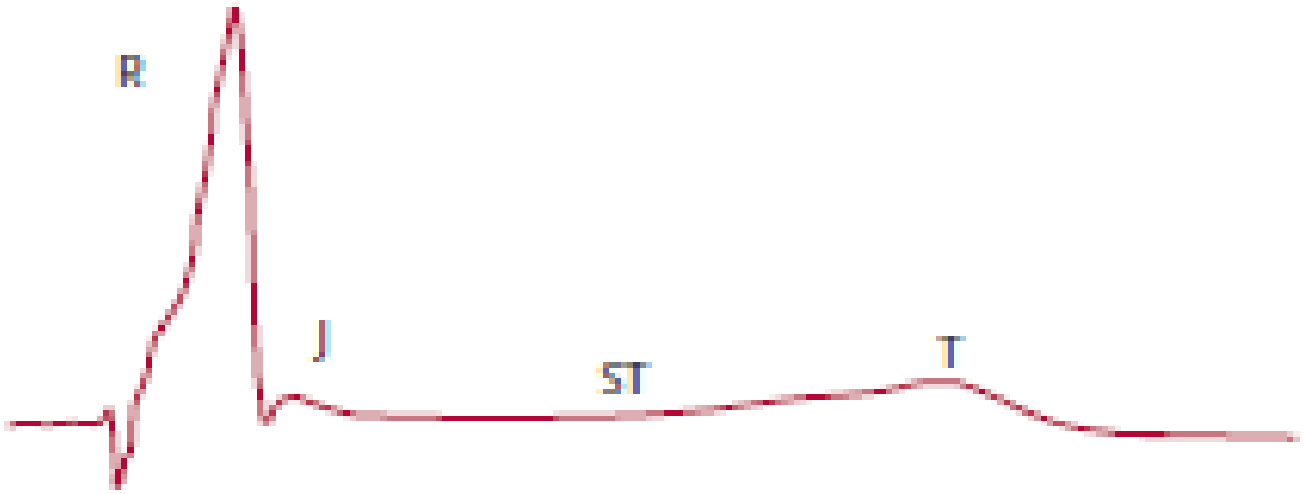
Exercise and channelopathies

Georgios Theodorakis

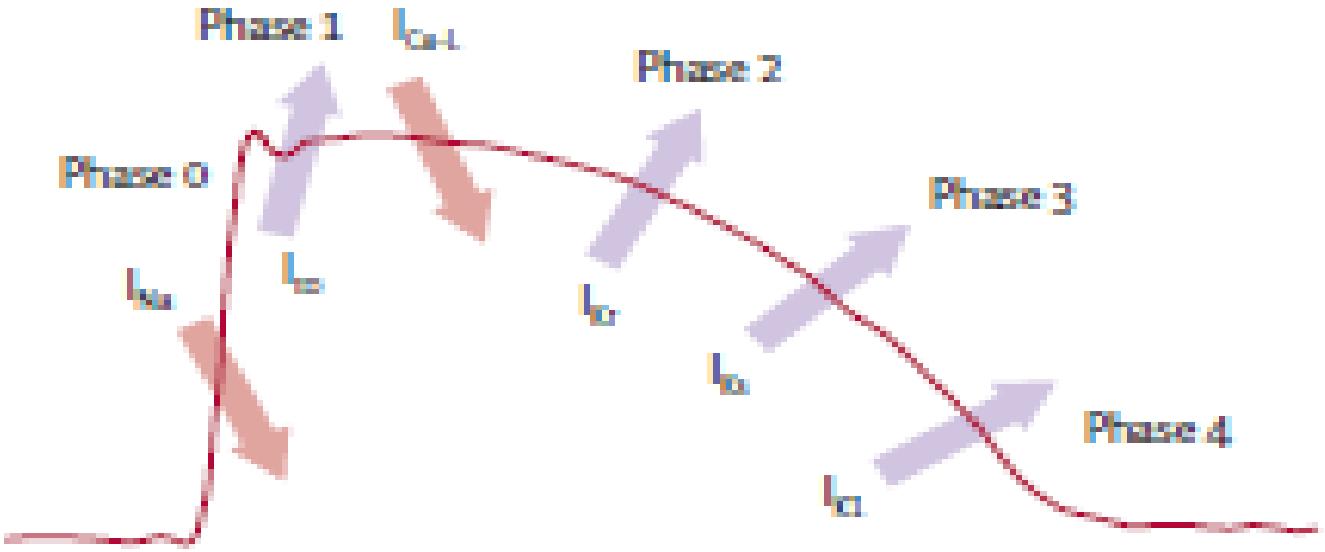
Channelopathies

- Long Q-T syndrome
- Short QT syndrome
- Brugada syndrome
- Catecholaminergic polymorphic ventricular tachycardia

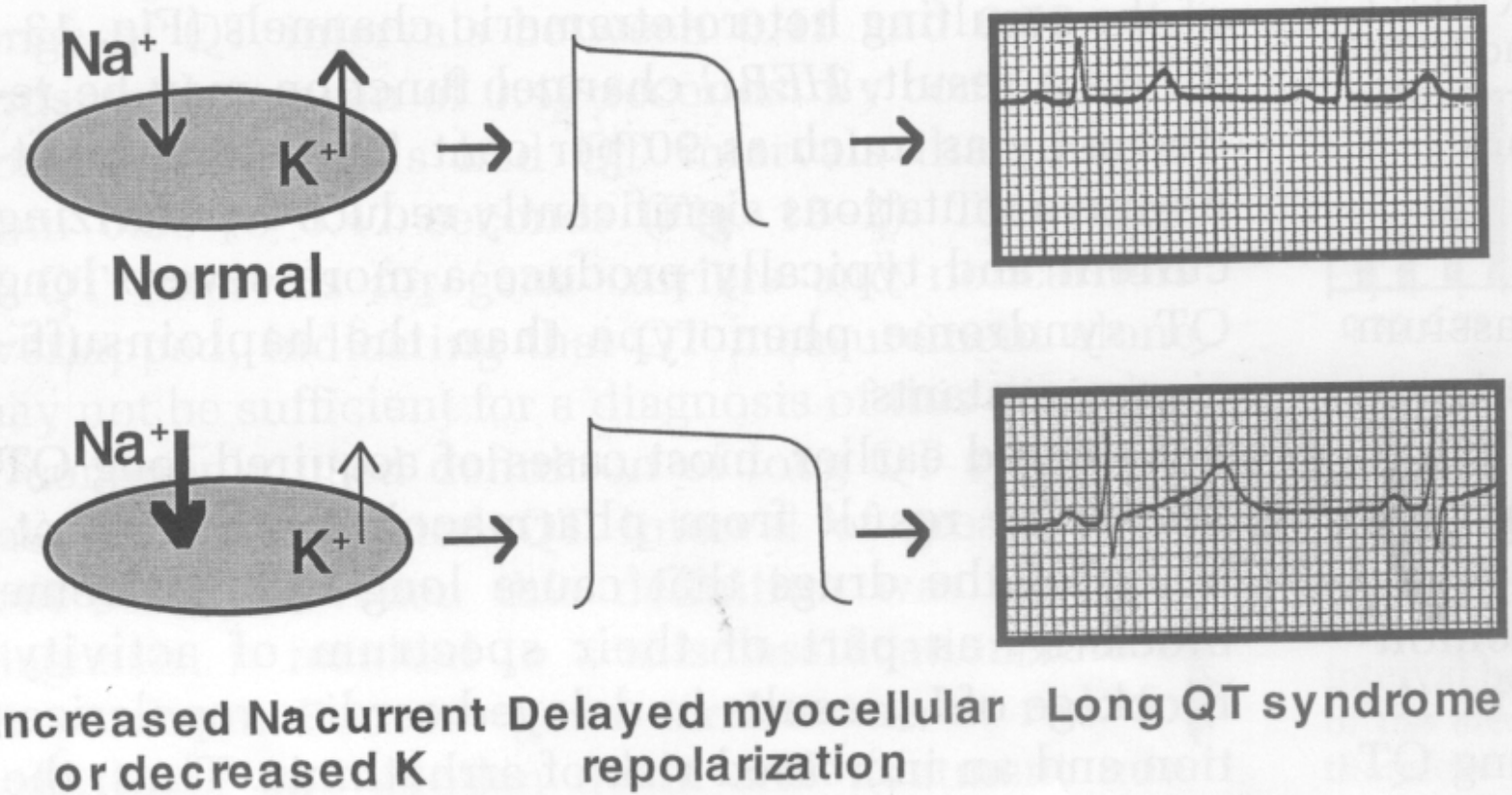
ECG



Action potential



Common cellular mechanism of LQT



Long QT Syndrome

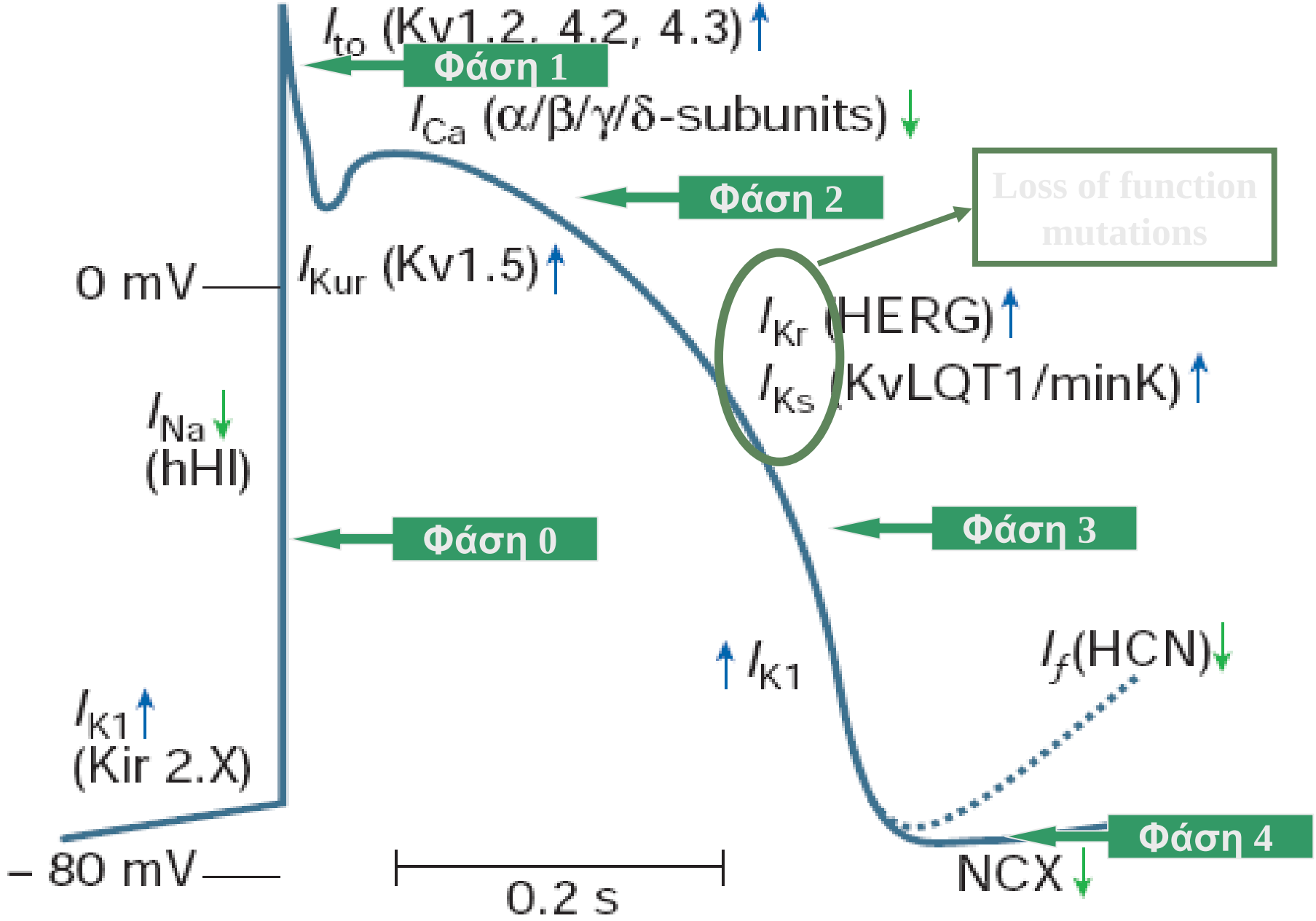
- Syncope during exercise or stress
- Sudden death
- Young age
- ECG Findings (long QTc >450 msec)
- TWA alternance
- Sinus bradycardia
- Chronotropic incompetence

	Points
ECG findings*	
QTc†	
≥480 ms	3
460–470 ms	2
450 ms (in men)	2
Torsades de pointes‡	2
T-wave alternans	1
Notched T wave in three leads	1
Low heart rate for age§	0·5
Clinical history	
Syncope‡	
With stress	2
Without stress	1
Congenital deafness	0·5
Family history¶	
Family members with definite LQTS‖	1
Unexplained sudden cardiac death at age <30 years among immediate family members	0·5

*Without medication or disorders known to affect such ECG features. †Calculated by Bazett's formula. ‡Mutually exclusive. §Resting heart rate below second percentile for age. ¶Same family member cannot be counted in A and B. ‖Defined as LQTS score ≥4 (scoring: ≤1, low probability of LQTS; 2–3, intermediate probability of LQTS; ≥4, high probability of LQTS).

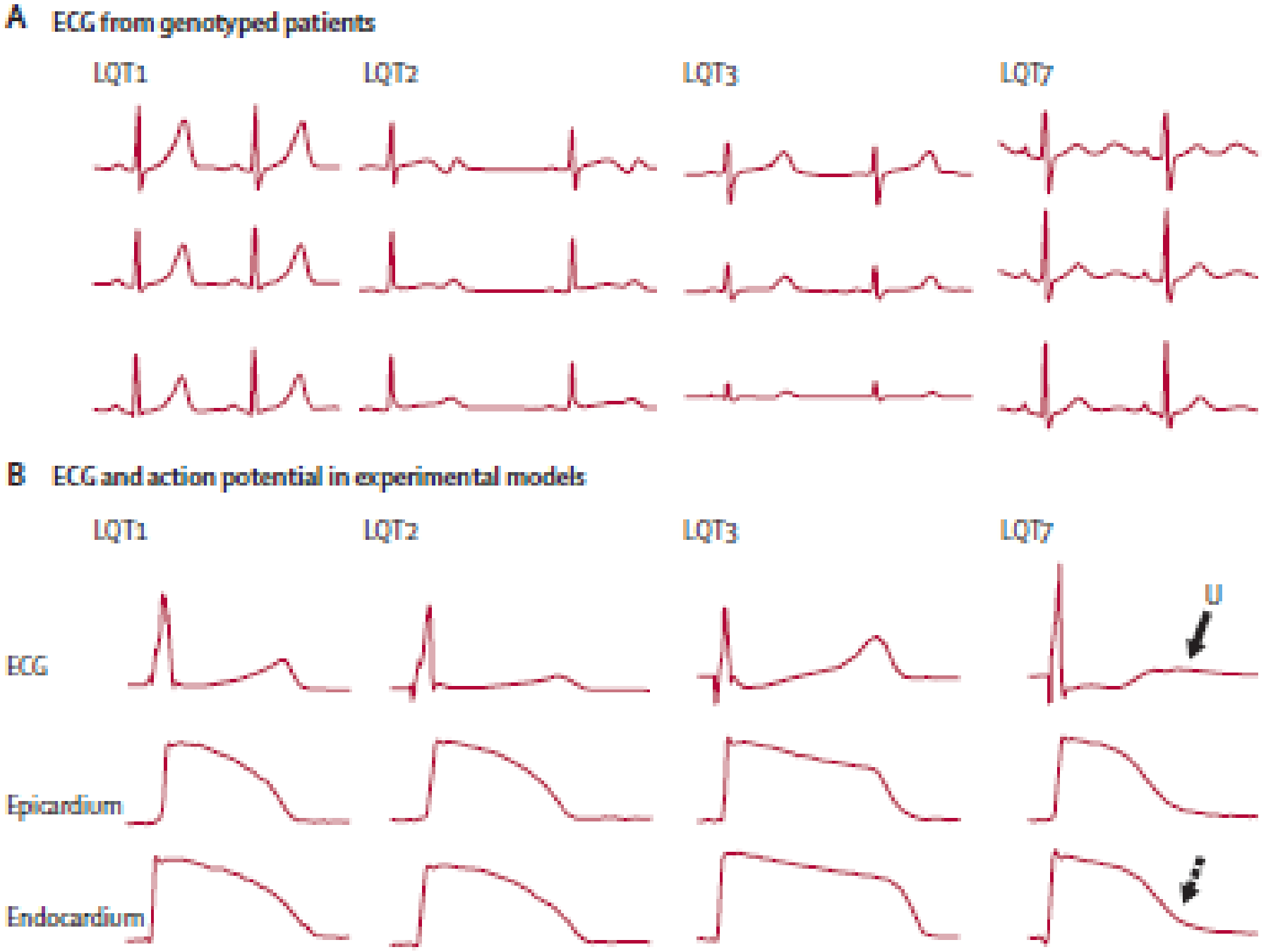
Table 2: Diagnostic criteria for LQTS in 1993

