Ventricular arrhythmias in the absence of organic heart disease.

Sami Viskin.

Tel Aviv Medical Center

2006.

Classification of ventricular arrhythmias.

By morphology

Monomorphic	RBBB pattern LBBB pattern
Polymorphic	Polymorphic VT Torsade de pointes Ventricular fibrillation

By duration

- Non-sustained
- Sustained

By symptoms

- Well tolerated
- Poorly tolerated
- Cardiac arrest

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Classification of ventricular arrhythmias continues.

By mechanism

Abnormal automaticity

Triggered activity: EADs

DADs

Reentry: macroreentry -BBRVT

microreentry – myocardial VT

By response to stimuli

Catecholaminergic

Tachycardia dependent

Bradycardia dependent

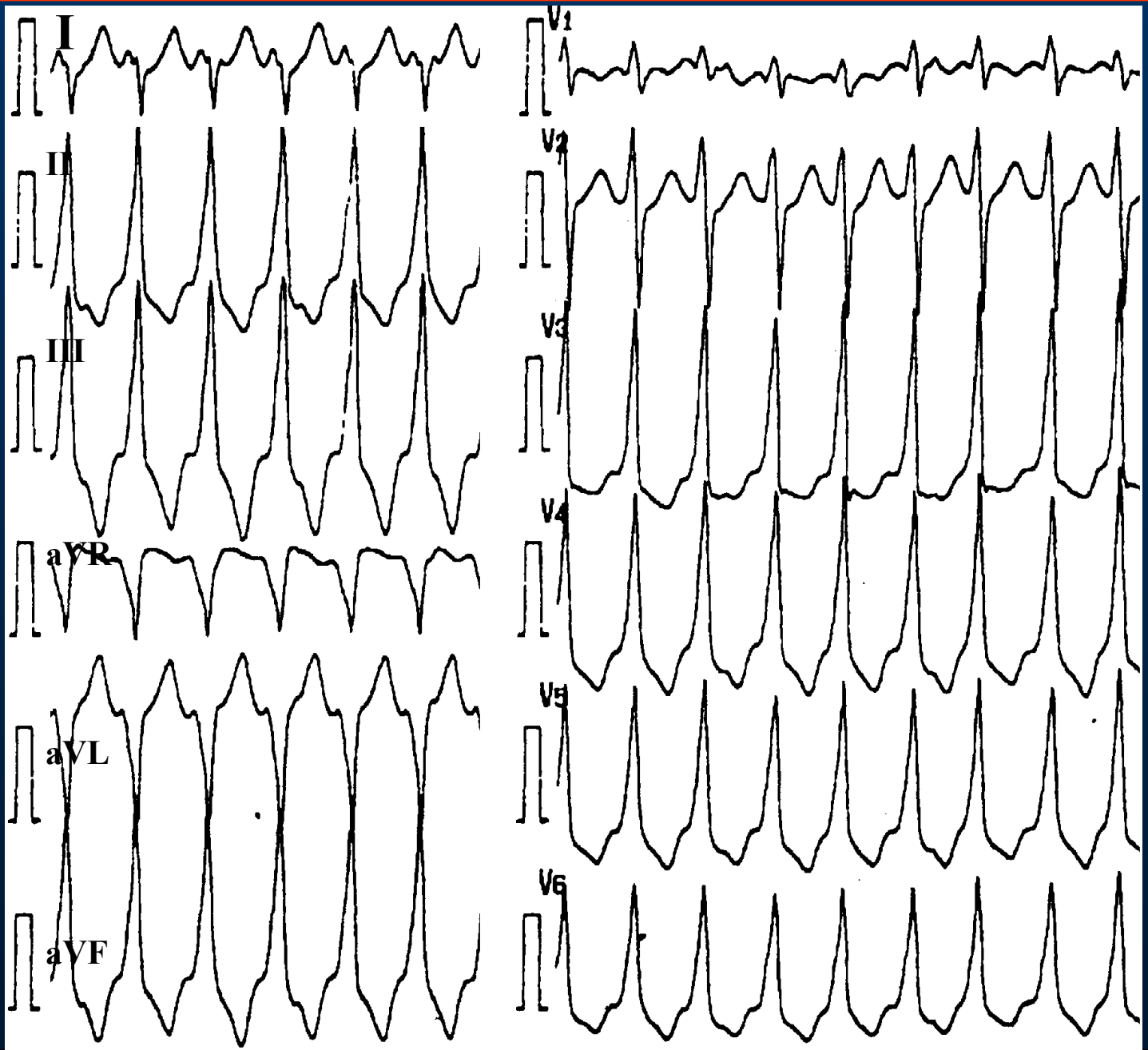
Response to drugs

ATP sensitive

Verapamil sensitive

Idiopathic monomorphic VT in the normal heart

Adenosine Sensitive LVOT VT



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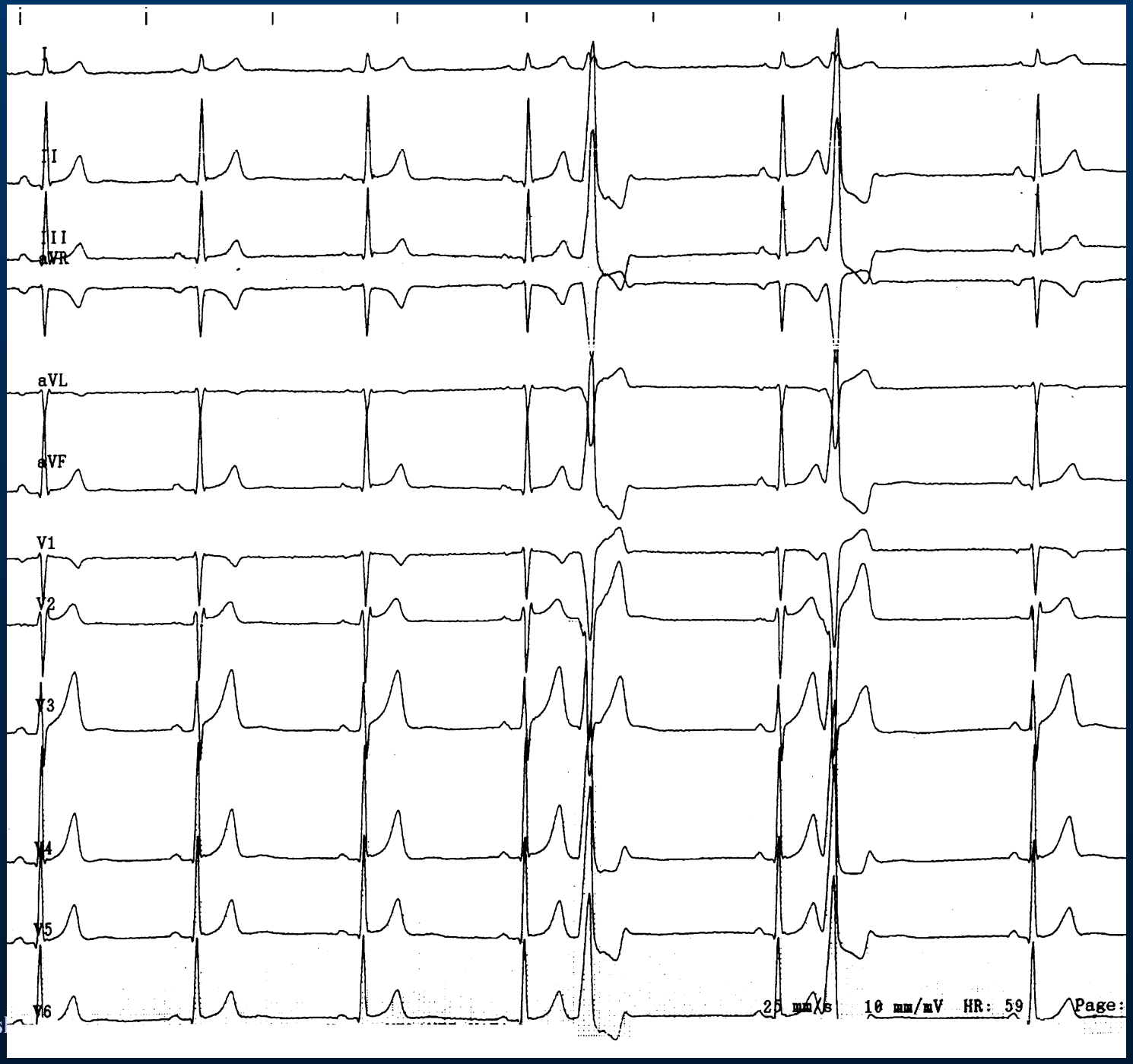

Idiopathic monomorphic VT in normal heart.

RVOT VT

75% - 90% of VT with no heart disease.

LBBB with inferior axis.

- Non-sustained repetitive VT
- Exercise-induced sustained VT

Adenosine sensitive

cAMP – mediated triggered activity

Idiopathic monomorphic VT in normal heart.

RVOT VT

Males = females.

Age = 30 – 50 years.

Palpitations, dizziness =90%

Syncope = 10%

Sudden death = rare

ECG in sinus = 10% RBBB

Echo: normal, slight RVOT enlargement, MVP

Cath: normal, RVED pressure + (25%)

SAECG: normal, RMS40 + or LPD+

MRI: focal wall thinning, abnormal motion antero-lateral RVOT
focal fatty infiltration

I-MIBG: regional sympathetic denervation in 50% in the LV

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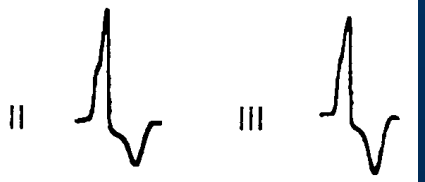
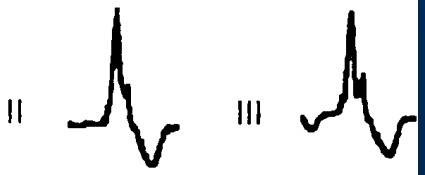
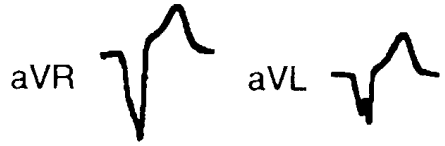
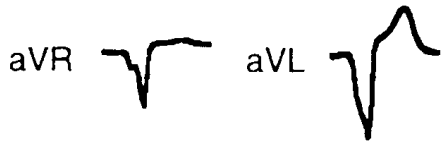
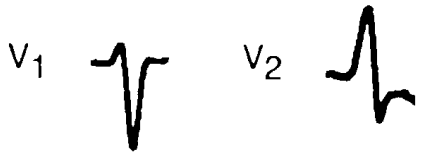
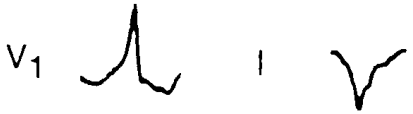
Idiopathic monomorphic VT in normal heart.

RVOT VT

Medical treatment	efficacy
• Beta-blockers:	25% - 50%
• Calcium blockers:	25% - 30%
• Beta-blockers + calcium blockers	
• Flecainide:	25% - 50%
• Sotalol, amiodarone:	50%

Radiofrequency ablation

Localization of site of origin of RVOT - VT

Location	Morphology	ECG
septal RVOT	QRS < 140 ms R (II/III)	
free-wall RVOT	QRS ≥ 140 ms RR'/Rr' (II/III)	
right superior RVOT	QS aVR > aVL	
left superior RVOT	QS aVL > aVR	
immediately beneath pulmonic valve	r ≥ 0.2 mV (V_1 and V_2)	
posterior LVOT (aortomitral continuity)	RBBB V_1, right inferior axis	

Idiopathic monomorphic VT in normal heart.

RVOT VT

Radiofrequency ablation

- Endocardial activation mapping:
  - Bipolar electrogram 10 – 45 msec before QRS
  - Not different from unsuccessful sites
  - Unipolar QS electrogram
- Pace mapping
  - More useful than activation mapping.
  - Identical pace-map achievable 8 mm away
- Success = 90% Recurrence =10%
- Complications: RBBB=1%, fatal perforation (1)

