (maximum diastolic membrane potential) due to a relatively high resting permeability to Na+ ions, which tends to maintain the membrane potential away from $E_K$.
    - Overall time course of APs is slower than that of atrial muscle.
Ionic Generation of Pacemaker Potential: (No voltage gated Na\(^+\) channels)

- during diastolic period, \(g_K\) increased during repolarization, turns off slowly. Decrease in \(g_K\) (reduced K\(^+\) efflux) unmasks any inward currents and results in depolarization. The inward current is carried by Na\(^+\) and later by Ca\(^{2+}\).
  - Early in the pacemaker potential, inward current is carried by Na\(^+\) through a proton-channel (Na\(^+\)/K\(^+\) primarily) opened by repolarization (negative voltages), the funny current (I\(_f\)). Near the end of the pacemaker potential, voltage gated Ca\(^{2+}\) channels open.

- Cardiac Action Potentials:
  - Depolarization is initiated by the pacemaker cells in the SA node (slow conduction - 0.05 m/s) \(\rightarrow\) spreads through atria (faster - 0.8-1.0 m/s) \(\rightarrow\) reaching AV node \(\rightarrow\) conducting bundle (Bundle of His – fast – 2-4 m/s) \(\rightarrow\) Purkinje fibers \(\rightarrow\) L + R bundle branches along interventricular septum (the first aspect of the ventricles to be activated) \(\rightarrow\) L + R endocardial surfaces \(\rightarrow\) endocardial cells \(\rightarrow\) epicardial cells \(\rightarrow\) base of heart.
    - The time course and shape of action potentials differ significantly in different parts of the heart (pacemaker regions, conducting fibers, atrial cells and ventricular cells).

- Two classes of APs: Nodal and Conduction/Muscular.
- Atrial AP has lower amplitude and less defined plateau than ventricular AP.
- Cells in SA node and AV node are similar. These cells are small and create small APs (conduct slowly).
  - Conduction from atria \(\rightarrow\) ventricles is via AV node only.
- All conduction in cardiac muscle is via electrical synapses (gap junctions).
- AV Delay: Because AV conduction is slow, atrial contraction is completed before ventricles contract.
  - AV conduction is one-directional and is rate-limiting (180-220/min – heart block).

Cardiac APs in Non-Pacemaker Cells:

- Non-pacemaker cells have large resting membrane potential (-90 mV – close to \(E_K\)) due to high resting permeability to K\(^-\) and a low permeability to Na\(^-\).
  - **Phase 0**: Rapid depolarization from MRP that overshoots that approaches +20 to +30 mV.
    - Voltage gated Na\(^+\) channels opened (\(g_{Na^+}\) ↑). Some K\(^-\) channels closed. Enhances inward flow of Na\(^-\).
  - **Phase 1**: Rapid repolarization to ~zero (begins plateau)
    - Rapid inactivation (closing) of Na\(^+\) channels (\(g_{Na^+}\) ↓). Some K\(^-\) channels re-opened.
  - **Phase 2**: Very slow repolarization (plateau – lasts 200-400 msec)
Rapid depolarization in Phase 0 opens Ca\(^{2+}\) channels (open very slowly) → influx of Ca\(^{2+}\) ions (these channels are voltage inactivated but much more slowly than Na\(^{+}\) channels). Progressive, slow increase in gK.

**Phase 3:** Rapid repolarization to MRP (ends plateau).
- Ca\(^{2+}\) channels mostly closed (g\(_{Ca}\) ↓). K\(^{+}\) channels open → K\(^{+}\) efflux → repolarization.

**Phase 4:** Diastolic interval between successive action potentials (atrial & ventricular filling).
- The action potential in all parts of the heart lasts for a significant fraction of a second (200-500 msec), in contrast with those recorded in nerve fibers and skeletal muscle (a few milliseconds).
- Very long Absolute Refractory period and very short Relative Refractory period.
  ▪ Therefore cells do not become excitable again until the AP is essentially terminated. The long refractory period prevents re-excitation until contraction is complete. Tetanic contractions are thus impossible (beneficial, as tetanic contraction would make it impossible for the heart to fill).

**While in skeletal muscle, the AP is a trigger for mechanical activity, in cardiac muscle, the AP lasts almost as long as the contraction, serving as a trigger and a modulator of magnitude and duration.** Duration of contractile activity α duration of contractile stimulus, and specifically, α length and height of plateau phase
  - The plateau phase varies under changes in physiological conditions.
    ▪ Period of contraction (emptying) = systole
    ▪ Period of relaxation (filling) = diastole

**Autonomic Effects on Heart Rate:** The ANS can modulate heart rate via action upon the AV node.
- Sympathetic stimulation → ↑ heart rate
  - increases the rate of rise of the pacemaker depolarization without change in MRP or threshold. Shortens the interval between APs, and therefore AP shortens (maintains diastolic filling time). ↓ interval duration
- Parasympathetic (vagal) stimulation → ↓ heart rate.
  - increases maximum diastolic potential (more negative) and decreases the rate of rise of the pacemaker potential.
    ▪ Acetylcholine, released by the vagus, increases membrane permeability to K\(^{+}\), thereby enabling the membrane to approach E\(_K\) more closely (hyperpolarization).

**Contraction and Calcium:**
- (1) During the initial stages of AP, intracellular Ca\(^{2+}\) is raised by the influx of extracellular Ca\(^{2+}\)
- (2) Influx of Ca\(^{2+}\) triggers the release of Ca\(^{2+}\) from the sarcoplasmic reticulum (SR) [L-type Ca\(^{2+}\) channel – DHPR]
- (3) Shortly after the peak, uptake of Ca\(^{2+}\) by the SR begins, but the [Ca\(^{2+}\)] does not drop below the level needed for contraction, because of the steady influx of Ca\(^{2+}\) during the plateau. At the end of the plateau, Ca\(^{2+}\) influx stops, Ca\(^{2+}\) pumping continues, [Ca\(^{2+}\)] drops below the contraction threshold, and the muscle relaxes. The AP thus not only triggers the contraction but also controls its magnitude and duration.

**Heart Sounds:**
1st: Closure of the AV valves at the beginning of ventricular systole. (The mitral valve component of the sound is best heard in the 5th intercostal space in the midclavicular line. The tricuspid valve component is best heard in the 5th intercostal space to the left of the sternum.)
2nd: Closure of the semilunar valves at the onset of ventricular diastole. (The aortic valve contribution to this sound is best heard in the second intercostal space to the right of the sternum. The pulmonic valve contribution is best heard in the second intercostal space to the left of the sternum.)
3rd: Vibrations of ventricular walls with rapid filling.
4th: Atrial systole.
Electrocardiography:
The body acts as a volume conductor: currents, produced by potential differences generated in the body, are conducted through body fluids and can be measured at the skin. The ECG can detect rhythm, conduction, and ventricle size. The dipole (a vector) created by membrane depolarization is “moving.” Positivity at the positive electrode (and negativity at the negative electrode) causes an upward deflection.

Vectors: The lead axis is determined by the orientation of paired electrodes as related to the direction of impulse movement. Multiple axes are created by the use of multiple electrodes, and the summative axis is given by: \( V = V_{\text{max}} \cos \theta \). Therefore, through the use of multiple leads in various axes, ECG determines direction and timing of impulse conduction.

- Einthoven’s Triangle: Provides geometric determination of a vector from any two of three leads (each of which forms the sides of an equilateral triangle with the heart at its center).

Each small box = 1mm x 1mm. Speed = 25mm/sec. \( 1 \) small box = 0.04 s.

- P-wave: atrial excitation
- QRS complex: ventricular excitation
- T-wave: ventricular repolarization
- PR Segment: AV delay
- PR Interval: Atrial depolarization and AV Conduction. WNL = 3-5mm (0.12-0.20s). If PR Interval WNL and P wave 2.5mm (0.08-0.1s), in sinus rhythm. If PR Interval >0.2s, AV Block
- ST Segment: Plateau phase. All ventricle is at same electrical level.
- Maximal ventricular contraction.
- QRS Duration: Conduction system \( \cdot \). WNL = 0.08-0.1s. Abnormal speed or shape indicates a change in conduction system.
- QT Interval: Duration of ventricular systole (depolarization-repolarization cycle). WNL= 0.3-0.4s.
- R-R Interval: Time between beats. HR = 60/sec/min)/R-RInterval
- The U wave is an inconstant finding, believed to be due to slow repolarization of the papillary muscles.

The dipole is constantly shifting during depolarization and repolarization. The last myocardial fibers to be depolarized are the first to repolarize. Therefore T-wave is not a downward deflection. The wave of depolarization in the left ventricle spreads from the endocardium outward to the epicardium, and the endocardial fibers have a delayed onset of repolarization, and the wave of repolarization begins at the epicardial surface and spreads inward toward the endocardium (opposite the sequence of depolarization).

- Other Leads: In addition to the three bipolar leads, nine augmented unipolar leads are used.
  - 3 Unipolar Augmented Limb Leads: \( aV_a \) (right arm), \( aV_l \) (left arm), and \( aV_f \) (left leg)
  - 6 Unipolar Chest Leads: Record in the transverse plane to provide information about anteriorly and posteriorly directed cardiac vectors (arranged \( V_1 - V_6 \) from right sternal margin to left axilla.)
• **Axis Deviation and Estimation of Heart Rate:**
  - **Heart Rate:** If Q-Q (R-R) Interval is:
    - 1 division (0.2s) = 300/min
    - 2 divisions (0.4s) = 150/min
    - 3 divisions (0.6s) = 100/min
    - 4 divisions (0.8s) = 75/min
    - 5 divisions (1.0s) = 60/min
    - 6 divisions (1.2s) = 50/min
  - **Mean Electrical Axis:** Computed from summation of Limb Leads I (largest upward deflection) and III (largest downward deflection).
    - -30° -- +105° is considered WNL.
    - < -30° = Left Axis Deviation (hypertension, aortic stenosis, or other left ventricular defect).
    - >105° = Right Axis Deviation (COPD, Pulmonary Embolism, or other pulmonary hypertension).

**Cardiac Output:** Defined as the volume of blood flowing in the circulatory system during a given time. It is equal to the volume ejected either by the left or the right ventricle per unit time (L/min). The output of the two ventricles is equal.

- **Cardiac Output = Stroke Volume x Heart Rate.**
- **Stroke Volume = EDV – ESV**
- **Ejection Fraction = SV/EDV (~60-65% in normal adult)**

• Cardiac Output is directly proportional to body surface area (expressed CO/m² = Cardiac Index)). A person weighing 70Kg has a surface area of about 1.7 sq. meters. A mean CO of 5 liters/min yields a cardiac index of 5.0/1.7 = 3 liters/min/m².

• **Fick Principle:**
  \[ CO = \frac{(O_2 \text{ uptake by the lung in ml/min})}{(A – V) O_2 \text{ difference in ml O}_2/\text{ml of blood}} \]

**Regulation of Stroke Volume:**
- **Preload:** The maximum resting tension is equivalent to the End Diastolic Pressure (EDP).
  - Increasing P_a and V_R (i.e. increased venous return) results in increased ventricular stroke volume and, at constant heart rate, increase in cardiac output.
  - Total Peripheral Resistance = Aortic Pressure / Cardiac Output \( V=IR \rightarrow R = V/I \)
  - **Starling’s Law of the Heart:** \( SV \alpha EDV \). “The energy of contraction (i.e. of ventricular muscle) is a function of the length of the muscle fiber.” As EDV increases, the length of cardiac muscle fibers increases, as does passive pressure (the EDP).

- Left ventricular performance curves relate preload, measured by EDP (or EDV) to cardiac performance, measured by stroke volume or CO. Cardiac performance for an individual with ventricular dysfunction (lower curve) is also shown. Starling’s law demonstrates that the heart can compensate for decreased force capability by increasing EDV.
  - **As stretch of muscles increase, the affinity of TN-C for Ca^{2+} increases.**
  - **Preload \( \alpha \) Stroke Volume**
  - **Length \( \alpha SV \) Pressure \( \alpha EDV \) (EDV = Preload)**
  - Generally the heart is prevented from filling to a point at which potential becomes negative (see muscle overlap diagram), because the heart is a very stiff muscle. .: overfill is prevented and the passive tension curve is much steeper than in skeletal muscle (stress relaxation of cardiac muscle is thus very low).

- **Superimposed active (a) and passive (p) length tension curves for cardiac (solid lines) and skeletal muscle (dotted lines).**
  - Increasing the venous return (or the preload on the ventricle) results in stretching of the ventricular muscle. This results in increased active wall tension development, an increase in the pressure of blood within the ventricle chamber and a resultant increase in stroke volume.
  - **As stretch of muscles increase (increasing sarcomere length), the affinity of TN-C for Ca^{2+} increases by an unknown mechanism (causing greater activation of the contractile apparatus).** Influence of length on function is called autoregulation or heteromeric regulation.
**Contractility:** EDV is constant during exercise, yet stroke volume increases, thus a family of Starling curves must exist such increased force generation is possible at a given EDV.

- Stimulation of the sympathetic nerves to the heart or infusion of epinephrine results in a greater than normal stroke volume at any EDV (influence $[\text{Ca}^{2+}]_i$). These stimuli shift the cardiac function curve to the left and upward, so that at any given EDV a greater stroke volume will result. This increased force capability at a given EDV is described as an increase in cardiac contractility.
  - A mediator that increases or decreases cardiac contractility has, respectively, a positive or negative "inotropic" effect. Since a change in contractility is independent of a change in length (i.e. not muscle based), the regulation is "homeometric".