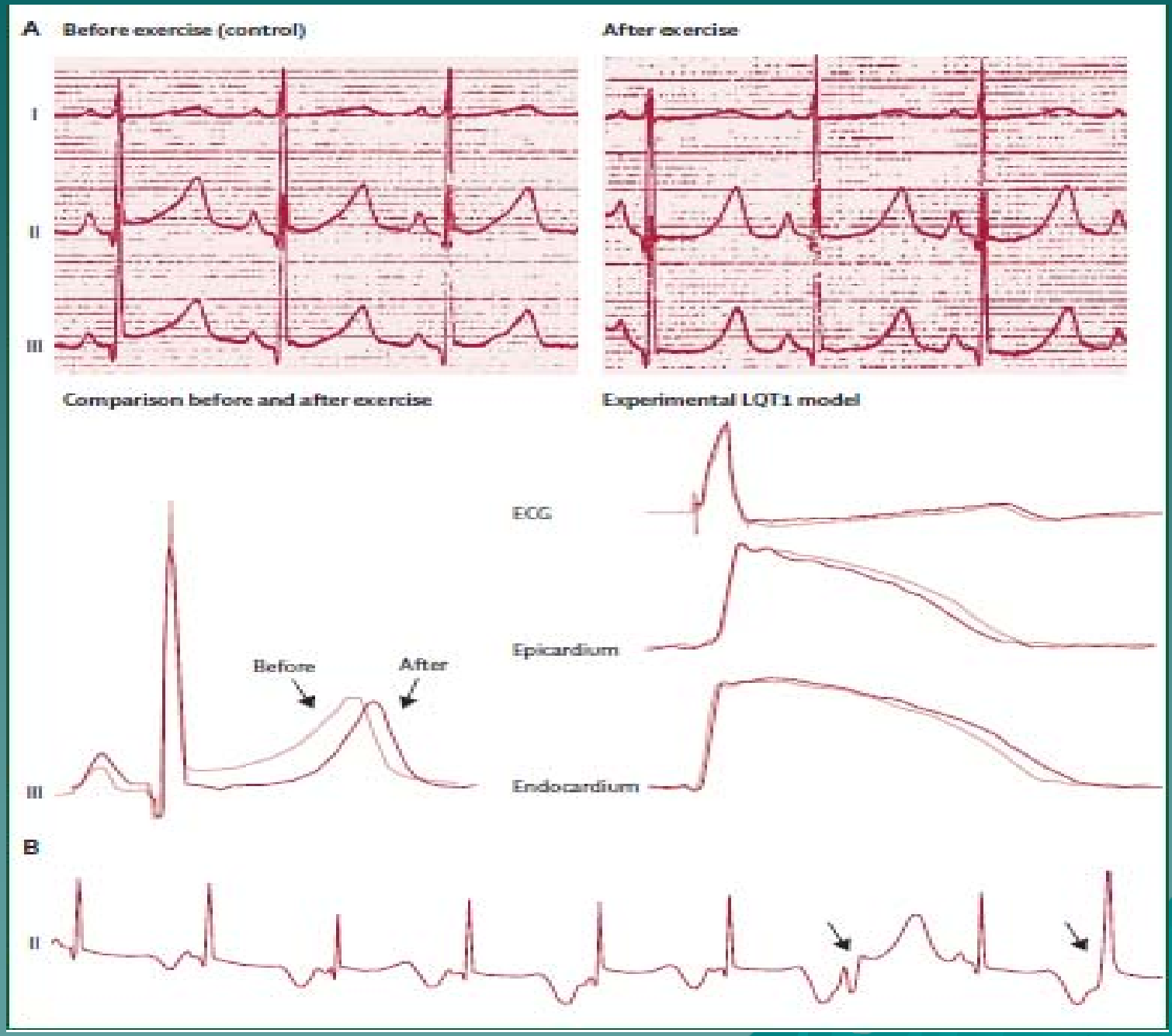
Το σύνδρομο μακρού QT



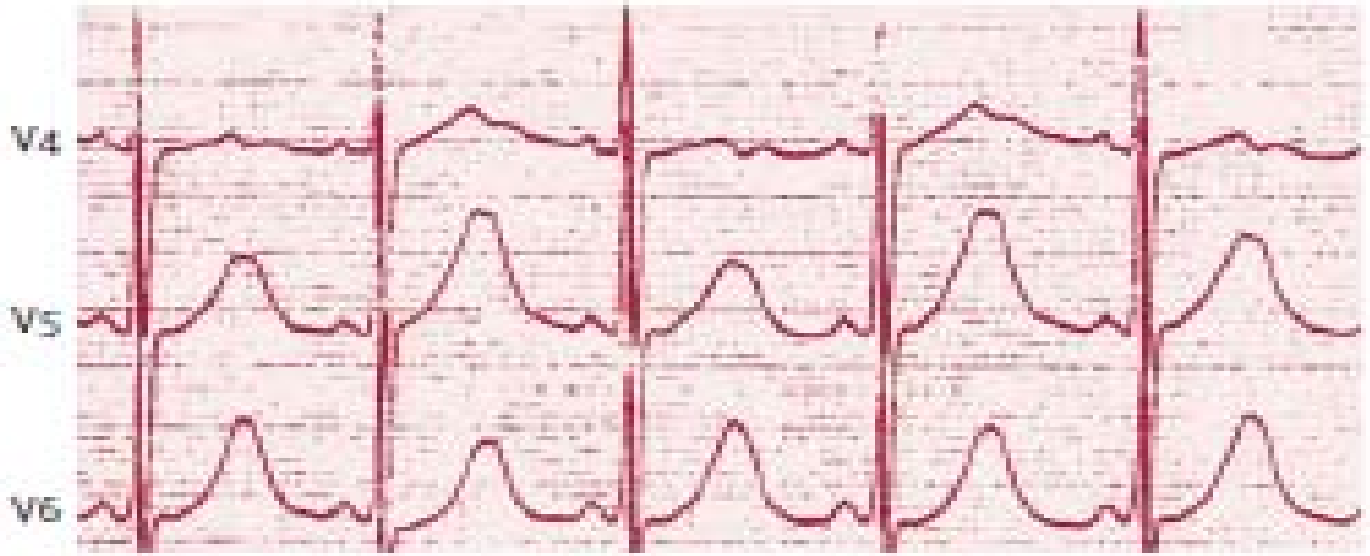
Long QT Syndrome (LQTS)* including Sudden Infant Death Syndrome (SIDS)[£]

Gene	Locus	Syndrome	Protein & subunit	Function & abnormality	Occurs In[¶]	Ref.
KCNQ1	11p15.5	LQTS1, SIDS[£]	$K_V7.1$ α	I_{Ks} ↓ KvLQT1	30-35%	74
KCNH2	7q35	LQTS2, SIDS[£]	$K_V11.1$ α	I_{Kr} ↓ HERG	25-30%	75
SCN5A	3p21	LQTS3, SIDS[£]	$Na_V1.5$ α	I_{Na} ↑	5-10%	12, 26
ANK2	4q25	LQTS4, ABS[$]	Ankyrin-B	$I_{Na,K}$ ↓ I_{NCX} ↓	1-2%	43-45
KCNE1	21q22.1	LQTS5	minK β	I_{Ks} ↓	1%	76-78
KCNE2	21q22.1	LQTS6, SIDS[£]	MiRP1 β	I_{Kr} ↓	rare	79
KCNJ2	17q23	LQTS7, ATS[#]	Kir2.1 α	I_{K1} ↓	rare	80, 81
CACNA1C	12p13.3	LQTS8, TS[&]	$Ca_V1.2$ α_{1c}	$I_{Ca,L}$ ↑	rare	82, 83
CAV3	3p25	LQTS9, SIDS[£]	Caveolin-3	I_{Na} ↑	rare	84, 85
SCN4B	11q23	LQTS10	$Na_V1.5$ β4	I_{Na} ↑	rare	86
KCNQ1	11p15.5	JLNS1[+]	$K_V7.1$ α	I_{Ks} ↓ KvLQT1	rare	87, 88
KCNE1	21q22.1	JLNS2[++]	minK β	I_{Ks} ↓	rare	78

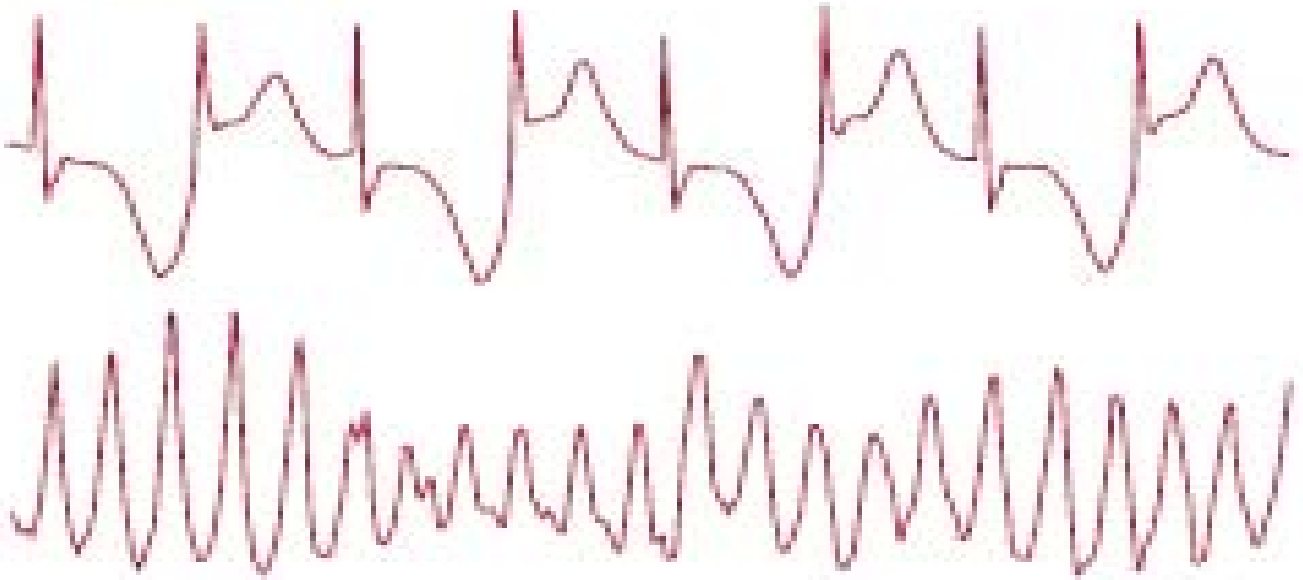

A
ECG from genotyped patients
LQT1
LQT2
LQT3
LQT7
B
ECG and action potential in experimental models
LQT1
LQT2
LQT3
LQT7
U
ECG
Epicardium
Endocardium


A
Before exercise (control)
After exercise
I
II
III
Comparison before and after exercise
Experimental LQT1 model
Before
After
III
ECG
Epicardium
Endocardium
B
II