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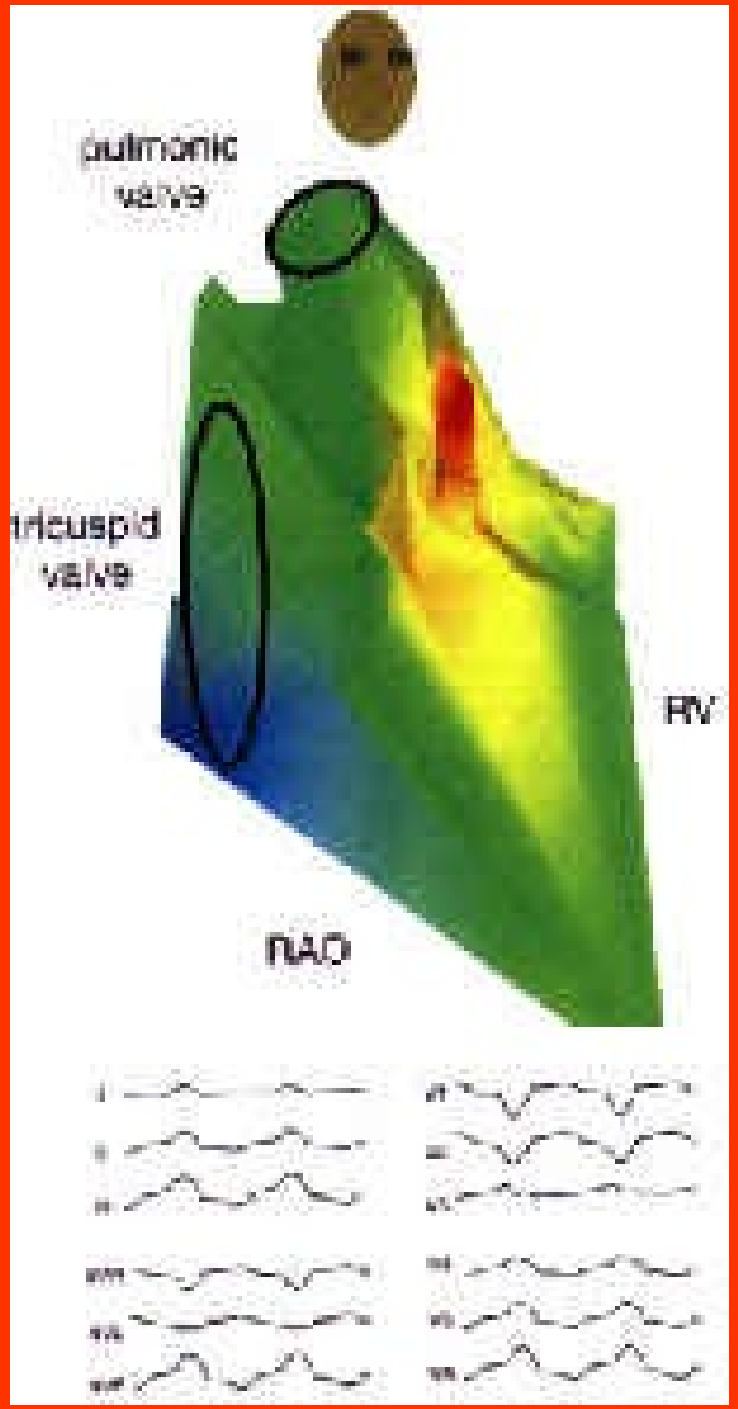
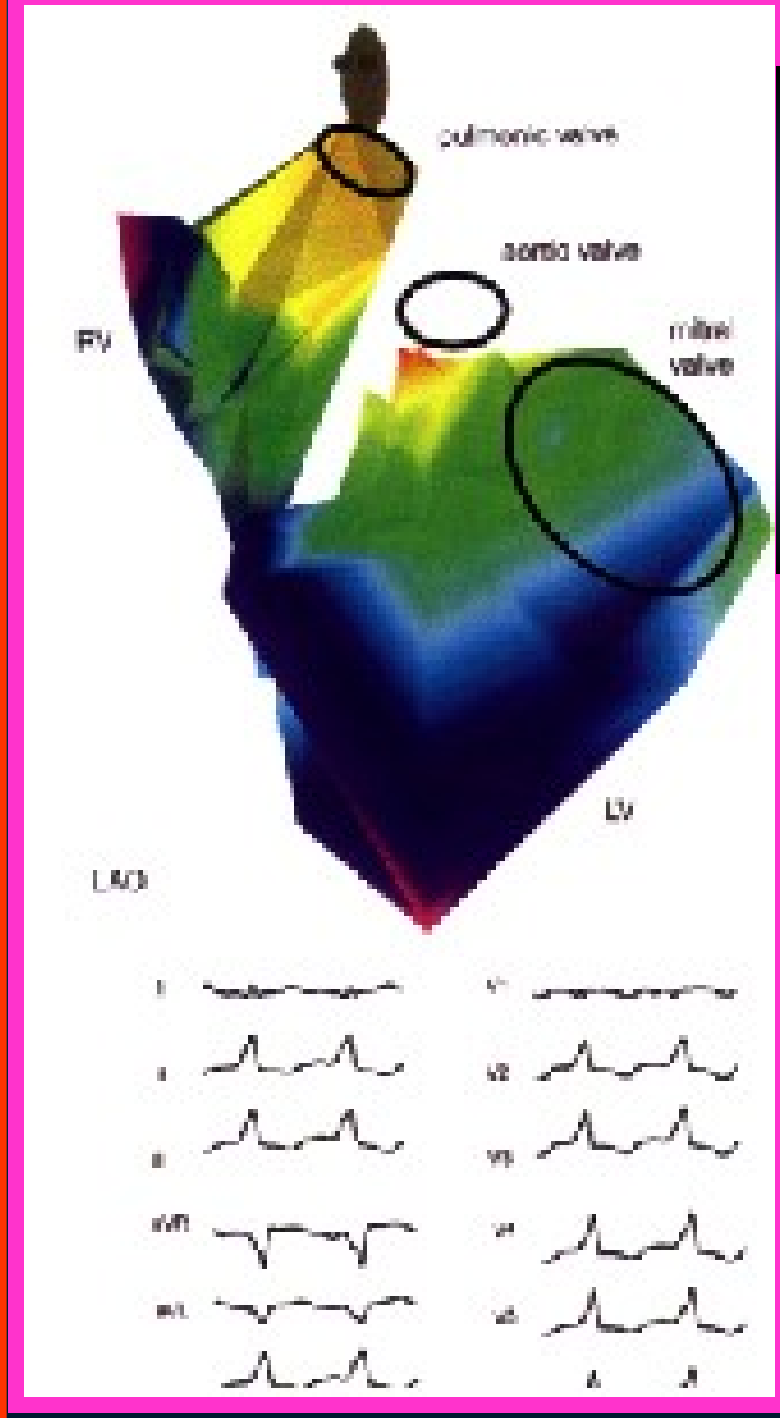




LVOT-VT

RBBB in V1

LBBB with R>S in V2

Idiopathic monomorphic VT in normal heart.

LV (verapamil sensitive) VT

Morphology: RBBBB + left axis **RS = 80 msec**

- Left superior axis 95% =Infero-posterior LV septum
- Right inferior axis 5% = antero-superior LV septum

Origin: left posterior fascicle region

Induction: atrial pacing

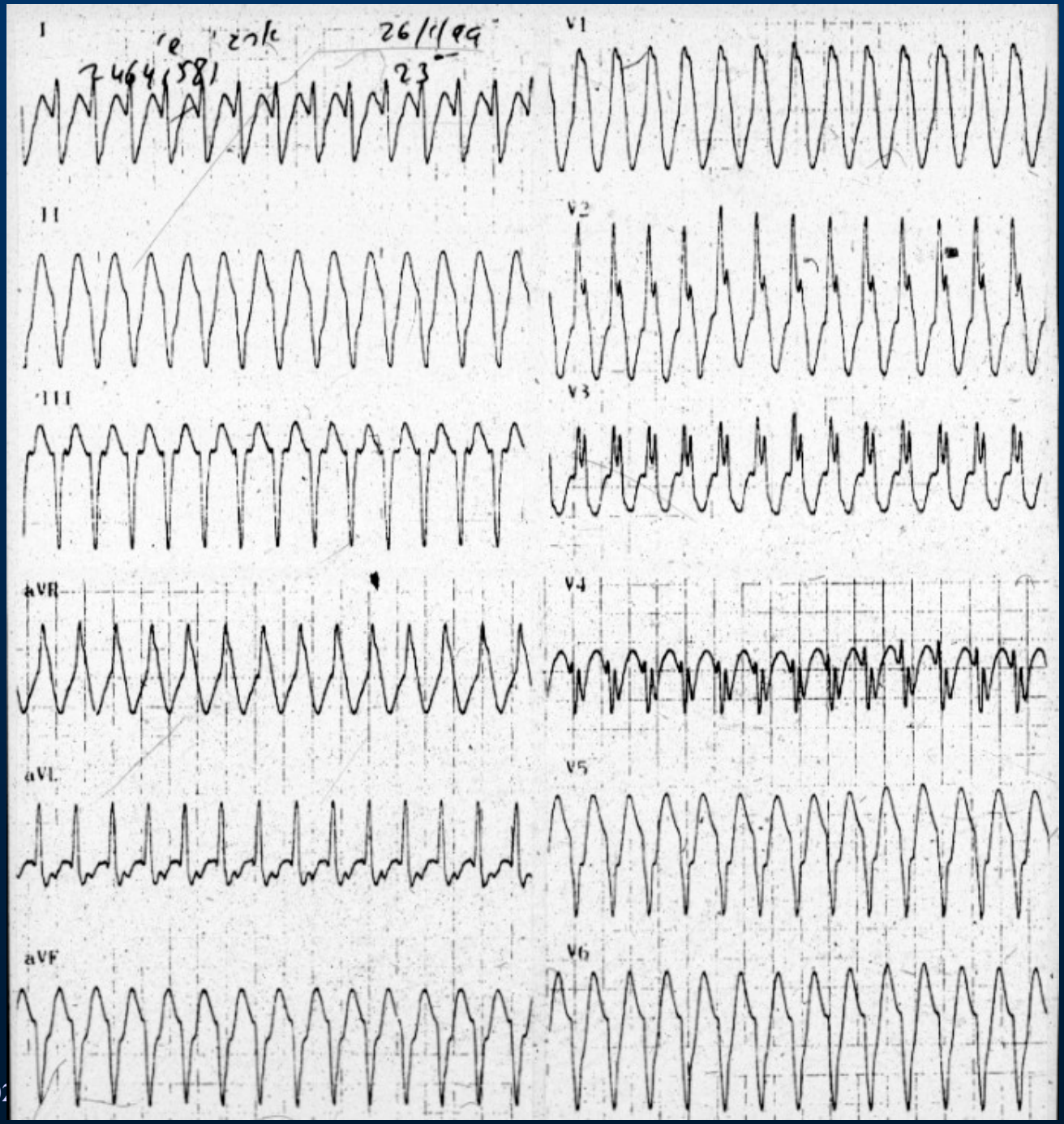
Termination: verapamil (Belhassen 1981)

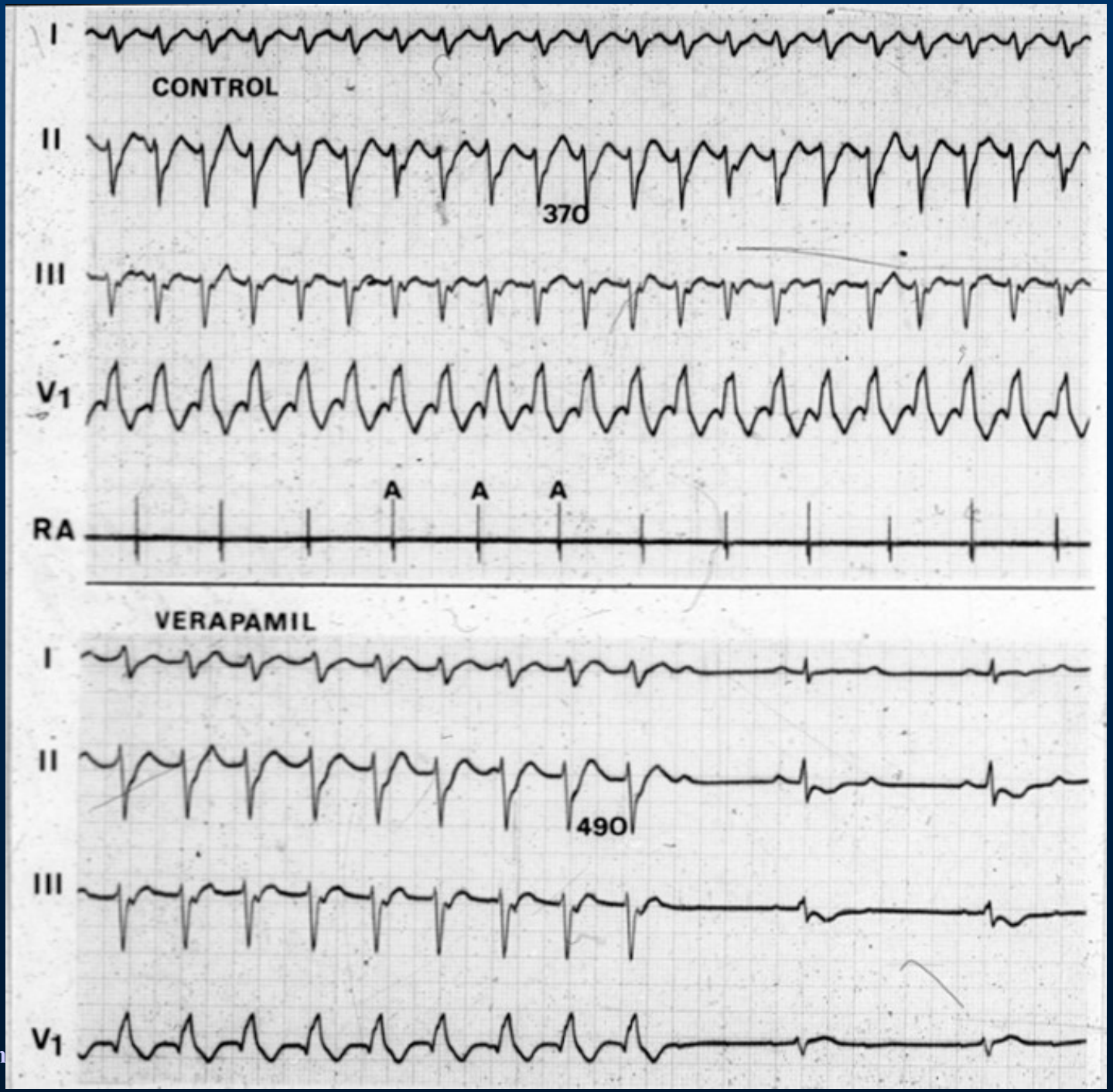
Age: 15 – 40 years (7 – 65 years)

Males = 80%

Usually sustained VT, well tolerated

Not catecholamine sensitive (usually)




I
CONTROL
II
370
III
V1
A
A
A
RA
VERAPAMIL
I
II
490
III
V1

Idiopathic monomorphic VT in normal heart.

LV (verapamil sensitive) VT

Circulation

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American Heart Association. Fighting Heart Disease and Stroke

(*Circulation.* 1996;93:497-501.)

Articles

Anatomic Substrate for Idiopathic Left Ventricular Tachycardia

Ranjan K. Thakur, MD; George J. Klein, MD; Chittur A. Sivaram, MD; Marco Zardini, MD; David E. Schleinkofer, MD; Hiroshi Nakagawa, MD; Raymond Yee, MD; Warren M. Jackman, MD

From the Arrhythm
Oklahoma Health S

False tendon
15/15 VT – 34/671 Control

Circulation

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American Heart Association. Fighting Heart Disease and Stroke

(*Circulation.* 1996;93:525-528.)

Articles

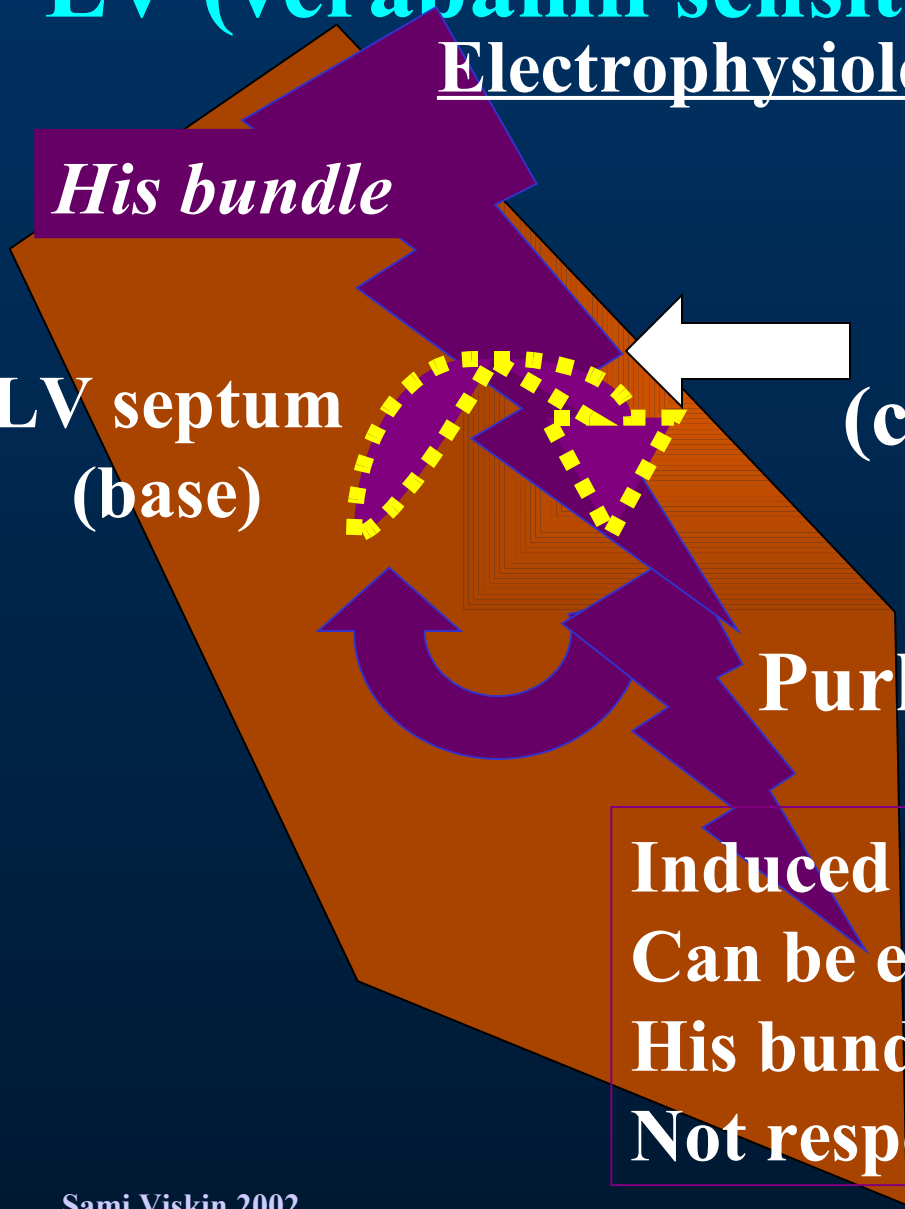
Left Ventricular Fibromuscular Band Is Not a Specific Substrate for Idiopathic Left Ventricular Tachycardia

False tendon
11/18 VT – 35/40 control

Idiopathic monomorphic VT in normal heart.

