Cardiac Pharmacology
(Introduction)

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Department of Pharmacology
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• Safe
• Quality Education
• World-class post secondary
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Pharmacology

DEFINITIONS:

**Pharmacology** is the study of how drugs exert their effects on living systems.

Pharmacologists work to identify drug targets in order to learn how drugs work. Pharmacologists also study the ways in which drugs are modified within organisms.

In most of the pharmacologic specialties, drugs are also used today as tools to gain insight into both normal and abnormal function.
Definitions

- **Pharmacokinetics**
  - The process by which a drug is absorbed, distributed, metabolized and eliminated by the body

- **Pharmacodynamics**
  - The interactions of a drug and the receptors responsible for its action in the body
The Life Cycle of a Drug
(pharmacokinetics)

• Absorption
• Distribution
• Degradation
• Excretion
Slow Absorption

- Orally (swallowed)
- through Mucus Membranes
  - Oral Mucosa (e.g. sublingual)
  - Nasal Mucosa (e.g. insufflated)
- Topical/Transdermal (through skin)
- Rectally (suppository)
Faster Absorption

• Parenterally (injection)
  – Intravenous (IV)
  – Intramuscular (IM)
  – Subcutaneous (SC)
  – Intraperitoneal (IP)

• Inhaled (through lungs)
Fastest Absorption

- Directly into brain
  - Intracerebral (into brain tissue)

General Principle: The faster the absorption, the quicker the onset, the higher the addictiveness, but the shorter the duration
Distribution: Depends on Blood Flow and Blood Brain Barrier

**FIGURE 1.8** Cross section of a blood capillary. Within the capillary are the fluids, proteins, and cells of the blood, including the red blood cells. The capillary itself is made up of cells that completely surround and define the central cylinder (or lumen) of the capillary. Water-filled pores form channels, allowing free flow of blood plasma and extracellular fluid.
• Excludes ionized substances;
• Active transport mechanisms;
• Not uniform – leaky (circumventricular areas)
Bioavailability

• The fraction of an administered dose of drug that reaches the bloodstream.

• What determines bioavailability?
  – Physical properties of the drug (hydrophobicity, pKa, solubility)
  – The drug formulation (immediate release, delayed release, etc.)
  – If the drug is administered in a fed or fasted state
  – Gastric emptying rate
  – Circadian differences
  – Interactions with other drugs
  – Age
  – Diet
  – Gender
  – Disease state
Depot Binding
(accumulation in fatty tissue)

• Drugs bind to “depot sites” or “silent receptors” (fat, muscle, organs, bones, etc)

• Depot binding reduces bioavailability, slows elimination, can increase drug detection window

• Depot-bound drugs can be released during sudden weight loss – may account for flashback experiences?
Degradation & Excretion

- Liver
  - Enzymes (cytochrome P-450) transform drugs into more water-soluble metabolites
  - Repeated drug exposure increases efficiency → tolerance

- Kidneys
  - Traps water-soluble (ionized) compounds for elimination via urine (primarily), feces, air, sweat
Excretion: Other routes

• Lungs
  alcohol breath
• Breast milk
  acidic ---> ion traps alkaloids
  alcohol: same concentration as blood
  antibiotics
• Also bile, skin, saliva ~
Metabolism and Elimination (cont.)

• Half-lives and Kinetics
  – Half-life:
    • Plasma half-life: Time it takes for plasma concentration of a drug to drop to 50% of initial level.
    • Whole body half-life: Time it takes to eliminate half of the body content of a drug.
  – Factors affecting half-life
    • age
    • renal excretion
    • liver metabolism
    • protein binding
First order kinetics

A constant *fraction* of drug is eliminated per unit of time.

When drug concentration is high, rate of disappearance is high.
Zero order kinetics

Rate of elimination is constant.

Rate of elimination is independent of drug concentration.

Constant amount eliminated per unit of time.

Example: Alcohol
Comparison

• First Order Elimination
  – [drug] decreases exponentially with time
  – Rate of elimination is proportional to [drug]
  – Plot of log [drug] or ln[drug] vs. time are linear
  – $t_{1/2}$ is constant regardless of [drug]

• Zero Order Elimination
  – [drug] decreases linearly with time
  – Rate of elimination is constant
  – Rate of elimination is independent of [drug]
  – No true $t_{1/2}$
Drug-drug Interactions

• Pharmacokinetic and pharmacodynamic
  – With pharmacokinetic drug interactions, one drug affects the absorption, distribution, metabolism, or excretion of another.
  – With pharmacodynamic drug interactions, two drugs have interactive effects in the brain.
  – Either type of drug interaction can result in adverse effects in some individuals.
  – In terms of efficacy, there can be several types of interactions between medications: cumulative, additive, synergistic, and antagonistic.
The condition in which repeated administration of a drug may produce effects that are more pronounced than those produced by the first dose.
Additive Effects

