CHANNELOPATHIES

Osama Diab
MD Cardiology
Prof. of Cardiology, Ain Shams University-Cairo
Consultant Electrophysiologist, Ain Shams University Hospitals

Hereditary disorders affecting ion channels, resulting in channel dysfunction manifested by a variety of clinical syndromes
Cardiac Channelopathies

- Congenital Long QT Syndrome
- Acquired Long QT Syndrome
- Short QT Syndrome
- Brugada Syndrome
- Catecholaminergic Polymorphic VT
- Sinus node dysfunction
- AV Conduction blocks (Degenerative HB/Lev-syndrome, LBBB, RBBB, congenital HB)
- Atrial standstill

Cardiac Action Potential

Voltage gated Na channels

L-Ca channels

Ca++

Na+

K+

3Na+

Na/K pump

Mg++, Ca++

K+

2K+
Sodium Channels

Alfa subunit is the core of Na channel: 4 domains of 6 membrane spanning regions (S1-S6), encoded by SCN5A gene. Beta subunits may regulate the channel activity.

Action Potential Abnormalities due to Na\(^+\) Channel Dysfunction

Activating mutation
(Reopening after closure)

LQT3
Schematic drawing illustrating transmembrane action potentials from a Purkinje fiber, a ventricular muscle fiber, and a surface electrocardiogram

Reopening of Na channels after closure leads to another influx of Na in late phases of action potential (after depolarization). When after depolarization reaches threshold of firing, another action potential occurs leading to isolated PVCs or runs of polymorphic VT.

**Long QT syndrome**

**LQT3**

- Activation of the Na+ channel. Channels may open repetitively during the action potential.

- Arrhythmia occurs at rest or during sleep.
LQT3

Action Potential Abnormalities due to Na⁺ Channel Dysfunction

Inactivating
(Premature closure)

Endocardium

Na⁺

Gradient

Epicardium

Endocardium

Syndrome

V1
Understanding Brugada

Schematic representation of right ventricle epicardial action potential (AP) changes thought to underlie the ECG manifestations of Brugada syndrome.
BRUGADA SYNDROME

- The second commonest cause of death (after accidents) in south east Asia in individuals below 20.
- Usually familial rarely sporadic.
- Inherited as autosomal dominant.
- Some forms of SCN5A gene mutation terminate the channel opening early only at high temperature. So VF may appear in febrile states.

Example of type 1, 2 and 3 Brugada-type ECG patterns
MANEUVERS THAT UNMASK OR ACCENTUATE BRUGADA ECG SIGN

1. Sodium channel blockers (flecanide, ajmaline)
2. Fevers, hot weather
3. Vagotonic agents
4. $\alpha$ adrenergic agonists
5. Beta blockers
6. Tricyclic antidepressants
7. Some antihistaminics
8. Cocaine

How Brugada syndrome is missed:
Diagnostic pitfalls

<table>
<thead>
<tr>
<th>Brugada Syndrome</th>
<th>Misdiagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope in hot weather or after a hot bath</td>
<td>Neurocardiogenic syncope</td>
</tr>
<tr>
<td>Fainting+fits during febrile episodes</td>
<td>Febrile convulsions</td>
</tr>
<tr>
<td>Agonal breathing during sleep</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>ST elevation in V1-3 that resolves</td>
<td>Anteroseptal MI coronary spasm</td>
</tr>
</tbody>
</table>
Brugada syndrome treatment strategy

- Symptomatic patients (SCD or syncope) plus Brugada ECG pattern → ICD (class I)
- Asymptomatic patients plus Brugada ECG pattern → EPS (class IIa)
  a. Inducible VT → ICD
  b. Non-inducible → Follow up

Action Potential Abnormalities due to Na\(^+\) Channel Dysfunction

**Inactivating mutation**
(Partial closure)

PCCD (Lev)
Congenital HB
Normal Action Potential Propagation

Na$^+$

His-Purkinje cells

Na Channel inactivating Mutation

Na$^+$

His-Purkinje cells
Most individuals with LQT1 show prolongation of the QT interval with infusion of isoprenaline. This can also unmask latent carriers of the LQT1 gene. Arrhythmic events during exercise and excitement improve with beta blockers.