LV (verapamil sensitive) VT

Electrophysiologic mechanism



Induced w programmed stimulation
Can be entrained from RVOT.
His bundle not part of the circuit
Not responsive to adenosine..unless..

Idiopathic monomorphic VT in normal heart.

LV (verapamil sensitive) VT

Therapy

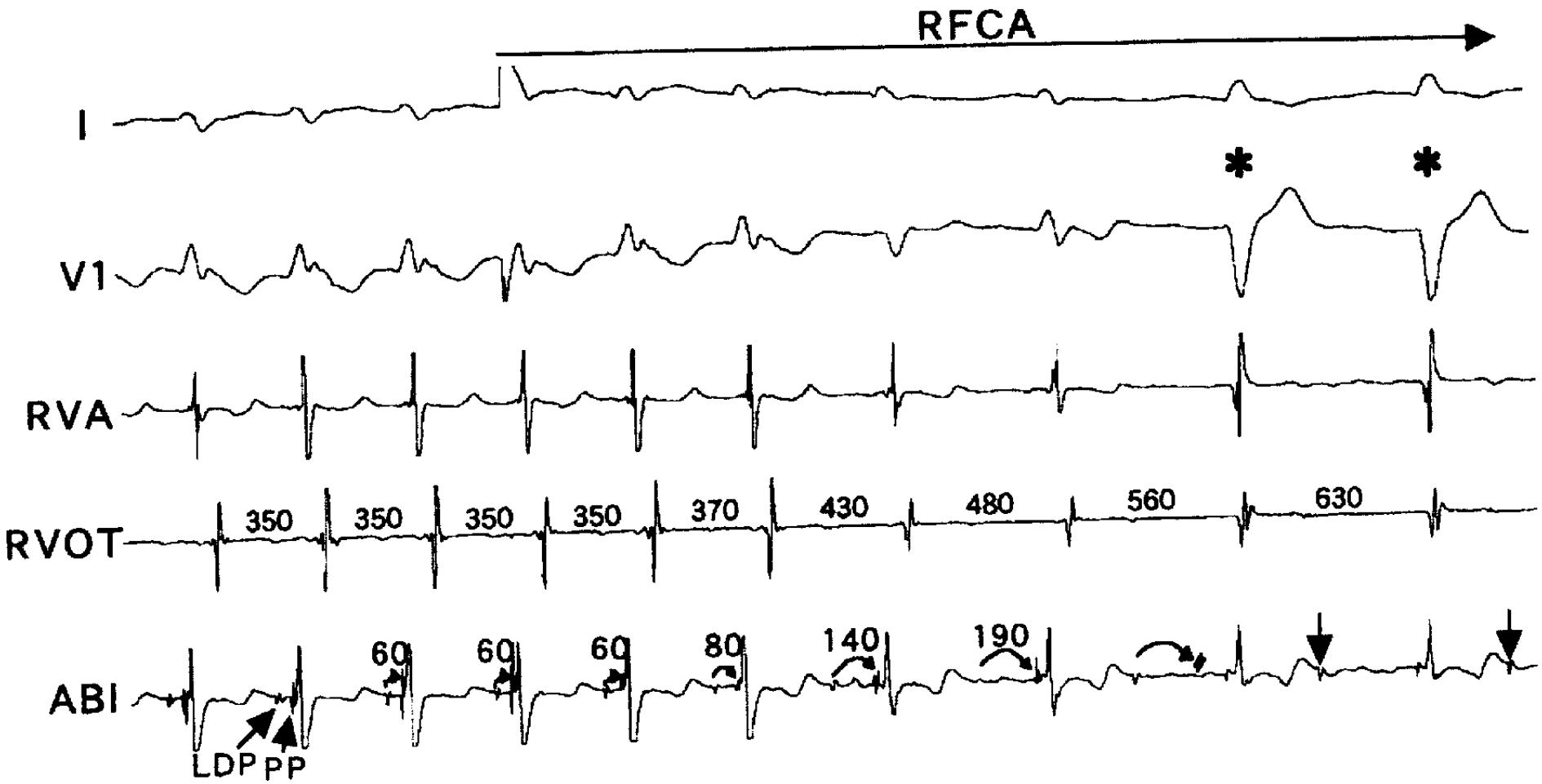
Acute termination: Verapamil

Chronic therapy: Verapamil 320 mg/day

Radiofrequency ablation:

Success: 90% **Complications: rare**

Radiofrequency ablation of LV – VT (verapamil sensitive)



LDP = left diastolic potential
PP= Purkinje-like pre-potential

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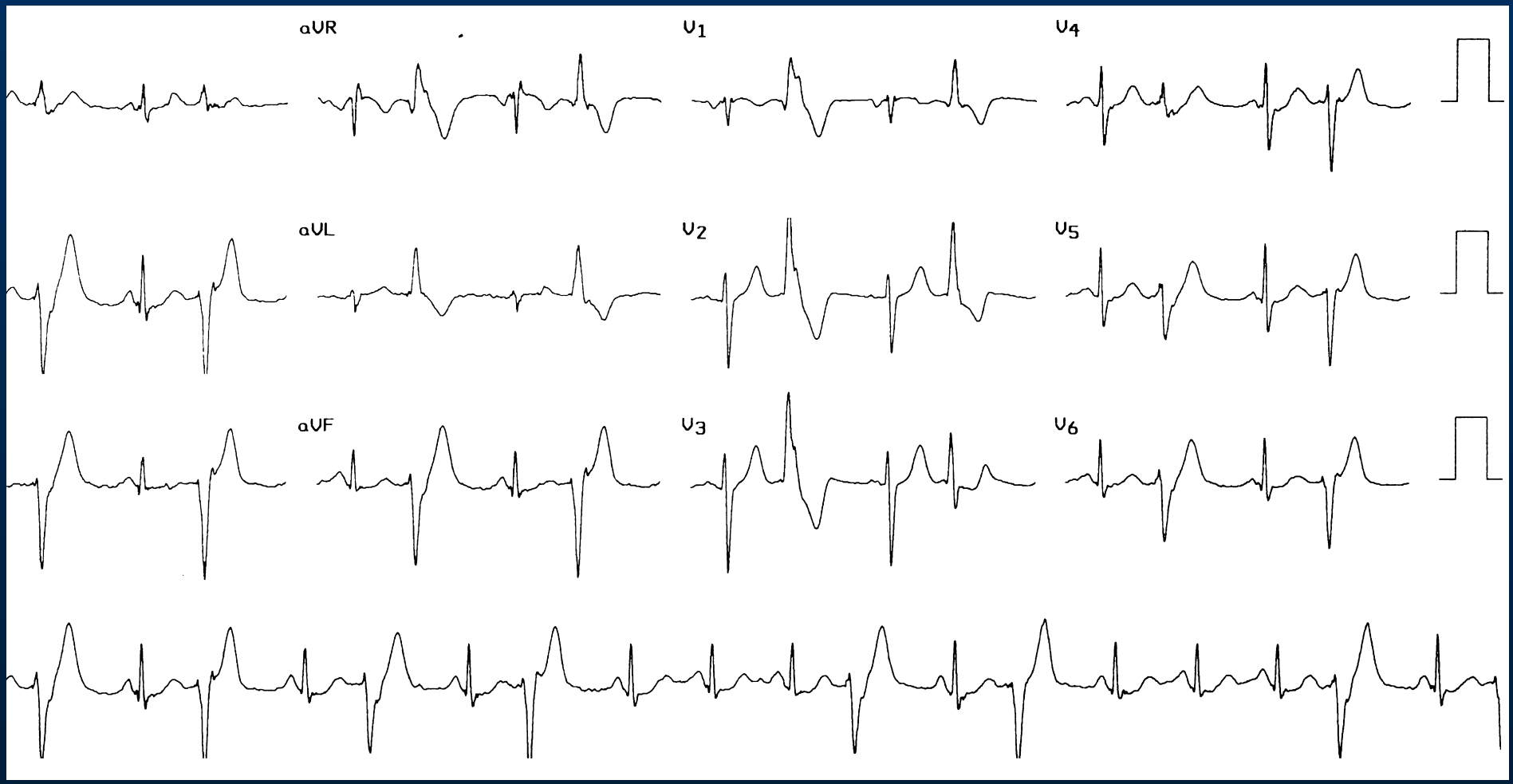
Tsuchiya, *Circulation* 1999

Idiopathic catecholamine sensitive monomorphic VT



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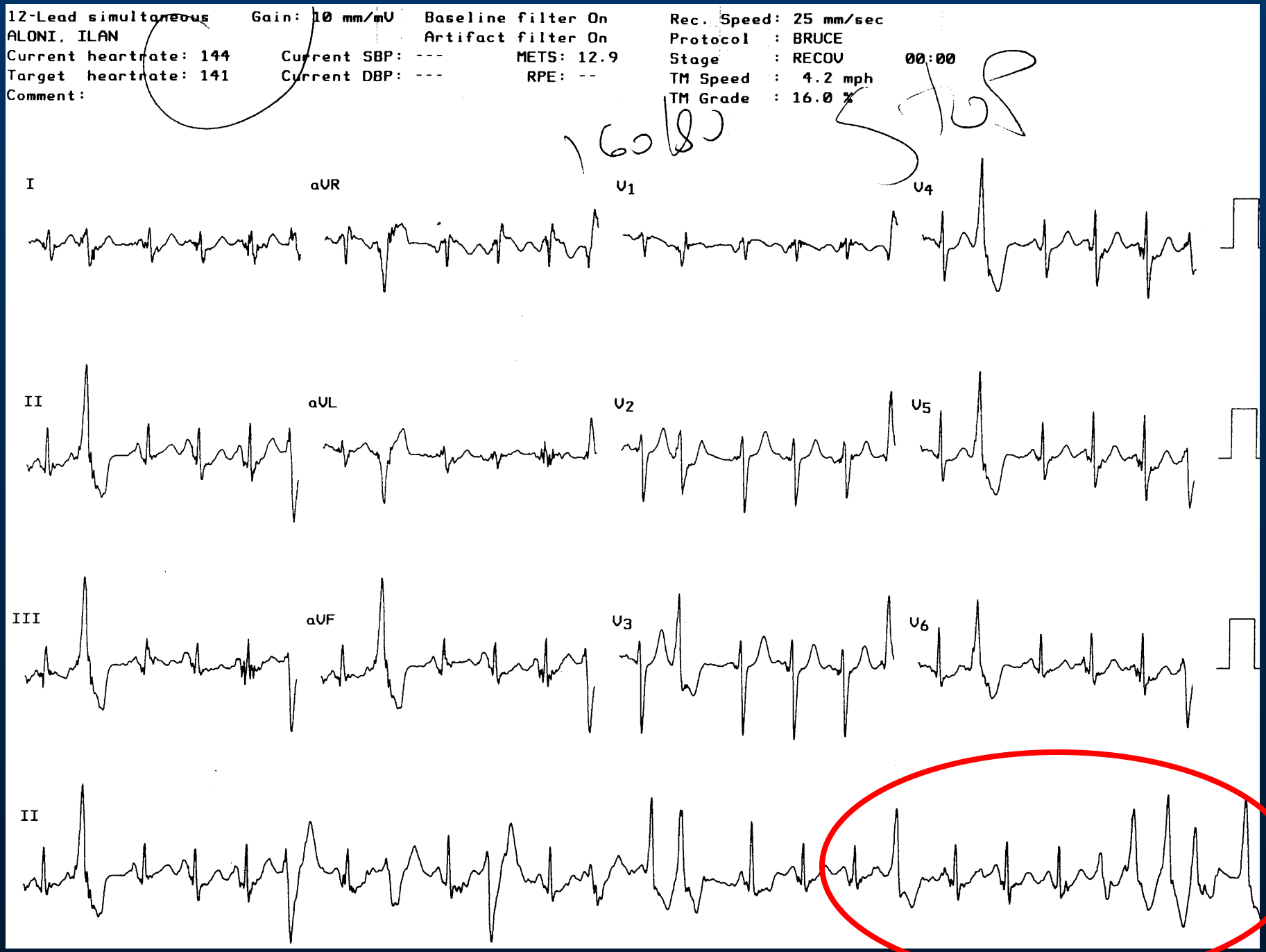
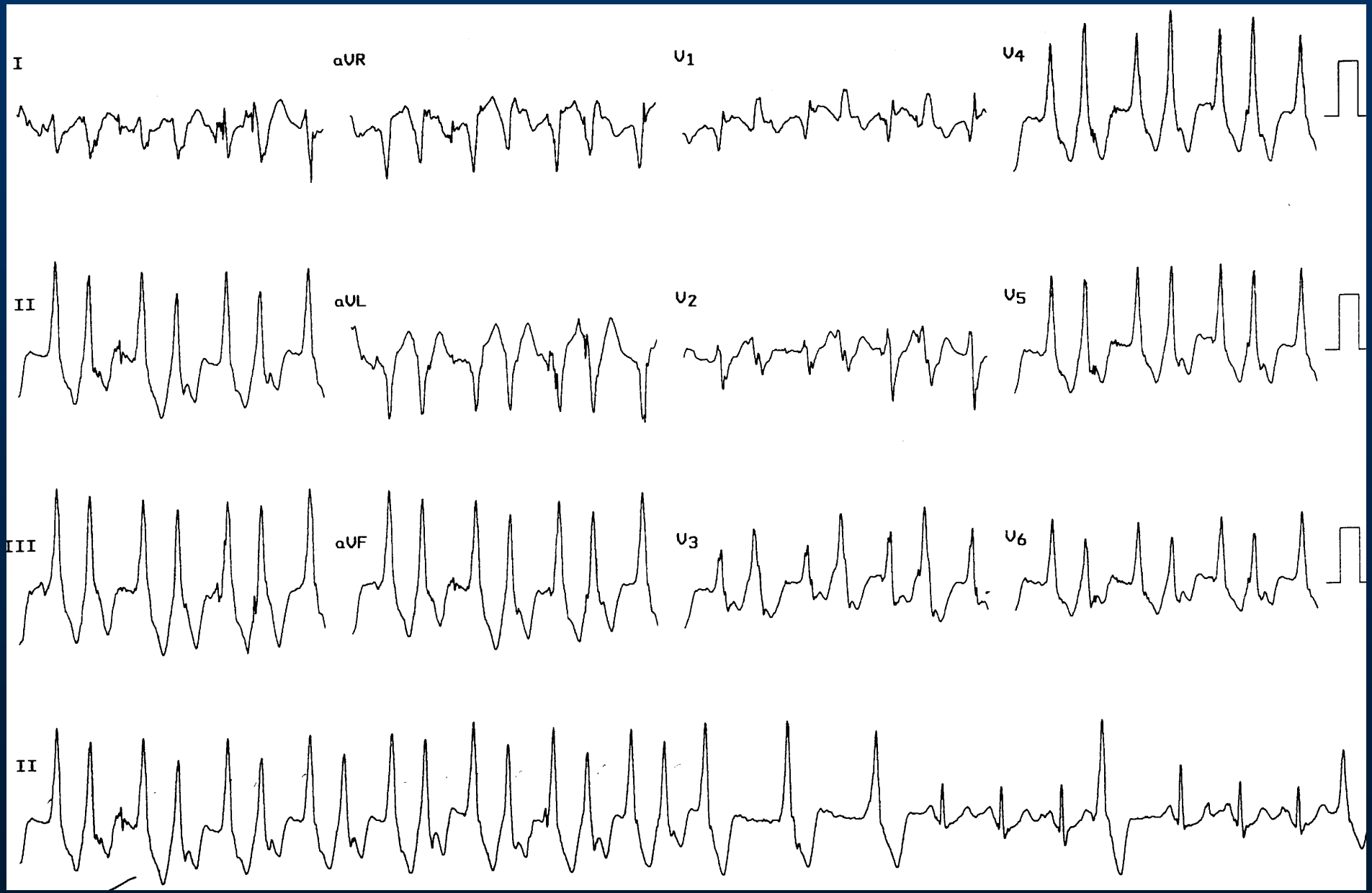

