AF, VT, VF Summit

Chicago, IL

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"Genetic and Cellular Basis of Lethal Cardiac Arrhythmia "

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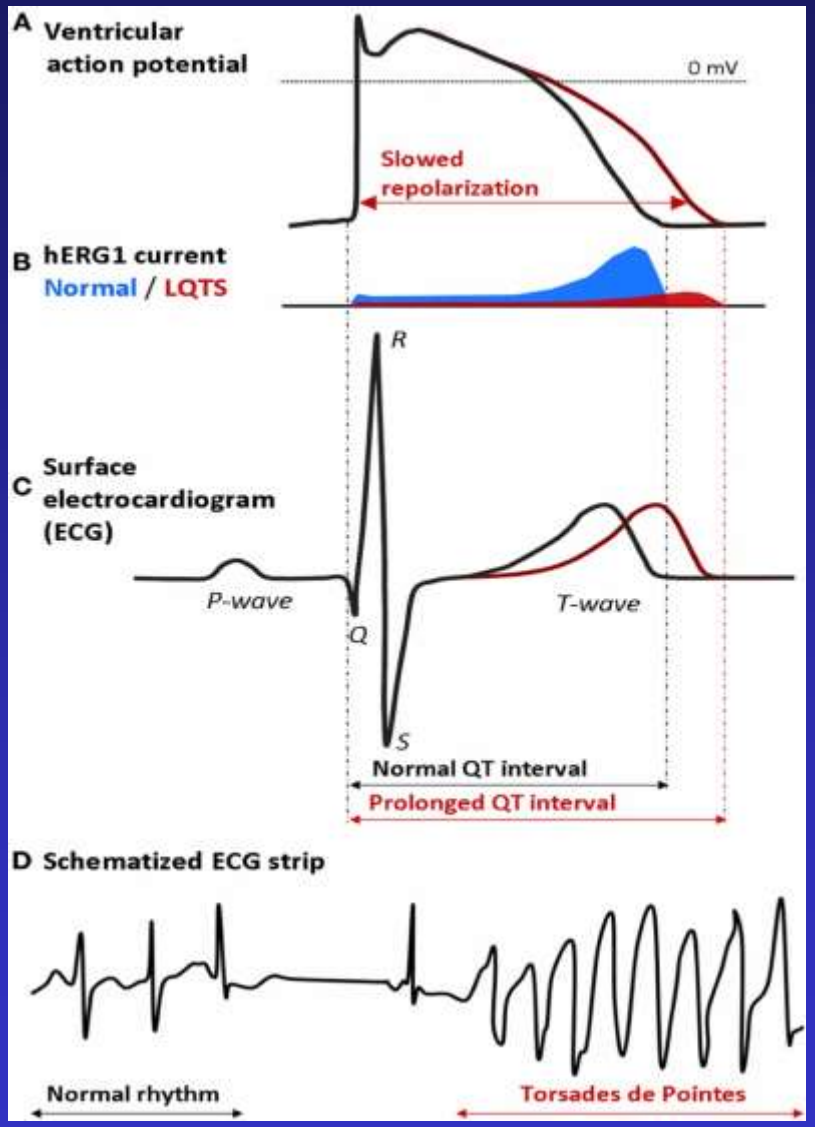
Inherited Cardiac Arrhythmia Syndromes

Common Link: Arrhythmogenic Substrate Develops as a Result of Amplification of Spatial Dispersion of Repolarization

• Long QT Syndrome	Preferential prolongation of APD of M cells
• Short QT Syndrome	Preferential abbreviation of APD of Epicardium
• Brugada Syndrome	Preferential abbreviation of APD of RV epicardium
• Early Repolarization Syndrome	Preferential abbreviation of APD in epicardium of the inferior LV

Long QT Syndrome (LQTS)



Grilo et al, Front Pharm 2010

Diagnosis:

QTc ≥450-480 ms

QTc > 500 ms – high risk

Gene Defects Responsible for the Long QT Syndrome

Chromosome		Gene	Ion Channel	
LQT1	11	*KCNQ1, KvLQT1*	↓ I_{Ks}	90 %
LQT2	7	*KCNH2, HERG*	↓ I_{Kr}	
LQT3	3	*SCN5A, $Na_V1.5$*	↑ Late I_{Na}	
LQT4	4	*Ankyrin-B, ANK2*	↑ Ca_i, ↑Late I_{Na} ?	
LQT5	21	*KCNE1, minK*	↓ I_{Ks}	
LQT6	21	*KCNE2, MiRP1*	↓ I_{Kr}	
LQT7*	17	*KCNJ2, Kir2.1*	↓ I_{K1}	
LQT8**	6	*CACNA1C, $Ca_V1.2$*	↑ I_{Ca}	
LQT9	3	*CAV3, Caveolin-3*	↑ Late I_{Na}	
LQT10	11	*SCN4B, NavB4*	↑ Late I_{Na}	
LQT11	7	*AKAP9, Yotiao*	↓ I_{Ks}	
LQT12	20	*SNTA1, α-1 Syntrophin*	↑ Late I_{Na}	
LQT13	11	*KCNJ5, Kir3.4*	↓ I_{K-ACh}	
LQT14	14	CALM1, Calmodulin	↑ I_{Ca} , ↑ Late I_{Na}	
LQT15	2	CALM2, Calmodulin	↑ I_{Ca} , ↑ Late I_{Na}	
LQT16	19	CALM3, Calmodulin	↑ I_{Ca} , ↑ Late I_{Na}	
LQT17	19	TRPM4, transient receptor potential cation channel	↓ $I_{non\text{-}selective\ cation\ channel}$	

* Andersen –Tawil Syndrome

** Timothy Syndrome

Congenital Long QT Syndrome (LQTS): Genetics

NIH-funded Clinical Genome Resource (ClinGen) has developed a framework to define and evaluate the clinical validity of gene-disease pairs

Strande et al, Am J Hum Gen 2017

New criteria developed by ACGM (American College of Genetics and Genomics)

Some of the minor genes **(ANK2,KCNE2, SCN4B, AKAP9, SNTA1, and KCNJ5)** have been designated as having limited- or disputed-evidence (as monogenic causes).

Disputed

LQTS subtype	Culprit gene
LQT1	*KCNQ1*[50]
LQT2	*KCNH2*[51]
LQT3	*SCN5A*[52]
LQT4	*ANK2*[47]
LQT5	*KCNE1*[53]
LQT6	*KCNE2*[54]
LQT7	*KCNJ2*[55]
LQT8	*CACNA1c*[56]
LQT9	*CAV3*[46]
LQT10	*SCN4B*[57]
LQT11	*AKAP9*[48]
LQT12	*SNTA1*[33]
LQT13	*KCNJ5*[44]
LQT14	*CALM1*[27]
LQT15	*CALM2*[27]

Minor LQTS genes

Strande et al, Am J Hum Gen, 2017

Guidicessi et al, Trend Card Med, 2018

Debate continues as to validity of the ClinGen criteria

It is important to continue to collect both clinical and experimental data concerning their involvement in the pathogenicity of the syndrome which will be reviewed and used to adjust the classifications as necessary

Drugs Associated with LQTS and Torsade de Pointes

Anesthetics
- Propofol

Antianginal
- Bepridil, Israpidine, Nicardipine

Antiarrhythmic Drugs

Class IA
- Quinidine, Procainamide
- Disopyramide

Class III
- N-acetylprocainamide, sotalol,
- Ibutilide, dofetilide

Antibiotics
- Erythromycin, Trimethoprim & Sulfamethaxazole, Pentamidine,
- Clarithromycin

Antihistamines
- Terfenedine, Astemizole, diphenhydramine

Muscle Relaxant
- Tizanidine

Antifungal Agents
- Ketoconazole
- Flucoconazole
- Itraconazole

Diuretics
- Indapamide

Gastrointestinal
- Cisapride

Lipid Lowering
- Probucol

Psychotropics
- Phenothiazines, Tricyclic antidepressants (Amitriptyline)
- Haloperidol, Pimozide

Immunosuppressives
- Tacrolimus

Sedative/Hypnotics
- Chloral hydrate

Positive Inotropic
- DPI 201-106
- BDF 9148

Toxins
- Anthopleurin-A, ATX-II
- Veratridine
- Arsenic
- Organophosphate insecticides
- Pyrethroids
- β – PMTX
- Liquid protein diets

Hypokalemia

The genetics underlying acquired long QT syndrome: impact for genetic screening

Hideki Itoh[1,2,3,4], Lia Crotti[5,6], Takeshi Aiba[8], Carla Spazzolini[5], Isabelle Denjoy[9], Véronique Fressart[2,3,4,10], Kenshi Hayashi[11], Tadashi Nakajima[12], Seiko Ohno[1], Takeru Makiyama[13], Jie Wu[1,14], Kanae Hasegawa[1], Elisa Mastantuono[7], Federica Dagradi[5], Matteo Pedrazzini[5], Masakazu Yamagishi[11], Myriam Berthet[2,3,4], Yoshitaka Murakami[15], Wataru Shimizu[8,16], Pascale Guicheney[2,3,4†], Peter J. Schwartz[5†], and Minoru Horie[1†*]

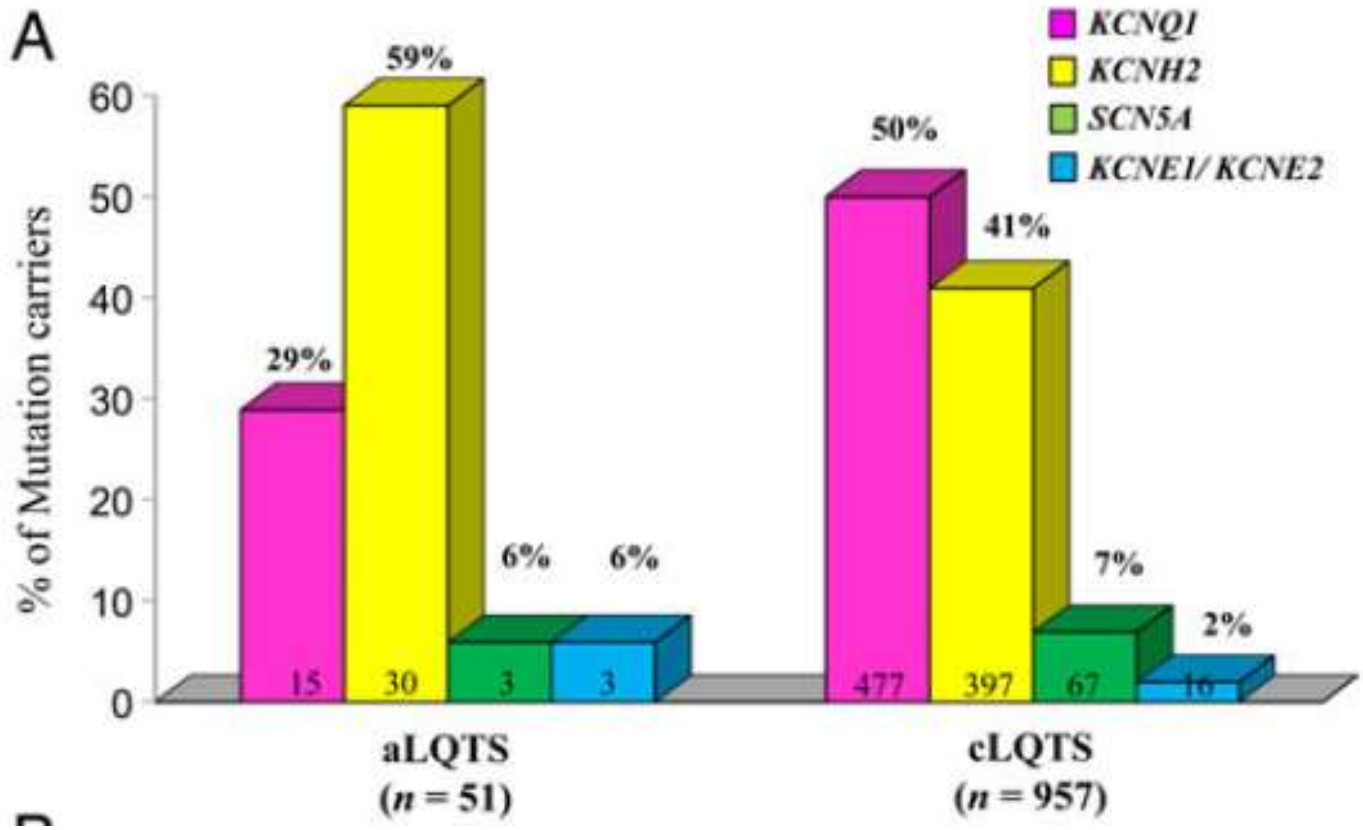
Aims Acquired long QT syndrome (aLQTS) exhibits QT prolongation and Torsades de Pointes ventricular tachycardia triggered by drugs, hypokalaemia, or bradycardia. Sometimes, QTc remains prolonged despite elimination of triggers, suggesting the presence of an underlying genetic substrate. In aLQTS subjects, we assessed the prevalence of mutations in major LQTS genes and their probability of being carriers of a disease-causing genetic variant based on clinical factors.

Methods and results We screened for the five major LQTS genes among 188 aLQTS probands (55 $\pm$ 20 years, 140 females) from Japan, France, and Italy. Based on control QTc (without triggers), subjects were designated 'true aLQTS' (QTc within normal limits) or 'unmasked cLQTS' (all others) and compared for QTc and genetics with 2379 members of 1010 genotyped congenital long QT syndrome (cLQTS) families. Cardiac symptoms were present in 86% of aLQTS subjects. Control QTc of aLQTS was 453 $\pm$ 39 ms, shorter than in cLQTS (478 $\pm$ 46 ms, $P < 0.001$) and longer than in non-carriers (406 $\pm$ 26 ms, $P < 0.001$). In 53 (28%) aLQTS subjects, 47 disease-causing mutations were identified. Compared with cLQTS, in 'true aLQTS', *KCNQ1* mutations were much less frequent than *KCNH2* (20% [95% CI 7–41%] vs. 64% [95% CI 43–82%], $P < 0.01$). A clinical score based on control QTc, age, and symptoms allowed identification of patients more likely to carry LQTS mutations.

Conclusion A third of aLQTS patients carry cLQTS mutations, those on *KCNH2* being more common. The probability of being a carrier of cLQTS disease-causing mutations can be predicted by simple clinical parameters, thus allowing possibly cost-effective genetic testing leading to cascade screening for identification of additional at-risk family members.

European Heart Journal 37:1454-1464, 2016

Mutations in acquired vs. congenital LQTS

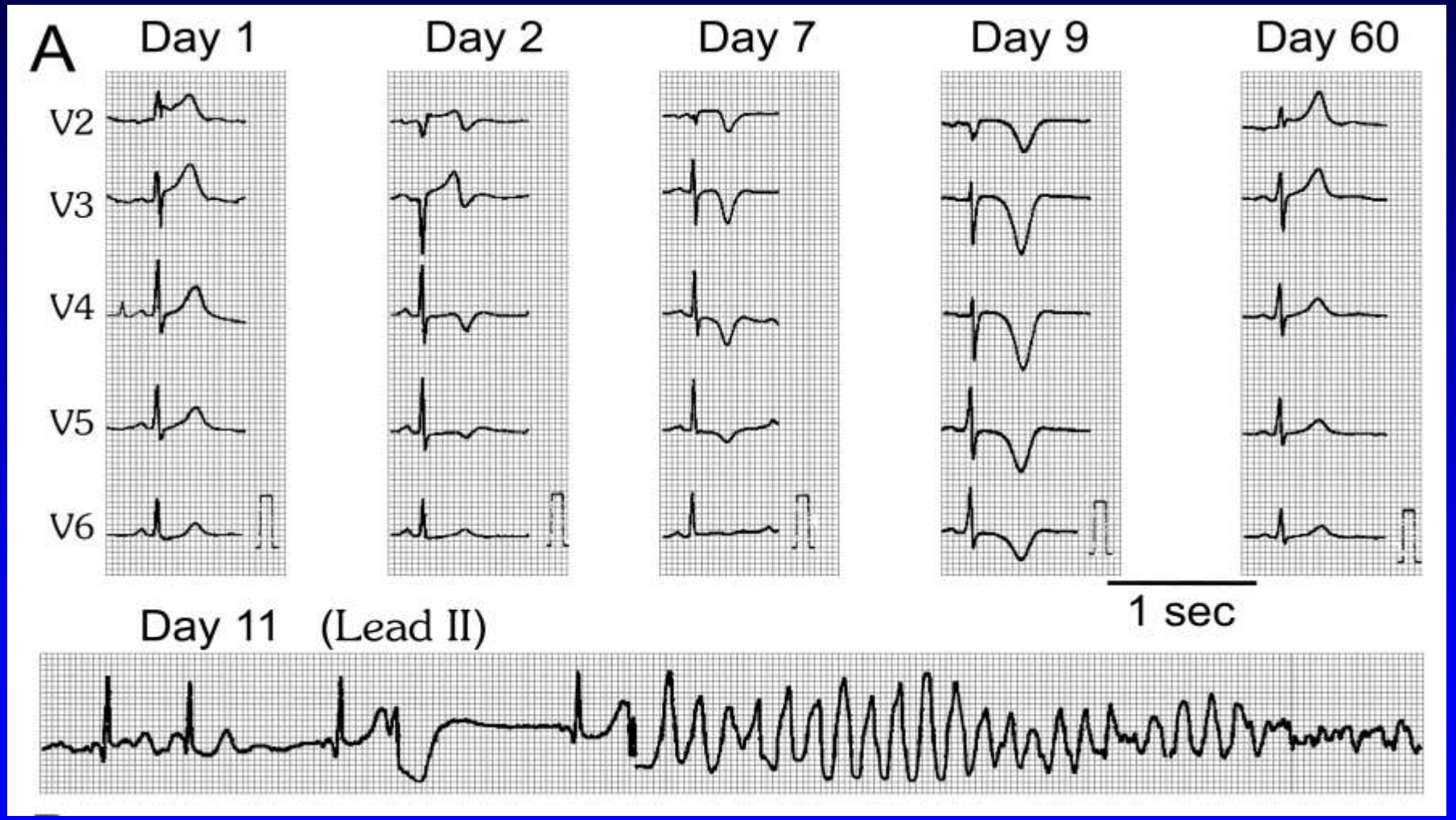


Itoh et al. European Heart Journal 37:1454-1464, 2016

Other Forms of Acquired Long QT Syndrome

- Hypertrophic Cardiomyopathy
- Dilated Cardiomyopathy
  Heart Failure
- Post MI (days 2-11)
  - ↓ I_{Kr}
  - ↓ I_{Ks}
  - ↑ **Late I_{Na}**
  - ↑ $I_{Na\text{-}Ca}$

Post-MI LQTS and TdP



Halkin et al. JACC 38: 1168-74, 2001
Crotti et al. Heart Rhythm, 9:1104-12, 2012

Torsades de pointes following acute myocardial infarction: Evidence for a deadly link with a common genetic variant

Lia Crotti, MD, PhD,*†‡ Dan Hu, MD, PhD,§ Hector Barajas-Martinez, PhD,§ Gaetano M. De Ferrari, MD,† Antonio Oliva, MD, PhD,§‖ Roberto Insolia, PhD,*† Guido D. Pollevick, PhD,§ Federica Dagradi, PhD,*† Alejandra Guerchicoff, PhD,§ Federica Greco, BSc,*† Peter J. Schwartz, MD, FACC, FAHA, FESC, FHRS,*†¶#** Sami Viskin, MD,‡‡ Charles Antzelevitch, PhD, FHRS, FACC, FAHA§

BACKGROUND Although QT prolongation following myocardial infarction (MI) is generally moderate, cases with marked QT prolongation leading to life-threatening torsades de pointes (TdP) have been described.

OBJECTIVE To investigate the genetic substrate of this phenomenon.

METHODS We studied 13 patients who developed TdP in the subacute phase of MI (2–11 days) and a group of 133 ethnically matched controls with uncomplicated MI. Long QT syndrome genes and the *KCNH2*-K897T polymorphism were screened by using denaturing high-performance liquid chromatography plus direct sequencing and a specific TaqMan assay, respectively.

RESULTS Two of the 13 patients (15%) who presented with QT prolongation and TdP were found to carry long QT syndrome mutations (*KCNH2*-R744X and *SCN5A*-E446K). Nine of the remaining 11 patients (82%) carried the *KCNH2*-K897T polymorphism, which was present in 35% of the controls ($P = .0035$). Thus, patients with an acute MI carrying the *KCNH2*-K897T polymorphism had an 8-fold greater risk of experiencing TdP compared with controls (95% confidence interval = 2–40).