Progressive Cardiac Conduction Defect “Progressive Familial Heart Block”
PCCD

- Also called Lenegre-Lev disease is one of the most common cardiac conduction disturbances.

It represents the major cause of pacemaker implantation in the world (0.15 implantations per 1,000 inhabitants per year in developed countries).

Progression has been shown from a normal electrocardiogram to right bundle branch block and from the latter to complete heart block.

SCN5A: A single gene subjected to different mutations – different clinical syndromes
Normal $\text{Na}^+$ channel function

Activating mutation (reopening after closure): LQT3

Normal $\text{Na}^+$ channel function

Premature closure (gating defect): Brugada
Partial closure (or ↓ number of channels): Conduction disease

Potassium Channels

Nobel Prize 2003

Roderick MacKinnon

Types of K channels:

1- Voltage gated K channels:
   - KvLQ1 channels (slow, Iks)
   - HERG channels (rapid, Ikr)

2- Inwardly rectifying K channels

Four subunits form the channel core, each is formed of 2-6 transmembrane segments (alfa subunits) + B subunits.
Voltage gated $K^+$ channels

Inactivating mutation

Voltage gated $K$ channels

Inwardly rectifier $K$ channels

Na/K pump

Long QT: 1,2,4,5,6

ECG

Long QT syndrome

LQT1

The most common type (50 percent of all cases).

The LQT1 gene is on chromosome 11, encoding for the voltage-gated potassium channel KvLQT1 (alpha subunit), which is responsible for the slowly activated delayed potassium rectifier current ($I_{ks}$).

Triggered by exercise or swimming

Could be autosomal dominant or an autosomal recessive pattern in the same family. Homozygous mutations leads to severe prolongation of the QT interval, and is associated with congenital deafness. This variant of LQT1 is known as the Jervell and Lange-Nielsen syndrome.
The second most common (40%).

Involves mutations of the human ether-a-go-go related gene (HERG) on chromosome 7 which is part of the rapid component of the potassium rectifying current (IKr).

Arrhythmia is triggered by sudden auditory stimuli (door bells, telephone rings).
$T$-peak to $T$-end = Transmural dispersion of repolarization
T-peak to T-end = Transmural dispersion of repolarization

Modified Schwartz score for the diagnosis of LQTS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG findings</strong></td>
<td></td>
</tr>
<tr>
<td>QTc ms ≥ 480</td>
<td>3</td>
</tr>
<tr>
<td>460–470</td>
<td>2</td>
</tr>
<tr>
<td>450 (in males)</td>
<td>1</td>
</tr>
<tr>
<td>Torsade de pointes</td>
<td>2</td>
</tr>
<tr>
<td>T wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T wave in three leads</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
</tr>
<tr>
<td>Syncopy</td>
<td>2</td>
</tr>
<tr>
<td>With stress</td>
<td>1</td>
</tr>
<tr>
<td>Without stress</td>
<td>0.5</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td></td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>Family members with definite LQTS</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained sudden cardiac death &lt; age 30 years</td>
<td>0.5</td>
</tr>
<tr>
<td>among immediate family members</td>
<td></td>
</tr>
</tbody>
</table>

Score ≥ 3.5: Definite LQTS  
Score 2-3: Intermediate probability  
Score ≤ 1: Low probability

Voltage gated $K^+$ channels
Activating mutation

Short QT

ECG

Short QT syndrome

- QT interval interval $\leq 300$ ms that doesn't significantly change with heart rate, tall and peaked T waves, and a structurally normal heart. Short QT syndrome appears to be inherited in an autosomal dominant pattern (activating mutation of HERG gene).

- In the electrophysiology lab, individuals with short QT syndrome are noted to have short refractory periods, both in the atria as well as in the ventricles, ventricular fibrillation and AF are frequently induced on programmed stimulation.

- TTT: ICD
Short QT

Calcium Channels

Types of Ca channels:
1. high voltage activated
   - L-type
   - N-type
   - P/Q-type
2. R-type (intermediate voltage activate)
3. T-type (low voltage activated)

Complex of several different subunits: α1, α2, β, γ, and δ. The α1 subunit is the one that decides most of the channel properties.
Calcium Release Channels
Ryanodine Receptors 2 (RyR2)

Structure: Tetramer comprised of 4 RYR2 polypeptides & FK506-binding proteins FKBP1A
Location: Sarcoplasmic reticulum

RyR2 gene mutation will increase sensitivity of sarcoplasmic Ca release channels to Ca influx from the membrane L-channels resulting in Ca load

Catecholamines
Activating mutation increases sensitivity of RyR2 to Ca

Catecholaminergic Polymorphic VT

Ca++ load

Catecholaminergic Polymorphic VT

- Described by Coumel et al in 1978.