The effect of two chemicals is equal to the sum of the effect of the two chemicals taken separately, eg., aspirin and motrin.
Synergistic Effects

The effect of two chemicals taken together is greater than the sum of their separate effect at the same doses, e.g., alcohol and other drugs
The effect of two chemicals taken together is less than the sum of their separate effect at the same doses.
Pharmacodynamics

- Receptor
  - target/site of drug action (e.g. genetically-coded proteins embedded in neural membrane)

- Lock and key or induced-fit models
  - drug acts as key, receptor as lock, combination yields response
  - dynamic and flexible interaction
Agonism and Antagonism

**Agonists** facilitate receptor response

**Antagonists** inhibit receptor response

(direct ant/agonists)
Modes of Action

• Agonism
  – A compound that does the job of a natural substance.
  – Does not effect the rate of an enzyme catalyzed reaction.

• Up/down regulation
  – Tolerance/sensitivity at the cellular level may be due to a change in # of receptors (without the appropriate subunit) due to changes in stimulation

• Antagonism
  – A compound inhibits an enzyme from doing its job.
  – Slows down an enzymatically catalyzed reaction.
Agonists/Antagonists

- Full
- Partial
- Direct/Competitive
- Indirect/Noncompetitive
- Inverse

A single drug can bind to a single receptor and cause a mix of effects (agonist, partial agonist, inverse agonist, antagonist)

Functional Selectivity Hypothesis:
Conformational change induced by a ligand-receptor interaction may cause differential functional activation depending on the G-protein and other proteins associated with the target receptor
Important implications of drug-receptor interaction

- drugs can potentially alter rate of any bodily/brain function
- drugs cannot impart entirely new functions to cells
- drugs do not create effects, only modify ongoing ones
- drugs can allow for effects outside of normal physiological range
Drug Effects

when a drug is used therapeutically, the desired action is termed the *therapeutic effect*

the effects of all drugs are dose-dependent

- the amount of drug that is administered determines both qualitative and quantitative aspects of its effects
- very low doses - no observable effects
- high enough doses - toxic reactions
Side Effects

any other action is a side effect

– side effects may be adverse, beneficial, or innocuous

– adverse drug reactions include
  ➢ toxic effects due to overmedication
  ➢ common side effects that appear at therapeutic dosages
  ➢ idiosyncratic side effects (e.g., allergic reactions) that are not clearly related to dose

– side effects vary from mild to life-threatening

– side effects may develop insidiously over a long period of time or may occur in an idiosyncratic and unpredictable fashion
Drug Combinations

• although it is not uncommon in clinical practice, there are few reports in the literature concerning the simultaneous use of more than one medication
• usually considered in
  treatment-resistant patients
  patients with comorbid diagnoses
• use of two different medications may permit lower doses of each and decrease the potential for side effects
• further research is needed evaluating the overall safety and efficacy of various drug combinations
Cardiac Pharmacology
(The Heart)

Yin Liu
Associate Professor
Department of Pharmacology
The Human Heart

• Beat ~2.5 billion times during a life time
  – The force of each beat is equivalent to squeezing a tennis ball as hard as you can

• Pump ~210 million liters of blood
  – This is equivalent to leaving your kitchen faucet on for ~45 consecutive years

• Travel ~3 billion km of blood vessels
  – This is equivalent of travelling to the Moon ~8500 times or going around Earth for ~75000 times
Introduction

• Human heart starts to develop during the 3rd week of embryonic life. Till then the needs of the embryo are met through simple diffusion of blood between the germ layers.
• Cardiogenesis in humans is associated with complex morphogenetic events
• The developing blood vessels and heart tube can be seen in an embryo at approximately 18 days.

• When looking down at this early embryo you can see multiple **blood islands** dispersed throughout the embryo.
Heart Development
Congenital Heart Disease

• Defect of the heart or its vessels presented at birth

• Affecting 1-5% of the overall population

• Caused by both environmental and genetic factors

Background

• Cardiovascular disease is the major cause of death in the US (>50% of all deaths)

• Cardiovascular function based on
  – Cardiac pumping ability
    • Pace-making electrical signals
    • Force of contraction
    • Height of ventricle discharge pressure
  – Integrity of vasculature
    • Presence of blockage
    • Muscular tone/structural integrity
    • Pressure drop needed to move blood to and through capillary beds
  – Blood volume/composition
    • Water, electrolyte, iron balances
    • Lipid and protein composition
Cardiovascular System Function

• Functional components of the cardiovascular system:
  – Heart
  – Blood Vessels
  – Blood

