Exercise and Sports in Pediatric and Congenital Cardiovascular Conditions

Beyond Beta-blockers: Moving to Gene-specific Therapies for Channelopathies

Maully Shah, MBBS, FACC, FHRS, CCEP, CCDS

Director, Cardiac Electrophysiology, CHOP

Professor of Pediatrics

University of Pennsylvania School of Medicine

Children's Hospital of Philadelphia℠
Cardiac Center

Perelman School of Medicine
University of Pennsylvania

Cardiology 2018

February 22, 2018

Cardiology 2018

21st Annual Update on Pediatric and Congenital Cardiovascular Disease

EFFECTIVE TEAMS, IMPROVING OUTCOMES

Cardiac Channeloathies in 2018

- Long QT Syndrome
- Catecholamine sensitive Polymorphic Ventricular Tachycardia
- Brugada Syndrome
- Short QT syndrome
- Early Repolarization syndrome

Uninterrupted use of Beta Blockers is the Primary Treatment..

+ Genotye specific therapies

for LQTS as well as CPVT

LQTS

I 

Beta-blockers are clinically indicated in LQTS, including those with a genetic diagnosis and normal QTc, unless there is a contraindication such as active asthma.

I 

Beta-blockers are recommended for patients with a diagnosis of LQTS who are asymptomatic with a QTc ≥ 470 msec.

II A 

Beta-blockers can be useful in patients with a diagnosis of LQTS who are asymptomatic with a QTc ≤ 470 msec.

HRS/EHRA/APHRS 2013, ACC/AHA/ HRS 2017

CPVT

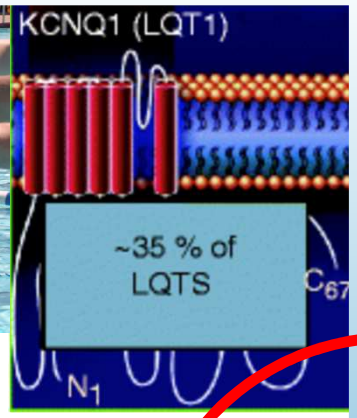
I 

Beta blockers are recommended in all patients with a clinical diagnosis of CPVT based on stress induced ventricular arrhythmias

II A 

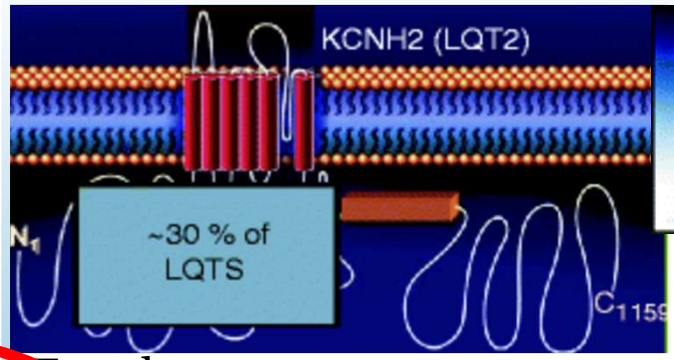
Therapy with beta blockers should be considered for gene positive family members even if they have a negative stress test

HRS/EHRA/APHRS 2013, ACC/AHA/ HRS 2017



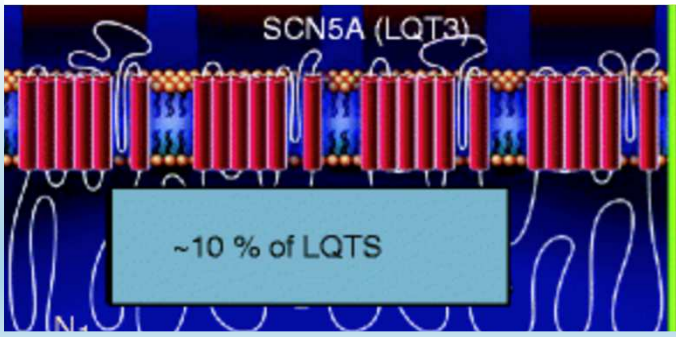
Males < 13 y ++
C loop region mutations ++
Exercise ++
Sleep/rest in females > 13 y++

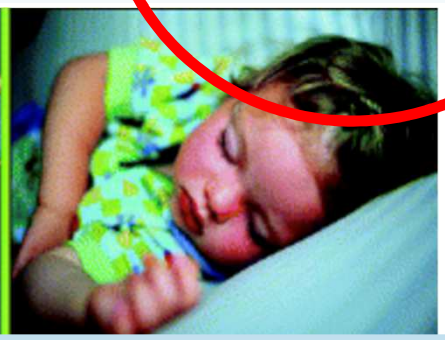
75%



Females > 15 y ++
Transmembrane Pore region ++
Auditory, sudden arousal ++
Post partum, pre-menopause period ++

Long QT Syndrome Genotype-Phenotype Correlations





Neonates 2:1 AV block++
ΔKP mutation++
Sleep/rest+

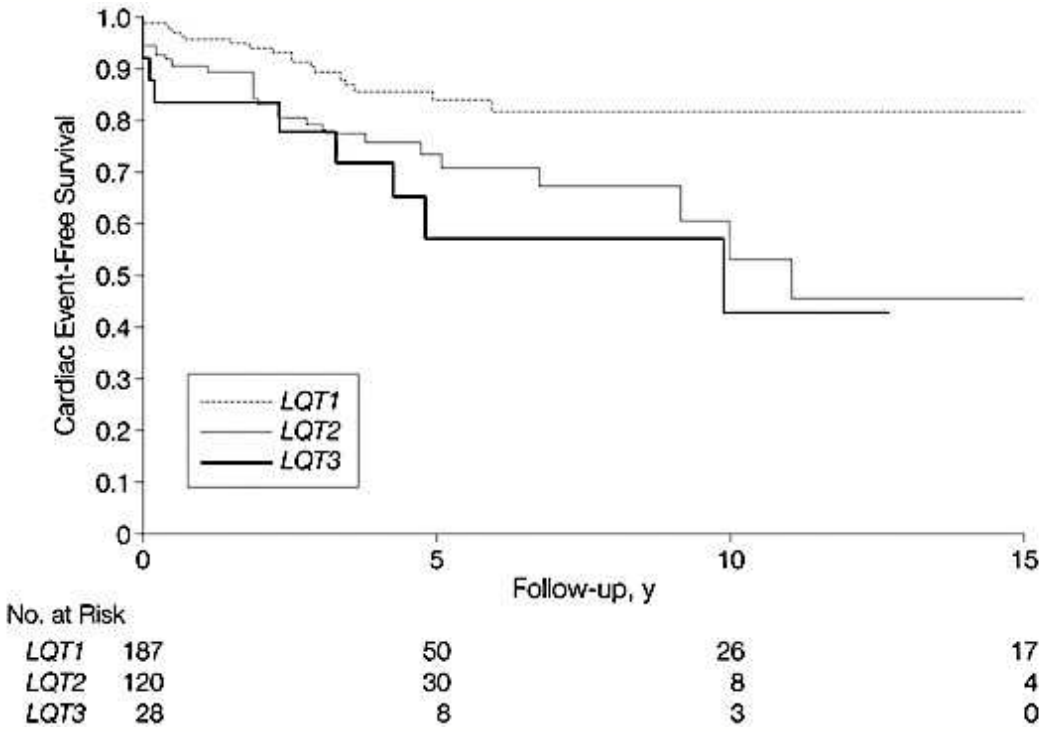
Remaining LQTS	Gene	Protein	Current
Type 4	Ankyrin B	Ankyrin	Na+/K+ ATPase and others
Type 5	KCNE1	MinK	Iks ↓
Type 6	KCNE2	MiRP1	Ikr ↓
Type 7	KCNJ2	Kir2.1	Ik1 ↓
Type 8	CACNA1C	CaV1.2	ICa-L ↑
Type 9	CAV3	Caveolin 3	INa ↑
Type 10	SCN4B	SCNβ4 subunit	INa ↑
Type 11	AKAP-9	Yotiao	Iks ↓
Type 12	SNTA-1	Syntrophin-α1	INa ↑
Type 13	KCNJ5	Kir3.4	IkAch ↓
Type 14	CALM1	Calmodulin 1	Defective Ca2+ signalling
Type 15	CALM2	Calmodulin 2	
Type 16	CALM3	Calmodulin 3	

Type 17 or CPVT3: Bi-allelic mutation in TECRL gene

Beta Blocker Response depends on the genotype

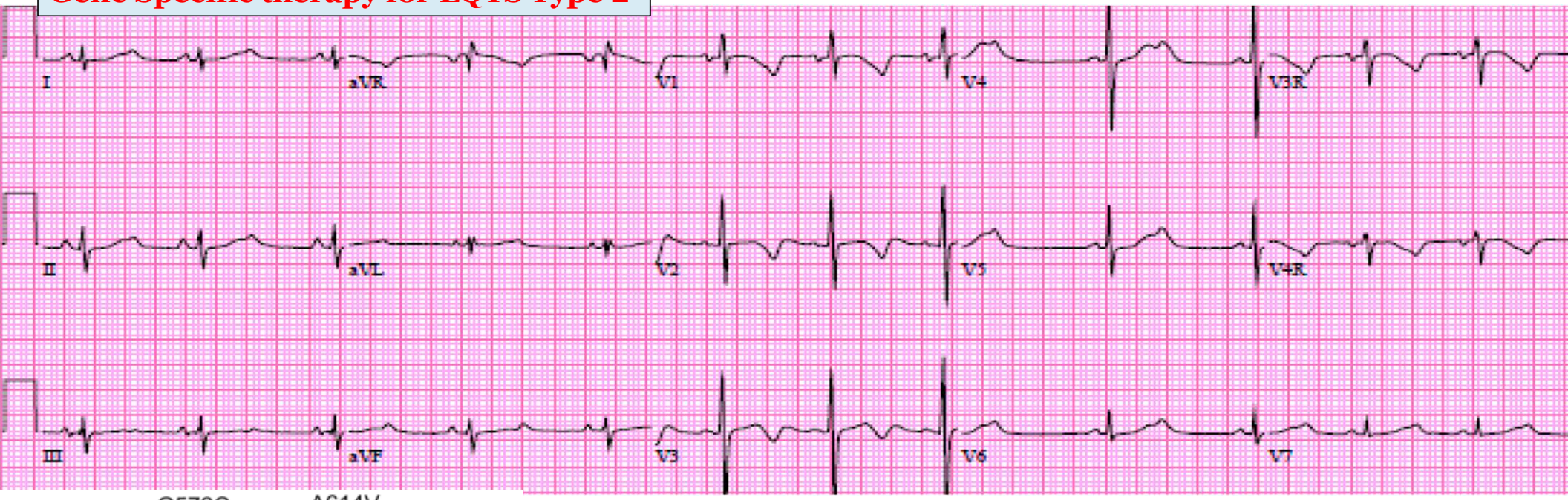
Cardiac events may occur particularly for patients with ***LQT2*** and ***LQT3*** genotypes despite β-blockers

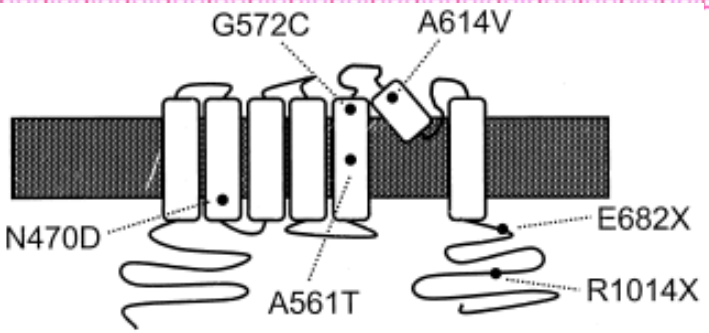
Genotype specific therapies



Priori, JAMA 2004

Gene Specific therapy for LQTS Type 2





Dysfunction of the hERG potassium channel - ↓ *I*Kr

↑ Serum K+ and extracellular K+ → ↑ Ikr

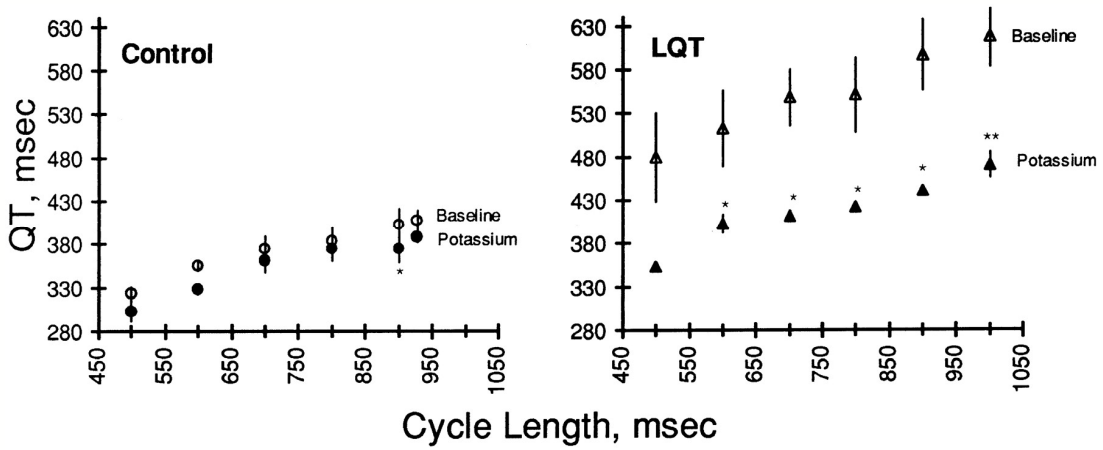
Oral potassium improves repolarization in patients with **LQTS Type 2**

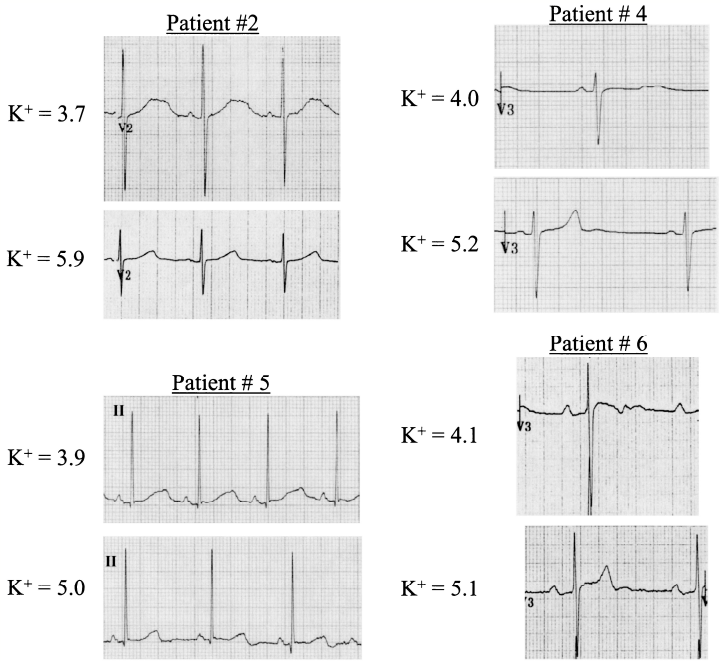
Genetically Defined Therapy of Inherited Long-QT Syndrome

Correction of Abnormal Repolarization by Potassium

Steve J. Compton, Robert L. Lux, Matthew R. Ramsey, Katie R. Strelich, Michael C. Sanguinetti, Larry S. Green, Mark T. Keating, Jay W. Mason

Effect of Potassium on Resting QT intervals and Morphology in Patients with LQT2

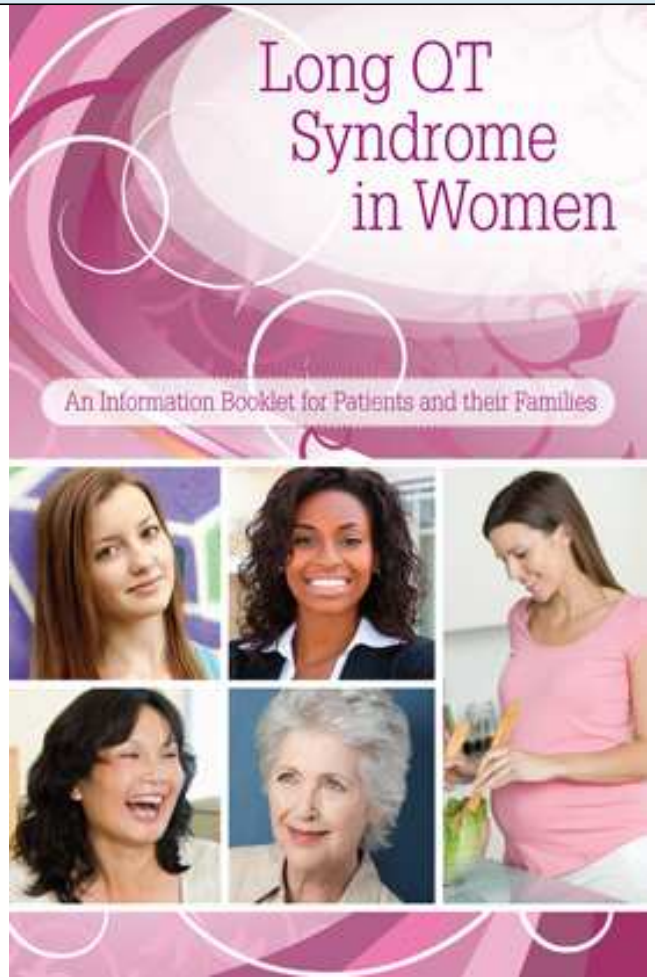




Compton et al. Circulation. 1996, Etheridge,et al JACC 3003

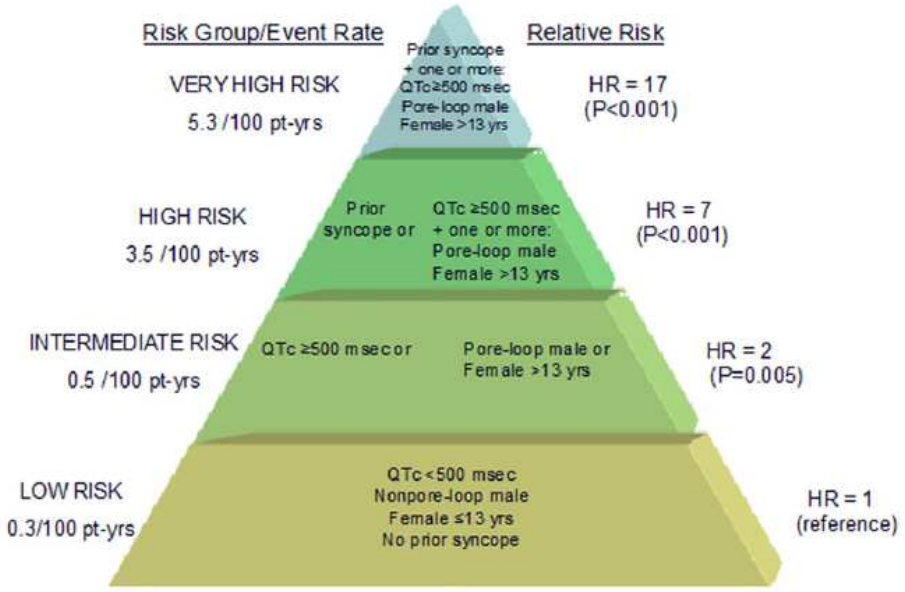
Patients given KCL and spironolactone to target serum K^+level 1.5 mEq/l above baseline

Gene Specific therapy for LQTS Type 2



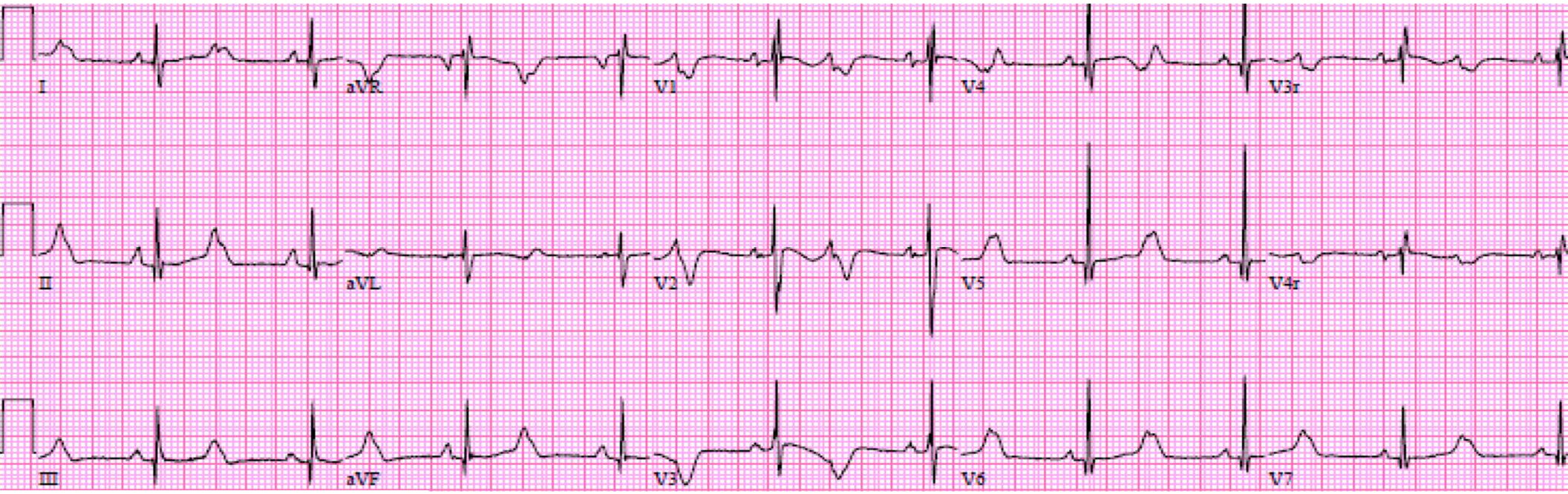
LQTS Type 2 females are at highest risk post puberty and post partum related to ↑ Estrogen

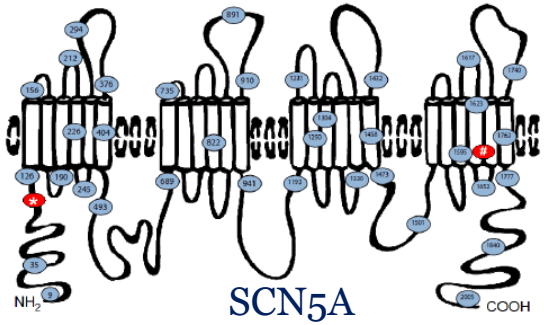
- Progesterone has protective effects against long QT–associated arrhythmias
- Avoid Estrogen only OCP



Nakamura, Circulation 2007

Gene Specific therapy for LQTS Type 3



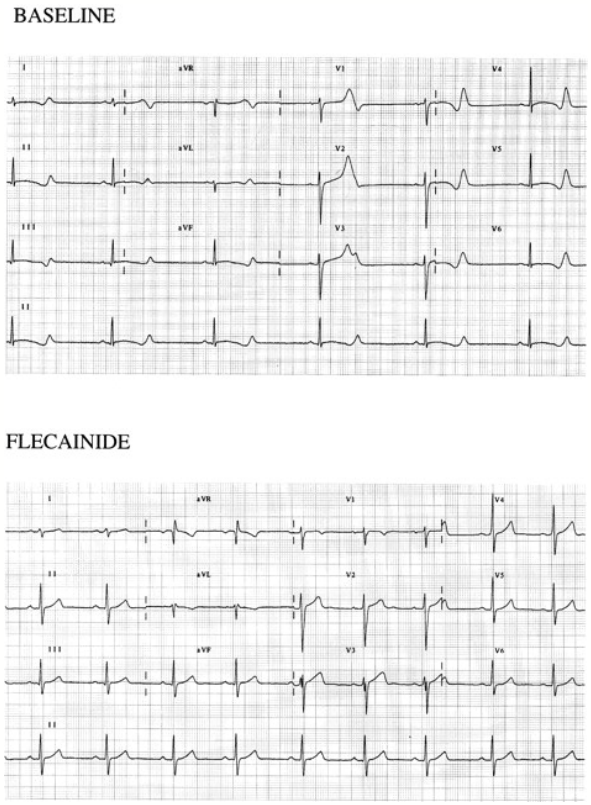


SCN5A

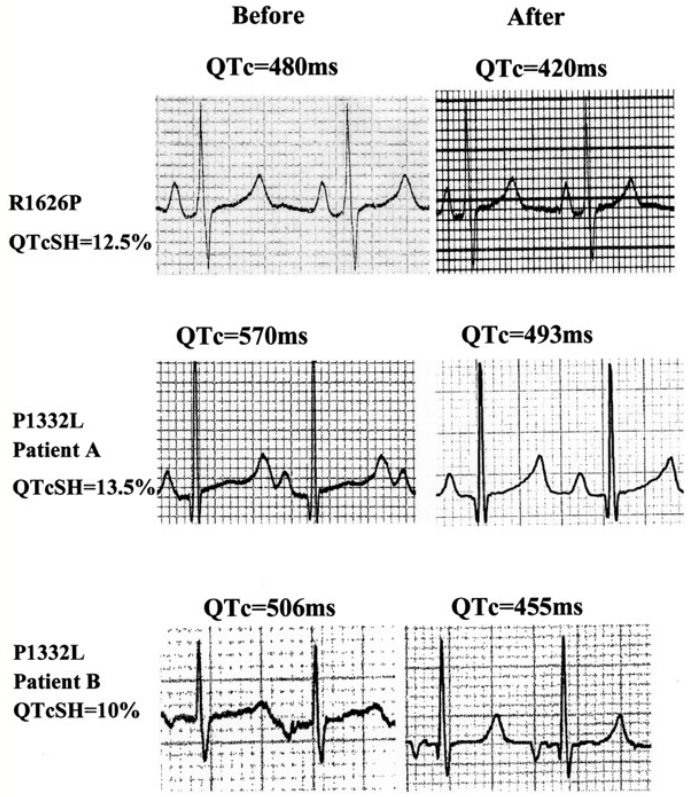
Dysfunction of Na Channel- ↑ INa

Na channel blocking agents could Attenuate I_{Na} in **LQTS Type 3**

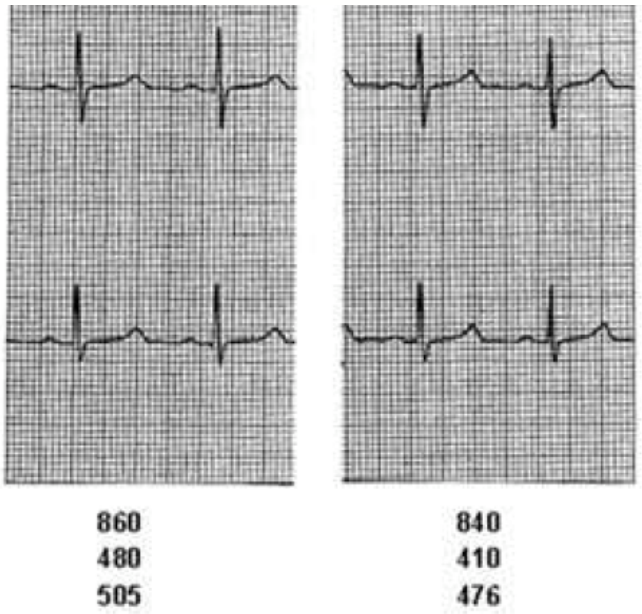
Flecainide (Class IC) in SCN5A D1790G mutation carrier