- $\Delta SV \propto \Delta \text{Contractility}$
  - Changes in contractility are of importance in regulating SV and CO. Sympathetic stimulation increases the force of ventricular contraction, and causes the ventricle to empty more completely. SV increases and the residual volume of blood in the ventricle, the ESV decreases. At rest, ventricular ejection fractions (EF) are about 50-67% of the end-diastolic volume; during exercise the EF can increase to 80%.
    - $\propto \uparrow \text{Contractility} \rightarrow \uparrow \text{Rate of Ejection} \rightarrow \uparrow \text{Pressure}_{LV}$
    - $\propto \uparrow \text{SV}/\text{EDV}$

### Effect of Epinephrine/Norepinephrine on Contraction and Relaxation of the Heart:
- E/NE binds to a $\beta_1$ receptor $\rightarrow \uparrow$ adenylate cyclase $\rightarrow \uparrow \text{cGMP} \rightarrow \uparrow \text{PKA} \rightarrow$ Phosphorylate Multiple Targets:
  - (1). Phosphorylation of voltage dependent $\text{Ca}^{2+}$ channel (L-type) in plasma membrane, $\uparrow g_{\text{Ca}} \rightarrow \uparrow \text{Ca}^{2+}$ release from SR $\rightarrow \uparrow$ activation of contractile apparatus.
  - (2). Phosphorylation inhibits Phospholamban (normally inhibits SR $\text{Ca}^{2+}$ pump) $\therefore$ SR reuptake of $\text{Ca}^{2+} \uparrow$.
  - (3). Phosphorylation of Troponin-I reduces affinity of TN-C for $\text{Ca}^{2+}$. Dissociation of $\text{Ca}^{2+}$ occurs more rapidly $\rightarrow$ inactivation of contraction.
  - (4). Phosphorylation of Titin decreases its stiffness ($\downarrow$ passive wall tension) $\rightarrow \uparrow$ filling of ventricle.
  - (5). Phosphorylation of Myosin Binding Protein C $\rightarrow \uparrow$ crossbridge cycling rate.
  - **NE/E increase speed and strength of ventricular contraction by increasing contractility, shortening the duration of the contractile response, increasing the crossbridge cycling rate, and facilitating ventricular filling. The interval-duration relationship is changed by E/NE (shorter AP with a higher amplitude).**

- Digitalis inhibits the $\text{Na}^+ - \text{K}^+$ ATPase pump $\rightarrow \uparrow [\text{Na}^+]_i$, $\rightarrow$ decreased driving force of $\text{Na}^+$ to power the $\text{Na}^+-$Ca$^{2+}$ exchanger. Ca$^{2+}$ levels remain high, and contractile force increases.

### Afterload:
- Afterload is equated with the aortic pressure (the force/area that opposes shortening of the ventricular myocytes).
  - Diastolic Pressure $1/\alpha \propto \text{Velocity of Shortening} \propto \text{Stroke Volume}$. 
During the isovolumetric phase of contraction, the pressure within the ventricular chamber rises until it reaches and slightly exceeds the arterial diastolic pressure. The semilunar valve opens and ejection begins.

- The higher the arterial diastolic pressure, the higher the ventricular pressure must be for valve opening and ejection to occur. Since the pressure within the left ventricular chamber at the onset of the rapid ejection phase of the cardiac cycle is nearly identical to the aortic diastolic pressure, the aortic pressure is considered the left ventricular muscle’s afterload;
  - The greater the load, the more slowly the cardiac muscle shortens. When aortic diastolic pressure †, ejection is delayed and the rate of ejection ‡.
  - If the duration of systole is unchanged, a slower ejection rate means that a smaller stroke volume is ejected.
  - The afterload therefore influences stroke volume (along with preload and cardiac contractility).


Pressure-Volume Relationships of Left Ventricle (EDPVR):
- Work = Force x Distance \( \Rightarrow \) Work = \( P \times V \) \( \Rightarrow \) Stroke Work = \( P \times SV \) [or \( P \times (EDV-ESV) \)].
- Minute Work = \( P \times SV \times HR \) \( \leftrightarrow \) Minute Work = \( P \times CO \)

Ventricular systole.
- **Isovolumetric contraction phase:** Begins shortly after ventricular excitation (QRS). A-V valves close, and ventricular pressure rises sharply. The first heart sound occurs, and is concurrent with the closure of the A-V valves. Atrial pressure increases slightly due to the A-V valves bulging backwards.
- **Ventricular ejection period:**
  - **Rapid ejection phase:** When pressure in the ventricle exceeds the aortic pressure (80 mm Hg), aortic valves open and blood is ejected into the aorta. Pressure in the ventricle rises steeply and exceeds that of the aorta very slightly. The blood flows rapidly through the aorta, and ventricular volume decreases accordingly. The atrial pressure falls due to the downward pull of the A-V ring as blood is ejected upward into the aorta. The atrial pressure then increases steadily due to venous return.
  - **Reduced ejection phase:** Aortic pressure is higher than that of the ventricle, but blood, because of its momentum, continues to flow into the aorta at a reduced velocity and causes further (though smaller) reduction of ventricular volume. The higher aortic pressure is due to the recoil forces of the stretched aorta (and large arteries) and coincides with the less forceful contraction of the ventricle. Both pressures continue to decline. Aortic pressure falls because

Note: (a) refers to the control loop.
- **Left:** † Preload & Fixed Afterload \( \leftrightarrow \) ‡SV
- **Center:** Fixed Preload & †Afterload \( \leftrightarrow \) ‡SV
- **Right:** † Contractility & Fixed Preload & Fixed Afterload \( \leftrightarrow \) ‡SV.

ESVPR = Starling curve (pressure represents maximum force the ventricle can generate at a given volume at that point in the cardiac cycle. At the end of the ejection phase, cardiac fibers are largely depolarized (not developing force).
the rate of flow out into peripheral vessels is greater than the rate of flow in during reduced ventricular ejection; ventricular pressure falls as more and more fibers begin to relax. (The major portion of the T wave (ventricular repolarization) is in this period.)

- **Ventricular diastole**
  - Isovolumetric relaxation phase: Ventricles relax and the reduction in pressure results in closure of the semilunar valves (2nd heart sound). Rebound of the elastic valves causes the dicrotic notch in the aortic pressure tracing. This period between the closure of the semilunar valves and the opening of the A-V valves is termed **isovolumetric diastole**; pressure drops markedly without any change in ventricular volume. Backflow of blood in the aorta after the aortic valves close is associated with some inward bulging of the valves, regurgitation through the aortic valves and flow into the coronary arteries. At the beginning of this phase the heart is already repolarized (see T wave).
  - Ventricular filling phase:
    - Rapid filling phase: Isometric relaxation phase ends when the ventricular pressure falls below the pressure in the atrium. The A-V valves open, and the ventricle begins to fill. Its volume increases rapidly, while the atrial pressure decreases. The aortic pressure continues to fall as the blood flows to the periphery (3rd heart sound)
    - Reduced filling phase: Increase in ventricular volume.
    - Atrial systolic phase: Further filling of only about 10-20% of the ventricular volume in a normal individual at rest. With exercise when the time for diastole is reduced, atrial contraction contributes a more significant fraction of ventricular volume. Atrial contraction also becomes important if a narrowing of an A-V valve (stenosis) increases resistance to flow between atrial and ventricular chambers.

- **Law of Laplace:**
  - Thin-walled vessels: Stretching pressure increases wall tension, until tension in an elastic wall is in equilibrium with the pressure exerting a force upon it.
    - \[ T = \frac{Pr}{2} \]
  - Thick-walled vessels: For thicker vessels, wall stress (\(\sigma\)) is tension (force) per unit area.
    - Wall Stress (\(\sigma\)) = \(\frac{Pr}{2h(\text{thickness})}\)
      - The more a vessel is filled, the greater the cardiac work required to empty it (SVxEDV).
        - To support or develop a given pressure, the wall stress required depends on the radius and on the wall thickness of the ventricle.
        - **Wall stress \(\sigma\) radius and \(1/\alpha\) wall thickness.** In chronic hypertension or aortic stenosis (obstruction), the compensatory ventricular wall thickening (hypertrophy) reduces the wall stress. In conditions of increasing ventricular radius, as might occur in systolic heart failure, the wall stress required to generate a given pressure increases.

**Circulation:**
- Small arteries and arterioles regulate flow to capillaries and serve as the **high pressure storage system.** By constricting (\(\uparrow\) resistance), they decrease flow. By dilating (\(\downarrow\) R), \(\downarrow\) Q. Endothelial walls of capillaries are the site of material exchange between blood and tissues (diffusion).
- Veins are thinner than arteries and are more distensible. They serve as the **volume storage system** (2/3 of total blood volume is in veins).
  - \(Q=\frac{\Delta P}{R}\) and \(C=\frac{\Delta V}{\Delta P}\)
    - Veins have relaxed volume (volume that can be contained without \(\uparrow\) pressure) 3-4x that of arteries. Veins are 56x more distensible (stretchable) than arteries.
      - **Specific Compliance\(\text{vein}\) = volume x distensibility.
    - Veins have 15-24x compliance of arteries.

**Arterial Blood Pressure:**
- During systole, large arteries expand during ejection to accommodate the SV (the actual change in arterial volume during ejection is about 50 – 70% of SV, as blood is flowing out of the artery into downstream vessels simultaneously). During diastole, elastic arterial walls recoil (without expenditure of energy) propelling remaining blood accommodated during systole through the circulation ("diastolic run off"). During systole \(Q_{in} > Q_{out}\) and volume and pressure increase. During diastole when \(Q_{in} = \text{zero},\) runoff continues and thus volume and pressure decrease.
Determinants of Arterial Blood Pressure: Volume and Compliance

Mean Arterial Pressure: 
\[ \text{MAP} = \frac{2}{3} (P_S - P_D) = CO \times TPR \]

- Because we spend more time in diastole than in systole.

\[ P_S \text{ = systolic BP, } P_D \text{ = diastolic BP, and } (P_S - P_D) \text{ = pulse pressure} \]

- Note that the above equation is physiologically wrong. It should be: \( \text{MAP} - P_{RA} = CO \times TPR \), but \( P_{RA} \) is usually \( \sim 0 \).

- CO and TPR influence volume.

Key of Compliance: Compliance defines the \( \Delta P \) for a given \( \Delta V \). Compliance is relatively constant, and \( \sim P \frac{1}{\alpha} V \)

- **Determinants of Arterial Blood Pressure: Volume and Compliance**
  - During systole, the ejected volume distends the aorta and aortic pressure ↓.
  - Peak pressure = aortic systolic pressure.
  - After ejection, \( P_v \) falls. When it drops below aortic pressure, the aortic valve closes (marked by the dicrotic notch).
  - During diastole, the aortic wall recoils, pushing the blood toward the periphery, and pressure continues to decline.
  - The trough of the pressure wave = diastolic pressure.
  - The difference between systolic and diastolic pressure is the pulse pressure.
  - Note that flow rate is constant even with a pulsating pressure because energy is stored in the walls of elastic vessels during systole, and that energy is used to drive arteriole → venous flow during diastole.

- **Mean Arterial Pressure:** \( P_D + \frac{1}{3} (P_S - P_D) = CO \times TPR \)
  - Because we spend more time in diastole than in systole.
  - Where \( P_S \) = systolic BP, \( P_D \) = diastolic BP, and \( (P_S - P_D) \) = pulse pressure
  - Note that the above equation is physiologically wrong. It should be: \( \text{MAP} - P_{RA} = CO \times TPR \), but \( P_{RA} \) is usually \( \sim 0 \).
  - CO and TPR influence volume.

- **Pulse Pressure is primarily determined by stroke volume.**
  - \( \Delta V = Q_{in} - Q_{out} \rightarrow \) If volume is constant, but ejection velocity ↑ (↓ time of runoff), a greater pulse pressure results.

  - Stroke volume \( \propto P_S \).
  - ↓ Ejection period (↑ ejection velocity) \( \rightarrow \) ↑ \( P_S \)
  - Decreases in aortic distensibility or compliance, (↑ age) \( \rightarrow \) ↓ pulse pressure for a given volume change.
  - \( TPR \frac{1}{\alpha} \) Rate of Runoff \( \rightarrow \) ↓ rate of decline of arterial volume and pressure. \( \rightarrow \) TPR \( \propto P_D \)
  - \( HR \propto P_D \) (↓ time for runoff between heartbeats.
  - In distal arteries the peak pressure may actually exceed that in the aorta. It should be noted, however, that the mean pressure (or total fluid energy) at sites distant from the aorta will always be less than that in upstream vessels so as to allow continued flow.

- Left: Compliance \( \text{Veins} \sim 20 \times \) that of arteries.
- Right: Distensibility or specific compliance (percentage of volume change per unit pressure) in a large artery and in a vein.
- High distensibility of the veins (A) at physiological pressures (<10 mmHg) compared with that of the arteries (B) at their normal pressures (75-150mmHg). At higher pressures, the distensibility of the arteries decreases (C).
- Note that pressure increases during systole because volume increases (ejection/SV) in arterial and then venous trees.
- Note that veins have greater distensibility but NOT 20 fold (actually \( \sim 6 \times \) that of arteries).
- Arterial compliance in older patients is severely decreased (for a given \( \Delta V \), a greater \( \Delta P \) must occur).
**Venous Return:** $P_V \sim 5$–$10$ mmHg; $P_{RA} \sim 0$–$2$ mmHg. In the steady state, cardiac output = total venous return (Starling’s Law) $\therefore Q_V = Q_A$ yet $P_V = 1/10 P_A$; venous resistance is very low.

| Venous Return: $CO = \frac{P_{A} - P_{RA}}{TPR} = \frac{P_{V} - P_{RA}}{R_{V} (\text{very low})}$ |

**Secondary Factors Influencing Venous Return:**
- **Skeletal Muscle Pumps:** Contraction of skeletal muscle raises tension around the soft walled veins and helps to propel venous blood toward the heart. During standing, slight rhythmic contractions of the muscle in the legs assist the venous return.
- **Respiratory Pump:** Intrapleural pressure becomes more negative during inspiration and descent of the diaphragm increases the intra-abdominal pressure. This drives pressure gradient between peripheral veins and the right atrium and promotes venous return.
- **Valves:** Ensure unidirectional flow towards the heart. Excess venous pressure and incompetence of these valves may lead to varicose veins.
- **Venomotor Tone:** Degree of contraction of smooth muscle in the walls of veins will influence venous compliance and the volume of blood contained within the venous system. Active venous wall tension $\Rightarrow$ venous pressure $\Rightarrow$ venous return. Venous compliance (relaxation) $\Rightarrow$ blood (pooling) in the venous system.
- **Downward Systolic Pull on Heart:** Systolic ejection $\Rightarrow$ heart drawn down $\Rightarrow$ atrial pressure (mechanical) $\Rightarrow$ venous return.
- **Gravity and Venous Pressure:** In a recumbent individual the difference in mean pressure between the aorta and downstream peripheral arteries is small. In a standing individual, hydrostatic pressure $\sim 90$ mmHg added to arterial and venous pressures in the feet. Lateral pressures (arterial and venous) in the head are reduced by $\sim 40$ mmHg. Pressure gradient between arteries and veins at the same level remains the same, $\therefore$ driving pressure gradients (differences in lateral pressures) between the arterial and the venous sides are constant.
  - Under gravitational force, transmural pressure and compliance of veins provides for venous volume in lower part of body ($\sim 500$ mL will pool $\sim 10\%$ body volume). As a consequence venous return is decreased, and arterial blood pressure falls. If no reflex adaptations occurred, such as an increased venomotor tone and peripheral resistance, the subject would faint.
- **Fluid will only flow from high to low total fluid energy (lateral pressure, kinetic energy, and gravitational potential energy)**
- **Venous return does not increase.** The extra pressure in the distal system drives blood back to the heart with no additional expenditure of energy.
  - Because of the effect of gravity, the external jugular vein is partially collapsed, but the main drainage from the head is through deep cervical veins that are protected from collapse by the surrounding structures. Collapse is also prevented in the cerebral vessels and sinuses by the surrounding tissues.