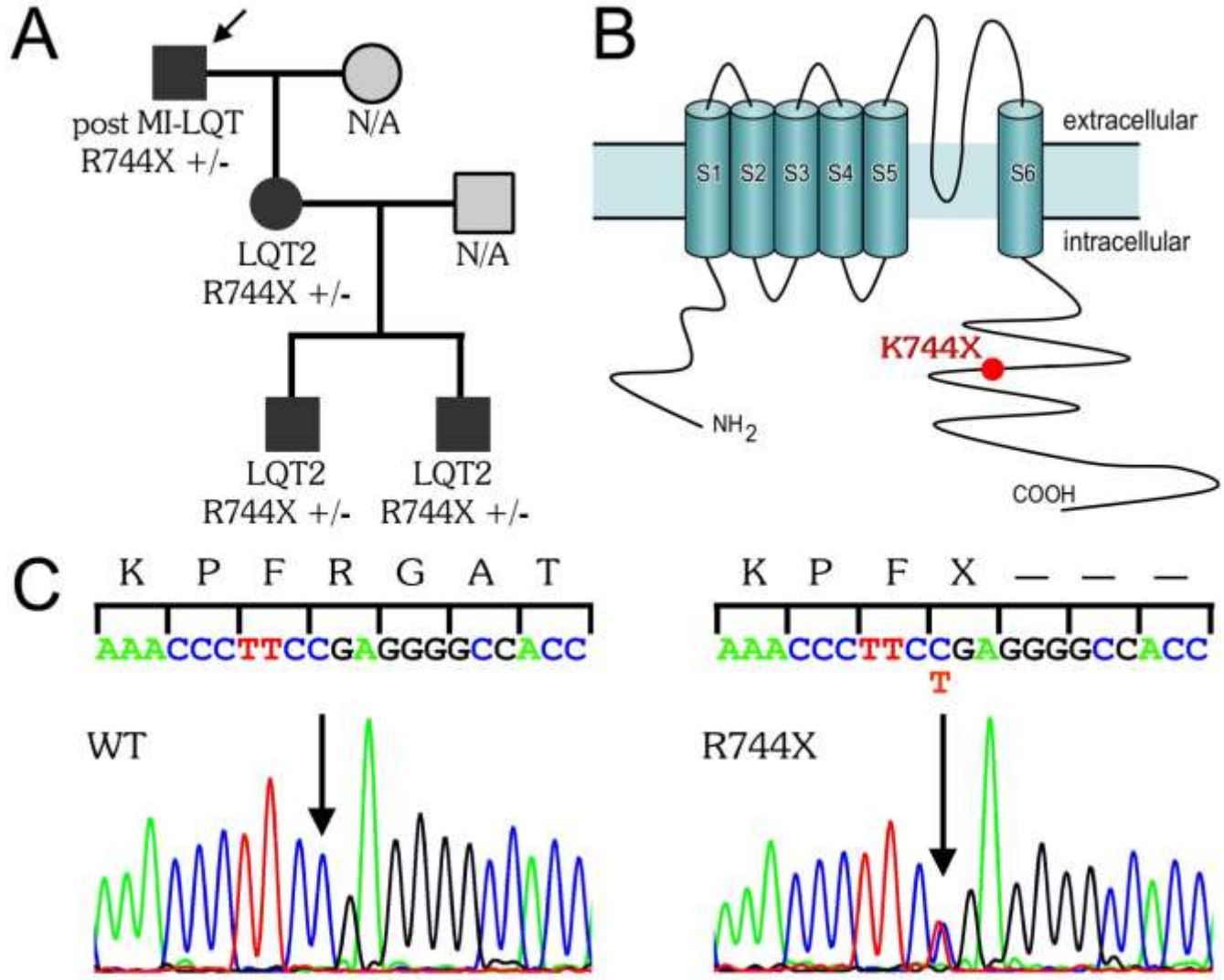
CONCLUSIONS Our data suggest that the common K897T polymorphism is associated with an increased risk of TdP developing in the subacute phase of MI. Our findings support the concept that the electrical remodeling associated with this healing phase of MI may unmask a genetic substrate predisposing to a time-limited development of life-threatening arrhythmias. They also provide the first line of evidence in support of the hypothesis that a common polymorphism, previously described as a modifier of the severity of LQTS, may increase the risk of life-threatening arrhythmias in a much more prevalent cardiac disease such as myocardial infarction.

KEYWORDS Long QT syndrome; Cardiac arrhythmia; Sudden cardiac death; Molecular genetics; Single nucleotide polymorphism

ABBREVIATIONS **ECG** = electrocardiogram; **HERG** = human ether-a-go-go-related gene; $\mathbf{I_{Kr}}$ = delayed rectifier potassium current; **LQTS** = long QT syndrome; **MI** = myocardial infarction; **QTc** = QT interval corrected for heart rate; **SCD** = sudden cardiac death; **SNP** = single nucleotide polymorphism; **TdP** = torsades de pointes; **VF** = ventricular fibrillation; **WT** = wild type

(Heart Rhythm 2012;9:1104–1112)

Post-MI LQTS and TdP



KCNH2

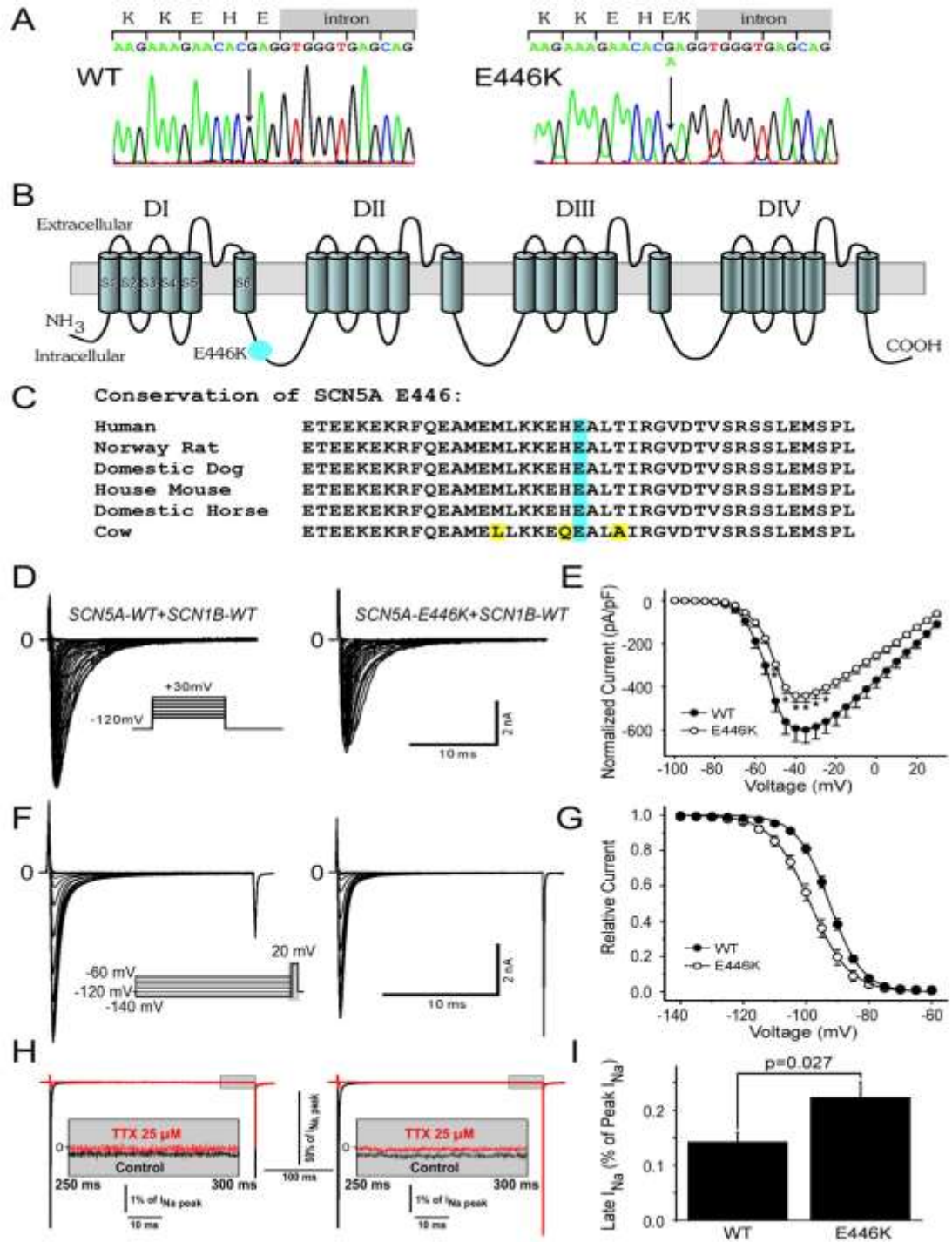
Crotti et al. Heart Rhythm, 9:1104-12, 2012

Post-MI LQTS and TdP

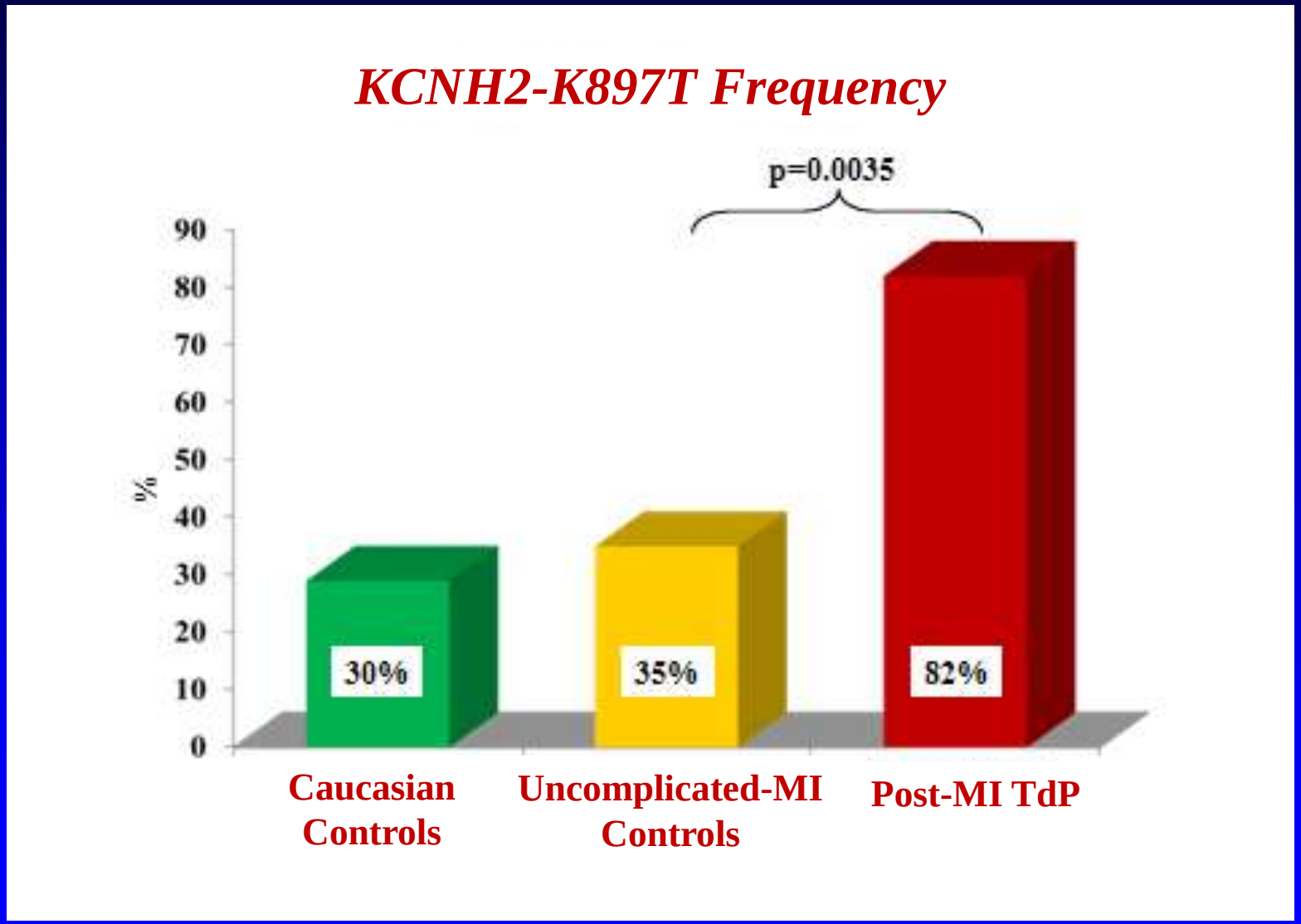
SCN5A-E466K missense mutation

LQT3 Increased I_{Na}

Crotti et al. Heart Rhythm, 9:1104-12, 2012



Post-MI LQTS and TdP



Crotti et al. Heart Rhythm, 9:1104-12, 2012

Post-MI LQTS and TdP

These data suggest that the common K897T polymorphism is associated with increased risk of TdP developing in the subacute phase of MI.

These findings support the concept that the electrical remodeling associated with this healing phase of MI may unmask a genetic substrate predisposing to a time-limited development of life-threatening arrhythmias.

KCNH2-K897T Is a Genetic Modifier of Latent Congenital Long-QT Syndrome

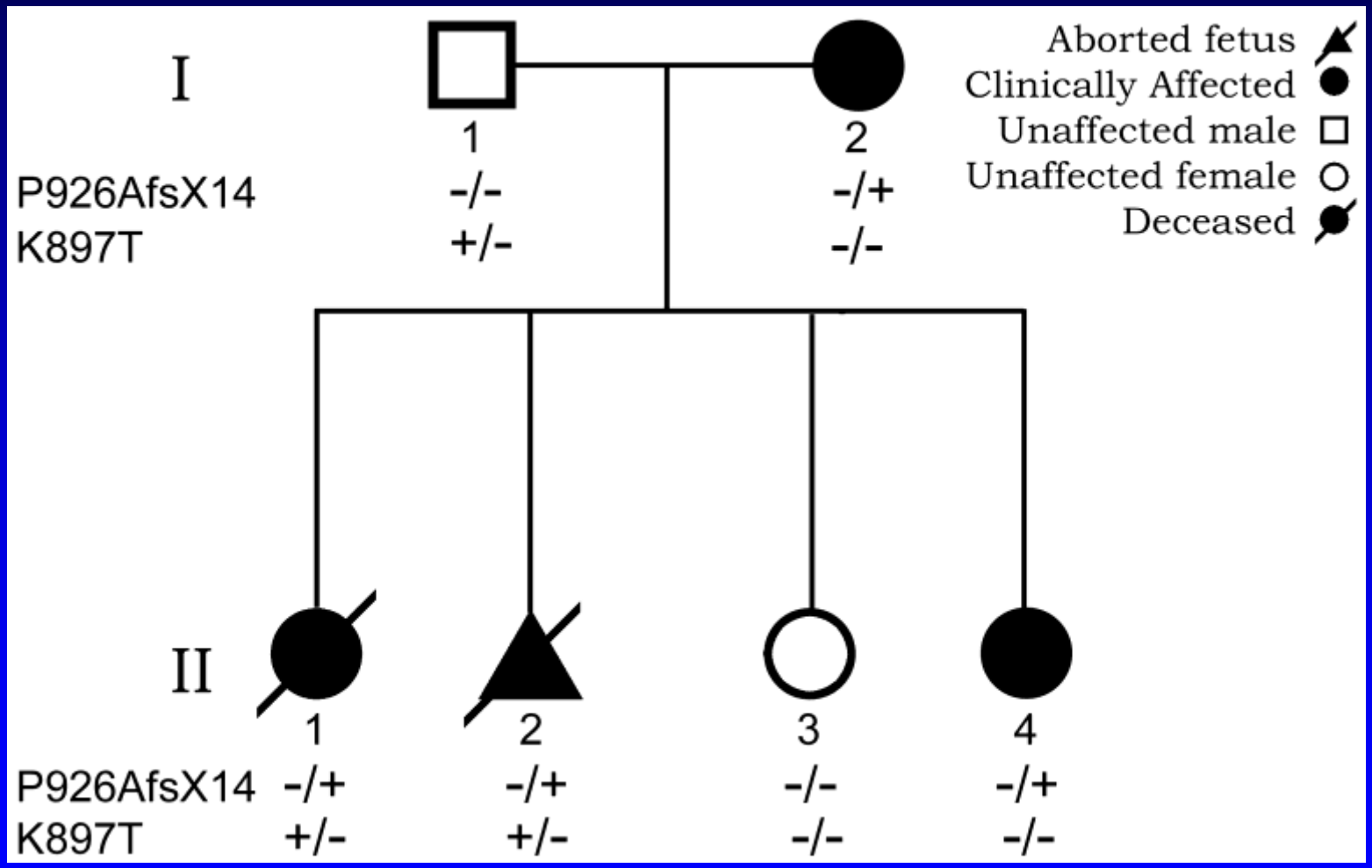
Lia Crotti, MD*; Andrew L. Lundquist, PhD*; Roberto Insolia, BSc; Matteo Pedrazzini, BSc; Chiara Ferrandi, BSc; Gaetano M. De Ferrari, MD; Alessandro Vicentini, MD; Ping Yang, PhD; Dan M. Roden, MD; Alfred L. George, Jr, MD; Peter J. Schwartz, MD

Background—Clinical heterogeneity among patients with long-QT syndrome (LQTS) sharing the same disease-causing mutation is usually attributed to variable penetrance. One potential explanation for this phenomenon is the coexistence of modifier gene alleles, possibly common single nucleotide polymorphisms, altering arrhythmia susceptibility. We demonstrate this concept in a family segregating a novel, low-penetrant *KCNH2* mutation along with a common single nucleotide polymorphism in the same gene.

Methods and Results—The proband is a 44-year-old white woman with palpitations associated with presyncope since age 20, who presented with ventricular fibrillation and cardiac arrest. Intermittent QT prolongation was subsequently observed (max QTc, 530 ms), and LQT2 was diagnosed after the identification of a missense *KCNH2* mutation (A1116V) altering a conserved residue in the distal carboxyl-terminus of the encoded HERG protein. The proband also carried the common *KCNH2* polymorphism K897T on the nonmutant allele. Relatives who carried A1116V without K897T were asymptomatic, but some exhibited transient mild QTc prolongation, suggesting latent disease. Heterologous expression studies performed in cultured mammalian cells and using bicistronic vectors linked to different fluorescent proteins demonstrated that coexpression of A1116V with K897T together resulted in significantly reduced current amplitude as compared with coexpression of either allele with WT-HERG. Thus, the presence of *KCNH2*-K897T is predicted to exaggerate the I_{Kr} reduction caused by the A1116V mutation. These data explain why symptomatic LQTS occurred only in the proband carrying both alleles.

Conclusions—We have provided evidence that a common *KCNH2* polymorphism may modify the clinical expression of a latent LQT2 mutation. A similar mechanism may contribute to the risk for sudden death in more prevalent cardiac diseases. (***Circulation*. 2005;112:1251-1258.**)

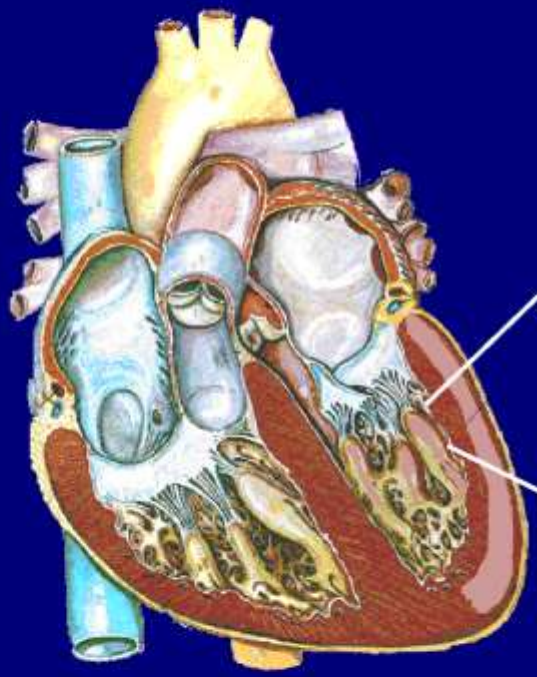
A Common Single Nucleotide Polymorphism (K897T) Can Exacerbate Long QT Type 2 Syndrome Leading to Sudden Infant Death