A Alternating amplitude in LQT1



B Alternating polarity in LQT1



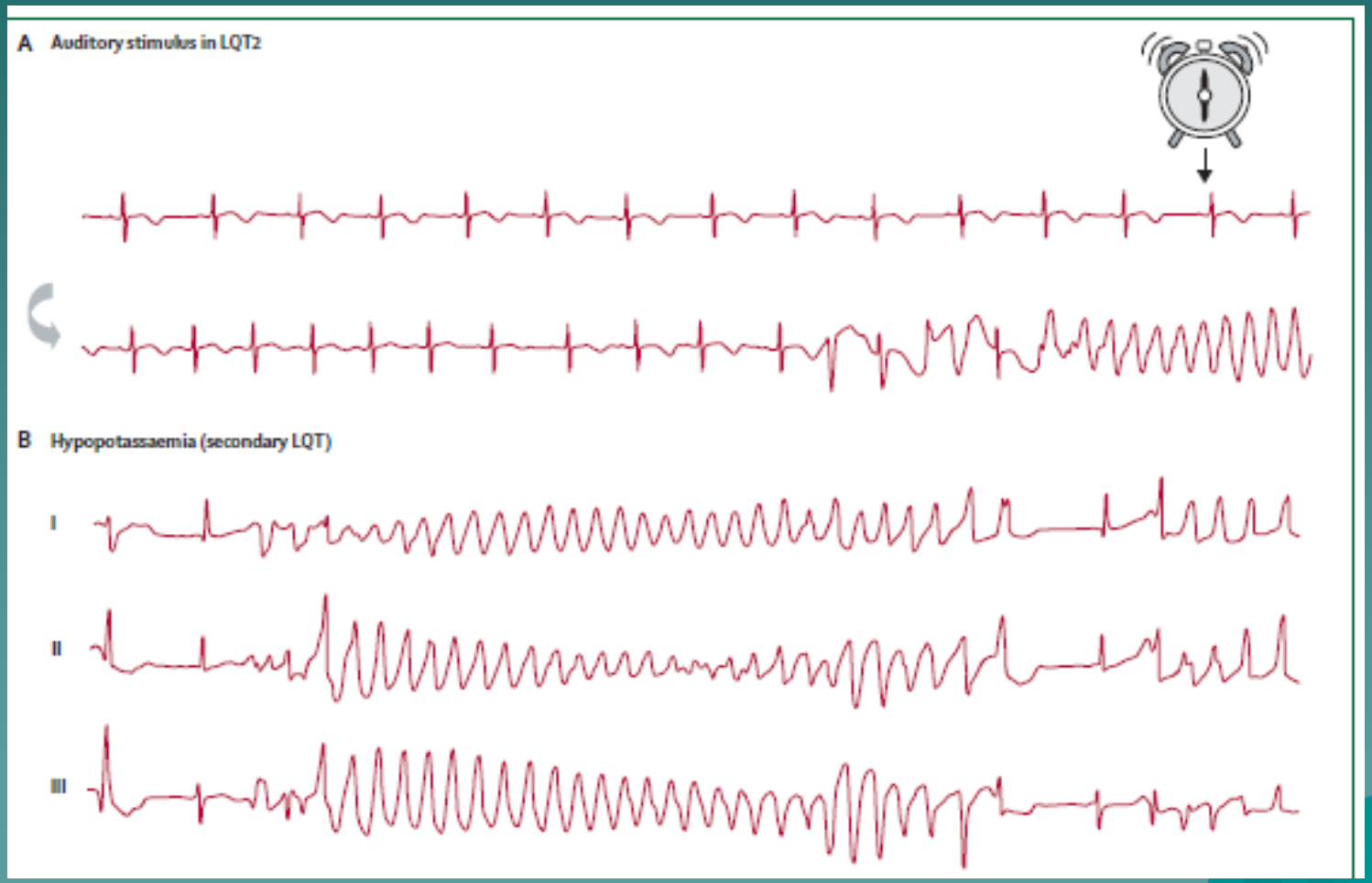

A Auditory stimulus in LQT2
B Hypopotassaemia (secondary LQT)
I
II
III

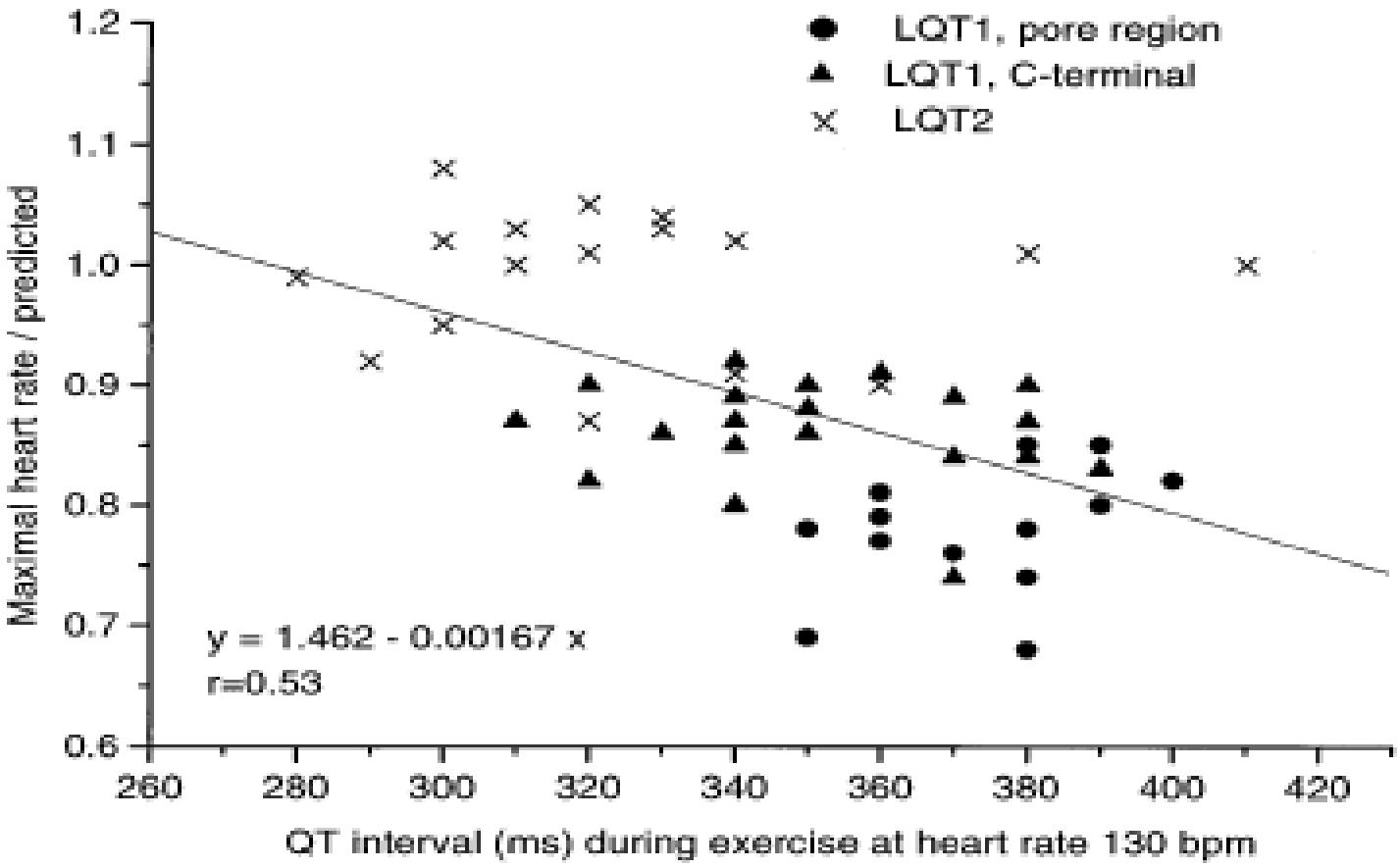
Table 4 Characteristics of LQT1, LQT2 and LQT3 models of LQTS in canine arterially-perfused left ventricular wedge preparations

	LQT1	LQT2	LQT3
ECG T wave pattern	Broad-based T wave	Low amplitude T wave, notched or birfurcated appearance	Late-appearing T wave
Rate dependence of QT interval	++	++	+++++
Sensitivity to catecholamines	+++++ (Sustained ↑ in TDR)	+++ (Transient ↑ in TDR)	– (↓ in TDR)
Torsades de Pointes (in the clinic)	Exercise-related	Startle alarm clock[77]	Rest/sleep
Effectiveness of beta-blockers	+++++	+++	–
Effectiveness of Na^+ channel blockers	+++	++++	+++++

TDR = transmural dispersion of repolarization.
+Small/low; +++++large/high.

Sinus Node Function and Ventricular Repolarization During Exercise Stress Test in Long QT Syndrome Patients With KvLQT1 and HERG Potassium Channel Defects

Heikki Swan, MD, Matti Viitasalo, MD, Kirsi Piippo, PHD, Päivi Laitinen, PHD, Kimmo Kontula, MD, Lauri Toivonen, MD
Helsinki, Finland



JACC Vol. 34, No. 3, 1999
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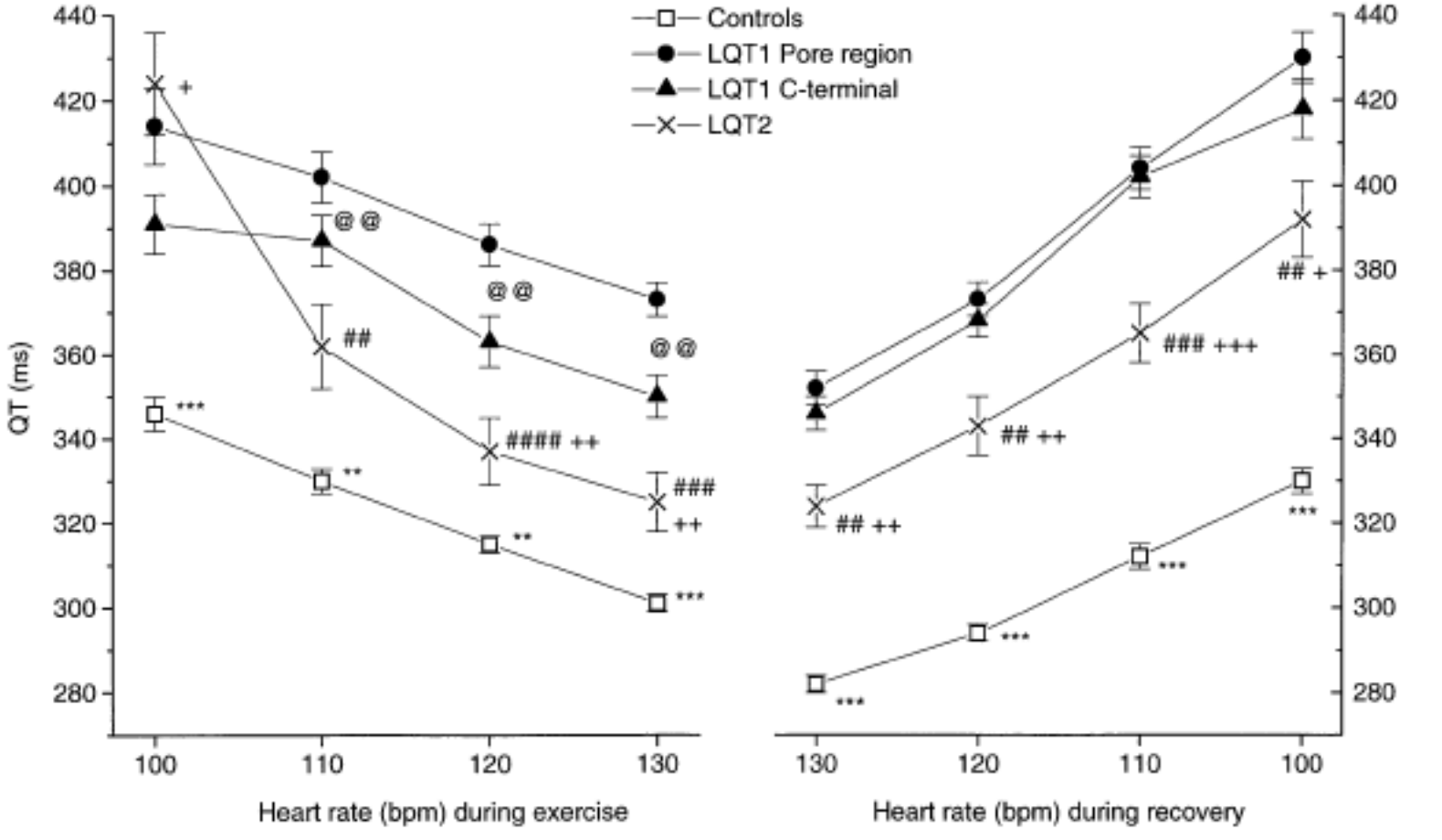

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Table 3. QT/Heart Rate Slopes (ms/min^{-1}) During Exercise and Recovery

	LQT1 patients			
	Pore region	C-terminus	LQT2 patients	Controls
QT/heart rate				
Exercise	−1.8 ± 1.1	−1.6 ± 0.7*	−2.2 ± 0.8*†	−1.4 ± 0.3†
p value‡	< 0.01	< 0.001	NS	NS
Recovery	−2.6 ± 1.3§	−2.4 ± 0.5§	−2.2 ± 0.6§	−1.5 ± 0.4

*$p < 0.01$ between LQT1 C-terminal group and LQT2 patients; †$p < 0.001$ between LQT2 patients and controls subjects; ‡between exercise and recovery phases; §$p < 0.001$ compared with control subjects.
QT = QT interval.

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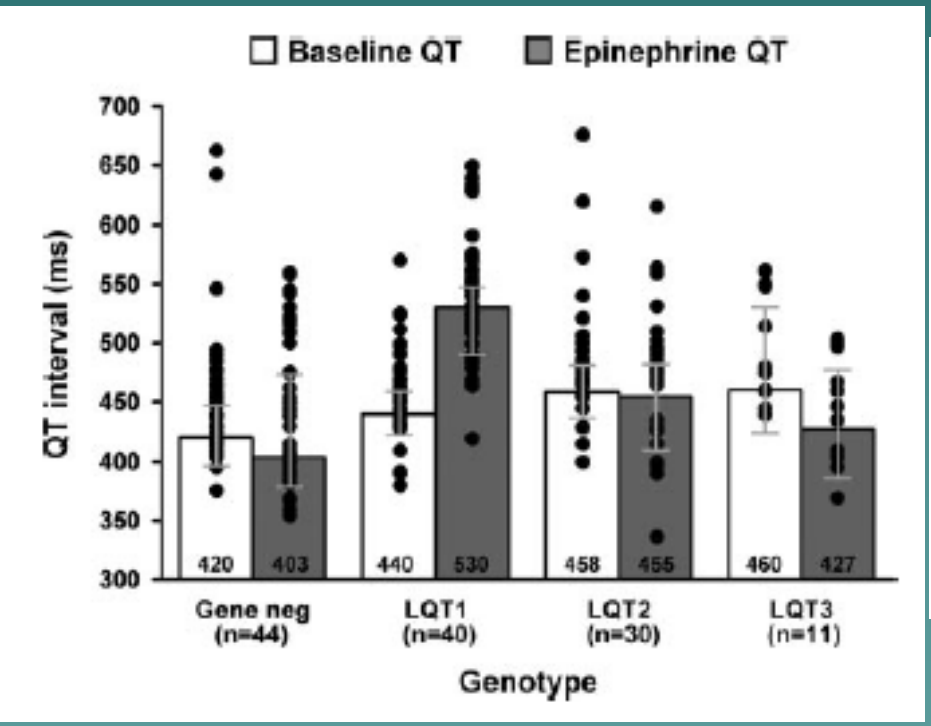
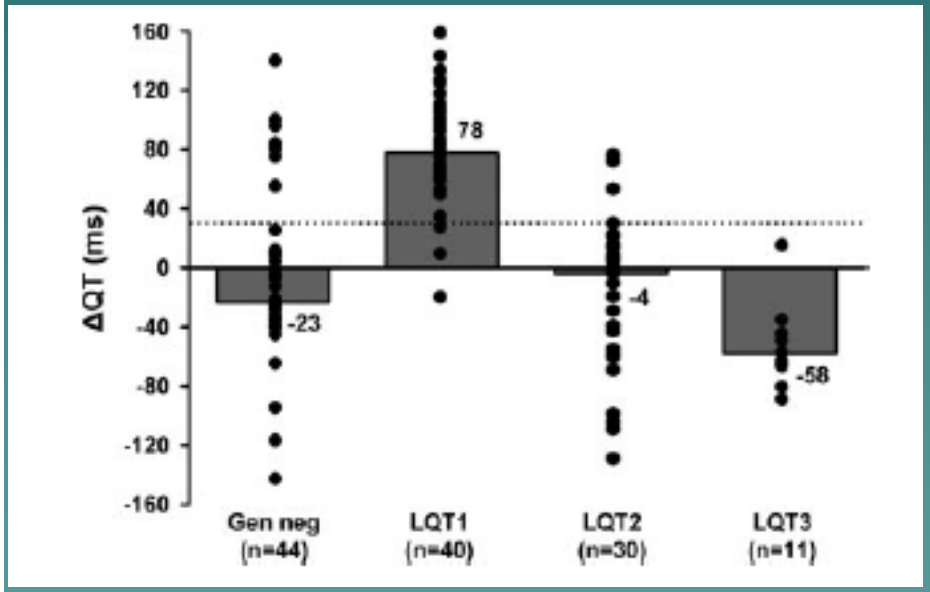
Epinephrine QT Stress Testing in the Evaluation of Congenital Long-QT Syndrome

Diagnostic Accuracy of the Paradoxical QT Response

Himeshkumar Vyas, MD; Joseph Hejlik, RN; Michael J. Ackerman, MD, PhD





$\leq 0.1\ \mu g \cdot kg^{-1} \cdot min^{-1}$

(*Circulation*. 2006;113:1385-1392.)

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TABLE 2. Validity of the Test at a ΔQT ≥30 ms

ΔQT	LQT1	Non-LQT1	
ΔQT ≥30 ms	37	12	Positive predictive value=76%
ΔQT <30 ms	3	73	Negative predictive value=96%
	Sensitivity=92.5%	Specificity=86%	n=125

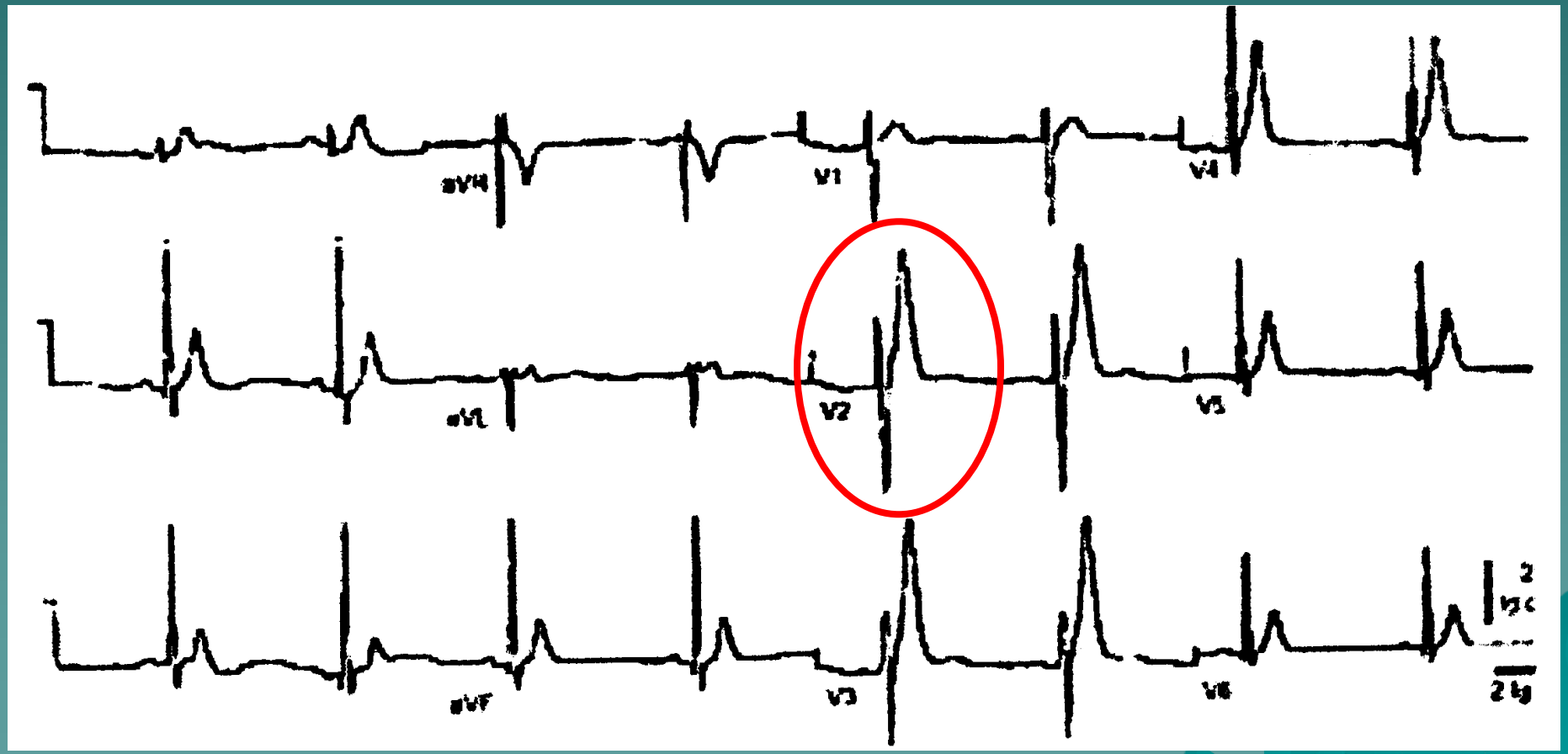
(*Circulation*. 2006;113:1385-1392.)

