THE UNIVERSITY OF TENNESSEE MEDICAL CENTER

CARDIAC CHANNELOPATHIES

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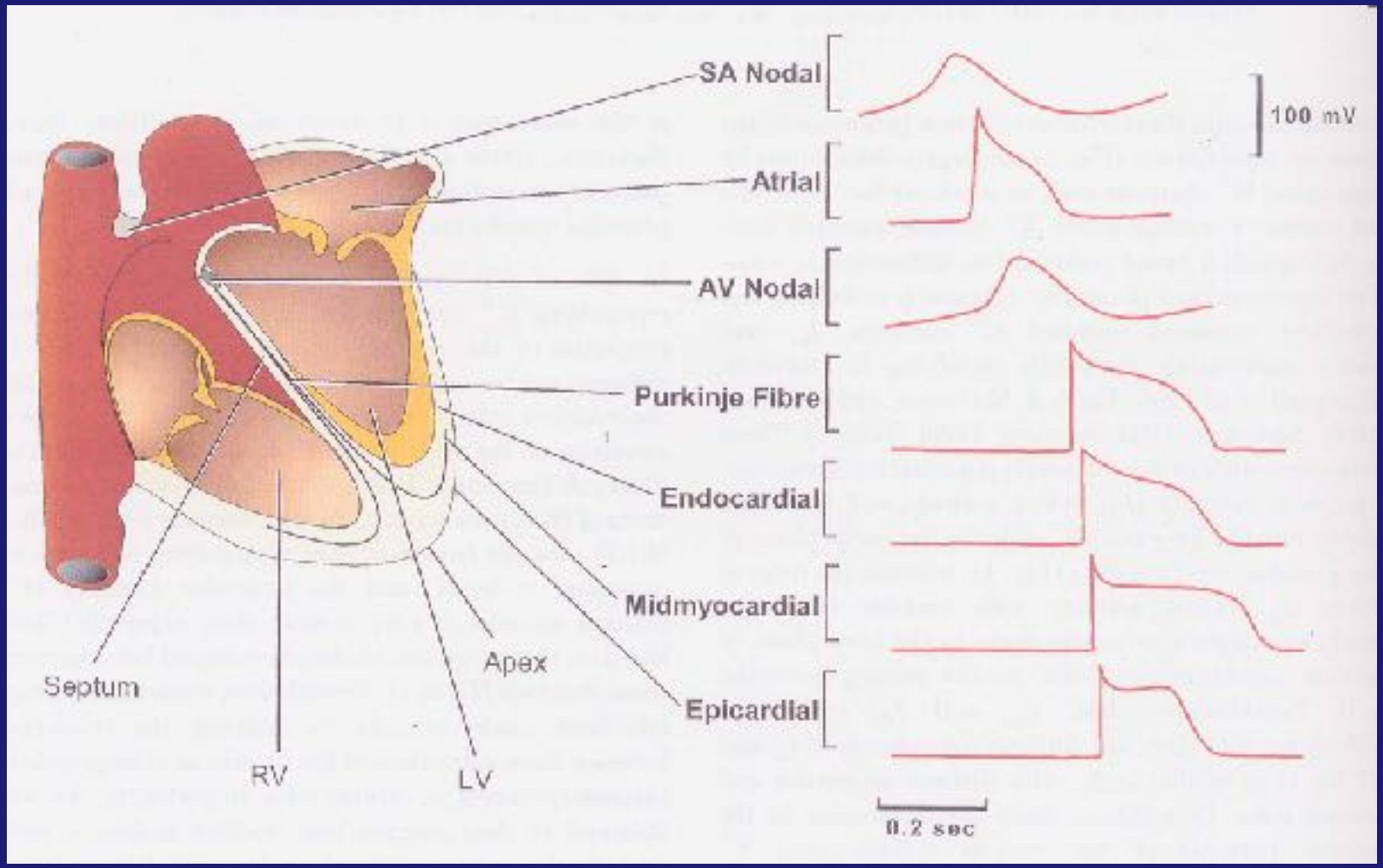
Outline

- Introduction
- Overview of cardiac action potential
- Structure of ion channels
- Long QT Syndrome
- Short QT Syndrome
- Brugada Syndrome
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)
- Idiopathic ventricular fibrillation
- Progressive cardiac conduction defect
- Ankyrin-B Syndrome

Introduction

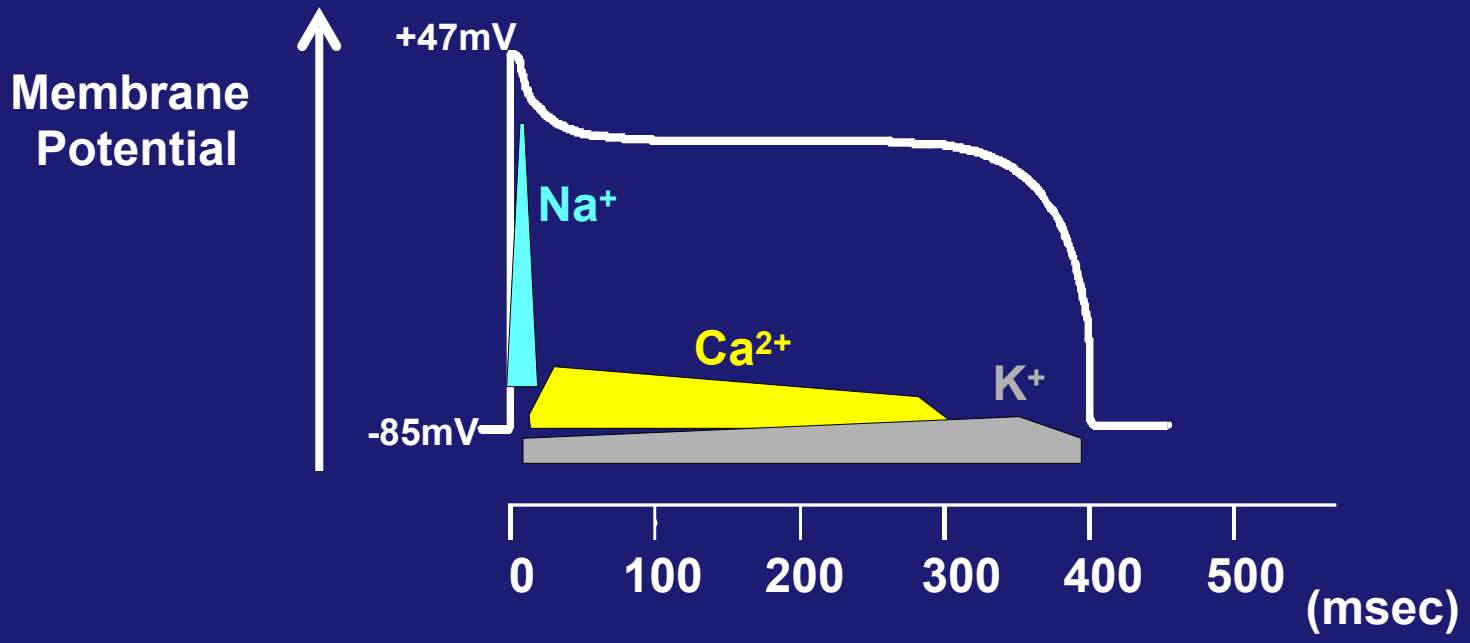
- Cardiac arrhythmias and conduction defects result from abnormalities in three main families of proteins:
  - Contractile proteins (e.g. HOCM)
  - Cytoskeletal proteins (eg. DCM)
  - Ion channels and their regulators