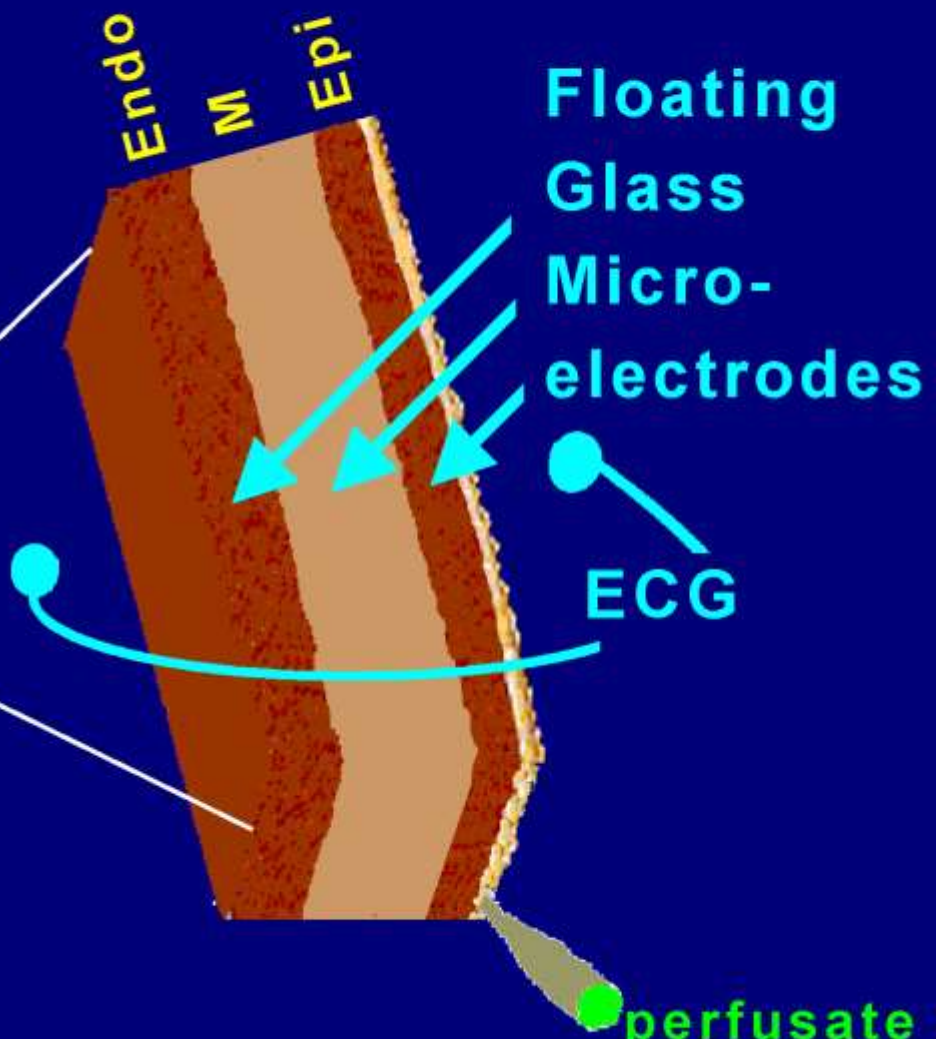


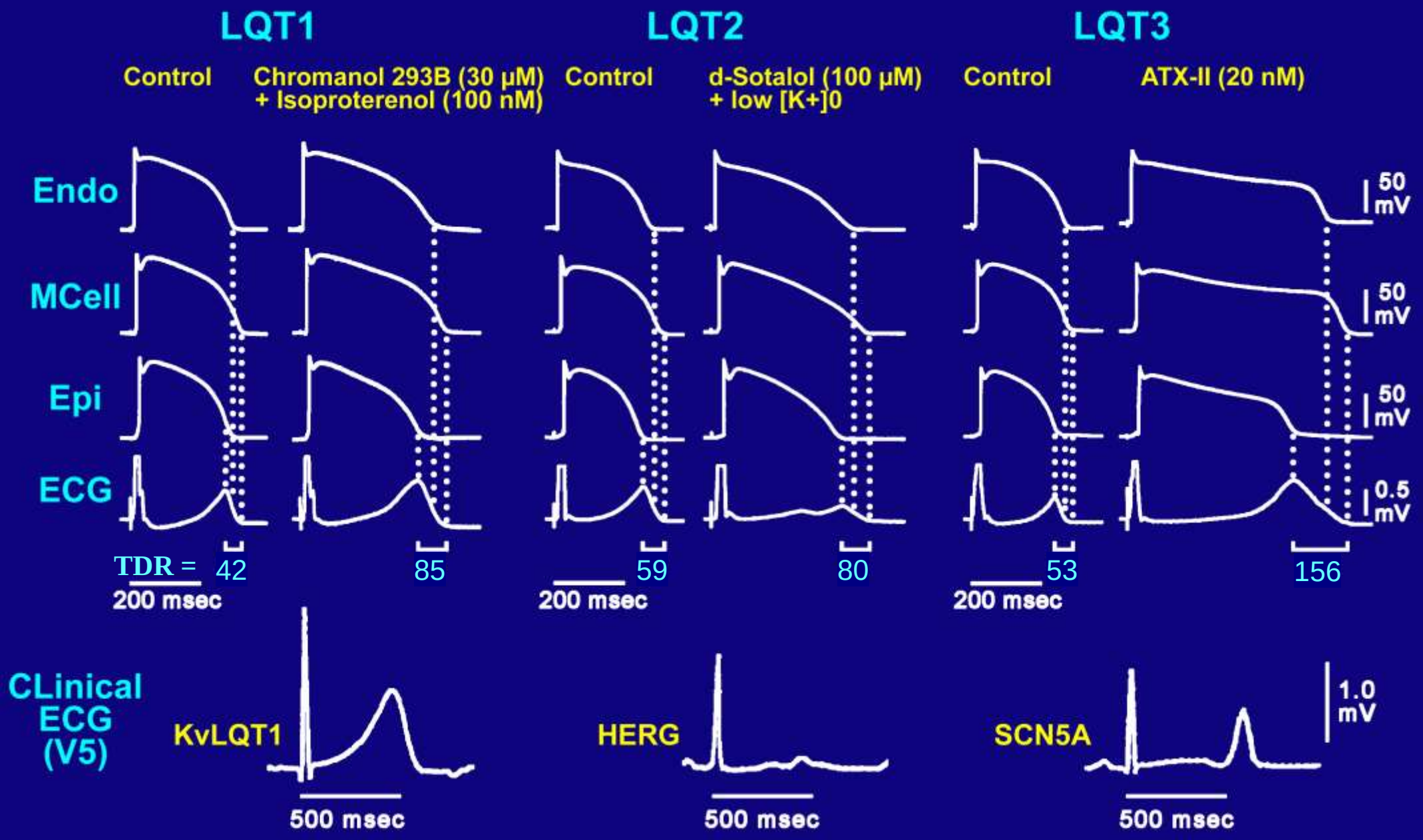
Nof et al. Circulation Cardiovascular Genetics , 3:199-206, 2010

Arterially Perfused Left Ventricular Wedge

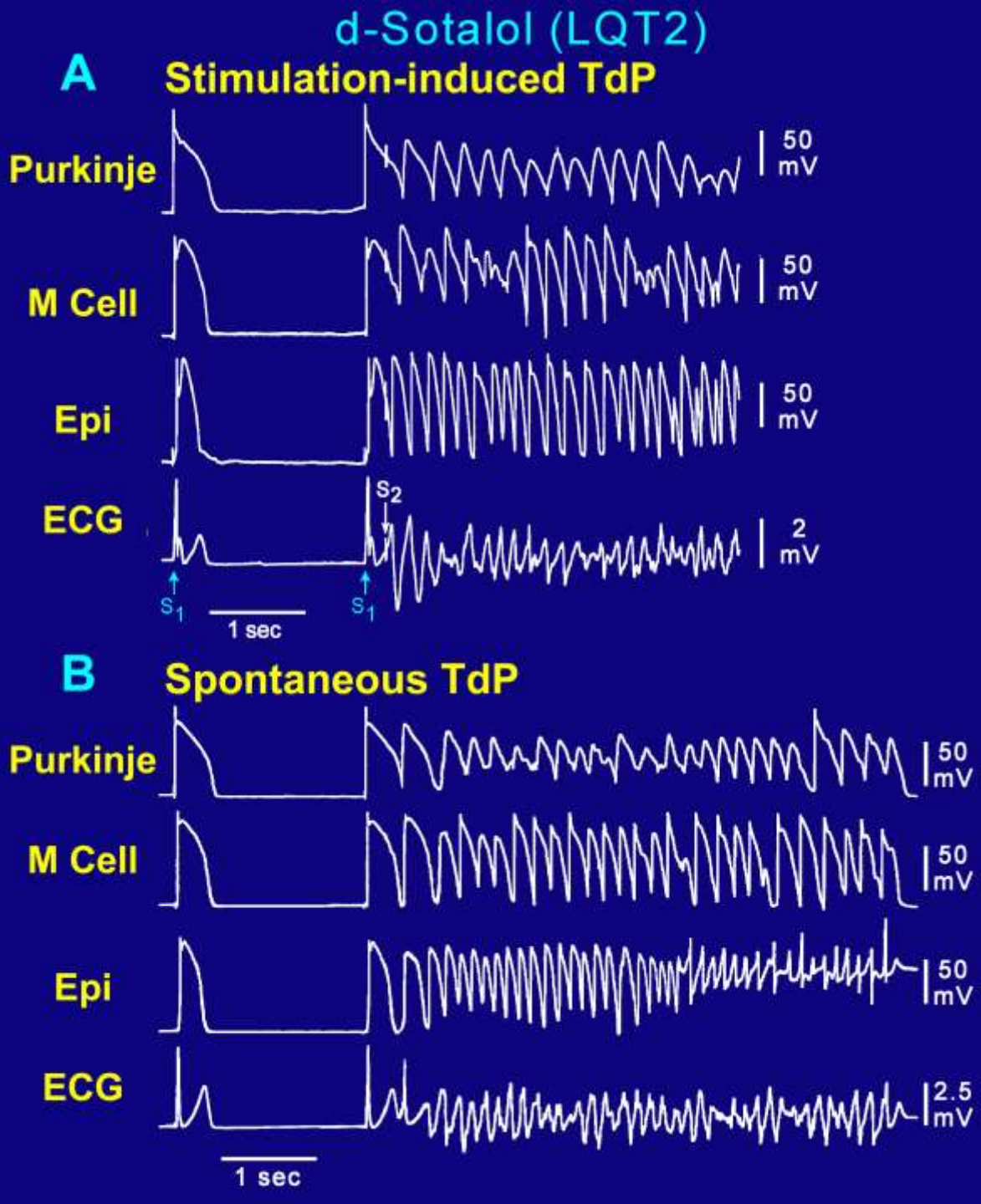
LQT1
LQT2
LQT3
LQT5
LQT6
LQT7
LQT8



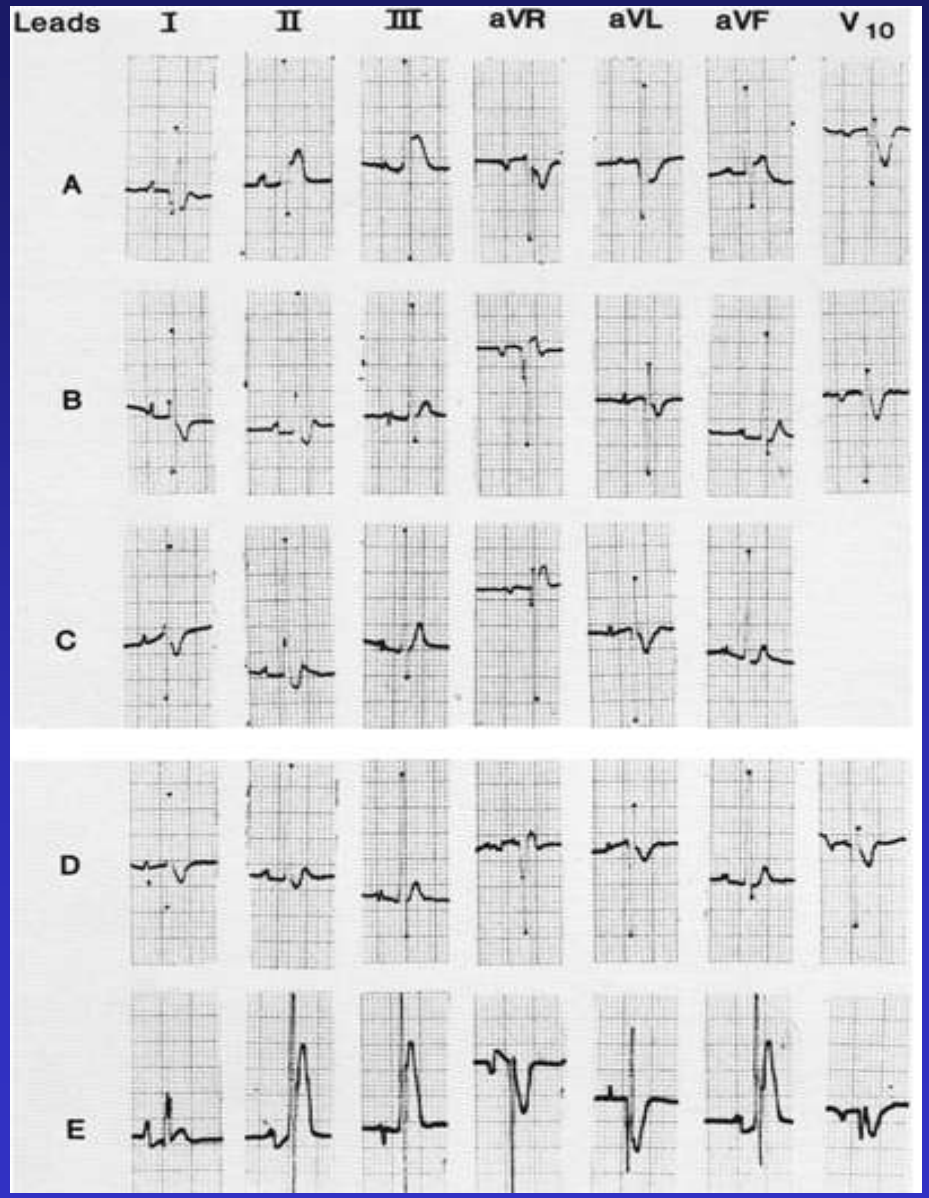




Antzelevitch and Shimizu. Curr Opin Cardiol 17, 43-51, 2002


d-Sotalol (LQT2)
A
Stimulation-induced TdP
Purkinje
M Cell
Epi
ECG
50 mV
50 mV
50 mV
2 mV
S2
S1
S1
1 sec
B
Spontaneous TdP
Purkinje
M Cell
Epi
ECG
50 mV
50 mV
50 mV
2.5 mV
1 sec

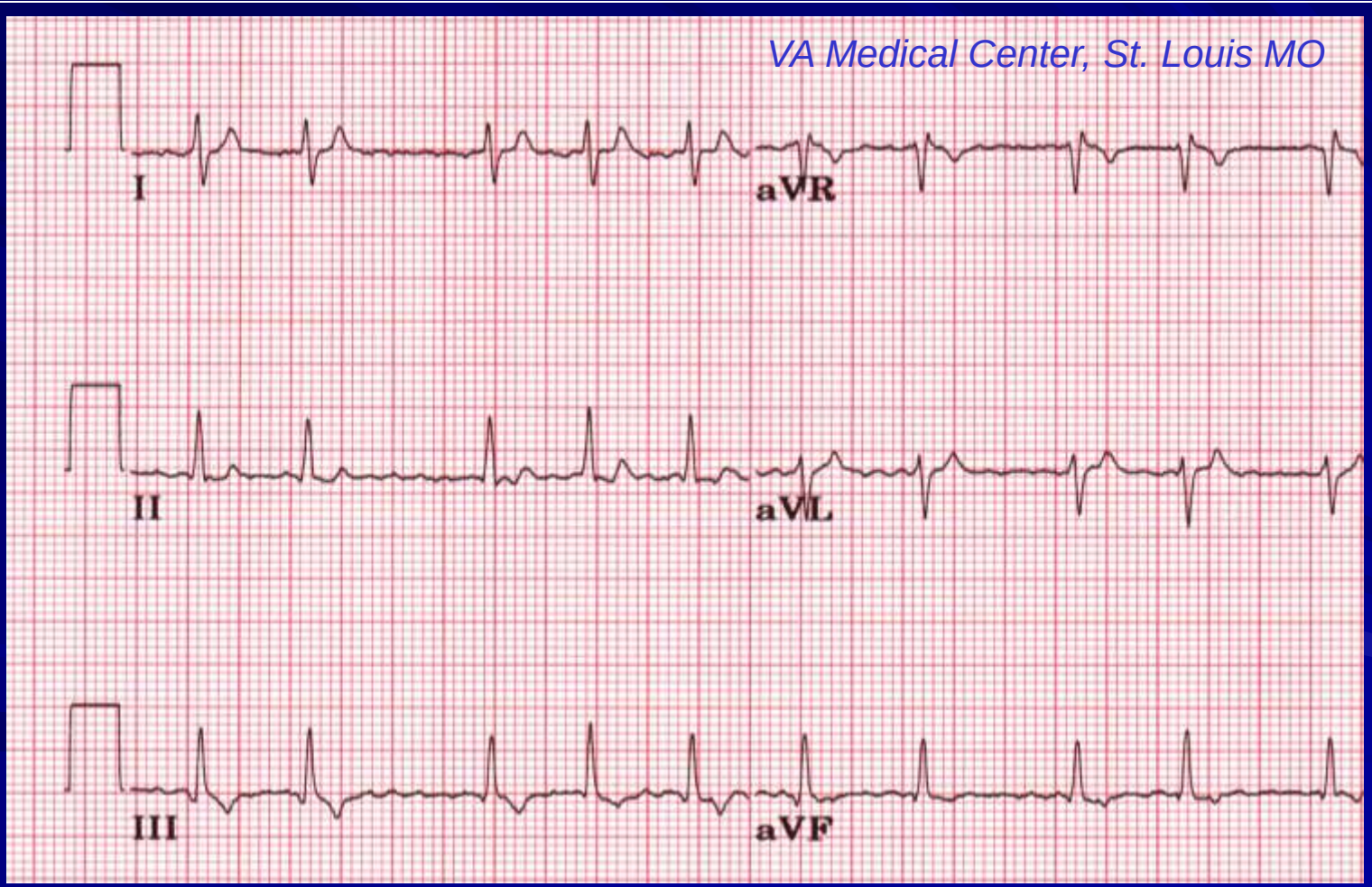
Short QT Syndrome



Eastern Grey Kangaroo

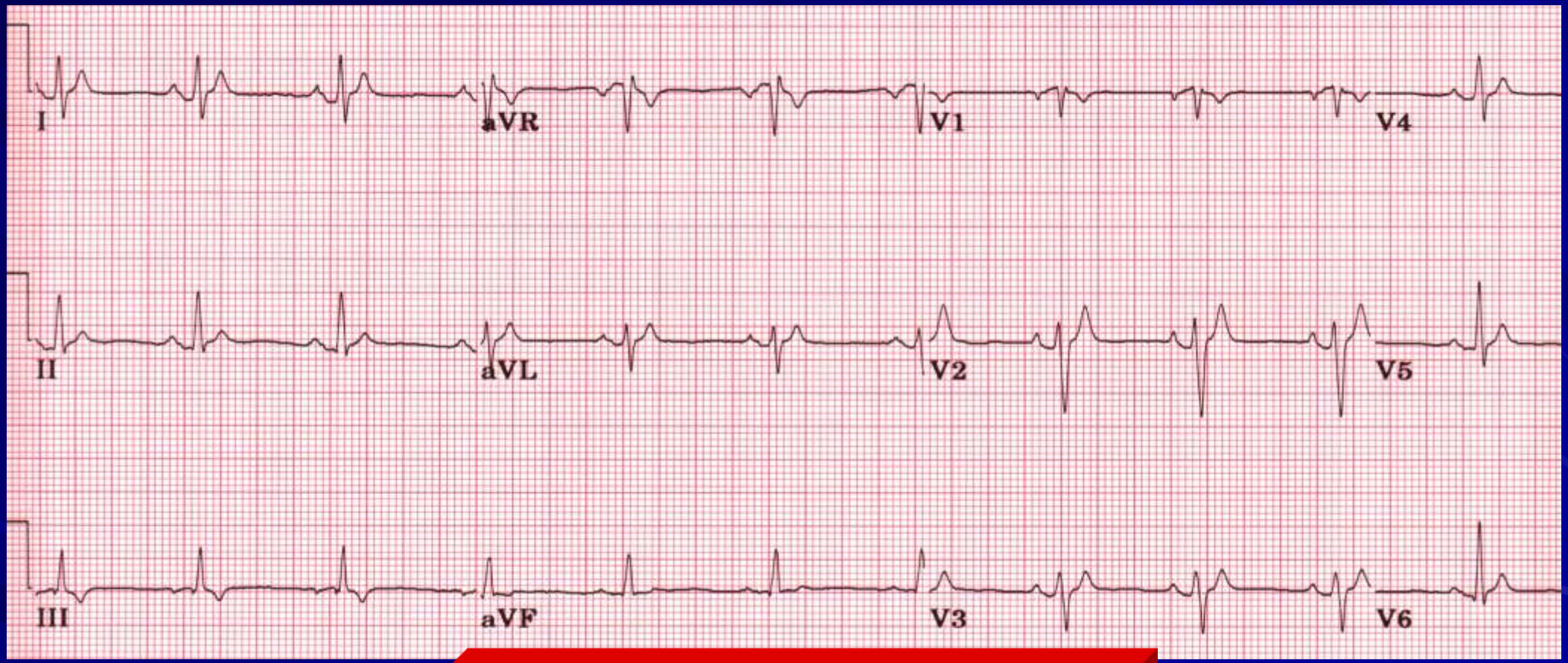
Rezakhani A et al. , Austr Vet J 1986

The history of Short QT Syndrome started with this ECG of a 17 year old female who presented with Atrial Fibrillation at the Clinic of Preben Bjerregaard in March, 1999



Gussak et al. Cardiology 2000; 94: 99–102

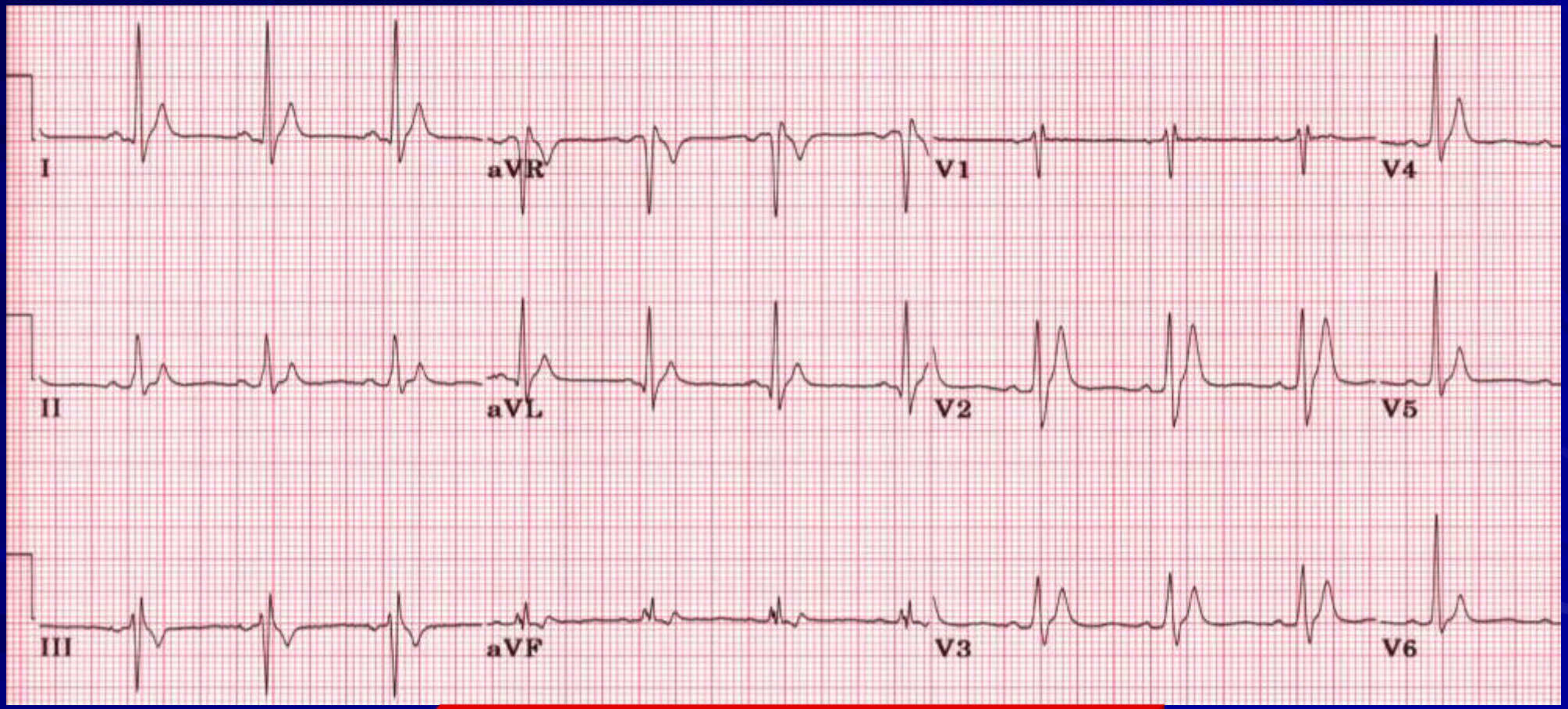
ECG of Index Patient
Sinus Rhythm and Short QT Intervals