SHORT QT SYNDROME

- Sudden death age 10-35 years
- Syncope
- Atrial fibrillation
- Exercise variable- Sleep
- Positive VT stim usually

Το σύνδρομο βραχέος QT

QT interval always <320 ms without significant dynamic changes during heart rate variations - tall and peaked T waves



Brugada R, et al. Circulation 2004;109:30-35

Το σύνδρομο βραχέος QT

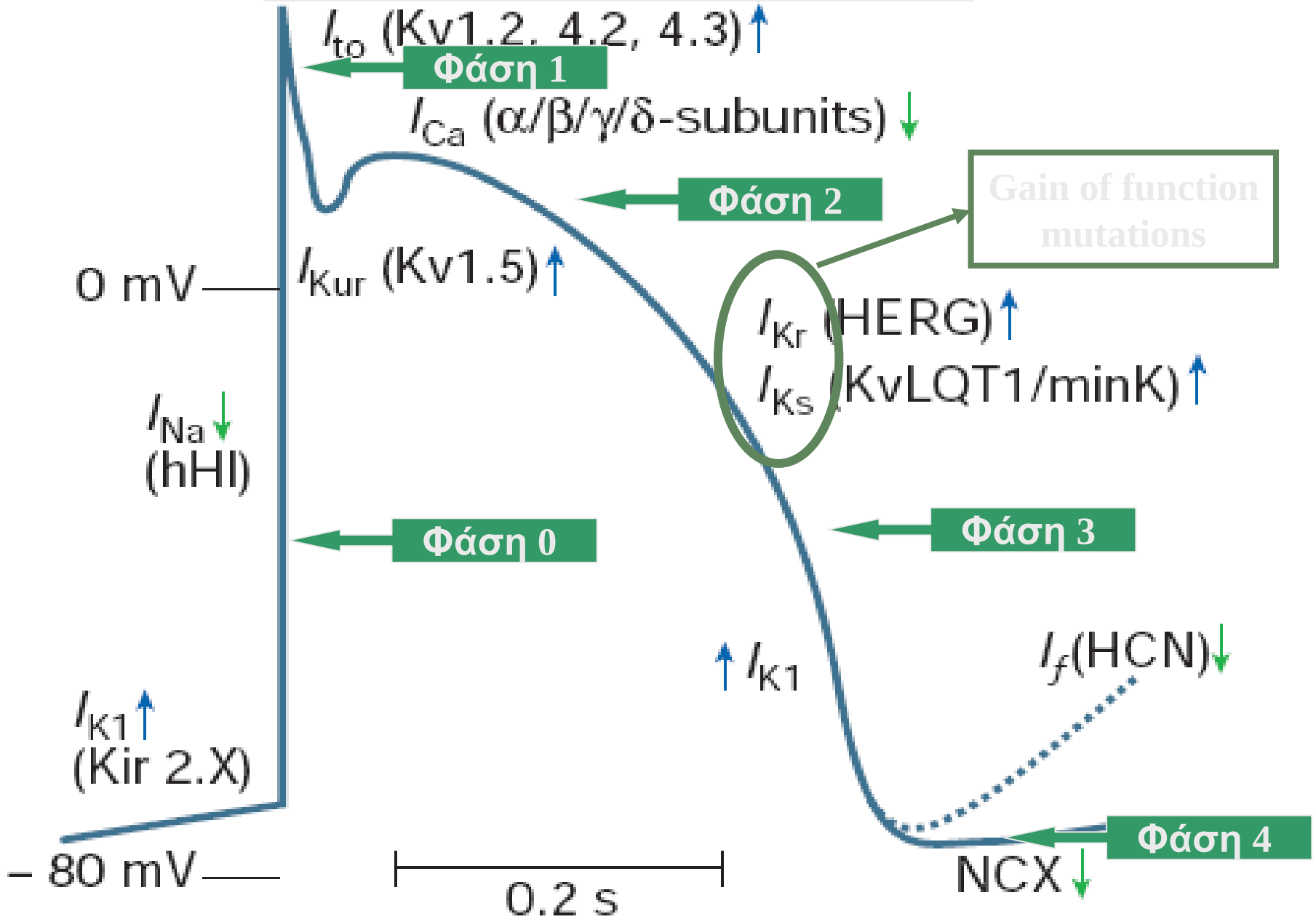
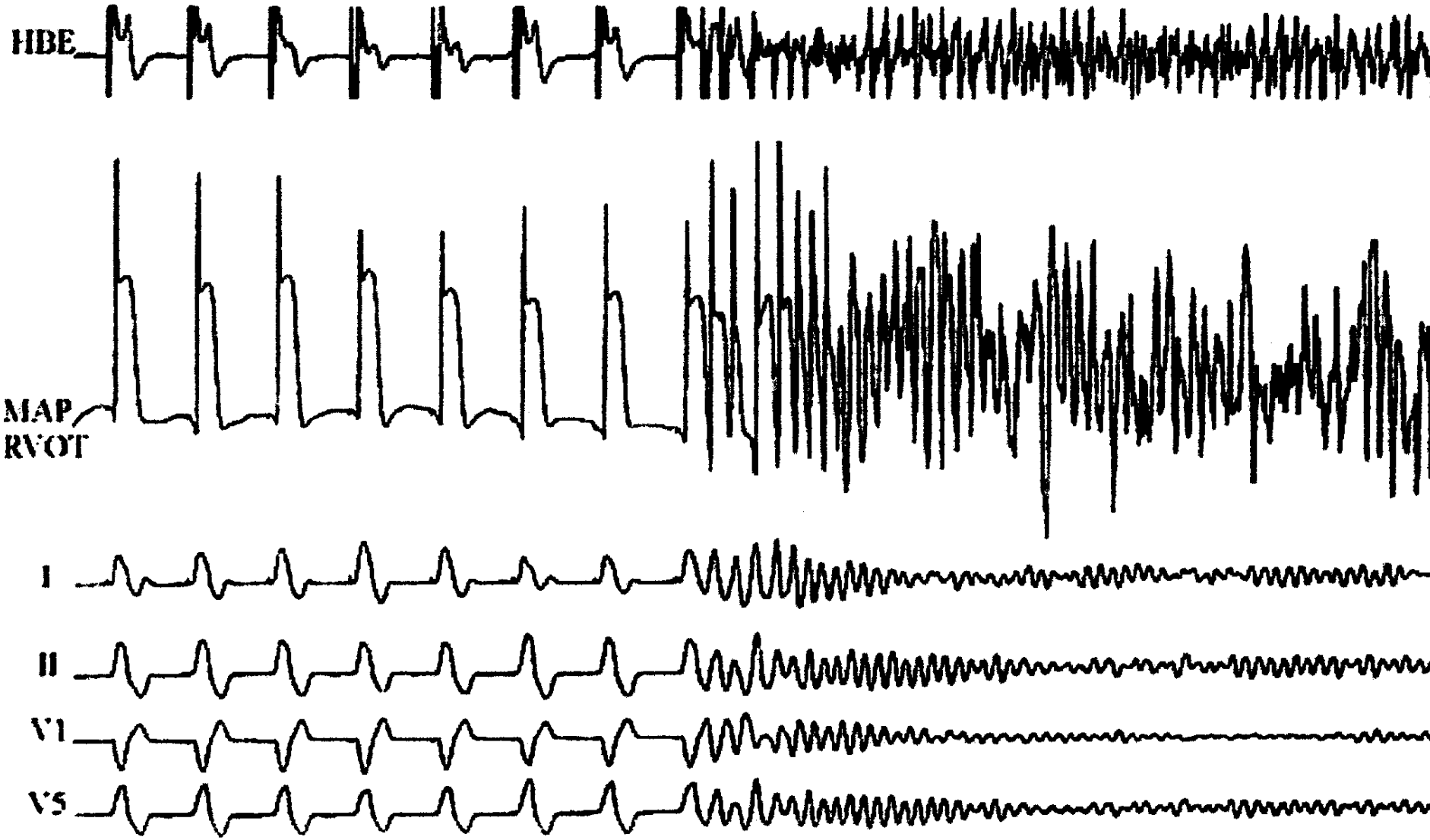


TABLE 2. Currently Known Mutations for Short QT Syndrome

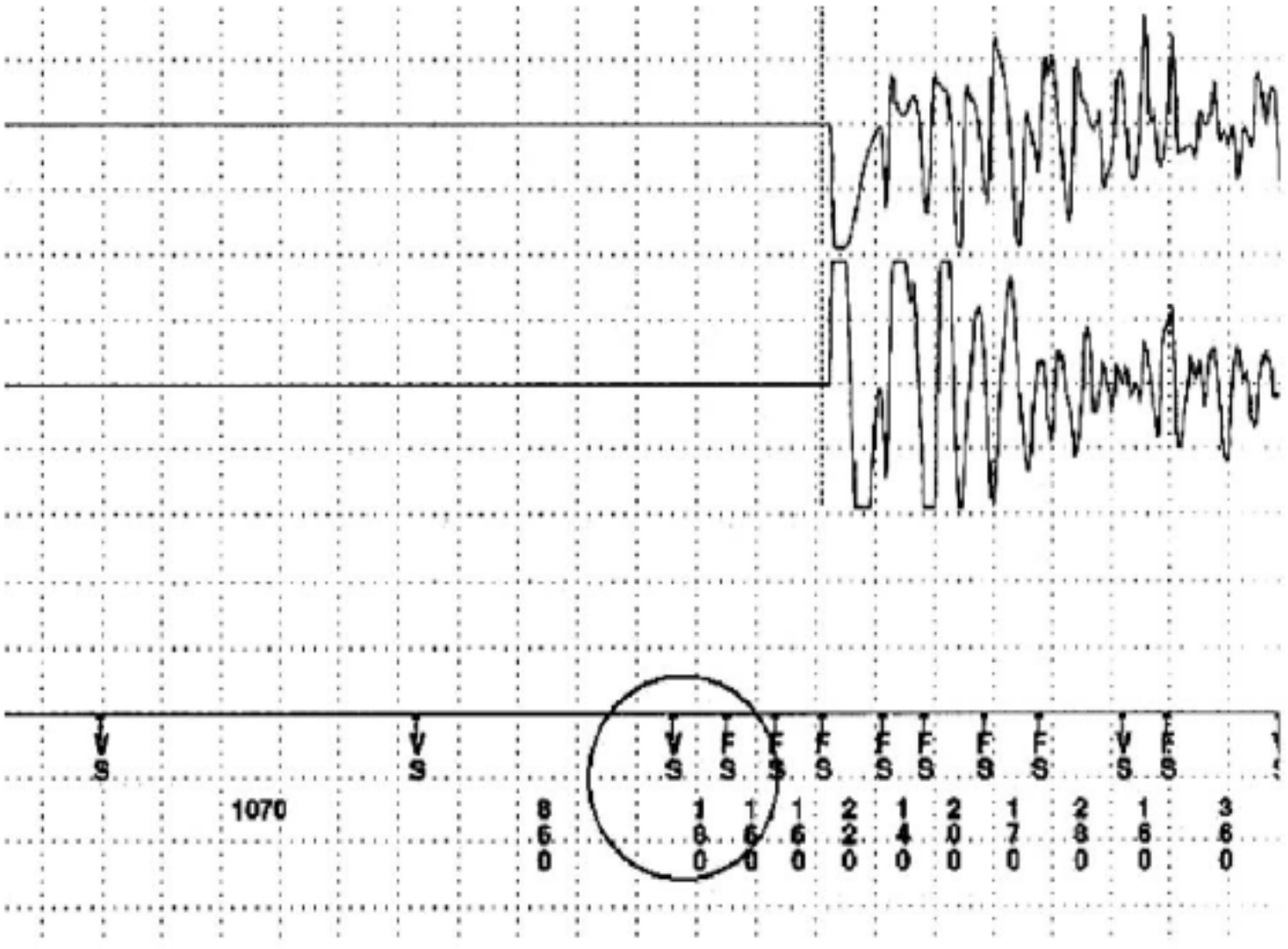
Short QT Syndrome	Gene	Ionic Channel Regulated	Mutation	Result	Comments
SQT1	*KCNH2* (HERG)[7]	IKr, the rapidly activating delayed rectifier potassium channel	Two different missense mutations	Gain in function of the channel - shortening the action potential	Loss of function results in LQT2. Associated with SIDS
SQT2	*KCNQ1* (KvLQT1)[10,11]	IKs, the slowly activating delayed rectifier potassium channel	Two different missense mutations	Gain in function of the channel - shortening the action potential	Loss of function results in LQT1
SQT3	*KCNJ2* (Kir2.1)[12]	IK1, the potassium inward rectifier current	Missense mutation	Gain in function with selective speeding of late repolarization	Loss of function results in LQT7 (Andersen syndrome)
Brugada syndrome and Short QT (overlap or SQT4 syndrome)	*CACNA1C* and *CACNB2*[13]	Calcium channel	Mutations in genes encoding the cardiac L-type calcium	Loss of function affects ST segment. ECG shows ST segment elevation in right precordial lead and short QT interval	Gain of function results in LQT8 (Timothy syndrome)

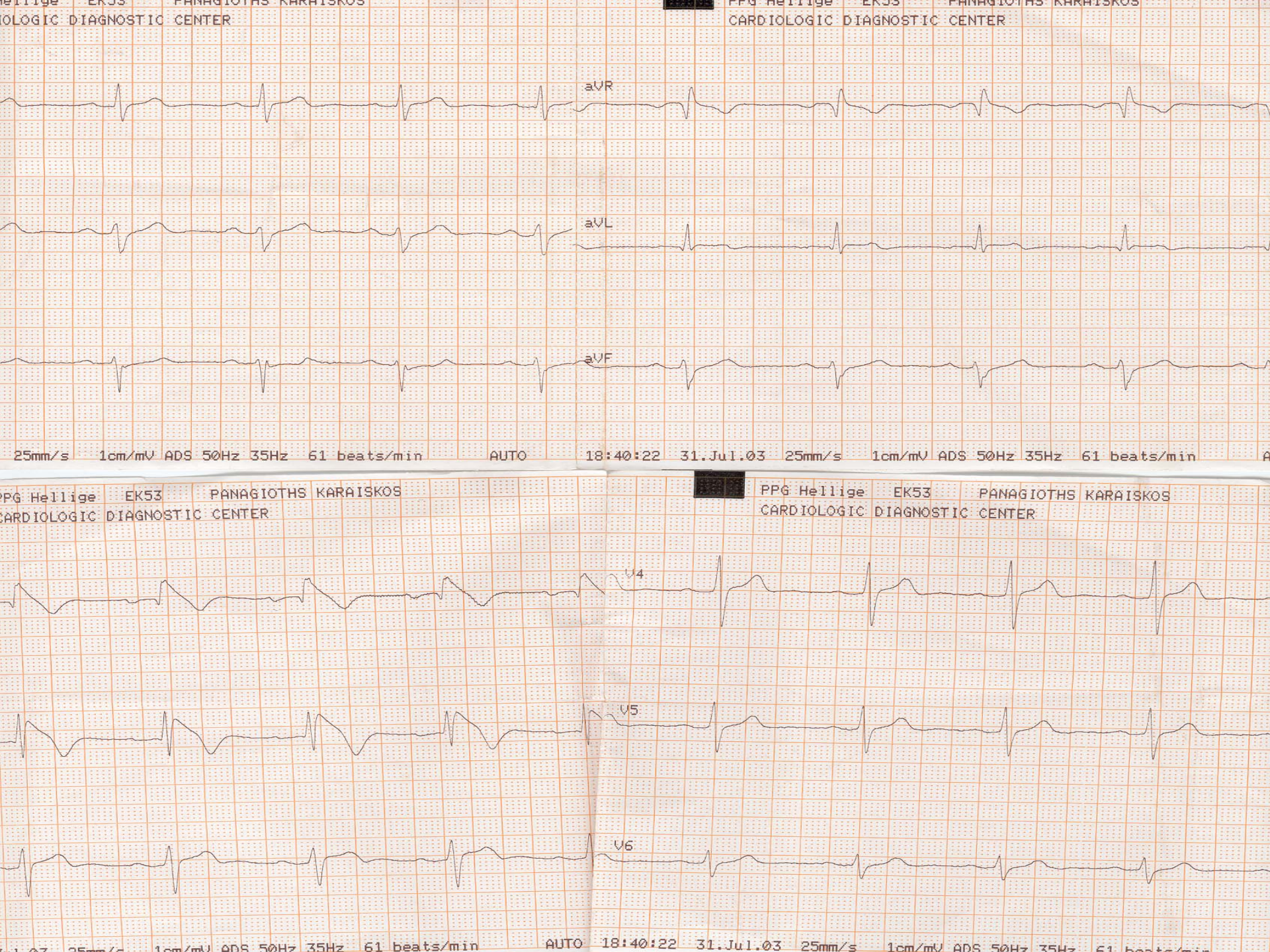
Short QT Syndrome

VF induction



Gaita F, et al: Circulation 2003;108:965-70


VS
1070
VS
VS
FS
FS
FS
FS
FS
FS
FS
VS
FS
850
1600
1600
1600
2200
1400
2000
1700
2800
1600
3600


PPG Hellige EK53 PANAGIOTHS KARAISKOS
CARDIOLOGIC DIAGNOSTIC CENTER
aVR
aVL
aVF
25mm/s 1cm/mV ADS 50Hz 35Hz 61 beats/min AUTO 18:40:22 31.Jul.03
V4
V5
V6