Action Potential Waveforms in Different Regions of the Heart



Nerbonne JM. J of Physiology 2000, 525.2;285

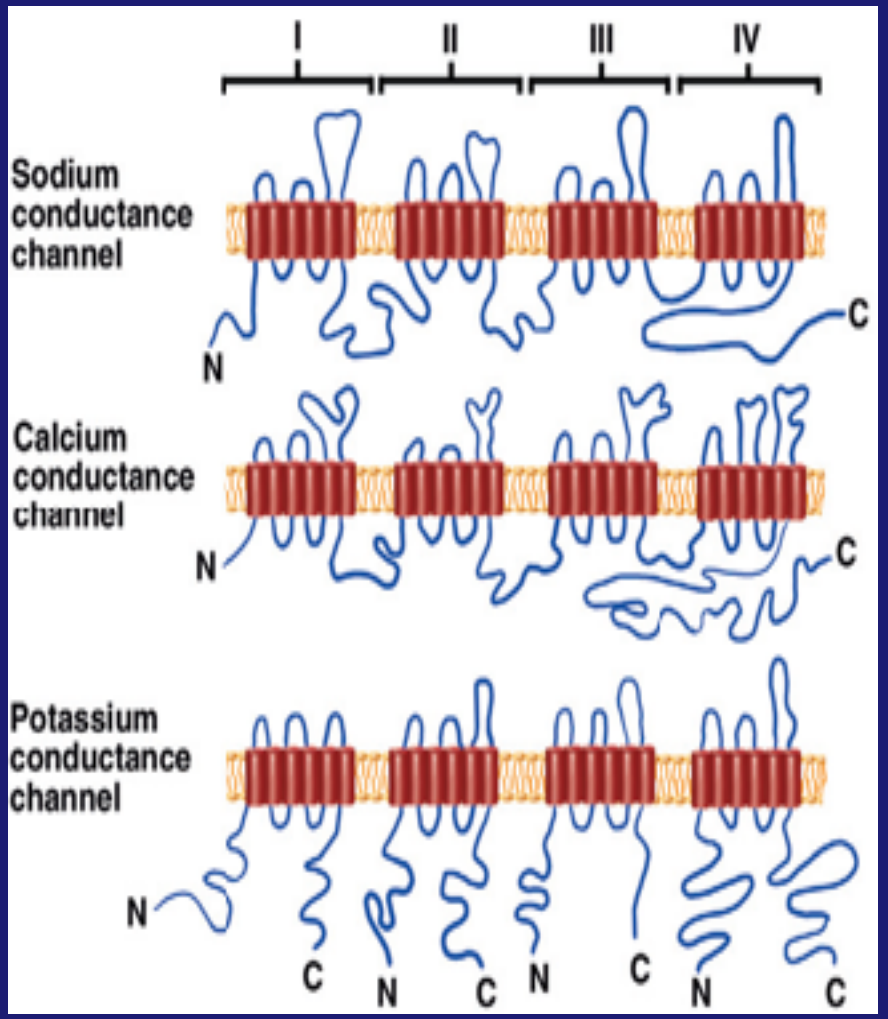
The Cardiac Action Potential



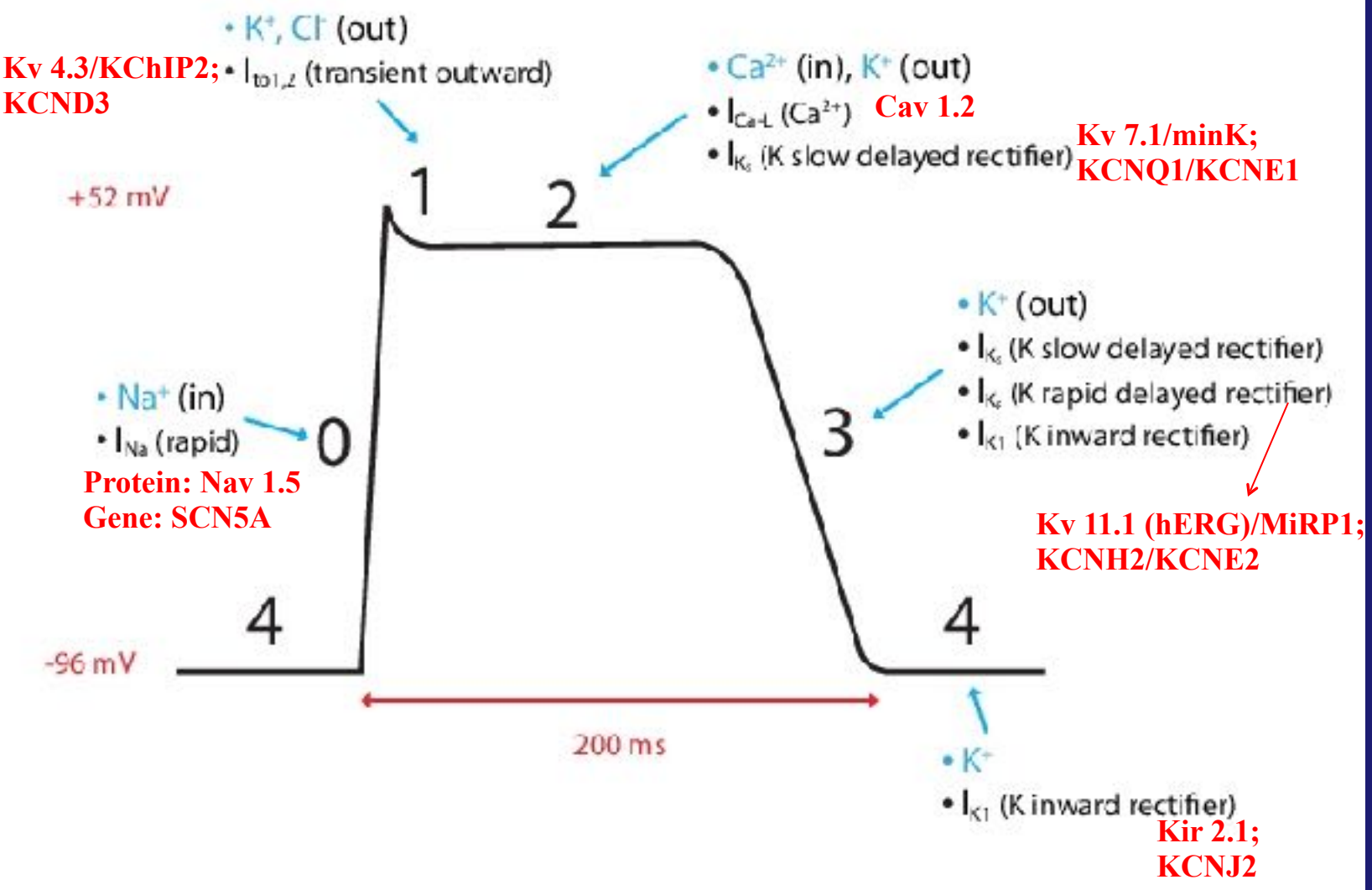
Structure of Ion Channels

ION CHANNEL = **Alpha Subunit (pore forming)** + **Auxillary subunits (β,γ,δ)**

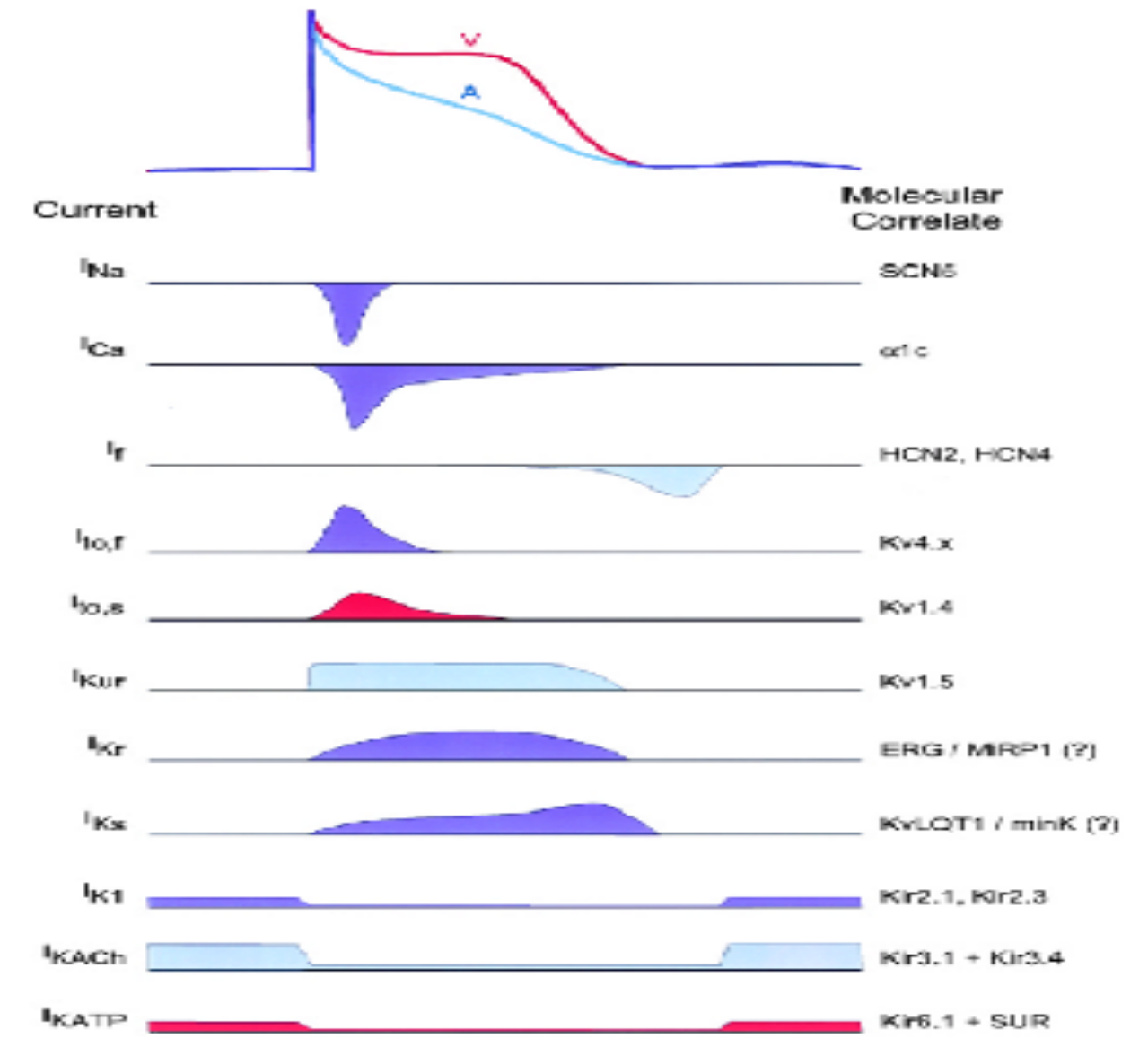
- Voltage-gated Na+ and Ca2+ channels:
  - single tetramer
  - four covalently linked repeats of the six transmembrane–spanning motifs.
- Voltage-gated K+ channels:
  - four separate subunits,
  - each containing a single six transmembrane–spanning motif.
- Inwardly rectifying K+ channels
  - In contrast to voltage-gated K+ channel alpha subunits, the Kir alpha subunits have only two (not six) transmembrane domains.