Mexiletine(Class IB) in specific mutation carriers

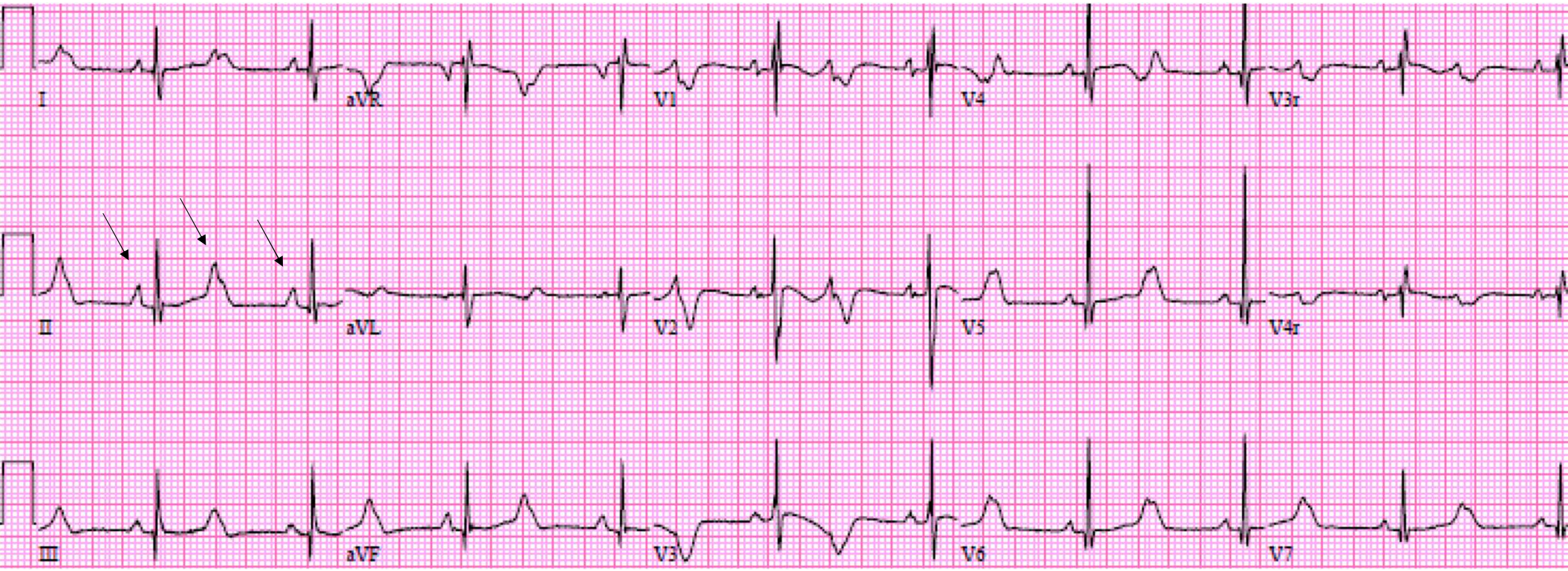


Ranolazine in SCN5A- Δ KP mutation carriers



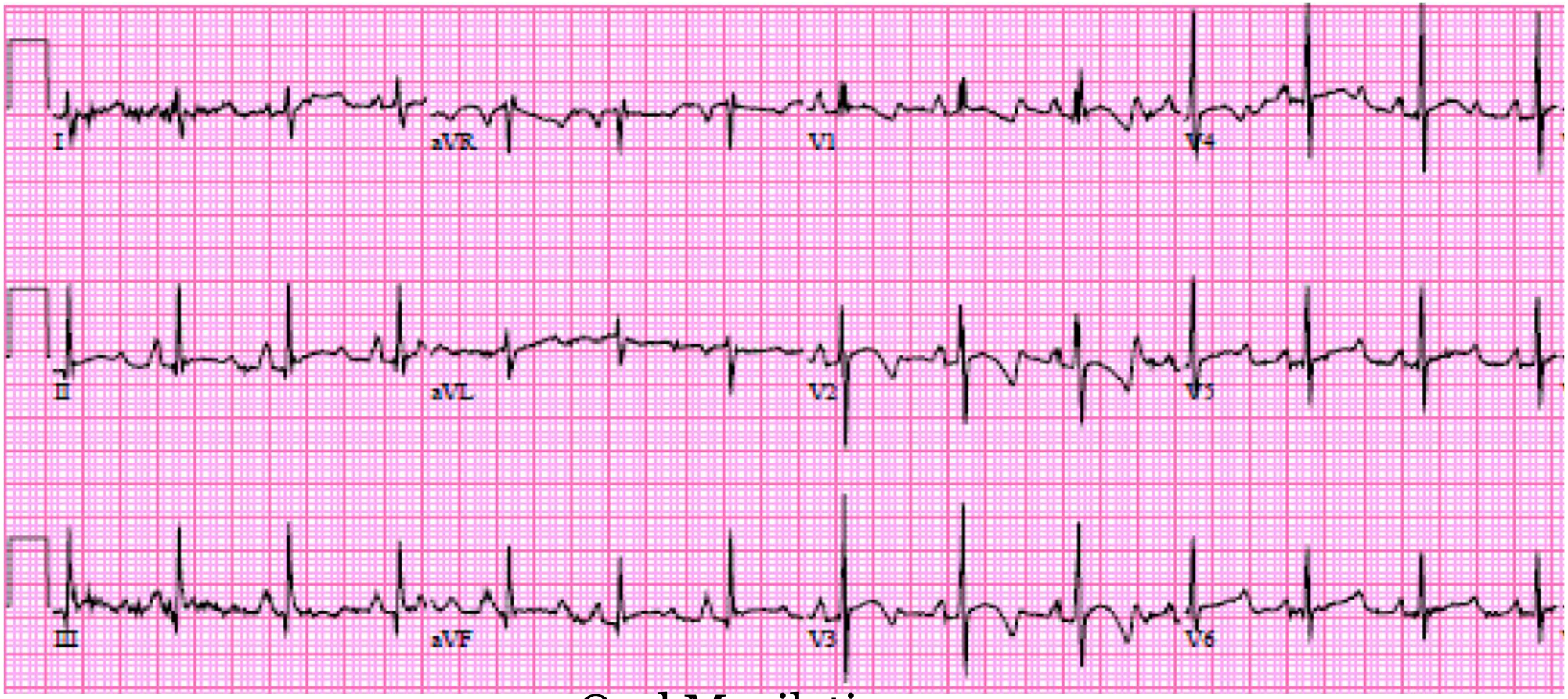
Ruan,Circulation. 2007, Benhorin, Circulation 2000, Schwartz, Circulation 1995, Moss, JCE 2008, Tan, Heart Rhythm 2017

24 month old with long QT syndrome 3 which resolved at 6 months of age and 2:1 AV block last week



QTc: 560 ms

Functional 2:1 AV block

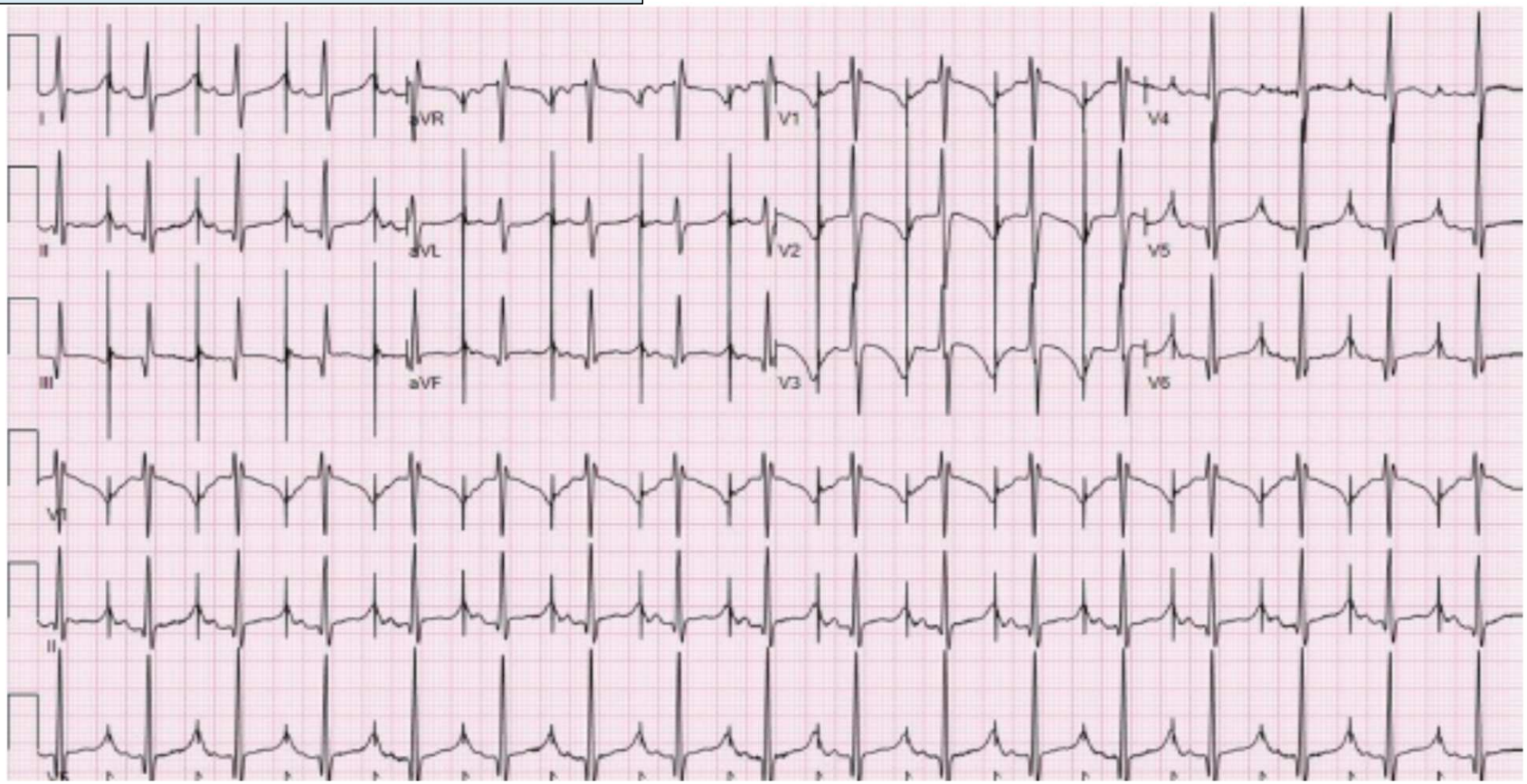


Oral Mexiletine:

QTc: 470 ms

1:1 AV conduction

Gene Specific therapy for LQTS Type 3



Increasing rate by Atrial Pacing Shortens the QT interval without sympathetic stimulation in LQT3

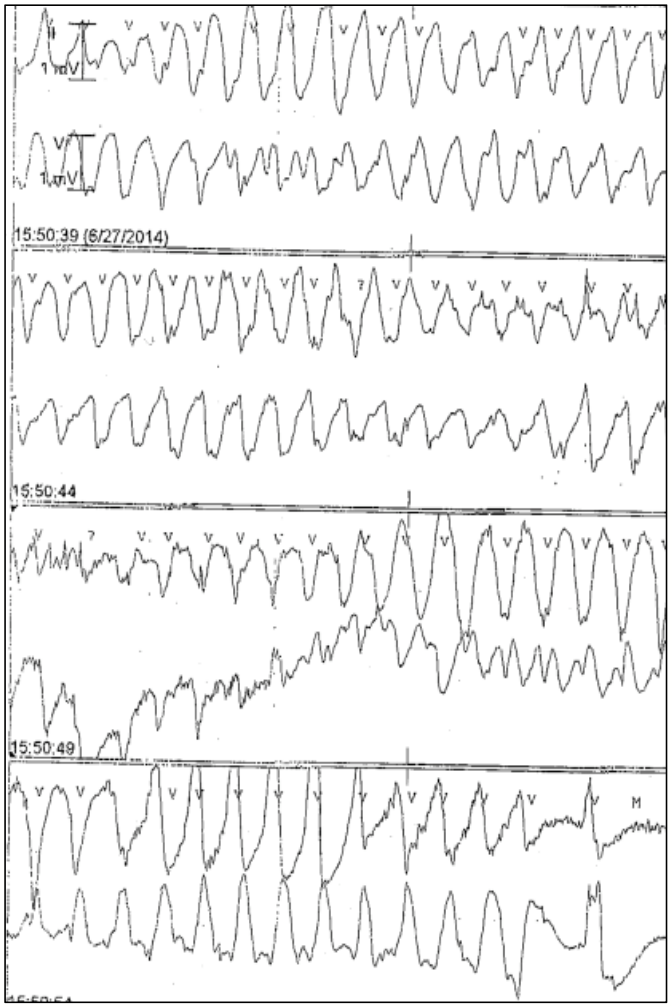
Gene Specific therapy for LQTS Type 3

Phenytoin as an effective treatment for polymorphic ventricular tachycardia due to QT prolongation in a patient with multiple drug intolerances

Neil Yager, Katherine Wang, Najiba Keshwani, Mikhail Torosoff

Class Ib anti-arrhythmic

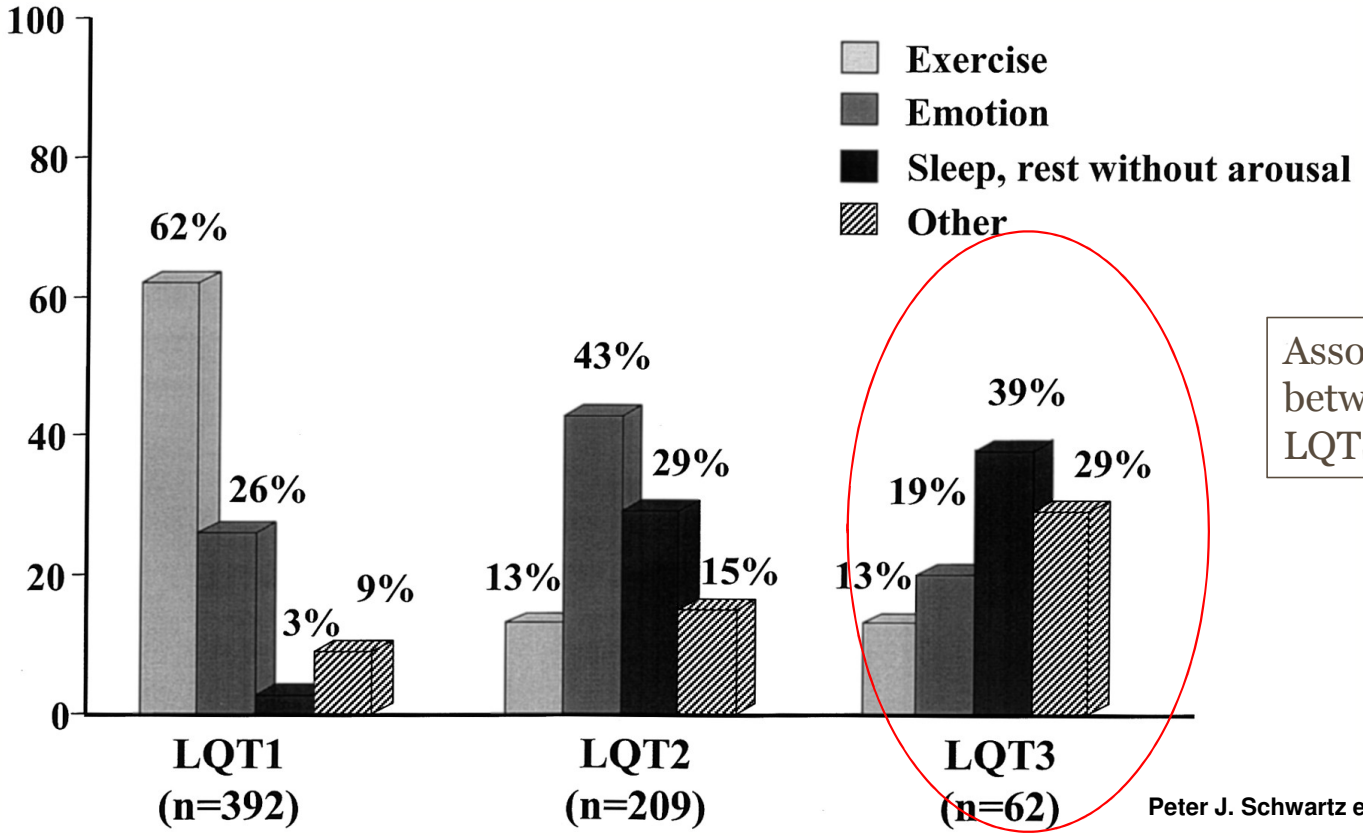
- Shortens action potential by inhibiting rapid inward I_{Na}
- ↓ I_{Ca2+}, reduces the rate of depolarization in the plateau phase of the action potential and increases the refractory period, thus preventing EADs



BMJ 2015

LIFESTYLE MANAGEMENT

Life Style Management in LQTS
Genotype Specific Triggers

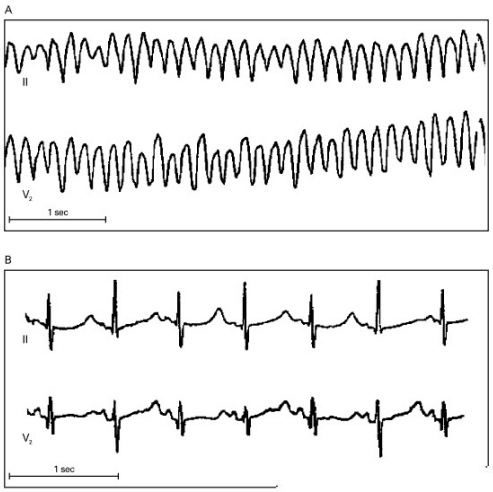


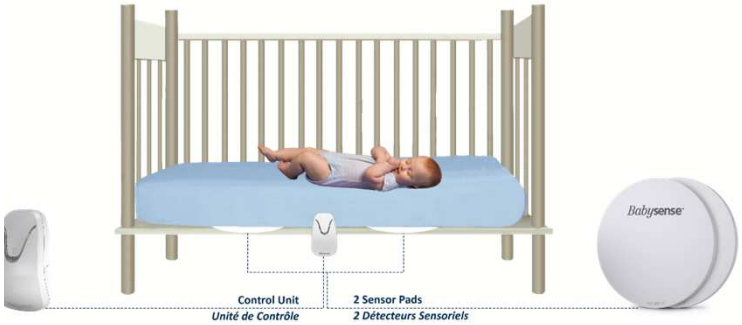
Association between SIDS and LQTS?

Peter J. Schwartz et al. Circulation. 2001;103:89-95

When Sleep is a trigger? How do you Reassure Parents?

Co-Sleeping?





Micro sensors?

Heart Rate Monitors?

AHA/ACC SCIENTIFIC STATEMENT

Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 10: The Cardiac Channelopathies 2015

Class I *(level of evidence C)*

Symptomatic athletes with any suspected or diagnosed cardiac channelopathy be restricted from all competitive sports until:

- ✓comprehensive evaluation has been completed by specialist
- ✓athlete and his or her family are well informed,
- ✓treatment program has been implemented,
- ✓athlete has been asymptomatic on therapy for 3 months

AHA/ACC SCIENTIFIC STATEMENT

2015

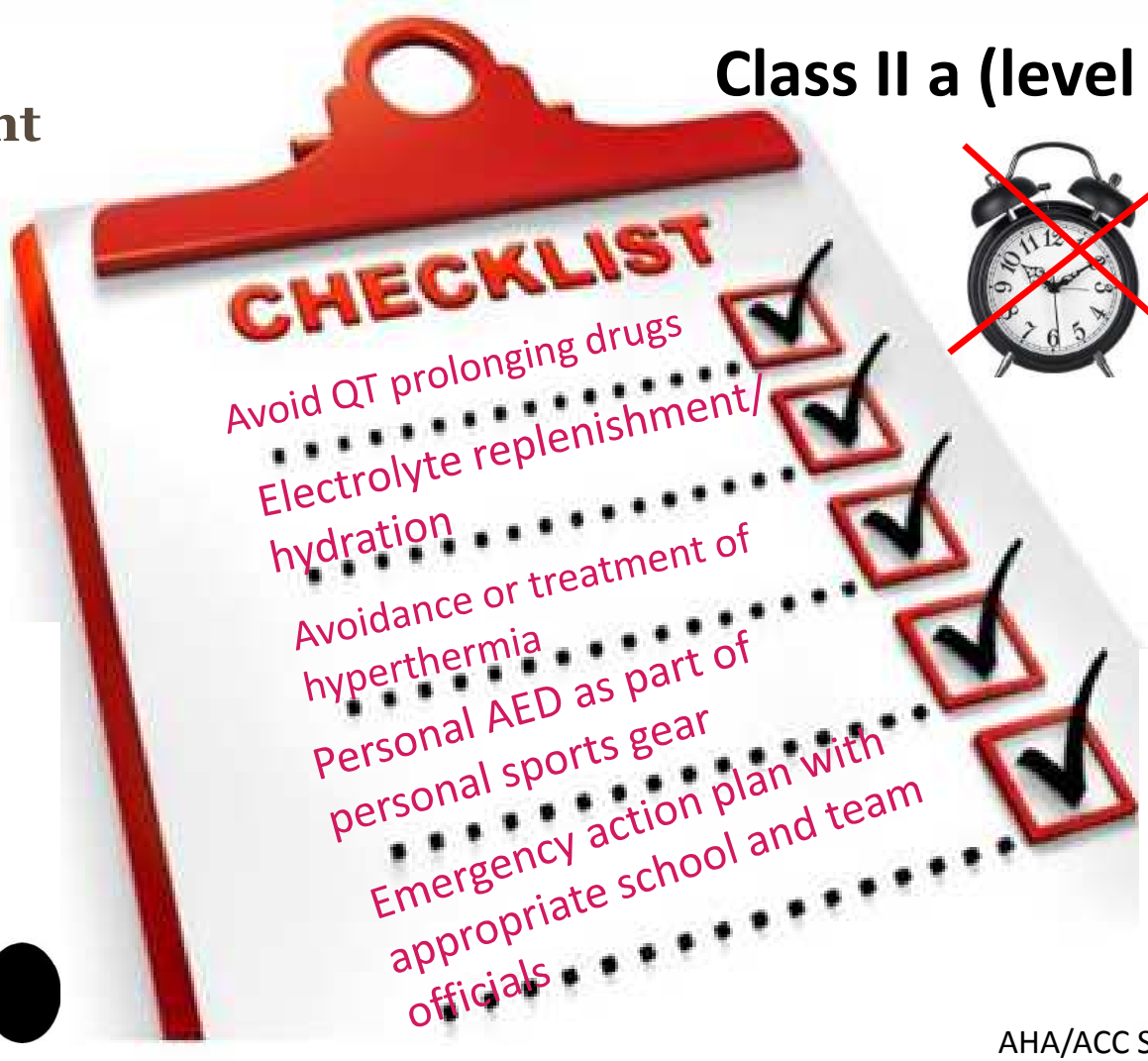
Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 10: The Cardiac Channelopathies

- Asymptomatic LQTS athletes (Genotype positive, phenotype negative) may participate in all competitive sports, **Class II a (LOC, C)**

- Competitive sports may be considered for an athlete with either previously symptomatic or ECG evidence of LQTS (> 470 ms in males, > 480 ms in females), **Class II b (LOC, C)**
  - ✓precautionary measures and disease specific treatments are in place and
  - ✓athlete is asymptomatic on treatment for at least 3 months
    - Except competitive swimming in previously symptomatic LQTS type I

Life Style Managemnt in LQTS

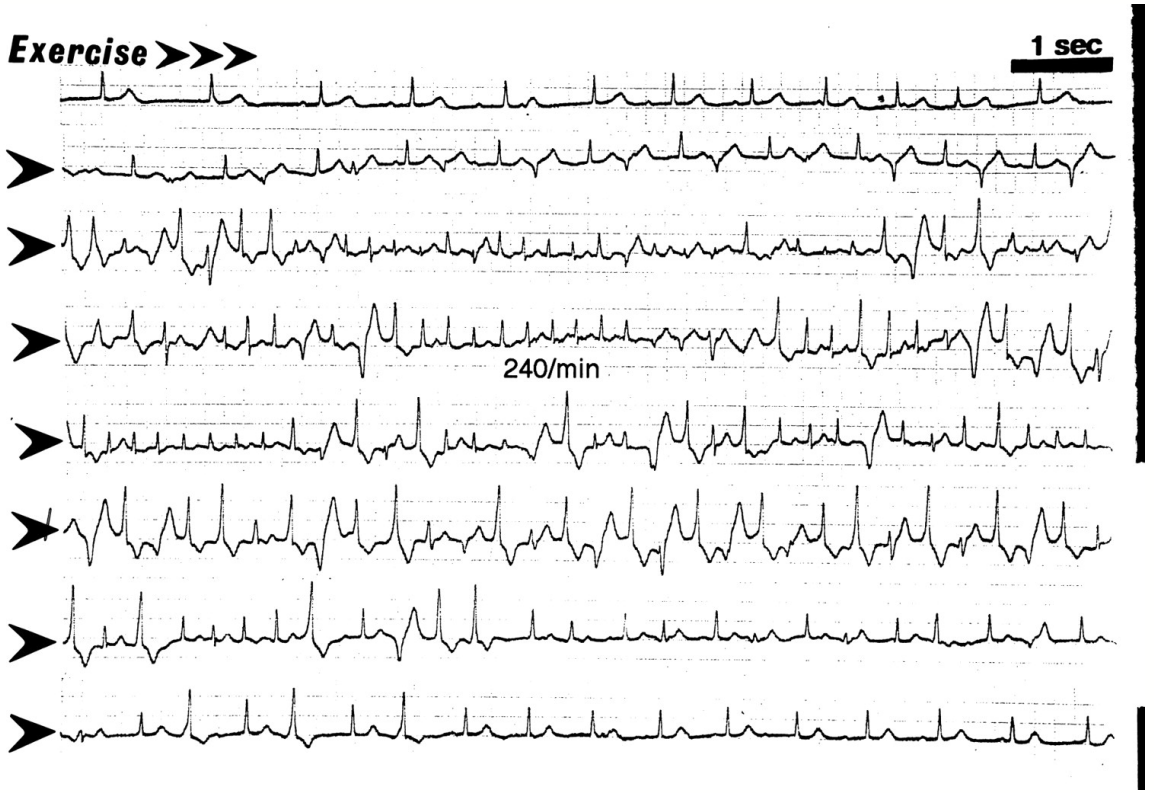
Class II a (level of evidence C)



AHA/ACC Statement Task Force 10, 2016

Catecholaminergic Polymorphic VT

- Affects young patients
- Baseline ECG is normal
- Exercise induced symptoms & ectopy
- Rx- beta blockers