**Regulation of the Cardiovascular System:** Three major effectors: the heart, arteries, and veins.

**Local Autoregulation of Blood Flow:**
- **The Myogenic Response:** Precapillary vessels are able to maintain fairly constant flow appropriate to the given metabolic needs of a tissue despite changes in perfusion pressures due to an increase or decrease in arteriolar resistance within the tissue. Smooth muscle fibers in the walls of resistance vessels have spontaneous, rhythmic oscillations in membrane potential that upon reaching threshold give rise to action potentials that in turn initiate contractions.
  - Distention activates stretch-sensitive cationic channels, promotes membrane depolarization and increases the rate of APs and thus contractile activity in vascular smooth muscle.
    - Perfusion pressure $\Rightarrow$ flow, but also distends vessels and triggers vasoconstriction. The response to the initial distension is a narrowing in vessel diameter that raises resistance and returns flow to normal.
    - Wall tension $\Rightarrow$ relaxation $\Rightarrow$ flow.
• **Chemical Regulation of Flow:**
  o When tissues increase their metabolic activity, \( Q \) to meet increased requirements for \( O_2 \), nutrients, and waste removal. If \( Q \) is inadequate to meet increased metabolic needs of a tissue, \( pO_2, pCO_2 \) and \( pH \) contribute to \( \downarrow R \) and \( \downarrow Q \) by decreasing contractile tension in vascular smooth muscle (vasodilation). Plasma [K+] and osmolality (reduce arteriolar tension) both are \( \downarrow \) in venous blood draining active muscle. Adenosine is another especially effective vasodilator that results from the below reaction in to an ischemic environment.

\[
\text{Myokinase} \\
2 \text{ADP} \leftrightarrow 2 \text{ATP} + \text{AMP} \\
5' \text{Nucleotidase} \\
\text{AMP} \rightarrow P_i + \text{Adenosine}
\]

• **Mechanisms of Vasodilation:**
  o **Hyperpolarization:**
    * During hypoxia \( (\downarrow pO_2) \), when ATP levels fall, \( K_{ATP} \) channels open, \( g_K \uparrow \rightarrow \) hyperpolarization. Increased conductance of \( K_{ATP} \) channels also occurs in response to reduced \( pH \) \( (\downarrow [H^+] \) ), hypercapnia \( (\downarrow pCO_2 \) and interaction of adenosine with its cell surface receptors. Small increases in extracellular \( K^+ \) can also hyperpolarize vascular smooth muscle by causing a different \( K^+ \) channel (\( K_{IR} \) ) to open. The membrane potential of vascular smooth muscle cells oscillates sufficiently above \( E_K \) that an increase in \( K^+ \) conductance hyperpolarizes the cell.
    o \( \downarrow \) \( [Ca^{2+}]_i \)
      * Mediated, in part, by *nitric oxide (NO)* (an endothelium-derived relaxing factor (EDRF))
        * \( \text{NO} \rightarrow \uparrow \text{cGMP} \rightarrow \uparrow \text{PKG} \rightarrow \text{Phosphorylation of Phospholamban} \rightarrow \downarrow \text{Ca}^{2+} \) conductance
        * Surface membrane \( \text{Ca}^{2+} \) channels and \( \uparrow \text{Ca}^{2+}-\text{ATPases} \) (resequester \( \text{Ca}^{2+} \) into SR).
  o **Inactivation of Myosin Light Chain Kinase:**
    * \( \uparrow \text{Adenosine} \rightarrow \uparrow \text{cAMP} \rightarrow \uparrow \text{PKA} \rightarrow \text{Phosphorylation of Myosin Light Chain Kinase (inhibition)} \rightarrow \) no contraction.
      * MLCK is modulated by the \( \text{Ca}^{2+}-\text{Calmodulin} \) complex.

**Extrinsic Control of CVS:**

• **Neural Regulation of CVS Effectors:**
  o **Resistance Vessels:**
    * **Sympathetic Nervous System (ANS):**
      * Primary regulator of Total Peripheral Resistance (TPR), via release of NE/E \( \rightarrow \text{vasoconstriction via } \alpha_1 \text{ receptors} \)
        o Large arteries and precapillary sphincters are relatively poorly innervated, but small arteries and arterioles receive a rich supply of post-ganglionic adrenergic fibers.
          * More extensive in skin than brain.
            * Basal tone is a function of autoregulatory responses and low level stimulation by vasoconstrictor fibers (1-3 impulses/sec). The full range of vasomotor activity can be reproduced by stimulating sympathetic constrictor nerves at rates between 0-10 impulse/sec.
              o Cholinergic vasodilatation is likely mediated by NO, which is released from endothelial cells lining blood vessels in response to ACh.
    * **Parasympathetic Nervous System (ANS):**
      * Directly innervate external genitalia and meninges of the brain.
      * Stimulation of salivary and other secretory glands indirectly produces vasodilatation by glandular release of the enzyme, *kallikrein (see below)*. Post-ganglionic parasympathetic peptidergic neurons that release *vasoactive intestinal polypeptide* (VIP) have been shown to contribute to salivary gland vasodilation as well.
        o These three peptides act by promoting NO release.
Although the parasympathetic nervous system can influence flow to certain tissues, overall control of blood pressure by modulation of vascular resistance is mediated by increases or decreases in sympathetic adrenergic nerve firing.

- **Capacitance Vessels:**
  - Veins and to a lesser extent muscular venules are also innervated by sympathetic vasoconstrictor nerves that release NE/E and fire at a low level during basal conditions. NE/E → vasoconstriction via α-1 receptors. Smooth muscle tension (and therefore venous capacitance) can be adjusted by increasing or decreasing sympathetic discharge. Contraction of venous smooth muscle cells raises pressure in the veins and propels blood toward the heart. The reduced venous compliance effectively shifts fluid from the veins to the arterial side of the system and raises arterial blood pressure. An increase in compliance has the opposite effect.
  - Parasympathetic does not regulate venous tone, and does not have a significant role in regulating total peripheral resistance in the circulation.

- **The Heart:**
  - The SA (R. vagus) and AV (L. vagus) nodes and the atria are more densely innervated than the ventricles
    - Sympathetic (T1-T5): \# HR and \# contractility via NE → β-1 receptors.
    - Parasympathetic (Vagal): &HR and & contractility (limited)
      - Vagal and sympathetic nerves are tonically active and have opposing influences.
      - Parasympathetic tone predominates. If vagus is cut, HR\(\downarrow\), if sympathetic is cut, HR\(\uparrow\). If both are cut, HR\(\uparrow\).

- **The Cardiovascular Control Center:** processes afferent signals from various receptors in the body as well as inputs from higher centers and makes cardiovascular adjustments through autonomic motor neurons.
  - Sympathetic:
    - Pressor: Rostral ventrolateral medulla. Spontaneously active. Excitatory on preganglionic sympathetics.
    - Depressor: Raphe Nuclei. Tonic inhibition of sympathetics. Tonaically restrains pressor under basal conditions.
      - Basal net effect is excitation.
  - Parasympathetic: Vagal preganglions in nucleus ambiguous and the dorsal motor nucleus. Tonic inhibition of heart (baroception).

Cardiovascular Reflexes:
- **The Baroreceptor Reflex:** Arterial baroreceptors are critically involved in the reflex control of arterial blood pressure
  - Adventitia of Carotid Sinuses → Glossopharyngeal (CN-IX) → Sinus or Hering nerves
    - Adventitia of Aortic Arch → Vagus (CN-X) – Aortic or Depressor nerves
      - Baroreceptors are mecanical stretch receptors activated by deformation of the artery wall. Firing frequencies of aferents increase when distending pressures rise and decrease when pressures fall.
        - Afferent activity is determined not only by instantaneous pressures but by rates of change of pressure
          - The threshold for firing of the sinus nerve (~60 mmHg) is lower than that of the aortic nerve.
Baroreceptor afferent fibers synapse in NTS, which in turn, in conditions of stretch (BP), activates the cardioinhibitory center and depressor. Depressor inhibits the pressor and preganglionic sympathetics. 

When mean arterial pressure ↓, baroreceptor afferents firing frequency ↓ depressor and cardioinhibitory areas to be excited less (inhibited) → pressor area to be activated (disinhibited) → sympathetic outflow → TPR and venous tone → HR and Contractility.

Individual Effects of Cardiovascular Reflexes:

**Arteriolar Tone:**
- ↑ TPR → ↓ runoff (rate of blood flow out of the arteries into veins (through arterioles, capillaries and venules) → ↓ venous volume (Venous return will be affected for a very brief period. Cardiac output will be affected for a very brief period, as well.) → Arterial blood volume ↑ (Q_in exceeds Q_out) → P_A ↑
- After a brief period of time new “steady state” assumed with ↓ flow from the arteries to the veins and ↓ flow from the veins through the heart to the arteries.
- ↑ TPR → ↓ runoff → ↑ MAP and ↓ Q (cardiac output and venous return ↓).

**Venous Tone:**
- ↓ BP → ↑ venous tone (↓ compliance via vasoconstriction) → ↑ venous return → ↑EDV → ↑SV → ↑ MAP
- An increase in venous tone has a minor effect on venous resistance but a significant influence on arterial blood pressure. Small volume Δs (venous → arterial) are sufficient to cause significant Δ MAP (if HR↓, runoff ↓, and P_Dias ↑).

\[
\frac{MAP - \uparrow P_{RA}}{\uparrow TPR} = \downarrow C.O.
\]

**Stimulation:**
- ↓BP → ↑ sympathetic firing and ↓ parasympathetic tone → ↑ HR and ↑ contractility
  - **↑ Contractility:**
    - ↑ contractility (ventricles to contract more forcefully and more rapidly at a given EDV and ↓: empty more completely) → ↑SV → ↓ ESV → ↑ MAP.
    - ↓ ESV → ↑ venous return (↓ mean atrial volume and pressure). Driving force for flow through the system is increased (↑P_A – ↓P_RA) → ↑ CO and ↑ venous return.
  - **↑ Heart Rate:**
    - ↑HR → ↓ runoff → ↓ EDV → ↓ SV/CO → ↓ P_S and ↑ P_D → ↑ Pulse pressure (↑ cardiac volume).
    - ↑ Driving force through system (↑ MAP and ↓ P_RA).

**Combined Baroceptive Reflexes:**
- ↑ TPR → ↑ MAP, ↓ CO
  - ↓ CV → ↑ MAP, ↑ CO
  - ↑ Contractility → ↑ MAP, ↑ CO
  - ↑ Heart Rate → ↑ MAP, ↑ CO
  - ↓ TPR → ↓ MAP, ↑ CO
  - ↑ CV → ↓ MAP, ↓ CO
  - ↓ Contractility → ↓ MAP, ↓ CO
  - ↓ Heart Rate → ↓ MAP, ↓ CO

**Hormonal Responses:**
- **(Nor)Epinephrine:** Released from adrenal medulla in response to sympathetic stimulation.
  - **Heart:**
    - β-1: ↑ HR; ↑ contractility (NE/E similar affinity)
Veins:
- α-1: ↓ compliance (NE/E similar affinity)
Arteries/Arterioles:
- α-1: vasoconstriction
- β-2: vasodilation
  - E has greater affinity for β-2 than for α-1; at \(\left[E\right]\), vasodilation occurs. However, at \(\left[E\right]\), α-1 signaling overrides that from β-2 and vasoconstriction occurs.
  - NE has a greater affinity for α-1 → vasoconstriction.

Angiotensin: Synthesis depends on the kidneys (renin), the liver (angiotensinogen), and endothelial capillary cells of the lungs (ACE).
- \(\uparrow\) sympathetic activation or \(\downarrow\) renal perfusion \(\rightarrow\) renin release from kidneys. Renin cleaves angiotensinogen (liver) \(\rightarrow\) angiotensin I. A-I is cleaved to angiotensin II by angiotensin converting enzyme (ACE) found in endothelial capillary cells of the lungs.
  - A-II mediates aldosterone secretion from the kidneys.
    - Aldosterone \(\rightarrow\) Na\(^+\) retention and \(\downarrow\) plasma volume

A-II actions:
- Potent vasoconstrictor
- Facilitates NE release from sympathetic nerves
- Controls aldosterone release (long term BP regulation by \(\uparrow\) Na\(^+\) retention \(\rightarrow\) \(\downarrow\) blood volume)
- Stimulates hypothalamic thirst mediators
- Promotes ADH (vasopressin) secretion from posterior pituitary.
  - ADH \(\uparrow\) H\(_2\)O retention and causes vasoconstriction.
    - Vagal firing inhibits release of ADH. When blood volume \(\downarrow\), vagal firing \(\downarrow\), and ADH is released.

Atrial Natriuretic Peptide (ANP):
- Released when atria are distended \(\rightarrow\) Na\(^+\) and H\(_2\)O loss in kidneys (a hypervolemic response), and vasodilation.
  - **The Bainbridge Response** (vaguely mediated):
    - Atrial distension \(\rightarrow\) vagal firing \(\rightarrow\) selective \(\uparrow\) HR (at SA node). When venous return \(\uparrow\), the Bainbridge response converts that return to CO (and avoids \(\uparrow\) cardiac volume by \(\downarrow\) cardiac filling time).

