بسم الله الرحمن الرحيم
Cardiac ion channels

By: Mohammed El-desoky
### Types of cardiac muscle action potential

<table>
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<th>Fast response</th>
<th>Slow response</th>
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<tr>
<td>atria, ventricles, His–Purkinje network</td>
<td>SAN and AVN</td>
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<tr>
<td>a high resting $K^+$ permeability between APs.</td>
<td>have a low $K^+$ permeability between APs and are automatic</td>
</tr>
<tr>
<td>APs generated by fast $Na^+$ current</td>
<td>APs is generated by $Ca^{+2}$ current</td>
</tr>
<tr>
<td><strong>Plateau</strong></td>
<td><strong>lack of a well-defined plateau</strong></td>
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<tr>
<td><strong>Stable RMP.</strong></td>
<td><strong>unstable RMP</strong></td>
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<tr>
<td>Rapid rise of action potential</td>
<td><strong>slow rise of the action potential</strong></td>
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</table>
SA node, A V node: "Slow response"
Fast response action potential
phases and primary currents in the ventricle muscle action potential:

A. **Phase 0**: rapid upstroke of the AP (Sodium Current).

B. **Phase 1**: small repolarization (Transient Outward Current)

C. **Phase 2**: plateau (Calcium Current)

D. **Phase 3**: final repolarization (Delayed Rectifier Current)

E. **Phase 4**: the resting potential (Inward Rectifier Current)
A. Phase 0: rapid upstroke of the AP (Sodium Current):

- fast Na+ current → The upstroke causes a voltage change (110–120 mV) within 1–2 msec.
- threshold to open some of the fast Na+ channels is -70 mV, then regenerative +ve feedback cycle.
- peak I Na occurs between -30 and -20 mV
The membrane potential never reaches $E_{Na} (+60 \text{ m.v})$ for several reasons:

1. Driving force for Na$^+$ influx is ↓

2. Beginning of Na$^+$ channels inactivation after about 1 msec; thus some Na$^+$ channels are already closing during the latter part of the upstroke.

3. Repolarizing currents are beginning to activate during the latter portion of the upstroke.
The current voltage curve for $I_{Na}$.
Phase 1: small repolarization phase (Transient Outward Current) (Ito):

- (I_{to}) turns on during the final portion of the AP upstroke; (the threshold for activation is - 30 mV).

- I_{to} is composed of two separate current carried through two distinct channels:
  - The first component is I_{to1}: is a K^+ current through Transient Outward voltage gated K channels.
  - The second component is I_{to2}: a Ca^{2+} activated Cl^- channel.
Under physiological conditions, Ito1 appears responsible for the vast majority of phase 1.

Ito2 may become more important in Ca\(^{+2}\) overload conditions → Ito2 would be activated → Cl influx → shorten the AP duration, thereby indirectly ↓ the duration of Ca\(^{+2}\) current → ↓ Ca\(^{+2}\) influx.

(Thus, activation of Ito2 acts as a negative feedback mechanism to reduce calcium overload)
Ito1 is characterized by Rapid activation followed by inactivation, so, there is some overlap between Ito1 and Ca ++ during the plateau.
C. Phase 2: plateau phase (Calcium Current)

Means:
a period of time in which the membrane potential remains relatively constant → long AP duration in cardiac cells.

Caused by: balance () inward & outward current.

The positive inward current is:
Ca+2 current through L-type calcium channels \( I_{CaL} \)

Significance: calcium induced Ca release from S.R.
The threshold for activation of I Ca is -40 mV, the current is maximal near 0 mV, & inactivate completely within a few hundred m.sce.

(2) There is a small contribution of the fast Na⁺ current to the plateau: a very small fraction of the INa inactivates slowly causing a late sodium current known as the “sodium window current”
ICa(L) is a major regulatory site in control of cardiac muscle contractility:

- Catecholamines $\rightarrow$ ++ β1R $\rightarrow$ ↑ cAMP $\rightarrow$ ++ cAMP-dependent protein kinase which phosphorylates the Ca$^{+2}$ channel $\rightarrow$ ↑ channel activity and ↑ force of contraction

- Acetylcholine $\rightarrow$ -- cAMP formation. Additionally, ACh stimulates cGMP production $\rightarrow$ ↓ I$_{CaL}$
NA + β1

ATP → AC → cAMP

PK

Ca^{+2}
The positive outward currents:

- **Outward K⁺ current during the plateau phase occurs through:** slowly activating k⁺ current known as the delayed rectifier k⁺ channels (particularly in latter part of the plateau)

- Additionally, Ito contributes to early plateau phase.
Phase 3: final repolarization phase (Delayed Rectifier Current)

Cause $\rightarrow$ outward current overcomes inward current.