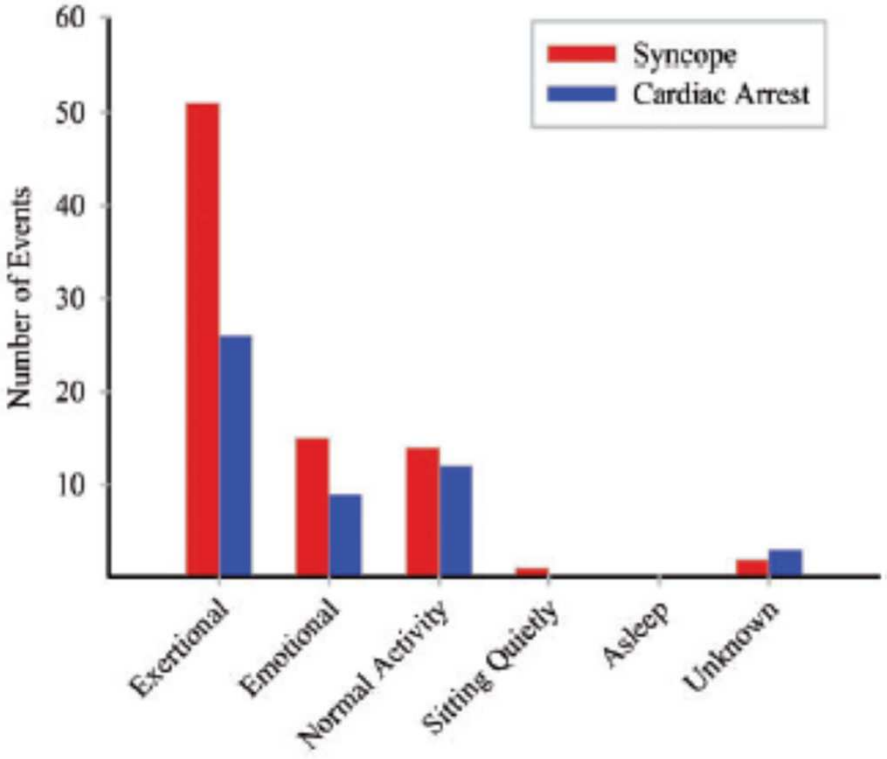
Leenhardt, A. et al. Circulation 1995;91:1512-1519

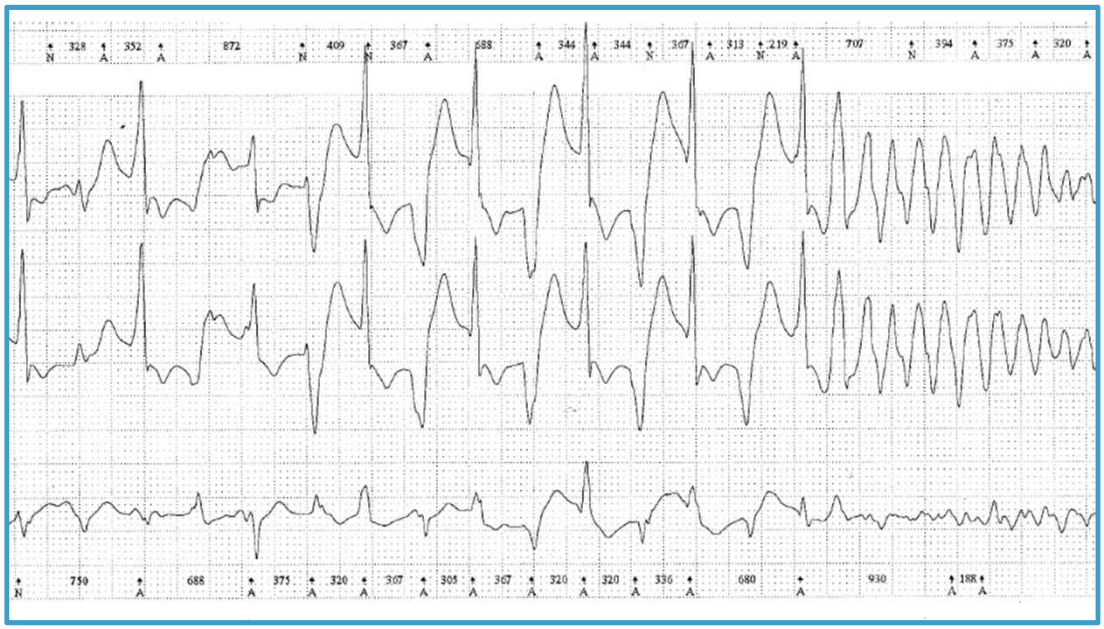
CPVT Genes

Name	Current	Gain/loss of function	Protein	Gene	
CPVT1	I_{rel}	Leak	RyR2	*RyR2*	65%
CPVT2	I_{rel}	Leak	Calsequestrin	*CASQ2*	3-5%
CPVT3	I_{K1}	Loss	Kir2.1	*KCNJ2*	
CPVT4	I_{NCX}, I_{NaK}, $InsP_3R$	Loss	Ankyrin-B	*ANKB*	

Priori et al., 2013; Leenhardt et al., 2012; Zumhagen et al., 2014

CPVT is a Lethal Disease: Baseline Risk is High

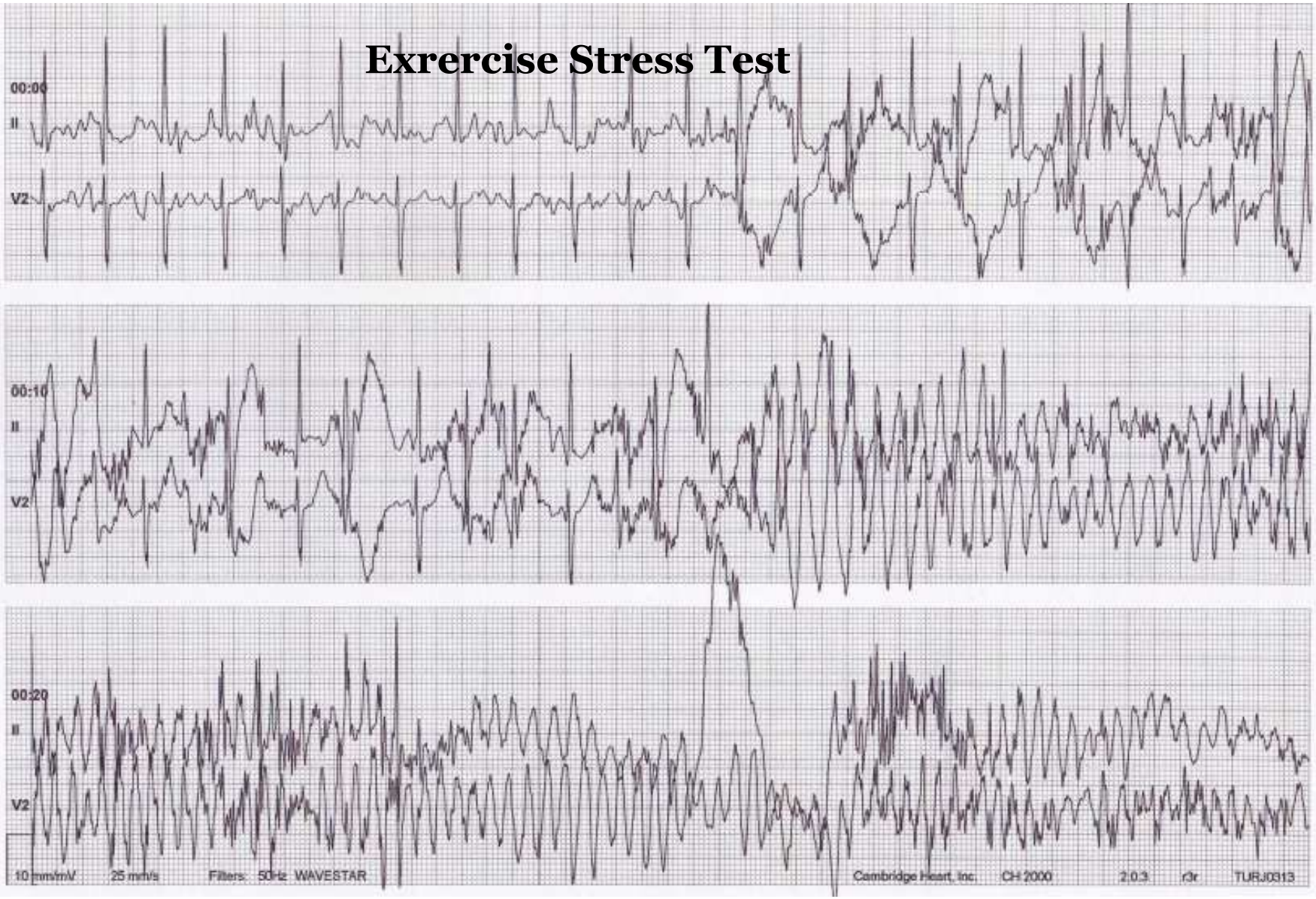


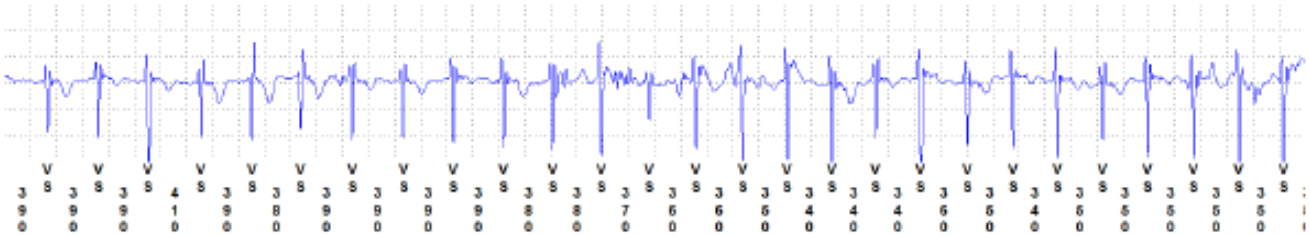


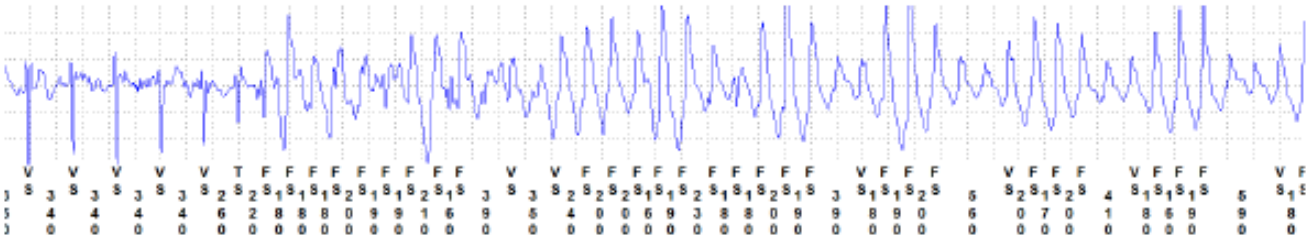
Holter recording of 8 year old boy with CPVT who was playing in the yard

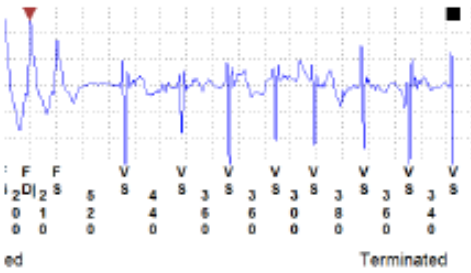
Roston et al, Europace 2017

Exrercise Stress Test







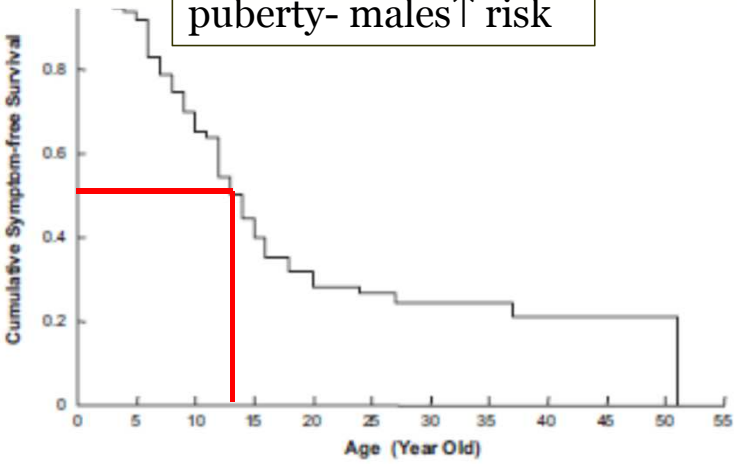


Tachy Detect

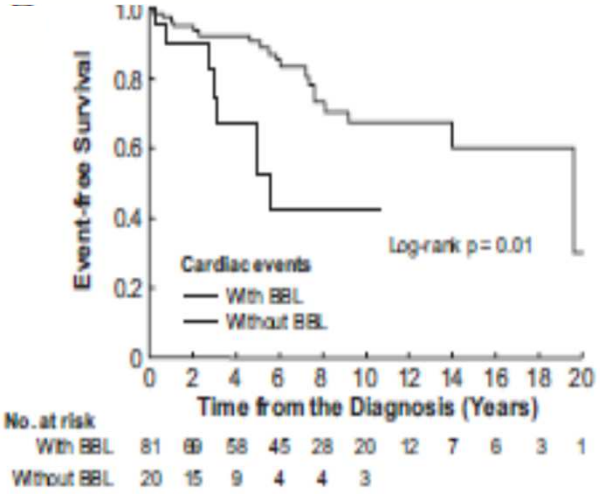
A Case of Nerves?

CPVT: Risk of Recurrent Events

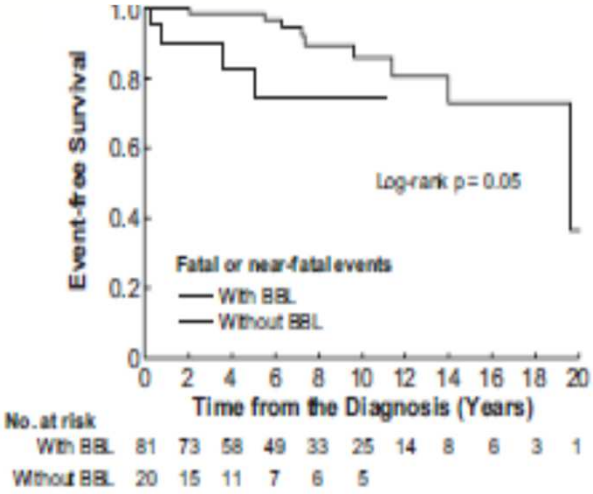
Pre- Diagnosis:
50% symptomatic by puberty- males↑ risk



Syncope with & without beta blockers



CA/ACA with & without beta blockers



- Estimated 8 year Cardiac event rate is 27% (with β blockers) and 52% (without β blockers)
- **β blockers are not 100% protective**

Hayashi, Circulation 2009

urnal of the American College of Cardiology
2006 by the American College of Cardiology Foundation
blished by Elsevier Inc.

Vol. 48, No. 5, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.07.010

CC/AHA/ESC PRACTICE GUIDELINES

ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death)
Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society

WRITING COMMITTEE MEMBERS

Douglas P. Zipes, MD, MACC, FAHA, FESC, *Co-Chair*
A. John Camm, MD, FACC, FAHA, FESC, *Co-Chair*

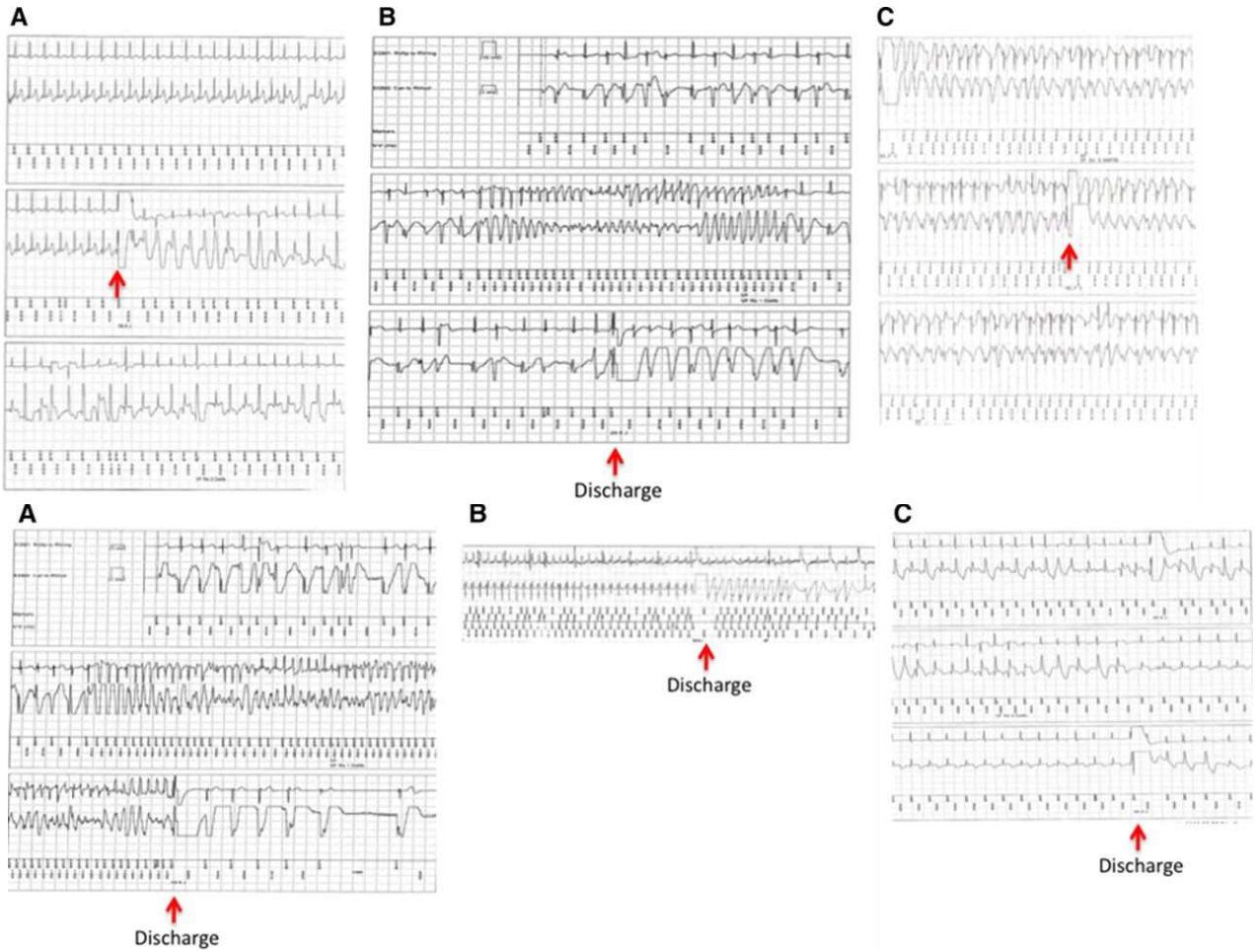
Martin Borggrefe, MD, FESC
Alfred E. Buxton, MD, FACC, FAHA
Bernard Chaitman, MD, FACC, FAHA
Martin Fromer, MD
Gabriel Gregoratos, MD, FACC, FAHA
George Klein, MD, FACC
Arthur J. Moss, MD, FACC, FAHA†
Robert J. Myerburg, MD, FACC, FAHA
Silvia G. Priori, MD, PHD, FESC*
Miguel A. Quinones, MD, FACC
Dan M. Roden, MD, CM, FACC, FAHA
Michael J. Silka, MD, FACC, FAHA
Cynthia Tracy, MD, FACC, FAHA

European Heart Rhythm Association Official Representative; †Heart Rhythm Society Official Representative

Class IIa

1. **Beta blockers can be effective in patients without clinical manifestations when the diagnosis of CPVT is established during childhood based on genetic analysis.** ***(Level of Evidence: C)***
2. **Implantation of an ICD with the use of beta blockers can be effective for affected patients with CPVT with syncope and/or documented sustained VT while receiving beta blockers and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***

ICD Treatment was successful for VF but not for Polymorhic VT and Bidirectional VT



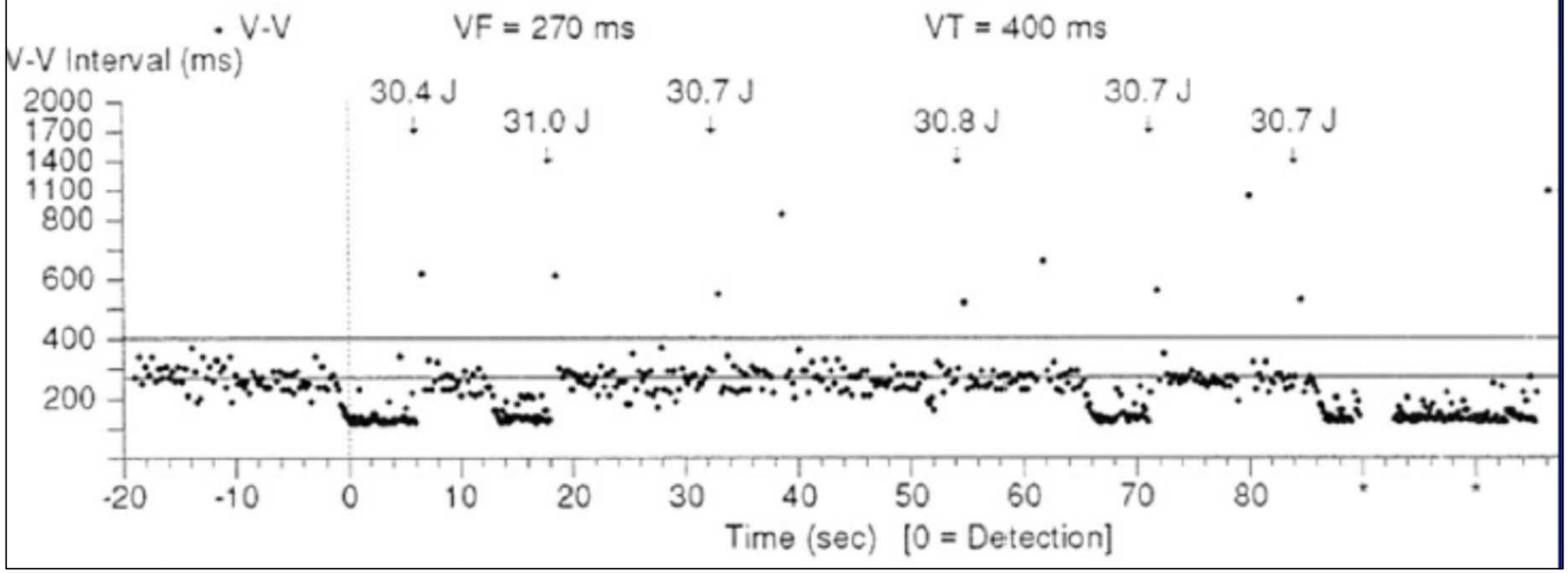
Christina Y. Miyake et al. Circ Arrhythm Electrophysiol.

Sudden cardiac death despite an implantable cardioverter-defibrillator in a young female with catecholaminergic ventricular tachycardia

Heart Rhythm 2006

Uwais Mohamed, MBBS,* Michael H. Gollob, MD,† Robert M. Gow, MB, BS,‡ Andrew D. Krahn, MD*

Date/Time	Type	V. Cycle	Last Rx	Success	Duration
Jan 11 09:15:58	VF	130 ms	VF Rx 6	No	14 min



Gene Specific therapy for CPVT 1 (RYR2)

Published in final edited form as:
Nat Med. 2009 April ; 15(4): 380–383. doi:10.1038/nm.1942.

Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans

Hiroshi Watanabe[1,5,6], **Nagesh Chopra**[1,6], **Derek Laver**[2,6], **Hyun Seok Hwang**[1], **Sean S Davies**[1], **Daniel E Roach**[3], **Henry J Duff**[3], **Dan M Roden**[1], **Arthur A M Wilde**[4], and **Björn C Knollmann**[1]

[1]Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA [2]School of Biomedical Sciences, University of Newcastle and Hunter Medical Research Institute, Callaghan, Australia [3]Libin Cardiovascular Institute, University of Calgary, Calgary, Alberta, Canada [4]Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Flecainide directly and indirectly affects RYR2 receptor and prevents premature sarcoplasmic reticulum release of Ca2+ into myocytes

Management of CPVT
In addition to Beta Blockers…
Flecainide is second line treatment

Class IIa

- Flecainide can be a useful addition to beta-blockers in patients who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers

2013HRS/EHRA/APHRS Guidelines

Molecular Medicine

Allele-Specific Silencing of Mutant mRNA Rescues Ultrastructural and Arrhythmic Phenotype in Mice Carriers of the R4496C Mutation in the Ryanodine Receptor Gene (*RYR2*)

Circ Res 2017

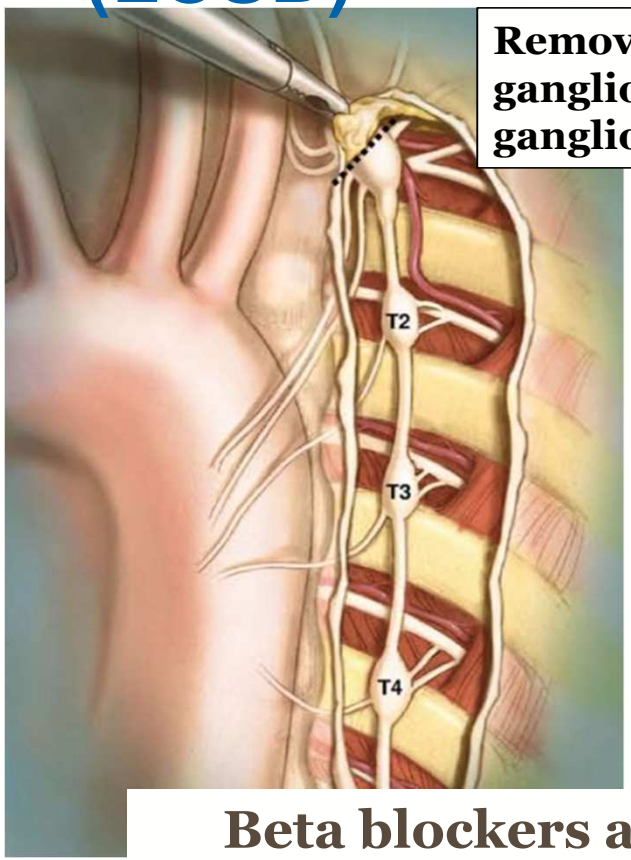
Rossana Bongianino, Marco Denegri, Andrea Mazzanti, Francesco Lodola, Alessandra Vollero, Simona Boncompagni, Silvia Fasciano, Giulia Rizzo, Damiano Mangione, Serena Barbaro, Alessia Di Fonso, Carlo Napolitano, Alberto Auricchio, Feliciano Protasi, Silvia G. Priori