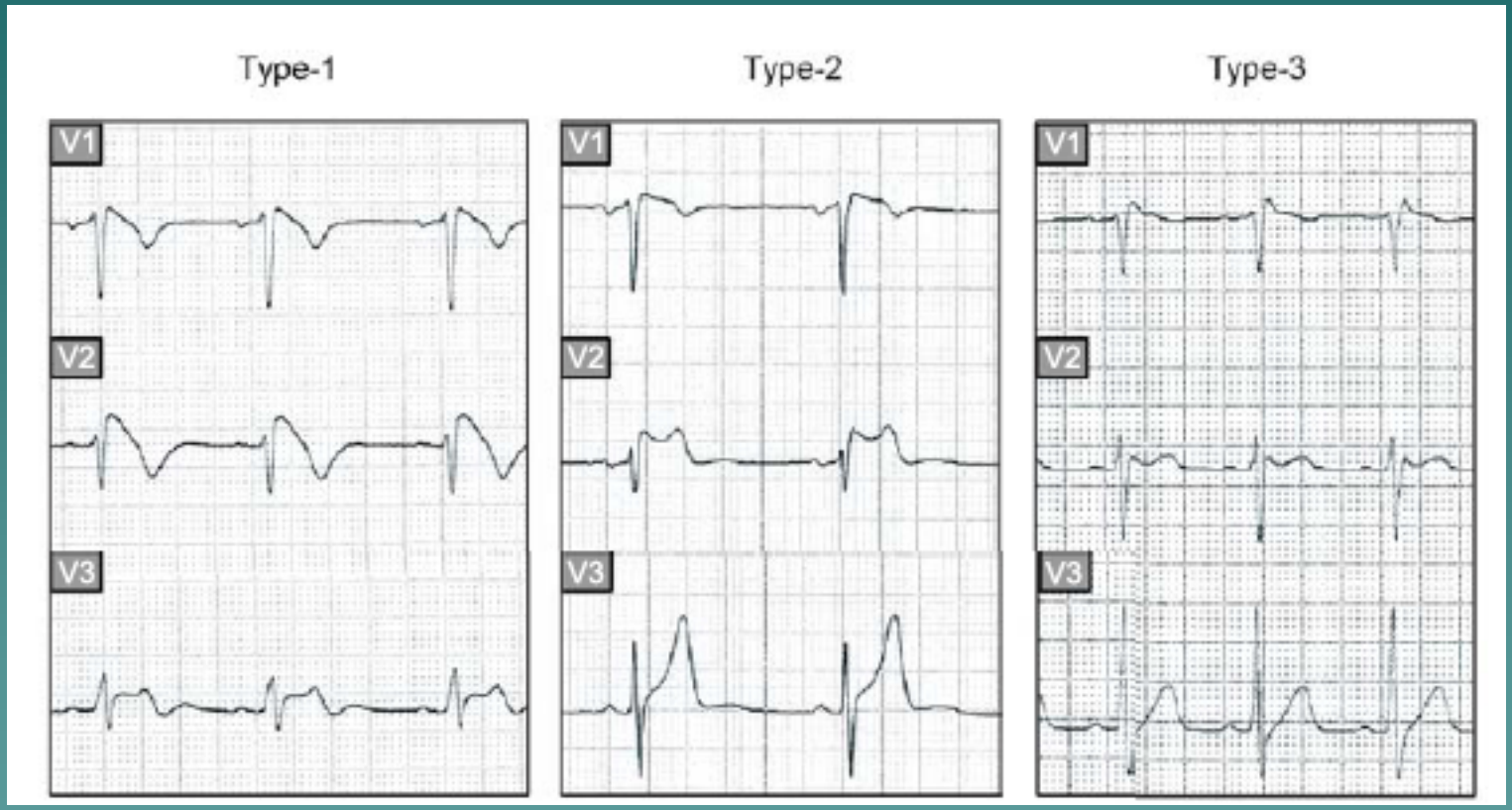
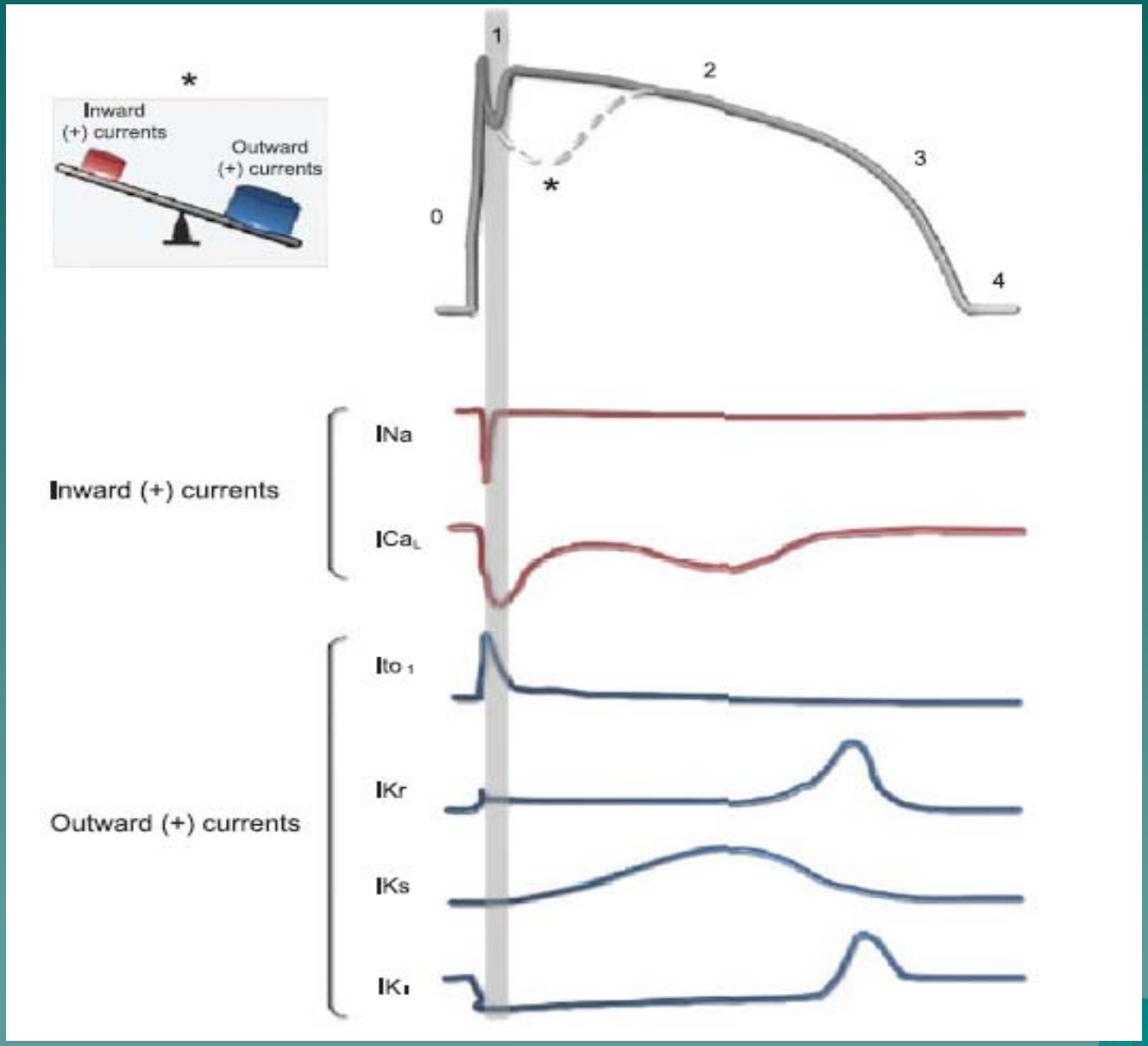

Type-1
Type-2
Type-3
V1
V2
V3
V1
V2
V3
V1
V2
V3

Table 1. Diagnostic criteria of the Brugada syndrome.[15]

Appearance of a type-1 ST-segment elevation (coved-type) ≥2 mm in more than one right precordial lead (V_1–V_3): • either spontaneously • or after sodium-blocker exposure	
AND	
One of the following:	
• Documented ventricular fibrillation • (Self terminating) polymorphic ventricular tachycardia • Inducibility of ventricular arrhythmias with programmed electrical stimulation	Documented ventricular arrhythmias
• Family history of sudden death before 45 years • Presence of a coved-type ECG in family members	Family history
• Syncope • Nocturnal agonal respiration	Arrhythmia-related symptoms
Other factor(s) that might account for the ECG abnormality should be ruled out.	

Brugada Syndrome

- Autosomal dominant trait
- SCN5A mutations were present in 38% of familial forms
- Age 30-40 years
- Sudden death (4%) Polymorphic VT
- Syncope


*
Inward
(+) currents
Outward
(+) currents
1
2
3
4
0
*
Inward (+) currents
INa
ICaL
Outward (+) currents
Ito 1
IKr
IKs
IK1

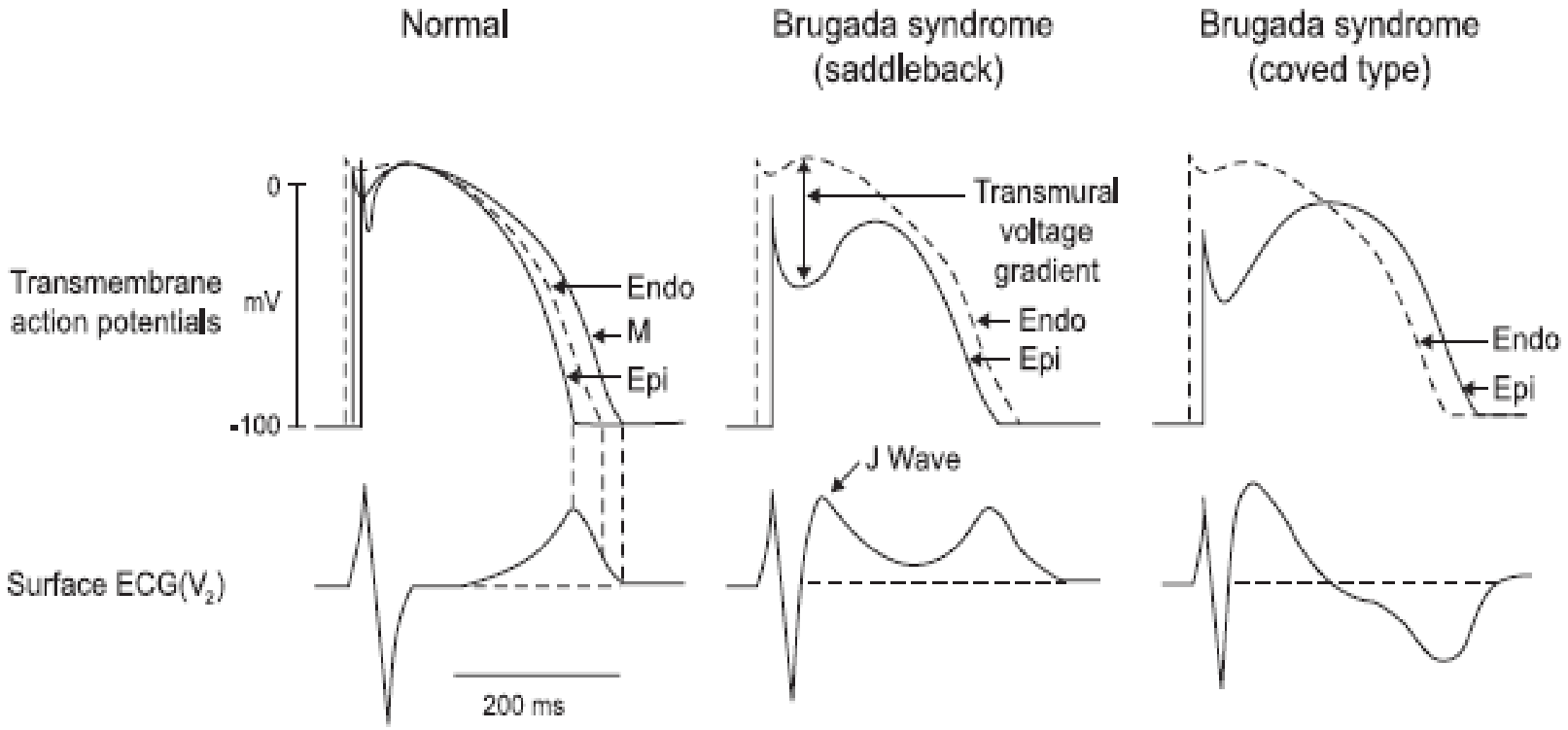
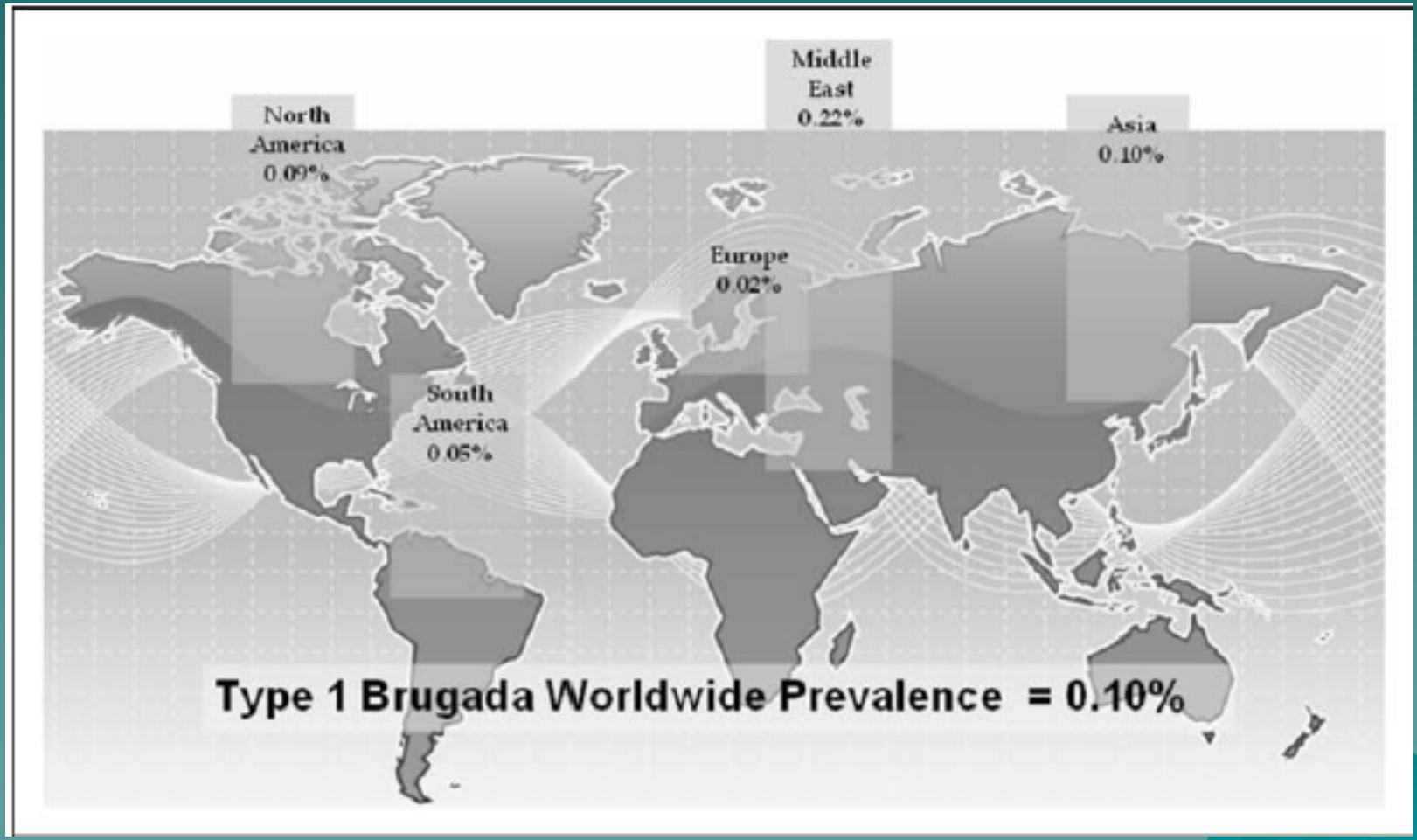
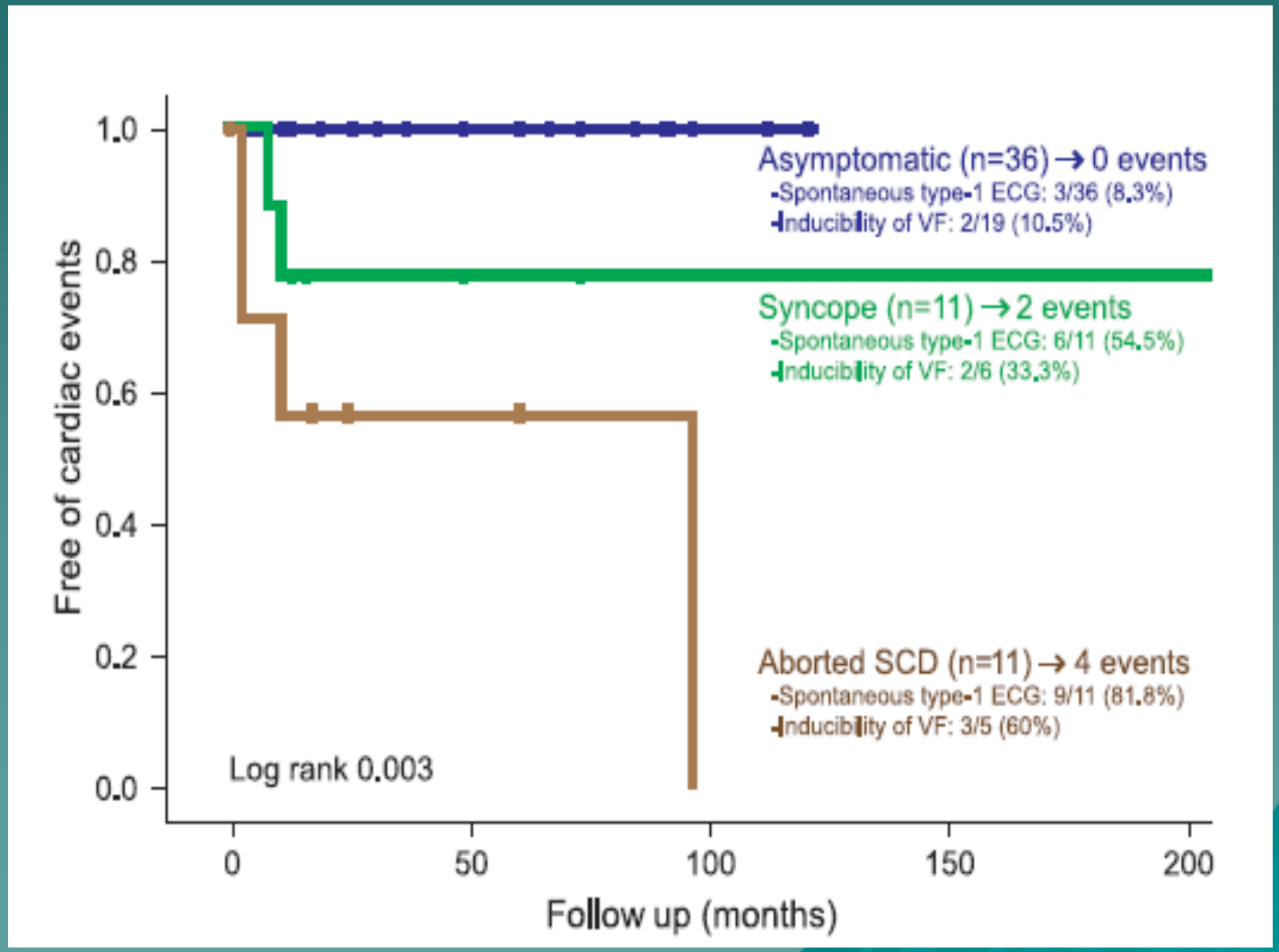