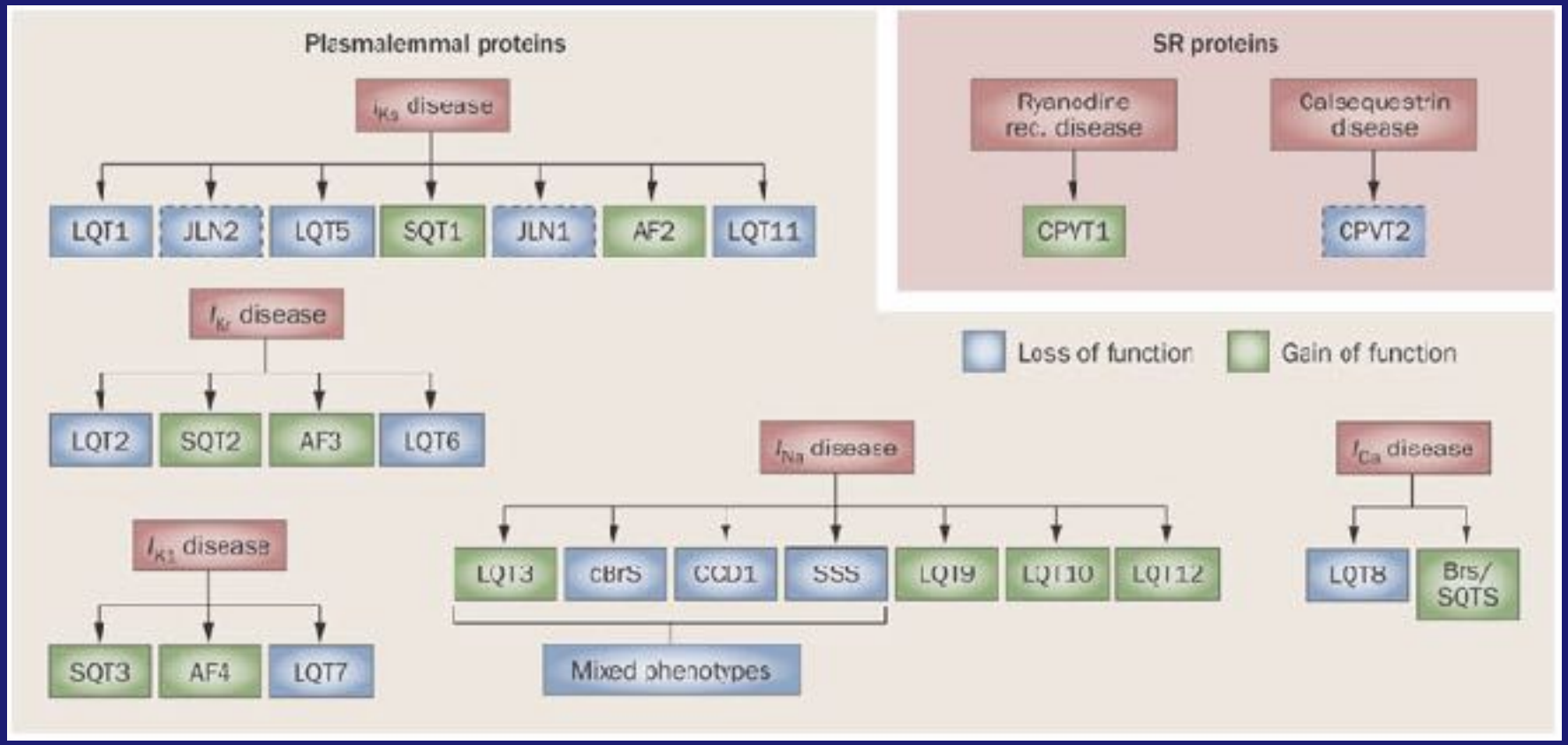
Relationship Between Cardiac Action Potential and Ion Channel Currents



Ionic Basis of the Action Potential in Mammalian Cardiomyocytes

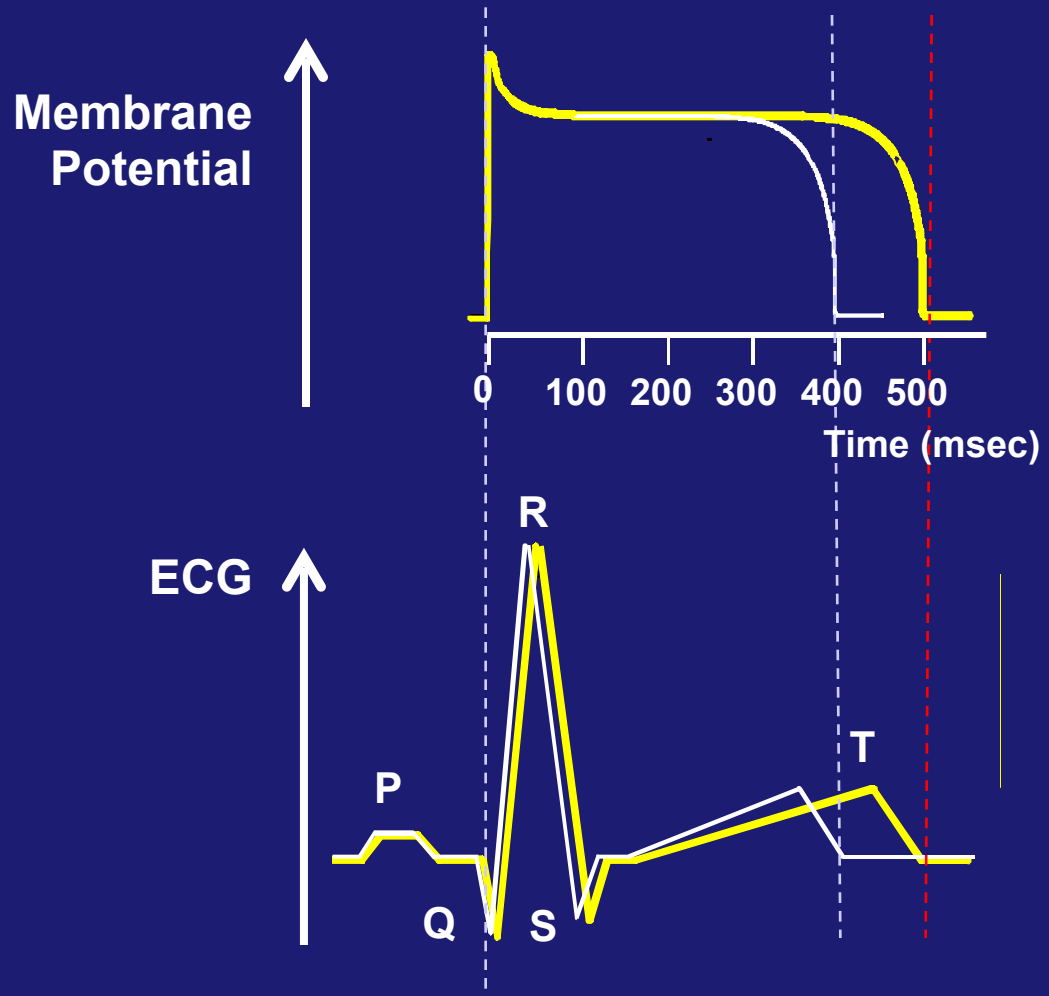


Overlap in Gene Mutations



Long QT Syndrome (LQTS)