• General functions these provide
  – Transportation
    • Everything transported by the blood
  – Regulation
    • Of the cardiovascular system
      – Intrinsic v extrinsic
  – Protection
    • Against blood loss
  – Production/Synthesis
Overview of the Cardiosvascular System

- Heart and Blood vessels
- Products transported to sustain all cells

<table>
<thead>
<tr>
<th>SUBSTANCE MOVED</th>
<th>FROM</th>
<th>TO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Materials entering the body</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td>Lungs</td>
<td>All cells</td>
</tr>
<tr>
<td>Nutrients and water</td>
<td>Intestinal tract</td>
<td>All cells</td>
</tr>
<tr>
<td><strong>Materials moved from cell to cell</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wastes</td>
<td>Some cells</td>
<td>Liver for processing</td>
</tr>
<tr>
<td>Immune cells, antibodies, clotting proteins</td>
<td>Present in blood continuously</td>
<td>Available for any cell that needs them</td>
</tr>
<tr>
<td>Hormones</td>
<td>Endocrine cells</td>
<td>Target cells</td>
</tr>
<tr>
<td>Stored nutrients</td>
<td>Liver and adipose tissue</td>
<td>All cells</td>
</tr>
<tr>
<td><strong>Materials leaving the body</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic wastes</td>
<td>All cells</td>
<td>Kidneys</td>
</tr>
<tr>
<td>Heat</td>
<td>All cells</td>
<td>Skin</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>All cells</td>
<td>Lungs</td>
</tr>
</tbody>
</table>

Table 14-1: Transport in the Cardiovascular System
The distribution of blood in a comfortable, resting person is shown here.

Dynamic adjustments in blood delivery allow a person to respond to widely varying circumstances, including emergencies.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Flow at rest ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>650 (13%)</td>
</tr>
<tr>
<td>Heart</td>
<td>215 (4%)</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>1030 (20%)</td>
</tr>
<tr>
<td>Skin</td>
<td>430 (9%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>950 (20%)</td>
</tr>
<tr>
<td>Abdominal organs</td>
<td>1200 (24%)</td>
</tr>
<tr>
<td>Other</td>
<td>525 (10%)</td>
</tr>
<tr>
<td>Total</td>
<td>5000 (100%)</td>
</tr>
</tbody>
</table>

Adapted from Chapman and Mitchell.
<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart</strong></td>
<td></td>
</tr>
<tr>
<td>Atria</td>
<td>Chambers through which blood flows from veins to ventricles. Atrial contraction adds to ventricular filling but is not essential for it.</td>
</tr>
<tr>
<td>Ventricles</td>
<td>Chambers whose contractions produce the pressures that drive blood through the pulmonary and systemic vascular systems and back to the heart.</td>
</tr>
<tr>
<td><strong>Vascular system</strong></td>
<td></td>
</tr>
<tr>
<td>Arteries</td>
<td>Low-resistance tubes conducting blood to the various organs with little loss in pressure. They also act as pressure reservoirs for maintaining blood flow during ventricular relaxation.</td>
</tr>
<tr>
<td>Arterioles</td>
<td>Major sites of resistance to flow; responsible for the pattern of blood flow distribution to the various organs; participate in the regulation of arterial blood pressure.</td>
</tr>
<tr>
<td>Capillaries</td>
<td>Sites of nutrient, metabolic end product, and fluid exchange between blood and tissues.</td>
</tr>
<tr>
<td>Venules</td>
<td>Sites of nutrient, metabolic end product, and fluid exchange between blood and tissues.</td>
</tr>
<tr>
<td>Veins</td>
<td>Low-resistance conduits for blood flow back to the heart. Their capacity for blood is adjusted to facilitate this flow.</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>Liquid portion of blood that contains dissolved nutrients, ions, wastes, gases, and other substances. Its composition equilibrates with that of interstitial fluid at the capillaries.</td>
</tr>
<tr>
<td>Cells</td>
<td>Includes erythrocytes that function mainly in gas transport, leukocytes that function in immune defenses, and platelets (cell fragments) for blood clotting.</td>
</tr>
</tbody>
</table>
Circulation Reviewed

• Heart – "four chambered"
  – Right atrium & ventricle
  – Pulmonary circuit
  – Left atrium & ventricle
  – Systemic circuit

• Blood Vessels – "closed circulation"
  – Arteries – from heart
  – Capillaries – cell exchange
  – Veins – to heart
Properties of Cardiac Muscle

– Aerobic muscle
– No cell division after infancy—growth by hypertrophy
– 99% contractile cells (for pumping)
– 1% autorhythmic cells (set pace)
Circulation Reviewed - it’s a closed circuit but “stuff” can get into the circuit in two places; which ones?

What is the general rule regarding the direction of blood flow through blood vessels? (capillaries, veins, arteries)

What is the exception to this general rule?
Why does blood flow? Think physics. . .