QT = 230 msec, QTc = 300 msec

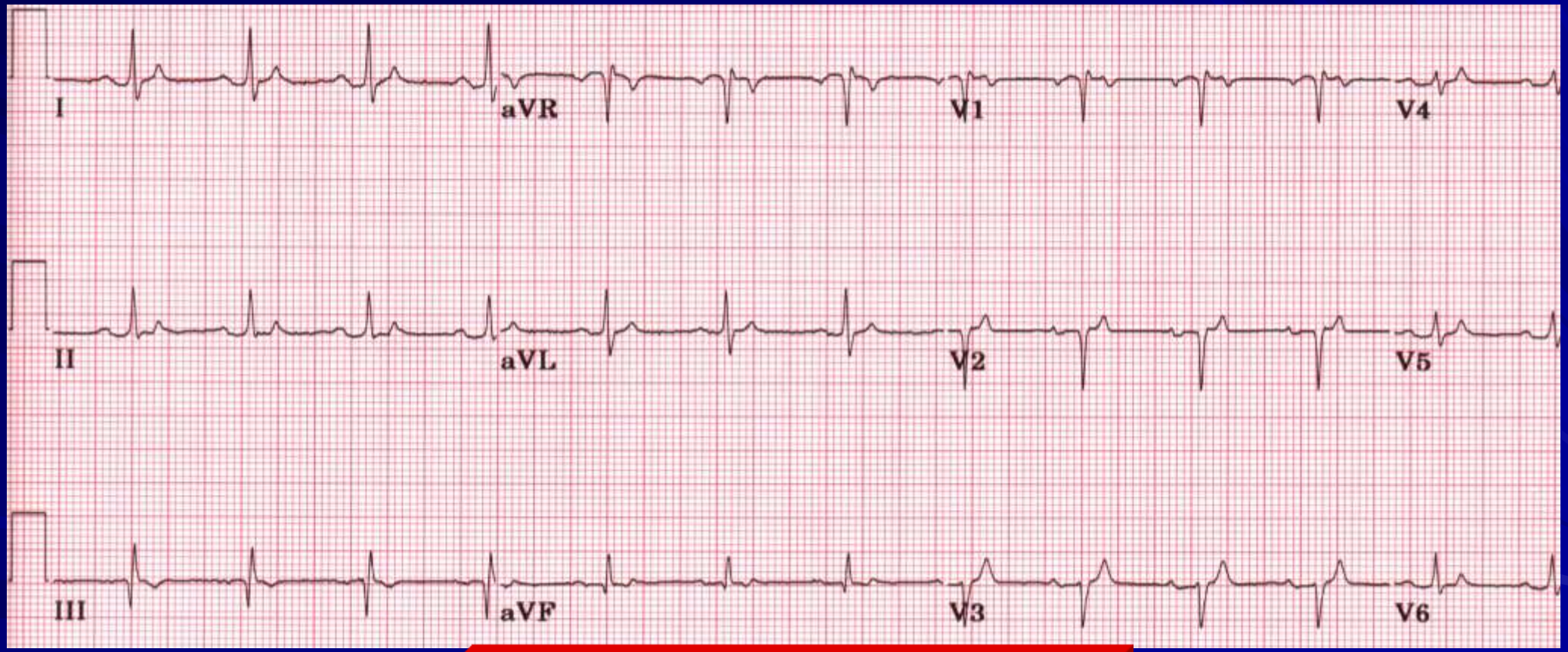
Gussak et al. Cardiology 2000; 94: 99–102.

ECG of Brother of Index Patient
Sinus Rhythm and Short QT Intervals



QT = 245 msec, QTc = 267 msec

ECG of Mother of Index Patient
Sinus Rhythm and Short QT Intervals



QT = 235 msec, QTc 289 msec

Gussak et al. Cardiology 2000; 94: 99–102.

Short QT Syndrome

Idiopathic Short QT Interval: A New Clinical Syndrome?

Ihor Gussak[a] Pedro Brugada[b] Josep Brugada[c] R. Scott Wright[a]
Stephen L. Kopecky[a] Bernard R. Chaitman[d] Preben Bjerregaard[d]

Cardiology 2000; 94(2):99–102.

ECG Phenomenon of Idiopathic and Paradoxical Short QT Intervals

Cardiac Electrophysiology Review 2002;6:49–53

Ihor Gussak,[1] Pedro Brugada,[2] Josep Brugada,[3] Charles Antzelevitch,[4] Mary Osbakken[1] and Preben Bjerregaard[5]

CER; 2002

Short QT Syndrome
A Familial Cause of Sudden Death

Fiorenzo Gaita, MD; Carla Giustetto, MD; Francesca Bianchi, MD; Christian Wolpert, MD; Rainer Schimpf, MD; Riccardo Riccardi, MD; Stefano Grossi, MD; Elena Richiardi, MD; Martin Borggrefe, MD

Circulation 2003; 108: 965-70

Diagnosis of Short QT Syndrome

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)

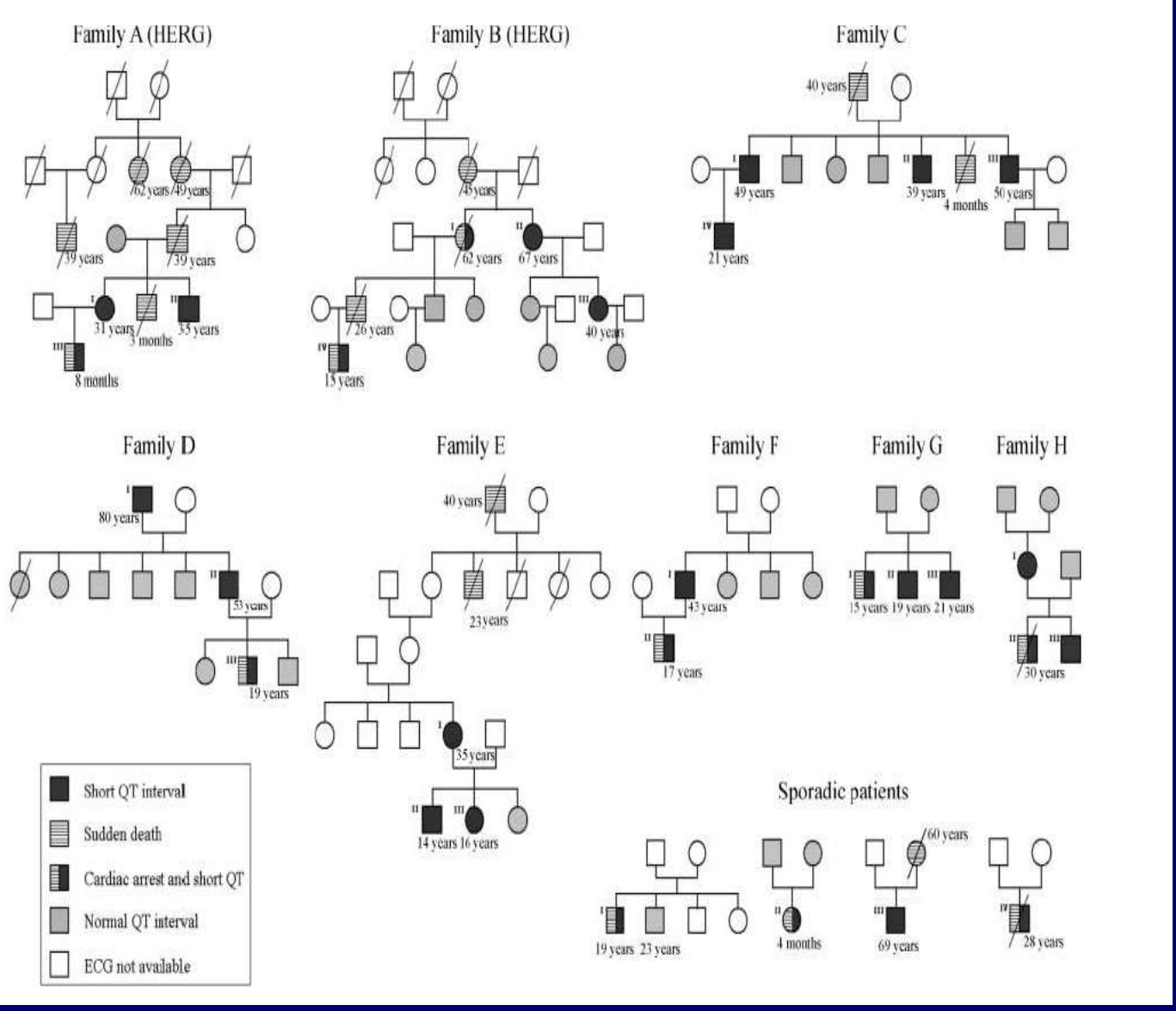
Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)

Authors/Task Force Members: Silvia G. Priori* (Chairperson) (Italy), Carina Blomström-Lundqvist* (Co-chairperson) (Sweden), Andrea Mazzanti† (Italy), Nico Blom[a] (The Netherlands), Martin Borggrefe (Germany), John Camm (UK), Perry Mark Elliott (UK), Donna Fitzsimons (UK), Robert Hatala (Slovakia), Gerhard Hindricks (Germany), Paulus Kirchhof (UK/Germany), Keld Kjeldsen (Denmark), Karl-Heinz Kuck (Germany), Antonio Hernandez-Madrid (Spain), Nikolaos Nikolaou (Greece), Tone M. Norekvål (Norway), Christian Spaulding (France), and Dirk J. Van Veldhuisen (The Netherlands)

Recommendations	Class[a]	Level[b]	Ref.[c]
SQTS is diagnosed in the presence of a QTc ≤340 ms.	I	C	This panel of experts
SQTS should be considered in the presence of a QTc ≤360 ms and one or more of the following: (a) A confirmed pathogenic mutation (b) A family history of SQTS (c) A family history of sudden death at age <40 years (d) Survival from a VT/VF episode in the absence of heart disease.	IIa	C	This panel of experts

QTc = corrected QT; SQTS = short QT syndrome; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Clinical Characteristics of Short QT Patients



29 SQTS patients - 25 from 8 families and 4 sporadic cases

21 males: 8 Females

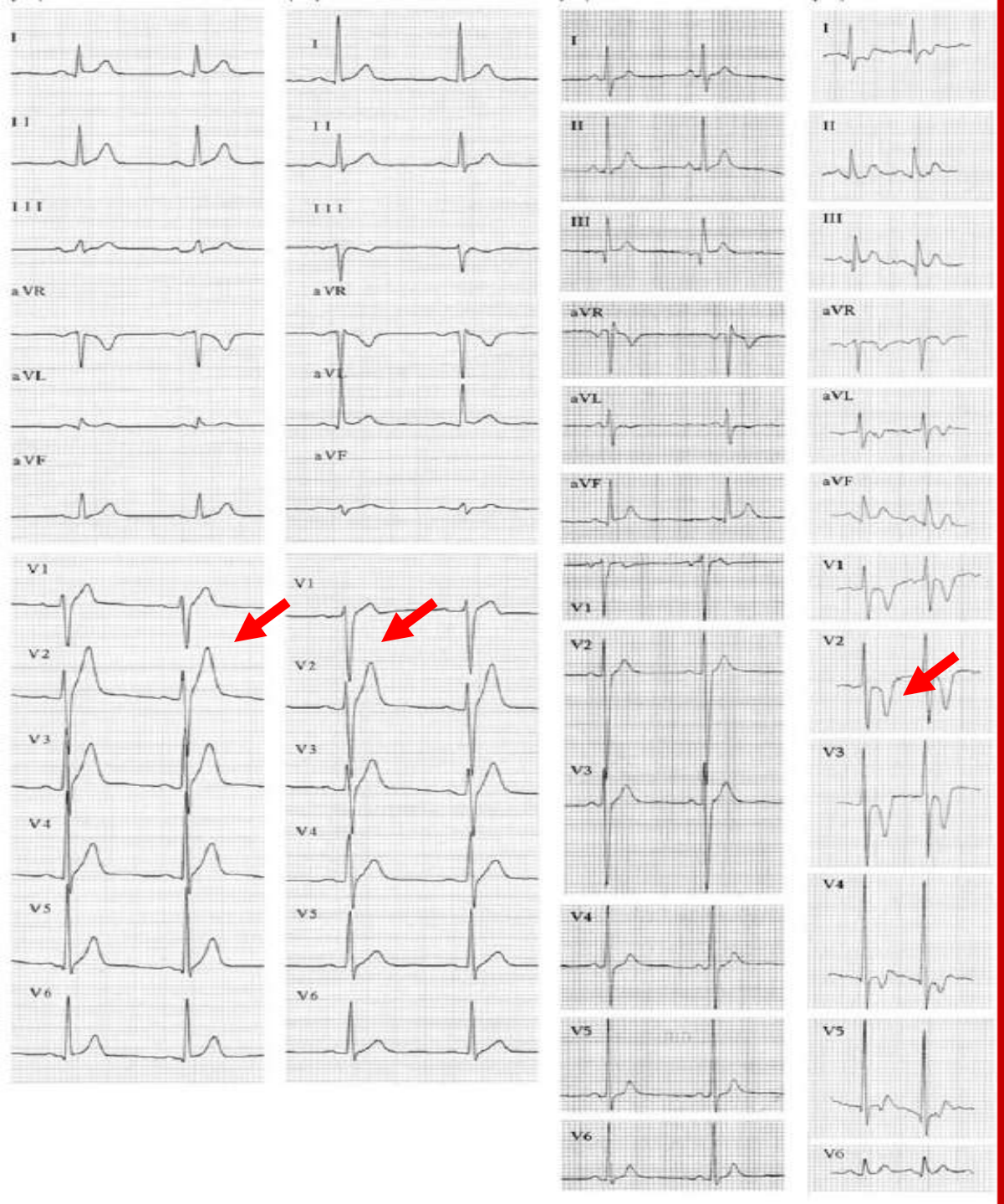
Median age at diagnosis = 30 (range: 4 mos – 80 yrs.)

Symptomatic: 18/29 62%

Cardiac arrest: 9/29 31%
Age range: 4 mos – 62 yrs.
(In 8 of the 9 SCA 1st symptom)
SCA: QTc = 300 ± 20 ms
Others: QTc = 309 ± 19 ms

AF or Flutter: 7/29 24%

Giustetto C et al, Eur Heart J, 2006



Tall peaked T waves Positive or Negative

↑ Tpeak-Tend Interval

= ↑ Transmural Dispersion of Repolarization (TDR)

Giustetto C et al, Eur Heart J, 2006

Short QT Syndrome

	QTc (ms)	Gene (Cardiac Ion Channel)	Reference
SQT 1	286 ± 6	*KCNH2* (I_{Kr}) ↑	*Brugada et al., Circulation 109:30, 2004*
SQT 2	302	*KCNQ1* (I_{Ks}) ↑	*Bellocq et al., Circulation 109:2394, 2004,*
SQT 3	315 - 330	*KCNJ2* (I_{K1}) ↑	*Priori et al., Circulation Research 96: 800, 2005*
SQT 4	331 - 370	*CACNB2b* (I_{Ca}) ↓	*Antzelevitch et al. Circulation 115:442, 2007*
SQT 5	346-360	*CACNA1C* (I_{Ca}) ↓	*Antzelevitch et al. Circulation 115: 442, 2007*
SQT 6	330	*CACNA2D1* (I_{Ca}) ↓	*Templin et al., European Heart Journal, 32:1077-88, 2011*
SQT 7	282 - 340	*SLC22A5* (↓carnitine - ↑ I_{kr})	*Roussel et al., Heart Rhythm 13:165-174, 2016*
SQT8	340	*SLC4A3* (↑pHi - ↓Cl_i^-)	*Thorsen et al., Nature Comm.* 8:1696, 2017

Calcium channel mutations often produce a combined SQTS/BrS phenotype

Carnitine deficiency induces a short QT syndrome

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BACKGROUND Short QT syndrome is associated with an increased risk of cardiac arrhythmias and unexpected sudden death. Until now, only mutations in genes encoding the cardiac potassium and calcium channels have been implicated in early T-wave repolarization.

OBJECTIVE The purpose of this study was to confirm a relationship between a short QT syndrome and carnitine deficiency.

METHODS We report 3 patients affected by primary systemic carnitine deficiency and an associated short QT syndrome. Ventricular fibrillation during early adulthood was the initial symptom in 1 case. To confirm the relationship between carnitine, short QT syndrome, and arrhythmias, we used a mouse model of carnitine deficiency induced by long-term subcutaneous perfusion of MET88.

RESULTS MET88-treated mice developed cardiac hypertrophy associated with a remodeling of the mitochondrial network. The continuous monitoring of electrocardiograms confirmed a shortening of the QT interval, which was negatively correlated with the plasma carnitine concentration. As in humans, such alterations coincided with the genesis of ventricular premature beats and ventricular tachycardia and fibrillation.

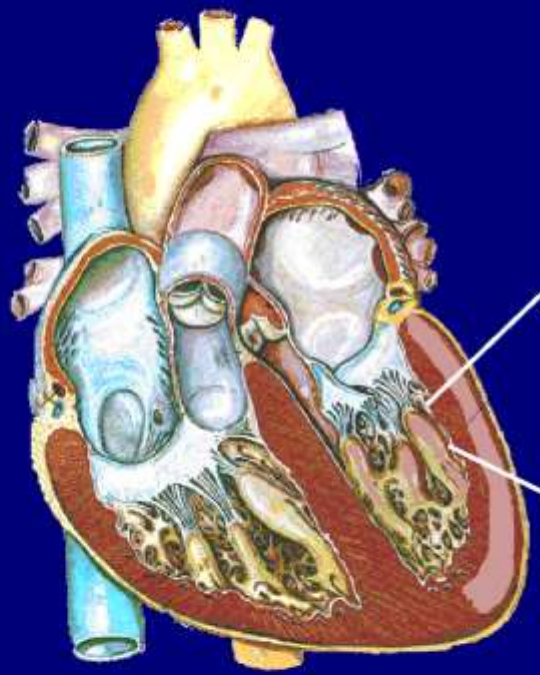
CONCLUSION Altogether, these results suggest that long-chain fatty acid metabolism influence the morphology and the electrical function of the heart.

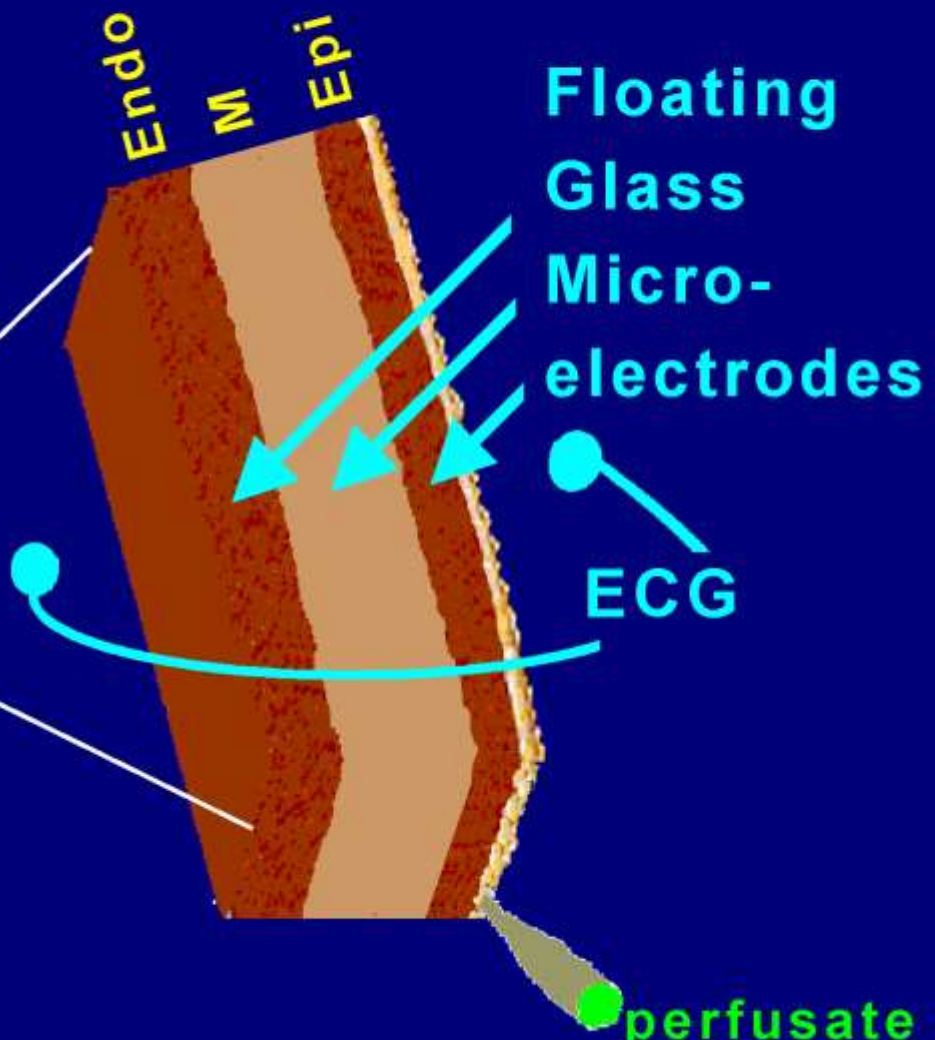
KEYWORDS Carnitine deficiency; Short QT syndrome; Electrophysiological remodeling; Sudden death; Ventricular arrhythmias