Figure 5. Proposed mechanism that underlies ST-segment elevation in Brugada syndrome. The accentuated notch present in epicardium but not in endocardium gives rise to transmural voltage gradient and J point elevation (Brugada saddleback). Further accentuation of the notch may be accompanied by a prolongation of the action potential in epicardium, which becomes longer than in endocardium, thus leading to the development of negative T waves in addition to the ST-segment elevation (Brugada coved-type). (Modified from reference 16 with permission.)


Middle East 0.22%
North America 0.09%
Asia 0.10%
Europe 0.02%
South America 0.05%
Type 1 Brugada Worldwide Prevalence = 0.10%


1.0
0.8
0.6
0.4
0.2
0.0
Free of cardiac events
0
50
100
150
200
Follow up (months)
Asymptomatic (n=36) → 0 events
-Spontaneous type-1 ECG: 3/36 (8.3%)
-Inducibility of VF: 2/19 (10.5%)
Syncope (n=11) → 2 events
-Spontaneous type-1 ECG: 6/11 (54.5%)
-Inducibility of VF: 2/6 (33.3%)
Aborted SCD (n=11) → 4 events
-Spontaneous type-1 ECG: 9/11 (81.8%)
-Inducibility of VF: 3/5 (60%)
Log rank 0.003

Natural History of Brugada Syndrome
Insights for Risk Stratification and Management

Silvia G. Priori, MD, PhD; Carlo Napolitano, MD, PhD; Maurizio Gasparini, MD; Carlo Pappone, MD; Paolo Della Bella, MD; Umberto Giordano, MD; Raffaella Bloise, MD; Carla Giustetto, MD; Roberto De Nardis, MD; Massimiliano Grillo, MD; Elena Ronchetti, PhD; Giovanna Faggiano, MD; Janni Nastoli, BS

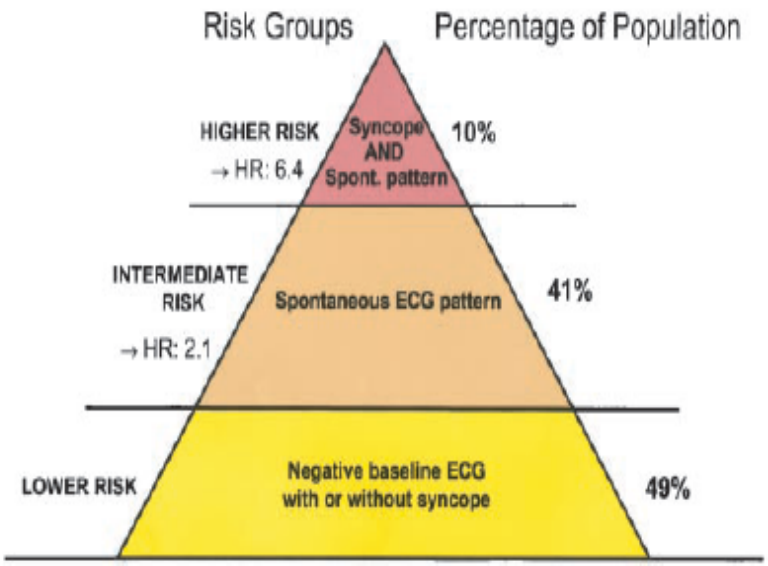


Figure 4. Risk stratification according to distribution of clinical variables in BS. Spont. Pattern indicates spontaneous positive ECG (see text for details).

TABLE 2. Performance of Clinical and Genetic Variables in Predicting the Occurrence of Cardiac Arrest in Brugada Syndrome Patients

	Positive Predictive Value, %	Negative Predictive Value, %	Sensitivity, %	Specificity, %	Accuracy, %
Male sex	13	96	90	26	33
Family history of SCD	7.5	87	22	65	61
Positive pharmacological test	7.9	95	88	17	22
SCN5A mutation	8.3	87	32	57	54
Outcome at PES (global)	14	86	66	34	38
PES (2 premature stimuli)	14	92	75	37	21
PES (3 premature stimuli)	10	82	50	33	52
Coved-type ST elevation	12	85	55	40	42
Syncope	24	91	36	85	80
Spontaneous ST elevation	19	94	77	53	56
Syncope and spontaneous ST elevation	44	91	36	94	86

IMAGES IN ELECTROPHYSIOLOGY

Type I Brugada electrocardiogram pattern during the recovery phase of exercise testing

Alexander Grimster, Oliver R. Segal*, and Elijah R. Behr

Cardiological Sciences, St George's Hospital, Blackshaw Road, London SW17 0QT, UK

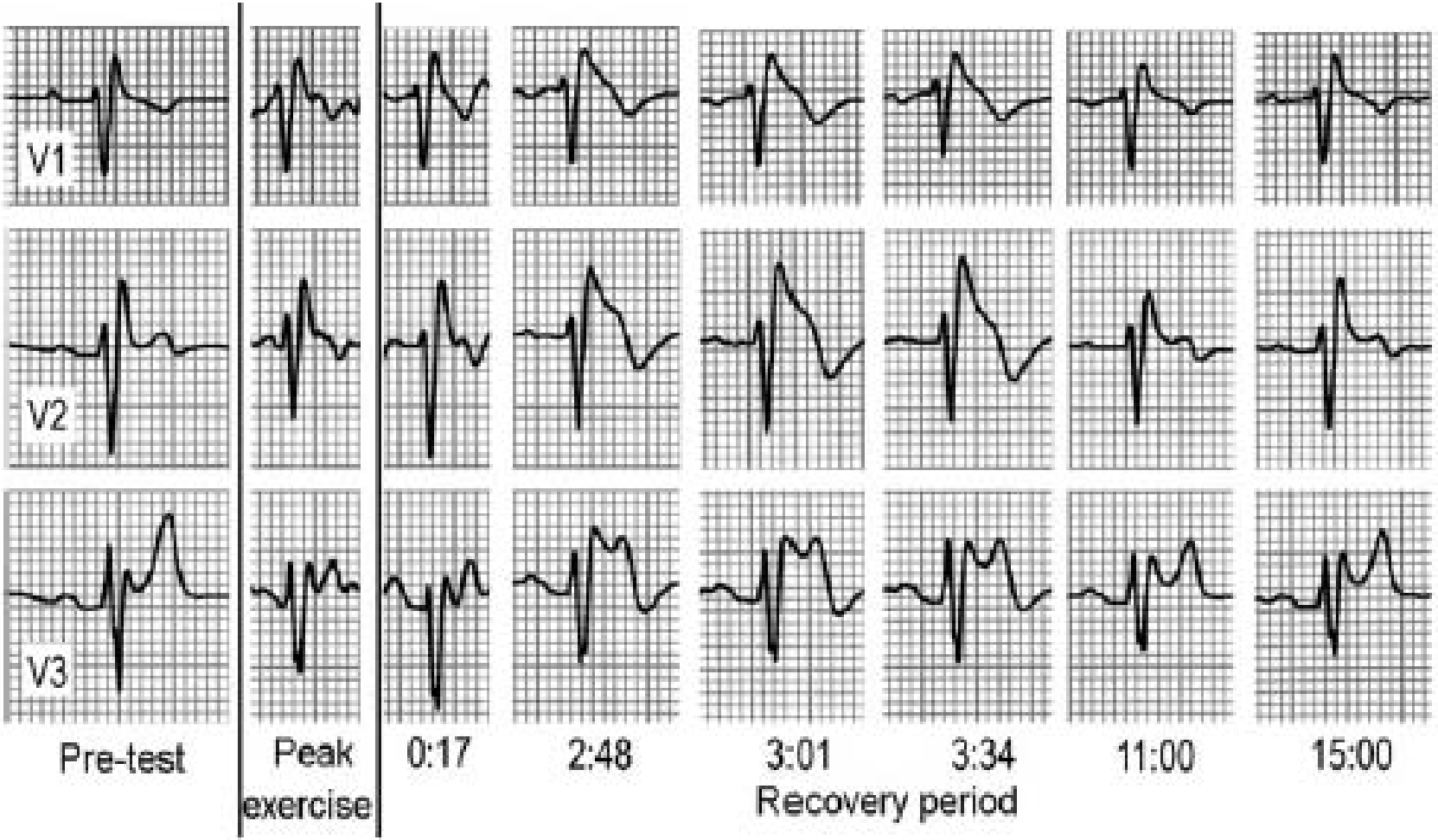
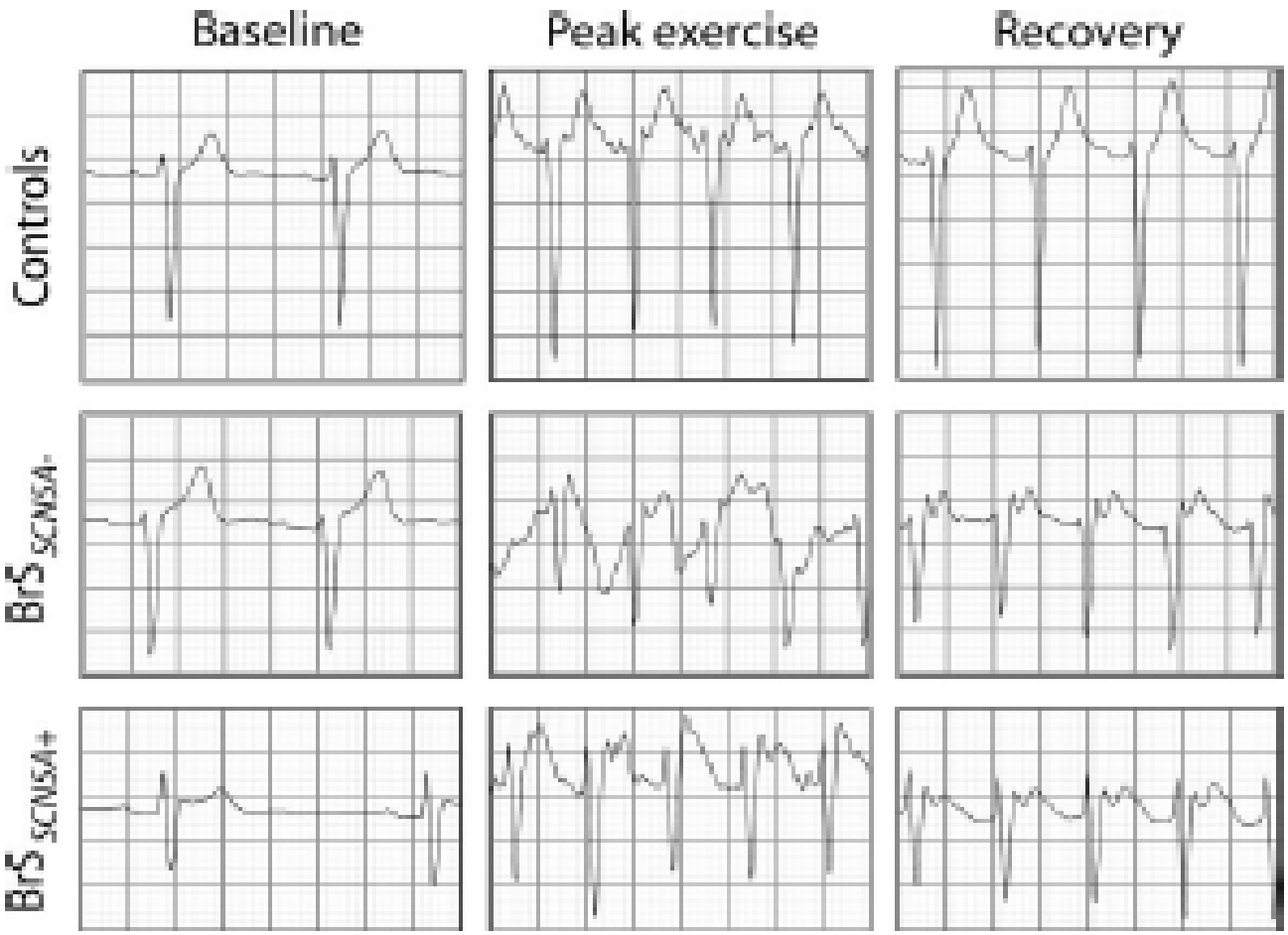


Figure 1 ST segment changes during recovery phase of exercise.