Feed-Forward Reflex (Cardiopulmonary Receptors): (anticipation response for an expected upcoming event)
- Vagal afferents stretch receptors are found in atria, ventricles, and pulmonary vessels (project to NTS and induce a pressor response when firing frequency decreases and a depressor response when there is an increase in impulse frequency).
- When EDV has increased and non-myelinated vagal afferents have an increased discharge associated with distention of the cardiac chambers, total peripheral resistance, for example, is immediately lowered. The "anticipated" increase in cardiac output is matched by an increased outflow from the arteries, and arterial blood pressure is not significantly altered.

Higher Processing: The Scared Response: (Cardiovascular Control Center \(\leftrightarrow\) Hypothalasms \(\leftrightarrow\) Cerebral Cortex)
- \(\uparrow\) HR, \(\uparrow\) contractility, \(\uparrow\) vaso- and arterio-constriction (except brain, heart, and skeletal muscle – dilation to \(\uparrow\) Q), \(\uparrow\) Q, \(\uparrow\) MAP, \(\uparrow\) CO.
  - MAP is not lowered by CVCC because the NTS is transiently inhibited by the hypothalamus such that \(\uparrow\) BP can be maintained.

Long-Term Regulation of Circulation: Primarily via adjustment of fluid balance:
- Capillary fluid shift, Angiotensin II levels, Aldosterone levels, ADH levels, ANP levels, and Renal function.
**Arrhythmias:**

**Bradycardia:** defined as a heart rate that is less than 60 beats per minute.

**Tachycardia:** defined as a heart rate greater than 100 beats per minute.

**Sinus arrhythmia:** The longest PP or RR interval exceeds the shortest such interval by 0.16 s (four small boxes) or more. Common in normal children and young persons. Triggered by peripheral reflexes: on inspiration activated stretch receptors in lungs lead to inhibition of vagal nuclei in the cardiovascular control center and increased heart rate.

**Premature atrial beat:** Results from an ectopic focus in the atria that depolarizes earlier than the SA node. P wave may have a shape and size different from normal. Path of the impulse through the A-V junction and ventricle is normal. If the impulse reaches the SA node before its spontaneous firing, the SA node is prematurely depolarized, and is prevented from firing at its expected time. The interval between the premature atrial beat and the next normal beat is therefore longer; it is equal to the duration of normal cardiac cycle plus the time required for the ectopic impulse to be conducted to the SA node.

**Atrial fibrillation:** P waves are replaced by irregular fluctuations (f-waves). The AV node is activated irregularly. Ventricular beats are irregular (AV node is receiving multiple inputs). Ventricular rate is somewhat protected. Due to either multiple irritable foci or to an irregular circuitous spread of the impulse from an ectopic focus. The atria do not contract effectively and have a ripple like motion. **Compatible with life.** During exercise, atrial fibrillation may compromise cardiac output.

**Premature junctional beat:** Supraventricular rhythm. QRS is narrow with normal contour (impulse conduction follows the normal path through specialized cells that allow for a rapid ventricular depolarization). P wave may be masked by the QRS, although in this ECG it is seen right after the QRS.

**Premature ventricular beats (PVC):** originate at ectopic foci in ventricles. Impulse spread is aberrant, (configurations of QRS and T are entirely different). The different morphology of the two PVCs in this ECG suggests the presence of at least two different ectopic foci. (A single ectopic site will produce PVCs with the same contour). The prolonged interval after the premature ventricular beat is called a compensatory pause. This ectopic beat does not disturb the normal SA rhythm. When normal SA impulse reaches ventricle, the latter is still refractory due to ectopic excitation. Normal beat originating in SA is blocked (the normal P wave is lost in the T wave of the ectopic beat).

**Ventricular tachycardia:** results from ectopic excitable focus in the ventricle. QRS and T are confluent and have an unusual appearance. Can be dangerous and develop into ventricular fibrillation. Mechanism is not known (many tachycardias are generated by a reentrant mechanism in which activity is initiated at a site which supports oneway conduction from this site through the rest of the atrial or ventricular muscle). V Tach is fatal unless overcome immediately, (e. electric shock) because the ventricle doesn't contract effectively.
Coronary and Microcirculation:

Capillary Exchange: The one layer of capillary endothelial cells permits rapid transmural exchange of $O_2$, nutrients, hormones, growth factors, removal of $CO_2$, and removal of waste products, between the blood and the surrounding interstitial space. Additionally, the $\frac{A}{S}$ cross-sectional area and low BP (more time for exchange) provide optimum conditions.

- **Endothelial Microstructure:** The ease of transfer of substances across the capillaries is related to the porosity of capillary endothelial structure.
  - Continuous Capillaries: No recognizable openings. Interconnected by tight junctions or gap junctions.
    - Low type: muscle, nerve, and adipose tissue
    - High type: lymph nodes
  - Fenestrated Capillaries: Small intercellular gaps.
    - Closed type: endocrine glands
    - Open type: renal glomeruli
  - Discontinuous Capillaries: Large intercellular gaps (sinusoidal).
    - Found in liver, bone marrow, and spleen.

- **Methods of Exchange:**
  - Diffusion: The primary method of gases, substrates, and waste product transfer. Occurs through cell membrane or pores.
    - Bidirectional flow.
    - There is no concentration gradient of $H_2O$ across capillary and thus no net $H_2O$ movement.

- **Ventricular Fibrillation:** is similar to that in the atria, (immediately life threatening). Often follows a period of ventricular tachycardia.

- **First degree AV block:** characterized by a prolonged (>0.2 s) P-R interval

- **Second degree AV block:** Not all P waves are followed by a QRS (occasional complete block at the A-V junction). Here: 4:3 Wenckebach (or Mobitz type I) 2nd degree block (progressive lengthening of the P-R interval until a beat is missed). The failed conduction of the 4th P wave allows time for the conducting system (AV node or downstream Purkinje fibers) to fully repolarize after the previous excitation, and the next PR interval has the shortest duration of the series. The process, however, repeats and culminates in another missed beat.

- **Third degree (Complete) block:** Impulse is unable to pass the AV junction. The ventricles develop an independent pacemaker and beat entirely independently of the impulses in the atria. Time intervals between the P waves are equal as are those between the QRS complexes. The P-P interval is shorter than the R-R interval. The low ventricular contraction rate may compromise cardiac output, if ventricular stiffness is high or contractile ability is reduced such that the slow heart rate cannot be compensated by an adequate increase in stroke volume to maintain cardiac output within normal limits. If the block occurs at the crest of the AV node, a junctional rhythm will take over and drive the ventricles producing narrow QRS complexes at the intrinsic rate of the AV node (40-55/min). This is the case in ECG tracing. If the site of block is below the AV node the rhythm is established by a ventricular pacemaker. If this pacemaker were below the bifurcation of the bundle of His, the resulting QRS complex would be wide and the rate would be low, 20 to 40/min.
• The ISF takes on composition of incoming blood.

**Fick’s 1st Law:** \( J = -DA \frac{dc}{dx} \) (\( J = \) quantity of substance moved over time, \( D = \) diffusion coefficient of substrate \((1/\sqrt{\text{MW}})\), \( A = \) surface area of diffusion pathway, and \( dc/dx = \) concentration difference of solutes)

**Fick’s 2nd Law:** \( Q = -PS(C_O-C_I) \) (\( Q = \) quantity of substance moved over time, \( P = \) capillary permeability of substance, \( S = \) surface area, \( C_O = \) concentration inside capillary, \( C_I = \) concentration outside capillary)

- **Filtration:** Movement out of capillary (whereas, movement into the capillary = re-absorption)
  - maintains blood volume
  - provides for intestinal fluid absorption as well as saliva, sweat, and urine production
  - → tissue edema
    - Dependent upon:
      - 1) Hydrostatic pressure (blood pressure within capillaries).
      - 2) Osmotic (oncotic) pressure (difference in concentration of proteins in plasma and interstitia).
- **Pinocytosis:** Relatively unimportant.
- **Starling’s Filtration Equation (Factors of Filtration):**
  - Intracapillary lateral pressure drives fluid out of the capillary into the interstitia, and the plasma colloid oncotic pressure (due to proteins) absorbs water into the capillaries.
  - Small interstitial oncotic pressure promotes ultrafiltration out of the capillary, and a small interstitial hydrostatic pressure may oppose ultrafiltration out of the capillary.

\[
F = K[(P_c - P_i) - (\sigma_p - \sigma_i)]
\]
where \( F = \) net movement of fluid (ml/min), \( K = \) specific hydraulic permeability of the capillary, \( P_c = \) lateral capillary pressure, \( P_i = \) lateral interstitial pressure, \( \sigma_p = \) colloid osmotic pressure (in plasma), and \( \sigma_i = \) colloid osmotic pressure in interstitia.

- Fluid is filtered out of the capillary at the arterial end and towards the middle and is reabsorbed at the venous end.
- Normally about 20 L/day of fluid are filtered through the capillaries and about 16-18 L are reabsorbed into the capillaries.
  - The remaining 2-4 L/day are returned to the blood by the lymphatic system.
  - Permeability \( 1/\alpha \) radius (size), and \( 1/\alpha \text{ MW} \) and is also effected by electrical charge and solubility properties.

**The Lymphatic System:** Acts as an interstitial drainage system. Lymph channels have closed blind endings, lie in interstitial spaces, and drain (via lymph nodes) into the SVC and subclavian veins. Content resembles plasma (except has \[\parallel\] protein).

- **Edema:** accumulation of excess fluid in the interstitial space
  - Increased capillary hydrostatic pressure (heart failure):
    - Left-side (pulmonary venous pressure \[\uparrow\], hydrostatic pressure \[\uparrow\], → pulmonary edema)
    - Right side: (systemic venous pressure \[\uparrow\] → pitting edema in dependent areas.
      - \[\uparrow\] capillary pressure and edema can result from renal failure (fluid retention).
• ↑ localized capillary pressure occurs from localized venous obstruction (DVT).
  
  o Lymphatic obstruction (tumors, parasites): ISF pressure ↑, and filtration ↓. The water/protein flux ratio consequently ↓, and the protein concentration in the interstitial space ↑.
  o Increased capillary permeability (endothelial breakdown): Response to infection, injury, and allergic conditions (excess liberation of histamine or histamine-like substances from mast cells that are stimulated by bradykinin). ↑ permeability is associated with ↑ localized capillary hydrostatic pressure due to vasodilatation of the arterioles.

Coronary Circulation: Delivers blood to supply the O₂ and nutrient demands of cardiac muscle. Contractions of the heart muscle tends to compress the vessels running through the ventricular walls during systole.

  o Anatomy:
    * Arterial supply:
      - R. Aortic Sinus → R. Coronary Artery → (R. atroventricular sulcus) → Posterior Interventricular Artery (Right dominant heart).
      - L. Aortic Sinus → L. Coronary Artery → Left Circumflex and Left Anterior Descending Branches (LAD=Anterior Interventricular). L. Circumflex → Posterior Descending (Left dominant heart).
    * Venous drainage: (primarily → right atrium via Coronary Sinus).
      - Right ventricular veins drain → Anterior Cardiac veins → right atrium.
      - Thebesian veins pass from venous ends of capillaries → cardiac chambers.

  o Physiology:
    * 10% of flow is O₂ utilization in coronary flow.
    * Myocardial capillary density is very high (~one capillary/myocyte).
    * Collaterals supply less than 10% of the normal flow.
    * The blood flow rate per unit weight of tissue is approximately 10 times the average value for the whole body.
    * Myocardium extracts 65–70% of the oxygen from the coronary blood. In contrast, the whole body average is only 25% at rest.
      * Increases in cardiac O₂ requirements must be met by an increase in coronary blood flow.
    * Coronary flow is greater during diastole than during systole, because contraction of the ventricular muscle surrounding the coronary vessels impedes the flow. The systolic reduction of flow is greater in the left than in the right ventricle, because the latter generates lower pressures. Systolic flow is also lower in the endocardial regions of the ventricles, which are under greater compression than the epicardial regions.

  o Regulation: Similar to other vasculature
    * Vasodilators: ↓pO₂, ↑[K⁺], and ↑adenosine, epinephrine (preferentially binds β-2 receptors).
      * Small coronary vessels contain predominance of β-2 while the large vessels contain α-1.
    * Sympathetic stimulation or injection of catecholamines causes relaxation of the small coronary vessels, (inhibited by β-2 blockers). Large coronary arteries constrict in the presence of sympathetic stimulation (inhibited by α-1 blockers).
      * The overall effect of sympathetic stimulation is to cause an increase in coronary flow that is enhanced by the effects of sympathetic activity on heart rate and contractility.

Congestive Heart Failure:

Overview and Epidemiology:

  o Risk Factors (Hypertension, Hyperlipidemia, Diabetes, Smoking, and Aging) → Coronary Atherosclerosis → Myocardial Infarction → Heart Failure
  o Toxins (EtOH), Chronic Hypertension, Myocarditis ( Infective or autoimmune) idiopathic/genetic manifestations can also lead directly to heart failure (without MI)
    * Therefore CHF is the common pathway for acute and chronic heart disease (including arrhythmia, ischemia, valvular disease, and congenital heart disease).
  o 400,000 cases of CHF diagnosed/year (increasing due to growing elderly population and increase in survivors of MI).
  o Patients with a diagnosis of CHF have high morbidity and mortality.
  o Terminology: Preload: The load (ventricular end-diastolic pressure) that establishes ventricular end-diastolic fiber length and ventricular end-diastolic volume. The major determinants of preload are LV volume and compliance. Afterload: The sum of the loads against which the myocardial fibers must contract during systole. The left ventricular afterload is left ventricular systolic pressure, which is influenced by aortic pressure. Contractility (Inotropic State of the Heart): The rate, extent, and/or force of myocardial fiber shortening during systole for a given set of loading conditions. Stroke Volume: Amount of blood pumped out with each heartbeat. Ejection Fraction: Percent of end-diastolic volume that is ejected with each contraction
(SV/EDV). The major determinants of myocardial oxygen demand are heart rate, contractility, left ventricular systolic pressure and left ventricular volume.

- **Inotropes** (catecholamines) ↵ contractility by ↨Ca²⁺ availability
- **Inotropes** (β-blockers, myocyte loss) ↩ contractility → apoptosis and MI

**Pathophysiology of Heart Failure:**

- **Definitions of Heart Failure:**
  - **Technical:** HF occurs when the heart fails to pump blood at a rate required by metabolizing tissues, or when the heart can only do so with an elevated filling pressure.
  - **Operational:** HF is a clinical syndrome resulting from clinical decompensation and characterized by the signs and symptoms of interstitial volume overload and/or inadequate tissue perfusion.

