Tutorial on Electrophysiology of the Heart

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DISCLOSURE

• Hold patents on blood test for arrhythmic risk, hLuc7A/RBM25 as antiarrhythmic targets, NAD$^+$ and mitochondrial anti-oxidants for treatment of arrhythmia
• Off label uses of NAD$^+$ and mitoTEMPO
• Owner of 3PrimeDx
Objectives

- Review normal cardiac cellular excitation
- Review generation and spread of electrical activity in the heart
- Understand three major mechanisms of arrhythmogenesis:
  - Automaticity
  - Triggered Activity
  - Reentry
- Review treatments
Review of Cellular Electrophysiology
Molecular and cellular correlates of the electrocardiogram (ECG)
Major Ion Channel Players

- All three major components (inward Na\(^+\) and Ca\(^{2+}\) and outward K\(^+\)) are voltage gated
- Four domains
- Each domain has 6 membrane spanning segments
Antiarrhythmic drugs:
State-dependent block of ion channels

- Increased affinity of channel blockers for open and inactivated states
- Relevant for antiarrhythmic effects of Class I drugs
RMP ≈ K⁺ Equilibrium potential

Nernst equation:

\[ E_K = -61 \log \left( \frac{[K^+]_i}{[K^+]_o} \right) = -96 \text{ mV} \]

RMP is determined primarily by 3 factors:

1) the concentration of ions on the inside and outside of the cell
2) the activity of electrogenic pumps (e.g., Na⁺/K⁺-ATPase and Ca²⁺ transport pumps)
3) the permeability of the cell membrane to K⁺
Changing the membrane potential

\[ E_{eq} = -61 \log \frac{[S]_i}{[S]_o} \]

\[ E_m = \frac{RT}{F} \ln \frac{P_K[K]_o + P_{Na}[Na]_o}{P_K[K]_i + P_{Na}[Na]_i} \]
Gap Junction Channels are made of Connexons
- Each channel is made of two connexons, one in the plasma membrane of each of the cells linked
- Each connexon is made of up to 6 connexin subunits
- The most abundant is Cx43, other (Cx 37, Cx 40, Cx 45) are only in small amounts
Concept of Refractoriness
Conduction System Properties

A. SAN

B. Atrium

C. AV node

D. His-Purkinje

E. Ventricles

SAN, AV node, His-Purkinje, and Ventricles are diagrammed with corresponding voltage changes:

- SAN: 0 mV, -50 mV
- Atrium: +30 mV, -75 mV
- AV node: 0 mV, -60 mV
- His-Purkinje: +40 mV, -90 mV
- Ventricles: +30 mV, -80 mV

1 sec. scale for voltage changes.
Conduction Velocity in Cardiac Tissue

• Velocity of spread of activation along tissue dependent on
  – Action potential upstroke speed (i.e., amount of depolarizing current)
  – Coupling of cells (gap junction function)

• Slow Conduction
  – Blocking sodium channels in working myocardium
  – Blocking calcium channels in nodal tissue
  – Affecting gap junction function
Differences Between Normal Physiology of Nodal and Working Myocardial Tissue

- **Nodal tissue**
  - Action potential dependent primarily on Ca$^{2+}$ ions (because RMP is -60mV → little Na$^+$ current)
  - AP has slow upstroke, therefore conduction velocity is slow
  - As rate of stimulation is increased, conduction velocity slows, refractory period increases
  - Behavior influenced profoundly by autonomic tone
Cellular Electrophysiology

Automaticity

The property of cardiac cells to depolarize spontaneously

Normally only cells of the SA node, the AV node, and His-Purkinje system possess automaticity.

SA Node
(Ca$^{2+}$)

Purkinje Fiber
(Na$^{+}$)
Autonomic effects on automaticity
Mechanisms of Arrhythmia
Mechanisms of bradyarrhythmia

Failure of impulse formation (e.g. sinus bradycardia)

Failure of impulse propagation (e.g. Mobitz II atrioventricular nodal block)
Mechanisms of tachyarrhythmia

Automaticity
- normal (e.g. sinus tachycardia)
- abnormal (e.g. reperfusion arrhythmias)

Triggered activity
- Early afterdepolarizations associated with action potential prolongation (torsades de pointes)
- Delayed afterdepolarizations associated with Ca\(^{2+}\) overload and depolarization (e.g. digoxin)

Reentry
- favored by slow conduction (low dV/dt or V\(_{\text{max}}\) )
- favored by cellular heterogeneity
Tachycardia
Enhanced Normal Automaticity

- Basal condition
- Increased slope of phase 4 depolarization
Characteristics of Arrhythmias Mediated by Automaticity

- Morphology of the initiating P or QRS is the same as subsequent complexes
- Exhibit progressive “warm-up” (acceleration in rate)
- Automatic tachycardias cannot be initiated by programmed electrical stimulation (PES) or pacing.
Triggered activity

**Early afterdepolarizations**

- Seen with bradycardia and prolonged action potentials
- Thought to be secondary to L-type Ca\(^{2+}\) channel recovery

**Delayed afterdepolarizations**

- Seen with tachycardia and cell Ca\(^{2+}\) overload
- Thought to be secondary to a Ca\(^{2+}\)– dependent transient inward current or sodium calcium exchange
Long QT Syndrome

Normally the QT interval is < ½ RR interval.

