CARDIOVASCULAR PHYSIOLOGY: THE HEART
Cardiac Muscle

• Conducting system
  – *Pacemaker cells*
  – 1% of cells make up the conducting system
  – Specialized group of cells which initiate the electrical current which is then conducted throughout the heart

• Myocardial cells (cardiomyocytes)

• Autonomic Innervation
  – Heart Rate
    • Sympathetic and Parasympathetic regulation
    • $\beta_1$ receptors (ADRB1), M-ACh receptors
  – Contractility
    • Sympathetic stimulus
    • Effects on stroke volume (SV)
Electrical Synapse

- Impulses travel from cell to cell
- Gap junctions
  - Adjacent cells electrically coupled through a channel
- Examples
  - Smooth and cardiac muscles, brain, and glial cells.
Conducting System of the Heart

- SA node is the pacemaker of the heart
  - Establishes heart rate
  - ANS regulation
- Conduction Sequence:
  - SA node depolarizes
  - Atria depolarize
  - AV node depolarizes
    - Then a 0.1 sec delay
  - Bundle of His depolarizes
  - R/L bundle branches depolarize
  - Purkinje fibers depolarize
  - Ventricles depolarize

Sinus Rhythm: Heartbeat Dance
Electrical Events of the Heart

- **Electrocardiogram (ECG)**
  - Measures the currents generated in the ECF by the changes in many cardiac cells

- **P wave**
  - Atrial depolarization

- **QRS complex**
  - Ventricular depolarization
  - Atrial repolarization

- **T wave**
  - Ventricular repolarization

- **U Wave**
  - Not always present
  - Repolarization of the Purkinje fibers
• Plateau cause by slow VG Ca⁺ channels & Ca⁺ inflow
  • this prolonged state of depolarization results in long period of refractory.
• Long refractory prevents heart from entering tetanus (which is a good thing as heart needs to relax to fill)
AP in Myocardial Cells

- **Plateau Phase**
  - Membrane remains depolarized
  - *L-type Ca\(^2+\) channels*
  - “Long opening” calcium channels
  - Voltage gated
    - Open at > -40 mV
  - Present in the T-Tubules
- RMP = -90 mV
- Threshold = -70 mV

- **Time for myocardial muscle twitch is for a single myocardial cell**
Excitation-Contraction Coupling

Myocardial Cell

1. Action potential enters from adjacent cell.
2. Voltage-gated Ca\(^{2+}\) channels open. Ca\(^{2+}\) enters cell.
3. Ca\(^{2+}\) induces Ca\(^{2+}\) release through ryanodine receptor-channels (RyR).
4. Local release causes Ca\(^{2+}\) spark.
5. Summed Ca\(^{2+}\) sparks create a Ca\(^{2+}\) signal.
6. Ca\(^{2+}\) ions bind to troponin to initiate contraction.
7. Relaxation occurs when Ca\(^{2+}\) unbinds from troponin.
8. Ca\(^{2+}\) is pumped back into the sarcoplasmic reticulum for storage.
9. Ca\(^{2+}\) is exchanged with Na\(^+\).
10. Na\(^+\) gradient is maintained by the Na\(^+\)-K\(^+\)-ATPase.
Excitation-Contraction Coupling
Myocardial Cell

- $\text{Ca}^{2+}$ entering through L-type $\text{Ca}^{2+}$ channels triggers the release of $\text{Ca}^{2+}$ from the ryanodine receptors in the SR
  - *Calcium induced calcium release*
- Cross-bridge cycling occurs
- Contraction ends when:
  - $\text{Ca}^{2+}$ is pumped back into the SR by $\text{Ca}^{2+}$/ATPase pumps
  - $\text{Ca}^{2+}$ is pumped out of the cell by $\text{Na}^{+}/\text{Ca}^{2+}$ exchangers
AP in Cardiac Pacemaker Cells

- Pacemaker potential
  - Slow depolarization
  - Automaticity (spontaneous, rhythmical)
  - Average heart rate (HR) is 72 beats per minute (bpm)
- \textit{F-type Na}^+ (HCN) channels open when the membrane potential is at negative values
- \textit{T-type Ca}^{2+} channels open briefly
  - Inward Ca^{2+} current
  - Final depolarizing boost to threshold

Nodal Cell RMP = -60 mV
Nodal Cell threshold -40 mV
HCN Channels
F-Type Na⁺ Channels

• Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels
  – Activated by cAMP

• Non-selective voltage gated ion channels
  – Heart, brain

• Creates a “Funny” current
Mechanical Events of the Heart

• **Cardiac Cycle**
  – Repeating sequence of *mechanical* phases that occur when the heart beats causing *pressure* changes which lead to *volume* changes

• **Mechanical Phases**
  – ***Systole***
    • Ventricular contraction which leads to ejection of blood
  – ***Diastole***
    • Ventricular relaxation which leads to filling with blood

• Cardiac cycle lasts 0.8 seconds (*time for the entire ventricle*)
  • 0.3 seconds in systole
  • 0.5 seconds in diastole
Cardiac Cycle
Ventricular Volumes

- **End-diastolic volume (EDV)**
  - Volume in the ventricles at the end of diastole
  - Volume in the ventricles at the end of ventricular relaxation
  - Volume in the ventricles at the end of ventricular filling
  - Average resting volume is 135 mL

- **End-systolic volume (ESV)**
  - Volume in the ventricles at the end of systole
  - Volume in the ventricles at the end of ventricular contraction
  - Volume left in the ventricles after the blood has been ejected from the ventricles
  - Average resting volume is 65 mL
Cardiac Cycle

• Isovolumetric Phase
  – Volume does not change in the ventricle
  – All valves closed