12-Lead simultaneous
Gain: 10 mm/mV
Baseline filter On
Artifact filter On
Rec. Speed: 25 mm/sec
ALONI, ILAN
Protocol : BRUCE
Current heartrate: 144
Current SBP: ---
METS: 12.9
Stage : RECOV 00:00
Target heartrate: 141
Current DBP: ---
RPE: --
TM Speed : 4.2 mph
Comment:
TM Grade : 16.0 %
160/80
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II



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Idiopathic monomorphic VT in normal heart.

	Adenosine sensitive	Verapamil sensitive	Propranolol sensitive
Origin	**RVOT**	Lf post fascicle	RV or LV
Morphology	**LBBB**	RBBB, Lf axis	RBBB, LBBB
Characteristic	**NSVT, Exercise SMVT**	SMVT	Exercise SMVT
Mechanism	**Triggered activity**	Reentry	Automaticity
Entrainment	**No**	Yes	No
Termination:			Beta-blockers
Adenosine	**Yes**	No	Transient
Verapamil	**Yes**	Yes	No

Polymorphic ventricular arrhythmias in the normal heart.

Catecholamine sensitive polymorphic VT

Long QT syndromes

Idiopathic VF and Brugada syndrome.

Short QT syndromes

scientific sessions 2005
Sessions: November 13–16
Exhibits: November 13–15
Dallas, Texas

basic science | clinical science | population science

American Heart Association
Learn and Live

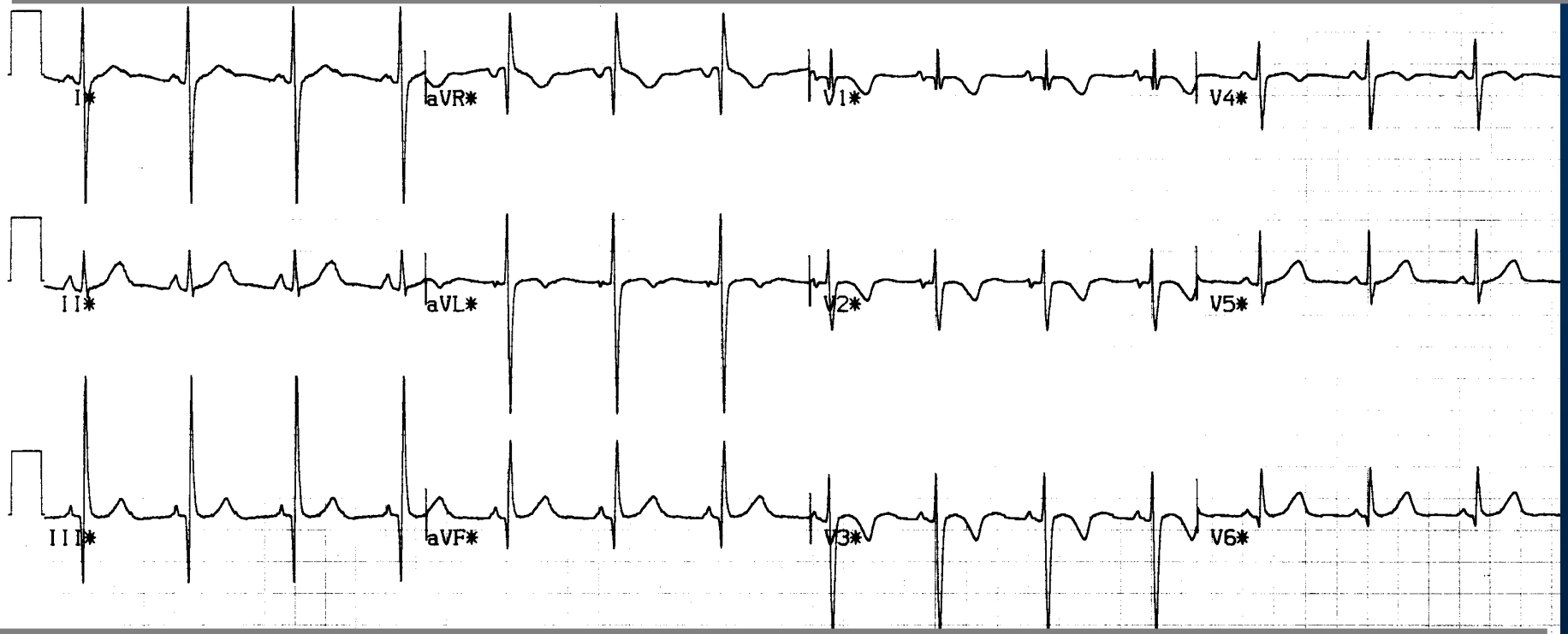
Cardiovascular Seminar:

Emerging Syndromes: Catecholaminergic Polymorphic VT, Malignant RVOT, Idiopathic VF

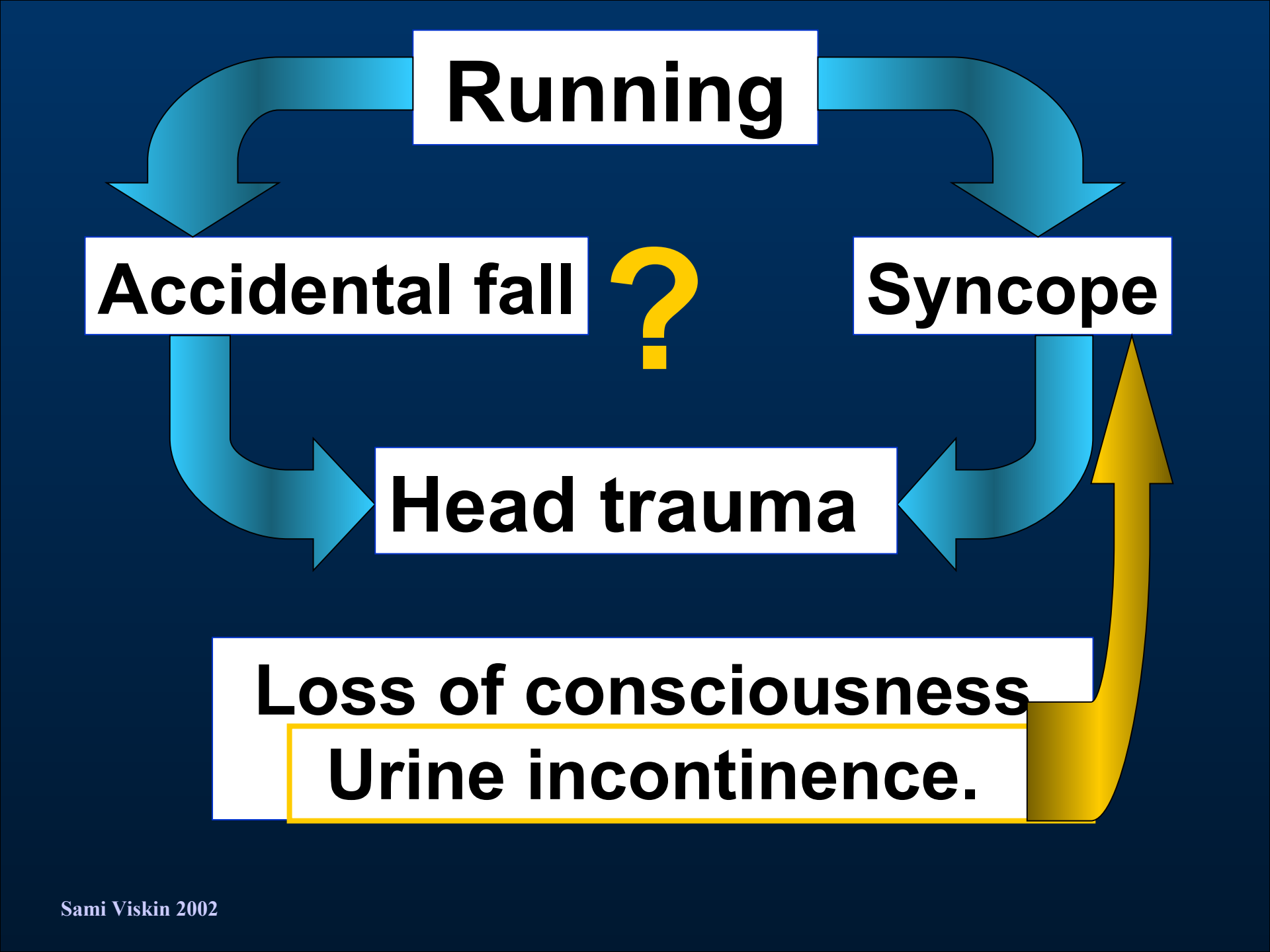
Sami Viskin.
Tel Aviv Medical Center, Israel.

Disclosures: None (unfortunately).

B.S.- 6 year old boy. Brought to the emergency room because of head trauma.