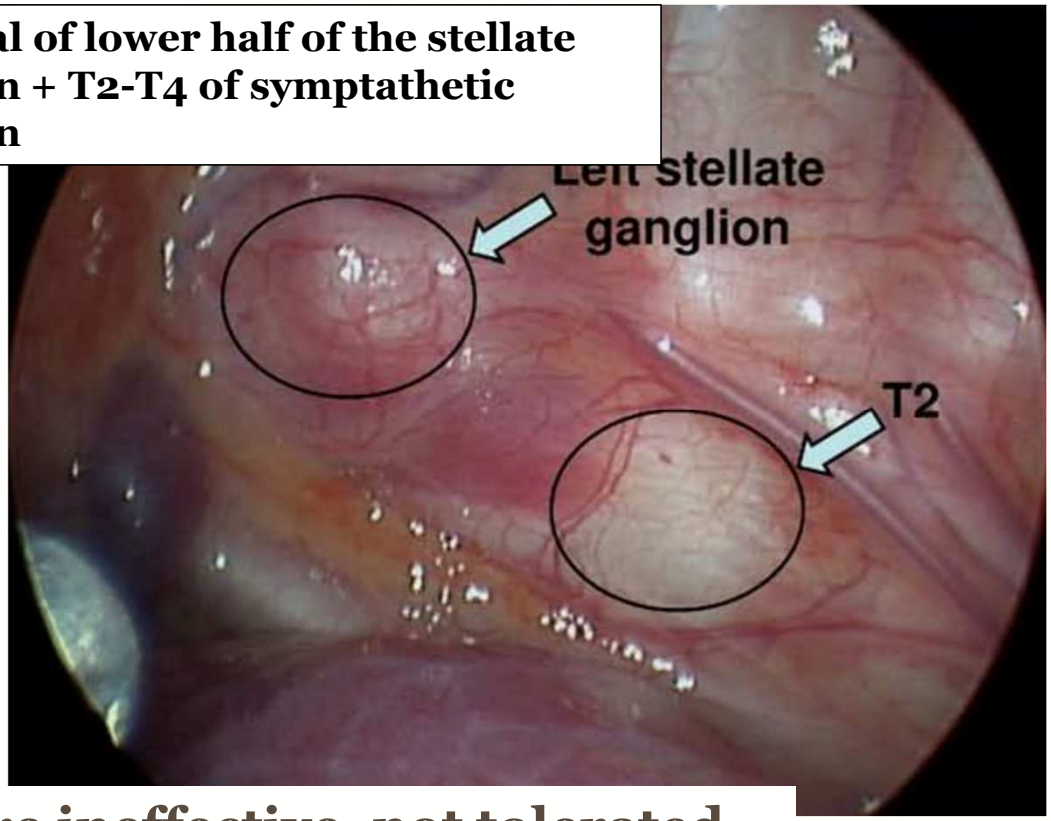
Single Delivery of an Adeno-Associated Viral Construct to Transfer the *CASQ2* Gene to Knock-In Mice Affected by Catecholaminergic Polymorphic Ventricular Tachycardia Is Able to Cure the Disease From Birth to Advanced Age

Marco Denegri, PhD*; Rossana Bongianino, MSc*; Francesco Lodola, PhD*; Simona Boncompagni, PhD; Verónica C. De Giusti, MD, PhD; José E. Avelino-Cruz, PhD; Nian Liu, MD; Simone Persampieri, MS; Antonio Curcio, MD, PhD; Francesca Esposito, MD; Laura Pietrangelo, MSc; Isabelle Marty, PhD; Laura Villani, MD; Alejandro Moyaho, PhD; Paola Baiardi, PhD; Alberto Auricchio, MD; Feliciano Protasi, PhD; Carlo Napolitano, MD, PhD; Silvia G. Priori, MD, PhD

Left (bilateral) Cardiac Sympathetic Denervation (LCSD)

Removal of lower half of the stellate ganglion + T2-T4 of symptathetic ganglion





Beta blockers are ineffective, not tolerated or contra-indicated, ICD storms in LQTS and CPVT

Collura, Heart Rhythm 2009

Implantable Cardioverter Defibrillator

- LQTS

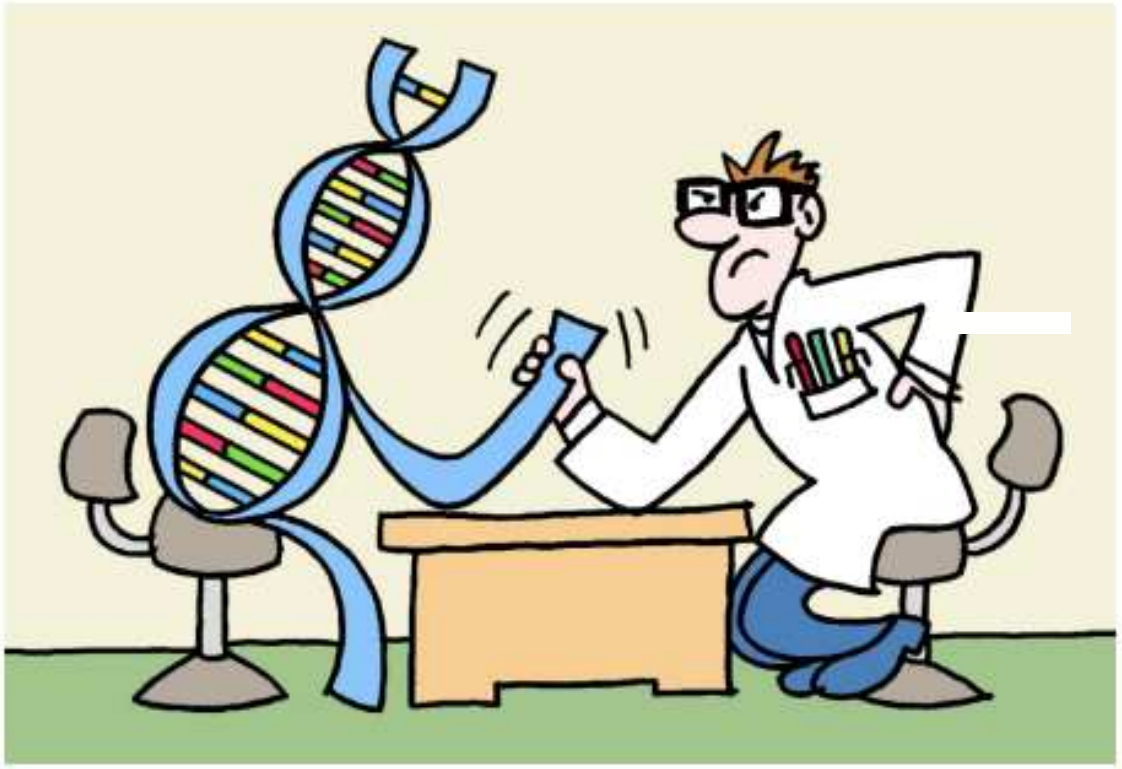
  Recommended for all survivors of cardiac arrest

- CPVT

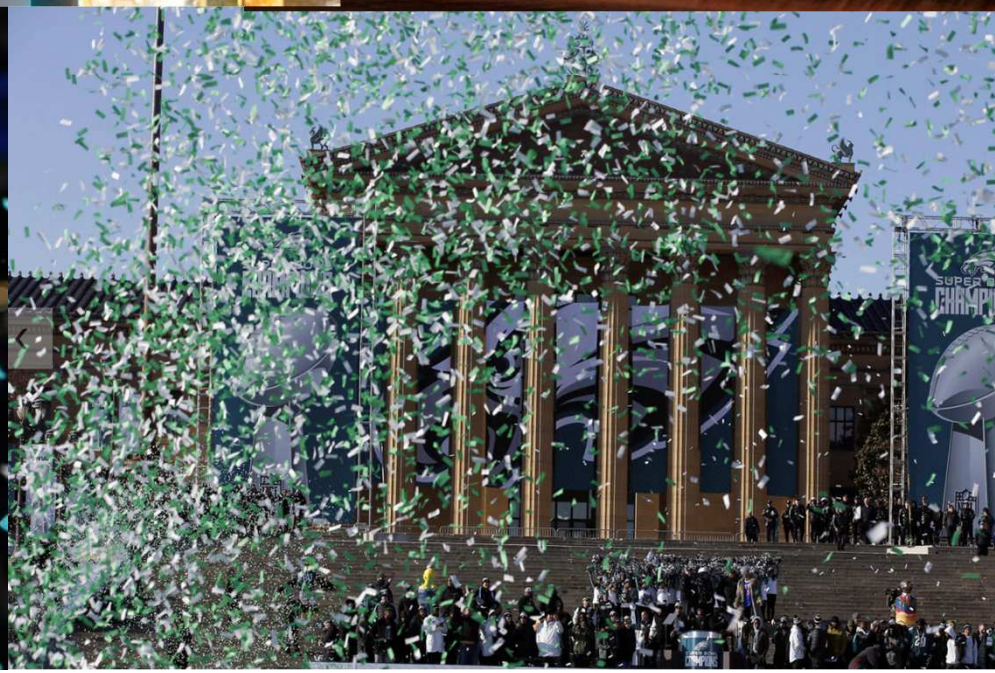
  Recommend for Cardiac arrest, recurrent syncope or VT despite optimal medical management and /or LCSD

2013HRS/EHRA/APHRS Guidelines

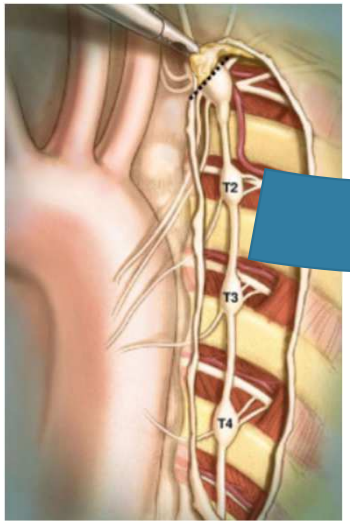
Treatment directed to the patient should trump treatment of the mutation !




The Children's Hospital of Philadelphia



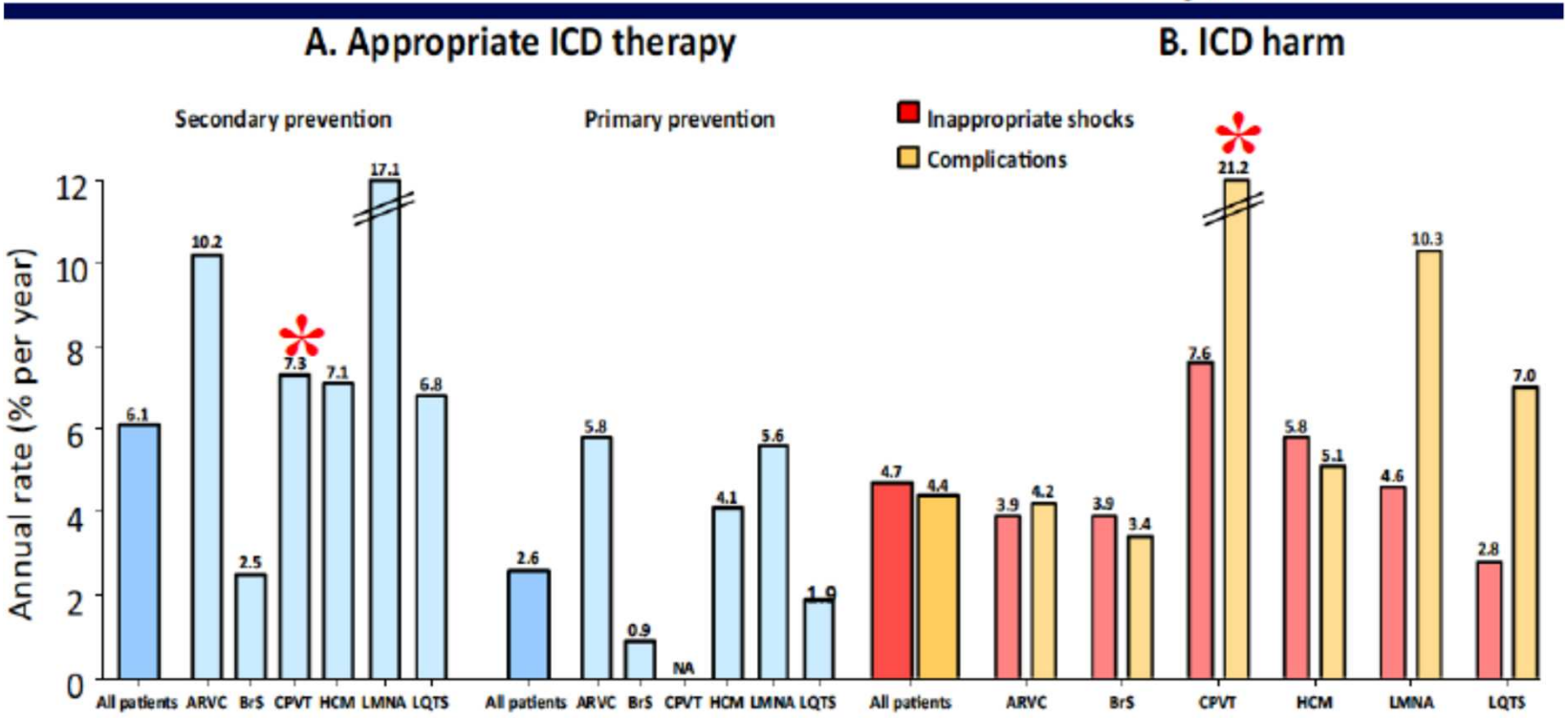
High risk channelopathy



Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications

Louise R.A. Olde Nordkamp, MD, PhD,* Pieter G. Postema, MD, PhD,* Reinoud E. Knops, MD,* Nynke van Dijk, MD, PhD,† Jacqueline Limpens, PhD,‡ Arthur A.M. Wilde, MD, PhD,*§ Joris R. de Groot, MD, PhD*

Heart Rhythm 2016



Life Style Management

Class I

- Limit /avoid competitive sports
- Limit/avoid strenuous physical exercise
- Limit exposure to stressful environments

2013HRS/EHRA/APHRS Guidelines
2017 ACC/AHA/HRS Guidelines

Left Cardiac Sympathetic Denervation (LCSD)

- Recommended for high-risk LQTS and CPVT
  - ICD is contra-indicated or refused and/or
  - Beta blockers are ineffective, not tolerated or contra-indicated
  - Recurrent ICD shocks

2013HRS/EHRA/APHRS Guidelines

Pharmacotherapy- NO RCTs

-Net effect of all drugs is to ↓ Ito

Available in the U.S.

Quinidine

-Ito blocker

-suppressed VF induction

-Prospective study of 25 patients: No arrhythmias at 6-219 months follow up

-? Asymptomatic patients

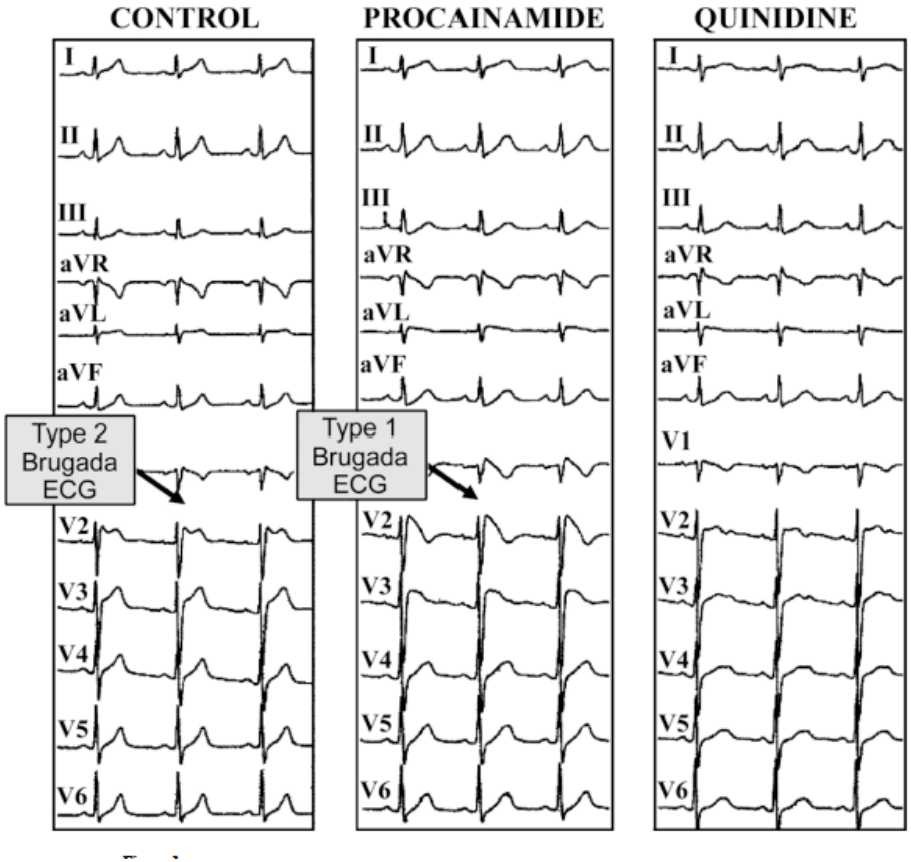
-can induce acquired LQTS

Cilostazol

-Phosophodiestrase III inhibitor

-↑cAMP and Heart rate

-↓ Ito, ↑ Ca^2



Belhassen , PACE 2009, Marquez, Heart Rhythm 2013, Kanlop, J Cardiovasc Med 2011, Shinohara, HeartRhythm 2014

Heart Rhythm. 2013 July ; 10(7): 1054–1062. doi:10.1016/j.hrthm.2013.03.011.

Effect of Wenxin Keli and Quinidine to Suppress Arrhythmogenesis in an Experimental Model of Brugada Syndrome

Yoshino Minoura, MD, PhD, Brian K. Panama, PhD, Vladislav V. Nesterenko, PhD, Matthew Betzenhauser, PhD, Hector Barajas-Martínez, PhD, Dan Hu, MD, PhD, José M. Di Diego, MD, and Charles Antzelevitch, PhD, FHRS
Masonic Medical Research Laboratory, Utica, NY 13501

Wenxin keli
☆☆☆☆☆
$12.80
ADD TO CART
Wishlist Compare

Chinese herbs-based antiarrhythmic drug

Beware Of Imitations!

Treatment of Arrhythmia Storms

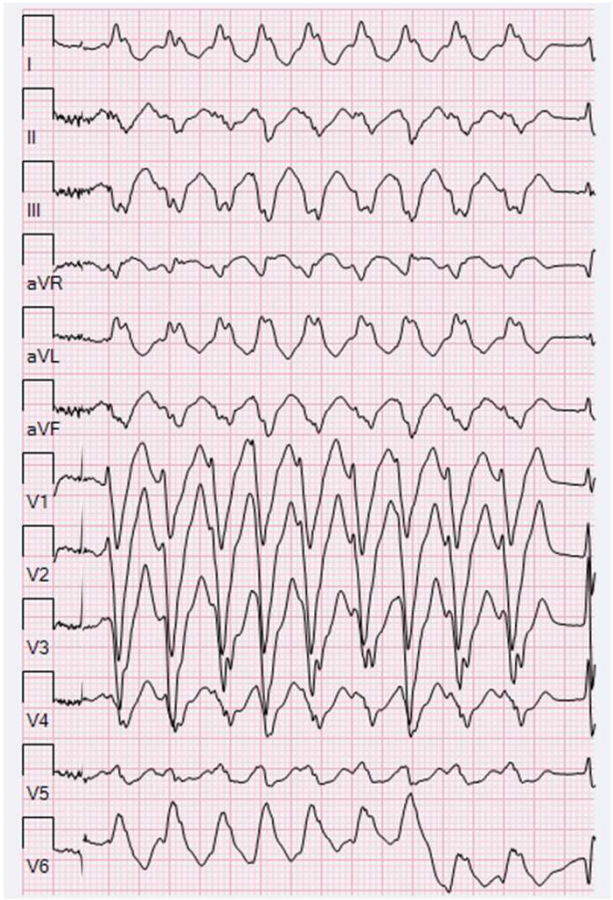
Isoproterenol

-↑ HR, ↑cAMP, ↑ Ca^2, ↓Ito

Milrinone

-Phosphodiesterase III inhibitor

- ↑cAMP, ↑ Ca^2, ↓Ito



Maury, Eurpace 2004, Watanabe, EurHeartJ 2006, Suzuki, JCE 2000, Szel, HeartRhythm 2013

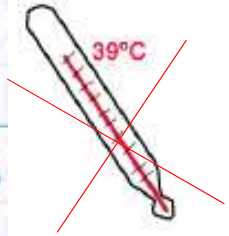
Brugada Syndrome (BrS): Management

Risk stratification and management in Brugada Syndrc		
Recommendations		
The following lifestyle changes are recommended in all patients with a diagnosis of Brugada syndrome: a. Avoidance of drugs that may induce ST-segment elevation in right precordial leads (www.brugadadrugs.org); b. Avoidance of excessive alcohol intake and large meals; c. Prompt treatment of any fever with antipyretic drugs.	I	
ICD implantation is recommended in patients with a diagnosis of Brugada syndrome who: a. Are survivors of an aborted cardiac arrest, and/or b. Have documented spontaneous sustained VT.	I	C
ICD implantation should be considered in patients with a spontaneous diagnostic type I ECG pattern and history of syncope.	IIa	C

Lifestyle changes

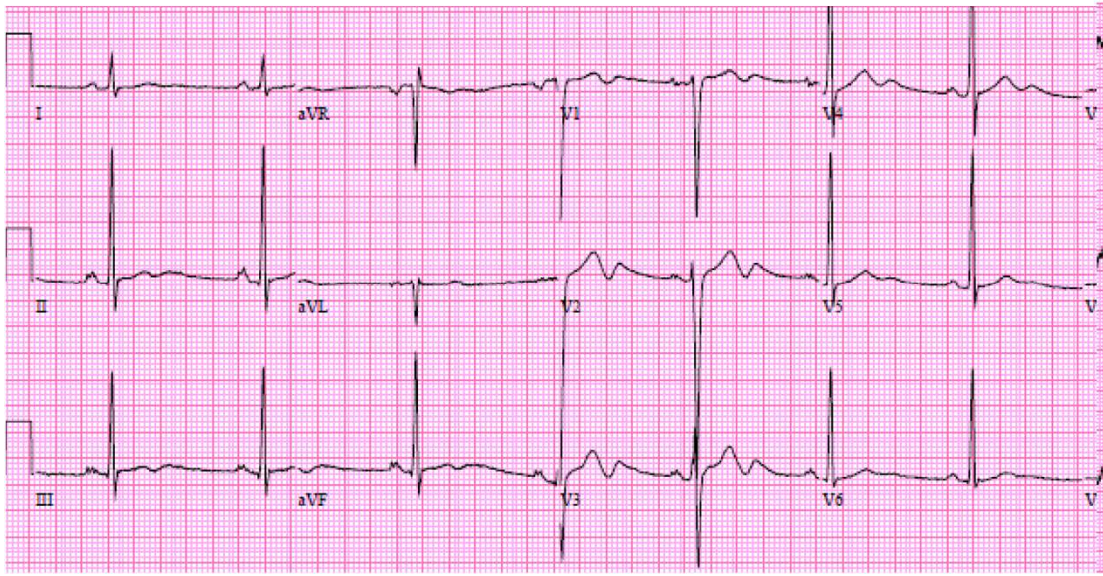
Secondary prevention

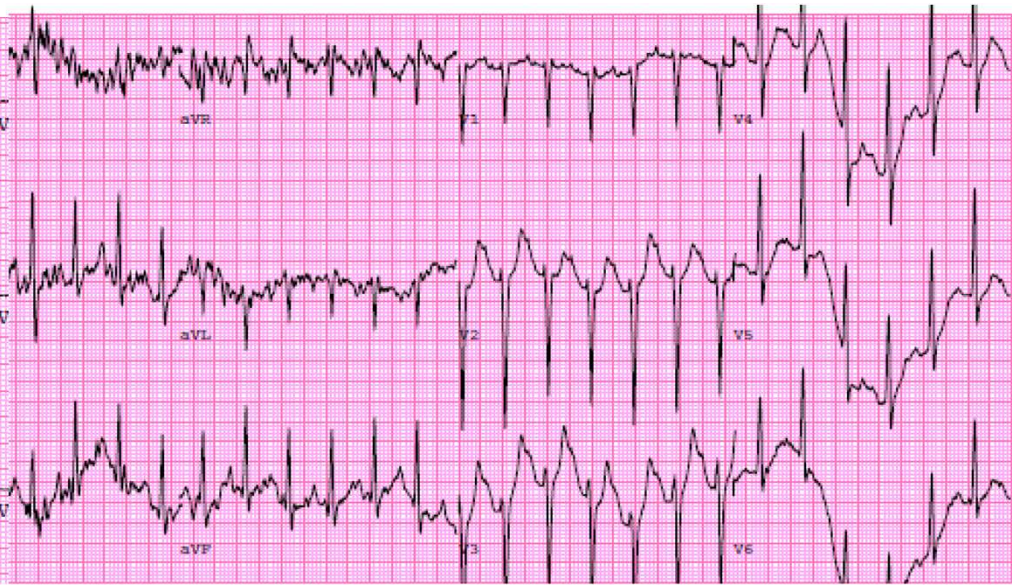
Primary prevention

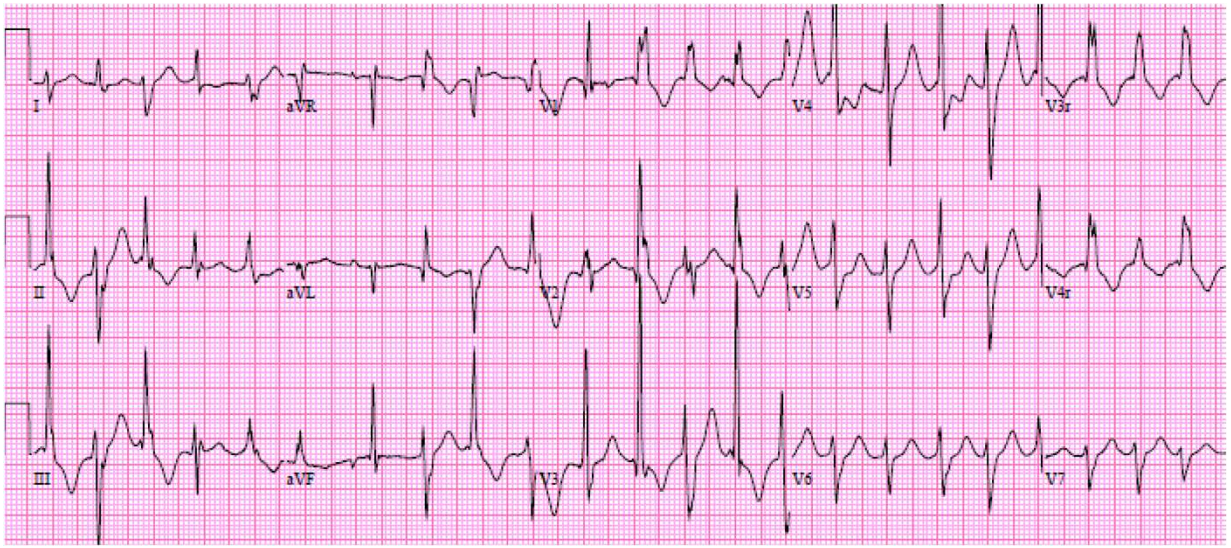


www.brugadadrugs.org

ICD implantation with the use of beta-blockers is recommended in LQTS patients with previous cardiac arrest.	I	B
ICD implantation in addition to beta-blockers should be considered in LQTS patients who experienced syncope and/or VT while receiving an adequate dose of beta-blockers.	IIa	B
Implantation of an ICD may be considered in addition to beta-blocker therapy in asymptomatic carriers of a pathogenic mutation in *KCNH2* or *SCN5A* when QTc is >500 ms.	IIb	C







Ventricular Ectopy		
Total VE Beats	:	55095 (45.3%)
Vent Runs	:	803
Beats	:	6393
Longest	:	56 Beats at 4:57:13 PM
Fastest	:	174 BPM at 1:59:32 PM
Triplets	:	720 Events
Couplets	:	852 Events
R on T	:	0
Bi/Trigemin	:	42048/463 Beats
Max VE/Minute	:	116 Beats at 4:56:00 PM
Max VE/Hour	:	3867 Beats at 10:25:00 PM
Mean VE/Hour	:	2,297.0
VE/1000	:	453.2

2015: Time for change?