$\downarrow$ inward current $\rightarrow$

is caused by $\downarrow$ Ca$^{2+}$ conductance due to Ca$^{2+}$-channels closure.

$\uparrow$ outward current $\rightarrow$

is caused by $\uparrow$ K+ efflux.
- A number of K currents may contribute to phase 3 of the action potential **through:**

(1) **outward delayed rectifier k channels (IK) which are three types:**

- a very slowly activating component (IKs)
- a more rapidly activating component (IKr)
- “ultrarapid-activating”’ (Ikur) (in atrial myocyte)

(2) **inwardly rectifying K⁺ current (I K1) also begins to contribute to late part of repolarization.**

(3) Some ventricular preparations also shows a Ca⁺² dependent IK( significance like I to2).
Ion Channels in Ventricular Muscle

- **K channels (I_{TO})**
- **“Ultra-rapid” K channels (I_{Kur})**
- **“Rapid” K channels (I_{Kr})**
- **“Slow” K channels (I_{Ks})**

- **Voltage-gated Na Channels**
- **Voltage-gated Ca Channels**

- Ventricular muscle membrane potential (mV)
  - 0
  - -50

- **I_{K1}**
- 200 msec
Phase 4: the resting potential (Inward Rectifier Current)

Phase 4 → the stable, negative potential that occurs ( ).

APs in non spontaneous cells.

-maintained by:

The Na–K pump.

-The resting potential is determined largely by the inward rectifier K channels (IK1).
Inward Rectifier ($I_{k1}$) Structure

Note: No “voltage sensor”

- P-Region
- Extracellular Fluid
- Inside
- Membrane

$M1$ and $M2$ domains with $H_2N$ and $HO_2C$ structures.
A **rectifier** is an electrical device that converts **alternating current** (AC), which periodically reverses direction, to **direct current** (DC), current that flows in **only one** direction.
Inward rectifier K channel isn’t Voltage sensitive

K^+  K^+
K^+  K^+
K^+  K^+
K^+  K^+

> - 96 mv
Inward Rectifier K Channels

-96 M.V

-30 M.V

K hump

Block by Mg & polyamines
Inward Rectification

Extracellular solution

Intracellular Solution

-30 mV

K⁺

Mg²⁺

polyamines

=30 mV

K⁺
The outward K current through inward rectifying channels is the only one occurring physiologically, as the membrane potential does not normally hyperpolarize beyond EK.
Additional currents contributing to the A.P:

(I) Na–K ATPase (Pump Current):
- Try role is to maintain ionic gradients that generate electrochemical driving forces for currents responsible for A.P.

(II) Na–Ca Exchange Current:
- **Normal mode:** Transport 3 Na in for one Ca out → generates a current.
- During the initial portion of the plateau → transiently works in the reverse mode & generates an outward current, then return to the normal mode.
3) PKA-Activated Chloride Channels (ICI-PKA):

- β-adrenergic R stimulation $\uparrow$ ICI-PKA $\rightarrow$ inward Cl-current generated can contribute to repolarization $\rightarrow$ A.P duration $\rightarrow$ prevent prolongation of AP.
Regional differences in action potentials:

A. Atria

Atrial cells APs characterized by a prominent phase 1 & phases 1, 2, and 3 tend to run together, resulting in a triangular shape, with a distinct plateau not always apparent, due to a large Ito & IKur.

B. Purkinje Fibers

Purkinje APs differs from ventricular cells in that they have a more prominent phase 1 and a longer plateau (phase 2) & may exhibit automaticity.
Slow response action potential

SA node

AV node
Slow Response Action Potential

- **Phase 0**
- **Phase 1** ➔ absent
- **Phase 2** ➔ Very brief
- **Phase 3** ➔ Not Separated Clearly From phase 2
- **Phase 4**

![Graph showing membrane potential over time](image)
SA Node Action Potential

SA node membrane potential (mV)

0
-50

200 msec

Voltage-gated L-Ca$^{+2}$ channels

Voltage-gated K$^{+}$ channels

$I_f$ or pacemaker channels
Sinoatrial Node

1- The most -ve potential the cell reaches ( ) APs is called maximum diastolic potential (MDP=-55m.v).

2- MDP is less negative than the resting potential of ventricular cells due to a lower K⁺ permeability (caused by a lack of IK1).