ABBREVIATIONS **ECG** = electrocardiogram/electrocardiographic; **I_{Kr}** = rapid potassium current; **LCFA** = long-chain fatty acid; **LV** = left ventricular; **OCTN2** = organic cation transport Na^+; **PCD** = primary carnitine deficiency

(Heart Rhythm 2016;13:165–174)

Arterially Perfused Left Ventricular Wedge

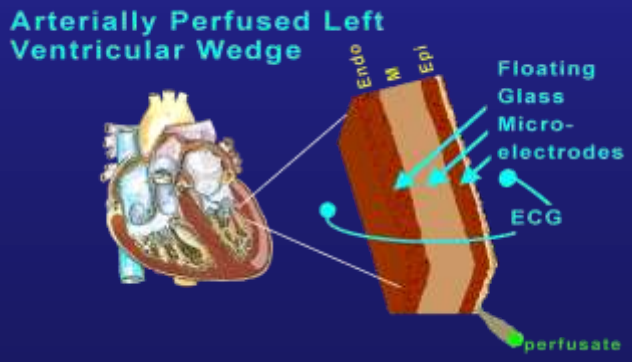


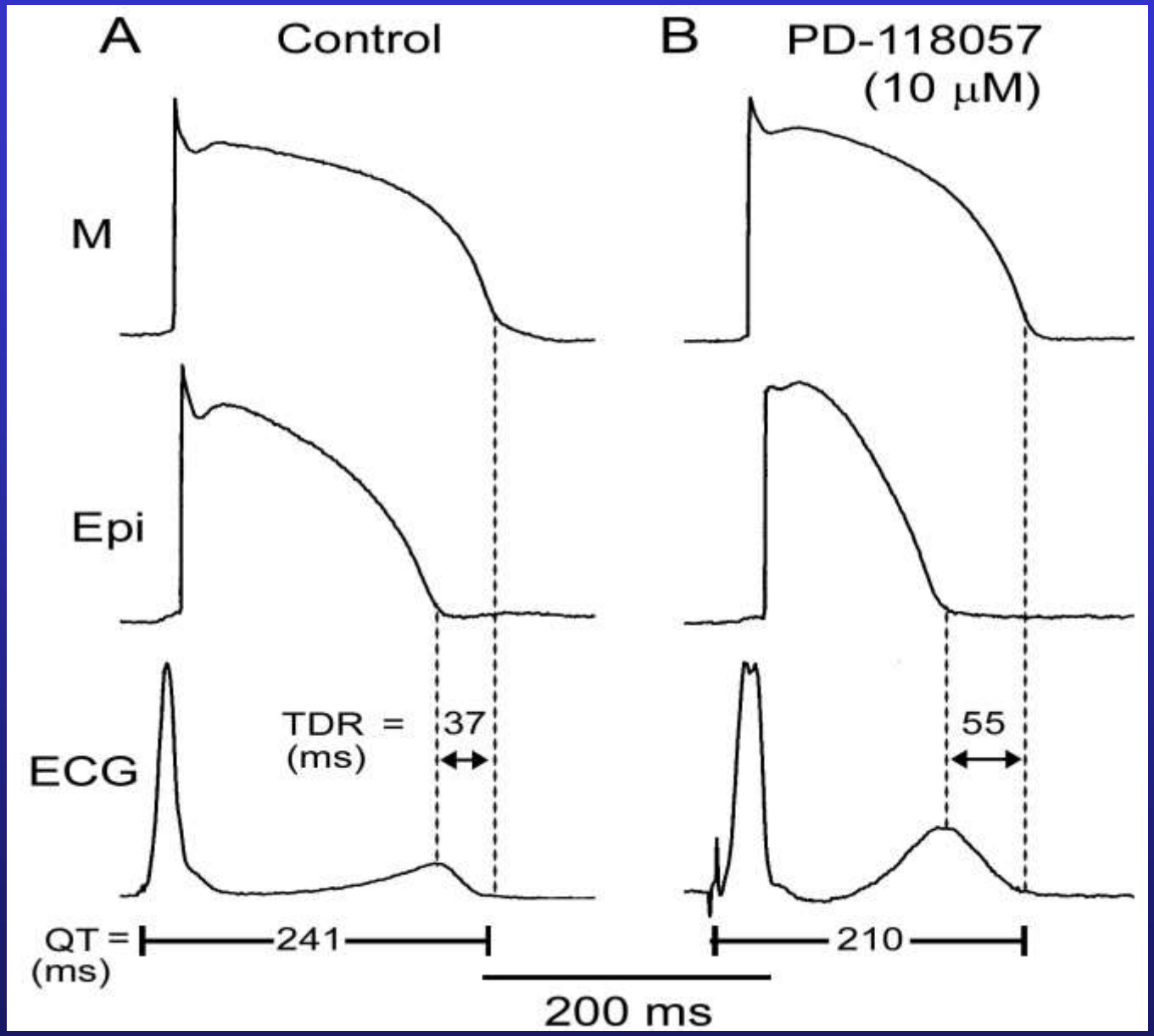


Short QT Syndrome

SQT1

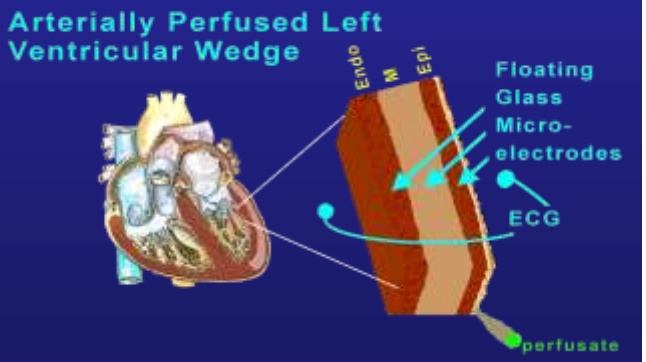
I_{kr} Agonist

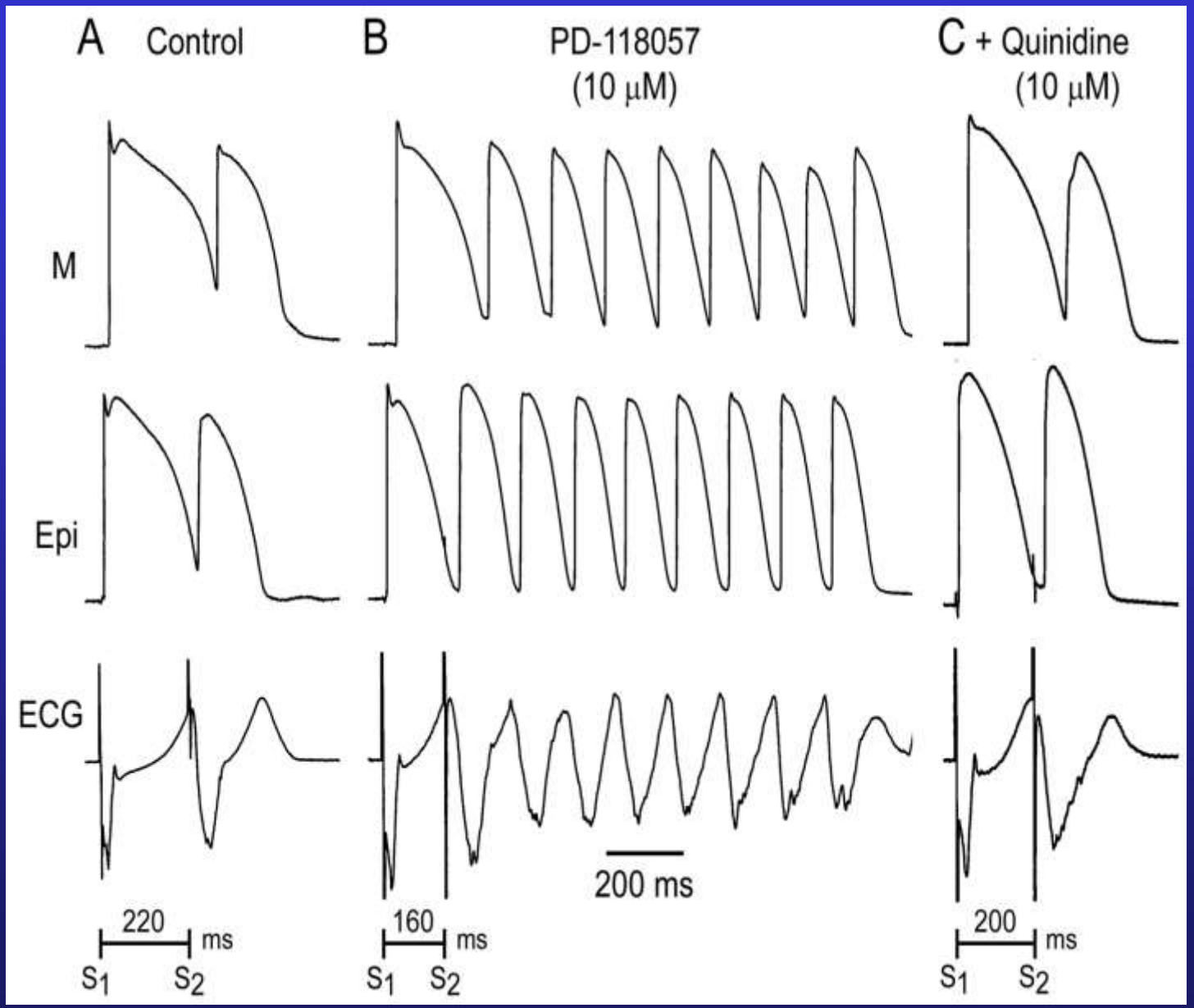




Patel and Antzelevitch. Heart Rhythm 5:585–590 , 2008

Short QT Syndrome



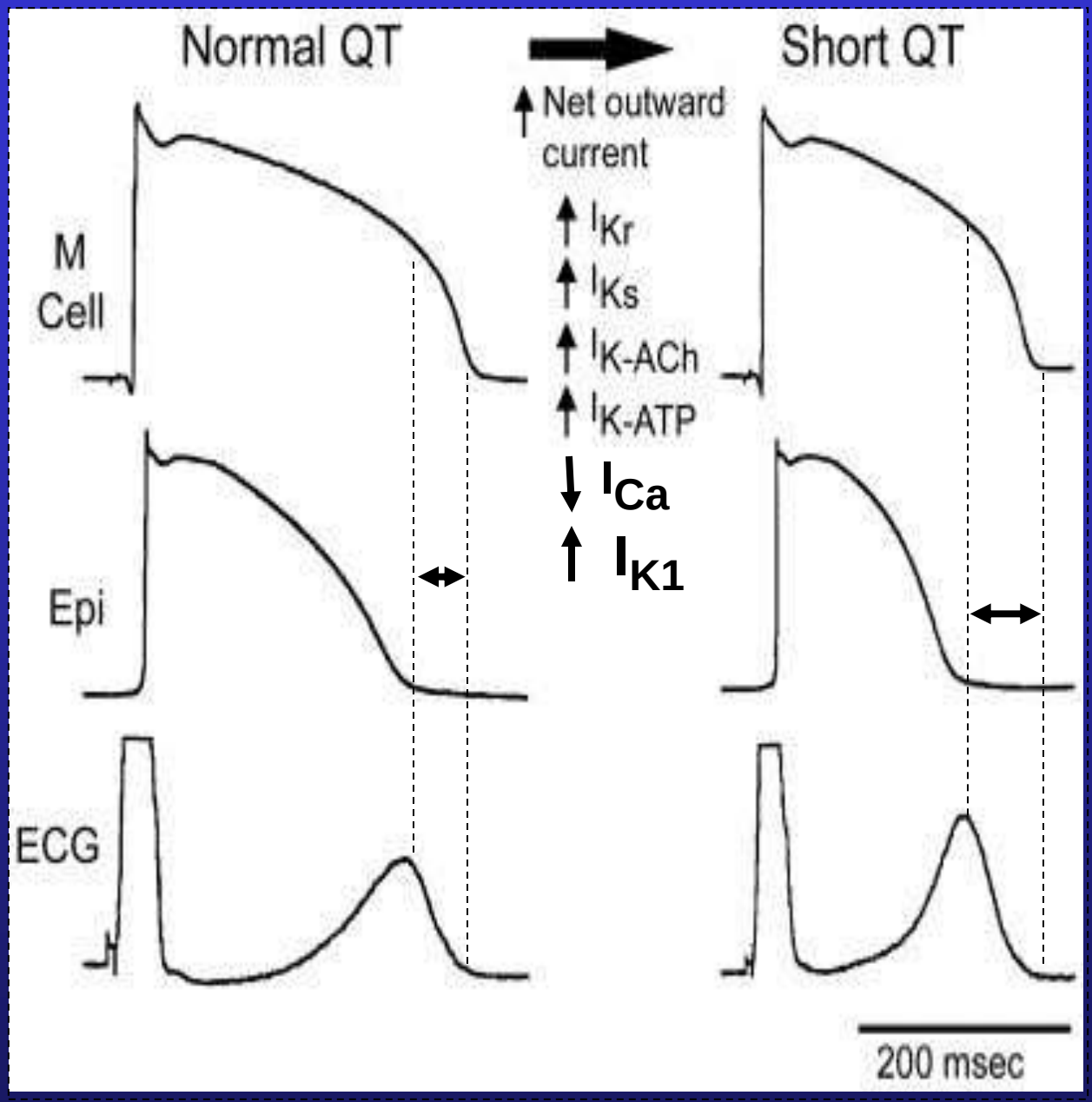


Patel and Antzelevitch. Heart Rhythm 5:585–590 , 2008

Short QT Syndrome

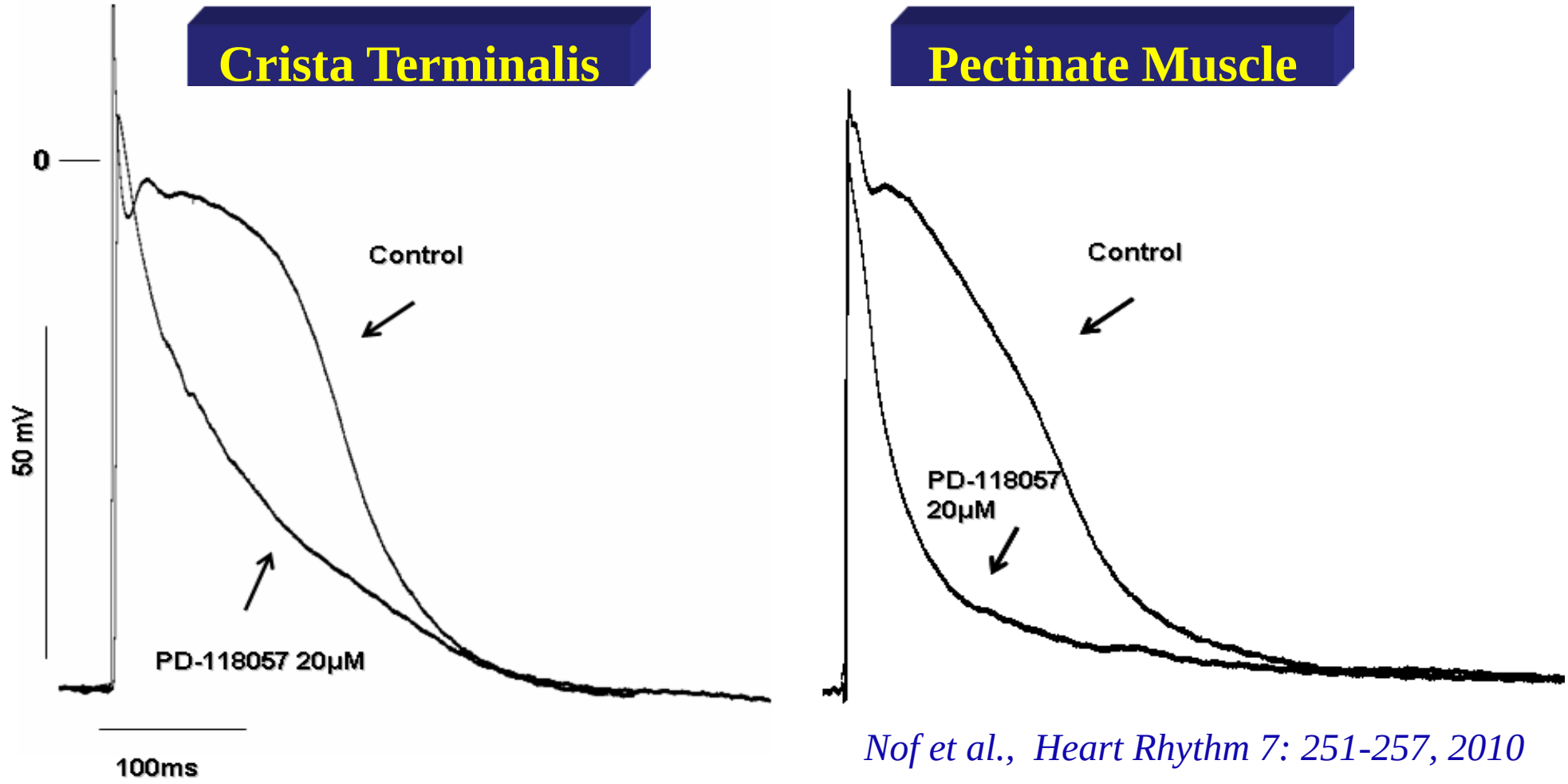
Arrhythmogenic Mechanism

↓ ERP ↑ TDR

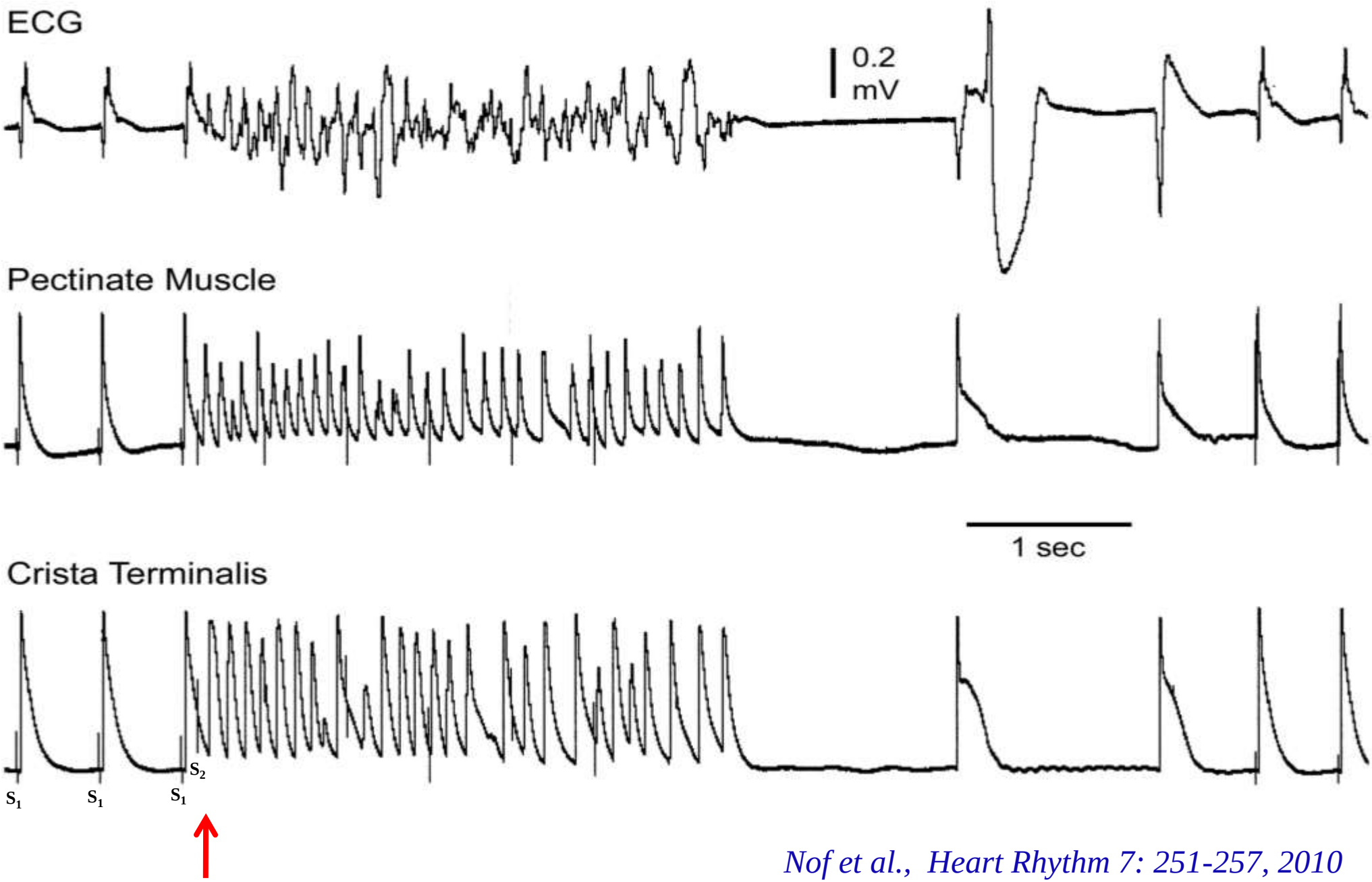


Extramiana and Antzelevitch, Circulation 110:3661-6. 2004
Antzelevitch & Francis, IPEJ 4: 46-49 , 2004

Heterogeneous Abbreviation of APD by I_{Kr} Agonist PD-118057 in Coronary-perfused Canine Right Atrium