- Observational evidence: athletes with either concealed, electrocardiographically manifest, or symptomatic LQTS who chose to remain competitive- no deaths/ > 1000 athlete year

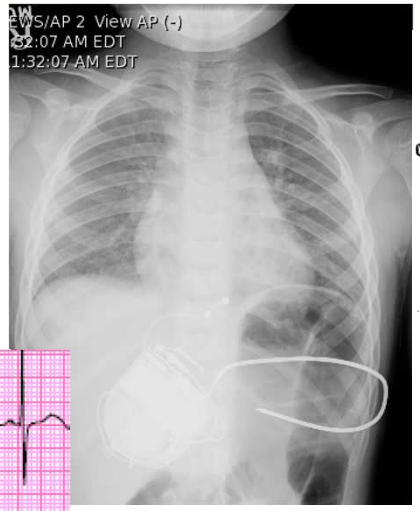
- Genetic testing is now a widely available clinical test used routinely in the evaluation of a patient with a suspected channelopathy

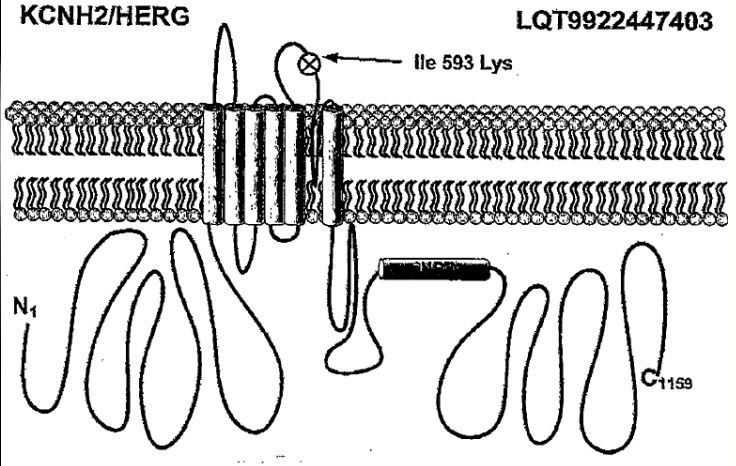
  (LQTS 1 Vs other types of LQTS)

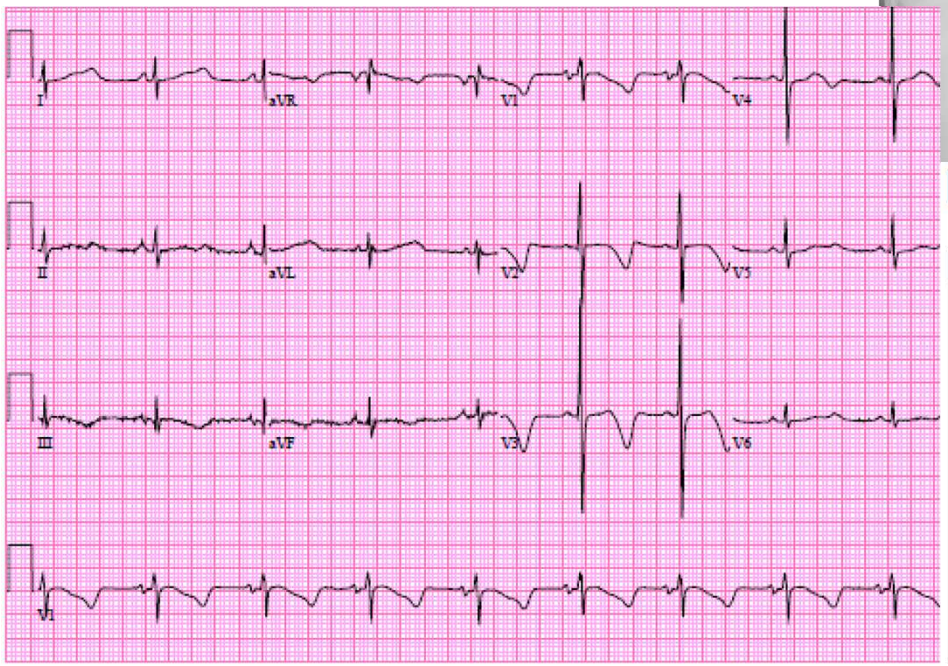
- No report of athletes with **concealed** channelopathic substrates in the United States experiencing their sentinel event during sport

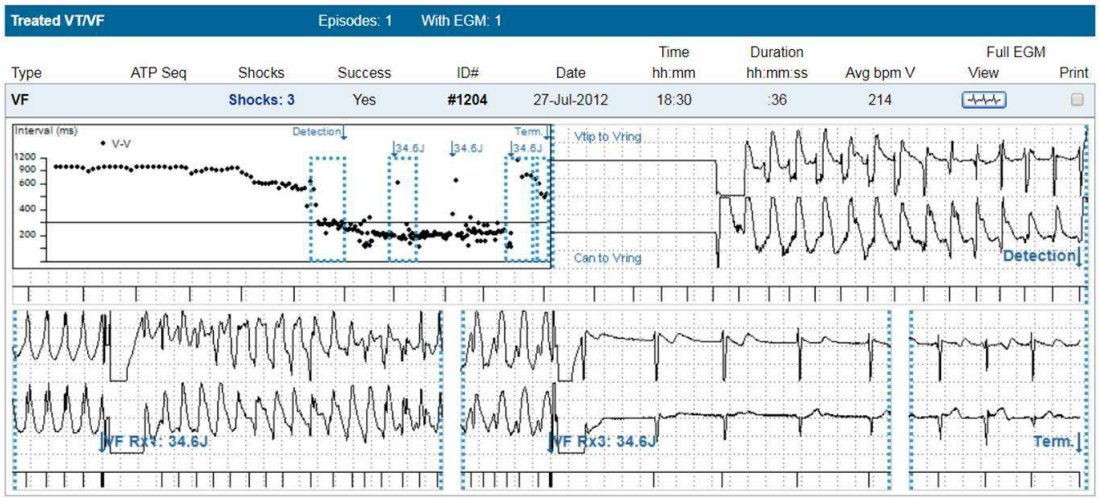
- Observational evidence from American ICD Sports Registry : athletes with an ICD can continue to participate with negligible mortality

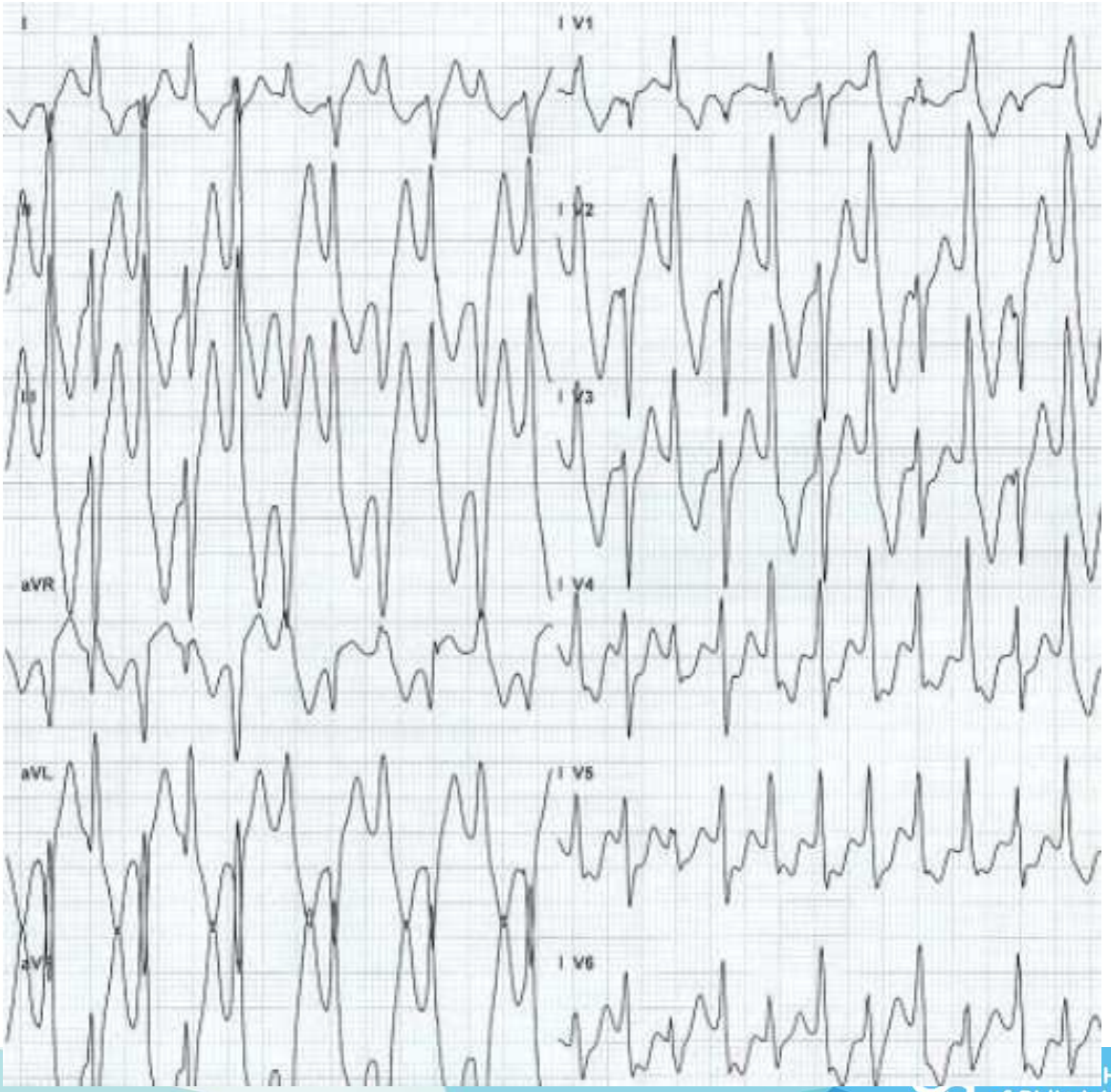
Aziz, JACC 2013, Johnson, BJSM 2013

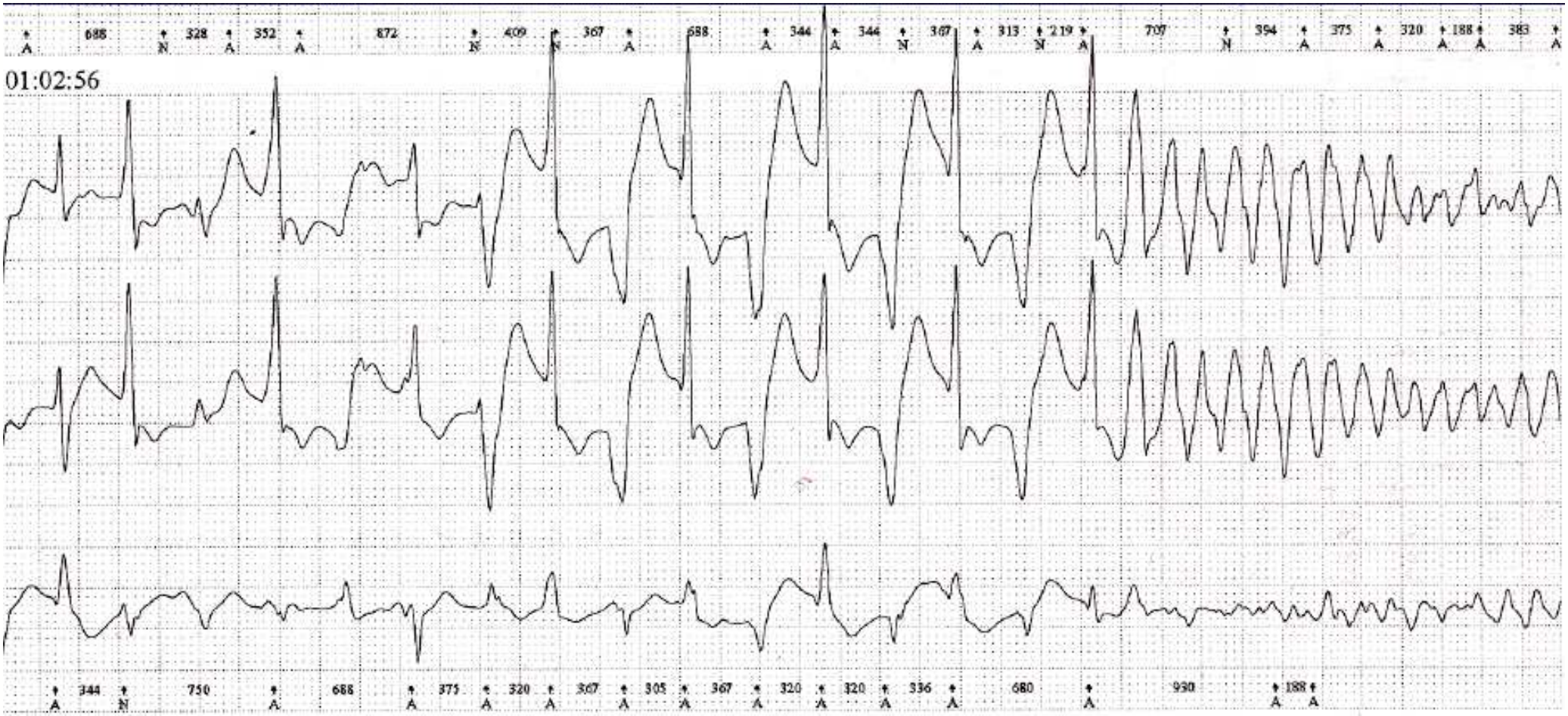

EWS/AP 2 View AP (-)
1:32:07 AM EDT
1:32:07 AM EDT


KCNH2/HERG
LQT9922447403
Ile 593 Lys
N1
C1159


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1


Treated VT/VF
Episodes: 1
With EGM: 1
Type
ATP Seq
Shocks
Success
ID#
Date
Time hh:mm
Duration hh:mm:ss
Avg bpm V
Full EGM View
Print
VF
Shocks: 3
Yes
#1204
27-Jul-2012
18:30
:36
214
Interval (ms)
V-V
Detection
34.6J
34.6J
34.6J
Term.
Vtip to Vring
Can to Vring
Detection
VF Rx1: 34.6J
VF Rx3: 34.6J
Term.


I
II
III
aVR
aVL
aVF
I V1
I V2
I V3
I V4
I V5
I V6

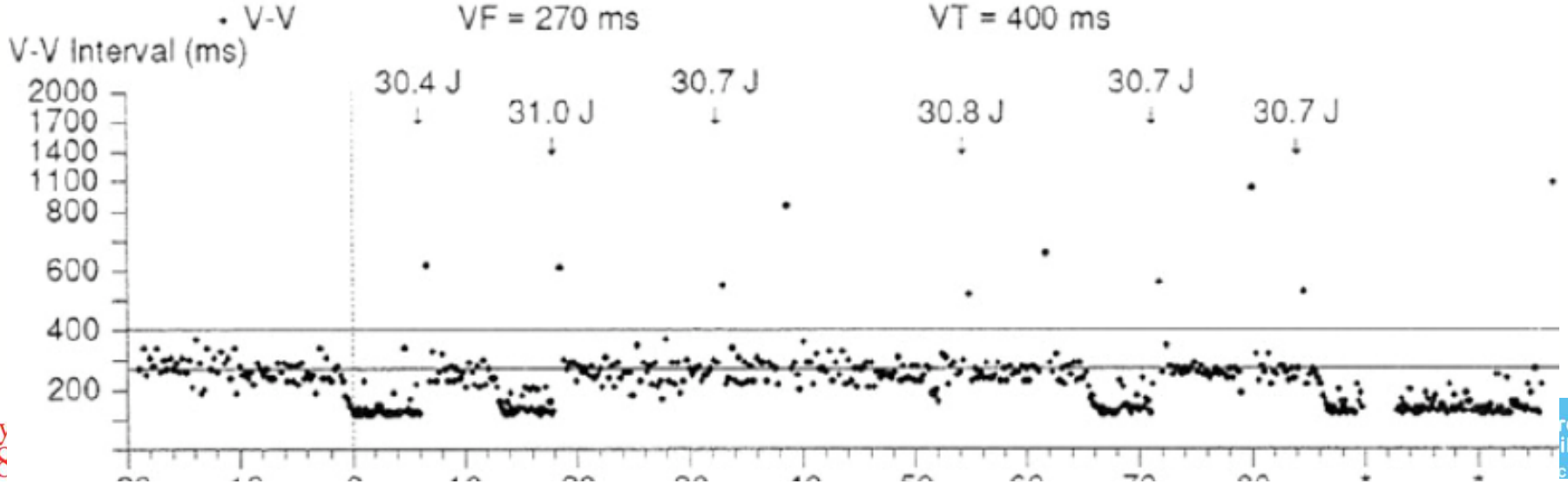

01:02:56

Sudden cardiac death despite an implantable cardioverter-defibrillator in a young female with catecholaminergic ventricular tachycardia

Heart Rhythm 2006

Uwais Mohamed, MBBS,* Michael H. Gollob, MD,† Robert M. Gow, MB, BS,‡ Andrew D. Krahn, MD*

Date/Time	Type	V. Cycle	Last Rx	Success	Duration
Jan 11 09:15:58	VF	130 ms	VF Rx 6	No	14 min




ADRENALINE
JUNKIE

nature medicine 2009

Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans

Hiroshi Watanabe[1,5,6], Nagesh Chopra[1,6], Derek Laver[2,6], Hyun Seok Hwang[1], Sean S Davies[1], Daniel E Roach[3], Henry J Duff[3], Dan M Roden[1], Arthur A M Wilde[4] & Björn C Knollmann[1]

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially lethal inherited arrhythmia syndrome in which drug therapy is often ineffective. We discovered that flecainide prevents arrhythmias in a mouse model of CPVT by inhibiting cardiac ryanodine receptor–mediated Ca^{2+} release and thereby directly targeting the underlying molecular defect. Flecainide completely prevented CPVT in two human subjects who had remained highly symptomatic on conventional drug therapy, indicating that this currently available drug is a promising mechanism-based therapy for CPVT.

Flecainide Suppresses Defibrillator-Induced Storming in Catecholaminergic Polymorphic Ventricular Tachycardia

ROBERT A. HONG, M.D.*, KAHEALANI K. RIVERA, M.D.*, ARKSARAPUK JITTIRAT, M.D.,† and JOON J. CHOI, M.D., PH.D.*

From the *The Queen's Medical Center, John A. Burns School of Medicine, Department of Internal Medicine, Division of Cardiology; and †John A. Burns School of Medicine, Department of Internal Medicine, Honolulu, Hawaii

PACE 2012

Effects of flecainide on exercise-induced ventricular arrhythmias and recurrences in genotype-negative patients with catecholaminergic polymorphic ventricular tachycardia

Hiroshi Watanabe, MD, PhD, FESC,[‾] Christian van der Werf, MD,[†] Ferran Roses-Noguer, MD,[‡] Arnon Adler, MD,[§] Naokata Sumitomo, MD,[‖] Christian Veltmann, MD,[¶] Raphael Rosso, MD,[§] Zahurul A. Bhuiyan, MD, PhD,[#] Hennie Bikker, PhD,[**] Prince J. Kannankeril, MD, MSCI,[††] Minoru Horie, MD, PhD,[‡‡] Tohru Minamino, MD, PhD,[*] Sami Viskin, MD,[§] Björn C. Knollmann, MD, PhD,[§§] Jan Till, MD,[‡] Arthur A.M. Wilde, MD, PhD[†]

Heart Rhythm 2013

Flecainide monotherapy is an option for selected patients with catecholaminergic polymorphic ventricular tachycardia intolerant of β-blockade

Gareth J. Padfield, MBChB, PhD,[*] Leenah AlAhmari,[*] Krystien V.V. Lieve, MD,[†] Tasneem AlAhmari,[*] Thomas M. Roston, MD,[*] Arthur A. Wilde, MD, PhD, FHRS,[†‡] Andrew D. Krahn, MD, FHRS,[*] Shubhayan Sanatani, MD, FHRS[*]

Heart Rhythm 2016

The Role of Flecainide in the Management of Catecholaminergic Polymorphic Ventricular Tachycardia

Krystien VV Lieve,[1] Arthur A Wilde,[1,2] Christian van der Werf[1]

1. Heart Centre, Academic Medical Centre, Amsterdam, The Netherlands;
2. Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders, Jeddah, Kingdom of Saudi Arabia

Arrhythmia & Electrophysiology Review 2016

Carvedilol and its new analogs suppress arrhythmogenic store overload–induced Ca^{2+} release

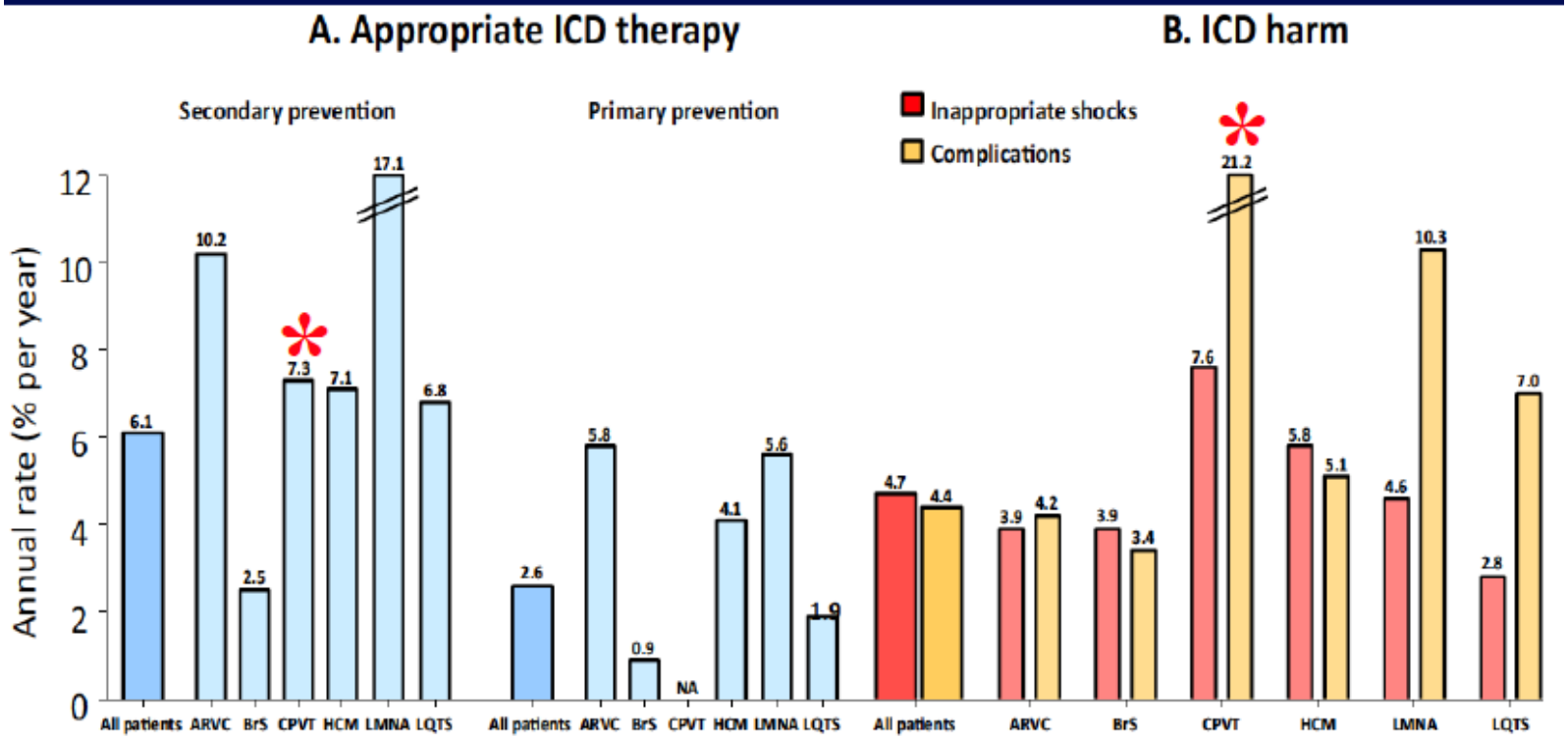
Qiang Zhou[1,2,8], Jianmin Xiao[1,8], Dawei Jiang[1], Ruiwu Wang[1], Kannan Vembaiyan[3], Aixia Wang[3], Chris D Smith[3], Cuihong Xie[1,2,8], Wenqian Chen[1], Jingqun Zhang[2], Xixi Tian[1], Peter P Jones[1,8], Xiaowei Zhong[1], Ang Guo[4], Haiyan Chen[2], Lin Zhang[1], Weizhong Zhu[5], Dongmei Yang[6], Xiaodong Li[7], Ju Chen[7], Anne M Gillis[1], Henry J Duff[1], Heping Cheng[6,8], Arthur M Feldman[5], Long-Sheng Song[4], Michael Fill[2], Thomas G Back[3] & S R Wayne Chen[1,2]

Nature Medicine 17 2011

Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications

Louise R.A. Olde Nordkamp, MD, PhD,[*] Pieter G. Postema, MD, PhD,[*] Reinoud E. Knops, MD,[*] Nynke van Dijk, MD, PhD,[†] Jacqueline Limpens, PhD,[‡] Arthur A.M. Wilde, MD, PhD,[*§] Joris R. de Groot, MD, PhD[*]

Heart Rhythm 2016



Efficacy of Implantable Cardioverter Defibrillators in Young Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

Success Depends on Substrate

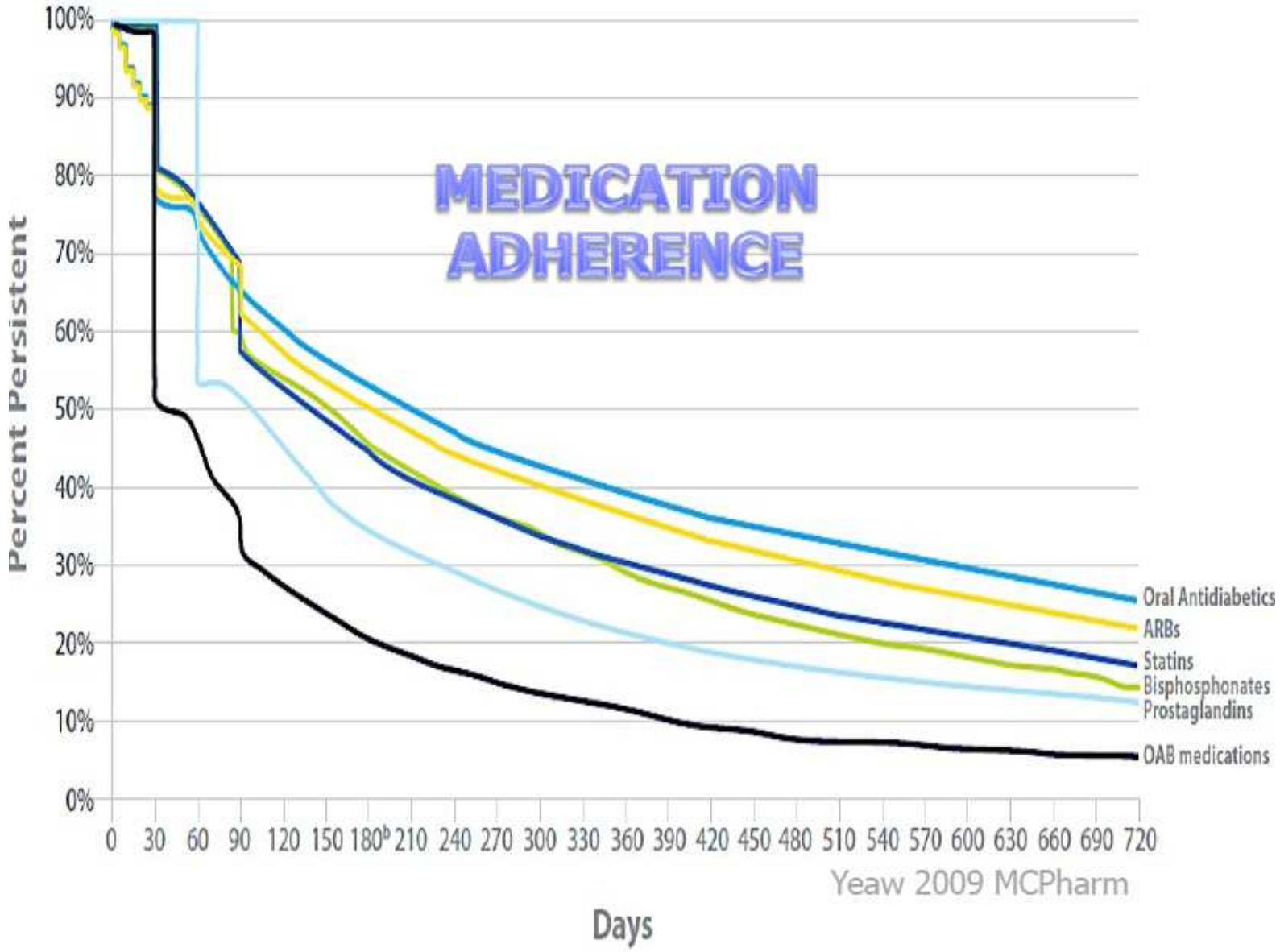
Circ Arr EP 2013

Christina Y. Miyake, MD; Gregory Webster, MD; Richard J. Czosek, MD; Michal J. Kantoch, MD; Anne M. Dubin, MD; Kishor Avasarala, MD; Joseph Atallah, MD, CM, SM