- $P\underline{\phantom{1}}\underline{\phantom{1}}\underline{\phantom{1}}\underline{\phantom{1}}$ $G\underline{\phantom{1}}\underline{\phantom{1}}\underline{\phantom{1}}\underline{\phantom{1}}$
What’s this mean?

• Pressure Gradient

What cardiovascular structure generates this pressure gradient?
The heart; why is the left side of the heart hypertrophied compared to the right side?
Blood Flow: Pressure Changes

Figure 14-2: Pressure gradient in the blood vessels
Functional Anatomy of the Heart

Chambers

- 4 chambers
  - 2 Atria
  - 2 Ventricles

- 2 systems
  - Pulmonary
  - Systemic
Functional Anatomy of the Heart

Valves

• Function is to prevent backflow
  – Atrioventricular Valves
    • Prevent backflow to the atria
    • Prolapse is prevented by the chordae tendinae
      – Tensioned by the papillary muscles
  – Semilunar Valves
    • Prevent backflow into ventricles
Atrioventricular Valve Action

(a) When the ventricles are relaxed, blood enters the atria, pushing the atrioventricular valve cusps down into the ventricles, opening the valves.

(b) When the ventricles contract, blood presses up against the atrioventricular valve cusps, forcing the valves closed. Contraction of the papillary muscles tightens the chordae tendineae, preventing the valve cusps from being pushed into the atria.
Semilunar Valve Action

(a) When the ventricles contract, blood presses up against the semilunar valve cusps, forcing the valves open and allowing blood to flow into the aorta and pulmonary artery.

(b) When the ventricles relax, blood in the aorta and pulmonary artery presses down against the valve cusps, forcing them to close.
The general route of the blood through the body is shown, including passage through the heart (colored box).
Functional Anatomy of the Heart

Intrinsic Conduction System

• Consists of “pacemaker” cells and conduction pathways
  – Coordinate the contraction of the atria and ventricles
Heart Structure – anatomy review

- Which two veins return deoxygenated blood to the heart? Which chamber is this, RA, LA, RV, LV?
- Deoxygenated blood is pumped to the lungs via what blood vessel?
- Oxygenated blood returns to the heart by what blood vessel? – To which chamber?
- Name the 4 heart valves.

Figure 14-7 g: ANATOMY SUMMARY: The Heart
Modulation of Contraction- what is the key ion?

Figure 14-12: Modulation of cardiac contraction by catecholamines
Action potential of a cardiac contractile cell

What is the Main difference Between this and The neuron Action potential?

There is a Physiological Reason for this difference; what Could it be?

<table>
<thead>
<tr>
<th>Phase</th>
<th>Membrane channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Na(^+) channels open</td>
</tr>
<tr>
<td>1</td>
<td>Na(^+) channels close</td>
</tr>
<tr>
<td>2</td>
<td>Ca(^{2+}) channels open; fast K(^+) channels close</td>
</tr>
<tr>
<td>3</td>
<td>Ca(^{2+}) channels close; slow K(^+) channels open</td>
</tr>
<tr>
<td>4</td>
<td>Resting potential</td>
</tr>
</tbody>
</table>

\(P_X = \text{Permeability to ion X}\)
Ionic mechanisms

• Resting potential
  – $K^+$ equilibrium potential
  – $Na^+$-inward background current
  – Electrogenic $Na^+$-$K^+$ pump
**Diagram of Membrane Transport**

- **Extracellular space**
- **[Na⁺]**
- **[Cl⁻]**
- **[K⁺]**

**Membrane: 3Na⁺**

**Na⁺/K⁺ pump:**
- 3Na⁺ → 2K⁺

**Nongated K⁺ channel:**
- K⁺

**Nongated Na⁺ channel:**
- Na⁺

**Cytoplasm: [A⁻]**

**ADP + Pi → ATP:**

**Cytoplasm:**
- [Na⁺]
- [A⁻]
- [Cl⁻]
- [K⁺]
The action potential of a myocardial pumping cell.

- **Phase 0**
  - Threshold potential (-70mV)
  - Opening of fast Na⁺ channel
  - Regenerative cycle

![Diagram of action potential cycle](image)

*Figure 12-13*
Phase 1
- Transient outward current, Ito K+ current
  - activated at −20 mV
  - opening for 5~10 ms
Phase 2

Inward current ↔ Outward current

\( \text{Ca}^{2+} \text{ & Na}^{+} \) \hspace{2cm} \text{(K}^{+} \text{ current)}

