Basics of Structure/Function of Sodium and Potassium Channels

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International Symposium of Inherited Arrhythmia Disorders and Hypertrophic Cardiomyopathy: A Comprehensive Update and Current Controversies

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Nothing to Disclose
15 Year Old with Syncope
Baseline Holter Tracing
Nightmare at 3:30 AM
Cardiac Arrhythmias

• Major cause of morbidity and mortality
• At least 250,000 sudden deaths per year in US
• Treatment is inadequate
• Most are associated with structural heart disease (MI, CHF)
• A lot is known about rare syndromes simple inheritance (long QT & Brugada syndromes)
Inherited Arrhythmopathies

- Long QT Syndrome
- Short QT Syndrome
- Brugada Syndrome
- Catecholaminergic Polymorphic VT
- Familial Atrial Fibrillation
- Progressive Conduction Defects (Lev, Lenegre)
- WPW
# Long QT Syndrome Loci/Genes

<table>
<thead>
<tr>
<th>Locus</th>
<th>Protein</th>
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<th>Current Current</th>
<th>Chromosome</th>
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<tbody>
<tr>
<td>LQT1</td>
<td>KvLQT1</td>
<td>KCNQ1</td>
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<td>KCNH2</td>
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<td>Ankyrin-B</td>
<td>ANK2</td>
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<td>LQT6</td>
<td>MiRP1</td>
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<td>SNTA1</td>
<td>↑ ( I_{Na} ) ?</td>
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Long QT Syndrome

- Autosomal Dominant (Romano Ward), Autosomal Recessive (Jervell & Lange Nielsen) Acquired (drugs, intracranial bleed, etc)
- Symptoms: Syncope, aborted SCD, Seizures, SIDS
- Dx: QTc prolongation, T-wave abnormalities, torsades de pointes, family history, stress test
- Molecular diagnosis: Familion, GeneDx
- Therapies: Avoid QT prolonging meds, Beta blockers, ?K+/aldactone, ?mexilitine
Long QT Syndrome: Mechanism of Ion Channel Mutations

- Fewer functional $K^+$ channels
  - Mutations that alter RNA or protein expression
  - Mutations that alter channel trafficking to membrane

- Abnormal channels
  - Nonfunctional $K^+$ channels
  - Dysfunctional $K^+$ channels: Abnormal kinetics
  - Dysfunction $Na^+$ channels: Persistent late current

- Dominant negative $K^+$ channel subunits
Arrhythmic Mechanisms - Initiation

- Triggered Activity: long APD $\rightarrow$ EADs
  - Early Afterdepolarizations
  - Action potential prolongation leading to reactivation of inward Ca$^{2+}$ currents

- Triggered Activity: long APD $\rightarrow$ DADs
  - Delayed Afterdepolarizations
  - Abnormal release of Ca$^{2+}$ from the SR triggers inward current via Na-Ca exchanger
Arrhythmic Mechanisms – Maintenance (Reentrant Substrate)

• Slow conduction
  – Abnormal Na\(^+\) currents
  – Abnormal intercellular connections

• Anatomical barriers \(\rightarrow\) block
  – Scar, fibrosis

• Functional barriers \(\rightarrow\) block
  – Dispersion of repolarization and refractoriness
  – Heterogeneities: Apex/base, endocardium/epicardium, Purkinje fibers
LQTS: Genotype-Phenotype

- Arrhythmia by genotype:
  - LQT1: Exercise
  - LQT2: Noise
  - LQT3: Rest
    (Schwartz et al., J Intern Med 2006; 259: 39)

- More malignant mutations
  - Dominant negative and pore K⁺ channel mutations
    (Moss et al., Circulation 2007;115:2481-89)

- Gene-specific therapies
  - LQT1, LQT2: β-blockade
  - LQT2: K⁺ + Aldactone
  - LQT3: Mexilitine, Ranolazine
LQT1: Beta-Blockers