Therapeutic approach for patients with catecholaminergic polymorphic ventricular tachycardia: state of the art and future developments

Europace 14 2012

Christian van der Werf[1], Aeilko H. Zwinderman[2], and Arthur A.M. Wilde[1]*


MEDICATION ADHERENCE
Percent Persistent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0 30 60 90 120 150 180[b] 210 240 270 300 330 360 390 420 450 480 510 540 570 600 630 660 690 720
Days
Oral Antidiabetics
ARBs
Statins
Bisphosphonates
Prostaglandins
OAB medications
Yeaw 2009 MCPharm

Self-reported non-adherence to immune-suppressant therapy in liver transplant recipients: demographic, interpersonal, and intrapersonal factors

Clinical Transplant
26 2012

Using a liberal definition, half of our surveyed adult liver recipients report non-adherence to their immune suppressants, which may be a bigger problem than often recognized. Missed physician office appointments may serve as important "tip-off" in identifying non-adherence to immune


DANGER
TEENAGER IN
REBELLION MODE

Successful treatment of catecholaminergic polymorphic ventricular tachycardia with bilateral thoracoscopic sympathectomy HR 5 2008

Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery HR 6 2009

EDITORIAL COMMENTARY

Cutting nerves and saving lives Peter J. Schwartz, MD, FHRS HR 6 2009

Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: Intermediate and long-term follow-up Bilateral > LCSD HR 11 2014

Safety and efficacy of renal denervation as a novel treatment of ventricular tachycardia storm in patients with cardiomyopathy HR 11 2014

EDITORIAL COMMENTARY

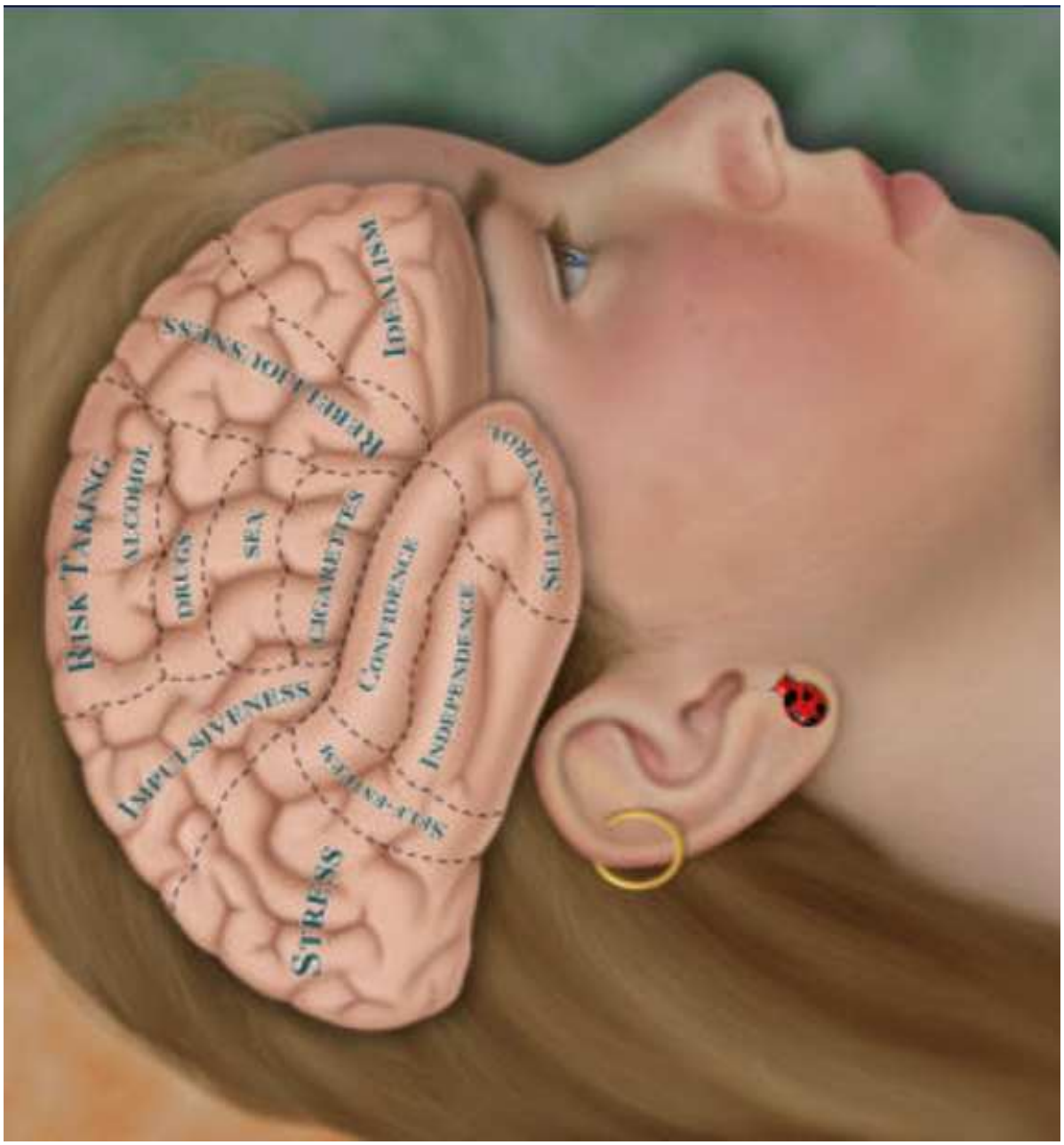
Interventional treatment of ventricular tachycardia and electrical storm: From ablation of substrate and triggers to autonomic modulation by renal denervation HR 11 2014

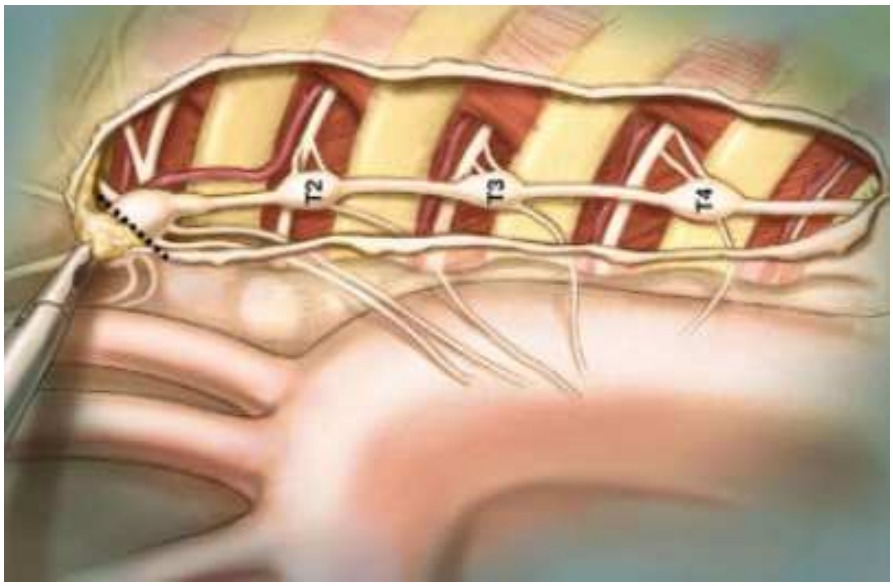
Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia

Circulation 2015

The Role of Left Cardiac Sympathetic Denervation

Gaetano M. De Ferrari, MD*; Veronica Dusi, MD*; Carla Spazzolini, DVM, MS*;
J. Martijn Bos, MD, PhD*; Dominic J. Abrams, MD, MRCP; Charles I. Berul, MD;
Lia Crotti, MD, PhD; Andrew M. Davis, MB, BS, MD; Michael Eldar, MD; Maria Kharlap, MD;
Asaad Khoury, MD; Andrew D. Krahn, MD; Antoine Leenhardt, MD; Christopher R. Moir, MD;
Attilio Odero, MD; Louise Olde Nordkamp, MD; Thomas Paul, MD; Ferran Rosés i Noguer, MD;
Maria Shkolnikova, MD; Jan Till, MD; Arthur A.M. Wilde, MD; Michael J. Ackerman, MD, PhD†;
Peter J. Schwartz, MD†

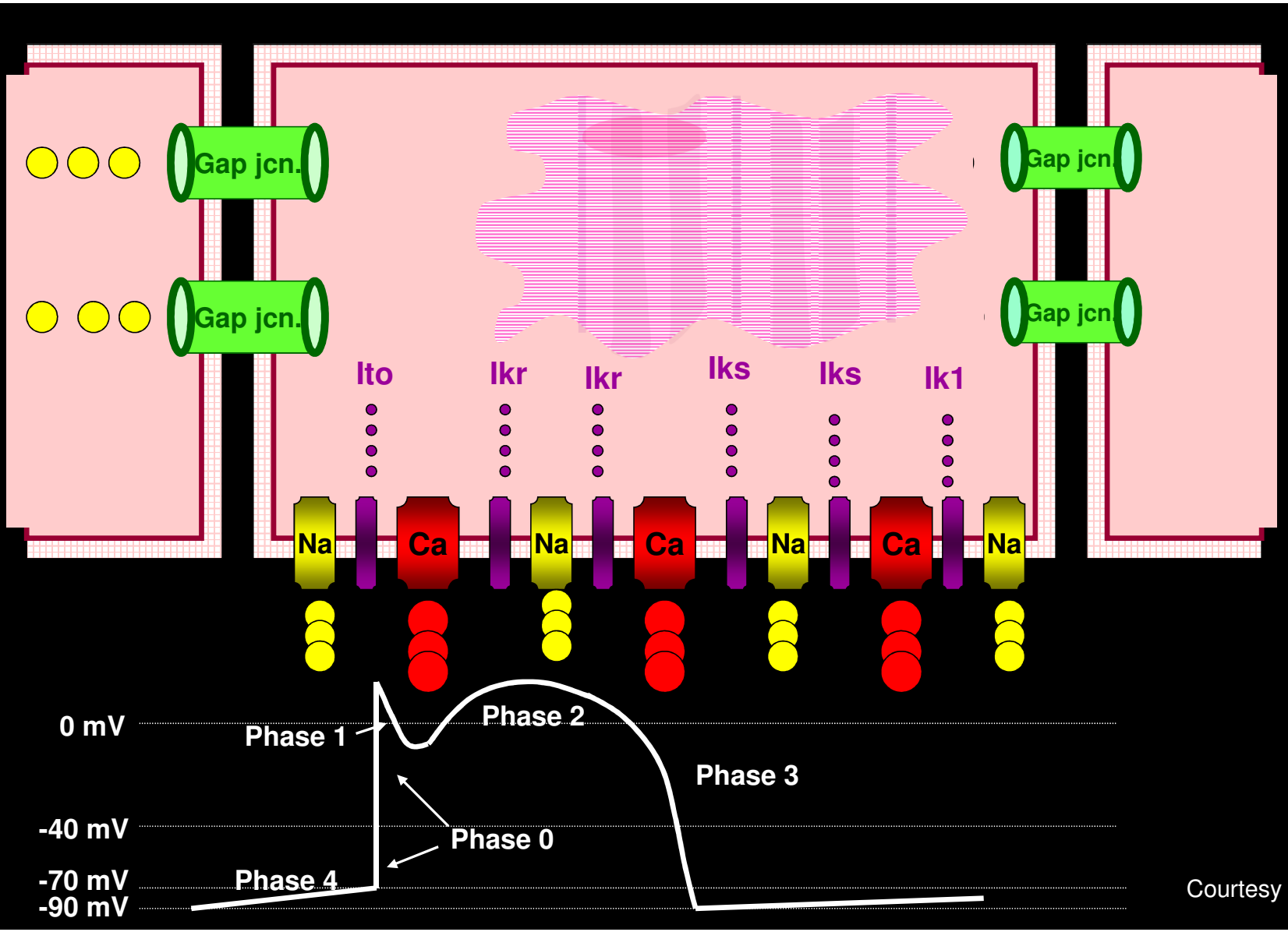

RISK TAKING
ALCOHOL
DRUGS
SEX
CIGARETTES
CONFIDENCE
INDEPENDENCE
IMPULSIVENESS
STRESS
OPENNESS
SELF-ESTEEM


T2
T3
T4

Recommendations	Class[a]	Level[b]
Therapy with beta-blockers should be considered for genetically positive family members, even after a negative exercise test.	IIa	C
Flecainide should be considered in addition to beta-blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers, when there are risks/ contraindications for an ICD or an ICD is not available or rejected by the patient.	IIa	C
Flecainide should be considered in addition to beta-blockers in patients with a diagnosis of CPVT and carriers of an ICD to reduce appropriate ICD shocks.	IIa	C

Left cardiac sympathetic denervation may be considered in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/ bidirectional VT/several appropriate ICD shocks while on beta-blockers or beta-blockers plus flecainide and in patients who are intolerant or have contraindication to beta-blockers.	IIb	C

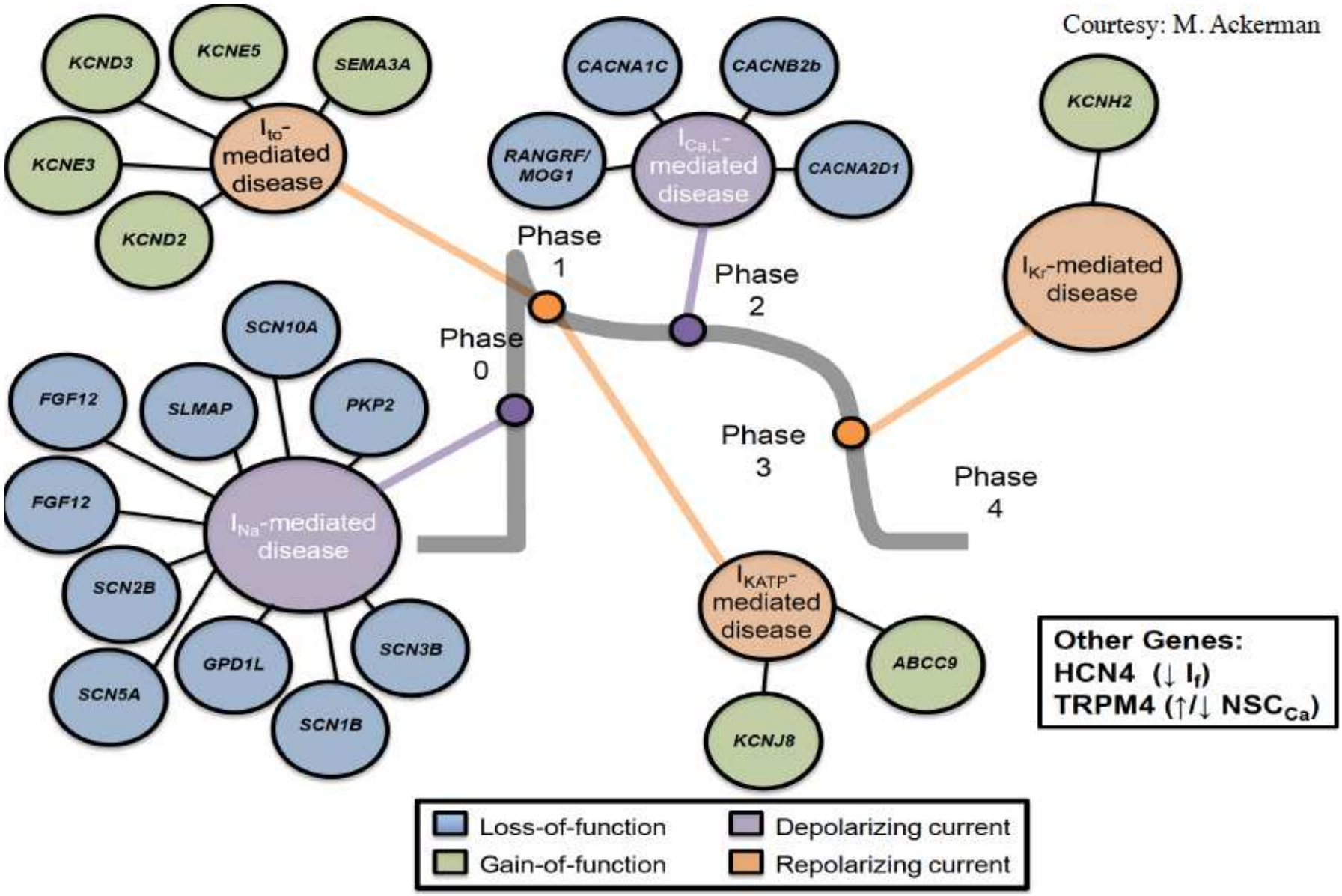
- For an athlete with previously symptomatic CPVT or
- an asymptomatic CPVT athlete with exercise-induced
- premature ventricular contractions in bigeminy,
- couplets, or nonsustained ventricular tachycardia,
- participation in competitive sports is not recommended
- except for class IA sports (Class III; Level of
- Evidence C). Exceptions to this limitation should be
- made only after consultation with a CPVT specialist.



Courtesy Dr. Ron Kanter

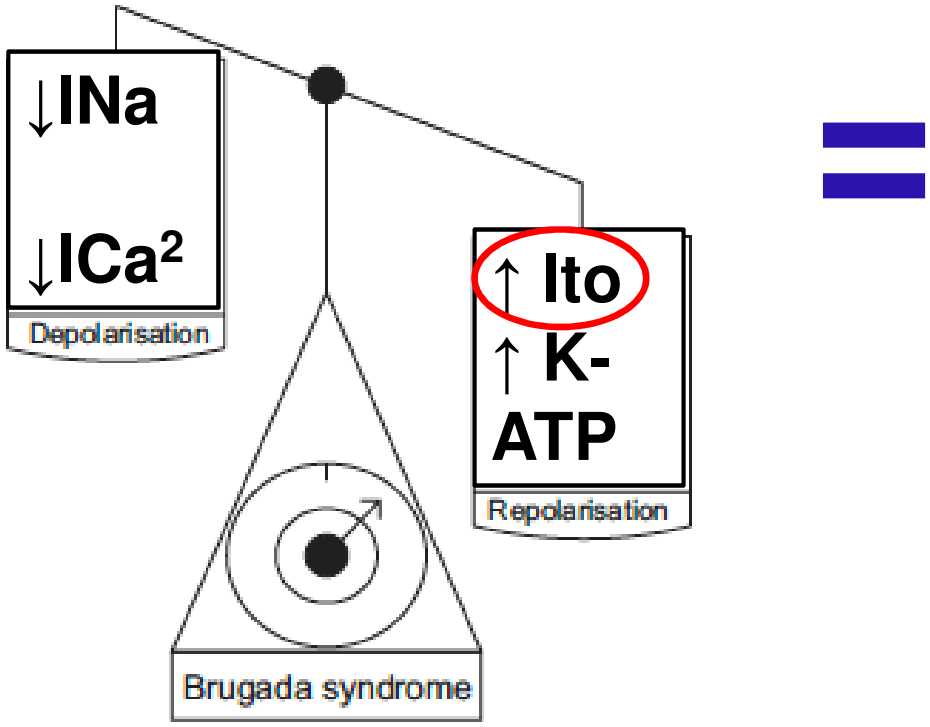
Name	Current	Gain/loss of function	Protein	Gene	Estimated Prevalence
BrS1	***INa***	*Loss*	*Nav1.5*	***SCN5A***	*11-28%*
BrS2	*INa*	*Loss*		*GPD1-L*	*Rare*
BrS3	*ICa,L*	*Loss*	*Cav1.2α1*	*CACNA1C*	*6.6%*
BrS4	*ICa,L*	*Loss*	*Cavβ2b*	*CACNB2b*	*4.8%*
BrS5	*INa*	*Loss*	*Navβ1*	*SCN1B*	*1%*
BrS6	*Ito*	*Gain*	*MiRP2*	*KCNE3*	*Rare*
BrS7	*INa*	*Loss*	*Navβ3*	*SCN3B*	*Rare*
BrS8	*IK-ATP*	*Gain*	*Kir6.1*	*KCNJ8*	*2%*
BrS9	*ICa,L*	*Loss*	*Cavα2d*	*CACNA2D1*	*2%*
BrS10	*Ito*	*Gain*	*Kv4.3*	*KCND3*	*Rare*
BrS11	*INa*	*Loss*		*MOG1*	*Rare*
BrS12	*IK-ATP*	*Gain*		*ABCC9, SUR2A*	*Rare*
BrS13	*INa*	*Loss*		*SLMAP*	*Rare*
BrS14	*INa*	*Loss*	*Navβ2*	*SCN2B*	Rare
BrS15	*INa*	*Loss*	*Plakophyllin*	*PKP2*	*Rare*
BrS16	*INa*	*Loss*		*FGF12, FHAF1*	*Rare*
BrS17	*INa*	*Loss*	*Nav1.8*	*SCN10A*	*16.7%*
BrS18	*INa*	*Gain*		*HEY2*	*Rare*
BrS19	*Ito*	*Gain*	*Semaphorin*	*SEMA3A*	*Rare*

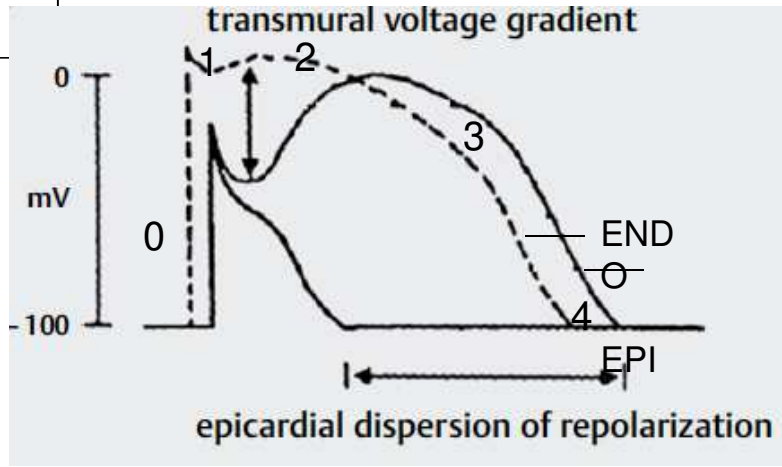
Obeyesekere et al 2015

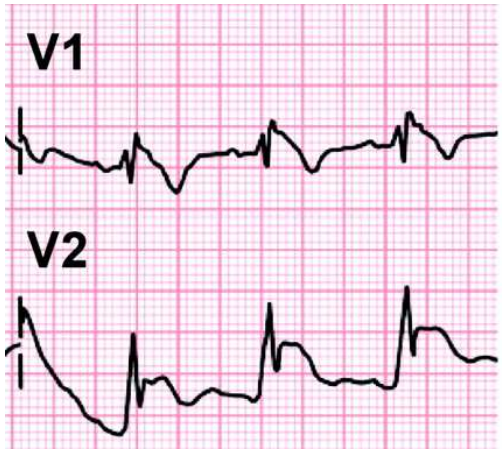

Courtesy: M. Ackerman
KCND3
KCNE5
SEMA3A
KCNE3
I_{to}-mediated disease
KCND2
CACNA1C
CACNB2b
RANGRF/MOG1
$I_{Ca,L}$-mediated disease
CACNA2D1
KCNH2
I_{Kr}-mediated disease
Phase 1
Phase 2
Phase 0
Phase 3
Phase 4
SCN10A
FGF12
SLMAP
PKP2
FGF12
I_{Na}-mediated disease
SCN2B
GPD1L
SCN3B
SCN5A
SCN1B
I_{KATP}-mediated disease
ABCC9
KCNJ8
Other Genes:
HCN4 (↓ I_f)
TRPM4 (↑/↓ NSC_{Ca})
Loss-of-function
Gain-of-function
Depolarizing current
Repolarizing current

