**Cardiovascular Physiology**

**Lecture 17**

**Myocardial Cell Action Potentials**

- 4 Phases:
  
  **A. Phase 0:** Rapid depolarization (+20mV)
  
  - Fast Na⁺ channels open

  **B. Phase 1:** Initial Repolarization
  
  - Fast Na⁺ channels close
  - Fast K⁺ channels open (few)

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**Ventricular Myocyte Action Potential**

- Phase 0: Rapid depolarization (+20mV)
  - Fast Na⁺ channels open

- Phase 1: Initial Repolarization
  - Fast Na⁺ channels close
  - Fast K⁺ channels open (few)
C. Phase 2: Plateau Phase (+10mV)
- Maintained depolarization
- Slow Ca\(^{2+}\) channels open (L-TYPE)
- Some Fast K\(^+\) channels close

\[\Rightarrow\] LONG REPOLARIZATION / Refractory Period

D. Phase 3: Rapid Repolarization (-85mV)
- Slow Ca\(^{2+}\) channels close
- Slow K\(^+\) channels open
E. Phase 4: Resting membrane potential
• No net movement of ion (−85 mV)

Plateau Phase: Refractory Phase
• Ensure Unidirectional cardiac Action potentials with interconnected cells

Plateau Phase on ECG
• Iso-electric periods on ECG
Effect of Myocardial Action Potential on Muscle Contraction

- **Action Potentials stimulate 2 Ca²⁺ Sources**

1. **Plateau Phase: Ca²⁺ influx**

   ![Diagram](image)

2. **Terminal Cisternae Ca²⁺**
   - **Ryanodine Receptor Channel:**
     - Ca²⁺ induced calcium release channels

   ![Diagram](image)

- **BOTH sources of Ca²⁺ increase cross bridge cycling**
  - Cardiac Contractions are NOT initially maximal
  - Cardiac Contraction strengths altered by Ca²⁺
Controlling Cardiac Tissue:

1. Rate Changes = **Chronotropic**
   - **Extrinsic Mediation:** Autonomic NS
     - a. Sympathetic Nervous System
       - Positive Chronotropic Effect
       - **Tachycardia:** Increased rate (>100 bpm)

Adrenergic Mechanism: 2 Effects

1. **cAMP** sensitizes HCN channels
   - Increases depolarization to threshold
   - Increases “ramp” to threshold

2. **cAMP** activates protein kinases
   - Phosphorylation increases activity of sacroplasmic active calcium pump
     - PHOSPHOLAMBAN
     - Increases clearance of Ca²⁺
     - Increases readiness for faster pacing
b. Parasympathetic Nervous System

- **Negative Chronotropic Effect**
- **Bradycardia**: Decreased rate (< 60 bpm)
2. **Contractility Changes** = *Inotropic Effect*

2 Controlling Sources

- **Intrinsic Control:** "Built in"
  
  a. **Length-Tension Relationship**
     
     - Degree of *Muscle Stretch*
     
     - *Increasing cardiac stretch increases contractility*

- **Resting cardiac cell length** is BELOW ideal
  
  - Increasing stretch *increases* **Cross bridge cycling**
  
  - *Increasing contractility*
Mechanism: **Ventricular filling**

\[ \text{Ventricular Filling} = \text{Stretch} = \text{Contractility} = \text{Positive Inotropic effect} \]

* Frank–Starling Law

b. **Excitation Contraction Coupling**

- Effect of frequency of myocardial Potentials on Contraction Strength
  - Greater frequency of Action Potentials increases cellular Ca\(^{2+}\)
    - Increase *influxing calcium*
    - Increase *ryanodine calcium release*
    - **Positive Inotropic Effect**
2. **Extrinsic Control**: “outside”
   a. **Sympathetic Nervous System**:
      - **Positive Inotropic Effect**
      - **Mechanism**: Direct affect

   - Norepinephrine: Binds $\beta_1$ receptors
     - cAMP activates protein kinases

1. Phosphorylate: **L-Type Voltage gated Ca$^{2+}$ channels**
   - Influx: more Ca$^{2+}$
   - More Ca$^{2+}$ produces Stronger contractions

2. Phosphorylate: **Ryanodine channels**
   - Release: more Ca$^{2+}$
   - More Ca$^{2+}$ produces Stronger contraction

3. Phosphorylate: **Phospholamban**
   - Reuptake Ca$^{2+}$ for faster
   - Faster Repolarization
   - Faster Pacing
   - Increase All Calcium movement
b. **Parasympathetic Nervous System**

- **Negative Inotropic Effect**
- Mechanisms: Direct & Indirect

> **Direct Effect:** *Muscarinic Receptors*

- Release Gi subunits
- Inhibit Adenylate cyclase and cAMP production
- Reduce intracellular Ca\(^{2+}\) and cross bridge cycling

  ✓ *Weaker contractions*

> **Indirect Effect:** *Muscarinic Receptors*

- Slows SA Node:
  - *Fewer Pacemaker potentials*
- Less influxing Calcium & cross bridge cycling

  ✓ *Weaker contractions*
Additional Cardiac Function Modifier

- **Adenosine**: Produced in response to **Hypoxia**
  - Large amounts of ATP hydrolyzed
- **Adenosine receptors**: G-protein moderated
  - Second Messenger Operated Response

Myocardial effect: **Slower Pacing**

Important mechanism to slow pacing when metabolic need is not met

"Cardiac Governor"

- **Mechanisms of action**: **Gi protein**
  1. **Inhibit Adenylate Cyclase**: Decrease cAMP
     - Decrease HCN priming
     - Increase potassium efflux
     - Slow Depolarization (If current)
     - Negative Chronotropic effect (pacing)

Adenosine Receptor: Nodal Cell
2. **Inhibit Adenylate Cyclase: Decrease cAMP**
   - Decrease L-Type Voltage gated channel
   - Slow conduction velocity (esp AV node)
     - *Negative Dromotrophic Effect*

- **Clinical Use:** Antiarrhythmic drug
  - Rapid treatment of Supraventricular Tachycardia
  - Especially in AV node re-entry