Long QT Syndrome



Na + current

K+ current

Long QT Syndrome

- Congenital LQTS: 1 in 2500 to 10,000 in the general population
- SCD is relatively common (3000 to 4000 annual sudden deaths in childhood in the United States)
- An untreated mortality rate of 50% in 10 years.
- The primary symptoms in patients with LQTS include palpitations, syncope, seizures, and cardiac arrest.
- Majority of patients are asymptomatic
  - One third present with syncope or malignant arrythmia (most common being torsades)

Long QT Syndrome

- Acquired *versus* inherited
- Mutations in seven genes have been identified thus far in patients with genetic LQTS
- Two defined patterns of inheritance:
  - Autosomal Dominant (Romano-Ward Syndrome): Includes LQT Syndrome 1 to 12.
  - Autosomal Recessive (Jervell Lang-Nielsen Syndrome): Associated with deafness. Thus far has only been described in LQT1 and LQT5 (i.e. the genes encoding for I_{ks} current).

Long QT Syndrome

- Andersen-Tawil syndrome (LQT7)
  - rare autosomal dominant ;
  - episodes of paralysis,
  - ventricular arrhythmias, and dysmorphic features ;
  - mutations in the gene KCNJ2, located on chromosome 17q23, which encodes the inward rectifying potassium channel Kir2.1
  - Characteristic T-U wave morphologies have also been identified in patients with Andersen syndrome:
    - Prolonged terminal T wave downslope
    - Biphasic U waves in limb leads
    - Wide T-U junction (in contrast to bifid T waves in LQT2)
    - Enlarged U waves

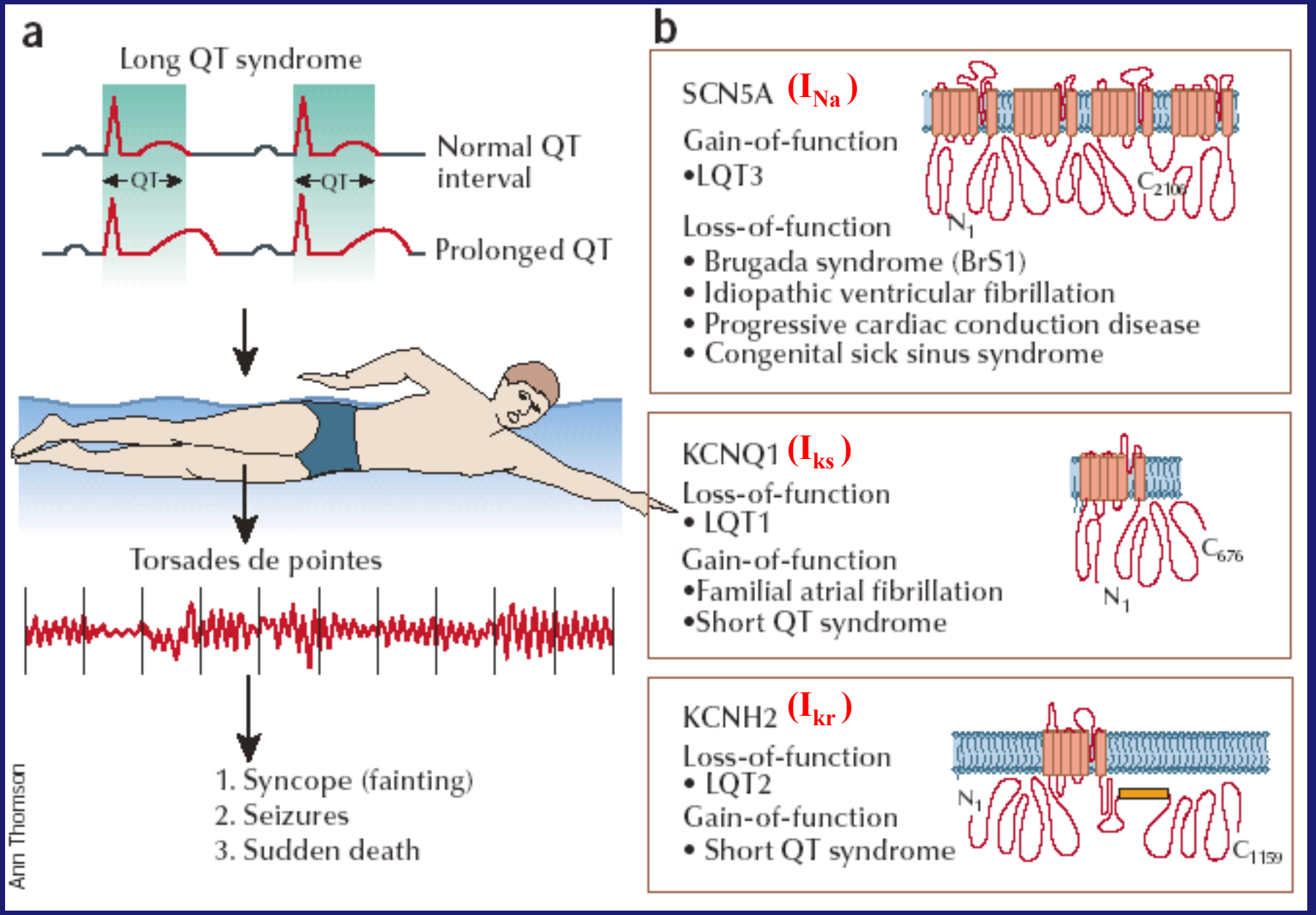
Inherited LQTS

Locus name	Chromosomal locus	Gene symbol	Protein (symbol)	Current	Action potential	In vitro characterization	Gene-specific therapy*	Clinical syndrome - heterozygous mutation	Clinical syndrome - homozygous mutation
LQT1	11p15.5	KCNQ1	I_{Ks} potassium channel α-subunit (KvLQT1)	↓ IKs	Delayed phase 3	Dominant negative suppression, trafficking defect, abnormal gating, reduced response	Beta-blockers†, potassium channel openers†	RAA	JLN
LQT2	7q35-q36	KCNH2	I_{Kr} potassium channel α-subunit (HERG)	↓ IKr	Delayed phase 3	Dominant negative suppression, trafficking defect, abnormal gating	Beta-blockers†, potassium supplement†, potassium channel openers, flecainide and	RAA	NR
LQT3	3p21	SCN5A	Cardiac sodium channel α-subunit (Nav 1.5)	↑ INa	Prolonged phase 2	Abnormal gating: sustained current, slower inactivation, faster recovery, increased window current	Sodium channel blockers (mexiletine)*	RAA	NR
LQT4	4q25-q27	ANK2	Ankyrin-B (ANK2)	↓ NaCl, Na/K ATPase, InsP3		Loss of expression and misslocalization	None proposed	RAA	NR
LQT5	21q22.1-q22.2	KCNE1	I_{Ks} potassium channel beta-subunit (MinK)	↓ IKs	Delayed phase 3	Dominant negative suppression, abnormal gating, reduced response to beta AR signal	Beta blockers, potassium supplement, potassium channel openers	RAA	JLN
LQT6	21q22.1-q22.2	KCNE2	I_{Kr} potassium channel beta subunit (MiRP)	↓ IKr	Delayed phase 3	Reduced current density and abnormal channel gating	Beta-blockers, potassium supplement, potassium channel openers, flecainide and thapsigargin	RAA	NR
LQT7/Andersen	17q23.1-q24.2	KCNJ2	I_{K1} potassium channel (Kir2.1)	↓ IK1	Delayed phase 3	Dominant negative suppression, nonfunctional channels, trafficking defect, abnormal gating	None proposed	HPP	NR
LQT8/Timothy	12p13.3	CACNA1C	Voltage-gated calcium channel, CaV1.2	↑ ICa	Delayed phase 3	Loss of inactivation	Calcium channel blockers*	RAA	None
LQT9	3p25	CAV3	Caveolin-3	↑ INa		Increased late INa	Sodium channel blockers (mexiletine)		
LQT10	11q23	SCN4B	Cardiac sodium channel beta-4 subunit	↑ INa	Prolong the action potential plateau	Increased late INa	Sodium channel blockers (mexiletine)	RAA and 2:1 AVB	
LQT11	7q21-22	AKAP9	A-kinase anchoring protein	↓ IKs		Reduced phosphorylation of the Iks channel	Beta-blockers		
LQT12	20q11.2	SNTA1	Syntrophin	↑ INa		Increased late ina	Sodium channel blockers (mexiletine)		