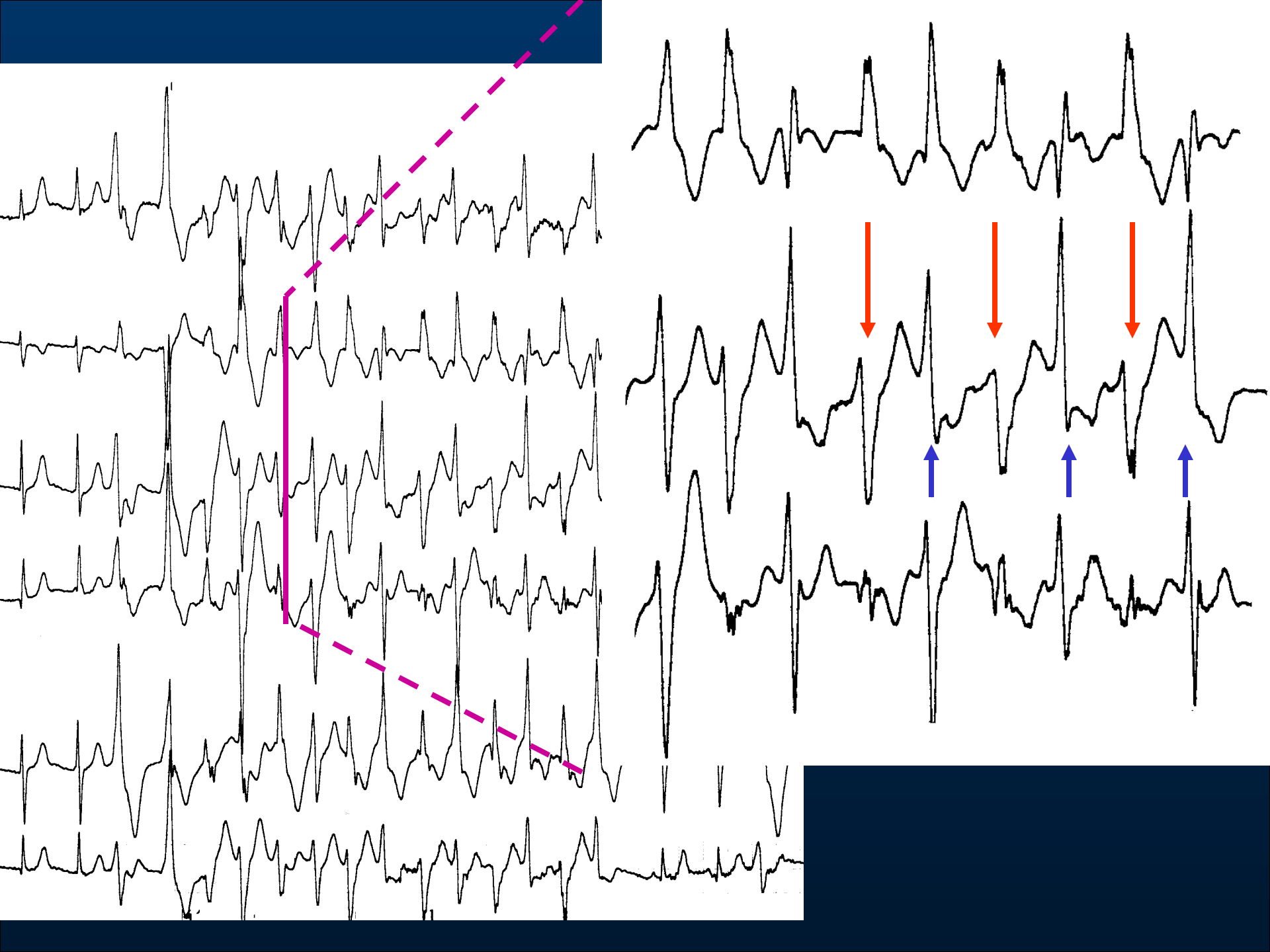


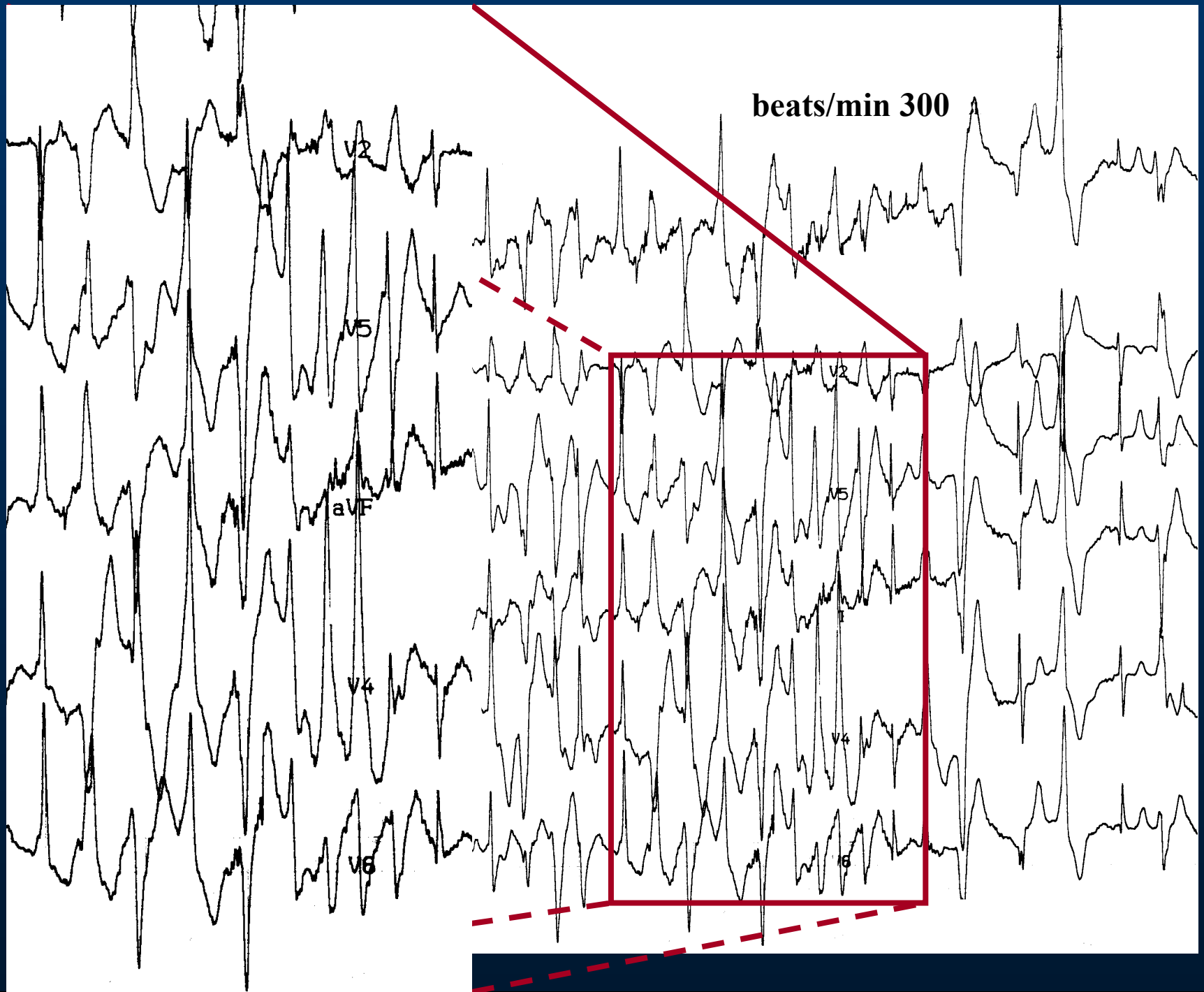
History: Running with friends ➔ fell forward ➔ hit his head, lost consciousness and passed urine.




BRUCE
EXERCISE 1
HR: 137bpm
Clock 1: 00:39
Clock 2: 00:39
Speed: 1.7mph
Grade: 10.0%
V2
V5
V4
V6


Speed: 0.9mph
Grade: 3.5%
40Hz
V2
V5
aVF
V4
V6
#2175 CASE 106G
3 A- H- S+ F+ 50 Sf23 H442 #2175 CASE 106G




beats/min 300
V2
V5
aVF
V4
V6
V2
V5
V4
V6

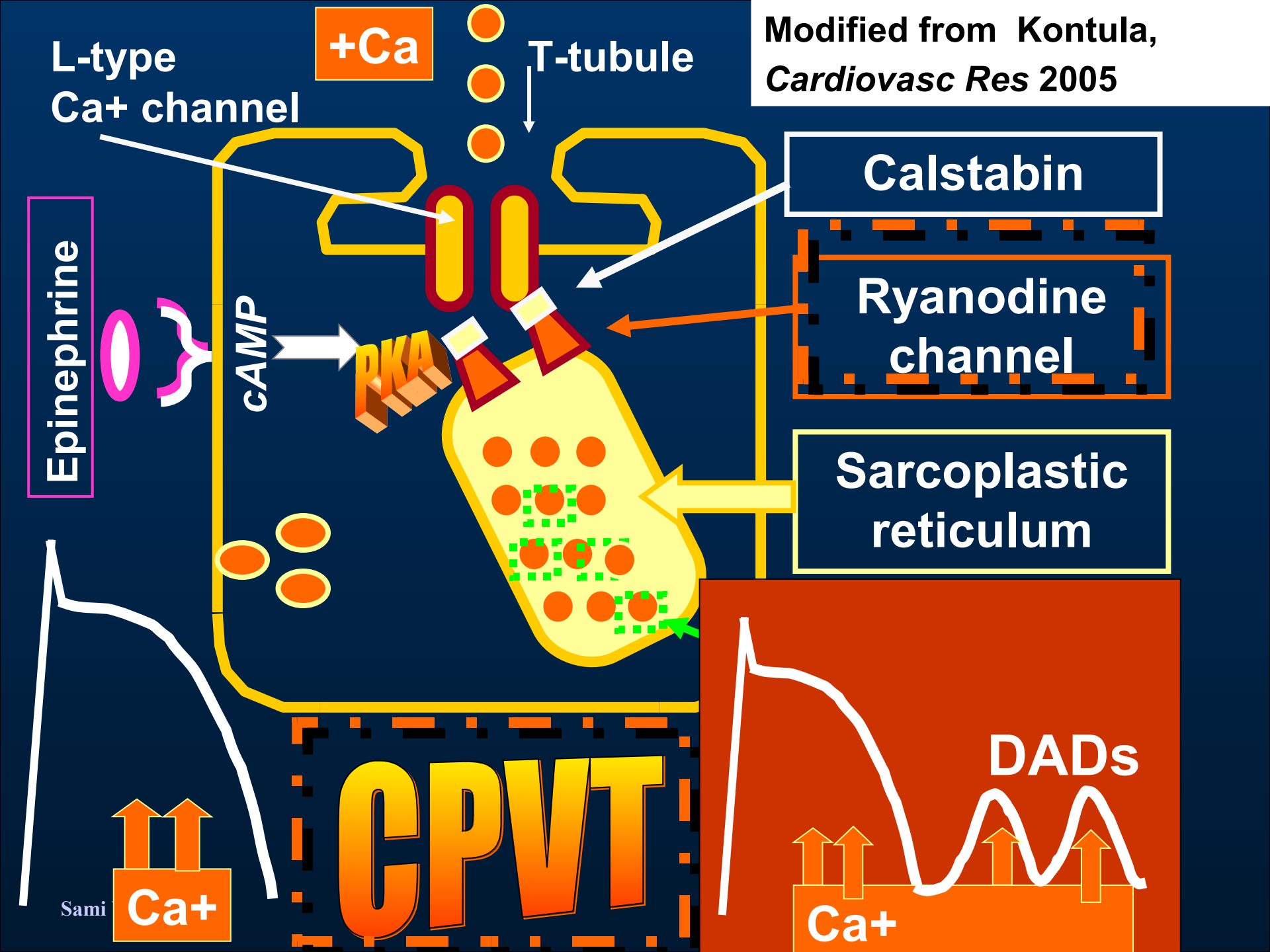
Catecholaminergic Polymorphic VT

Genetic disorder:

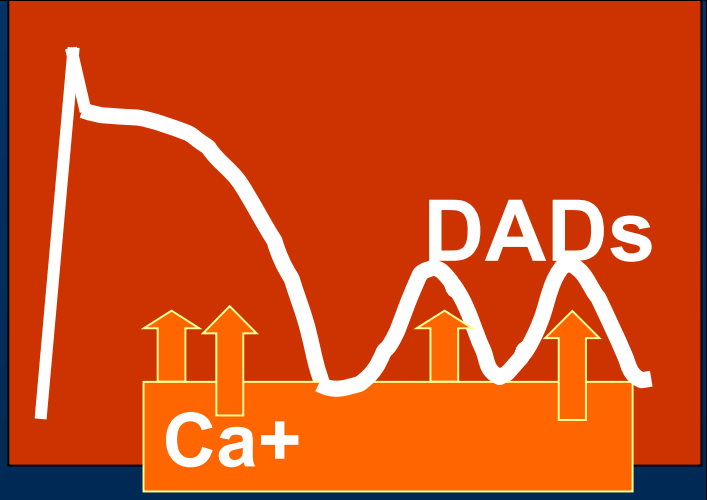
RyR2 **CASQ2** **KCNJ2** **Ankyrin-B**

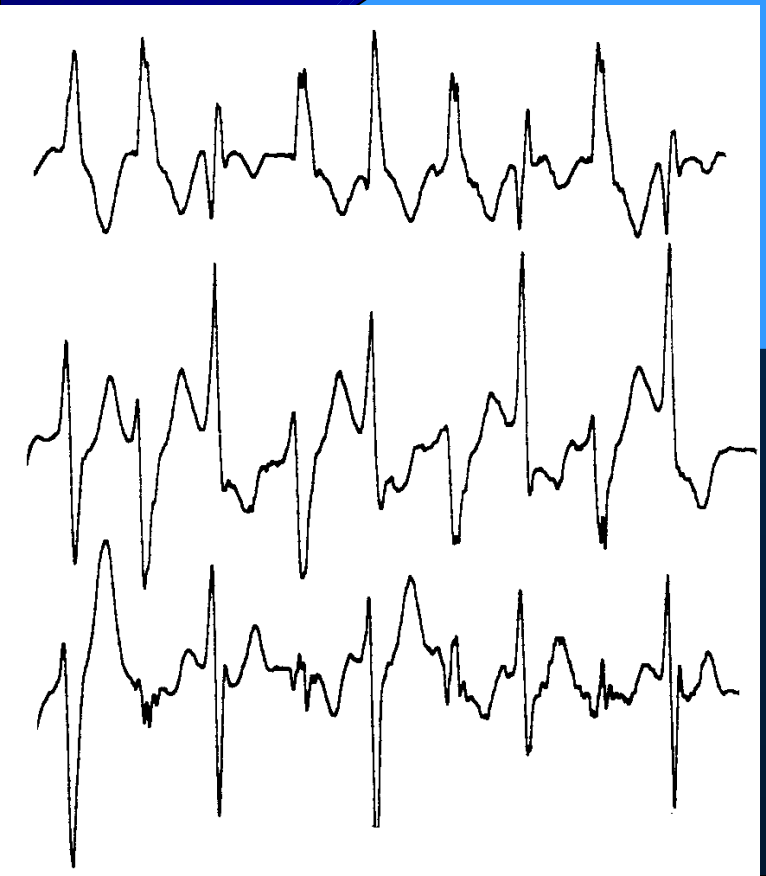
Age: 3-20, both genders.

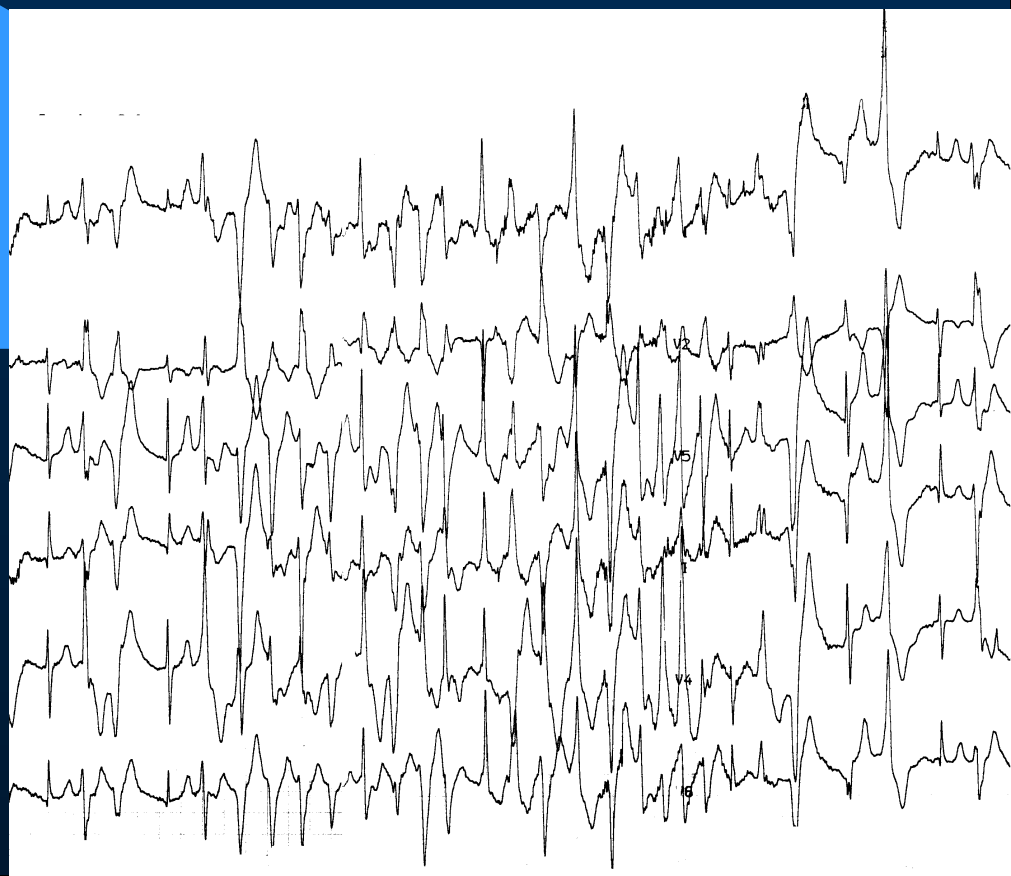
Syncope or cardiac arrest triggered by exercise/emotional stress.


Modified from Kontula, *Cardiovasc Res* 2005
L-type Ca+ channel
+Ca
T-tubule
Calstabin
Ryanodine channel
Epinephrine
cAMP
PKA
Sarcoplastic reticulum
Ca+
CPVT
DADs
Ca+
Sami

How do we get from here to here?