Figure 12-12
<table>
<thead>
<tr>
<th></th>
<th><strong>L-type</strong></th>
<th><strong>T-type</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of current</td>
<td>long-lasting</td>
<td>transient</td>
</tr>
<tr>
<td>Activation kinetics</td>
<td>slower</td>
<td>faster</td>
</tr>
<tr>
<td>Inactivation kinetics</td>
<td>slower</td>
<td>faster</td>
</tr>
<tr>
<td>Threshold</td>
<td>high (-35mV)</td>
<td>Low (-60mV)</td>
</tr>
<tr>
<td>cAMP/cGMP-regulated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Phosphorylation-regulated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Openers</td>
<td>Bay-K-8644</td>
<td>-</td>
</tr>
<tr>
<td>Blockers</td>
<td>varapamil</td>
<td>Tetramethrin</td>
</tr>
<tr>
<td></td>
<td>nifedipine, diltiazem</td>
<td>Ni^{2+}</td>
</tr>
<tr>
<td>Inactivation by [Ca^{2+}]_{i}</td>
<td>Yes</td>
<td>slight</td>
</tr>
<tr>
<td>Patch-clamp recording</td>
<td>run-down</td>
<td>relatively stable</td>
</tr>
</tbody>
</table>
Phase 3

Inactivation of Ca\textsuperscript{2+} channel

Outward K\textsuperscript{+} current dominates

I\textsubscript{K}: Progressively increased
I\textsubscript{K1}: Regenerative K\textsuperscript{+} Outward Current

Figure 12-12
Phase 4

$\text{Na}^+\text{-Ca}^{2+}$ exchange

Sarcolemmal $\text{Ca}^{2+}$ pump

$\text{SR Ca}^{2+}$ pump

$\text{Na}^+\text{-K}^+$ pump

Figure 12-12
a, The key ion channels (and an electrogentic transporter) in cardiac cells. K+ channels (green) mediate K+ efflux from the cell; Na+ channels (purple) and Ca2+ channels (yellow) mediate Na+ and Ca2+ influx, respectively. The Na+/Ca2+ exchanger (red) is electrogentic, as it transports three Na+ ions for each Ca2+ ion across the surface membrane.

b, Ionic currents and genes underlying the cardiac action potential. Top, depolarizing currents as functions of time, and their corresponding genes; centre, a ventricular action potential; bottom, repolarizing currents and their corresponding genes.

From the following article:
Cardiac channelopathies
Eduardo Marbán
Nature 415, 213-218 (10 January 2002)
doi:10.1038/415213a
Myocardial Physiology

Contractile Cells

- **Skeletal Action Potential vs Contractile Myocardial Action Potential**

*(a) Skeletal muscle fast-twitch fiber*: The refractory period (yellow) is very short compared with the amount of time required for the development of tension.

*(c) Cardiac muscle fiber*: The refractory period lasts almost as long as the entire muscle twitch.
Myocardial Physiology
Contractile Cells

• Plateau phase prevents summation due to the elongated refractory period
• No summation capacity = no tetanus – Which would be fatal
Myocardial Physiology
Contractile Cells

• Initiation
  – Action potential via pacemaker cells to conduction fibers

• Excitation-Contraction Coupling
  1. Starts with CICR (Ca$^{2+}$ induced Ca$^{2+}$ release)
     • AP spreads along sarcolemma
     • T-tubules contain voltage gated L-type Ca$^{2+}$ channels which open upon depolarization
     • Ca$^{2+}$ entrance into myocardial cell and opens RyR (ryanodine receptors) Ca$^{2+}$ release channels
     • Release of Ca$^{2+}$ from SR causes a Ca$^{2+}$ “spark”
     • Multiple sparks form a Ca$^{2+}$ signal
Myocardial Physiology
Contractile Cells

- **Excitation-Contraction Coupling cont...**
  2. $\text{Ca}^{2+}$ signal ($\text{Ca}^{2+}$ from SR and ECF) binds to troponin to initiate myosin head attachment to actin

- **Contraction**
  - Same as skeletal muscle, but...
  - Strength of contraction varies
    - Sarcomeres are not “all or none” as it is in skeletal muscle
      - The response is graded!
        » Low levels of cytosolic $\text{Ca}^{2+}$ will not activate as many myosin/actin interactions and the opposite is true
Myocardial Physiology
Contractile Cells

- Relaxation
  - $\text{Ca}^{2+}$ is transported back into the SR and
  - $\text{Ca}^{2+}$ is transported out of the cell by a facilitated $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX)
  - As ICF $\text{Ca}^{2+}$ levels drop, interactions between myosin/actin are stopped
  - Sarcomere lengthens
The relationship between the electrocardiogram (ECG), recorded as the difference between currents at the left and right wrists,

and

an action potential typical of ventricular myocardial cells.