3- The slope of phase 4 depolarization determines the rate of AP generation and heart rate.
Phase 4 (diastolic depolarization)

-Six currents participate in pacemaker potential:

1. **funny current (If)** → Depolarize the membrane to threshold of L&T type Ca channel

2. **T-type Ca channel**: opening of T-type channels can depolarize the cells further toward the threshold for L-type channels because T channels have lower threshold.
Two outward K currents

1- delayed rectifying K channels (Ik)

2- I K.Ach

3- L-type Ca channel: contribute to late part of pacemaker potential & is the major depolarizing force during phase 0

4- Na-Ca exchanger operates because of ↑Ca inside cardiac muscles due to previous Ca channels
Phase 4

$if$

$icat$

$ical$

Na-Ca exchanger

$ik$

$ikach$
The Upstroke (Phase 0)
much slower upstroke and is generated by inward Ca\textsubscript{2} current, ICa(L).

(I Na is negligible in SA node cells)

phase 1&2
There is generally no phase 1 and a brief plateau (phase 2) in nodal cells.

Phase 3
Repolarization returns the cell to MDD by K efflux through\textit{(Delayed outward rectifier, I_k)}.
Atrioventricular Node

Cells of the AV node are like SAN but, the rate of phase 4 depolarization in AV nodal cells is much slower than SA nodal cells. Thus, SA node cells fire APs before AV node cells fire, that is why SA node cells are the normal pacemaker cells of the heart.
funny, $I_f$

I-Called Funny channels because of unusual property:

1- If is a slowly nonselective cation current activating i.e., it is carried by a mixture of both Na$^+$ and K$^+$ ions.

2- If is a inward depolarizing current activated by hyperpolarization

II-Called HCN (Hyperpolarization-activated cyclic Nucleotide-gated) → because it is activated by hyperpolarization & modulated by cAMP
Modulation of automaticity

- If and ICa(L) are both enhanced by norepinephrine, and inhibited by acetylcholine.
- NE → ↑ the slope of the phase 4 depolarization, the threshold is reached sooner, and heart rate increase
- ACh → ↓ the slope of phase 4 depolarization, the threshold is reached more slowly, and heart rate decreases.
- ACh also activates another specific K current, IK(ACh), which hyperpolarizes the cell,
Autonomic influences alter the rate of pacemaker
(A) Chloride Channels in Heart.

(B) Calcium Channels in Heart.

(C) K⁺ Channels in the Heart.

(D) Na Channels in Heart.
(A) Chloride Channels in Heart

1) PKA-Activated Chloride Channels (ICl-PKA):
- β-adrenergic R stimulation ↑ ICl-PKA → inward Cl-current
  generated can contribute to repolarization → ↓ A.P duration → prevent prolongation of AP in sympathetic stimulation

2) Calcium-Activated Chloride Channels (I_{Cl-Ca}):
(1) I Cl-Ca generates a transient outward current (Ito2), which contributes to early repolarization in many cardiac cells.
(2) This is why hypercalcemia cause short QT interval.
**Major Calcium Channels in Heart**

<table>
<thead>
<tr>
<th>Property</th>
<th>L-type Ca channels</th>
<th>T-type Ca ++ Channels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Threshold</strong></td>
<td>Low (-40 M.V)</td>
<td>High (-70 M.V)</td>
</tr>
<tr>
<td><strong>maximum current</strong></td>
<td>around 0 Mv</td>
<td>-20 mV.</td>
</tr>
<tr>
<td><strong>Inactivation</strong></td>
<td>slow</td>
<td>Fast</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>large</td>
<td>Small (conductance threefold smaller than L-type Ca++ channel)</td>
</tr>
<tr>
<td><strong>Major function in the heart</strong></td>
<td>SAN pacemaker AP AVN conduction Plateau of fast response A.P Excitation contraction coupling</td>
<td>In node tissue</td>
</tr>
<tr>
<td></td>
<td>dihydropyridines (DHPs), phenylalkylamines (PAAs), and benzothiazepines (BTZs).</td>
<td>amlodipine.</td>
</tr>
</tbody>
</table>
(C) K⁺ Channels in the Heart
(I)voltage-gated K+ channels (Kv) 
(regulated by membrane potential) 

(A) Transient outward K+ channels (I<sub>to</sub>) 

(B) Delayed rectifier K+ channels (IK) → 

- \( I_{kur} \) → for ultra rapid rectifier K+ channels (only in atrial muscles). 
- \( I_{kr} \) → for rapid rectifier K+ channels 
- \( I_{ks} \) → for small rectifier K+ channels
(II)G-protein-activated muscarinic k channels (Ikach)

Diagram:

- ACh binds to the m-receptor (outside).
- GTP binds to Gi, activating the K+ channel.
- Pi + GDP released, leading to increased GTP binding.
- Ado and P1-receptor activation indicated on the right.
Inwardly rectifying K+ channels (Kir) are regulated by intracellular polyamines and Mg²⁺.