- **Frank-Starling Relationships:** Preload α Length of Contraction ↣ Preload α Force of Contraction

**Pathophysiology of CHF:**

- **Pressure Overload:** Stenosis (outflow obstruction) or systemic hypertension.
- **Volume Overload:** Valvular regurgitation; High output states such as: AV shunt or a congenital abnormality → hypertrophy (↑outflow).
- **Loss of Muscle:** MI → ischemic necrosis
- **Decreased Contractility:** Volume/pressure overload often due to cardiomyopathy.
- **Restricted Filling:** Pericardial effusion or constriction, ventricular hypertrophy.

**Categories of Heart Failure:**

- **Systolic vs. Diastolic Dysfunction:**
  - **Systolic Dysfunction:** Impairment of ventricular ejection (↓contractility, ↓ejection fraction, left ventricular dilation, ↑LVEDV, ↑LV diastolic filling pressure → ↑pulmonary pressure.).
    - Post-MI, 1° dilated cardiomyopathy, myocarditis
    - Result is chamber dilation (↑EDV) and ↑HR (↑CO by ↑ number of strokes/min)
    - Best treatment is ↑contractility, or ↓afterload.
    - The ejection fraction (EF) is the most useful clinical index of systolic dysfunction (normal EF is 50% to 70%) and is ↓ in systolic dysfunction. LVEDV is ↓ in systolic dysfunction.
  - **Primary (“Pure”) Diastolic Dysfunction:** Failure of filling (without systolic dysfunction)
    - Associated with left ventricular hypertrophy (LVH) and supranormal contraction and ejection fraction. Increased resistance to diastolic filling results from the increased LV mass and from interstitial fibrosis and subendocardial ischemia (often present with LVH). Being resistance to filling results in an elevated LV diastolic (filling) pressure, which, transmitted to the pulmonary capillaries, causes pulmonary congestion.
• Hypertension, hypertrophy, fibrosis CMP, aging (∆ compliance and ↑ pressure at any given volume.)
• ↑ LV diastolic (filling) pressure is required to achieve any given LV volume.
• Best treatment is ↑ preload :: ↑ filling time (↓ HR).
• Common finding is pulmonary congestion with normal EF

- Secondary Diastolic Dysfunction: Diastolic dysfunction (resistance to diastolic filling due to limited dilation and distensibility) secondary to systolic dysfunction.
  - Law of Laplace: LV wall stress ∝ radius \((\sigma = Pr/2h(\text{thickness}))\).
  - LV dilation (compensatory response), ↑ LV performance/SV (↑ preload) - Starling’s Law. But LV dilation implies $\Delta$ tension to generate a given pressure. Laplace’s law dictates that LV wall stress increases as the radius increases. Chronically dilated, failing ventricles have increased levels of wall stress $\Rightarrow$ mechanical disadvantage in terms of their ability to shorten during systole.

- Secondary Diastolic Dysfunction:
  - LV ejection (stroke volume) is decreased.
  - Movement of the loop to the right indicates ventricular dilation (abnormal ↑ LV volume during diastole, and a secondary $\Delta$ LV diastolic pressure due to $\Delta$ LV diastolic volume), resulting $\Delta$ in EF. The area within the loop (stroke volume) is decreased.
  - The slope of the diastolic pressure-volume curve is a measure of ventricular compliance (myocardial stiffness). Preload-dependent $\Delta$ in stiffness ($\Delta$ in diastolic compliance)
  - Patients with systolic and LV dilation and hyper-distension often have secondary diastolic dysfunction
  - Primary diastolic dysfunction shown by the dashed line, indicating that left ventricular diastolic pressures are abnormally $\Delta$ relative to diastolic ventricular volume. Diagnosis of primary diastolic dysfunction requires an upward shift of the diastolic segment of the pressure-volume loop. In contrast, systolic failure is associated with a right shifted, narrower loop, since it indicates failure of contractile function.

- RV Failure:
  - Caused by hypertension, coronary artery disease [CAD], aortic stenosis or insufficiency, mitral insufficiency
  - During diastole LV, LA, and pulmonary veins are continuous with the pulmonary capillary bed. $\therefore$ LV diastolic pressure determines pulmonary capillary pressure $\therefore$ presence or absence of pulmonary congestion/edema. LV diastolic pressure $\Delta$ in heart failure because of $\Delta$ in LV diastolic volume (LV dilation and distension) or from $\Delta$ in LV wall stiffness (decreased diastolic compliance or distensibility).
  - LV ejection (stroke volume) is influenced by the $P_a$ (afterload), which is in turn affected by TPR.
  - TPR $\propto$ LV SV.

- RV Failure:
  - Caused by pulmonary disease.
  - RV ejection and SV are influenced by pulmonary vascular resistance (PVR) and pulmonary capillary pressure that elevate pulmonary artery pressure and RV afterload.
  - The most common cause of RV failure is LV failure $\Rightarrow$ $\Delta$ LV $P_a$ $\Rightarrow$ $\Delta$ LA, PV, and PC pressures, all $\Delta$ RV afterload $\Rightarrow$ RV hypertrophy and eventual RV failure.)
Venodilation can reduce RA pressure, RV filling, pulmonary capillary pressure, LA pressure, and LV filling (↓preload).

Venoconstriction ↑ venous return by decreasing the size of the systemic venous "reservoir."

**Pulmonary Edema:** Pulmonary-alveolar capillary membrane fluid movement is regulated by the pulmonary capillary wedge pressure (PCWP- moves fluid → pulmonary interstitium) and the colloid osmotic pressure (COP-moves fluid from interstitium → capillary).

- COP normally exceeds PCWP (keeps lung parenchyma dry), but when PCWP exceeds COP, interstitial pulmonary edema occurs if lymphatic capacity is exceeded.

The pulmonary capillaries are in direct continuity with the pulmonary veins, (PV), left atrium (LA), and left ventricles (LV) in diastole when the mitral valve is open. In the absence of mitral stenosis or mitral insufficiency, the left ventricular diastolic pressure (LVDP) is approximately equal to the PCWP.

The pulmonary capillaries are in direct continuity with the pulmonary veins, (PV), left atrium (LA), and left ventricles (LV) in diastole when the mitral valve is open. In the absence of mitral stenosis or mitral insufficiency, the left ventricular diastolic pressure (LVDP) is approximately equal to the PCWP.

**Backward Heart Failure:** When ventricular filling pressures are ↑ pulmonary congestion (LV filling pressure increase) and systemic congestion (RV filling pressure ↑). **Backward failure is synonymous with diastolic dysfunction.**

- **Forward Heart Failure:** ↓ in cardiac output and in organ perfusion. Kidneys retain sodium and water and create fluid overload and edema. **Forward failure is synonymous with systolic dysfunction.**

- **High-Output vs Low-Output Failure:** Most CHF, cardiac output is low. However, some unusual forms of CHF are associated with high cardiac output, (result of decreased systemic vascular resistance and/or increased metabolic demand) [e.g., thyrotoxicosis, anemia, cirrhosis, Paget's disease, AV fistula].

**Neurohumoral Δ in CHF:** Net effect is to ↑ both arteriolar and venous constriction CHF patient and to ↓extracellular fluid volume.

- ↑ sympathetic tone →↑ catecholamines circulation → vasoconstriction and ↑ resistance
- Activation of the renin-angiotensin-aldosterone system → vasoconstriction and ↑ resistance
  - →↑ secretion of ADH
- ↑ secretion of atrial natriuretic factor → vasodilation, ↓TPR, ↑Na+/H2O loss.

**Normal Compensatory Mechanisms that Overshoot in CHF:** With moderate depression of cardiac contractility, the below mechanisms maintain circulatory function, but they can become counterproductive → CHF

- **Preload (↑ intravascular volume):** ↑ due to Na+/H2O retention and ↑ venous tone
  - Renal (H2O/Na+ retention) due to RAAS/ADH, volume expansion, and vasoconstriction → ↑preload, ↑ CO, but with ↑ filling pressure.
  - TPR: As CO↓, TPR ↑, maintaining MAP (the neurohumoral responses regulating this may lead to detrimental effects in a CHF patient).
- **Heart Rate:** ↑sympathetic tone and ↓parasympathetic tone → O2 demand (not beneficial)
- **Hypertrophy:** ↑filling pressures result from decreased compliance due to hypertrophy (in turn resulting from wall stress due to ↑EDV/P).
- **LV Dilation:** Early compensation for heart failure, but fails to maintain stroke output.
- **Summary:** Volume expansion Δ fluid distribution (→ tissue congestion), ↑diastolic wall stress, and ↑ metabolic demands. Neurohumoral activation results in ↑ preload (intravascular fluid expansion and vasoconstriction—diastolic wall stress ↑), ↑ afterload (↑ arterial constriction and systolic wall stress ↑) → pathological myocardial remodeling.

**Common Symptoms of CHF:**

- **Easy Fatigability:** ↓CO
- **Weakness:** ↓CO
- **Dyspnea:** difficulty breathing → pulmonary congestion (due to ↑ LV filling pressure)
  - Orthopnea: cannot breath while lying down
- **Oliguria:** ↓ urine output
  - **Nocturia:** ↓ nocturnal urination
- **Dependent Edema:** ↑venous pressure and ↑Na+ retention
Summary: Cardiac output \rightarrow> fatigue, cool extremities, mental obtundation, and organ dysfunction. Tissue congestion results from interstitial volume overload and \rightarrow> dyspnea (LF failure – pulmonary congestion), as well as dependent edema and ascites (RH failure– systemic congestion).

Classification of CHF:
- Class I - Symptom free
- Class II - Slight limitation of physical activity
- Class III - Moderate limitation of physical activity
- Class IV - Severe limitation of physical activity

Treatment of CHF:
- \beta blockers: Reduction in CO and renin release \rightarrow> ↓ cardiac workload and \rightarrow> ↓ O2 demand.
  - \beta_1: inhibits increase in HR
  - \beta_2: inhibits vasodilation
- Spironolactone (Aldosterone inhibitor – urgent application for survival):
- Hydralazine/Nitrates: vasodilation
  - Venodilation \rightarrow> ↓ venous return and ↓ filling pressures
  - Arteriodilation \rightarrow> ↓ systemic pressure and ↓ afterload.

Myocardial Remodeling: Drastic Δ in structure (all dimensions) and function of the heart as a consequence of ↓ ventricular wall stress (hemodynamic load ↓). Hypertrophy first normalizes stress on the myocardium, but equilibration to a new steady state does not occur, and wall stress becomes pathological, at which point continued dilation is harmful. This can lead to myocyte hypertrophy, which can in turn lead to myocyte apoptosis, and changes in the cardiac interstitium (collagenous structural reformation). Stimulation of remodeling include: mechanical strain (inhibited by nitrates/hydralazine, diuretics, and ACE inhibitors), A-II (inhibited by ACE inhibitors and diuretics), catecholamines (inhibited by \beta-blockers), aldosterone (inhibited by spironolactone), O2 radicals, etc.

GI Physiology

Motility:

Mastication: Rhythmic movement of jaws, tongue, and lips to mechanically shear food while mixing it with salivary secretions \rightarrow> increased surface area. Initiation of mastication is voluntary, but rhythmicity is a reflex to tactile stimuli.

Deglutition:
- Mechanics:
  - (1) Oral Phase: Elevation of tongue against hard palate. Soft palate raises and closes off nasopharynx. Initiation of swallowing is voluntary, but once initiated, swallowing is reflexively controlled.
  - (2) Pharyngeal phase: Contraction of pharyngeal muscles and opening of UES [food prevented from entering airway by elevation of larynx and closure of glottis, downward tilt of epiglottis, and cessation of respiration].
  - (3) Esophageal phase: Coordinated wave of contraction toward LES.
    - Initiated vagally, but carried via myenteric plexus.
    - LES opens as a result of peristalsis.
      - Primary Peristalsis: wave of contraction associated with swallowing
      - Secondary Peristalsis: result of distension by residual bolus.
      - Esophageal pressure is ~30-120mmHg. Velocity of peristalsis is 3-5cm/sec therefore food reaches LES 5-10sec post-initiation of swallowing.
    - As the LES opens, the fundus and body of stomach relax. Relaxation without change in pressure is proportional to amount of food added.
- Control:
  - Voluntary initiation (upper 1/3 of esophagus is striated skeletal muscle innervated directly by vagi)
  - Reflex processes initiated by swallowing center in the medulla (glossopharyngeal and vagus afferent reflexes). A peristaltic wave, once initiated, can proceed in a vagally denervated esophagus and therefore its propagation is dependent upon the myenteric plexus (between circular and longitudinal muscle layers). The vagus innervates and modulates the plexus but does NOT innervate esophageal smooth muscle directly.
• Peristalsis in the esophagus and function of the LES requires myenteric neuronal control (stretch relaxation is not sufficient).
  • LES tonically constricted with pressure greater than that of the fundus of the stomach. **LES is modulated by myenteric plexus (inhibitory and excitatory) and thus indirectly by the vagus.**
    - Inhibitory Control: VIP, NO
    - Excitatory Control: ACh
    - Hormonal Control: Progesterone (decreased tone)

**Gastric Motility:**
- **Receptive Relaxation:** Fundus and body relax in response to LES opening (neurally mediated via myenteric plexus and vagus).
- **Stress Relaxation:** Smooth muscle stretch due to mechanical stress. Allows increase in **volumexans** increase in pressure.
- **Gastric Peristalsis and BER:** The stomach antrum periodically contracts peristaltically when distended by food, driving chyme toward the pylorus → mechanical breakdown of foodstuff.
  - A pacemaker located on the greater curvature of the stomach drives slow wave depolarizations (the basic electrical rhythm) (3-4/minute) that are sub-threshold and are thus necessary but NOT sufficient for gastric peristalsis.
    - Initiated by interstitial cells of Cajal in the longitudinal muscle layer.
    - **Longitudinal conduction (caudal) is slow, and circular conduction (lateral) is fast.**
  - **The BER is conducted to and propagated by cells within the smooth muscle layers NOT by neurons.**
    - The BER is the same in Fed and Unfed states.
  - The BER defines frequency and direction of peristaltic contraction.
    - During the fed state, action potentials are generated due to distension and neuro-hormonal stimulation (possibly **Gastrin** → ACh release in stomach) → contraction.
      - Action potentials are phase-locked to the BER frequency.
    - Stretch activated receptors results from membrane conductance changes → depolarization. Stretch activated receptors are non-selective (Na⁺, K⁺, Mg²⁺, and Ca²⁺).
      - **Distension → opening of these channels → local membrane depolarization → voltage gated channels open → influx of Ca²⁺ → contraction.**
  - Distension leads to an initial rise in wall tension, but may then lead to a fall in wall tension (stress relaxation).