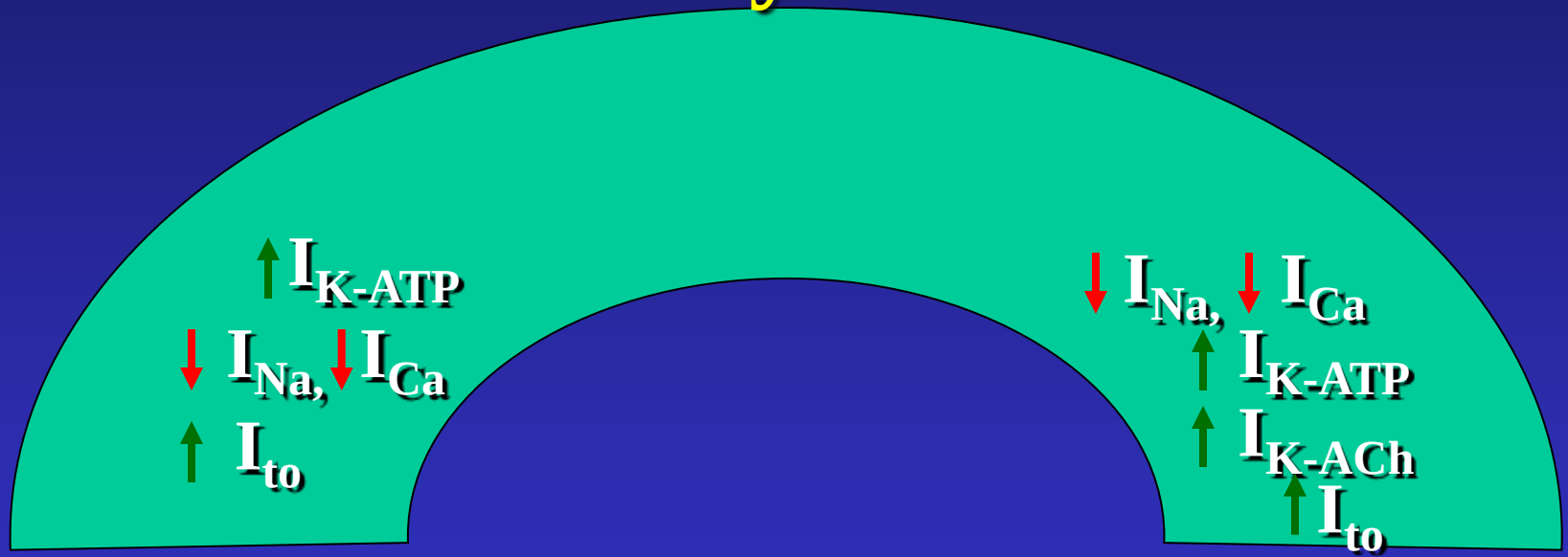
Nof et al., Heart Rhythm 7: 251-257, 2010



Nof et al., Heart Rhythm 7: 251-257, 2010

Outward shift of repolarizing current during early phase of the action potential

J Wave Syndromes



RVOT

Brugada Syndrome

Inferior LV

Early Repolarization Syndrome

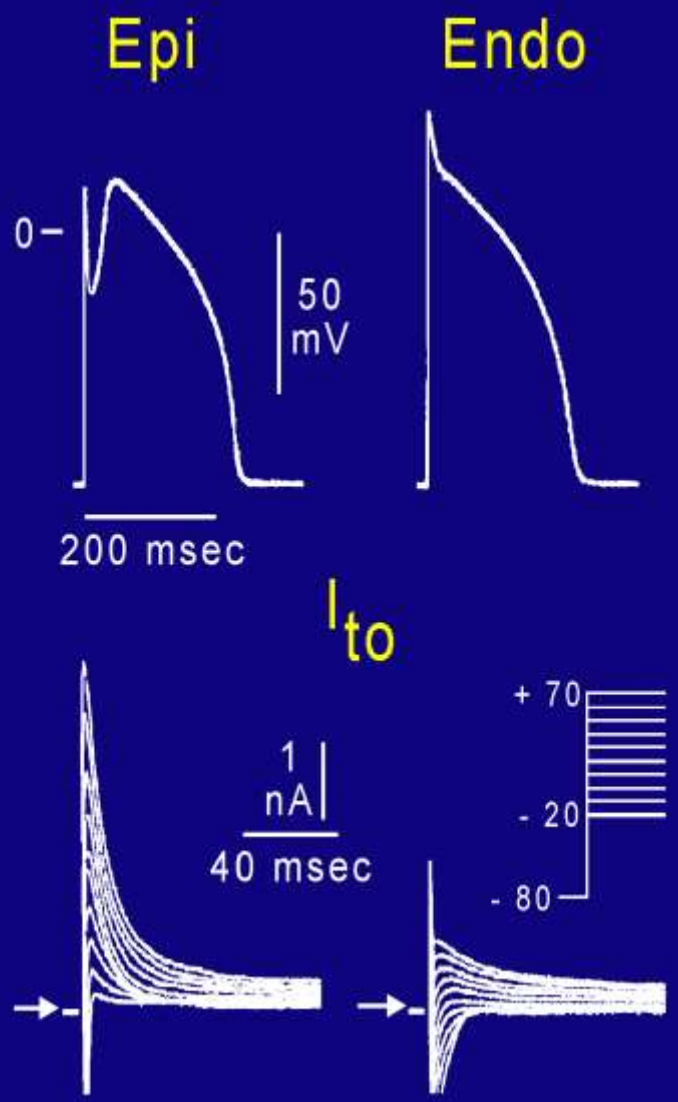
Phase 2 Reentry ?

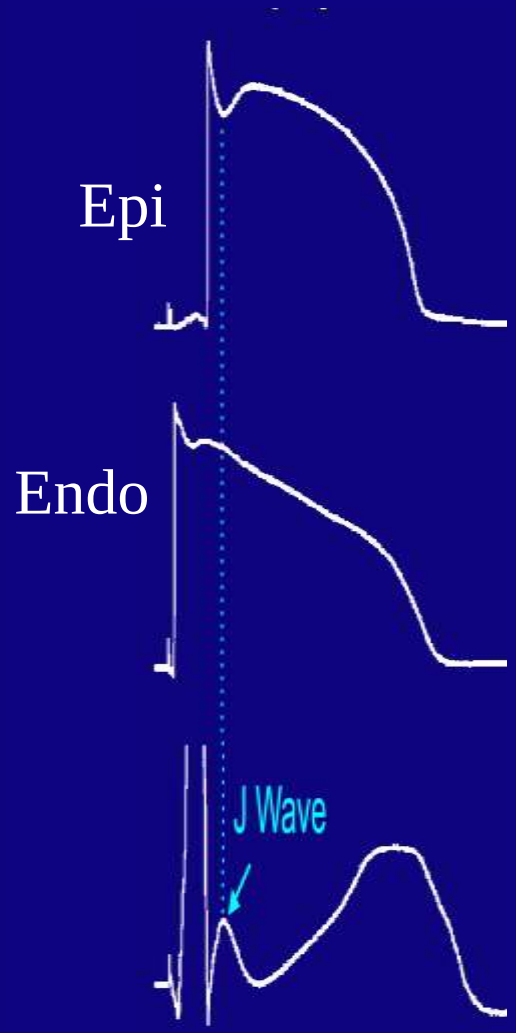
Continuous Spectrum Between BrS and ERS

- Brugada (BrS) and Early Repolarization (ERS) Syndromes share similar ECG characteristics, clinical outcomes, risk factors and arrhythmic characteristics.

- Although BrS and ERS differ with respect to the magnitude and lead location of abnormal J wave manifestation, they can be considered to represent a continuous spectrum of phenotypic expression, termed J wave syndromes, and to share a common arrhythmic platform related to amplification of I_{to}-mediated J waves.

Cellular Basis for the J Wave





Transmural distribution of the I_{to}-mediated action potential notch is responsible for the inscription of the electrocardiographic J wave

Yan and Antzelevitch. Circulation 93:372-379, 1996

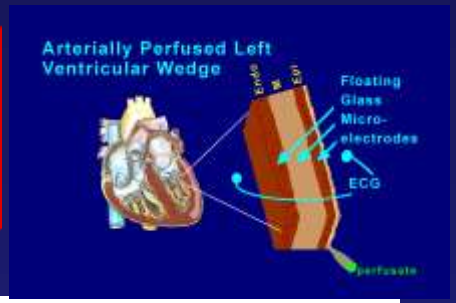
Similarities between Brugada and Early Repolarization Syndromes and Possible Underlying Mechanisms

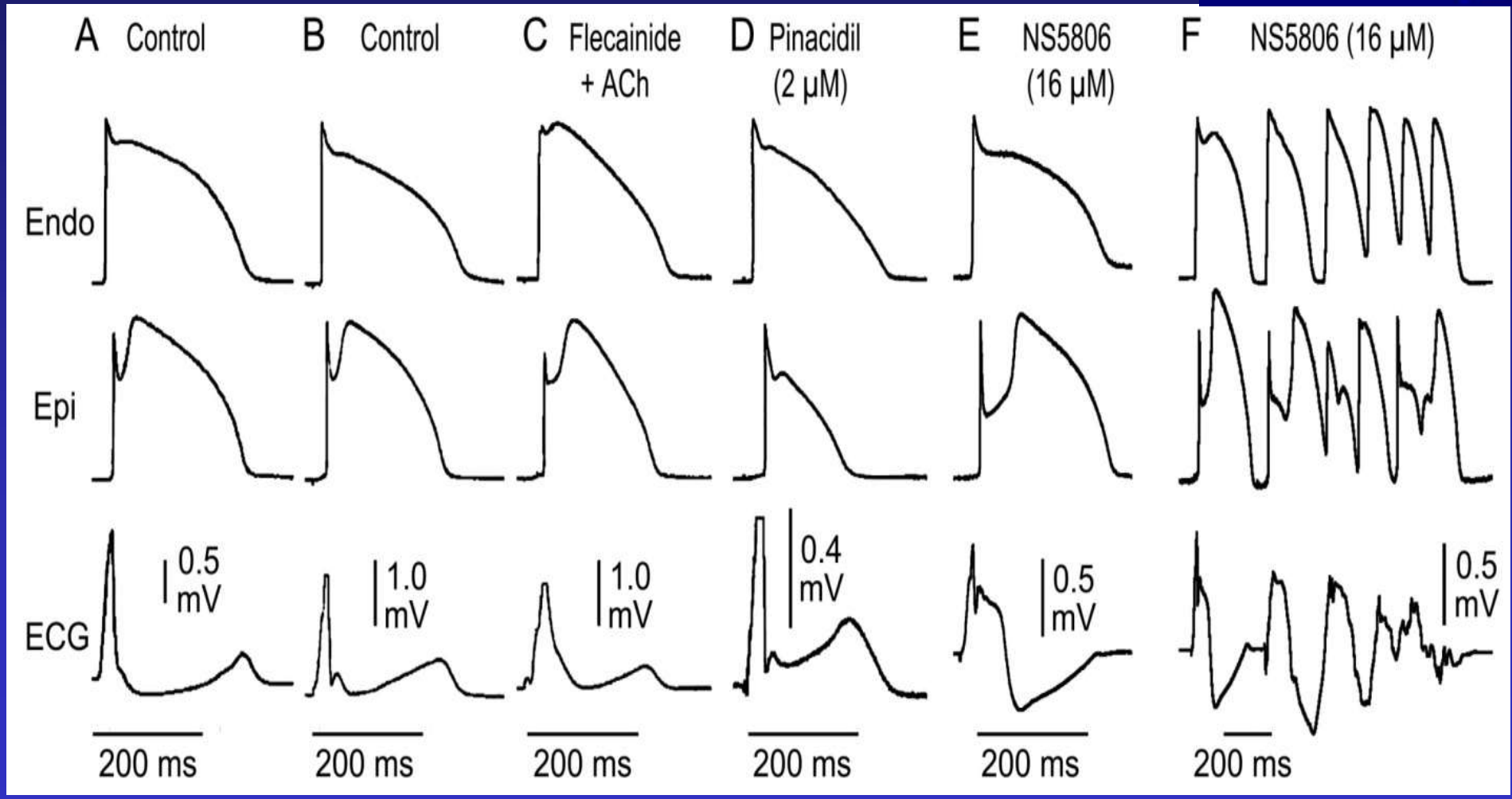
	BrS	ERS	Possible Mechanism(s)
Male Predominance	Yes (>75%)	Yes (>80%)	Testosterone modulation of ion currents underlying the epicardial AP notch
Average age of first event	30-50	30-50	
Associated with mutations or rare variants in KCNJ8, CACNA1C, CACNB2, CACNA2D, SCN5A, ABCC9, SCN10A	Yes	Yes	Gain of function in outward currents ($I_{K\text{-}ATP}$) or loss of function in inward currents (I_{Ca} or I_{Na})
Dynamicity of ECG	High	High	Autonomic modulation of ion channel currents underlying early phases of the epicardial AP
VF often occurs during sleep or at a low level of physical activity	Yes	Yes	Higher level of vagal tone and higher levels of I_{to} at the slower heart rates.
VT/VF trigger	Short-coupled PVC	Short-coupled PVC	Phase 2 reentry
Ameliorative response to quinidine and bepridil	Yes	Yes	Inhibition of I_{to} and possible vagolytic effect
Ameliorative response to Isoproterenol, denopamine and milrinone	Yes	Yes	Increased I_{Ca} and faster heart rate
Ameliorative response to cilostazol	Yes	Yes	Increased I_{Ca}, reduced I_{to} and faster heart rate
Ameliorative response to pacing	Yes	Yes	Reduced availability of I_{to} due to slow recovery from inactivation
Vagally-mediated accentuation of ECG pattern	Yes	Yes	Direct effect to inhibit I_{Ca} and indirect effect to increase I_{to} (due to slowing of heart rate)
Effect of sodium channel blockers on unipolar epicardial electrogram	Augmented J waves	Augmented J wave	Outward shift of balance of current in the early phases of the epicardial action potential
Fever	Augmented J waves	Augmented J waves	Accelerated inactivation of I_{Na} and accelerated recovery of I_{to} from inactivation.
Hypothermia	Augmented J waves	Augmented J waves	Slowed activation of I_{Ca}, leaving I_{to} unopposed. Increased phase 2 reentry, but reduced pVT due to prolongation of APD (Morita et al, 2007)

Differences between Brugada and Early Repolarization Syndromes and Possible Underlying Mechanisms

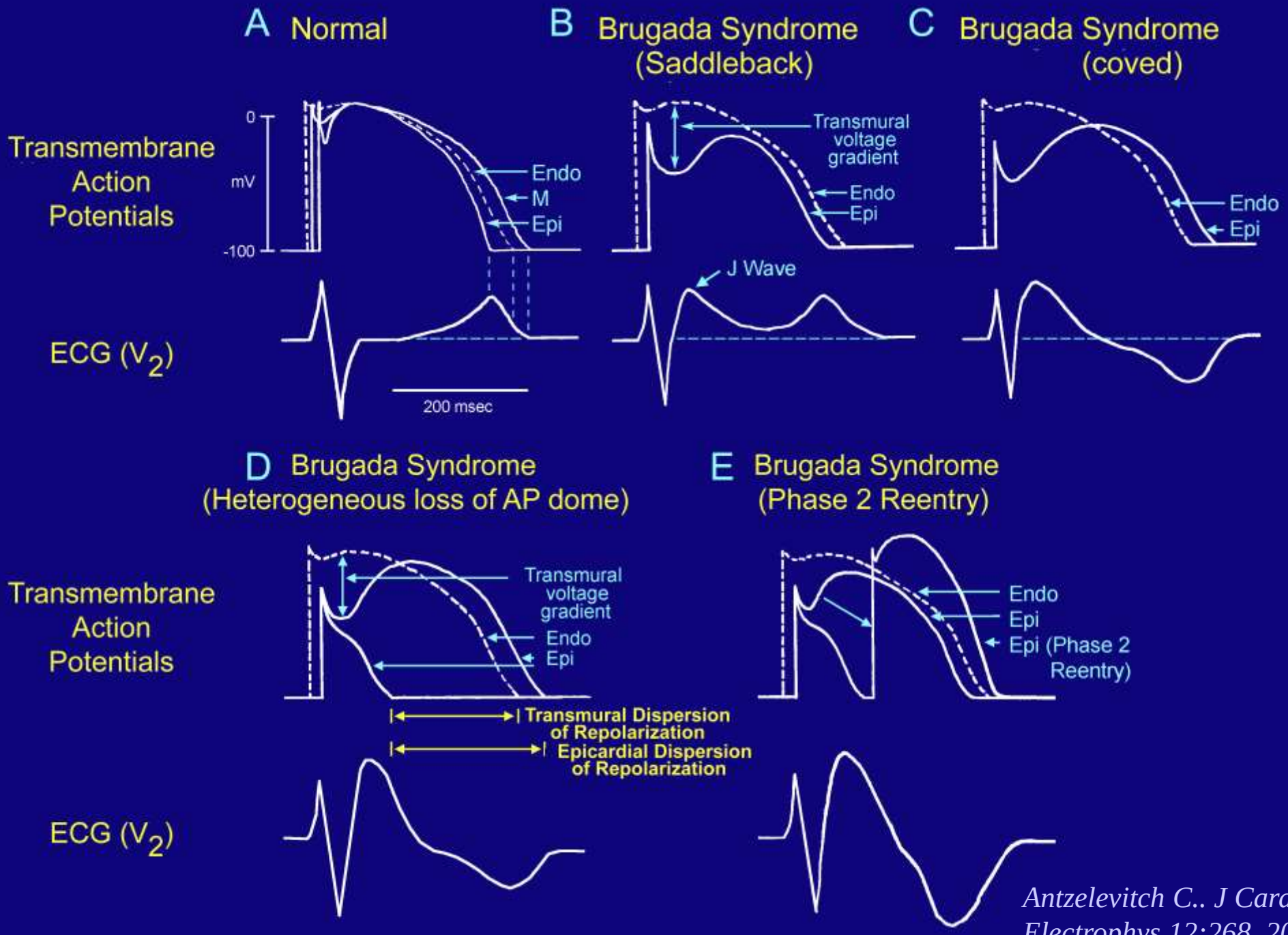
	BrS	ERS	Possible Mechanism(s)
Region most involved	RVOT	Inferior LV wall	Higher levels of I_{to} and/or differences in conduction
Leads affected	V1-V3	II, II aVF V4, V5, V6; I, aVL Both: infero-lateral	
Regional difference in prevalence			Europe: BrS = ERS Asia: BrS > ERS
Incidence of late potential in SAECG	Higher	Lower	
Inducibility of VF during an EPS	Higher	Lower	
Effect of sodium channel blockers on the surface ECG	Increased J wave manifestation	Reduced J wave Manifestation	Reduction of J wave in the setting of ER is due largely to prolongation of QRS. Accentuation of repolarization defects predominates in BrS, whereas accentuation of depolarization defects predominates in ERS.