40-55%

35-45%

8-10%


a
Long QT syndrome
QT
QT
Normal QT interval
Prolonged QT
Torsades de pointes
1. Syncope (fainting)
2. Seizures
3. Sudden death
Ann Thomson
b
SCN5A (I_{Na})
Gain-of-function
•LQT3
Loss-of-function
• Brugada syndrome (BrS1)
• Idiopathic ventricular fibrillation
• Progressive cardiac conduction disease
• Congenital sick sinus syndrome
N_1
C_{2100}
KCNQ1 (I_{ks})
Loss-of-function
• LQT1
Gain-of-function
•Familial atrial fibrillation
•Short QT syndrome
N_1
C_{676}
KCNH2 (I_{kr})
Loss-of-function
• LQT2
Gain-of-function
• Short QT syndrome
N_1
C_{1159}

LQT: Triggers of Arrhythmia

- Genotype-phenotype correlations have been performed:
  - LQT1: Events related to swimming (occurring either immediately after diving into water or during recreational or competitive swimming activities)

  - LQT2: Events triggered by auditory stimuli, such as an alarm clock or telephone ringing

  - LQT3: At highest risk of events when at rest or asleep

LQT: Prognosis

- The clinical course of LQTS is influenced by the specific analysis from the International Registry:
  - High risk (≥50 percent) – patients with QTc ≥0.50 sec who have LQT1 or LQT2 or (if male) LQT3
  - Intermediate risk (30 to 49 percent) – female patients with LQT3 and QTc ≥0.50 sec or patients with QTc <0.50 sec who have LQT3 or (if female) LQT2
  - Low risk (<30 percent) – patients with QTc <0.50 sec who have LQT1 or (if male) LQT2

LQT: Management

- The mortality rate in LQTS is reduced with earlier identification of affected patients and treatment:
  - beta blocker therapy,
  - sports restriction in some
  - avoidance of medications known to lengthen the QTc interval.

- High-risk patients including those with persistent symptoms despite beta blocker therapy may benefit from ICD implantation or left cardiac sympathetic denervation.

- Beta blockers are extremely protective in LQT1 patients, moderately protective in LQT2, and may not be sufficiently protective for those with LQT3. Consequently, targeting the pathologic, LQT3-associated late sodium current with agents such as mexiletine, flecainide, or ranolazine may represent a gene-specific therapeutic option for LQT3.

Short QT syndrome

Short QT syndrome

- Newly described in 2000
- Although not properly defined, QT<330 ms should raise high suspicion
- Three gene mutations identified so far: KCNH2 (I_{kr}), KCNQ1 (I_{ks}), KCNJ2 (I_{ki}).
- Clinically episodes of syncope, atrial fibrillation and/ or life-threatening cardiac arrhythmias.
- Tx: ICD. Research underway with class III antiarrhythmics that prolong QT (eg. Quinidine).

Brugada Syndrome

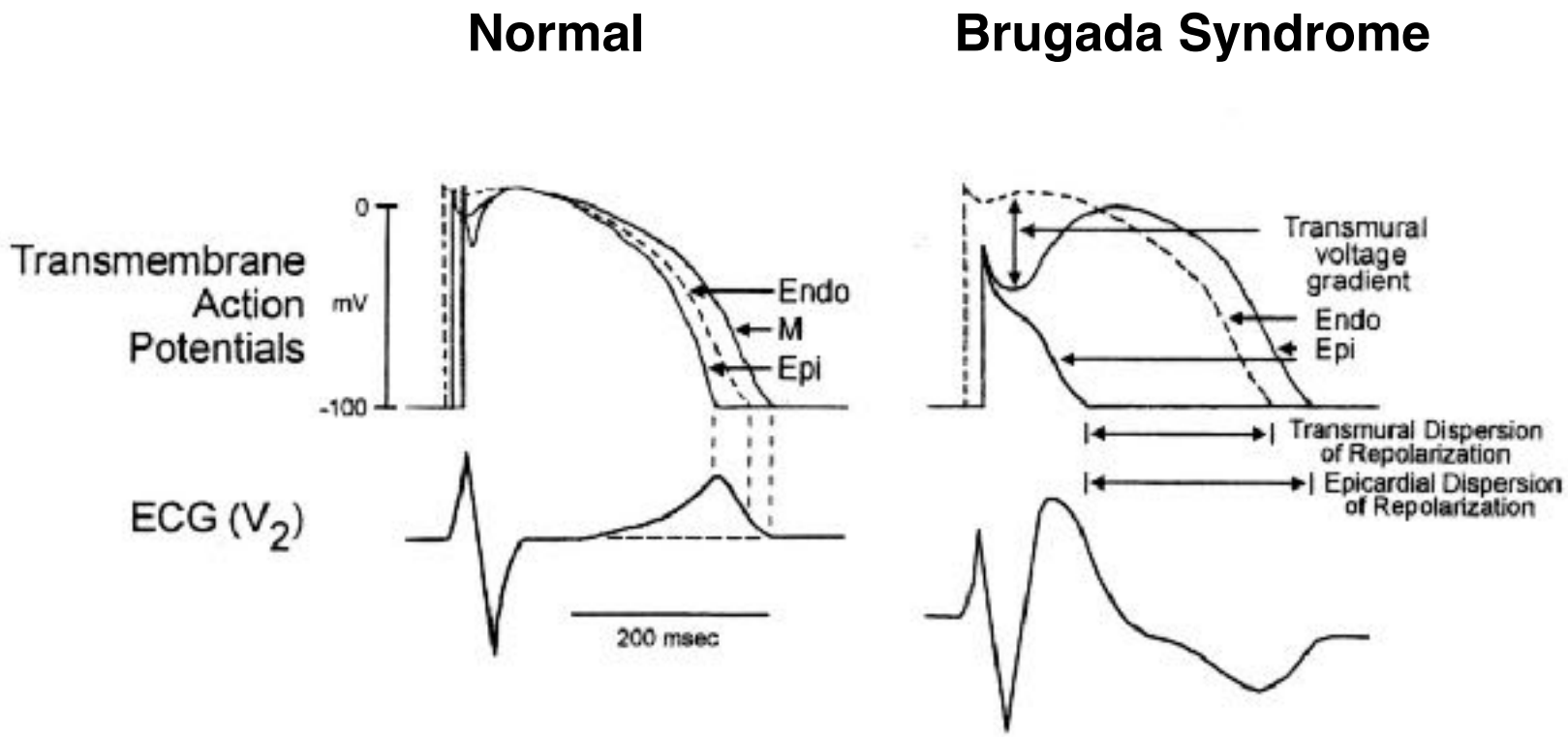
Brugada Syndrome

- Gene mutations of SCN5A (sodium channel), resulting in a loss of sodium channel function (either decreased expression or acceleration of inactivation) has been found in 10 to 30 percent of patients with Brugada syndrome.
  - In contrast, patients with congenital LQTS have SCN5A mutations that results in a gain in sodium channel function.
- Autosomal dominant transmission with incomplete penetrance
- A distinct clinical syndrome with syncope episodes and sudden cardiac death (fast polymorphic VT)