- **The pyloric sphincter prevents all but small chyme particles from entering the duodenum therefore the increasing pressure on the remaining chyme during peristaltic contraction (anteropulsion) → retropulsion → shearing force that homogenizes chyme mechanically.

  - **Entero-gastric reflex:** Distension of the duodenum → decreased emptying of stomach.
    - The stomach normally empties ~3%/minute.

  - **Migrating Myoelectric Complex:** Strong peristaltic contractions that occur every 75-90 minutes during inter-digestive periods that sweeps the entire length of the stomach and SI. Serves to clean out the stomach and SI. Responsible for **borborygmi** (abdominal gurgling). **Motilin** (hormone of SI) may be responsible for initiating MMCs.

**Small Intestinal Motility:**
  - **Segmentation Contractions:** Short and local annular (ring-like) contractions that drive backward and forward movement of chyme to further homogenization and to mix chyme with intestinal secretions. **Peristalsis in SI is local and minor form of motility.**
    - A gradient of segmentation contraction rate is found that corresponds with a gradient in force exerted on the chyme (duodenal muscle is thicker and stronger than ileal muscle), thus propelling the chyme distally.
      - **Duodenum:** 12/minute and **ileum:** 8-9/minute.
    - Segmentation contractions are controlled by BERs (control maximum frequency of segmentation), which are in turn controlled by multiple pacemakers found throughout the SI.
      - BER is subthreshold, thus **distension and myenteric plexi** (and in turn vagi) drive action potential generation.
    - **Gastro-ileal reflex:** Increased gastric activity → relaxation of the ileocecal sphincter (normally closed).
Colonic Motility:
- **Annular Constrictions:** Lead to sacculations (haustra), which chew up fecal matter increasing surface area.
- **Peristalsis:** Propels fecal matter → sigmoid colon.

Defecation:
- Segmental contraction of the rectum propels contents retrograde into the sigmoid colon (therefore rectum is usually empty). Sweeping contractions along the sigmoid colon fills rectum → defecation.
  - *Internal anal sphincter* opens reflexively under pressure, but the *External anal sphincter* is under voluntary control.

Extrinsic Neurogenic Control of Motility:
- **Vagus:** 80% *Afferent* (respond to stretch etc for vago-vagal reflexes as well as relay to higher control centers) and 20% *Efferent*.
- **Sympathetic:** Primary targets are blood vessels and submucosal and myenteric plexi. Primarily *inhibitory* via inhibition of myenteric motor neurons
  - *Excitatory* of blood vessels, LES, and pyloric sphincter.
    - Constriction of blood vessels → restricted delivery of nutrients, decreased smooth muscle metabolism, and decreased muscle contraction.
- **Parasympathetic:** Generally *excitatory* → increased motor activity.
  - *Inhibitory* (relaxation) in fundus of stomach and LES.

Endocrine and Paracrine Control of Motility:
- **Excitatory:** Gastrin, CCK, Motilin, Prostaglandins, and Serotonin.
- **Inhibitory:** Gastric Inhibitory Peptide (GIP), Somatostatin, Vasoactive Intestinal Peptide (VIP), and Secretin

Gastric Function and Secretions:

Gastric Function:
- Stores and mixes food
- Secretes acid, proteolytic enzymes (pepsin: *bacteriostasis and digestion*), and intrinsic factor (IF) [2-3Liters/day]
  - **Parietal cells** (HCl and IF), **chief/peptic cells** (pepsinogen), **mucous neck cells** (alkaline mucous), **endocrine cells** (G-cells: gastrin), and **paracrine cells** (ECL cells: histamine; D-cells: somatostatin)
    - **Cardiac Region:** mucous secreting cells
    - **Fundus and Corpus (Oxyntic Area):** parietal cells, chief cells, mucous neck cells, ECL cells, and D-cells.
    - **Pyloric Antrum:** mucous secreting cells, G-cells, and D-cells
- **HCl Secretion/Parietal Cells:**
  - **Parietal Cell characteristics:** large mitochondrial content, intracellular canaliculi (infolding of apical membrane), many intracellular vesicles (containing H⁺-K⁺ ATPases).
  - **Stimulation:** Vesicles fuse with PM and position H⁺-K⁺ ATPase pump at luminal border. Apical K⁺ and Cl⁻ channels are also present, as well as a basal HCO₃⁻ - Cl⁻ neutral antiporter.
  - **Function:** Acid serves to kill ingested bacteria, to denature dietary protein, and to provide pH for maximal pepsin activity. *As secretion continues, [H⁺] and [Cl⁻] increases, [Na⁺] decreases, and [K⁺] is approximately constant.*

**R-Proteins and IF:**
- **Vitamin B₁₂** (cobalamin) is necessary for DNA synthesis and is only available through dietary sources. B₁₂ binds R-protein (glycoprotein secreted by salivary and gastric glands) in stomach preferentially over...
intrinsic factor (secreted by parietal cells). In SI, R-proteins are degraded by pancreatic proteases, while IF is not. Therefore, B_{12} binds IF IF-B_{12} complex is internalized by receptor-mediated endocytosis in the ileum. IF is degraded in lysozymes. B_{12} is exocytosed to plasma with transcobalamin. Lack of IF and thus B_{12} absorption → pernicious anemia (RBCs don’t mature normally).

Pepsin/Chief Cells:
- Secrete pepsinogens (inactive zymogen). Below pH 4.0, pepsinogens converted to pepsins (active). pH optima for pepsins = 1.8-3.5. Pepsins are irreversibly inactivated at pH ~5+. Pepsins have broad peptide specificity, but preferentially attack peptide bonds involving aromatic amino acids.

Gastric Mucosal Barrier: protects stomach against its own secretions by forming a layer of mucous and protective bicarbonate barrier. Mucosal cells are joined by tight junctions preventing H^{+} passing into underlying tissue. Prostaglandins are also released following mucosal damage (particularly by NSAIDs and EtOH): decrease acid secretion by parietal cells, increase mucous production, and dilate arteries (increases blood flow and removes acid and pepsin). If cells lost in barrier, and pepsin penetrates wall, restitution rescales denuded area by conformation change (less than 60 minutes).

Control of Gastric Secretion:
- Cephalic Phase: conditioned response (vagal)
  - Vagus: stimulates secretion from all cells in the system except D-cells, which it inhibits.
  - ECL cell: releases histamine (promotes HCl secretion from Parietal cells and potentiates action of gastrin and ACh) in response to cholinergic and gastrin stimulation (CCKB2 receptor – competitively inhibited by CCK – less potent agonist).
  - Parietal Cell: releases HCl in response to cholinergic and histamine stimulation. HCl secretion is inhibited by cimetidine (blocks H_{2} receptor).
  - D-Cell: when pH of chyme in antrum <3, neurally released calcitonin gene related peptide (CGRP) stimulates D-cell release of somatostatin (blocks G-cell secretion of gastrin).
  - G-Cell: gastrin release stimulated by cholinergic neurons (ACh and Gastrin Releasing Polypeptide – GRP).
    - Gastrin family proteins only differ in size: share common four C-terminal amino acid residues.

- Gastric Phase: Protein buffers pH of gastric acid therefore pH rises, somatostatin levels decrease, and gastrin secretion increases (accounts for 90% of gastrin secretion).
  - (1) Distension Reflexes: Distension (mechanoceptive) of the stomach activates short and long vago-vagal reflexes to cholinergic stimulation of gastric secretory cells (see above).
  - (2) Chemical Stimulation: Peptides and amino acids in pyloric antrum directly stimulate G-cells.

Intestinal Phase:
- The putative hormone entero-oxynin stimulates duodenal gastrin release.
- Enterogastrones inhibit acid secretion (and gastrin release) in response to acidified chyme.
  - Secretin: released from S-cells when pH of chyme is <4.5. Secretin inhibits acid (ECL cells) and gastrin (stimulates D-cells and inhibits G-cells) release, but stimulates pepsinogen release from chief cells.
  - Gastric Inhibitory Peptide: released from K-cells in response to free fatty acids and carbohydrates (glucose). GIP inhibits acid (ECL cells) and gastrin (stimulates D-cells and inhibits G-cells) release.
  - Cholecystokinin (CCK): secreted from I-cells in response to FFAs, peptides, and amino acids. Competitively inhibits histamine release from ECL cells by binding to CCK2/B receptor (shares homologous sequence with gastrin). Affinity for receptor is similar to gastrin, but CCK is a much weaker agonist and therefore histamine secretion is reduced.

Salivary and Pancreatic Secretions: (salivary = neural control, gastric = neural and hormonal control, pancreatic = primarily hormonal control).
Salivary Secretions:
- 3 pairs of glands:
  - **Parotid**: serous secretion
  - **Submandibular**: mixed secretion
  - **Sublingual**: mucous secretion
    - The secretory unit is the salivon: composed of the terminal acini → intercalated duct → striated duct → excretory duct.
  - ** Constituents of saliva**: water, electrolytes, amylase (breaks down starch), mucous, and lingual lipase.
    - Lubricate food, mediate taste, facilitate speech, cleanse the mouth, dilute noxious stimuli, begin starch and lipid breakdown, and provide an ideal environment for the health of teeth.

- **Water and Electrolyte Secretion**: fluid composition is similar to an ultrafiltrate of plasma:
  - During secretion, Na⁺ and Cl⁻ are partially reabsorbed, and K⁺ and HCO₃⁻ are secreted into the tubules.
  - Ion absorption exceeds secretion and H₂O permeability is low, therefore saliva is hypotonic and alkaline. At high flow rates, saliva becomes isotonic as Na⁺ and Cl⁻ reabsorption is incomplete.

  - **Amylase**: 30% of salivary protein. Requires Cl⁻ and neutral pH for optimal activity. Amylase can only cleave interior α-1,4 glycosidic linkages in glucose polymers of starch. Products of starch digestion are thus mixtures. 50% of starch broken down in stomach due to salivary amylase.

  - **Other Secretions**: Mucins (glycosylated proteins of mucous)
    - Phosphorylated Proline-Rich Peptides (PRPs): regulate mineralization of teeth.
    - Histatins: anti-fungal.
    - Lysozyme: antibacterial.
    - Lactoferrin: chelates iron (restricting availability to microorganisms).
    - Lingual Antimicrobial Peptide (LAP).
    - Epidermal Growth Factor: aids in wound healing.

Regulation of Salivary Secretion:
- **Entirely neural control**: ~0.5-1 liter of saliva produced daily.
  - Mostly parasympathetic (sympathetic is 15% of parasympathetic). Increased secretion is associated with ↑ blood flow.
    - Causes of ↑ Blood Flow: (1) release of vasoactive intestinal polypeptide (VIP), (2) release of kallikrein.
      - Kallikrein cleaves kininogen → kallidin (later → bradykinin). Kallidin and bradykinin are vasodilators.
        - Vasodilation → ↑ salivary flow → ↑ hydrostatic pressure → ↑ filtration → ↑ hematocrit (~55%).
    - Lack of salivation is due to inhibition of salivary centers at higher levels. Therefore no excitation of salivary glands occurs (but not inhibited per se).

Pancreatic Secretions:
- Characterized by RER, extensive golgi, and many apical zymogen granules. **Secretes ~2L of fluid daily. Digestive enzymes are released in an alkaline fluid that neutralizes acidified chyme in the duodenum. Neutralization protects the mucosa from injury and maintains a pH optimum for pancreatic digestive enzymes.**
  - **Water and Electrolyte Secretion**: The primary secretion of acinar cells contains enzymes in a fluid with an ionic composition similar to that of plasma. Secretion is modified in ducts where an isotonic alkaline-rich (HCO₃⁻) fluid is secreted.
Pancreatic Protective Processes: (1) Inactive precursors of enzymatic secretions, (2) Packaging: all secretions contain N—terminal signal sequence tethering them to RER. Recognizes and attaches growing polypeptide to an ER translocation protein→ golgi→ condensing vacules→zymogen granule storage→release (keeps enzymes sequestered), (3) Trypsin inhibitor in vesicles: if trypsin is accidentally activated before release, inhibitors protects against damage.

Pancreatic Enzymes:
- **Proteases**:
  - **Endopeptidases** (cleave interior peptide bonds): (1) Trypsin (C-terminal basic amino acids), (2) Chymotrypsin (C-terminal aromatic residues), (3) Elastase (elastin)
  - **Exopeptidases** (cleave terminal peptide bonds): (1) Carboxypeptidase A: C-terminal aromatic and non-polar residues, (2) Carboxypeptidase B: C-terminal basic residues.
- **Lipolytic Enzymes**:
  - Lipase: reacts with triglycerides→2-monoglycerides and FFAs
  - Phospholipase A2: cleaves FFAs from the 2- position of phospholipids.
  - Cholesterol Esterase: Hydrolyzes cholesterol esters→cholesterol and FFAs.
- **Glycolytic Enzymes**:
  - Amylase cleaves interior α-1,4 glycosidic bonds.
- **Nucleic Acid Hydrolases**:
  - Ribonuclease and Deoxyribonuclease.

**Activation of Proteases and Phospholipase A2**: **Enteropeptidase (enterokinase)** is found in the brush border of cells lining the duodenum. Enteropeptidase converts trypsinogen→trypsin. Trypsin then activates proteases and PA2 from zymogenic precursors.

**Regulation of Pancreatic Secretion**: **CCK** (enzyme rich secretion from acinar cells) and **Secretin** (bicarbonate rich secretion from duct cells).
- **Cephalic Phase**:
  - Vagal stimulation→Pancreatic ACh release (acinera cell stimulation) and VIP release (duct cell stimulation).
  - Gastrin can bind to the receptor for CCK (CCK-1/A) [competitive inhibition]. Affinity of gastrin for CCK-1/A is significantly less than that of CCK.
- **Gastric Phase**:
  - Distension by food in stomach stimulates pancreatic secretion via vago-vagal reflexes to the pancreas and by releasing gastrin (→AC.h and VIP release).
- **Intestinal Phase**: (vast majority of pancreatic secretion)
  - **CCK** (major agonist of acinar cells): released from I-cells due to presence of peptides, amino acids, and FFAs. CCK stimulates production and secretion of enzyme rich solution from pancreatic acinar cells and potentiates secretin.
  - **Secretin** (major agonist of duct cells): released from S-cells due to presence of chyme with pH <4.5. Secretin augments CCK and is the major agonist for duct cell secretion of an alkaline rich fluid.
    - In duct cells, secretin and VIP stimulation is mediated by cAMP→PKA→phosphorylation of CFTR→clogging of mucous in duct cells and ducts→decreased quantities of digestive enzymes in intestines, and pancreatic degradation.