• Volume Change Phase
  – Volume changes
  – 1 set of valves open
  – Ventricular filling
    • AV valves open
  – Ventricular ejection
    • SL valves open
Cardiac Cycle
Systole

• **Isovolumetric Ventricular Contraction**
  – Ventricle contracts
    • Muscle fibers developing tension
    • Muscle fibers do not shorten
    • Increasing pressure inside the ventricles
  – All valves closed
  – No blood ejection
  – Ventricular volume remains the same
Cardiac Cycle
Systole

• **Ventricular Ejection**
  – Pressure in the ventricles exceed pressure in aorta/pulmonary trunk
  – Semilunar valves open
  – Blood forced into aorta/pulmonary trunk
  – Muscle fibers shorten

  – **Stroke volume (SV)**
    • Volume of blood ejected during systole
    • $SV = 135 \text{ mL (EDV)} - 65 \text{ mL (ESV)}$
    • Average SV is 70 mL/beat (0.07 L/beat)
Cardiac Cycle
Diastole

• *Isovolumetric Ventricular Relaxation*
  – Ventricle begins to relax
  – Semilunar valves close
  – AV valves closed
  – No blood entering or leaving the ventricles
  – Ventricular volume remains the same
Cardiac Cycle

Diastole

• **Ventricular Filling**
  – AV valves open
  – Blood flows from atria to ventricles
  – 80% of ventricular filling is passive
  – Atrial contraction occurs at the end of diastole
    • Atrial kick moves the remaining 20% of blood in atria into ventricles
Pressure Changes
Volume Changes
ECG
Heart Sounds

- **Lub**
  - Soft sound
  - Closing of the AV valves
  - Onset of systole

- **Dup**
  - Louder sound
  - Closing of the semilunar valves
  - Onset of diastole
Cardiac Output (CO)

• Volume of blood pumped out of the ventricles expressed as L/min
  – Volume of blood flowing through either the pulmonary or systemic circuit per minute

• CO = HR x SV

• CO = 72 beats/min x 0.07 L/beat

• CO = 5.0 L/min

• Total blood volume is pumped around the circuit once each minute
  – 1,440 per day!
Control of Heart Rate

HR is a variable that determines CO

- 100 BPM without nerve or hormone influence on the SA node
- However, SA node is under constant influence of nerves and hormones
  - Activity of the parasympathetic nerves causes a decrease in heart rate
  - Activity of sympathetic nerves causes an increase in heart rate
Control of Heart Rate

*HR is a variable that determines CO*

- **Sympathetic stimulation**
  - Increases slope
  - Increases F-type Na\(^+\) channel permeability
  - Faster depolarization

- **Parasympathetic stimulation**
  - Slope decreases
  - Hyperpolarizes plasma membrane of SA node
  - Increases K\(^+\) permeability
Control of Heart Rate

*HR is a variable that determines CO*

- **Epinephrine**
  - Increases HR
  - Binds to beta-adrenergic receptors in the SA node

- **Heart rate is also sensitive to changes in:**
  - Body Temperature
  - Plasma electrolyte concentrations
    - $K^+$
    - $Ca^{2+}$
Control of Stroke Volume

$SV$ is a variable that determines $CO$

- Ventricles do not completely empty during contraction
- More forceful contraction can produce an increase in SV by causing greater emptying
- 3 main factors
  1. Changes in EDV (*preload*)
  2. Changes in contractility
  3. Changes in *afterload*
     - arterial pressures against which the ventricles pump
     - Increase in total peripheral resistance (TPR)
Starling’s Law of the Heart

*Relationship between EDV and SV*

- Ventricles contract more forcefully during systole when it has been filled to a greater degree during diastole
- **SV increases as EDV increases**
- **SV is Dependent of EDV**
- Increase in venous return forces an increase in CO by increasing EDV which increases SV
Sympathetic Regulation

- Sympathetic nerves innervate the entire myocardium
- NE and Epi bind to beta-adrenergic receptors to increase *contractility*
  - Increases strength of contraction at any given EDV
  - SV is independent of EDV
  - Leads to an increase in ejection fraction
Ejection Fraction (EF)

- EF quantifies contractility
- EF = SV/EDV
- Under resting conditions, average is between 50–75%
- Increased contractility causes increased EF
Sympathetic Regulation

- Increased sympathetic activity
  - Increases HR without decreasing CO
  - Increases contractility
  - Ventricles contract more forcefully to compensate for the increase in HR
Sympathetic Regulation of Myocardial Contractility

Norepinephrine and Epinephrine bind to β-adrenergic receptors on the cell membrane, activating adenyl cyclase and increasing cAMP levels. cAMP activates a cAMP-dependent protein kinase, which phosphorylates thin filaments, enhancing the interaction between thick and thin filaments. This increases cross-bridge cycling and force generation, leading to an increase in the force and velocity of contraction.

1. Norepinephrine and Epinephrine bind to β-adrenergic receptors.
2. Adenyl cyclase is activated, increasing cAMP levels.
3. Active cAMP-dependent protein kinase is activated.
4. Phosphorylation of thin filaments increases the interaction with thick filaments.
5. Increased cross-bridge cycling leads to force generation.

Intramembrane fluid compartments include DHP receptor and Ryanodine receptor in the sarcoplasmic reticulum.
Control of Cardiac Output Summary

End-diastolic ventricular volume \rightarrow \text{Plasma epinephrine} \rightarrow \text{Cardiac muscle} \rightarrow \text{Cardiac output}

Activity of sympathetic nerves to heart \rightarrow \text{SA node} \rightarrow \text{Cardiac output}

\text{Cardiac output} = \text{Stroke volume} \times \text{Heart rate}