Early Repolarization Patterns



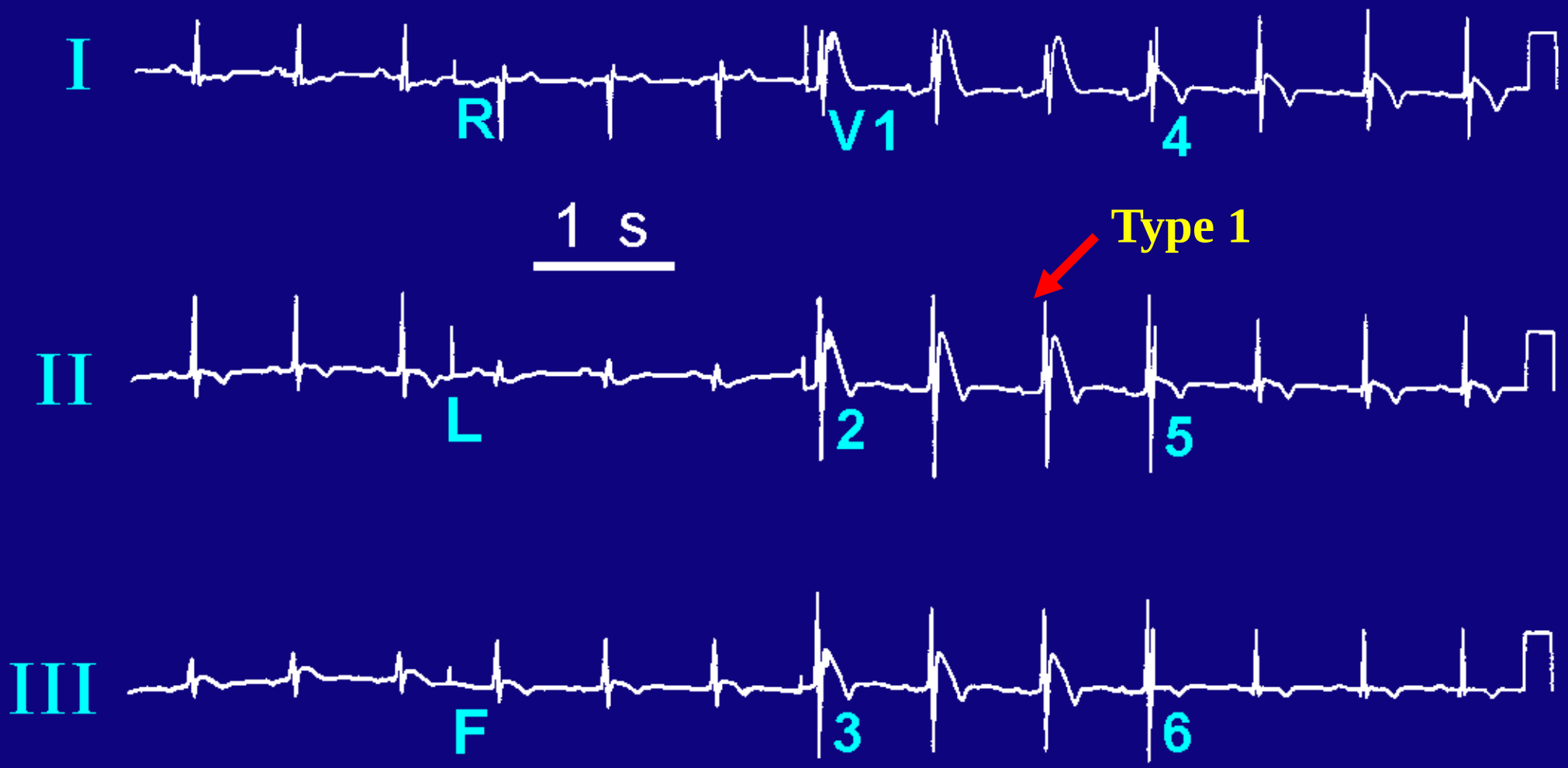


Modified from Antzelevitch et al, JACC, 2011



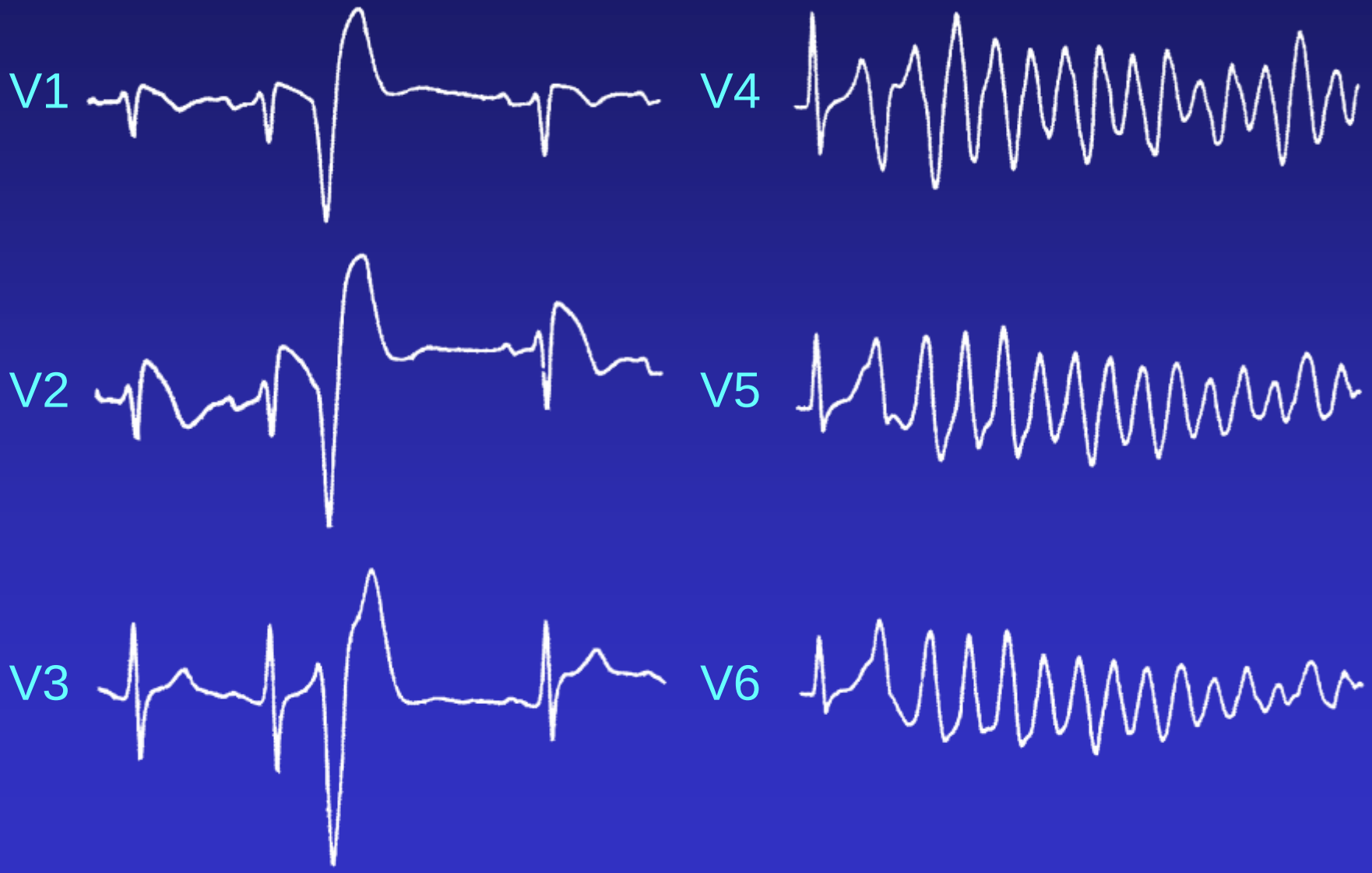
Antzelevitch C.. J Cardiovasc Electrophys 12:268, 2001

Brugada Syndrome



Brugada and Brugada, JACC 1992;20;1391-96

Ventricular Arrhythmias in Brugada Syndrome



Genetic Basis for Brugada Syndrome - *Causative Genes*

	Locus	Ion Channel	Gene/Protein	% of Probands
BrS1	3p21	I_{Na}	*SCN5A*, $Na_v1.5$	11-28%
BrS2	3p24	I_{Na}	*GPD1L*	Rare
BrS3	12p13.3	I_{Ca}	*CACNA1C*, $Ca_v1.2$	6.6%
BrS4	10p12.33	I_{Ca}	*CACNB2b*, $Ca_v\beta2b$	4.8%
BrS5	19q13.1	I_{Na}	*SCN1B*, *$Na_v\beta1$*	1.1%
BrS6	11q13-14	I_{to}	*KCNE3*, *MiRP2*	Rare
BrS7	11q23.3	I_{Na}	*SCN3B*, $Na_v\beta3$	Rare
BrS8	12p11.23	$I_{K\text{-}ATP}$	*KCNJ8*, Kir6.1	2%
BrS9	7q21.11	I_{Ca}	*CACNA2D1*, $Ca_v\alpha2\delta$	1.8%
BrS10	1p13.2	I_{to}	*KCND3*, *$K_v4.3$*	Rare
BrS11	17p13.1	I_{Na}	*RANGRF*, MOG1	Rare
BrS12	3p21.2-p14.3	I_{Na}	*SLMAP*, Sarcolemma Associated Protein	Rare
BrS13	12p12.1	$I_{K\text{-}ATP}$	*ABCC9*, *SUR2A*	Rare
BrS14	11q23	I_{Na}	*SCN2B*, $Na_v\beta2$	Rare
BrS15	12p11	I_{Na}	*PKP2*, Plakophilin-2	Rare
BrS16	3q28	I_{Na}	*FGF12*, FHAF1	Rare
BrS17	3p22.2	I_{Na}	*SCN10A*, $Na_V1.8$	5-16.7%
BrS18	6q	I_{Na}	*HEY2 (trasncriptional factor)*	Rare
BrS19	1p36.3	I_{to}	*KCNAB2*, $Kv\beta2$	Rare

Genetic Basis for Brugada Syndrome

New Candidate Genes

Locus	Ion Channel	Gene/Protein
12p12.1	↓ $I_{K/Na-Ca}$	*TRPM4,* Transient Receptor Potential Melastatin Protein 4
7q31.31	↑ I_{to}	*KCND2*/Kv4.2

Modulatory Genes

15q24-q25	↓ I_f	*HCN4*
7q35	↑ I_{kr}	*KCNH2, HERG*
Xq22.3	↑ I_{to}	*KCNE5 (KCNE1-like)*
7p12.1	↑ I_{to}	*SEMA3A, Semaphorin*

Reclassification of pathogenicity of Brugada Syndrome variants classified as deleterious and causative of the inherited syndrome

Recent efforts have led to exhaustive studies of genes and variants previously identified as pathogenic and causative of inherited cardiac arrhythmia syndromes using *American College of Medical Genetics and Genomics and Association for Molecular Pathology guidelines*. This has been performed for BrS led by **Michael Gollob and co-workers**.

The result is that 20 of the 21 genes identified as being causative of the disease have been reclassified as ***disputed*** with regards to any assertions of disease causality.

Circulation. 2018 Jun 29. pii: CIRCULATIONAHA.118.035070. doi: 10.1161/CIRCULATIONAHA.118.035070. [Epub ahead of print]

Reappraisal of Reported Genes for Sudden Arrhythmic Death: An Evidence-Based Evaluation of Gene Validity for Brugada Syndrome.

Hosseini SM[1], Kim R[2], Udupa S[3], Costain G[4], Jobling R[5], Liston E[5], Jamal SM[4], Szybowska M[6], Morel CF[6], Bowdin S[5], Garcia J[7], Care M[8], Sturm AC[9], Novelli V[10], Ackerman MJ[11], Ware JS[12], Hershberger RE[13], Wilde AAM[14], Gollob MH[15]; NIH-Clinical Genome Resource Consortium.

Author information

Abstract

Background -Implicit in the genetic evaluation of patients with suspected genetic diseases is the assumption that the genes evaluated are causative for the disease based on robust scientific and statistical evidence. However, in the past 20 years considerable variability has existed in the study design and quality of evidence supporting reported gene-disease associations raising concerns of the validity of many published disease-causing genes. Brugada syndrome (BrS) is an arrhythmia syndrome with a risk of sudden death. More than 20 genes have been reported to cause BrS and are assessed routinely on genetic testing panels in the absence of a systematic, evidence-based evaluation of the evidence supporting the causality of these genes. ***Methods*** -We evaluated the clinical validity of genes tested by diagnostic laboratories for BrS by assembling three gene curation teams. Using an evidence-based semi-quantitative scoring system of genetic and experimental evidence for gene-disease associations, curation teams independently classified genes as demonstrating Limited, Moderate, Strong or Definitive evidence for disease causation in BrS. The classification of curator teams was reviewed by a Clinical Domain Expert Panel who could modify the classifications based on their independent review and consensus. ***Results*** -Of 21 genes curated for clinical validity, biocurators classified only 1 gene (*SCN5A*) as Definitive evidence, while all other genes were classified as Limited evidence. Following comprehensive review by the Clinical Domain Expert Panel, all 20 genes classified as Limited evidence were re-classified as Disputed in regards to any assertions of disease causality for BrS. ***Conclusions*** -Our results contest the clinical validity of all but one gene clinically tested and reported to be associated with BrS. These findings warrant a systematic, evidence-based evaluation for reported gene-disease associations prior to use in patient care.

Hosseini et al. Circulation 2018

Genetic basis and molecular mechanism for idiopathic ventricular fibrillation

Qiuyun Chen, Glenn E. Kirsch, Danmei Zhang, Ramon Brugada, Josep Brugada, Pedro Brugada, Domenico Potenza, Angel Moya, Martin Borggrefe, Gunter Breithardt, Rocio Ortiz-Lopez, Zhiqing Wang, Charles Antzelevitch, Richard E. O'Brien, Eric Schulze-Bahr, Mark T. Keating, Jeffrey A. Towbin & Qing Wang

Ventricular fibrillation causes more than 300,000 sudden deaths each year in the USA alone. In approximately 5–12% of these cases, there are no demonstrable cardiac or non-cardiac causes to account for the episode, which is therefore classified as idiopathic ventricular fibrillation (IVF). A distinct group of IVF patients has been found to present with a characteristic electrocardiographic pattern. Because of the small size of most pedigrees and the high incidence of sudden death, however, molecular genetic studies of IVF have not yet been done. Because IVF causes cardiac rhythm disturbance, we investigated whether malfunction of ion channels could cause the disorder by studying mutations in the cardiac sodium channel gene *SCN5A*. **We have now identified a missense mutation, a splice-donor mutation, and a frameshift mutation in the coding region of *SCN5A* in three IVF families.** We show that sodium channels with the missense mutation recover from inactivation more rapidly than normal and that the frameshift mutation causes the sodium channel to be non-functional. Our results indicate that mutations in cardiac ion-channel genes contribute to the risk of developing IVF.

NATURE 392:294-296, 1998

Genetic Basis for Brugada Syndrome

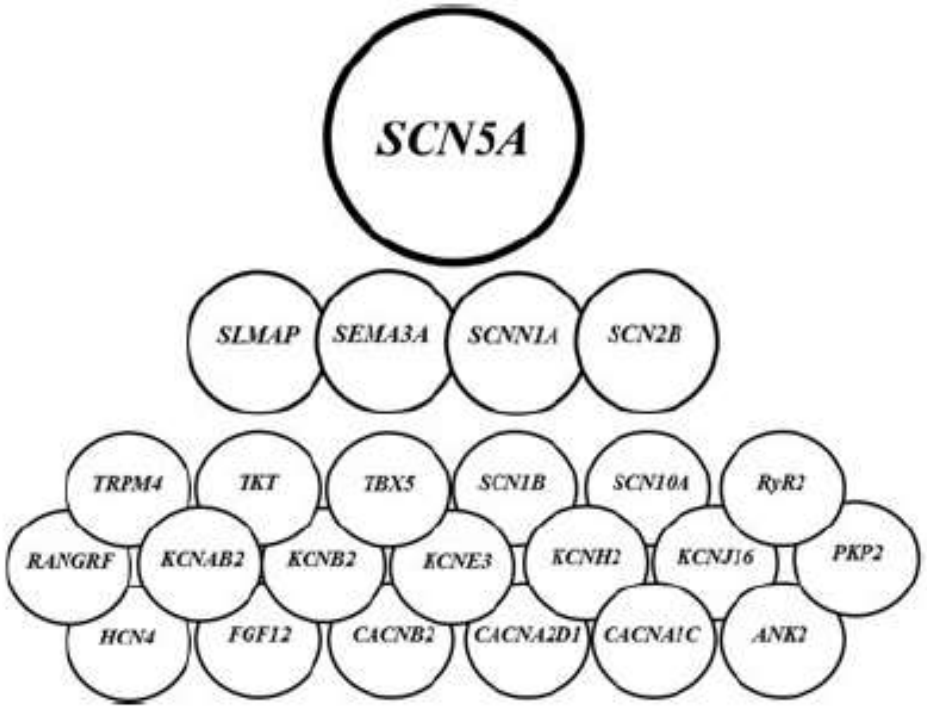
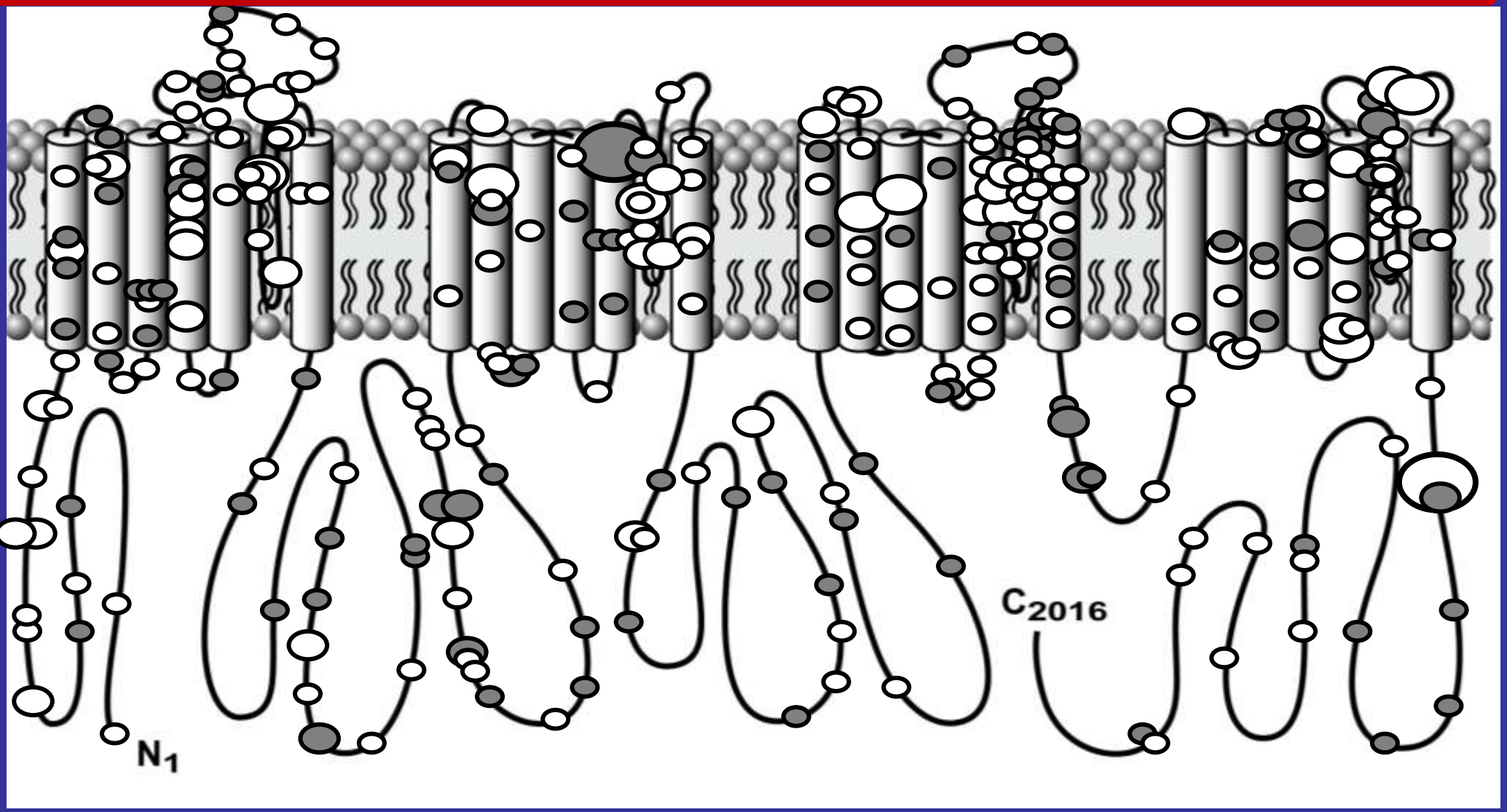


FIGURE 2 Identification of pathogenic and likely pathogenic genes for BrS following ACMG/AMP guidelines. In addition to *SCN5A*, the main gene associated with BrS, 23 other minor genes carry at least one pathogenic or/and likely pathogenic rare variant for BrS. ACMG/AMP: American College of Medical Genetics and Genomics/Association for Molecular Pathology; BrS: Brugada syndrome

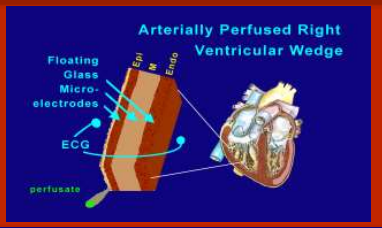
Campuzano et al.- Human Mutation 2019

Worldwide Brugada Syndrome Consortium
Genetic screening of 2111 BrS patients at 9 international centers
293 SCN5A Mutations



Kapplinger ... Ackerman. Heart Rhythm, 2009

ST Segment Elevation and Phase 2 Reentry Following *Combined I_{Na} and I_{Ca} Block*



A Control

B Terfenadine (5 μM)

C Terfenadine

D Terfenadine

Endo

Epi 2

Epi 1

ECG

TDR

EDR

50 mV

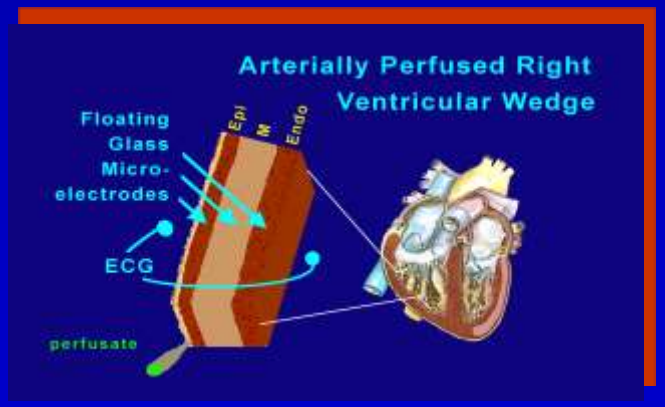
1 mV

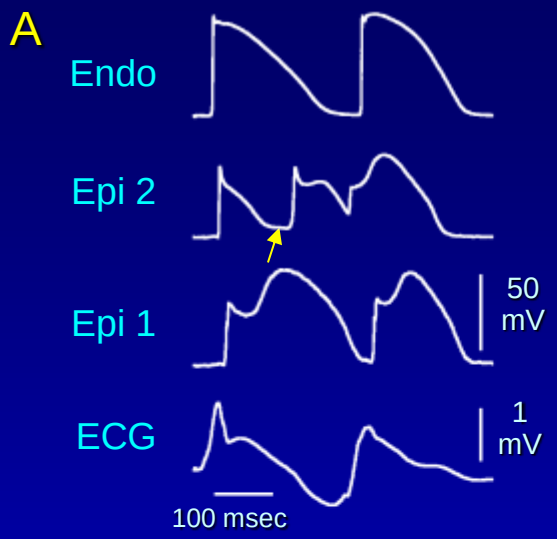
100 msec

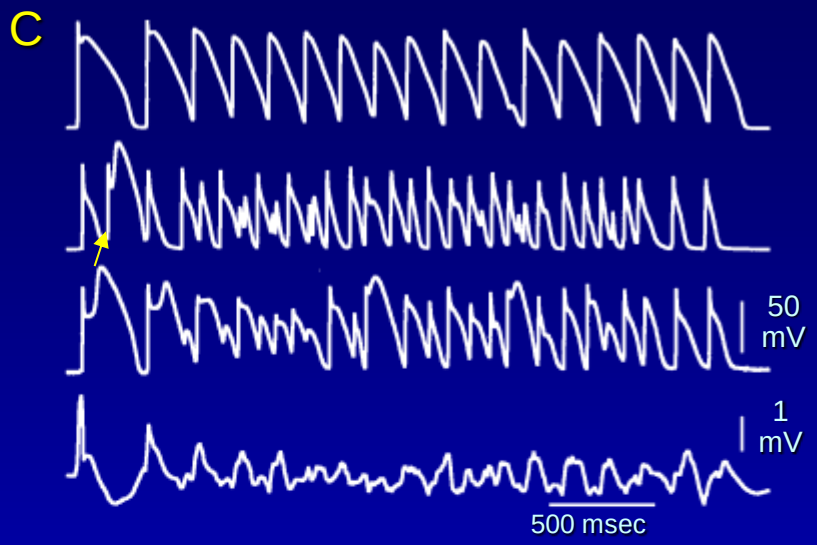
Fish and Antzelevitch, Heart Rhythm1:210-217, 2004