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**Intestinal Absorption:**

**The Absorptive Surface:**

- **Small Intestine is the site of most digestion.**
  - The enterocyte is the mature intestinal epithelial cell.
  - Carbohydrates, proteins, and fats are absorbed in the upper half of the SI, along with most minerals, water, and vitamins. Most Vitamin B12–IF complex and bile salts are absorbed in the distal one-third of the SI.
  - Enterocytes are replaced by continuous mitotic activity in the crypts of Lieberkühn (enterocyte stem cells).
  - Cells slide up a villus until they are shed from the tip (3-4 days in humans).
  - The enterocytes mature as they leave the crypt region, and they have a full complement of enzymes and transporter proteins when they appear on the side of the villi.
    - Each cell is covered on its apical surface with a brush border of 1,500-3,000 microvilli.
      - Brush border is rich in glycoproteins, hydrolytic enzymes, and carrier proteins.
      - 10% of brush border cells are goblet cells (make mucous).
      - 10% of brush border cells are lymphocytic.
      - Brunner’s glands are found in the brush border of the duodenum (secrete alkaline mucous).
  - SI has very large surface area (mucosa is in folds of Kerckring – valvulae conniventes) and epithelium is arranged in villi (0.5-1mm long). Epithelial cells are bound together by tight junctions.
    - Tight junctions are impermeable to macromolecules, but are variably permeable to ions and water (more leaky in proximal SI and more tight at the colon). Maintain asymmetrical distribution of transporter and enzyme proteins across membrane.

**Carbohydrate Digestion and Absorption:**

- Carbohydrate intake ~250-800g. It is the principal source of calories.
  - 60% glucose polymers (starch).
  - 30% sucrose.
  - 10% lactose.
  - Only monosaccharides can be absorbed, yet there are few monosaccharides in the diet.
    - Amylase (salivary and pancreatic): degrades interior α-1,4 glycosidic linkages.
    - Lactase: specific for lactose → galactose + glucose
    - Sucrase: can degrade maltose and maltotriose (→ glucose) in addition to sucrose → fructose + glucose
    - Maltase: maltose and maltriose → glucose
    - α-Dextrinase: can degrade maltose and maltotriose in addition to α-dextrins → glucose
    - Cellulose: cannot be absorbed by humans (some animals can use as a food source as it can be degraded by certain bacteria).
      - Glucose and galactose share a common sodium-dependent transport mechanism for which these compete (SGLT1).
        - Basolateral exit is non-competitive and downhill (GLUT2) – shared by fructose.
      - Fructose is taken up by sodium-independent specific carrier (GLUT5).
        - Some fructose → ATP and some → glucose.
  - Most ingested carbohydrate is absorbed in the first 20% of the SI—The carbohydrate capacity of the SI is nearly impossible to saturate.

**Carbohydrate Malabsorption Syndromes:**

- Deficiency in digestive enzymes of brush border: symptoms include intestinal distension, borborygmi, and diarrhea.
  - Lactose Malabsorption Syndrome: deficiency in lactase (50% of adults) → undigested lactose not absorbed and thus passes on to colonic bacteria which metabolize it producing gas and metabolites that are agonistic to colonic motility (lactose intolerance). Hereditary.
  - Glucose-galactose Malabsorption Syndrome: Defect in SGLT1 transporter of glucose and galactose. Ingestion of these sugars → severe diarrhea. Fructose is well tolerated. Hereditary.
  - Oral Sugar Tolerance Test: oral dose of sugar given and sugar levels in blood and feces measured. If intolerant of ingested sugar, diarrhea ensues and sugar appears in feces but NOT blood (no absorption).
Digestion and Absorption:

- Most ingested protein is absorbed in SI (GI tract absorbs ingested protein and 10-30g of secretion protein daily).
  - Minute amounts of intact protein and large peptides are absorbed by receptor-mediated endocytosis.
  - Small amounts digested by pepsin in stomach
  - Majority of protein is digested in the SI (by brush border and pancreatic proteases—see enteropeptidase activation).
    - 50% of protein is digested and absorbed in the duodenum.
    - Small peptides (2-4 amino acids in length) are 3-4x more concentrated than single amino acids in intestines. Rate of transport of di- and tripeptides is greater than rate of transport for single AAs.
      - Apical proton-dependent transport pump (PepT1).
      - Cytosolic peptides hydrolyze di- and tripeptides into single AAs, which cross the basolateral membrane via two transport mechanisms, which are further specific for groups of AAs (neutral, acidic, etc.): (1) Na⁺ dependent, and (2) Na⁺ independent.
        - Small, hydrophobic AAs can freely diffuse across the basolateral membrane.

- Protein Malabsorption Syndromes: Hereditary disorders of specific transporters are recognized by presence of AAs in urine. These conditions do not result in malnutrition, as di- and tripeptides are still absorbed.

Water and Electrolyte Absorption:

- Intestine absorbs 9L H₂O daily (7L from GI secretions and 2L ingestion).
  - Little H₂O absorption occurs in duodenum, but chyme made isotonic here. Since duodenum is highly water permeable, hypertonicity of chyme delivered from stomach forces H₂O movement from blood to lumen.
  - Large amount of H₂O absorption occurs in jejunum (more) and ileum. Little H₂O absorption occurs in colon (1L/day).
    - Intestinal H₂O absorption is secondary to Na⁺ reabsorption.
      - Standing Osmotic Gradient Hypothesis: Transport of Na⁺ into intracellular spaces raises osmolality → large osmotic water flow into intracellular spaces (due to high permeability of H₂O in SI) → raised hydrostatic pressure → fluid driven into capillaries → fluid becomes isotonic
  - Na⁺ is absorbed along entire SI (highest rate in jejunum).
    - In jejunum, Na⁺ transport is enhanced by glucose, galactose, and AA absorption (all use Na⁺ coupled processes).
    - In ileum, rate is slower (fewer carrier proteins).
    - In colon, Na⁺ is absorbed at a lower rate (against a larger electrochemical gradient) due to tightness of colonic cell-junctions. Absorption in colon is primarily via Na⁺-selective channels stimulated by aldosterone.
Micelles from bile (consist of salts, cholesterol, and lecithin) cannot be absorbed without pre-solubilization.

Lipid Digestion and Absorption:

- **Ion Absorption (Calcium, Iron, and Vitamins):**
  - **Calcium:** Paracellular (passive – adequate or high Ca\(^{2+}\) intake) and Transcellular (active – low Ca\(^{2+}\) intake) pathways.
    - Transcellular Pathway:
      - **Entry:** down the electrochemical gradient via voltage-insensitive Ca\(^{2+}\) channels.
      - **Intracellular Diffusion:** Rate-limiting (requires calbindin to buffer and transport Ca\(^{2+}\)).
      - Calbindin is a product of vitamin D.
      - **Extrusion:** Ca\(^{2+}\) - ATPase (synthesis stimulated by vitamin D)
  - **Iron:** required for hemoglobin, myoglobin, cytochromes, and many enzymes, but can be deleterious by catalyzing formation of free-radicals that attack cell membranes, proteins, and DNA. Therefore, iron is sequestered by proteins (transferrin – plasma; ferritin – cells) and its absorption is highly regulated.
    - 1-2mg iron absorbed daily (small fraction of that ingested). Most absorption occurs in upper duodenum (low pH and localized ferrireductase convert insoluble ferric (Fe\(^{3+}\)) to absorbable ferrous (Fe\(^{2+}\)) forms.
    - Ferrous iron crosses apical membrane via protein carrier (Divalent Metal Transporter 1 – DMT1). Iron binds ferritin (irreversible – released in feces) or mobilferrin (reversible – similar to calbindin) in enterocytes. Mobilferrin buffers iron, and facilitates diffusion to the basolateral membrane. Ferroportin (Ireg1) is the basolateral carrier protein, as well as transferrin receptors. Iron appears in blood bound to transferrin.
    - Regulation: (1) Amount of apoferritin (ferritin without bound iron) – synthesized by mucosal cells. [Apoferritin] increases when iron stores are high and decreases when stores are low. Translation of apoferritin mRNA is regulated by cytosolic iron concentration. (2) Hepcidin – liver peptide that binds and degrades iron transporter ferroportin (basolateral). Therefore, synthesis of hepcidin is increased by iron loading, and suppressed by anemia, hypoxia, or high rate of erythropoiesis.

- **Vitamins:**
  - See B\(_12\) above.
  - Vitamin C (ascorbic acid), Thiamin (Vit B\(_1\)), biotin, and others are co-transported with Na\(^+\).
  - Dietary folate is deconjugated and absorbed by an anion exchanger in proximal SI.
  - Lipid soluble vitamins (A, D, E, and K) dissolve in mixed micelles and leave intestine in lymph.

Lipid Digestion and Absorption: Triglyceride is responsible for 40% of caloric intake but are not soluble in water and therefore cannot be absorbed without pre-absorptive processing. The object of lipid solubilization is to incorporate dietary lipids within micelles from bile (consist of salts, cholesterol, and lecithin – a phospholipids).

- **Solubility:** Aqueous solubility: In order for a molecule to be soluble in water, it must have accessible polar groups that can bind water (hydrophilic groups). Ionized hydrophilic groups (e.g. COO\(^-\), PO\(_4\)^{2-}, NH\(_3\)) are more strongly polar than non-ionized hydrophilic groups (e.g. OH, COOR). Hydrocarbon chains are non-polar (hydrophobic), and their hydrophobicity increases in proportion to the number of carbon atoms in the molecule.
Cholesterol is relatively insoluble and forms a stable monolayer at the aqueous-air interface and, at increased concentration, a floating oil layer. Sodium-taurocholate (bile salt) also forms a monolayer at the air-water interface, but at increased concentrations, it forms aggregates in a specific manner (micelles) that are water-soluble. In mixtures of both Na+-taurocholate and cholesterol, the bile salt increases the maximum solubility of cholesterol about 500,000 times, since the hydrophobic portion of cholesterol can pack within the hydrophobic portion of the bile salt micelle.

- **Process of Lipid Digestion:**
  - **Emulsification** (dispersion): Mechanical emulsification occurs as a result of gastric mixing/homogenization.
    - Enzymes lipolyzing fats can only act on the surface, therefore it is necessary to increase surface area (increases rate of hydrolysis and solubilization of triglycerides).
    - Lecithin and formation of FFAs and diglycerides by lingual lipase (serous glands of tongue) and gastric lipase (chief cells) stabilize emulsification products.
    - Emulsion droplets are very large (macroscopic).
  - **Release of CCK**: CCK released in response to presence of FFAs and certain AAs.
    - CCK triggers gall bladder contraction (bile release) and pancreatic lipase (and protease) release from pancreatic zymogenic stores.
  - **Pancreatic Lipolysis** (degredation): Hydrolysis is the result of the action of pancreatic lipase (secreted in active form – pH optima ~6-7; destroyed by pH<3). Colipase protects pancreatic lipase from denaturation by bile salts and anchors the lipase to the oil-water interface. Esterase hydrolyzes cholesterol esters, and phospholipase hydrolyzes the 2-acyl bond of lecithin.
    - Lipolytic enzymes are all carboxylesterases.
    - Lipase acts upon a triglyceride, reducing it to two FFAs and one molecule of 2-monoglyceride.
  - **Micellar Solubilization by Bile Acids** (dissolve): micellar dispersion increases rate of fat absorption by increasing the concentration of lipolytic products in the aqueous phase 1000x. Rate of diffusion 1/6th that of FFAs. Therefore micellar solubilization increases flux by 150x.
  - **Lipid Processing:**
    - Hydrolysis followed by micellar dispersion: long-chain triglycerides
    - Micellar dispersion without hydrolysis: fat soluble vitamins (A, D, E, K,) and cholesterol
    - Hydrolysis only: hydrolytic products are water soluble [medium chain triglycerides – 8-12 carbons]
  - **Uptake and Enterocyte Transformation** (Passive Diffusion and Absorption): FFAs and monoglycerides are absorbed in the proximal SI (passive xport), while bile salts are absorbed in the distal ileum (active xport) – cholesterol uptake is carrier mediated.
    - Micelles are not absorbed intact (see above).
- Micelles are essentially a buffer for FFAs and monoglycerides, keeping saturation maximal such that the rate of absorption increases (expansion of micelles with FFAs increases the capacity for cholesterol solubilization).
- Bile salts are 95% conserved. Human body has a small pool of bile salts that is recycled ~3x/meal. The 5% of the total supply lost in feces daily serves as a method of eliminating cholesterol.
- Triglyceride Resynthesis: FFAs and monoglycerides are re-esterified to triglyceride at the cytoplasmic surface of the ER and are transported into the ER lumen of enterocytes.
  - Monoglyceride Acylation Pathway: 2-monoglyceride is acylated with fatty acid-CoA.
  - Phosphatidic Acid Pathway: Glucose is converted to glycerol phosphate, which is esterified with fatty acid-CoA \( \rightarrow \) phosphatidic acid. Dephosphorylation gives diglyceride, which is acylated to triglyceride.
- Chylomicron Formation: Resynthesized triglycerides aggregate to form spherical structures stabilized with free cholesterol and lecithin.
- Lymphatic Transportation: Chylomicrons are exocytosed into interstitial fluid \( \rightarrow \) lacteals \( \rightarrow \) lymphatics \( \rightarrow \) cisternal chyli \( \rightarrow \) SVC (via thoracic duct).
  - Medium chain fatty acids are water soluble and diffuse directly into portal blood (not in chylomicrons) and are oxidized by liver and thus are not taken up by adipose tissue.
- Absorption from Blood (Adipose Absorption): The majority of triglycerides in chylomicrons are hydrolyzed into glycerol and FFAs by lipoprotein lipase (synthesized by adipocytes and lives on endothelial cell membranes). Heparin causes activation of lipoprotein lipase and its release from tissues into blood. Lipoprotein lipase is thus destroyed by heparinase.