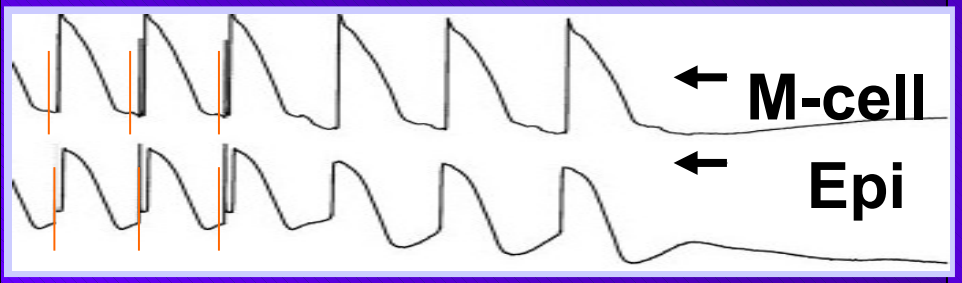




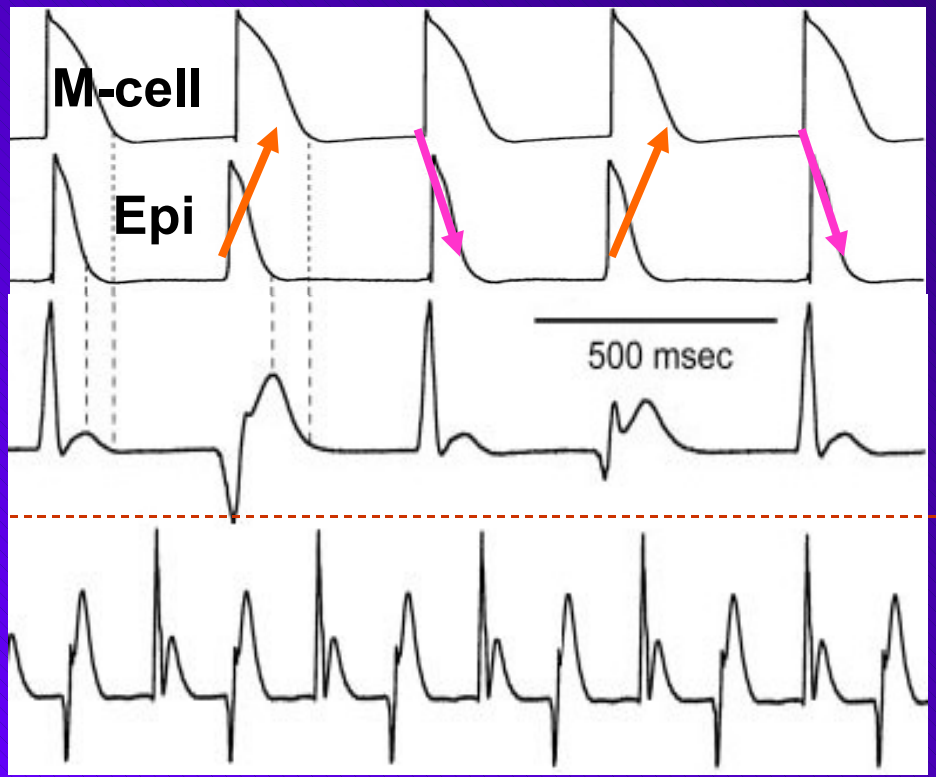
A model of CPVT (caffeine and isoproterenol) in the arterially perfused canine wedge preparation.

Nam, Burashnikov, Antzelevitch. *Circulation* 2005.

1. Caffeine + rapid pacing
➔ DADs from epicardium



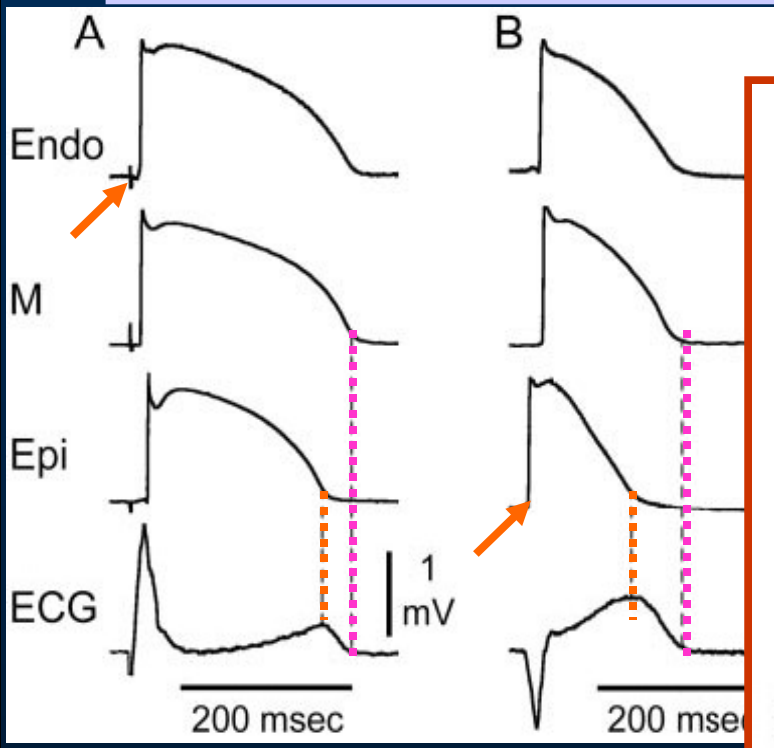
2. ➔ Alternating origin of DADs (epi and M cell)



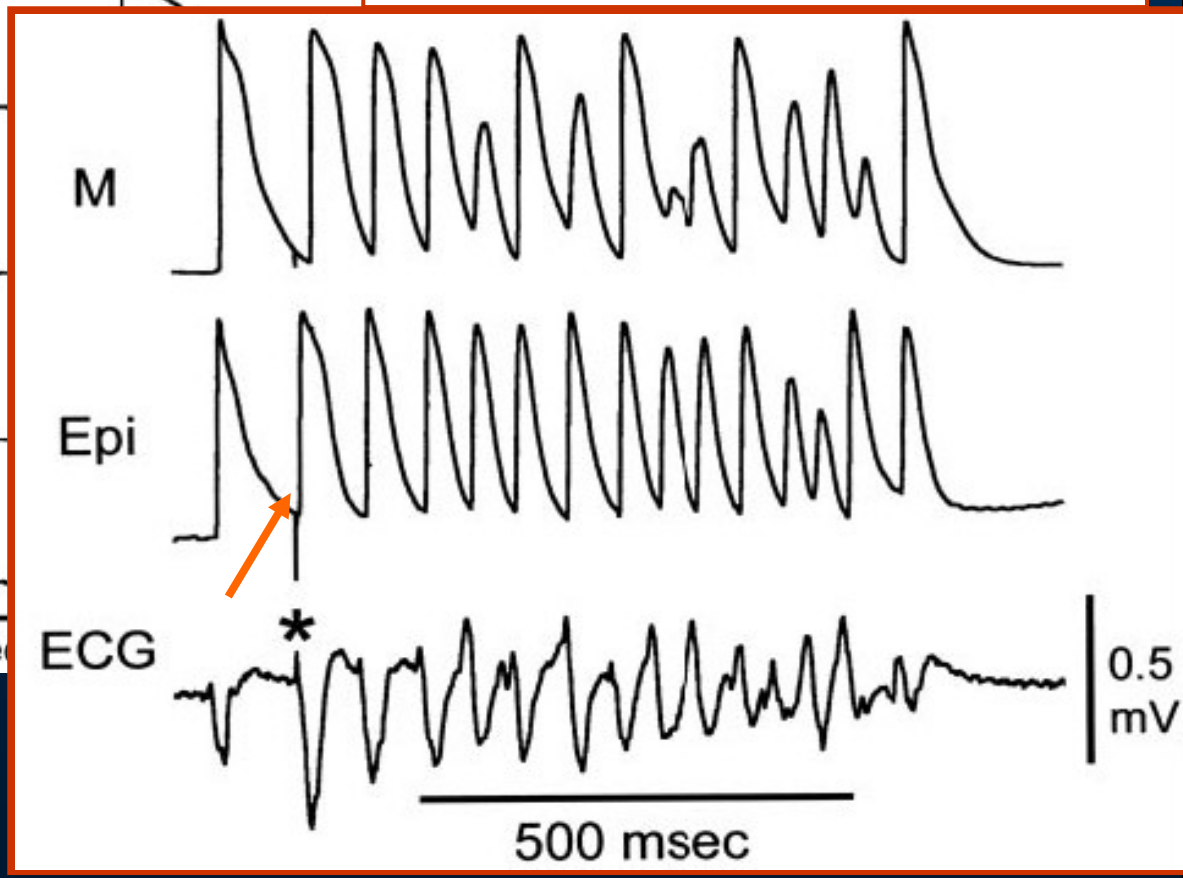
A model of CPVT (caffeine and isoproterenol) in the arterially perfused canine wedge preparation.

Nam, Burashnikov, Antzelevitch. *Circulation* 2005.

3. **Site of origin affects dispersion of repolarization**

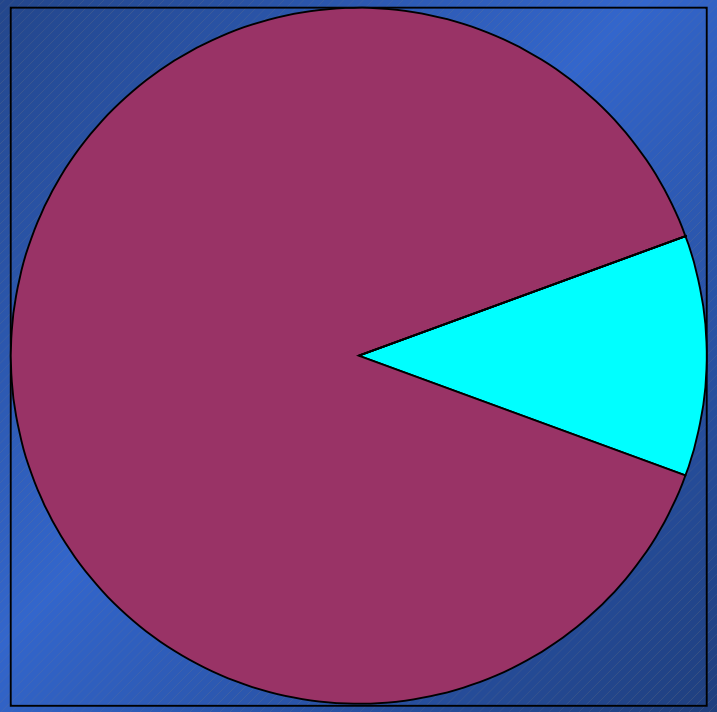


4. Single extrastimuli during epicardial VT ➔polymorphic VT

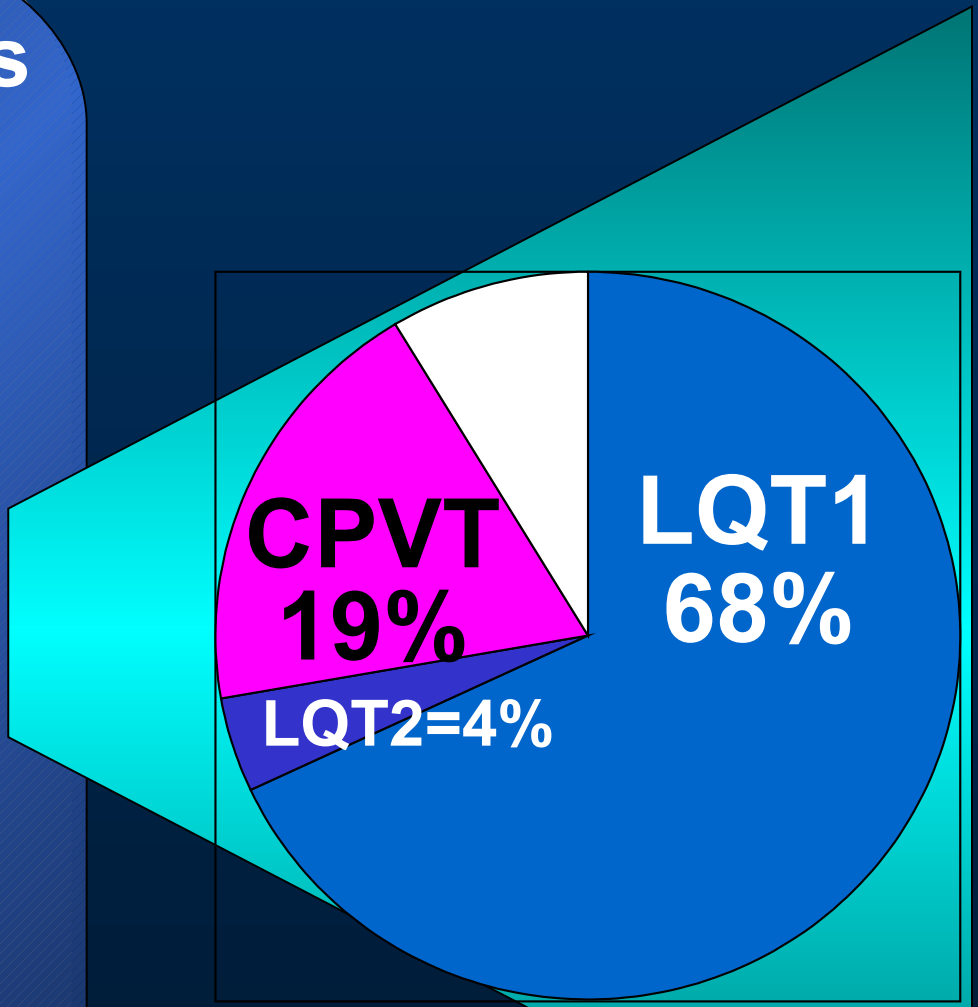


CPVT as cause for drowning

Consecutive referrals for genetic testing
N = 388.