Electrocardiogram (ECG)
- P wave: the sequential depolarization of the right and left atria
- QRS complex: right and left ventricular depolarization
- ST-T wave: ventricular repolarization
• PR interval: time interval from onset of atrial depolarization (P wave) to onset of ventricular depolarization (QRS complex)

• QT interval: duration of ventricular depolarization and repolarization

• ST segment: the time period between the end of the QRS complex and the beginning of the T wave, during which each myocyte is in the plateau phase (phase 2) of the action potential
Myocardial Physiology
Autorhythmic Cells (Pacemaker Cells)

• Characteristics of Pacemaker Cells
  – Smaller than contractile cells
  – Don’t contain many myofibrils
  – No organized sarcomere structure
    • do not contribute to the contractile force of the heart
Myocardial Physiology
Autorhythmic Cells (Pacemaker Cells)

• Characteristics of Pacemaker Cells
  – Unstable membrane potential
    • “bottoms out” at -60mV
    • “drifts upward” to -40mV, forming a pacemaker potential
  – Myogenic
    • The upward “drift” allows the membrane to reach threshold potential (-40mV) by itself
    • This is due to
      1. Slow leakage of K\(^+\) out & faster leakage Na\(^+\) in
         » Causes slow depolarization
         » Occurs through I\(_f\) channels (f=funny) that open at negative membrane potentials and start closing as membrane approaches threshold potential
      2. Ca\(^{2+}\) channels opening as membrane approaches threshold
         » At threshold additional Ca\(^{2+}\) ion channels open causing more rapid depolarization
         » These deactivate shortly after and
      3. Slow K\(^+\) channels open as membrane depolarizes causing an efflux of K\(^+\) and a repolarization of membrane
Myocardial Physiology

Autorhythmic Cells (Pacemaker Cells)

• Characteristics of Pacemaker Cells

(a) The pacemaker potential gradually becomes less negative until it reaches threshold, triggering an action potential.

(b) Ion movements during an action and pacemaker potential

(c) State of various ion channels

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- Normal pacemaker
  - SA node

- Latent pacemaker (Ectopic pacemaker under pathophysiological conditions)
  - AV node
  - Bundle of His
  - Purkinje fibers
Conducting velocity

SA node → Atria → A-V node
0.05 m/s → 0.4 m/s → 0.02~0.05 m/s

His bundle → Purkinje fiber → Ventricle
1.2~2.0 m/s → 2.0~4.0 m/s → 1.0 m/s

Atrioventricular delay: Asynchronization of atrial and ventricular depolarization to provide adequate cardiac output
Factors Affecting Conductivity

- Structural factors
  - Diameter of cardiac cells
  - Gap junctions at Intercalated disk

- Physiological factors
  - The velocity and amplitude of phase 0 depolarization
  - Excitability of adjacent region
Purkinje cells: Fast response autorhythmic cells
Ionic mechanism

- Phase 0~3: similar to ventricular cells
- Phase 4:
  - (1) $I_f$: Funny current, Pacemaker current
  - (2) $I_k$: Decay
Characteristics of $I_f$ channel

- $\text{Na}^+$, $\kappa^+$

- Voltage- & time-dependent
  
  Activation — Repolarized to -60mV
  
  Full activation — Hyperpolarized to -100mV
  
  Inactivation — Depolarized to -50mV
Sinoatrial cells
Sinoatrial cells: Slow response autorhythmic cells

- Maximal repolarization potential -70mV
- Threshold potential -40mV
- Phase 0, 3, 4
Ionic mechanism

- Phase 0: $I_{Ca} (I_{Ca,L})$
Phase 3:

- Inactivation of L-type Ca\(^{2+}\) channel
- Outward K\(^{+}\) current (I\(_{k}\))
• Phase 4:
  - $I_k$ decay
    - Inactivated when repolarized to -60mV
  - $I_{Ca,T}$
    - Activated when depolarized to -50mV
  - $I_f$
Conducting system of the heart

- Superior vena cava
- Atrioventricular node
- Bundle of His
- Left atrium
- Left ventricle
- Right atrium
- Right bundle branch
- Right ventricle
- Purkinje fibers
- Inferior vena cava
- Interventricular septum
- Left bundle branch
The sinoatrial node is the heart’s pacemaker because it initiates each wave of excitation with atrial contraction. The Bundle of His and other parts of the conducting system deliver the excitation to the apex of the heart so that ventricular contraction occurs in an upward sweep.
Conduction in Atria

The electrical impulses from SA node spread through the entire right and left atrial muscle mass, triggering contraction of the right and left atrium.
Delay at A-V Node

- The impulses from S-A node travel to atrioventricular (A-V) node.
- A-V node is located in lower end of the interatrial septum near the tricuspid valve.
Delay at A-V Node

- Conduction speed in A-V node is slow (delay).

- This delay allows time for the atria to finish contraction and empty their contents into the ventricles before ventricles start to contract.