(i) Classical Kir channels (IK1)

(ii) ATP-sensitive K+ channels in the heart (IKATP):

inhibited by physiological levels of intracellular ATP → in E depleted heart (hypoxia) → open → ↑k efflux → ↓ plateau phase → ↓ reduce contractility so, is E sparing
(iii) Na+ activated K+ channels (IKNa):

This channel is activated by ↑(Na) i as in pathological conditions, such as ischemia & digitalis intoxication.

(iv) Arachidonic acid-activated K channel [IK(AA)] and phosphatidylcholine- activated K channel [IK(PC)]:

activated by ischemia
Pathophysiology of cardiac action potential

- After depolarization.
- Ischemia.
- Channelopathies.
- Antiarrhythmic drugs.
After depolarization.

- Are spontaneous depolarization that appears during repolarization (phase 3) or shortly after repolarization (phase 4).

- When small ➔ cause small oscillation of membrane potential.

- When large ➔ cause triggered response which are important causes of lethal arrhythmias.

- Two Types:
  - Early afterdepolarization (EAD)
  - Delayed afterdepolarization (DAD)
Early after depolarization

- **Occurs at** the end (phase 2) or early phase 3.

- **Causes** more likely to occur when the action potential is prolonged as in heart rate is slow & certain antiarrhythmic drugs such as quinidine,

- **Mechanism:** When action potentials are sufficiently prolonged, the Ca++ channels have sufficient time to recover from inactivation before the cell fully repolarizes to trigger an EAD.

- Can cause torsades de pointes (polymorphic V-tach)
$I_K$ blockade ($I_{Ks}$, $I_{Kr}$) or $I_{Na}$ increase

- $I_{Na}$
- $-80mV$
- $0mV$
- $I_{Ca}/I_{Na}$
- $I_{Kr}$
- $I_{Ks}$
- $I_{K1}$

Action potential duration

Early afterdepolarizations (EAD)

torsades de pointes

QT duration dispersion
Delayed After depolarizations

- Occur at near the very end of repolarization or just after full repolarization (phase 4)

- Causes: in conditions of marked ↑ HR & ↑ [Ca++]i as in digitalis toxicity

- Mechanism: ↑ intracellular Ca++ stimulates

  - Oscillatory release of Ca++ from the SR.
  - Na+- Ca++ exchanger creates a net inward cation current that contributes to DADs.
Vulnerable period

- This period coincides with the downslope of the T wave of the ECG.
  (at nearly the same time as supernormal phase)
Ischemia

There is shortening of the AP during ischemia due to:

1- Activation of ATP sensitive K channels IK (ATP)

2-arachidonic acid-activated K channel [IK(AA)] and the phosphatidylcholine- activated K channel [IK(PC)]

3-Na+ activated K+ channels (IK Na)

- **Significance**: to reduce contractility → decreases energy demands of the cell → This mechanism contributes to the survival of the myocardial cell during temporary ischemia.
Arhythmia is common due to:

1-regional shortening of the AP can also lead to arrhythmias due to the decrease of refractory periods.

2-↑K⁺ in ECF ➔ causes depolarization of the cell ➔ voltage inactivation of sodium channels. Thus, APs in the ischemic area will have a reduced INa ➔ slow AP ➔ slow conduction through the region and enhanced likelihood of arrhythmias. (Long pathway).
Channelopathies

- Channelopathies are disorders caused by mutations in ion channel genes which ↑ the risk of fatal arrhythmia.

Examples:

1. Long QT syndrome
2. Short QT syndrome
3. Burgada syndrome
Long QT syndrome

**Definition**: a disorder in which the QT interval of the ECG is longer than normal.

**Correspond mainly to**: the plateau period of the ventricular action potential.

**Caused by**:

- **Congenital**: mutations that produce either a gain of function on sodium current (LQT3) or calcium currents (LQT4), or a loss of function on potassium (LQT1, LQT2, LQT5, LQT6, LQT7)
- **Acquired**: induced by some antiarrhythmic drugs.
Action potential phases
0: Upstroke
1: Early-fast repolarization
2: Plateau
3: Repolarization
4: Diastole
long QT syndrome → prolongation of the myocyte refractory period → extends the vulnerable period during which extra stimuli can evoke tachycardia or fibrillation → so, Patients with long QT syndrome are predisposed to a dangerous type of ventricular tachycardia called *torsades de pointes* "twisting of points"
**FIGURE 5.14**
Relationship of the ventricular action potential (B) to the electrocardiogram (ECG) (A). ECGs recorded from patients with long QT syndrome show a prolonged QT interval that reflects the longer duration of the action potential. (C) Electrocardiogram recorded from a patient showing *torsade de pointes*. 
In General, APs are longer in females than males, resulting in a greater Q-T interval. This suggests that the repolarizing currents may be smaller in females than males → greater incidence of Torsades de Pointes arrhythmias.
Antiarrhythmic drugs
### Vaughan Williams Classification System Of Anti-arrhythmic Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Basic Mechanism</th>
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</table>
| I-Sodium Channel Blockade     | depress Na channels and block conduction in atria, purkinje fibers & ventricles $\rightarrow$ $\uparrow$ refractoriness and prolong action potential, so, they are useful for rapid tachyarrhythmia.  
Such as: quinidine, procainamide. |
| II-Beta-blockade              | $\beta$-adrenergic blockers $\rightarrow$ inhibit Ca channels opening & If $\rightarrow$ $\downarrow$ AVN conduction also, $\downarrow$ DAD. |
| III-potassium-channel blockade| inhibit repolarizing K current, therefore prolong action potential duration.  
Such as: amidarone |
| IV-Calcium channel blockade   | Block L-type calcium-channels; most effective at SA and AV nodes; reduce rate and conduction.  
Such as: verapamil & deltiiazem |
Class Ia drugs

used for atrial flutter, fibrillation
prevention of ventricular tachycardia, fibrillation

Na$^+$ channel block

- ↑ threshold
- ↓ automaticity
- ↓ automaticity

Delayed recovery from inactivation

- ↑ Refractory period

Slows conduction
Class II drugs (beta-blockers)

e.g. propranolol

- $I_f$ reduces heart rate
- $I_{Ca,L}$ reduces $\text{Ca}^{2+}$ overload
- $\text{DADs}$ suppresses triggered activity

- Suppresses AV re-entry &
  - Controls ventricular response to atrial fibrillation or flutter

- Reduces AV conduction
- Increases AV refractoriness
Class III drugs

Used for ventricular tachyarrhythmias, atrial fibrillation, flutter

Blocks $I_{Kr}$

Prolongs action potential

- Prolongs refractory period
- Suppresses re-entry

EADs
- Can cause torsades de pointes
Class IV drugs (verapamil, diltiazem)

Controlling ventricular response to atrial fibrillation or flutter

↑ Threshold in SA node
↓ AV conduction
↑ AV refractoriness
↓ Heart rate
Mechanisms of Arrhythmias: 1

● Important to understand because treatment may be determined by its cause

● 1. **Automaticity**
   - Raising the resting membrane potential
   - Increasing phase 4 depolarization
   - Lowering the threshold potential
     ● e.g. increased sympathetic tone, hypokalamia, myocardial ischaemia
Mechanisms of Arrhythmias: 2

2. **Triggered activity**
   - from oscillations in membrane potential after an action potential
   - *Early Afterdepolarization*
     - Torsades de pointes induced by drugs
   - *Delayed Afterdepolarization*
     - Digitalis, Catecholamines

3. **Re-entry**
   - from slowed or blocked conduction
     - Re-entry circuits may involve nodal tissues or accessory pathways
Ventricular fibrillation is often initiated when a premature impulse arrives during the vulnerable period of the cardiac cycle. During this period the excitability of cardiac cells varies spatially. Some fibers are still in their effective refractory periods, others have almost fully recovered their excitability, and still others are able to conduct impulses, but only at very slow conduction velocities. Consequently, the action potentials are propagated over the chambers in many irregular wavelets that
Brugada Syndrome

- Cause → a genetic mutation located on the \textit{SCN5A} gene on chromosome 3 which codes for sodium ion channels.
- This mutation leads to either complete loss of channel function or an accelerated recovery from activation.
- This can generate heterogeneity of repolarization and increase the chance of intramyocardial re-entry circuits, which may induce ventricular tachyarrhythmias.
Acquired Long QT Syndrome

- A decreased outward potassium current can occur as a result of:
  - Class IA antiarrhythmic drugs (quinidine, procainamide and disopyramide)
  - Class III antiarrhythmic drugs (sotalol)
Congenital Long QT Syndrome

- In LQT3: mutations of the SCN5A gene for the sodium channel leads to gain-of-function with persistent inward sodium current in the plateau phase (failure to inactivate sodium channels)

- Loss-of-function mutations in the same gene may lead to different presentations (Brugada syndrome)