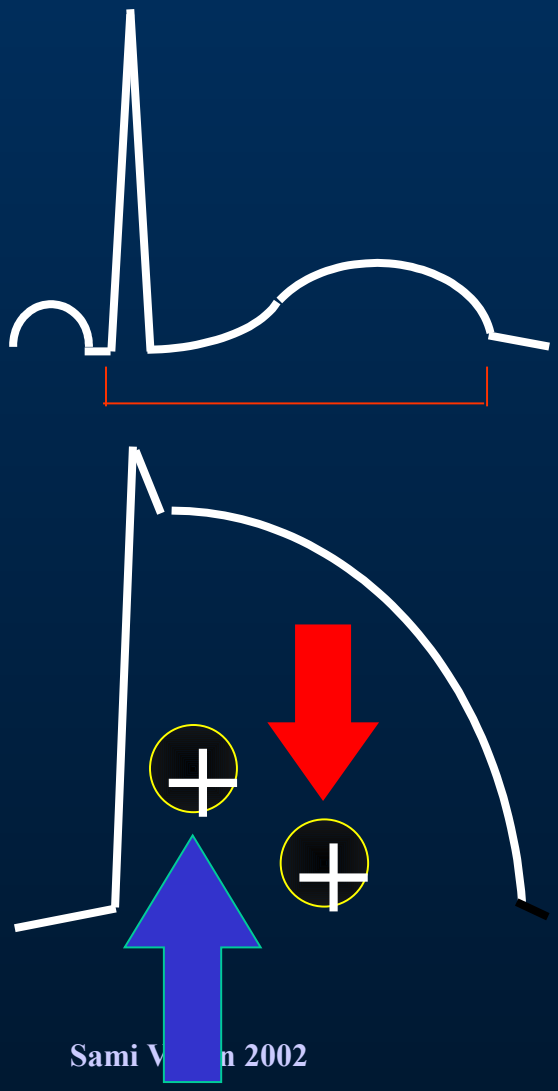
Swimming-related arrhythmias =11%

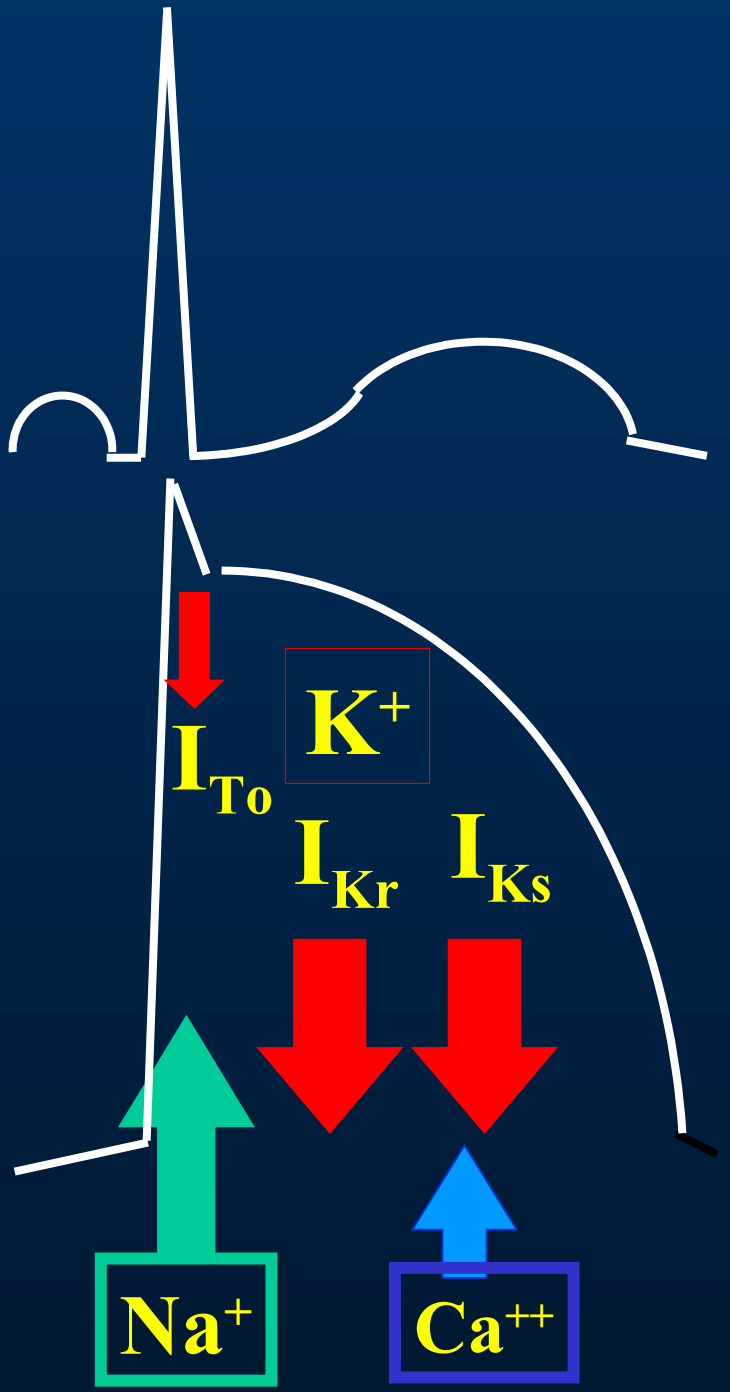


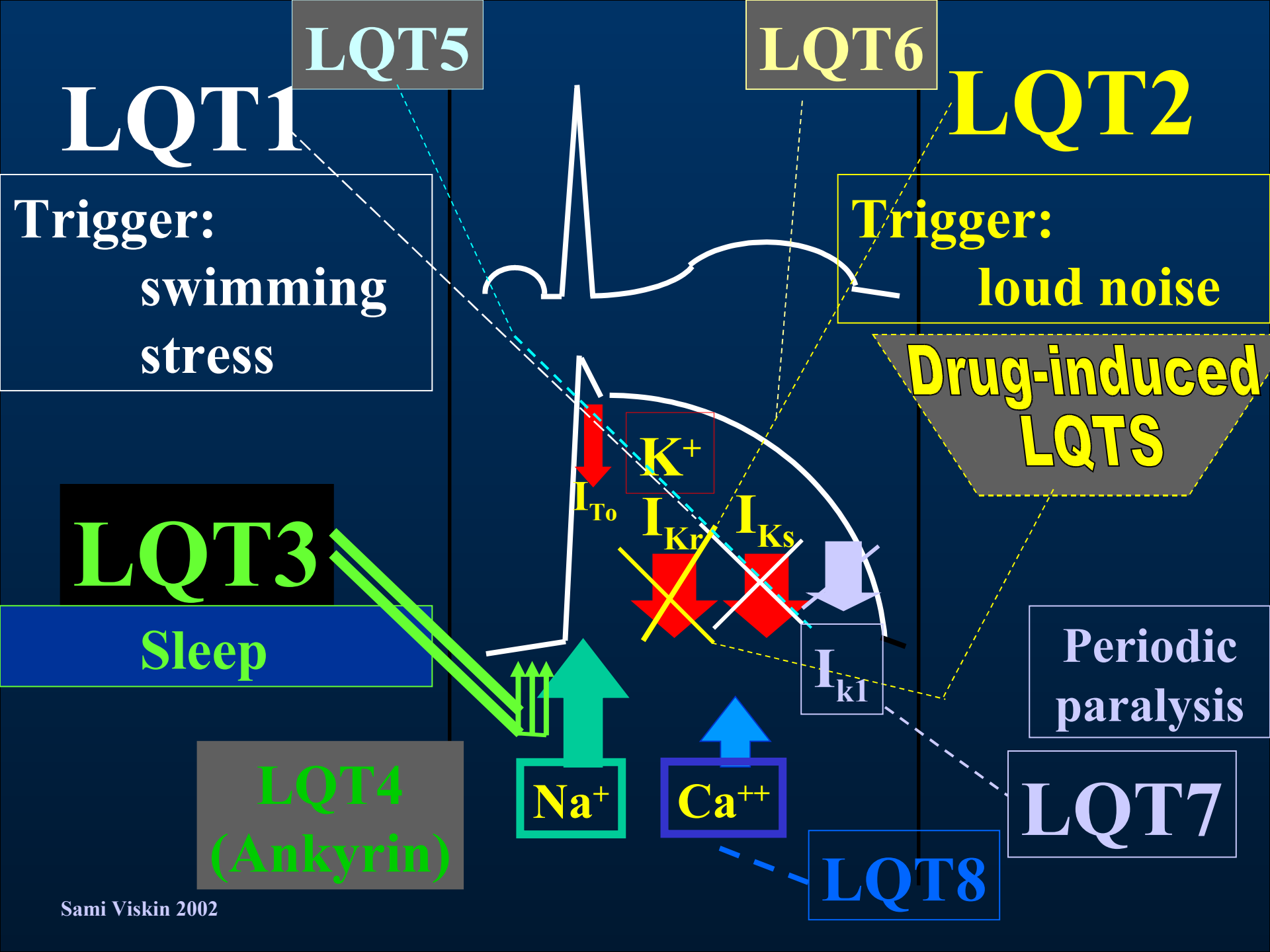
Choi, Ackerman,
Circulation 2004


HR: 146bpm
Speed: 4.9mph
Grade: 0.0%
25mm/s
10mm/mV
40Hz
Maximal exercise (no drugs)
I
II
V2
V5
aVF
V4
V6

The QT interval






LQT5
LQT6
LQT1
LQT2
Trigger:
swimming
stress
Trigger:
loud noise
Drug-induced
LQTS
K+
ITo
IKr
IKs
IkI
LQT3
Sleep
Periodic
paralysis
LQT4
(Ankyrin)
Na+
Ca++
LQT7
LQT8
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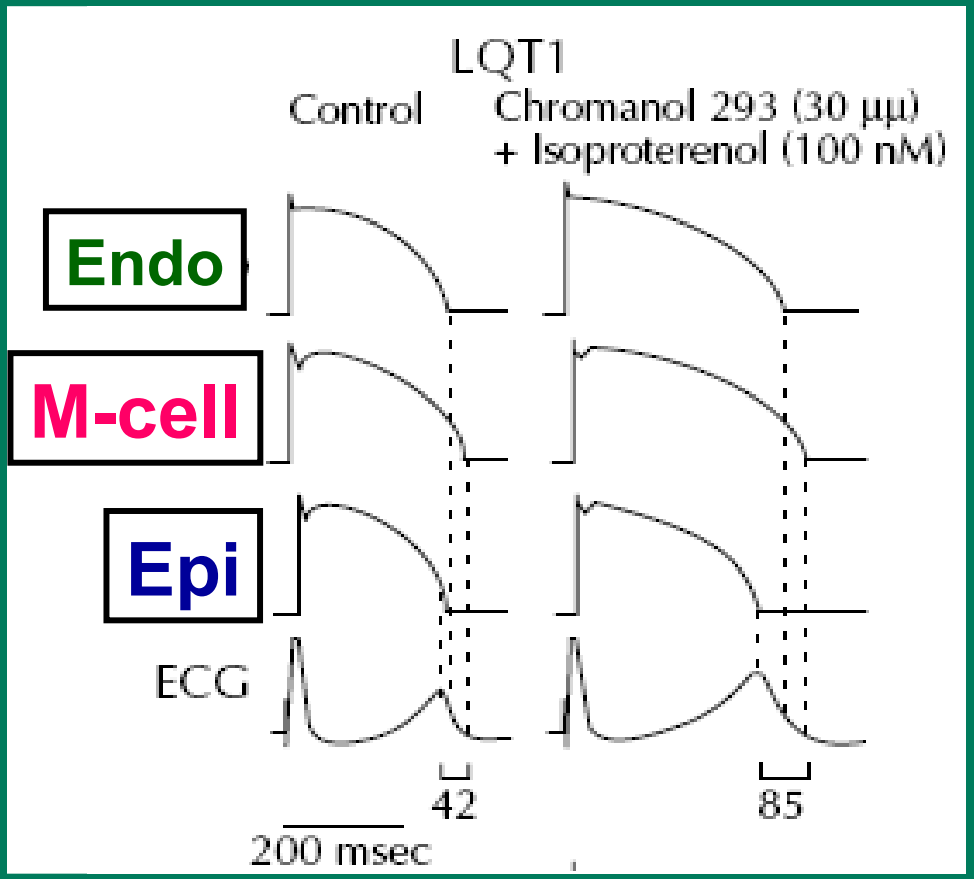
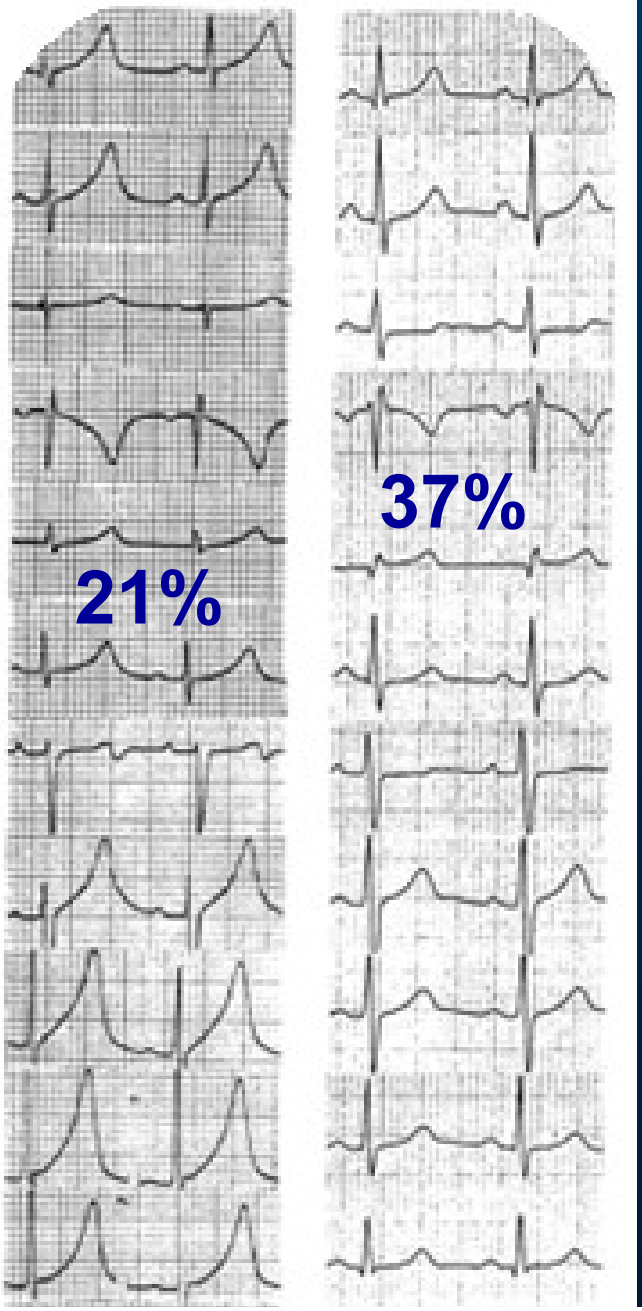
LQT1: *KCNQ1* : I_{Ks}



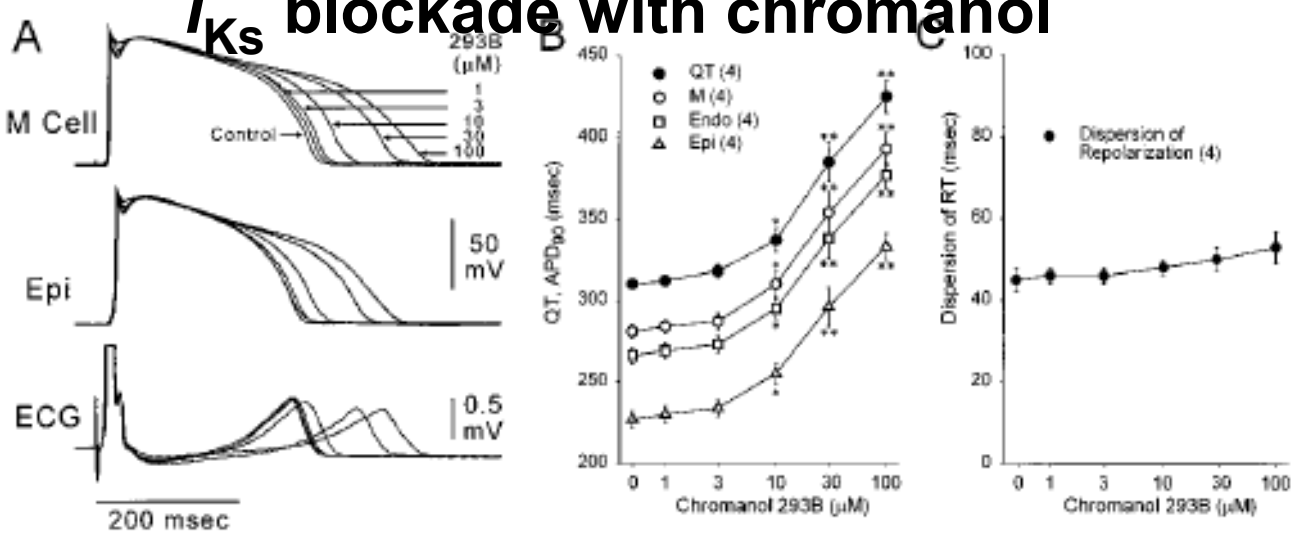
Yan, Antzelevitch. *Circulation* 1998.