Brugada Syndrome

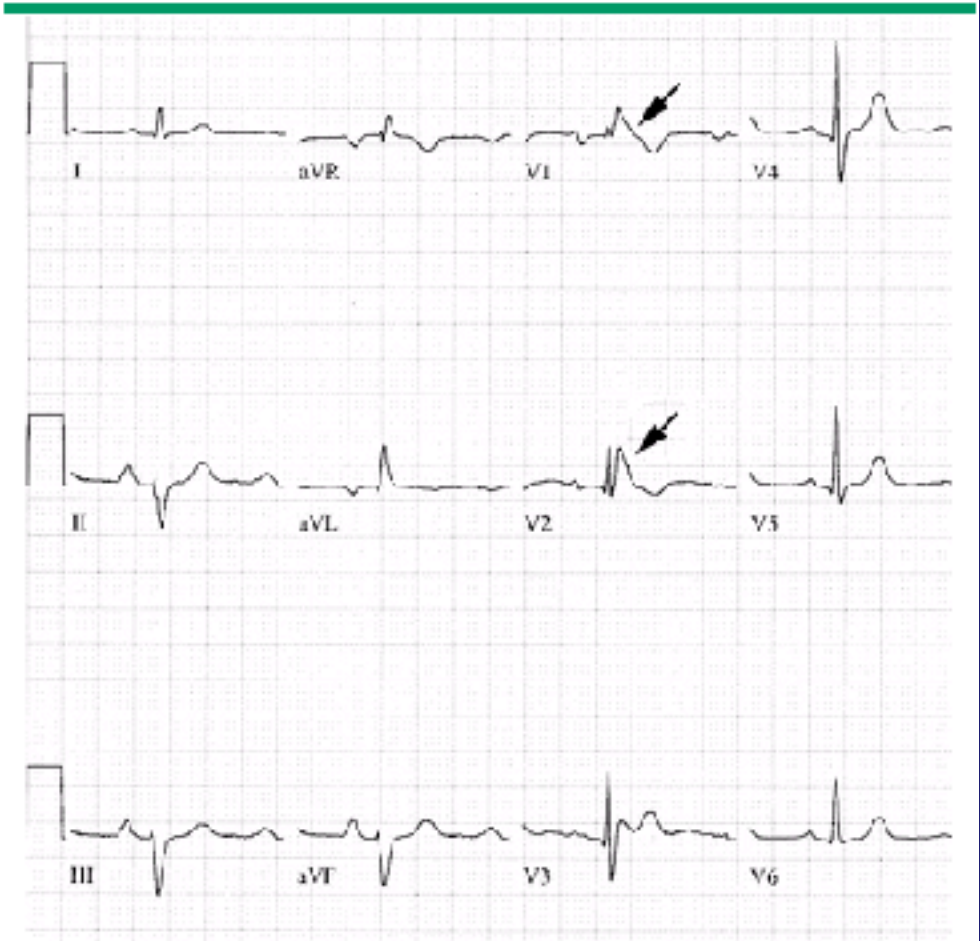
- This syndrome is estimated to be responsible for 20-50% of all sudden death in patients with an apparently normal heart.
- Prevalence varies from 5-50:10,000; largely depending on geographic location (endemic in southeast Asia).
- SUDS (Sudden Unexpected Death Syndrome) in Southeast Asia is a form of Brugada syndrome; most common cause of death in young males in Thailand.
- Male: Female 10:1

Loss of Normal Heterogeneity with Increased Dispersion of Repolarization



The right ventricle is most affected in Brugada syndrome, and particularly (but not specifically) the right ventricular outflow tract.

12-lead electrocardiogram (ECG) from a patient with the Brugada syndrome shows downsloping ST elevation

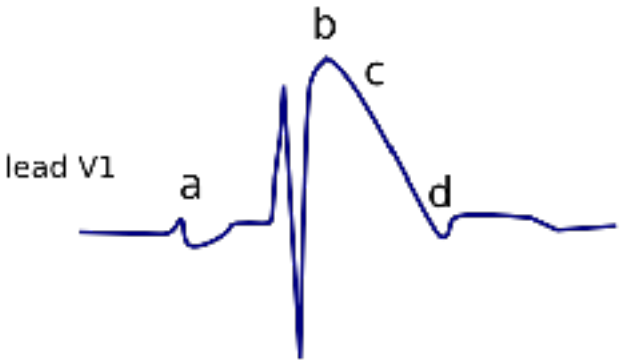


ST segment elevation and T wave inversion in the right precordial leads V1 and V2 (arrows); the QRS is normal. The widened S wave in left lateral leads that is characteristic of right bundle branch block is absent.

Courtesy of Dr Rory Childers, University of Chicago.

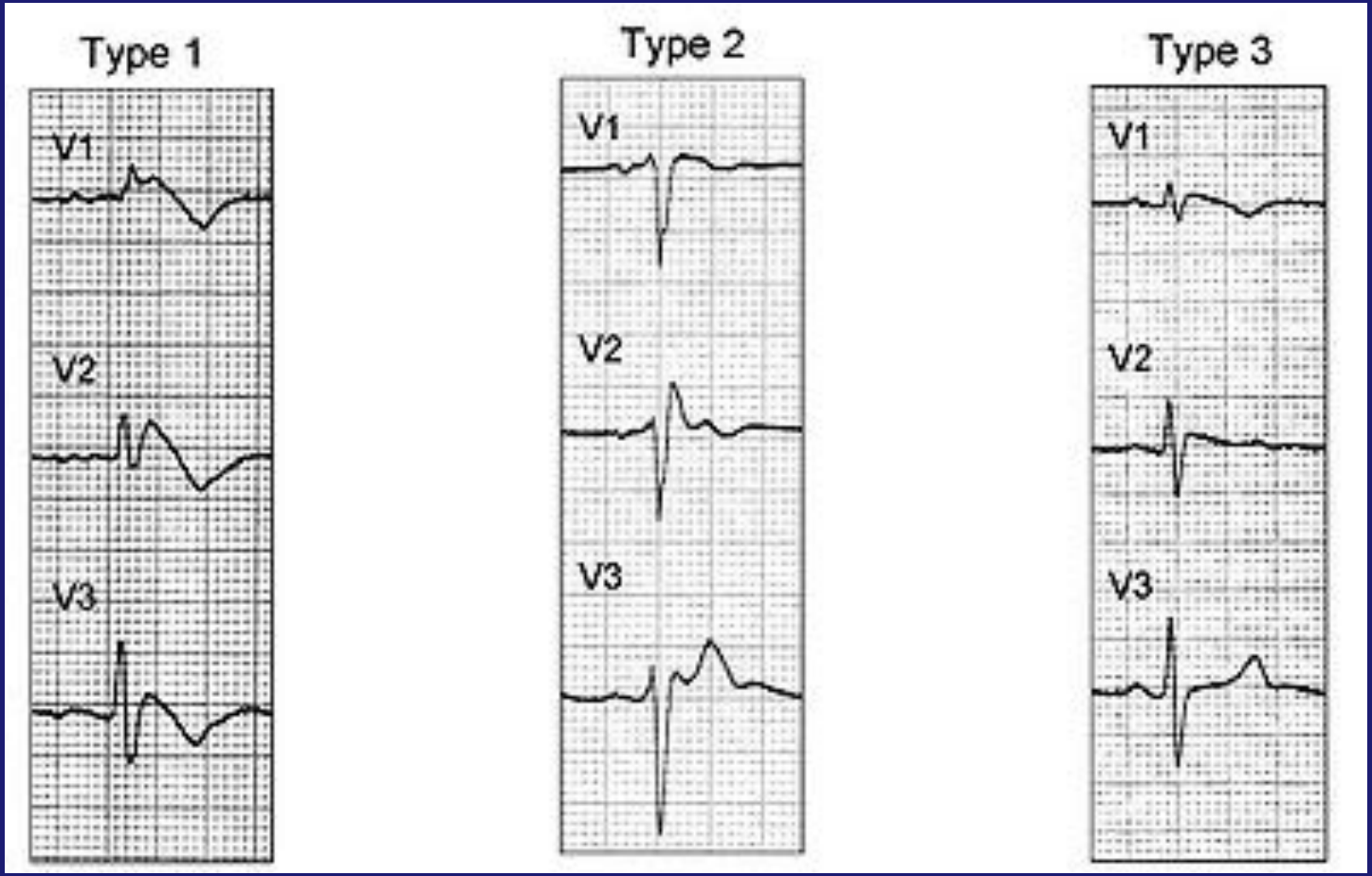
UpToD

RBBB pattern and >2mm ST segment elevation in V1-V3 in the absence of ischemia, electrolyte imbalance, and structural heart disease



ECG characteristics in Brugada Syndrome
a. Broad P wave with some PQ prolongation
b. J point elevation
c. Coved type ST segment elevation
d. Inverted T wave