- A-V node is the only normal route that impulses from SA node are transmitted into ventricles.
From AV node to Ventricles

*His bundle*

- left branch (anterior/posterior division)

- right branch
Rapid Conduction in Ventricles

After the delay at A-V node, the impulses rapidly spread to the ventricles via specialized fibers, *Purkinje fibers*.

1) *Purkinje fibers*
   - located in the subendocardial layer
   - fastest conduction (4 m/s)

2) *Ordinary ventricular myocardial cells*
   able to conduct AP at a slower speed
Rapid conduction in the ventricles

\[\downarrow\]

**simultaneous** excitation of the ventricles

\[\downarrow\]

functional syncytium
Note:

- Each electrical impulse can trigger cardiac muscle contraction normally only once.
- A normal heart generates 60 to 100 impulses in 1 minute at resting state.
Extrinsic Regulation of HR

• Neural Influences override intrinsic rhythm
  – Sympathetic: catecholamines
    • Epinephrine
    • Norepinephrine
  – Parasympathetic
    • Acetylcholine

• Cortical Input
• Peripheral Input
Myocardial Physiology
Autorhythmic Cells (Pacemaker Cells)

• Altering Activity of Pacemaker Cells
  – Sympathetic activity
    • NE and E increase $I_f$ channel activity
      – Binds to $\beta_1$ adrenergic receptors which activate cAMP and increase $I_f$ channel open time
      – Causes more rapid pacemaker potential and faster rate of action potentials

Sympathetic Activity Summary:
- increased chronotropic effects ↑heart rate
- increased dromotropic effects ↑conduction of APs
- increased inotropic effects ↑contractility

![Graph showing the effect of sympathetic stimulation on membrane potential](image)
Cardiac Accelerator Nerves

Sympathetic Fibers
- Innervate SA node & ventricles
- Increase heart rate
- Increase contractility
- Increase pressure
Myocardial Physiology
Autorhythmic Cells (Pacemaker Cells)

• Altering Activity of Pacemaker Cells
  – Parasympathetic activity
    • ACh binds to muscarinic receptors
      – Increases $K^+$ permeability and decreases $Ca^{2+}$ permeability = hyperpolarizing the membrane
        » Longer time to threshold = slower rate of action potentials

Parasympathetic Activity
Summary:
- Decreased chronotropic effects $\downarrow$ heart rate
- Decreased dromotropic effects $\downarrow$ conduction of APs
- Decreased inotropic effects $\downarrow$ contractility
Vagus Nerve

Parasympathetic Nerve
• Innervates SA node & AV node
• Releases acetylcholine
• Slows heart rate
• Lowers pressure
Cortical Influences on Heart Rate

- Cerebral cortex impulses pass through cardiovascular control center in medulla oblongata.
  - Emotional state affects cardiovascular response
  - Cause heart rate to increase in anticipation of exercise
Peripheral Influences on HR

Peripheral receptors monitor state of active muscle; modify vagal or sympathetic

• Chemoreceptors
  – Monitor $pCO_2$, $H^+$, $pO_2$

• Mechanoreceptors
  – Heart and skeletal muscle mechanical receptors

• Baroreceptors
Peripheral Influence on HR

• Baroreceptors in carotid sinus and aortic arch.
  – ↑ pressure $\rightarrow$ ? HR & contractility
  – ↓ pressure $\rightarrow$ ? HR & contractility
Blood Flow Regulation

• During exercise, local arterioles dilate and venous capacitance vessels constrict.
Blood Flow Regulation

• Flow = pressure gradient × vessel radius
  vessel length × viscosity

• Blood flow Resistance Factors
  1. Viscosity or blood thickness
  2. Length of conducting tube
  3. Radius of blood vessel
Blood Flow Regulation

• 1 of every 30 or 40 capillaries is open in muscle at rest

• Opening “dormant” capillaries during exercise
  – Increases blood flow to muscle
  – Reduces speed of blood flow
  – Increases surface area for gas exchange
Local Factors Resulting in Dilation

- ↓ tissue $O_2$ produces potent vasodilation in skeletal and cardiac muscle
- Increased temperature
- Elevated $CO_2$
- Lowered pH
- Increased ADP
- Nitric Oxide (NO)
- Ions of $Mg^{+2}$ and $K^+$
- Acetylcholine
Blood Flow Neural Factors

- Sympathetic nerves (adrenergic): norepinephrine general vasoconstrictor
- Sympathetic nerves (cholingeric): acetylcholine vasodilation in skeletal and cardiac muscle.
Blood Flow Humoral Factors

- Sympathetic nerves to adrenal medulla causes release of epinephrine & norepinephrine into blood (humor).
Blood Flow Humoral Factors

Sympathetic Nerves to Adrenal Medulla
epi & norepi in blood
vasoconstriction
except in skeletal muscle
Neural Factors of Flow Control