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



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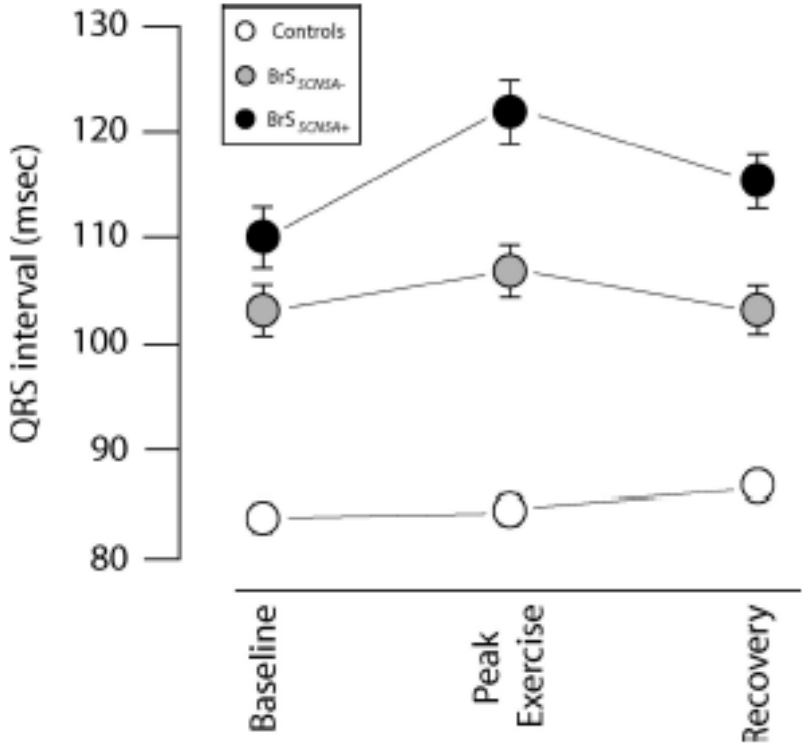

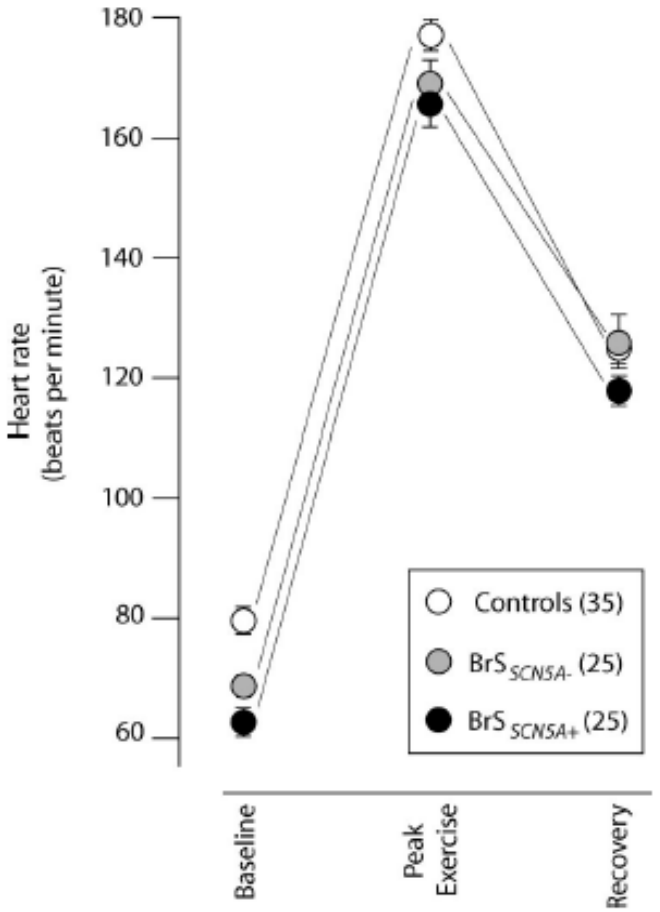

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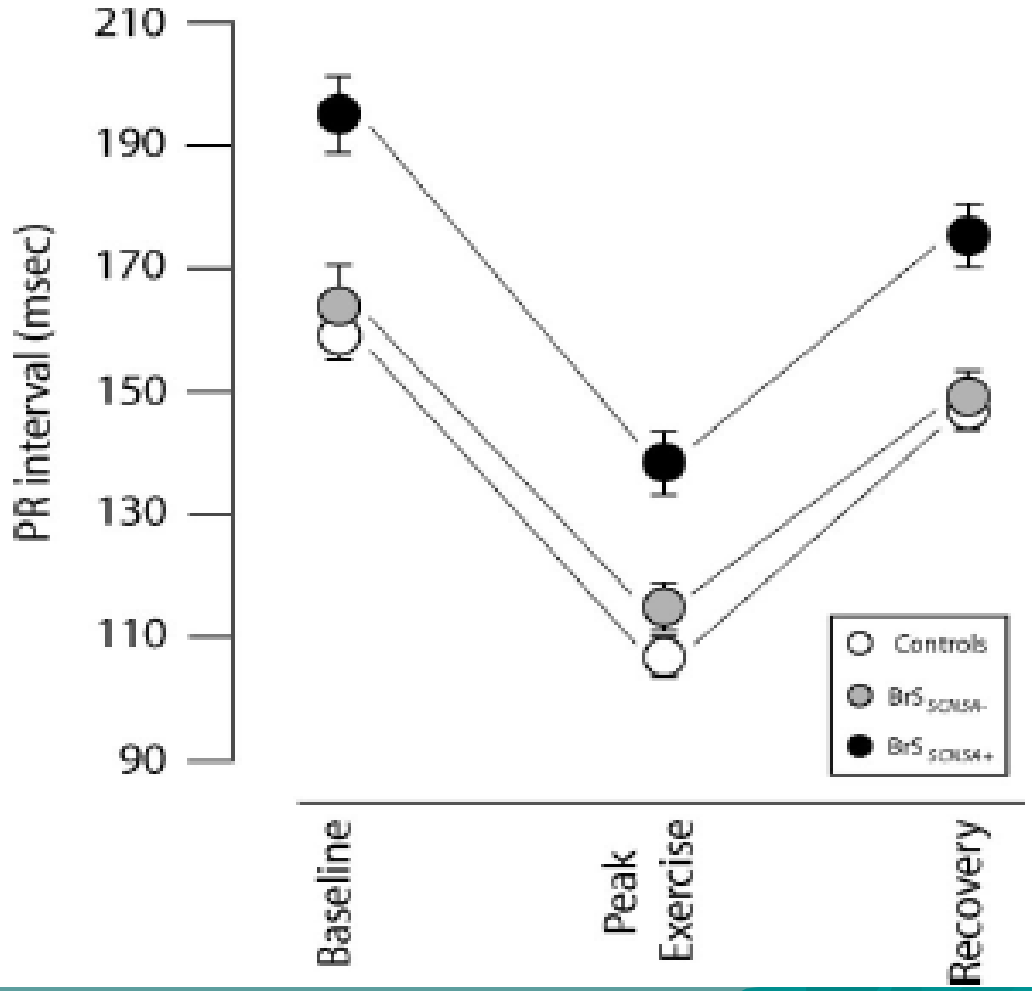
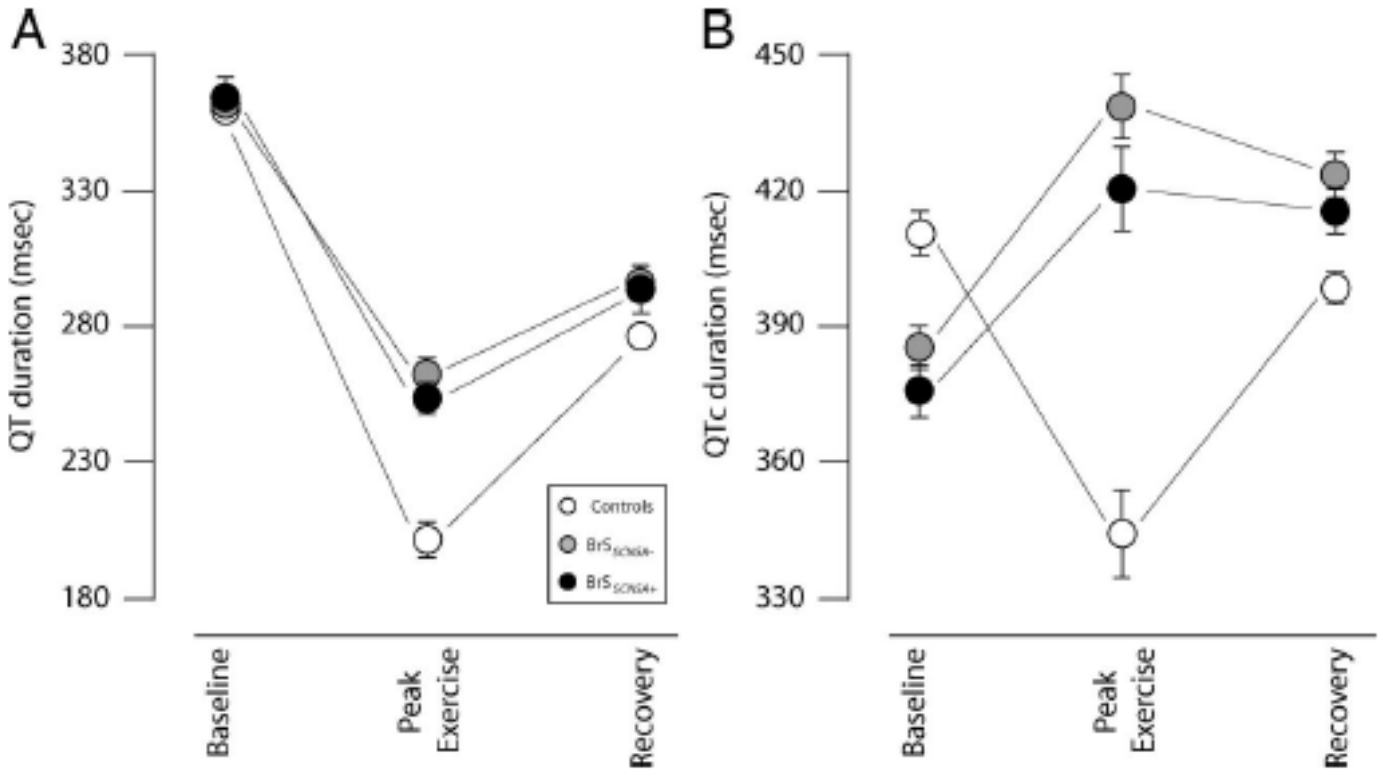
Arthur A.M. Wilde, MD, PhD; Hanno L. Tan, MD, PhD

Circ Arrhythmia Electrophysiol October 2009



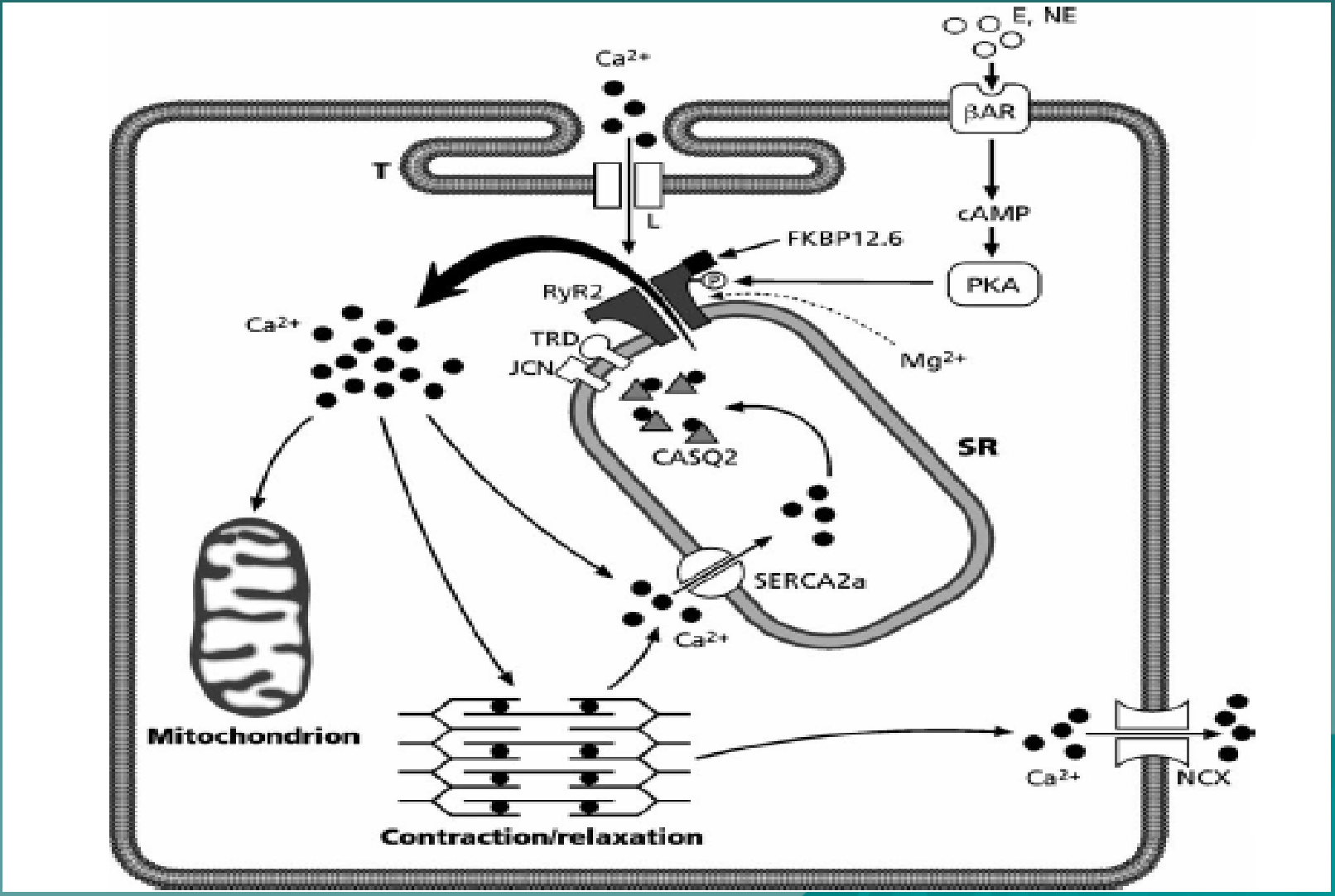
Exercise-Induced ECG Changes in Brugada Syndrome