QT interval = 540 msec
Cause of Torsades: EADs

Nattel and Carlsson *Nature Reviews Drug Discovery* 5, 1034–1049
Reentrant Tachycardia

~ 95% of clinical arrhythmias

Absolute requirement:
   Unidirectional conduction block

Favoring conditions:
   Slow conduction such as occurs with fibrosis

   Anisotropy of conduction or other electrophysiological properties such as \(\geq 2\) pathways for impulse conduction that can be joined proximally and distally
Unidirectional block and reentry

Anatomic obstacle  Bidirectional block  Unidirectional block  Reentry
Rotors: a new concept in reentry
Specific examples of arrhythmia
ATRIAL FIBRILLATION AND FLUTTER

Disorganized electrical pulses in the heart’s upper chambers (atria) cause the rhythm of the lower chambers to be fast and irregular.

Arrhythmia origin = ★

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Atrial fibrillation versus atrial flutter
Atrial fibrillation risks and characteristics

- Atrial fibrillation
  - Age
  - HTN
  - DM
  - FH
  - Obesity
  - Males
  - Atherosclerosis/prior MI
  - Surgery
  - Hyperthyroidism
  - LV dysfunction
  - Valvular disease
Complications of atrial fibrillation

Tachycardia

- SOB
- Lightheadedness
- Edema
- ↓ Exercise tolerance
- Myopathy

Stroke
Thrombus formation and stroke risk in atrial fibrillation
Atrial Fibrillation: Mechanisms
Ventricular Tachycardia and Fibrillation

Abnormal electrical pulses in the heart’s lower chambers (ventricles) disrupt the normal firing of the SA node causing the heart to beat rapidly.

Arrhythmia origin = ★
Ventricular fibrillation versus tachycardia

Ventricular Fibrillation

Ventricular Tachycardia

Sinus Node
Right Atrium
AV Node
Right Ventricle
Left Ventricle
Left Atrium
Sudden Death
Defining the Problem of Sudden Cardiac Death (SCD)

Etiologies of Sudden Death

- An estimated 13 million people had CHD in the U.S. in 2002. ¹
- Sudden death was the first manifestation of coronary heart disease in 50% of men and 63% of women. ¹
- Approximately 50% of CHD deaths are sudden²
- Incidence of SCD in the US is 1-2/1000²
- CHD accounts for at least 80% of sudden cardiac deaths in Western cultures.³

Etiologies of Sudden Death

- 80% Coronary Heart Disease
- 15% Cardiomyopathy
- 5% Other*  

* ion-channel abnormalities, valvular or congenital heart disease, other causes


Treatments of Arrhythmia
Pacemaker Indications

- Sinus node dysfunction
- Sinus bradycardia with symptoms
- Symptomatic chronotropic incompetence
- Sinus node dysfunction and syncope
- HR < 40 while awake

AV block
- Complete AV block
- High degree AV block
- Symptomatic AV block
- Mobitz II
- Exercise induced 2\textsuperscript{nd} or 3\textsuperscript{rd} degree AV block
- Bifascicular block and syncope

Iatrogenic
- Neurocardiogenic syncope
- Long QT

Heart failure and resynchronization
Vaughan Williams classification

Class I – Na\(^+\) blockers
- Class Ia – blocks Na\(^+\) and K\(^+\) channels
- Class Ib – blocks Na\(^+\) channels with rapid kinetics
- Class Ic – blocks Na\(^+\) channels with slow kinetics

Class II - β blockers

Class III – blocks K\(^+\) channels

Class IV – Ca\(^{2+}\) channel blockers. Dihydropyridines are not effective antiarrhythmic drugs
Getting Rid of Reentry

- The critical wavelength is $\text{APD} \times \text{CV} =$ the minimum path length required for reentry
- $\text{K}^+ \text{ channel block}$
- Prolong the refractory period
- $\text{Na}^+ \text{ channel block}$
- Critically slow conduction
Proarrhythmia

- Class I proarrhythmia may be drug induced
- Brugada syndrome
- Class III proarrhythmia is related to QT prolongation
Finding (Mapping) and ablating arrhythmias
Surgery for arrhythmias

Before Abnormal electrical pathways

Sinus (SA) node

Atrioventricular (AV) node

Scars block abnormal pathways

After

Atrial fibrillation

Before

Maze procedure (Normal rhythm restored)

After
Implanted cardiac defibrillators (ICDs)
SOCS-HEFT results: ROC curve for prediction of sudden death
Raising sodium current to treat arrhythmias

A. Preparation

B. Optical Action Potentials

C. Activation Map

D. Conduction Velocity

- Time (ms)
- 0 1 2 3
- Fluorescence
- 0 1 2 3
- 0 1 2 3
- Velocity (cm/sec)
- 0 1 2 3
- 0 1 2 3
- Pacing Cycle Length (ms)
- 2000 1000 800 600
Summary

• Ion channels and ion movement across a membrane underlie cardiac electrophysiology
• Conduction moves from the high right atrium to the ventricles
• There are five mechanisms of arrhythmia
  – Failed automaticity
  – Failed conduction
  – Enhanced or abnormal automaticity
  – Triggered activity
  – Reentry
• Treatments
  – Pacemaker
  – Blocking ion channels – all drugs have proarrhythmia
  – Ablation
  – ICDs
  – Raising ion channels