Neural Factors

- Sympathetic: norepinephrine (adrenergic) vasoconstrictor
- Sympathetic: acetylcholine (cholinergic) vasodilation in muscle
- Local Metabolites more powerful than sympathetic vasoconstrictors
Integrated Response

Factors Affecting Neural Control of Cardiovascular Function

- Cerebral Cortex
  - Emotional factors
  - Motor cortex
- Hypothalamus
  - Input from cortex
  - Body temperature

- Medulla Oblongata
  - Vasomotor center
  - Cardio-accelerator center
  - Cardio-inhibitor center

- Chemoreceptors
  - \( \uparrow \text{PCO}_2, \uparrow \text{H}^+ \)
  - \( \downarrow \text{PO}_2 \), leads to general vaso-constriction.

- Muscle Receptors
  - Mechanical: \( \uparrow \) movement leads to \( \uparrow \) sympathetic outflow
  - Metabolic: \( \uparrow \) activity causes \( \uparrow \) in metabolites, which leads to \( \uparrow \) sympathetic outflow

- Systemic Receptors
  - Baroreceptors (aortic and carotid bodies):
    - Respond to \( \uparrow \) MAP
    - leads to \( \uparrow \) parasympathetic outflow and \( \downarrow \) sympathetic outflow
  - Stretch receptors (right atrium):
    - \( \uparrow \) Venous return
    - leads to \( \uparrow \) sympathetic outflow

\( \uparrow \) Increase
\( \downarrow \) Decrease
Heart Sounds

Four heart sounds can be recorded via phonocardiography, but normally only two, the first and the second heart sounds, are audible through a stethoscope.
First heart sound:

- occurs when the atrioventricular (AV) valves close at the beginning of ventricular contraction.

- generated by the vibration of the blood and the ventricular wall

- is louder, longer, more resonant than the second heart sound.
Second heart sound

- occurs when **aortic and pulmonary semilunar valves close** at the beginning of ventricular dilation

- generated by the vibration of the blood and the aorta

- Aortic valve closes slightly before pulmonary valve.
MYOCARDIAL PERFORMANCE

Physiological Algorithm

Blood pressure

Systemic vascular resistance

Cardiac output

Heart rate

Stroke volume

End-diastolic volume

End-systolic volume

rhythm

preload; compliance

contractility; afterload
**Heart Rate**
the number of heart beats in 1 minute. Normal value: 60-100/min

**Stroke volume**
the volume of blood pumped out by each ventricle per each contraction.
Cardiac Output (CO)

the amount of blood pumped out by each ventricle in 1 minute.

Cardiac output = stroke volume x heart rate

Example:

70 ml x 75 beat/min = 5,250 ml/min
Ejection Fraction

= stroke volume ÷ end-diastolic ventricular volume

70 ml ÷ 130 ml = 54%

End of diastole

End of systole
**Ejection Fraction**

*increases during exercise*

\[
120 \text{ ml} \div 133 \text{ ml} = 90\%
\]
**Preload**

the force that stretches the muscle before contraction.

**Afterload**

the force that stretches muscle during contraction.
**Preload** to ventricles = *ventricular end diastolic pressure*

- the degree of stretch of the ventricular muscle cells just before they contract.
- determined by ventricular filling.
Afterload to left ventricle: *aortic arterial pressure*

Afterload to right ventricle: *pulmonary arterial pressure*

*Afterload to the left ventricle is greater than that to the right ventricle.*
Factors on Cardiac Output

1) **Preload:**

2) **Afterload:**

3) **Contractility:**

4) **Heart Rate:**
Factors on Cardiac Output

1) **Preload:**

\[ \text{↑ Preload} \implies \text{↑ cardiac output} \]
Factors on Cardiac Output

1) **Preload:**

$\uparrow$ Preload $\Rightarrow$ $\uparrow$ cardiac output
Factors on Cardiac Output

1) **Preload:**

2) **Afterload:**

\[ \text{↑ afterload} \Rightarrow \text{↓ CO} \]
Factors on Cardiac Output

1) **Preload:**

2) **Afterload:**

3) **Contractility:**

\[ \uparrow \text{contractility} \Rightarrow \uparrow \text{CO} \]
Factors on Cardiac Output

1) **Preload:**

2) **Afterload:**

3) **Contractility:**

4) **Heart Rate:**

...dual effects...

\[ \uparrow{CO} = \uparrow{Heart Rate} \times Stroke Volume \]
Factors on Cardiac Output

1) **Preload:**

2) **Afterload:**

3) **Contractility:**

4) **Heart Rate:**

Dual effects

\[ \downarrow \text{CO} = \uparrow \text{Heart Rate} \times \downarrow \text{Stroke Volume} \]

\[ 300\% \quad 400\% \]