Lipid Summary:

<table>
<thead>
<tr>
<th>Emulsification</th>
<th>Lipolysis</th>
<th>Solubilization</th>
<th>Diffusion</th>
<th>Uptake</th>
<th>Transport to Smooth ER</th>
<th>Triglyceride Resynthesis</th>
<th>Chylomicron Formation</th>
<th>Lymphatic Transport</th>
<th>Circulation</th>
<th>Adipose Absorption</th>
<th>Liver</th>
</tr>
</thead>
</table>

The Liver:

Anatomy and Histology:

- The celiac artery supplies the liver, spleen, the stomach the gallbladder, and part of the duodenum. The superior mesenteric artery supplies entire SI and right side of the LI; the inferior mesenteric artery supplies the rest of the colon. Venous blood draining the gut, including the entire colon, enters the portal system. Blood from the spleen, pancreas, gallbladder and most of the stomach empties into the portal vein. All portal blood has passed through one capillary system in each of these organs and will enter a second capillary system in the liver.
- The liver consists of hexagonal lobules. The center of each lobule is a central vein that empties into the hepatic vein and then into the IVC. Portal triads (portal vein, hepatic artery, and bile duct, as well as lymphatics and nerves) are found at the corners. Portal vein empties into hepatic sinusoids (large capillaries lined with a porous endothelium that allows all proteins and lipoproteins, but not blood cells, to pass through into the space of Disse).
- The hepatic artery supplies 25% of the blood (the portal vein supplying the other 75%), empties into the hepatic sinusoids. The two blood supplies mix high oxygen from the hepatic artery and low oxygen, nutrient-rich blood from portal vein.
  - The hepatic artery and portal vein are not necessary for survival of the liver. (The liver partially atrophies without portal input).
  - Digestion products flow to the liver in the portal vein (fatty acids, amino acids, sugars, vitamins, etc.) as well as hormones from the pancreas (insulin and glucagon) and from the GI tract (gastrin, secretin, CCK) as well as bilirubin, a product of red cell breakdown in the spleen.
  - The pressure in the sinusoids is extremely low.
  - Small tracts (canaliculi) are between double layers of hepatic cells. They empty into the Duct of Herring \( \rightarrow \) Bile Duct \( \rightarrow \) common hepatic duct \( \rightarrow \) porta hepatis.
    - Biliary secretions (water and electrolytes, bile salts, cholesterol, phosphatidylcholine, bilirubin) run towards the porta hepatis, while blood flows in the opposite direction towards the central vein.
      - Lymphatics begin in the Space of Disse (between the endothelial cell and the hepatic cell). Lymph that is formed in the space of Disse is basically blood plasma without the cells. Lymph passes out of the lobule into lymph channels on the exterior part of the lobule and then follows the hepatic artery, the portal vein and the bile duct down to the porta hepatis, where it exits the liver to enter the cysterni chyli.
      - Hepatocytes are surrounded on most of the surface by sinusoidal blood.
Hepatocytes are full of cellular machinery, ribosomes, smooth and rough endoplasmic reticulum, Golgi apparatus, secretory and uptake (endocytic) vesicles, mitochondria, lysosomes and peroxisomes. These cells are major metabolic factories.

Metabolism:

- **Sugars and Amino Acids:**
  - Glucose is synthesized in the liver (packaged during fed state → glycogen). During fasting state/exercise, glycogen is mobilized to produce glucose.
  - Other sugars are metabolized in liver. Sugars are also converted to complex polysaccharides.
  - Amino acids are catabolized → urea (urea cycle).
  - Transamiation (AAs from sugars) and gluconeogenesis (AAs to sugars) occur in liver.

- **Lipids:**
  - Fatty acids are synthesized from acetate.
  - Beta-oxidation catabolizes lipids for energy during fasting states.
  - Complex lipids (triacylglycerol, cholesterol ester, phospholipids, and glycolipids) are formed and assembled into lipoproteins (secretion) or fat droplets (storage).
  - Triacylglycerols are NOT secreted in bile.
  - Cholesterol is synthesized from acetate (HMG CoA reductase).
    - Cholesterol is:
      - catabolized → bile salts.
      - packaged in lipoproteins (VLDL) and secreted into blood stream.
      - secreted into bile
  - Liver synthesizes all of the major phospholipids [phosphatidylcholine (PC), lecithin], phosphatidyl ethanolamine (PE), phosphatidyl serine (PS), phosphatidyl inositol (PI) and sphingolipids. Phospholipids (mainly PC) are secreted as components of lipoproteins into the blood stream; phospholipids are also secreted into bile.

- **Proteins:**
  - Most plasma proteins (e.g. albumin, clotting factors, fibrinogen, and most plasma apolipoproteins) are synthesized in the liver (γ-globulins come from lymphoid tissue, and protein hormones are synthesized by specific organs).
    - The body pool of albumin is ~5g per kg or about 350g total in a 70kg person.
    - 40% of that is intravascular and 60% extra vascular.
    - Liver catabolizes ~300mg per kg per day or ~21gm per person a day.
    - The rate of breakdown is balanced by the rate of synthesis. Synthesized albumin is secreted into the space of Disse.
      - Average lifetime of albumin is ~12-16 days.

**Bilirubin:** Golden-brown pigment derived from heme. Elevated bilirubin in plasma → jaundice.

- **Formation:** RBCs broken-down in spleen. Iron released from heme (recycled by transferrin), and tetrapyrotyl ring of heme is converted to bilirubin (compact highly insoluble hydrophobic molecule with hydrophilic residues sequestered in center).
  - Bilirubin is soluble in plasma due to tight binding to albumin (8 sites for FFAs and 1 site for bilirubin – 1:1 ratio; also binds drugs and toxins). As level of circulating bilirubin increases (above 0.6mM (4g/dl) – the concentration of albumin), it moves into tissues (skin and conjunctiva of eye) → yellow color.
    - Bilirubin can cross the blood-brain barrier → kernicterus, seizures, and brain damage (especially in infants).

- **Uptake, Conjugation, and Secretion:** Bilirubin-Albumin complex enters hepatic sinusoid via portal vein. Binds specific carriers → binding proteins → ER → esterification (by glucuronol transferase addition of glucuronic acid) → bilirubin diglucuronide → transported into bile canaliculus by ATP Binding Cassette transporters → bile duct system → intestines → colon → degradation into dipyroles (give dark color to feces) → fecal excretion.
  - *Biliary tract obstruction or hepatic injury → light colored stool.*
**Bile Salts and the Enterohepatic Circulation**: Bile salts bind albumin in plasma, and move through hepatocytes in a method similar to that of bilirubin.

- **Formation, Conjugation, Secretion, and Uptake**: Cholesterol is metabolized to bile salts in the liver.
  - After significant processing, the salt-precursors are conjugated with **glycine** or **taurine**, producing salts that are acid resistant detergents.
  - Conjugated bile salts are transported to the lumen of canaliculi by a specific ABC transporter **Bile Salt Export Protein (BSEP)** to intestines to enhance absorption of FFAs and monoglycerides.
  - The pool of bile salts is ~3g, and the pool circulates 6-10X/day (2-3x/meal), therefore total circulation is ~24g/day. Approximately 0.4g (5%) is lost daily in feces, and ~0.4g (5%) is synthesized daily such that the pool is fairly constant.
  - Bile salt synthesis is dependent upon the rate of return of bile salts. High rates of return depress synthesis and vice-versa.
  - Bile salts are rapidly absorbed in the ileum (~30 minutes after secretion), and can be resecreted ~10 minutes after ileal uptake.
  - In the ileum, **Ileal Bile Acid Transporters (IBAT)** bind and translocate bile salts across the enterocyte membrane, where it is bound by an **Ileal Lipid Binding Protein (ILBP)**. The salt enters the portal system binds to albumin, and is taken up by a carrier, **Na+-Taurocholate Cotransport Protein (NTCP)**, that transports it across the sinusoidal membrane of hepatocytes, and back to BSEPs.

**Cholesterol and Phosphatidylcholine (PC) Synthesis and Secretion by ABC transporters and the Formation of Cholesterol/PC Micelles**:

- **Increases in cholesterol secretion or decreases in bile salt secretion lead to gallstone formation**.
  - PC secretion rate is a bile salt secretion rate.
  - Bile salts, cholesterol, and PC are transported to lumen of canaliculi by three separate specific ABC transporters. They are **combined into micelles on the luminal side of the canicular membrane**.
    - Cholesterol is synthesized in the liver, in peripheral tissues, and is absorbed in the diet. All cholesterol eventually enters hepatic circulation and once in the liver is treated like synthesized cholesterol.
      - Cholesterol net uptake is determined by the balance of absorption (Neiman-Pick-like protein – NCPL-1 transporter) and secretion (ABCG5/8 transporter).
        - Cholesterol absorption in the intestine can vary widely from person to person and between species. Newly absorbed cholesterol is excreted back into the gut lumen, thus cholesterol absorption is limited (normally 30-60% of cholesterol entering the intestine is absorbed).
      - **ABCG5/8 (key regulator of body cholesterol and responsible for both hepatic and intestinal secretion of cholesterol)** is upregulated by high cholesterol and down regulated by low cholesterol.

**Potential Defects**: (1) **Hyperbilirubinemia**: over production of unconjugated bilirubin (extensive RBC hemolysis – hemolytic anemias etc). (2) **Uptake Carrier Defect**: unconjugated hyperbilirubinemia. (3) **Glucuronyl Transferase Defect**: neonatal jaundice is caused by common, spontaneous increase in hemolysis at birth, and by poorly developed glucuronyl transferase. Possibly due to genetic mutation (more severe) → death due to severe unconjugated hyperbilirubinemia. (4) **ABC transporter Defect**: conjugated bilirubin glucuronide backs up into plasma (conjugated hyperbilirubinemia) → Dubin-Johnson disease (largely asymptomatic due to a defect in only one ATP transporter – others exist and thus back up is mild). (5) **Bile Flow Obstruction**: most common cause of conjugated hyperbilirubinemia (gallstones, cancer, etc).
Inactivation of ABCG5 or 8 → blockage of cholesterol secretion in the liver and increased absorption of cholesterol and similar plant sterols → Sitosterolemia: poor biliary excretion of sterols, increased absorption of plant sterols, hypercholesterolemia, hypercholesterolemia, and early coronary atherosclerosis.

If bile salt transporters have disrupted function, an increased concentration of bile salts build up in the plasma and the liver. Micelles are not formed, but PC and cholesterol are released in vesicles. If PC transporter K/O, bile salt is transported, but no cholesterol is solubilized. Therefore phospholipids must be solubilized by bile salt. PC can then solubilize cholesterol. If the sterol transporter is K/O, severe atherosclerosis results.

Cholesterol gallstones: Non-obese patients with gallstones have low bile salt secretion rates, while obese patients have double the normal cholesterol secretion rates. Reduction of body weight to normal can return cholesterol secretion rates to normal.

(a) Lipoproteins:
- **Uptake**: Three types of transmembrane transport:
  - **(1): Diffusion**: Albumin binds FFAs released from adipose tissue during fasting or exercise and from chylomicrons following lipolysis by lipoprotein lipase (LPL). Each albumin can bind 10-15 FFAs (but usually only binds 1-2). FFAs bound in excess of 1:1 ratio are transferred to hepatocytes and are bound intracellularly by Fatty Acid Binding Protein (FABP) → enter intracellular pool of fatty acids.
  - **(2): Receptor Mediated Endocytosis**: ~50% of low-density lipoprotein (LDL) is removed by peripheral tissues (the cholesterol is used for cell membrane formation, etc.). The other ~50% is removed by the liver. LDL binds to the hepatic LDL-R and undergoes receptor mediated endocytosis. LDL is released intracellularly and shuttled to lysosomes for degradation. LDL-R is recycled to the extracellular surface. In Familial Hypercholesterolemia, LDL-R is deficient, and therefore, LDL is high. Remnants of chylomicrons (cholesterol and FFAs left after the action of LPL) are endocytosed by chylomicron remnant receptors (CMrem-r) similar to LDL-R.
    - LDL-R synthesis is regulated by the levels of cholesterol in the liver (synthesis 1α pool).
      - FFA uptake from albumin, HDL uptake of cholesterol ester, and chylomicron remnant uptake are not so precisely regulated.
  - **(3): Receptor Mediated Selective Uptake**: High Density Lipoprotein (HDL) contains free and esterified cholesterol. Excess unesterified (free) cholesterol is transferred to plasma apoA-I and HDL. Most of this cholesterol is esterified by LCAT. This cholesterol ester is drawn into the liver by Scavenger Receptor Type B-1 (SR-B1) and is hydrolyzed to cholesterol and FFA. This cholesterol is secreted into mixed micelles in bile canaliculi.

- **Synthesis, and Secretion:**
  - Albumin can be thought of as a lipoprotein because it can bind hydrophobic substances (in particular FFAs). But albumin is synthesized in the liver sans FFAs. Ribosomal carried mRNA for albumin is targeted to the ER, then exocytosed into the sinusoidal space via the golgi.
  - **Apolipoprotein A-I** is the major apoprotein of HDL. Translated apoA-1 is translocated into the ER and there (or in the golgi) phospholipids (PC) are added to ApoA-1 to produce nascent HDL, which is secreted into the sinusoidal space. Nascent HDL binds cholesterol and PC via ABCA-1 transport from cells in peripheral tissues.
• The plasma enzyme **Lecithin Cholesterol Acyl Transferase (LCAT)** converts cholesterol → cholesterol ester and forms mature plasma HDL.

• mRNA for **apoB** also targets ribosomes to the ER → two possible fates for apoB: (1) it is combined with triglyceride, phospholipids, and cholesterol to form nascent VLDL that is secreted into plasma, or (2) if not enough lipid substrate is present, apoB is degraded.

  • **Control for secretion of VLDL (nascent) is post-translational and governed by lipid substrate availability.**
    - ~100g VLDL (nascent) is secreted daily.
    - Once VLDL is secreted into the plasma, it picks up cholesterol, other apolipoproteins (cofactors for LPL), its triglyceride is removed by LPL, and it is converted into LDL.

(1) Diffusion, (2) Receptor Mediated Endocytosis, and (3) Receptor Mediated Selective Uptake.
CM=chylomicron remnant. CE=cholesterol ester. The pH in the endocytic compartments is very low.