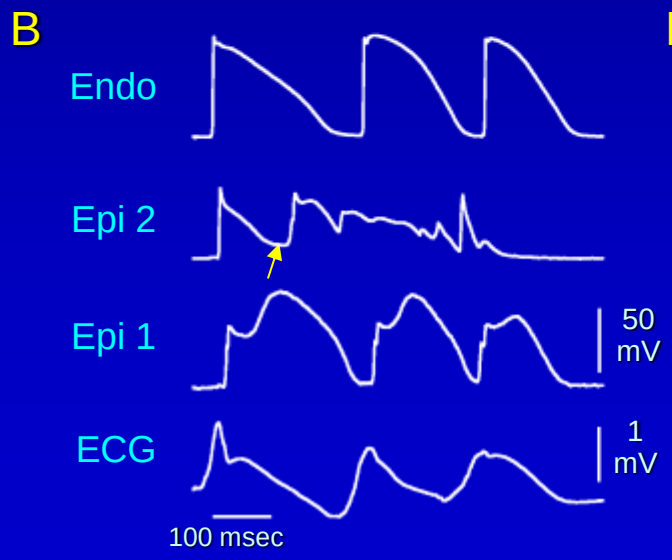
Terfenadine-induced VT/VF

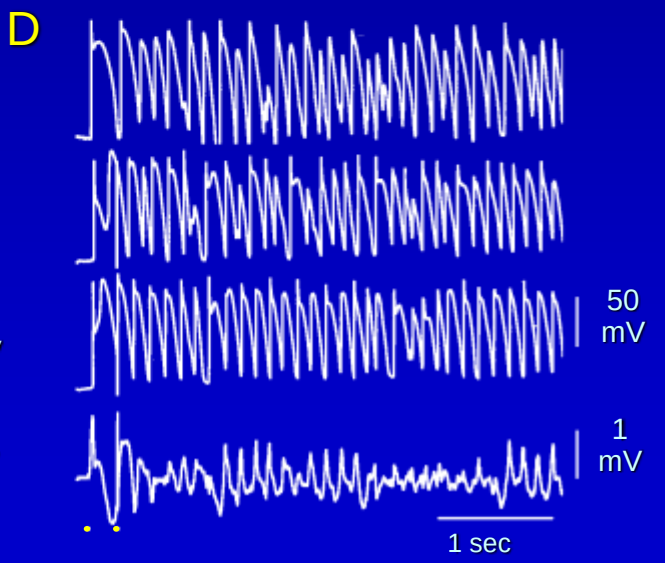
Brugada Syndrome





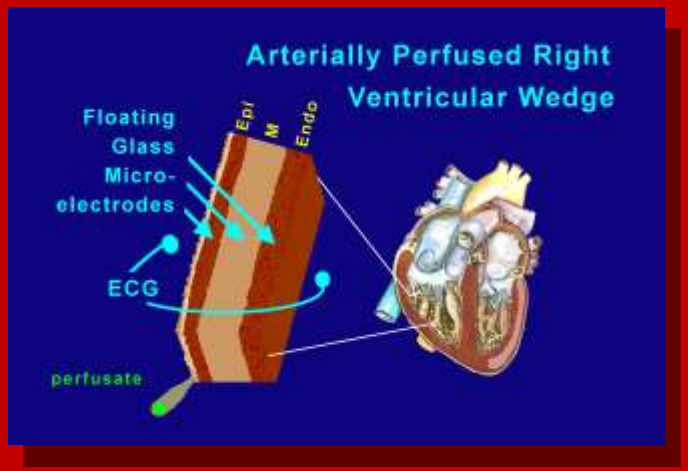




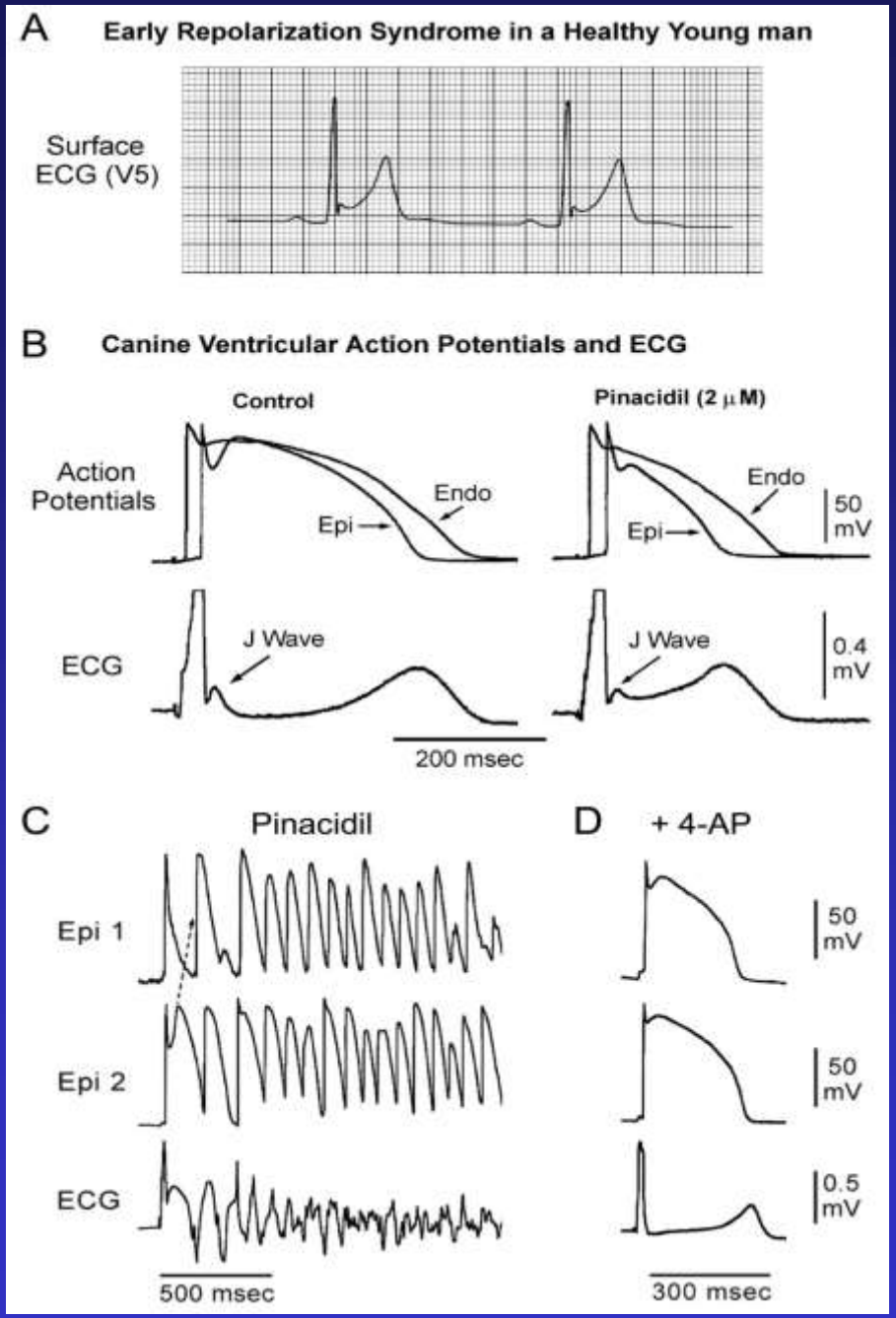


Fish and Antzelevitch, Heart Rhythm1:210-217, 2004

Early Repolarization Pattern Predisposes to Development of Polymorphic VT/VF via a Brugada Syndrome-like Mechanism



Yan an Antzelevitch, Circulation, 1999
Gussak and Antzelevitch, J Electrocardiol, 2000



Antzelevitch and Yan, Heart Rhythm7:549-58, 2010

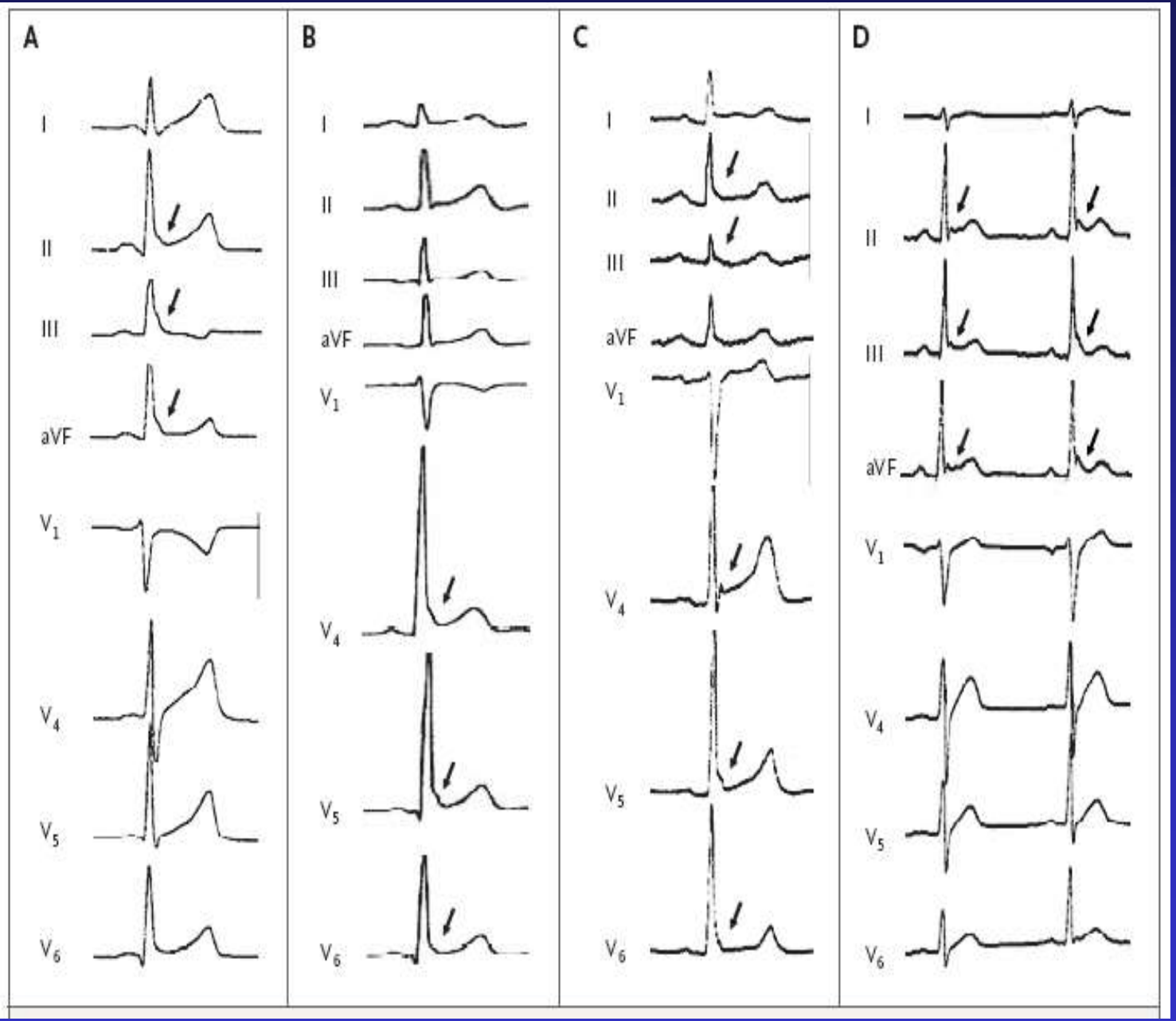
Early Repolarization Pattern and SCD

31% of IVF

vs.

5% of Controls

ER was defined as QRS-ST junction elevation of > 0.1 mV manifested as QRS slurring or notching

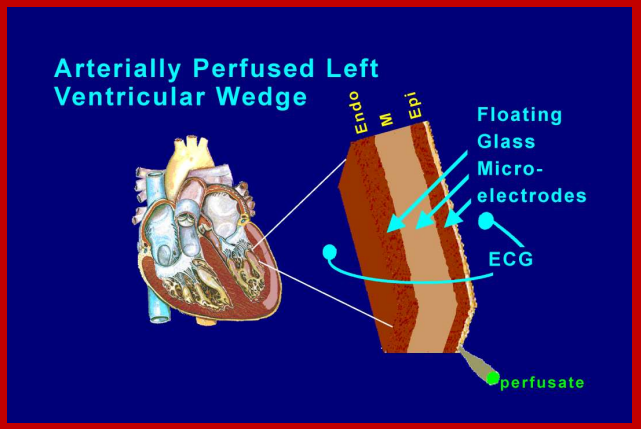


Haïssaguerre et al., N Engl J Med 358:2016-23, 2008

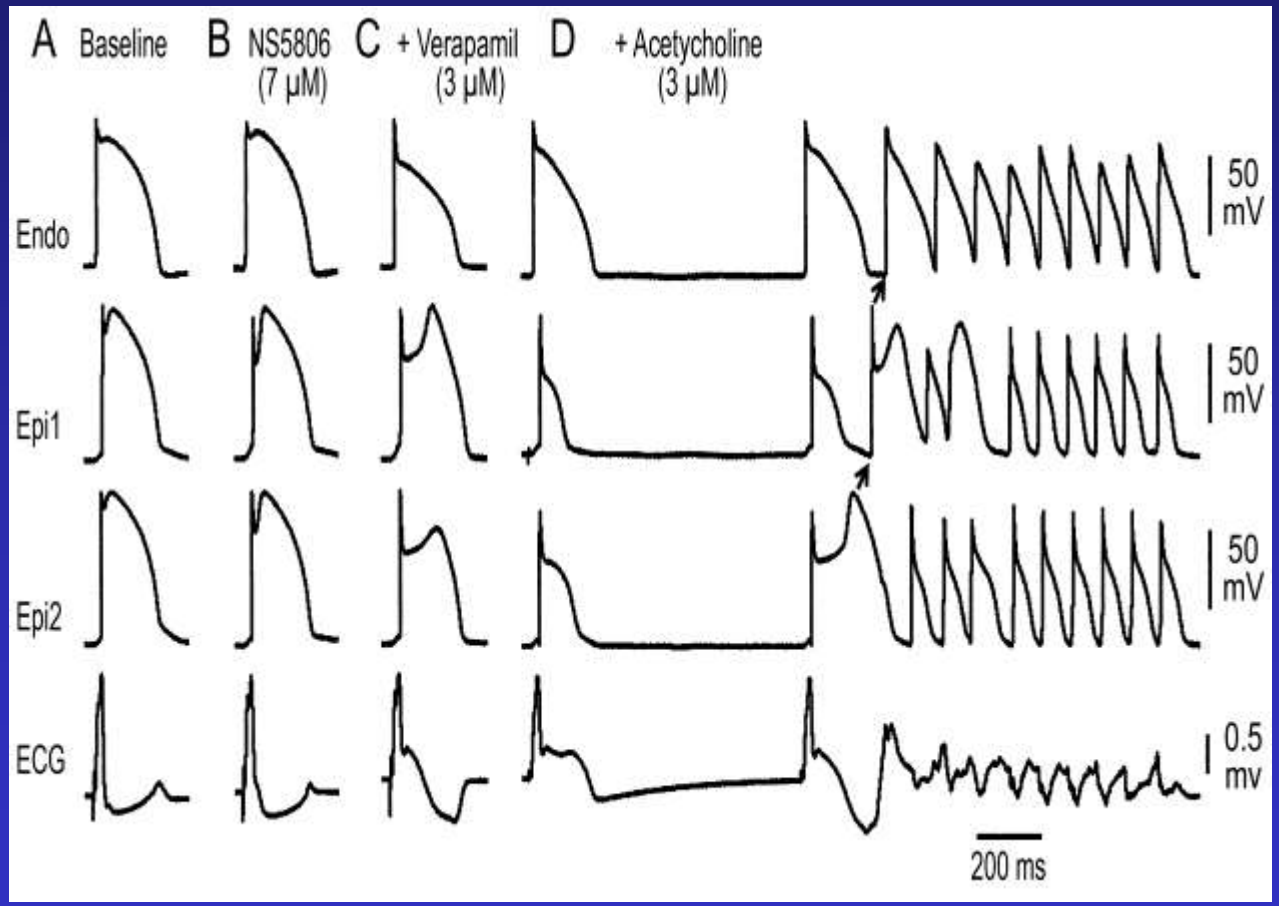
Genetic Basis for Early Repolarization Syndrome

	Locus	Ion Channel	Gene/Protein	% of Probands
ERS1	12p11.23	↑ $I_{K\text{-}ATP}$	*KCNJ8, Kir6.1*	
ERS2	12p13.3	↓ I_{Ca}	*CACNA1C*,$Ca_V1.2$	4.1%
ERS3	10p12.33	↓ I_{Ca}	*CACNB2b*, $Ca_v\beta_{2b}$	8.3
ERS4	7q21.11	↓ I_{Ca}	*CACNA2D1*, $Ca_v\alpha 2d$	4.1%
ERS5	12p12.1	↑ $I_{K\text{-}ATP}$	*ABCC9, SUR2A*	
ERS6	3p21	↓ I_{Na}	*SCN5A*, $Na_V1.5$	
ERS7	3p22.2	↓ I_{Na}	*SCN10A*, $Na_V1.8$	

Cellular Basis for Vagally-mediated potentiation of Early Repolarization Syndrome Phenotype



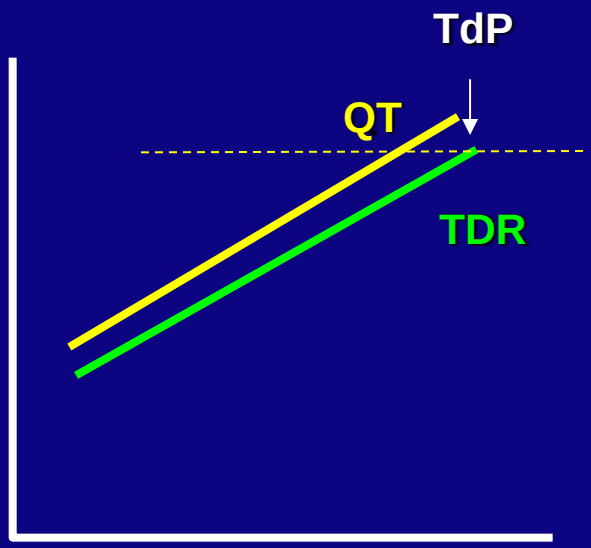
Pharmacologic modeling of I_{CA} loss of function mutations (CACNA1C, CACNB2, CACNA2D1)



Koncz….Antzelevitch, J Mol Cell Cardiol. 68:20-8, 2014

Polymorphic VT (PVT)

Long QT Syndrome

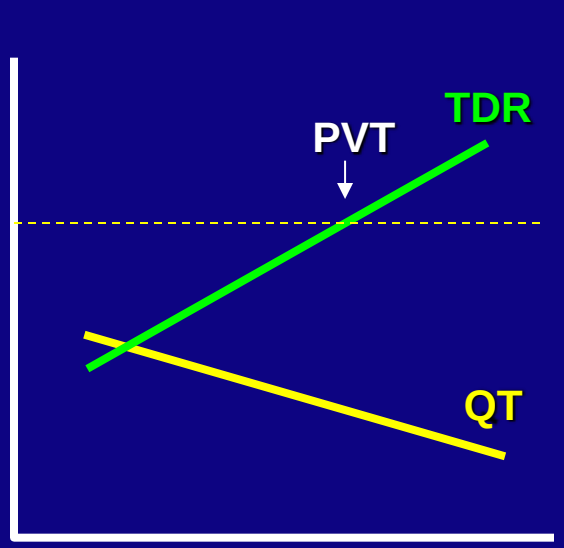


[Drug]
[Disease]

$\downarrow I_{Kr}$, I_{Ks}, I_{K1}, $I_{K\text{-}ACh}$,
$\uparrow I_{Na}$, I_{to}, $I_{K\text{-}ATP}$

Dofetilide
Sotalol, Quinidine

Short QT Syndrome

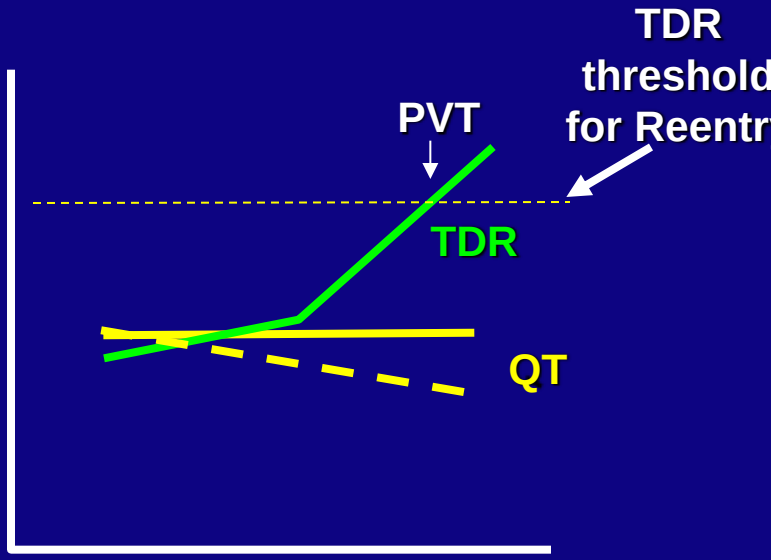


[Drug]
[Disease]

$\uparrow I_{Kr}$, I_{Ks}, I_{K1}
$\uparrow I_{K\text{-}ATP}$, $\downarrow I_{Ca}$

Pinacidil
Digitalis

J Waves Syndromes BrS, ERS



[Drug]
[Disease]

$\downarrow I_{Na}$, I_{Ca}
$\uparrow I_{K\text{-}ATP}$, $I_{K\text{-}ACh}$

Ajmaline, Procainamide

Action Potential Studies

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Perfused Wedge Studies

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Voltage Clamp Studies

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HRS/EHRA Consensus Statement
(Ackerman et al., Europace 2011)
Expert Consensus Recommendations

Section # - Disease	Diagnostic	Prognostic	Therapeutic
Section I - LQTS	+++	+++	++
Section III – BrS	+	+	-
Section V – SQTS	+/-	-	- (+)
– ERS	+	?	-

- *Relative strength (- = negligible to +++ = strong) of the contribution/impact of the genetic test for diagnosis, prognosis and choice of therapy.*

- **Identification of causative mutations in the proband is important in that it permits the identification of family members who may be at risk and who may require close clinical follow-up.**