Brugada Syndrome: ECG

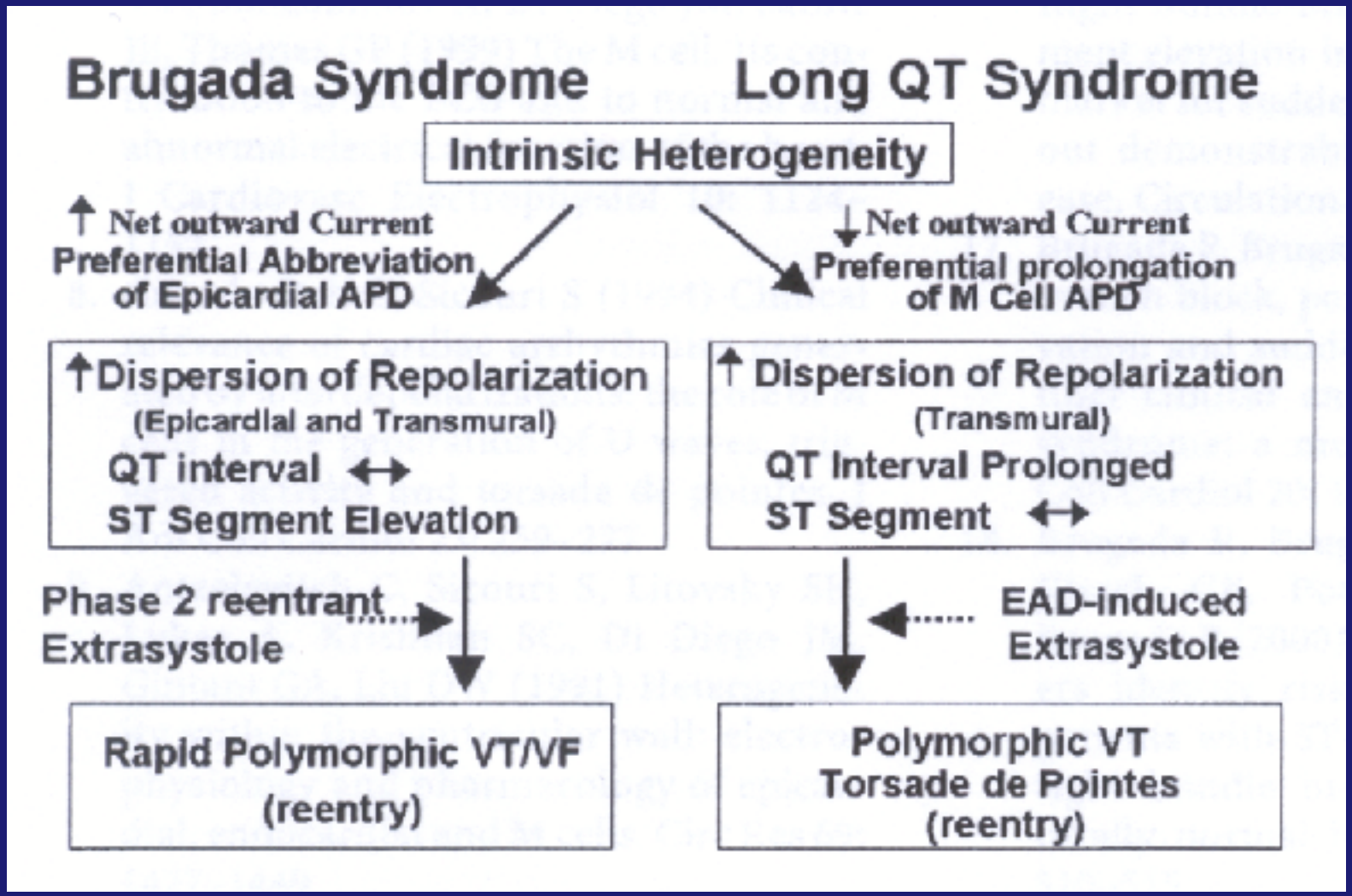


Brugada Syndrome: Factors / Drugs that Enhance ECG Pattern

- Na+ channel blockers
- alpha agonists, vagotonic agents, beta blockers
- fever
- alcohol, cocaine
- severe ischemia
- tricyclic antidepressants, antihistaminics

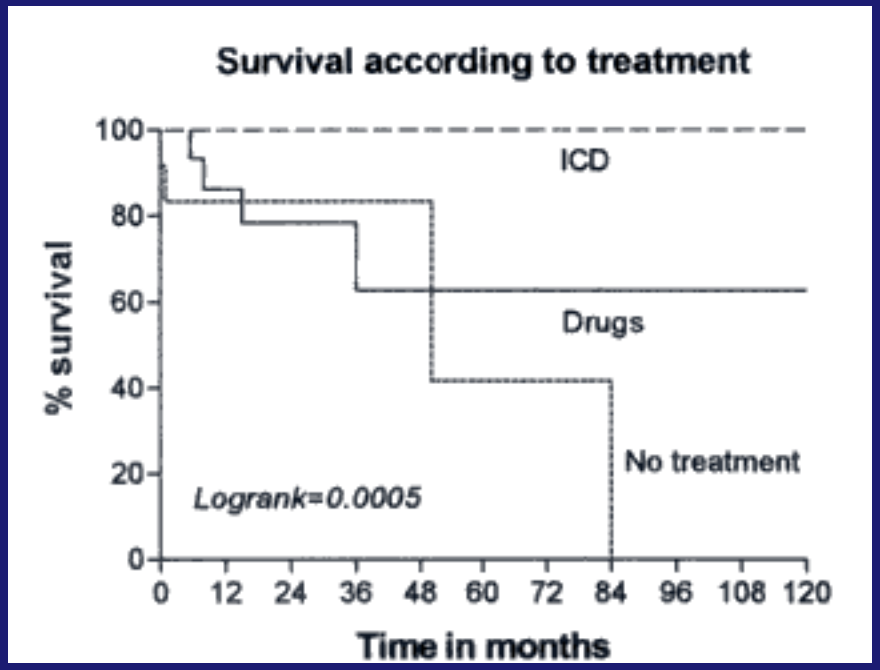
Brugada Syndrome: Diagnostic Criteria

- **Major criteria:**
  - 1. presence of ECG marker (Type 1) in structurally normal hearts
  - 2. appearance of ECG marker after administration of Na+ channel blockers (Type 2&3)
- **Minor criteria:**
  - 1. family history of sudden cardiac death
  - 2. syncope of unknown origin
  - 3. documented ventricular tachycardia/fibrillation
  - 4. genetic mutation of ion channels


Brugada Syndrome
Long QT Syndrome
Intrinsic Heterogeneity
↑ Net outward Current
Preferential Abbreviation
of Epicardial APD
↓ Net outward Current
Preferential prolongation
of M Cell APD
↑ Dispersion of Repolarization
(Epicardial and Transmural)
QT interval ↔
ST Segment Elevation
↑ Dispersion of Repolarization
(Transmural)
QT Interval Prolonged
ST Segment ↔
Phase 2 reentrant
Extrasystole
EAD-induced
Extrasystole
Rapid Polymorphic VT/VF
(reentry)
Polymorphic VT
Torsade de Pointes
(reentry)

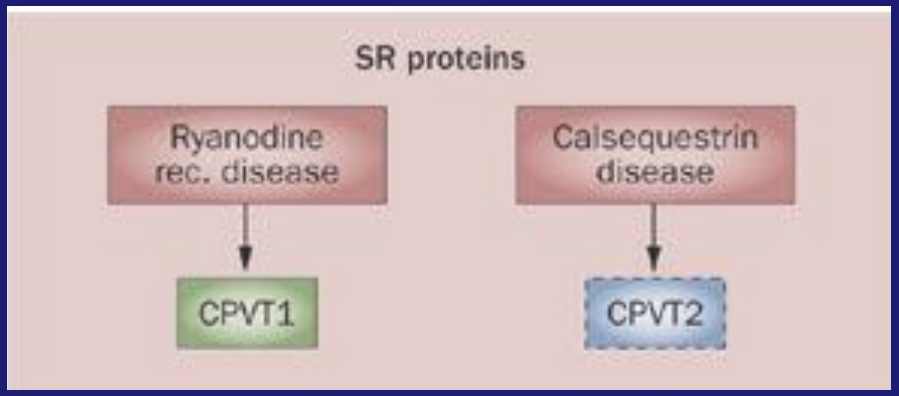
Brugada: Management

- Although pharmacologic therapy has been tried, the only therapy with proven efficacy in preventing sudden death is an implantable cardioverter-defibrillator (ICD).



Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

CPVT



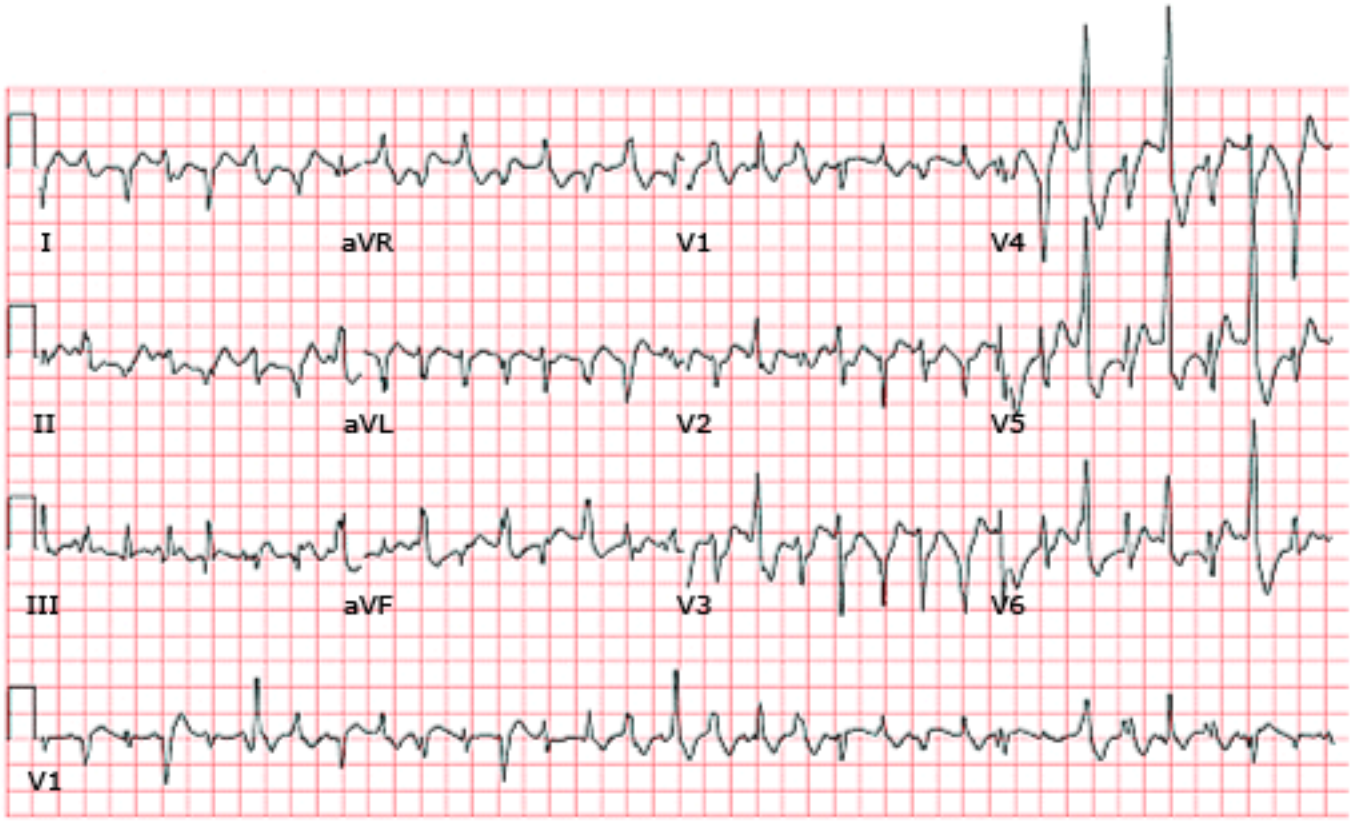
- Raynodine receptors (RyR2 gene)
  - Responsible for release of calcium from the sarcoplasmic reticulumn and are activated by incoming calcium; therefore they are a activated Ca channels.
  - Autosomal Dominant
- Calsequestrin 2 gene
  - Encodes a major calcium reservoir protein within the sarcoplasmic reticulum.
  - Autosomal recessive

CPVT

- At risk for VT (specifically bidirectional VT), ventricular fibrillation, and sudden death, especially in association with stress or exercise.
- At rest, the ECG typically demonstrates frequent premature ventricular contractions (PVC) and nonsustained polymorphic VT.
  - The QT interval is normal, which distinguishes it from LQTS, and there are no ST segment changes differentiating it from Brugada syndrome.

- At present, therapies include beta blockers, flecainide, and ICD or left cardiac sympathetic denervation for high risk patients and those with symptoms despite beta blocker therapy.
- Avoid competitive sports

12-lead ECG in child with catecholaminergic polymorphic ventricular tachycardia (CPVT)



This is the ECG of a five-year-old with recurrent exertional syncope. The ECG demonstrates bidirectional VT. This child underwent genetic testing and was positive for the RyR2 mutation.

Idiopathic Ventricular Fibrillation

- Absence of identifying structural or genetic abnormalities to explain the VF or the out-of-hospital cardiac arrest
- May account for as much as 10% of sudden deaths, especially in the young.
- About 30% of IVF-labeled individuals will have recurrent episodes of VF.
- Like BrS, loss of function SCN5A mutations have been identified.
  - Identified mutations in other arrhythmia susceptibility genes, such as *ANKB*, which encodes for ankyrin-B, and *RYR2*, which encodes for the cardiac ryanodine receptor.

Idiopathic V-fib

- J-point elevation (1 mm above baseline) on inferolateral electrocardiographic leads (so-called early repolarization)
  - was significantly overrepresented (31%)
  - was greater in magnitude in subjects who experienced cardiac arrest caused by IVF compared with age-, gender-, race-, and level of physical activity–matched controls.

- These patients with early repolarization were more often males and had a personal history of syncope or cardiac arrest during sleep

Progressive Cardiac Conduction Defect

- Lev-Lenègre disease
- Progressive (age-related) alteration of impulse propagation through the His-Purkinje system, with right or left bundle branch block and widening of the QRS complex, leading to complete atrioventricular (AV) block, syncope, and occasionally sudden death.
- Over 30 PCCD-associated mutations in *SCN5A (loss of function), autosomal dominant.*
- PCCD is the prevailing phenotype in BrS-associated *SCN5A* mutation carriers, where the penetrance of conduction defects was 76%.

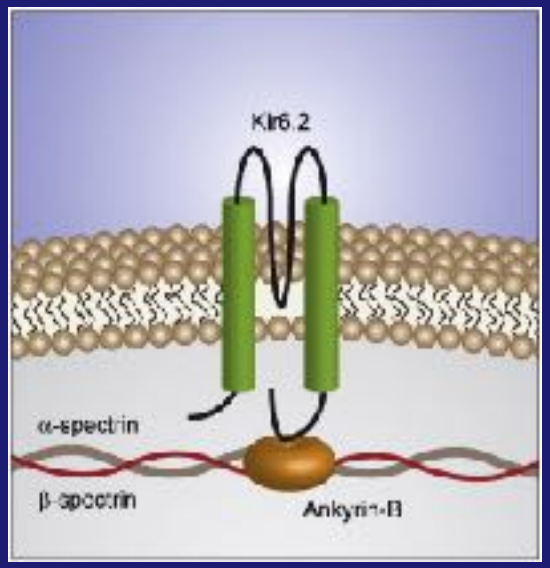
Sick Sinus Syndrome

- Inappropriate sinus bradycardia, sinus arrest, atrial standstill, tachycardia-bradycardia syndrome, or chronotropic incompetence
- Acquired: Commonly occurs in older adults (1 in 600 cardiac patients older than 65 years) with acquired cardiac conditions.
- Idiopathic: No identifiable cardiac anomalies; can occur at any age, including in utero.
  - Additionally, familial forms of idiopathic SND consistent with autosomal dominant inheritance with reduced penetrance and recessive forms with complete penetrance have been reported.
- So far implicated three genes—*SCN5A*, *HCN4 (*encodes the so-called I_f or pacemaker current and plays a key role in automaticity of the sinus node), and *ANKB*.

Ankyrin-B Syndrome

ANK2 gene → Ankyrin-B protein

Involved in anchoring the Na^+,K^+-ATPase, Na^+/Ca^{2+} exchanger, and InsP3 receptor to specialized microdomains in the cardiomyocyte transverse tubules.



- Loss of function mutations of *ANK2* were shown originally to cause a dominantly inherited cardiac arrhythmia with an increased risk for SCD associated with a prolonged QT interval
- LQT4 → more correctly renamed SSS with bradycardia, or the ankyrin-B syndrome.

References

- Braunwald's Heart Disease Textbook, 9th Edition
- Hurt's The Heart Textbook, 13th Edition

GO VOLS!!