Ionic Basis for Brugada Pattern

-Loss of AP dome in subepicardial cardiac myocytes







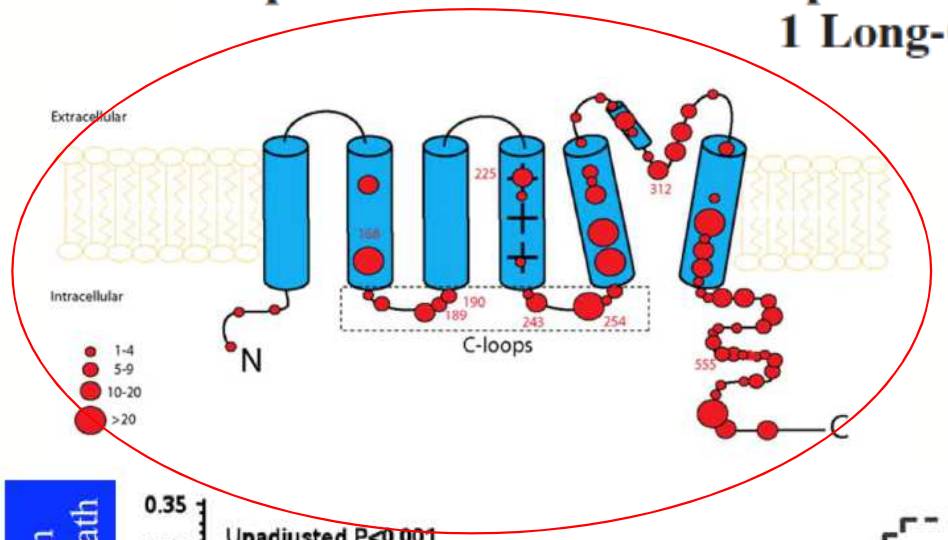
Brugada Syndrome in Children

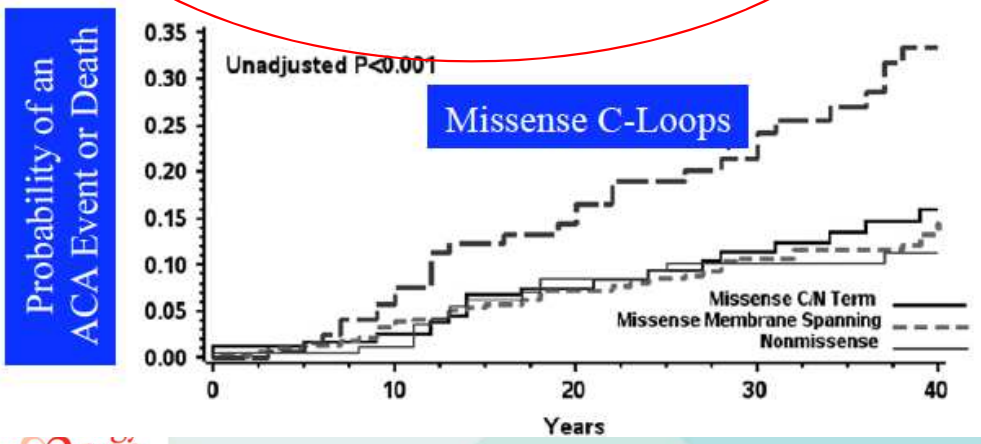
- Pediatric literature

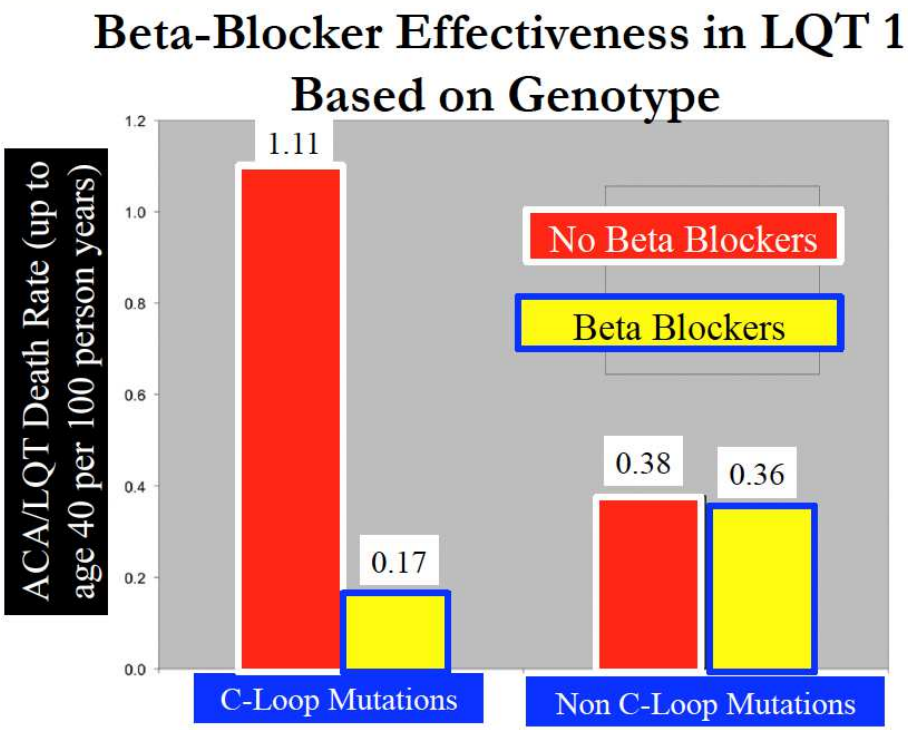
– Probst (*Circulation 2007*): 11 of 30 children (13 centers)
– Chockalingam (*HRS 2012):* 10 of 30 children (4 centers)
– Conte (*JACC 2015*): 10 of 40 children (single centers)
– Probst *(HRS 2016)*: 21 of 106 children (many centers)

Mutations in Cytoplasmic Loops of the KCNQ1 Channel and the Risk of Life-Threatening Events

Implications for Mutation-Specific Response to β-Blocker Therapy in Type 1 Long-QT Syndrome







Barsheshet, Circulation 2012

- - - - Chockalingam et al 2012

Treatment Strategies in Symptomatic Children with Brugada Syndrome

- Many children only at risk during fever
  - Strict use of anti-pyretics and hospital admission during febrile illnesses
  - Control of post immunization fever
- Quinidine as an alternative to an ICD appears to be effective
- ICD (try to avoid ICD implantation)
- β-blockers in BrS/conduction delay phenotype (loss of function SCN5A) as adjunct to ICD to prevent ICD storm
  - Rationale: ↑conduction delay at faster high rates - ↑risk of VT, atrial arrhythmias
  - Controversial -Not recommended in adults

Chokalingam Circulation EP 2012, Probst Heart Rhythm 2016

Largest Pediatric Study

Impact of clinical and genetic findings on the management of young patients with Brugada syndrome.

Andorin, Antoine; Behr, Elijah R; Denjoy, Isabelle; Crotti, Lia; Dagradi, Federica; Jesel, Laurence; Sacher, Fréderic; Petit, Bertrand; Mabo, Philippe; Maltret, Alice; Wong, Leonie C H; Degand, Bruno; Bertaux, Géraldine; Maury, Philippe; Dulac, Yves; Delasalle, Béatrice; Gourraud, Jean-Baptiste; Babuty, Dominique; Blom, Nico A; Schwartz, Peter J; Wilde, Arthur A

106 patients, age 11±6 years

- One-third spontaneous BrS pattern
- Symptomatic 25% (aborted SCD/VT 6%, syncope 14%, other 5%)
- 58 of 75 (77%) genetically tested patients: SCN5A mutation

Treatment:

ICD (21%): 2 appropriate shocks, 41% had complications

Quinidine (10%): 8/10 patients had no arrhythmias

Outcome (Follow up 54 months):

Life threatening arrhythmias in 10%

Fever as a trigger in 27%

Diagnosis and Management of Pediatric Brugada Syndrome: A Survey of Pediatric Electrophysiologists

BRONWYN U. HARRIS, M.D.,* CHRISTINA Y. MIYAKE, M.D.,†
KARA S. MOTONAGA, M.D.,* and ANNE M. DUBIN, M.D.*
From the *Division of Pediatric Cardiology, Lucile Packard Children's Hospital at Stanford, Palo Alto, California; and †Division of Pediatric Cardiology, Texas Children's Hospital, Houston, Texas

Treatments Used in Pediatric Patients with BrS

Treatment	MD's Recommendation in Symptomatic Patients	MD's Recommendation in Asymptomatic Patients
ICD	97%	24%
Antipyretics	76%	93%
Pharmacologic	31%	9%
Quinidine	58%	60%
β-blocker	37%	20%
Mexiletine	5%	–
Not specified	16%	40%
Admission during fever	3%	2%
AED	2%	2%

AED = automated external defibrillator; BrS = Brugada syndrome; ICD = implantable cardioverter defibrillator.

PACE 2015

Impact of clinical and genetic findings on the management of young patients with Brugada syndrome.

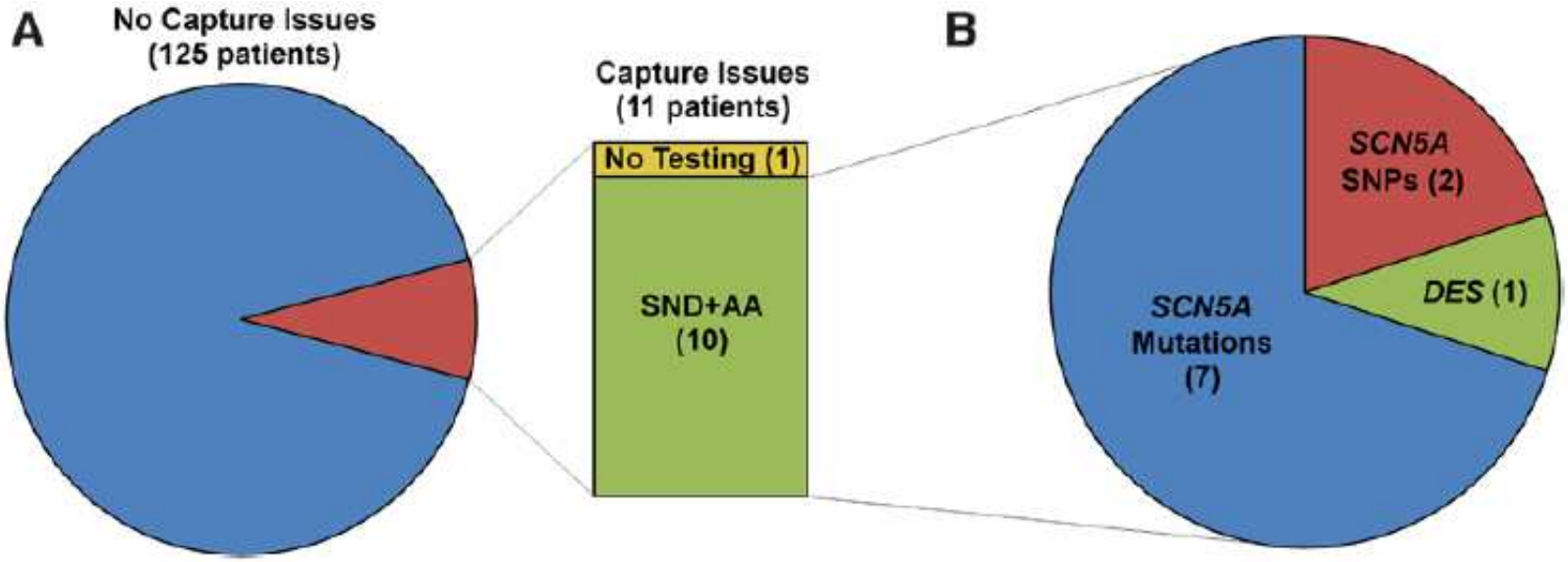
Andorin, Antoine; Behr, Elijah R; Denjoy, Isabelle; Crotti, Lia; Dagradi, Federica; Jesel, Laurence; Sacher, Fréderic; Petit, Bertrand; Mabo, Philippe; Maltret, Alice; Wong, Leonie C H; Degand, Bruno; Bertaux, Géraldine; Maury, Philippe; Dulac, Yves; Delasalle, Béatrice; Gourraud, Jean-Baptiste; Babuty, Dominique; Blom, Nico A; Schwartz, Peter J; Wilde, Arthur A

in 4 patients. Three demonstrated intermittent complete loss of ventricular capture after implantation: 1 has recurrent syncope, 2 eventually died. Genetic testing performed in 10 demonstrated 7 patients with 6 distinct *SCN5A* mutations, all predicted to be severe loss-of-function mutations by bioinformatic analyses. In the remaining patients, although putative pathogenic mutations

Conclusions—This study suggests that significant capture issues at implant may be because of loss-of-function *SCN5A* mutations, providing new insights into *SCN5A* function. Recognition of this association may be critical for planning device implantation strategies and patient follow-up. (***Circ Arrhythm Electrophysiol.* 2015;8:1105-1112.**

Loss-of-Function *SCN5A* Mutations Associated With Sinus Node Dysfunction, Atrial Arrhythmias, and Poor Pacemaker Capture

David Y. Chiang, Jeffrey J. Kim, Santiago O. Valdes, Caridad de la Uz, Yuxin Fan, Jeffrey Orcutt, Melissa Domino, Melissa Smith, Xander H.T. Wehrens, Christina Y. Miyake

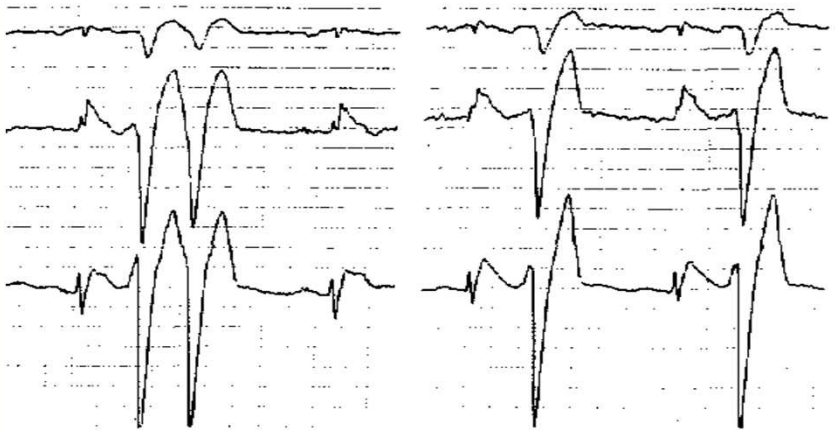


Circulation EP 2015

Baseline

Isoprotcrenol
1.5 μ g/min div

Acetylcholine



Miyazaki, JACC 1996

Recommendations for Competitive Athletics

- Asymptomatic (Genotype positive, phenotype negative)
  - Full participation with precautionary measures
    - Avoid drugs that exacerbate BrS
    - Electrolyte/hydration replenishment
    - Avoidance of hyperthermia or training related-related heat exhaustion or heat stroke
    - Prompt treatment for hyperthermia, febrile illnesses
    - Acquisition of a personal AED
    - Establish an emergency medical plan with school or team officials
- Symptomatic and/or Phenotype positive
  - Full participation with precautionary measures
  - Asymptomatic on appropriate treatment for 3 months

AHA/ACC Scientific Statement 2015

Two Studies on Exercise in Brugada Syndrome

50 males with BrS (SCN5A + and SCN5A-) vs. 35 controls

- ↑ QRS duration with exercise in BrS(SCN5A+)
- J point elevation and Coved pattern in earlyrecovery
- No VT/VF with exercise

Exercise-Induced ECG Changes in Brugada Syndrome

Ahmad S. Amin, MD; Elisabeth A.A. de Groot, BSc; Jan M. Ruijter, PhD;
Arthur A.M. Wilde, MD, PhD; Hanno L. Tan, MD, PhD

Background—Ventricular arrhythmia occurrence during exercise is reported in Brugada syndrome (BrS). Accordingly, experimental studies suggest that BrS-linked *SCN5A* mutations reduce sodium current more at fast heart rates. Yet, the effects of exercise on the BrS ECG phenotype have not been studied. We aimed to assess ECG responses to exercise in BrS and determine whether these responses are affected by the presence of an *SCN5A* mutation.

Methods and Results—ECGs at baseline, at peak exercise, and during recovery were analyzed from 35 male control subjects, 25 BrS men without *SCN5A* mutation (BrS_{SCN5A-}), and 25 BrS men with *SCN5A* mutation (BrS_{SCN5A+}; 15 with missense mutation and 10 with mutation leading to premature truncation of the protein). No differences existed in clinical phenotype between BrS groups. At baseline, BrS_{SCN5A-} and BrS_{SCN5A+} patients had lower heart rates, wider QRS, shorter QT_c, and higher peak J-point amplitudes than control subjects; BrS_{SCN5A+} patients also had longer PR than BrS_{SCN5A-} and control subjects. Exercise resulted in PR shortening in all groups, more QRS widening in BrS_{SCN5A+} than in BrS_{SCN5A-} and control subjects, and less QT shortening in BrS_{SCN5A-} and BrS_{SCN5A+} than in control subjects. The latter resulted in QT_c shortening in control subjects but QT_c prolongation in BrS_{SCN5A-} and BrS_{SCN5A+}. Finally, the increase in peak J-point amplitude during exercise was similar in all 3 groups but resulted in a coved-type pattern only in BrS_{SCN5A-} and BrS_{SCN5A+}.

Conclusions—Exercise aggravated the ECG phenotype in BrS. The presence of an *SCN5A* mutation was associated with further conduction slowing at fast heart rates. Possible mechanisms that may explain the observed ECG changes are discussed. (***Circ Arrhythmia Electrophysiol.* 2009;2:531-539.**)

Key Words: Brugada syndrome ■ arrhythmia ■ exercise ■ tachycardia ■ *SCN5A*, mutation ■ ECG

93 patients with BrS (SCN5A + and SCN5A-) vs. 106 controls

- ST↑ ≥0.05 mm in 37% of BrS
- ST ↑ correlated with ↑ HR recovery
- Risk factor for subsequent VT/VF in both symptomatic and asymptomatic patients

Journal of the American College of Cardiology
Vol. 56, No. 19, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.06.033

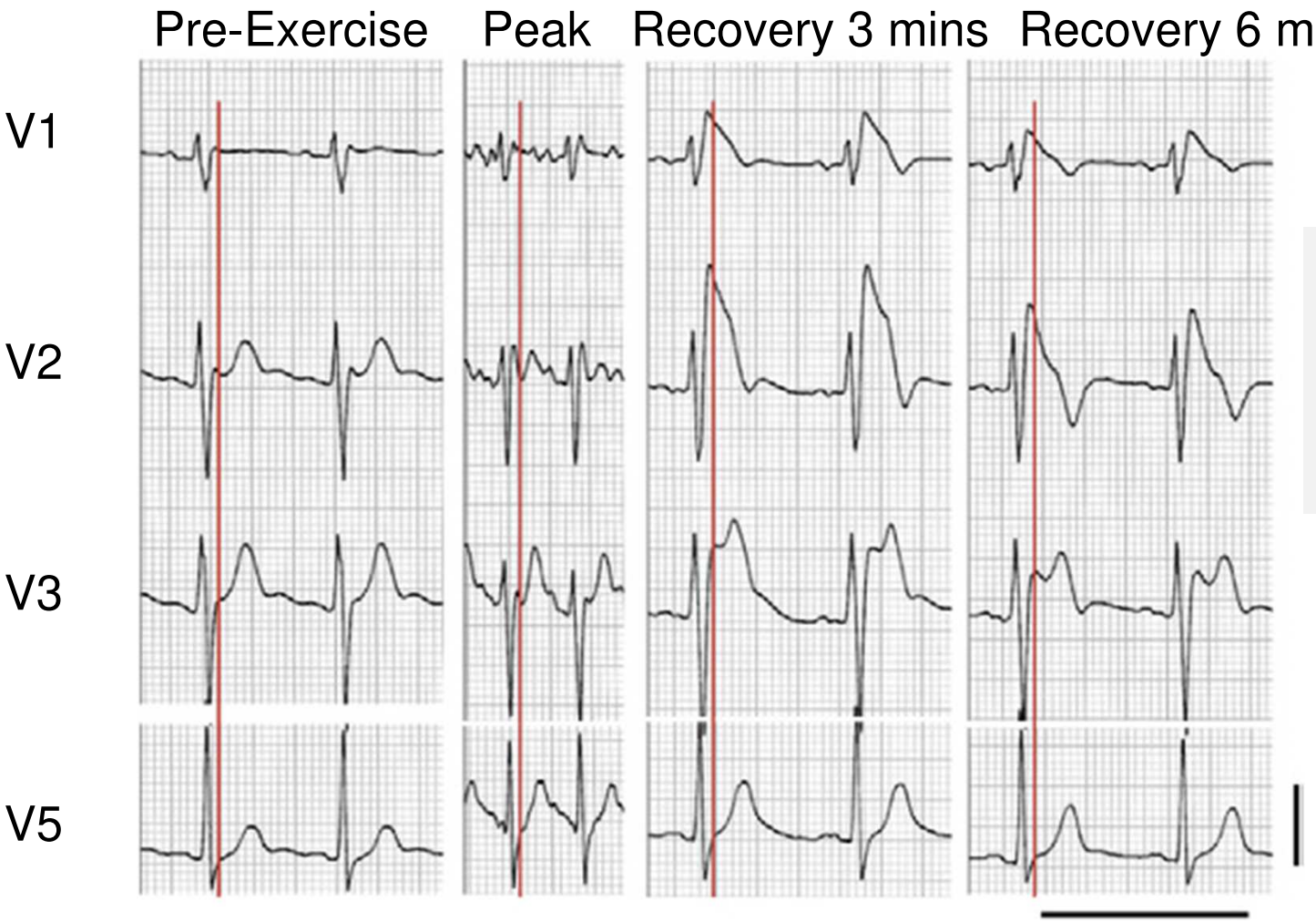
Published by Elsevier Inc.

Heart Rhythm Disorders

Augmented ST-Segment Elevation During Recovery From Exercise Predicts Cardiac Events in Patients With Brugada Syndrome

Hisaki Makimoto, MD,* Eiichiro Nakagawa, MD, PHD,† Hiroshi Takaki, MD, PHD,*
Yuko Yamada MD,* Hideo Okamura, MD,* Takashi Noda, MD, PHD,* Kazuhiro Satomi, MD, PHD,*
Kazuhiro Suyama, MD, PHD,* Naohiko Aihara, MD,* Takashi Kurita, MD, PHD,‡
Shiro Kamakura, MD, PHD,* Wataru Shimizu, MD, PHD*

Suita and Osaka, Japan



Exacerbation of BrS Pattern in Recovery after Exercise

Makimoto, JACC 2010

Exercise in Brugada Syndrome

EXERCISE

Acute Sympathetic Stimulation
Parasympathetic Withdrawal

↑ Hear Rate
-↓ ST Elevation

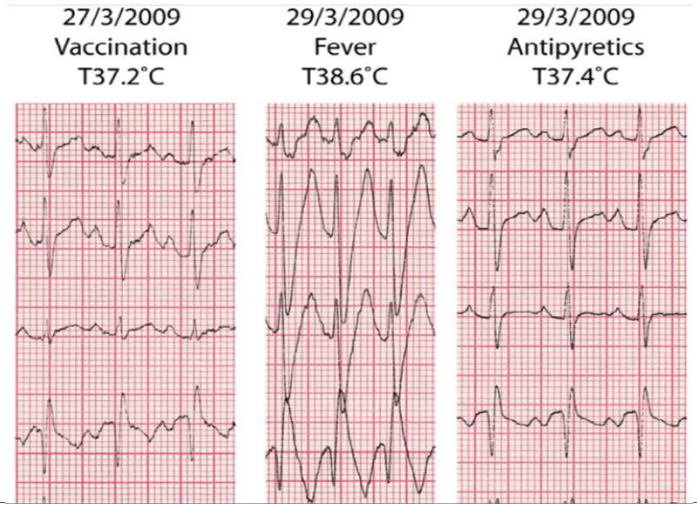
? ↓ Ventricular Arrhythmia susceptibility during sports

RECOVERY FROM EXERCISE

Vagal rebound

Rapid Heart rate Recovery
-↑ ST segment Elevation
-↓ Hear Rate at rest

? ↑ Ventricular Arrhythmia Susceptibility AFTER sports
-especially in conditioned athletes



OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

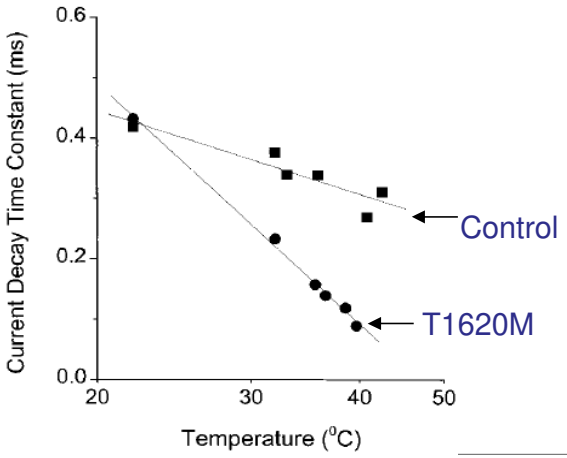
PEDIATRICS

Fever-Induced Life-Threatening Arrhythmias in Children Harboring an *SCN5A* Mutation

AUTHORS: Priya Chockalingam, MBBS,[a] Lukas A. Rammeloo, MD,[b] Pieter G. Postema, MD,[a] Jarda Hruda, MD,[b] Sally-Ann B. Clur, MD,[c] Nico A. Blom, MD, PhD[c] and Arthur A. Wilde, MD, PhD[a]

abstract

Cardiac channelopathies caused by *SCN5A* mutation are well tolerated



Cellular Biology

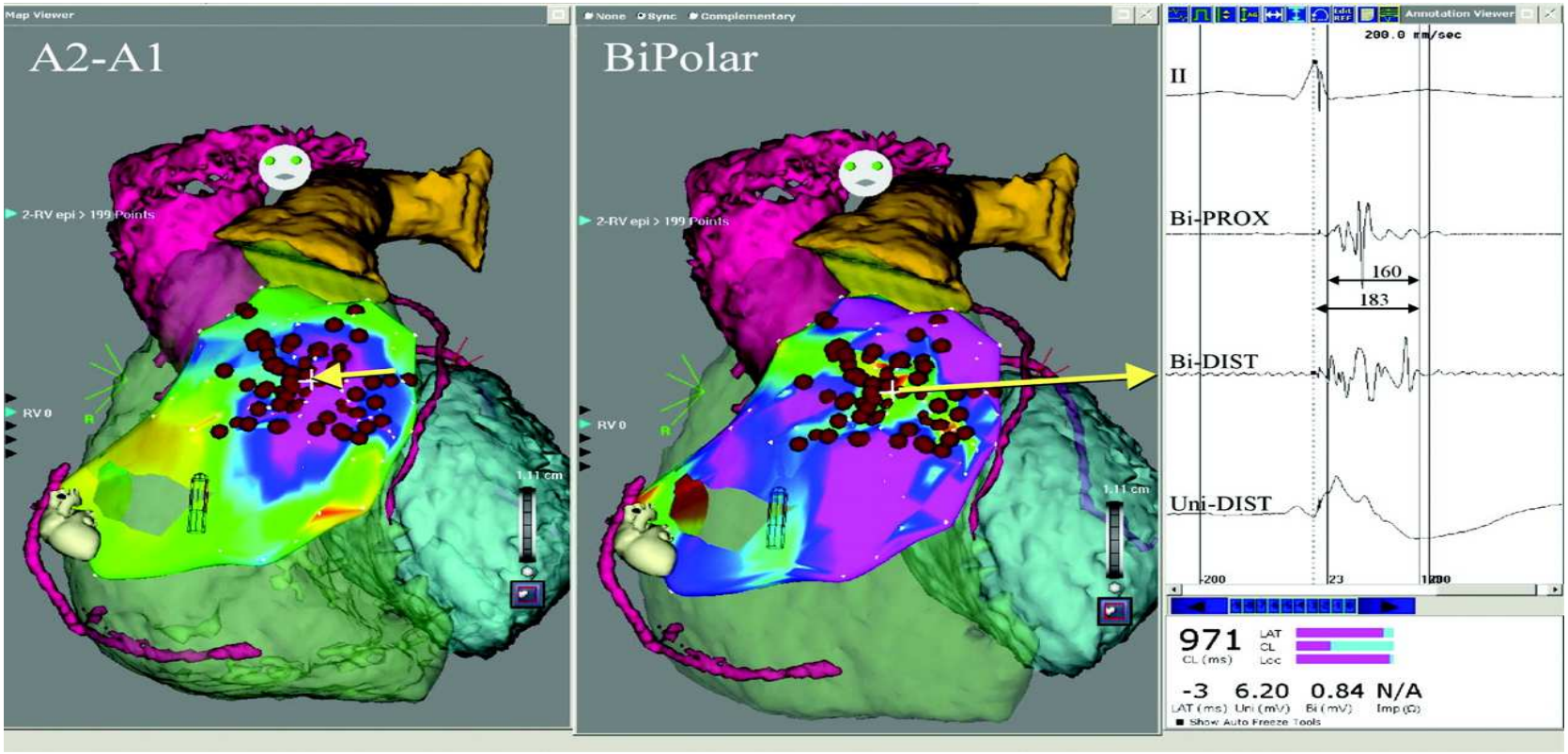
Ionic Mechanisms Responsible for the Electrocardiographic Phenotype of the Brugada Syndrome Are Temperature Dependent