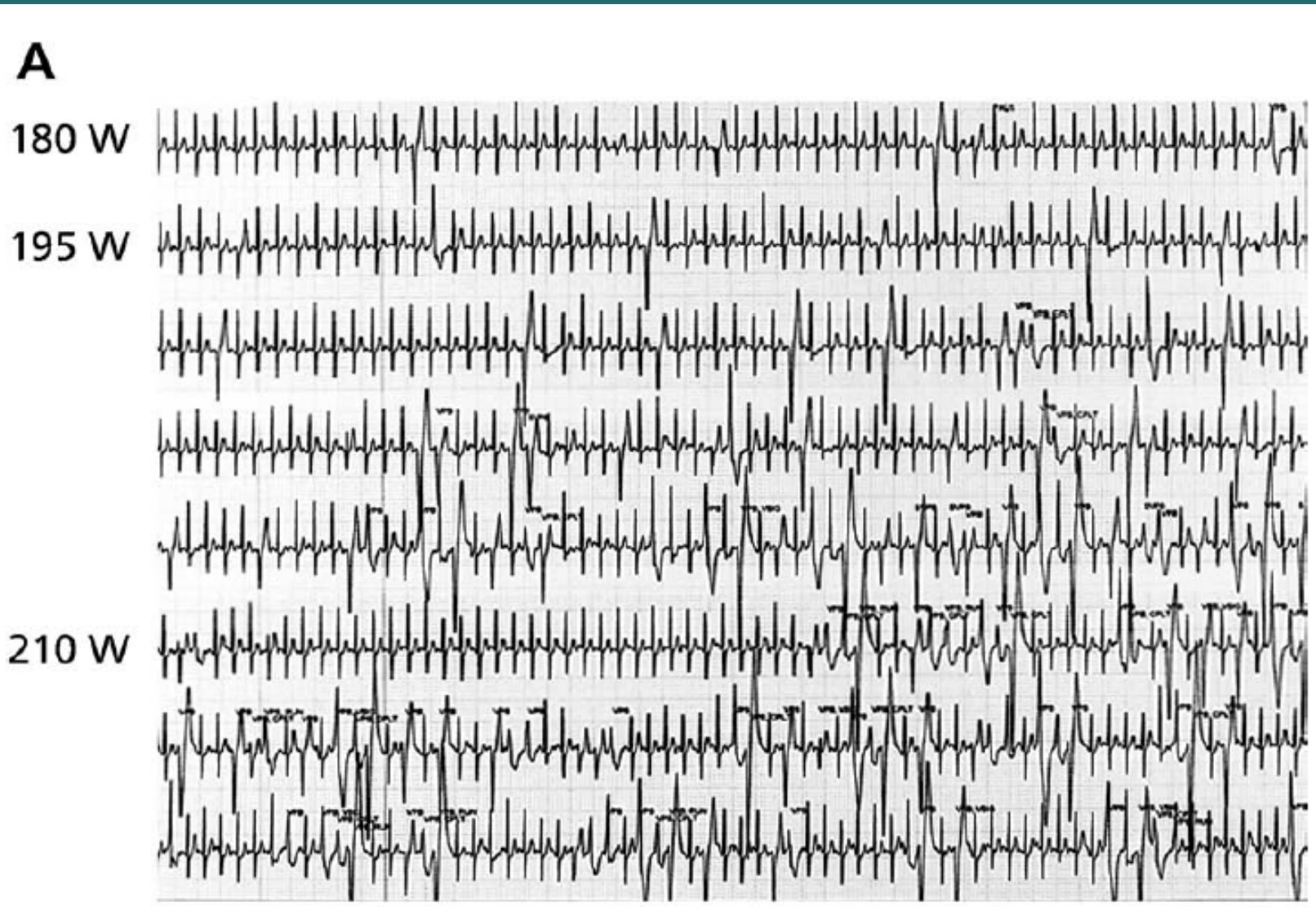
Ahmad S. Amin, MD; Elisabeth A.A. de Groot, BSc; Jan M. Ruijter, PhD;
Arthur A.M. Wilde, MD, PhD; Hanno L. Tan, MD, PhD



Circ Arrhythmia Electrophysiol October 2009

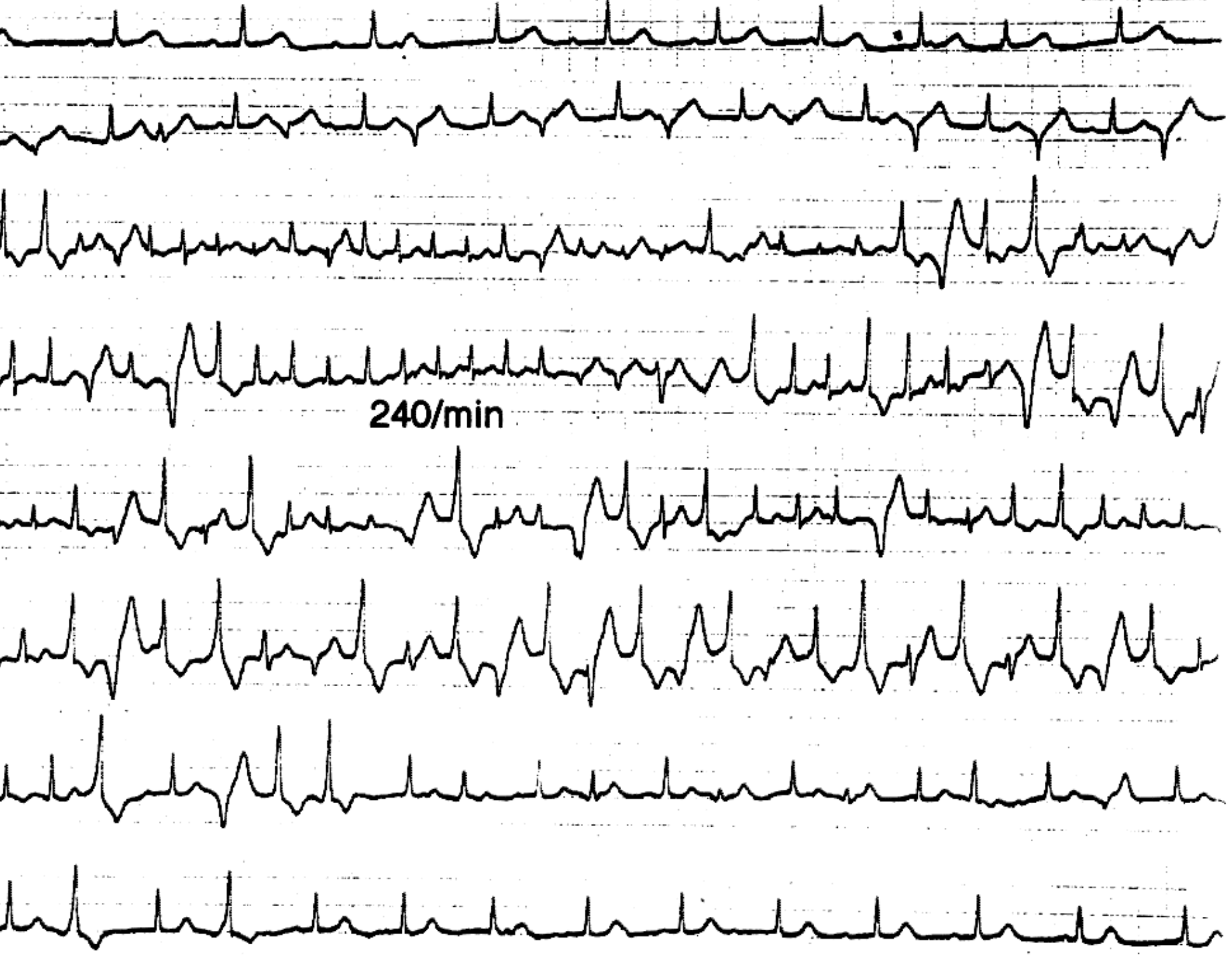
Ryanidine channels mutations CPVT

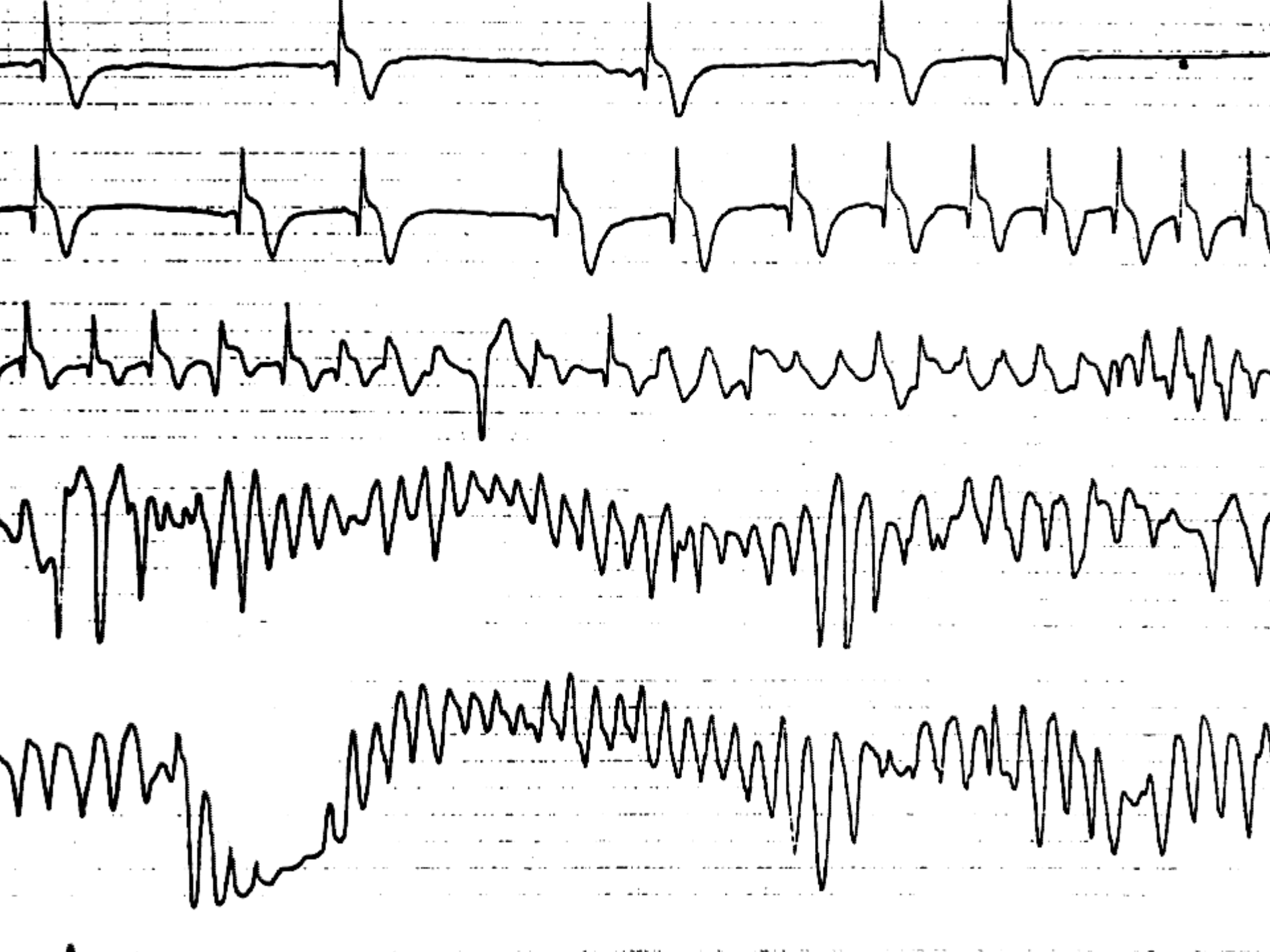


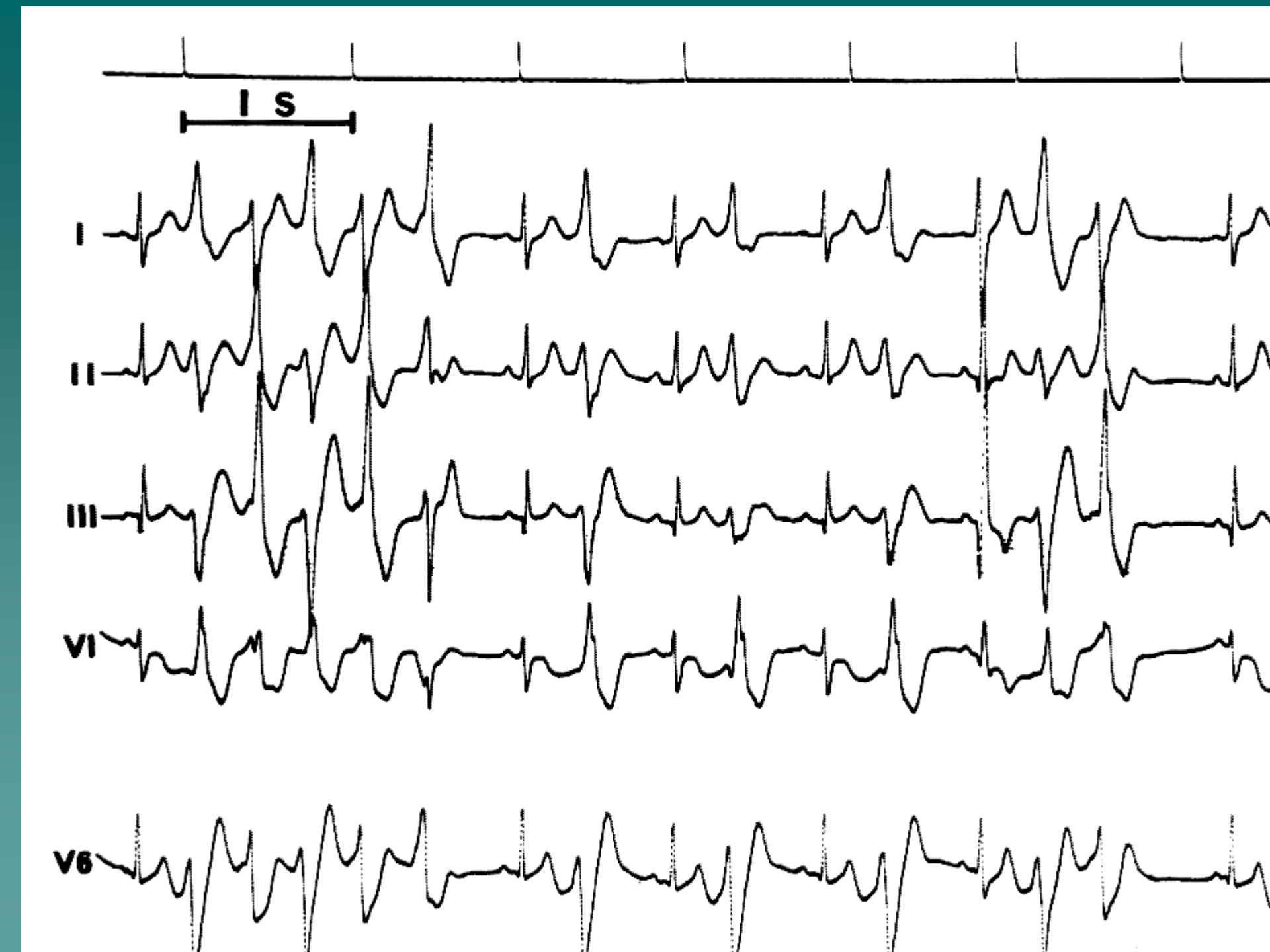

A
180 W
195 W
210 W

CPVT

- Syncope
- Sudden death
- VT during exercise- swimming
- 30% mortality
- EPS negative


240/min




1 S
I
II
III
VI
V6

Patients	Age Diag (years)	Age 1st Sync (years)	Gender	Symptoms	Familial Forms	Resting Heart Rate (beats/mn)	QRS Axis (degrees)	QT_c (ms)	VPB Threshold (beats/mn)
1	16	15	F	Syncope (exercise)	–	65	60	416	120
2	11	4	F	Syncope (exercise)	–	60	0	412	130
3	7	4	M	Syncope (exercise)	–	70	30	430	105
4	12	8	F	Syncope (exercise)	–	70	75	410	130
5	9.5	9	F	Syncope (exercise)	–	60	90	400	105
6	10	8	M	Syncope (exercise)	+	55	30	380	120
7	13	10	F	Syncope (exercise)	+	55	−30	380	130
8	6.5	4	M	Syncope (exercise)	–	60	50	410	150
9	7	5	M	Syncope (exercise)	?	75	30	425	110
10	11	8	M	Syncope (exercise)	–	60	30	400	110
11	3.5	3	M	Syncope (exercise)	+	75	75	435	120
12	4	4	M	Syncope (exercise)	–	68	50	430	115
13	7	7	M	Syncope (exercise)	–	55	30	420	110
14	7	7	F	Syncope (exercise)	+	60	80	435	130
15	15	12	F	Syncope (exercise)	+	45	−30	360	115
16	12	–	M	No, family request	+	52	−30	370	145
17	7	7	F	Syncope (exercise)	–	70	60	350	145
18	4	4	M	Syncope (exercise)	–	50	40	400	110
19	14	13	M	Syncope (exercise)	–	42	80	430	130
20	16.5	16	F	Syncope (exercise)	–	70	60	395	115
21	15	9	M	Syncope (exercise)	+	51	60	396	130
Mean ±SD	9.9±4	7.8±4	9F/12M		familial forms: 7	60.3±9	40±36	404±25	122±13

Exercise and Channelopathies

- Long Q-T syndrome LQT1 +
- Short QT syndrome ?
- Brugada syndrome -/+
- Catecholaminergic polymorphic + ventricular tachycardia