- KCNQ1/KCNE1 $K^+$ channels encode $I_{KS}$; Mutations of KCNQ1/KvLQT1 cause LQT1 form of LQTS
- Increased $I_{KS}$ responsible for QT shortening with increased heart rate and $\beta$-adrenergic stimulation
- $\beta$-Blockers more effective in LQT1 than LQT2 or LQT3 (Priori et al., *JAMA* 2004;292:1341-44)
- Yotiao (AKAP) associates KCNQ1 to PKA & PP1. The KCNQ1-G589D mutation disrupts the macromolecular complex and causes LQT1 (Marx et al., *Science* 2002;295:496-9)
**LQT2: K⁺ and Aldactone**

- KCNH2 K⁺ channels encode $I_{Kr}$; HERG mutations cause the LQT2 form of LQTS
- HERG K⁺ channels have lower open probabilities with lower extracellular [K⁺]
- K⁺ supplements and aldactone can increase blood K⁺ and shorten the QT interval in LQT2 patients (Etheridge et al., *JACC* 2003;42:1777-82)
LQT3: Mexilitine

- Mutations that alter inactivation of the SCN5A Na\(^+\) channel lead to a late inward Na\(^+\) current; SCN5A mutations cause the LQT3 form of LQTS

- Mexilitine blocks late currents in vitro, in SCN5A mutant LQT3 mice, and decreases QTc in LQT3 subjects

(Wang et al., JCI 1997;99:1714-20) (Schwartz et al., Circulation 1995;92:3381-6)
Brugada Syndrome Family

Proband presented with syncope and got an AICD
T353I Mutation in Conserved Region of SCN5A
Mutant Channels Have Decreased Peak $I_{Na}$

(Pfahnl et al., Heart Rhythm 2007; 4: 46-53)
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Brugada Syndrome

- Characterized by a right bundle branch block pattern (RBBBp) and ST elevation in the right precordial leads (STE) of the EKG which can vary from day to day (Brugada & Brugada, 1992)
- Autosomal dominant, male predominance
- No structural heart disease
- Rare, but more common in Southeast Asia (Bangungut, Pokkuri, Lai Tai, SUDS).
Brugada Syndrome

- Syncope, aborted SCD, Family history
- Typical ECG pattern (coved vs. saddleback)
- Na\(^+\) channel blockers (e.g. ajmaline, flecainide, procainamide) exacerbate the ECG findings and are used diagnostically (Brugada et al., 2000)
- EP study: HV prolongation, inducible VF
- Molecular diagnosis: Familion, GeneDx
- Therapies: ICD, ?Quinidine
Brugada Syndrome: A Disorder of Depolarization

- Reduced depolarizing current in the epicardial cells of the RV (Antzelevitch, 1998)

- The repolarizing current $I_{to}$ leads to:
  - loss of the action potential plateau
  - premature repolarization of the epicardium
  - transmural current flow with STE
  - reentrant arrhythmias
Brugada Syndrome:
Arrhythmia Mechanisms

Truncated Epicardial APs

Phase 2 Reentry
Brugada: Quinidine & Isoproterenol

• Mutations that decrease inward $I_{Na}$ lead to premature repolarization in the RV epicardium where outward $I_{to}$ is large.

• Quinidine blocks $I_{to}$, decreases ST elevation in some subjects, suppresses inducible VT/VF during EP study, and may decrease spontaneous arrhythmias (Belhassen et al., *Circulation* 2004;110:1731-7).

• Isoproterenol decreases ST elevation in the right precordial leads and suppresses VT storm, perhaps by increasing $I_{Ca}$ (Jongman et al., *Neth Heart J* 2007;15:151-4).
Long QT and Brugada Syndromes: Disorders of Repolarization/Depolarization

- A number of dysfunctional $K^+$ channels, $Na^+$ channels, $Ca^{2+}$ channels, and ion channel related proteins cause disease.

- These inherited disorders have catalyzed a huge amount of work on cardiac ion channels.

- Genotype-specific therapies exist, but they have not been proven to prevent arrhythmias or sudden cardiac death; Multicenter randomized controlled trials are needed.