Robert Dumaine, Jeffrey A. Towbin, Pedro Brugada, Matteo Vatta, Dmitri V. Nesterenko, Vladislav V. Nesterenko, Josep Brugada, Ramon Brugada, Charles Antzelevitch

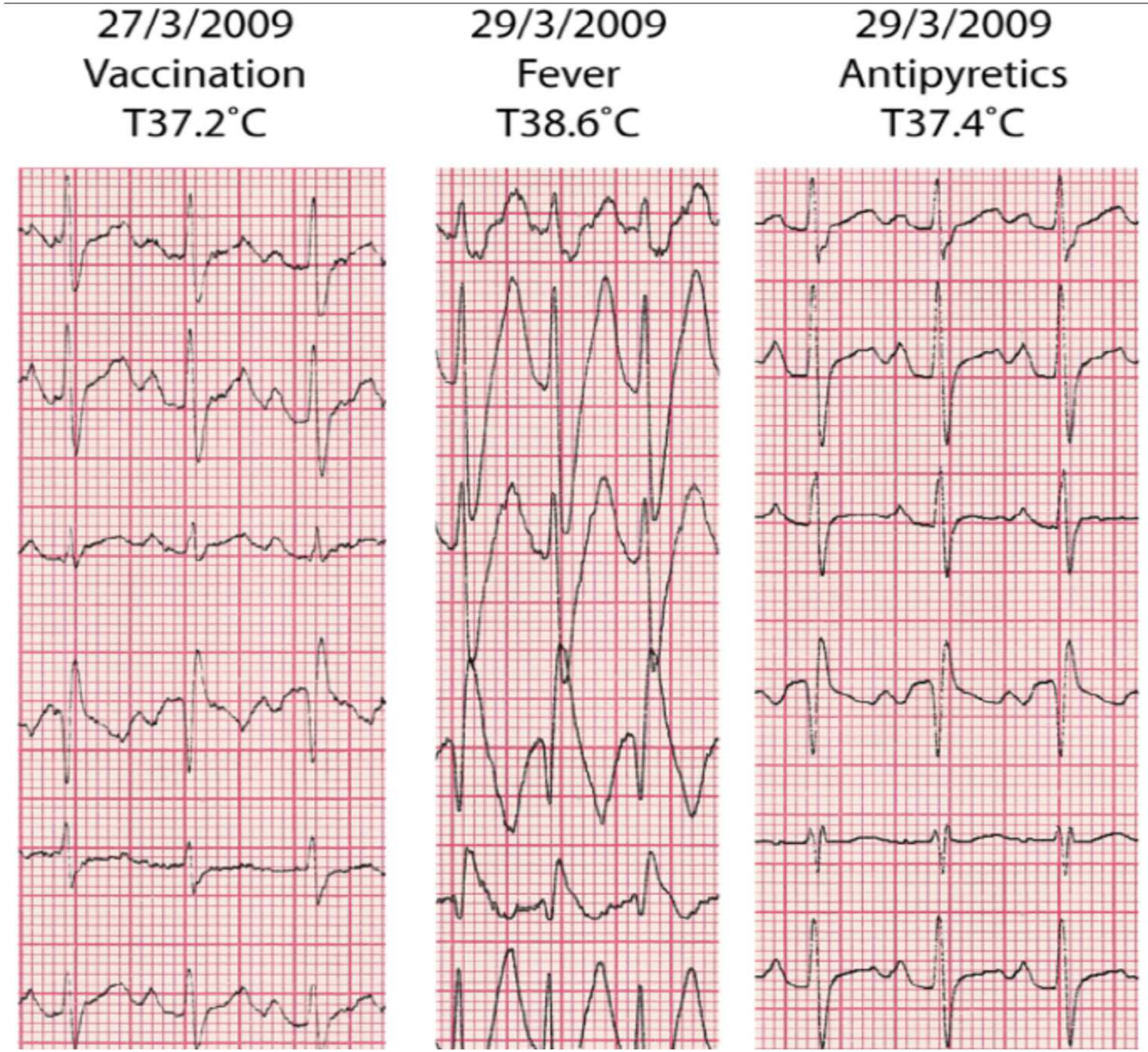
ORIGINAL ARTICLES

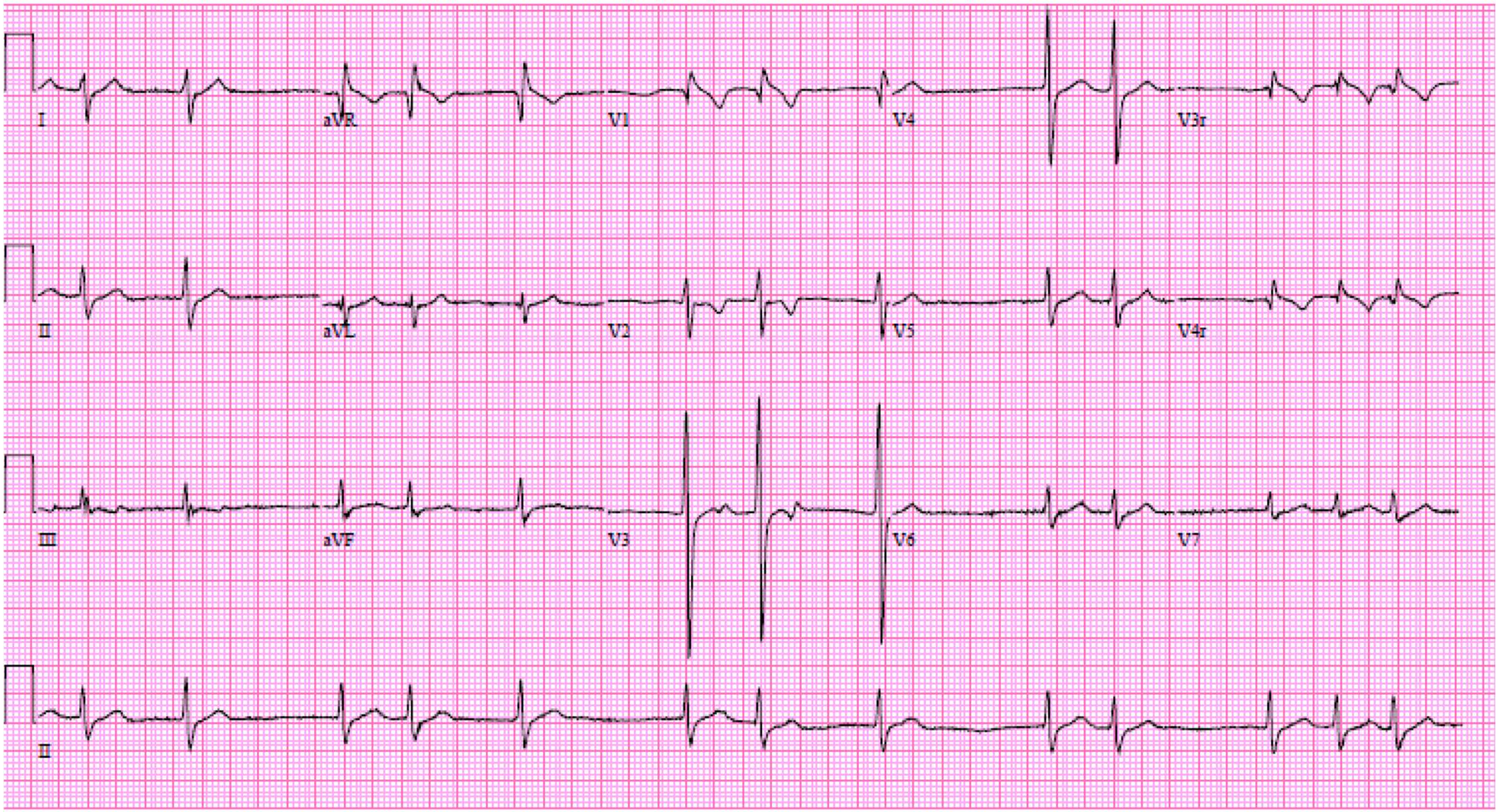
Prevention of Ventricular Fibrillation Episodes in Brugada Syndrome by Catheter Ablation Over the Anterior Right Ventricular Outflow Tract Epicardium

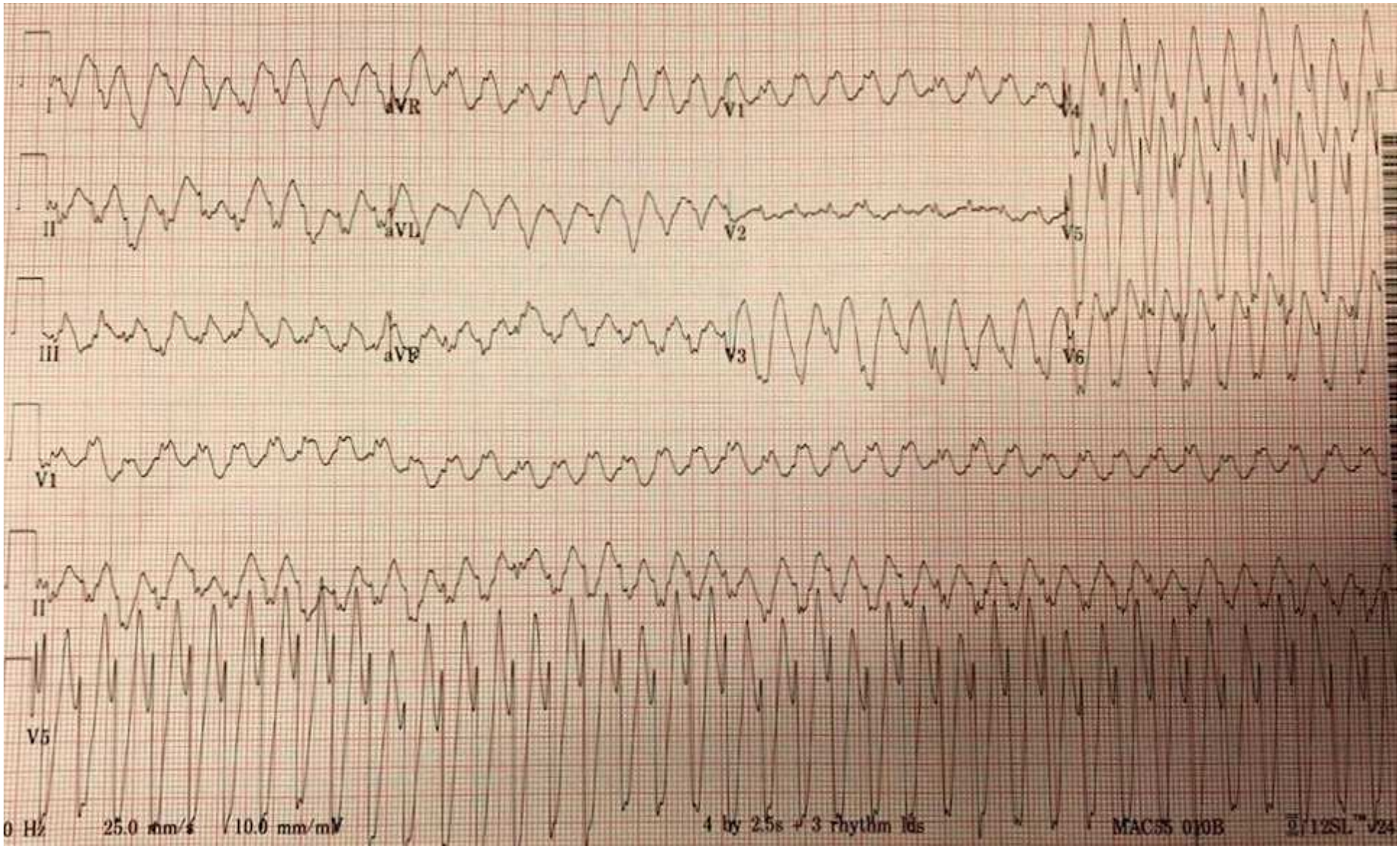
Koonlawee Nademanee, Gumpanart Veerakul, Pakorn Chandanamattha, Lertlak Chaothawee, Aekarach Ariyachaipanich, Kriengkrai Jirasirirojanakorn, Khanchit Likittanasombat, Kiertijai Bhuripanyo, Tachapong Ngarmukos



Circulation. 2011;123:1270-1279


27/3/2009
Vaccination
T37.2˚C
29/3/2009
Fever
T38.6˚C
29/3/2009
Antipyretics
T37.4˚C


I
aVR
V1
V4
V3r
II
aVL
V2
V5
V4r
III
aVF
V3
V6
V7
II


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5
0 Hz
25.0 mm/s
10.0 mm/mV
4 by 2.5s + 3 rhythm lds
MAC35 010B
12SL™ v24

Test(s) Requested: Brugada Syndrome (BrS) Panel

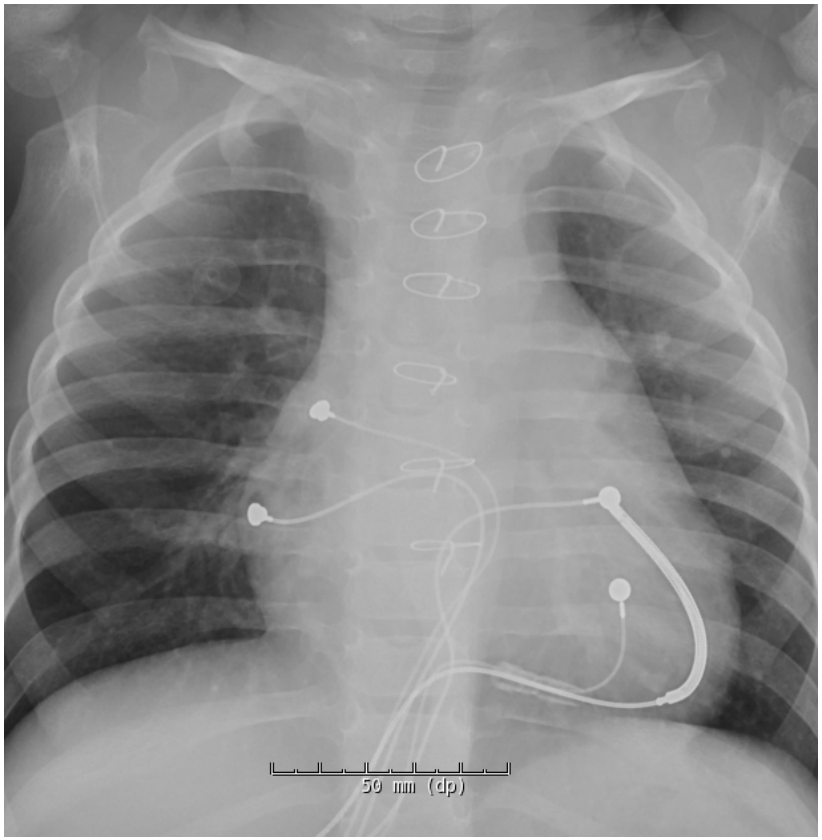
Genes Evaluated: SCN5A (BrS1), GPD1L (BrS2), CACNA1C (BrS3), CACNB2 (BrS4), SCN1B (BrS5), KCNE3 (BrS6), SCN3B (BrS7)

Result: **SEE INTERPRETATION**

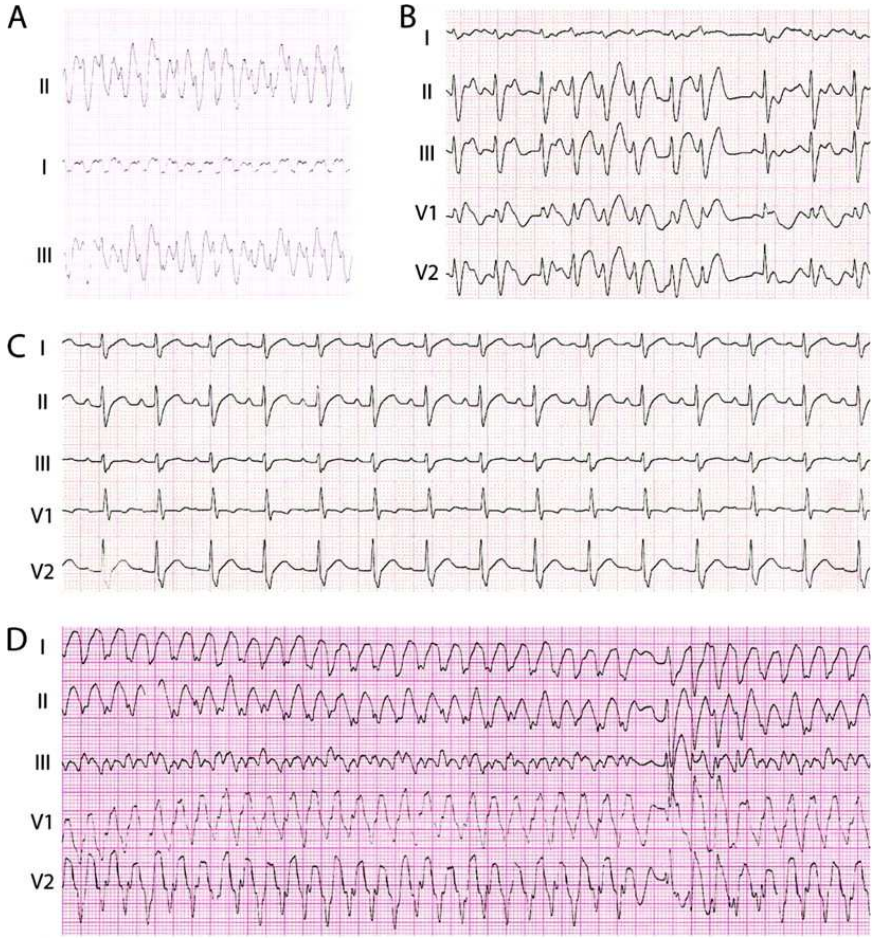
Gene	Coding DNA	Variant	Zygosity	Classification
SCN5A	c.3911 C>T	p.Thr1304Met (T1304M)	Heterozygous	Likely Pathogenic Variant
SCN5A	c.655 C>T	p.Arg219Cys (R219C)	Heterozygous	Likely Pathogenic Variant
SCN5A	c.5126 C>T	p.Thr1709Met (T1709M)	Heterozygous	Variant of Uncertain Significance
CACNB2	c.56 C>T	p.Ser19Leu (S19L)	Heterozygous	Variant of Uncertain Significance

No definitive pathogenic variants were detected by sequence analysis of 7 genes in this individual.

Interpretation: **This individual is heterozygous for missense variants in the SCN5A gene that are likely pathogenic. This individual is also heterozygous for variants of uncertain significance in the SCN5A and CACNB2 genes.**


50 mm (dp)

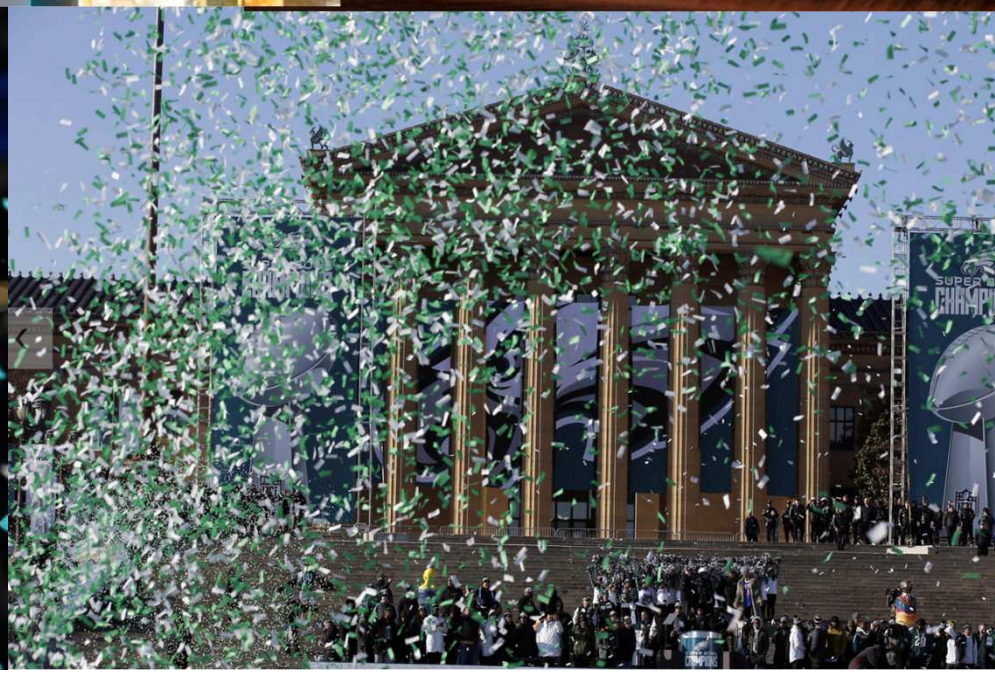
Ambulance rhythm strip (A) and ECG on admission (B), both showing wide-complex tachycardia, which could have been supraventricular tachycardia with aberrant conduction or VT (less likely).



Priya Chockalingam et al. Pediatrics 2011;127:e239-e244


SUPER BOWL
CHAMPIONS


The Children's Hospital of Philadelphia



Sahaja Yoga: The Yoga of Self-Realization

www.Psy-Minds.com

Risk stratification and management in Catecholaminergic Polymorphic Ventricular Tachycardia

Recommendations	Class[a]	Level[b]	
The following lifestyle changes are recommended in all patients with a diagnosis of CPVT: avoidance of competitive sports, strenuous exercise and stressful environments.	I	C	
Beta-blockers are recommended in all patients with a clinical diagnosis of CPVT, based on the presence of documented spontaneous or stress-induced VAs.	I	C	
ICD implantation in addition to beta-blockers with or without flecainide is recommended in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope or polymorphic/bidirectional VT despite optimal therapy.	I	C	
Therapy with beta-blockers should be considered for genetically positive family members, even after a negative exercise test.	IIa	C	461, 462
Flecainide should be considered in addition to beta-blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers, when there are risks/ contraindications for an ICD or an ICD is not available or rejected by the patient.	IIa	C	463
Flecainide should be considered in addition to beta-blockers in patients with a diagnosis of CPVT and carriers of an ICD to reduce appropriate ICD shocks.	IIa	C	463
Left cardiac sympathetic denervation may be considered in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/ bidirectional VT/several appropriate ICD shocks while on beta-blockers or beta-blockers plus flecainide and in patients who are intolerant or have contraindication to beta-blockers.	IIb	C	464, 465
Invasive EPS with PVS is not recommended for stratification of SCD risk.	III	C	14

Risk stratification and management in Catecholaminergic Polymorphic Ventricular Tachycardia		
Recommendations	**Class[a]**	**Level[b]**
The following lifestyle changes are recommended in all patients with a diagnosis of CPVT: avoidance of competitive sports, strenuous exercise, and stressful environments.	I	C
Beta-blockers are recommended in all patients with a clinical diagnosis of CPVT, based on the presence of documented spontaneous or stress-induced VAs.	I	C
ICD implantation in addition to beta-blockers with or without flecainide is recommended in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope, or polymorphic/ bidirectional VT despite optimal therapy.	I	C

ICD programming: **long delays before shock** - painful shocks can increase sympathetic tone - trigger arrhythmias - malignant cycle of ICD shocks and death.

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
V2
V3
V4
V5
V6
V7
V3R
V4R

B-Blocker therapy resulted in 83% reduction in cardiac events in females with LQT3 but not in males where the incidence of cardiac events is significantly less

-Typically use other Na-channel blockers as "**Add On**" therapy to B-blockers

ORIGINAL RESEARCH ARTICLE

Clinical Aspects of Type 3 Long-QT Syndrome

An International Multicenter Study

BACKGROUND: Risk stratification in patients with type 3 long-QT syndrome (LQT3) by clinical and genetic characteristics and effectiveness of β-blocker therapy has not been studied previously in a large LQT3 population.

METHODS: The study population included 406 LQT3 patients with 51 sodium channel mutations; 391 patients were known to be event free during the first year of life and were the focus of our study. Clinical, electrocardiographic, and genetic parameters were acquired for patients from 7 participating LQT3 registries. Cox regression analysis was used to evaluate the independent contribution of clinical, genetic, and therapeutic factors to the first occurrence of time-dependent cardiac events (CEs) from age 1 to 41 years.

RESULTS: Of the 391 patients, 118 (41 males, 77 females) patients (30%) experienced at least 1 CE (syncope, aborted cardiac arrest, or long-QT syndrome–related sudden death), and 24 (20%) suffered from LQT3-related aborted cardiac arrest/sudden death. The risk of a first CE was directly related to the degree of QTc prolongation. Cox regression analysis revealed that time-dependent β-blocker therapy was associated with an 83% reduction in CEs in females (P=0.015) but not in males (who had many fewer events), with a significant sex × β-blocker interaction (P=0.04). Each 10-ms increase in QTc duration up to 500 ms was associated with a 19% increase in CEs. Prior syncope doubled the risk for life-threatening events (P<0.02).

CONCLUSIONS: Prolonged QTc and syncope predispose patients with LQT3 to life-threatening CEs. However, β-blocker therapy reduces this risk in females; efficacy in males could not be determined conclusively because of the low number of events.

Arthur A.M. Wilde, MD, PhD*
Arthur J. Moss, MD*
Elizabeth S. Kaufman, MD*
Wataru Shimizu, MD, PhD*
Derick R. Peterson, PhD
Jesaia Benhorin, MD
Coeli Lopes, PhD
Jeffrey A. Towbin, MD
Carla Spazzolini, DVM, MS
Lia Crotti, MD, PhD
Wojciech Zareba, MD, PhD
Ilan Goldenberg, MD
Jørgen K. Kanters, MD, PhD
Jennifer L. Robinson, MS
Ming Qi, PhD
Nynke Hofman, PhD
David J. Tester, BS
Connie R. Bezzina, PhD
Marielle Alders, PhD
Takeshi Aiba, MD, PhD
Shiro Kamakura, MD, PhD
Yoshihiro Miyamoto, MD, PhD
Mark L. Andrews, BBA
Scott McNitt, MS
Bronislava Polonsky, MS
Peter J. Schwartz, MD
Michael J. Ackerman, MD, PhD

*Drs Wilde, Moss, Kaufman, and Shimizu contributed equally.

Correspondence to: Arthur A.M. Wilde, MD, PhD, Academic Medical Center, Department of Clinical and Experimental Cardiology, Meibergdreef 9; 1105 AZ The Netherlands. E-mail a.a.wilde@amc.nl

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

Recommendations	Class[a]	Level[b]
Beta-blockers are recommended in patients with a clinical diagnosis of LQTS.	I	B
ICD implantation with the use of beta-blockers is recommended in		

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013

Class I

1. The following lifestyle changes **are recommended** in all patients with a diagnosis of LQTS:
   a) Avoidance of QT-prolonging drugs (www.qtdrugs.org)
   b) Identification and correction of electrolyte abnormalities that may occur during diarrhea, vomiting, metabolic conditions or imbalanced diets for weight loss.
2. Beta-blockers **are recommended** for patients with a diagnosis of LQTS who are:

on beta-blocker therapy.

8. LCSD **can be useful** in patients with a diagnosis of LQTS who experience breakthrough events while on therapy with beta-blockers/ICD.
9. Sodium channel blockers **can be useful**, as add-on therapy, for LQT3 patients with a QTc >500 ms who shorten their QTc by >40 ms following an acute oral drug test with one of these compounds.

Oral Beta- blockers are still **first line** therapy for preventing life threatening arrhythmias in **all** Long QT Syndromes