- Affected individuals present with syncopal events and with a distinctive pattern of highly reproducible, stress-related, bidirectional VT in the absence of both structural heart disease and a prolonged QT interval.

- A family history of juvenile sudden death and stress-induced syncope is present in approximately one third of cases.

- Likely involves calcium overload–mediated, delayed afterdepolarizations due to increased calcium sensitivity of RyR2.
Bidirectional VT reproducibly elicited by exercise stress testing

Catecholaminergic Polymorphic VT
Inherited Conduction defects

- HCN channel inactivating mutation
- Na channel inactivating mutation
- Gap junction inactivating mutation

SND, AV conduction defects, Atrial standstill

Pacemaker Action Potential

- If
- Ca++
- L-Channels
- Ca++
- K+
- T-Ca Ch
- Volt. Gated K Channels

Diastolic Depolarization
**Pacemaker Action Potential**

**The funny current (I_f)**

If is a mixed Na+ and K+ inward current which is responsible for generation of the diastolic depolarization and pacemaker firing.

Has been well characterized by DiFrancesco in 1993.

**HCN Channels**

*(Hyperpolarization activated Cyclic Nucleotide-Gated Channels)*

They are good target for autonomic nervous system.

Structure of HCN channels.
Novel reports describing HCN gene mutation

**S672R Mutation of HCN4 gene**

*(Milanesi et al., 2006)*

**A.** Templates used for homology modeling for the open (MthK channel in red) and closed (KcsA channel in blue) channel.  
**B.** Final models of the spHCN channel in the open (red) and closed state (blue).

**HCN Channel Inactivating Mutation**

Inactivating mutation

↓

**Sinus Node Dysfunction**

If

Sinus bradycardia
Inactivating mutation

Sinus Node Dysfunction

HCN Channel Inactivating Mutation

Sinus pauses

HCN Channel Inactivating Mutation

Catecholamines

Chronotropic incompetence
Most individuals with LQT1 show prolongation of the QT interval with infusion of isoprenaline. This can also unmask latent carriers of the LQT1 gene. Arrhythmic events during exercise and excitement improve with beta blockers.

### Sinus Node Dysfunction (SND)

- 3 cases in 5000 patients older than 50 years.
- Accounts for approximately half of all patients requiring a pacemaker.
- In a significant portion of patients, SND appears in the absence of identifiable cardiac abnormalities or other associated conditions ("idiopathic" SND).

### Action Potential Abnormalities due to Na⁺ Channel Dysfunction

SCN5A gene

Inactivating mutation

(Partial closure)

PCCD (Lev)

Congenital HB

ECG
Normal Na⁺ channel function

Partial closure (or ↓ number of channels): Conduction disease

Normal Action Potential Propagation

His-Purkinje cells
Na Channel inactivating Mutation

His-Purkinje cells

Progressive Cardiac Conduction Defect
“Progressive Familial Heart Block”

PCCD

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Progression has been shown from a normal electrocardiogram to right bundle branch block and from the latter to complete heart block.
Gap junctions are dynamic structures because connexons are able to open and close. Elevated intracellular calcium and low intracellular pH are established stimuli for rapid closing of connexons.

**Gap junction inactivating mutation:**
- Cx43,45 (His-Purkinje specific) mutation: AV conduction defects
- Cx40 (atrial specific) mutation: causes atrial standstill

**Normal Action Potential Propagation**

His-Purkinje cells
Normal AV conduction
Gap junction inactivating mutation

His-Purkinje cells
AV block

Atrial standstill

Characterized by:

(1) Absence of P wave in any lead of the standard electrocardiogram.
(2) Slow junctional escape rhythm
(3) Lack of atrial response to atrial pacing
(4) Absence of atrial wall movement on fluoroscopy; & mitral A wave on the echocardiogram.
Differential Diagnosis

Slow Atrial Fibrillation

Management

VVIR Pacing

Anticoagulation
Thank You