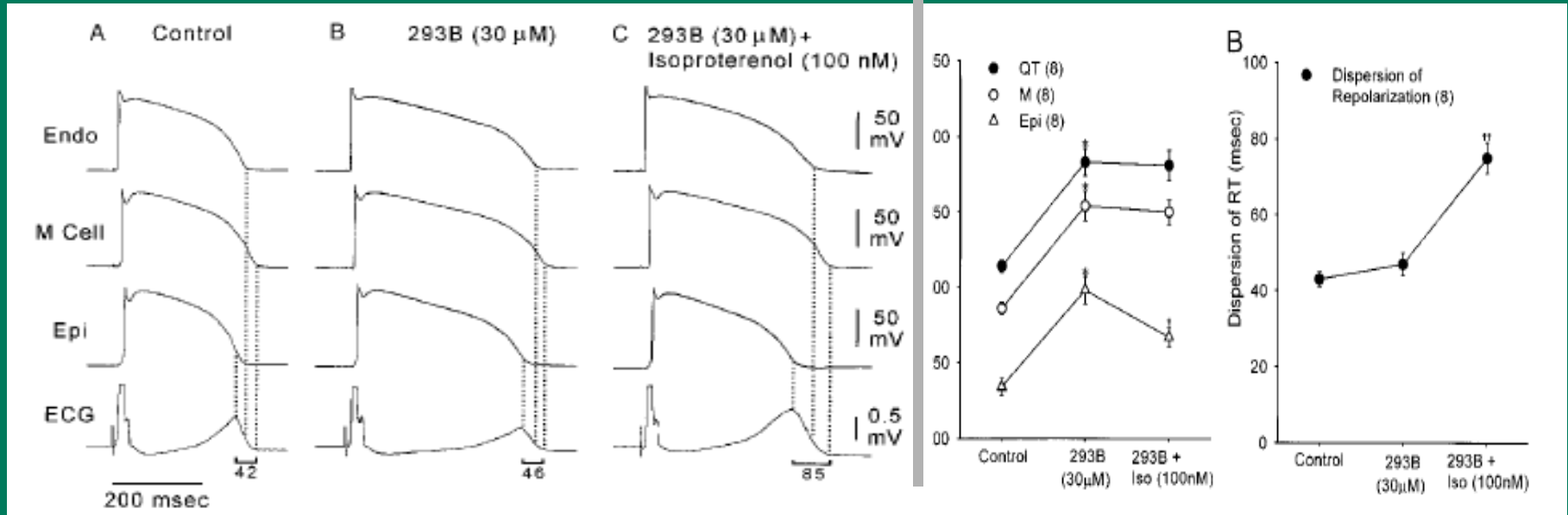
Zhang. Circulation 2000.

LQT1

I_{Ks} blockade with chromanol



Isoproterenol during *I*Ks blockade

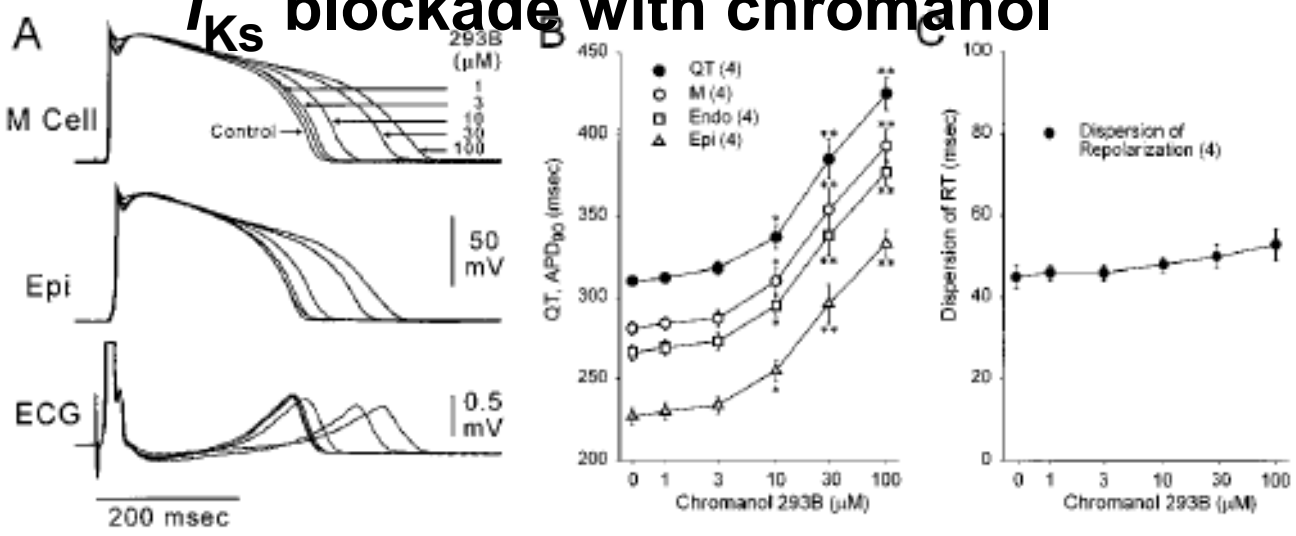


Shimizu, Antzelevitch *Circulation* 1998.

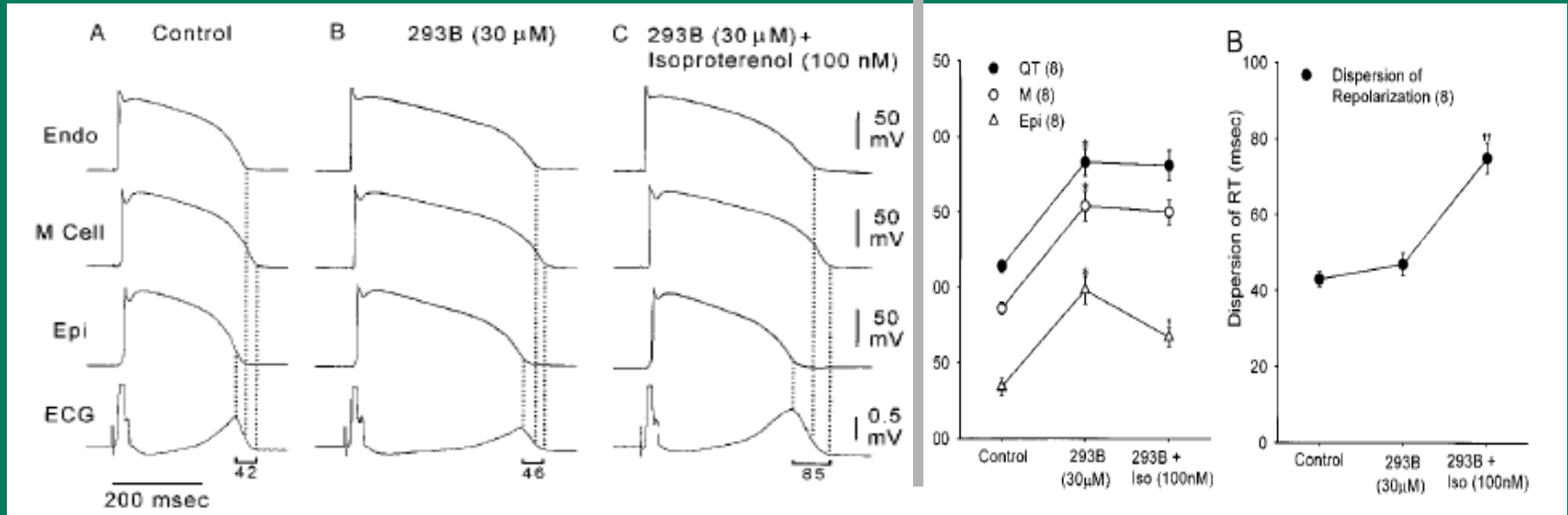
LQT1

Stress 62%

I_{Ks} blockade with chromanol



Isoproterenol during *I*Ks blockade



Shimizu, Antzelevitch *Circulation* 1998.

LQT1 Excellent response to beta-blockers.

Clinical research

EUROPEAN SOCIETY OF CARDIOLOGY

Low incidence of cardiac events with β-blocking therapy in children with long QT syndrome

E. Villain[a,*], I. Denjoy[b,c,d], J.M. Lupoglazoff[c,d], P. Guicheney[c], B. Hainque[e] V. Lucet[f], D. Bonnet[a]

European Heart Journal (2004) 25, 1405–1411

[a] Cardiologie Pédiatrique, Hôpital Necker-Enfants-Malades, 149 Rue de Sevres, 75015 Paris Cedex, Paris, France
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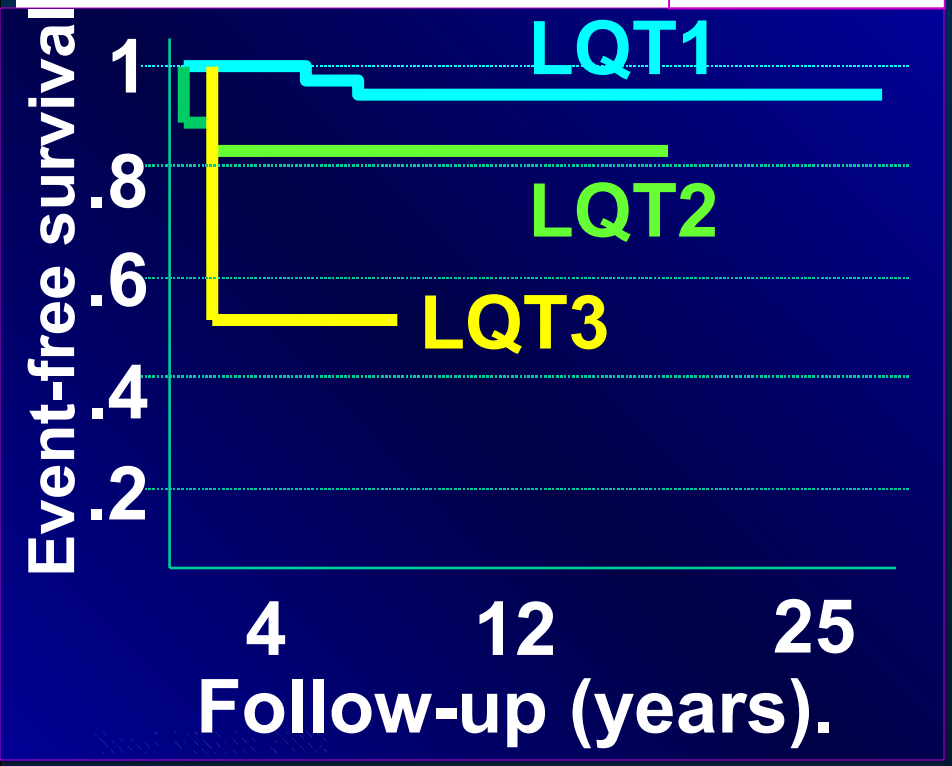
[c] INSERM U582, Institut de Myologie, Hôpital Pitié-Salpêtrière, Paris, France
[d] Cardiologie Pédiatrique, Hôpital Robert Debré, Paris, France
[e] Biochimie, Hôpital Pitié-Salpêtrière Paris
[f] Cardiologie Pédiatrique, Château des Côtes, Les Loges en Josas, France

EHJ 2004



BRIEF REPORT

Association of Long QT Syndrome Loci and Cardiac Events Among Patients Treated With β-Blockers

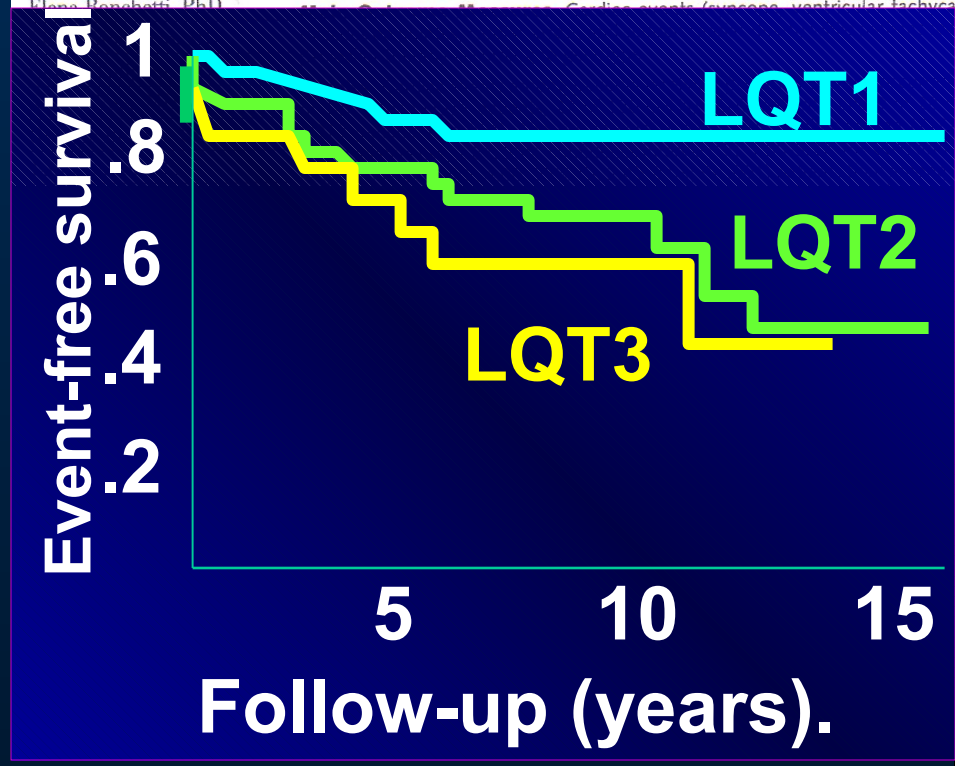
JAMA 2004

Silvia G. Priori, MD, PhD
Carlo Napolitano, MD, PhD
Peter J. Schwartz, MD
Massimiliano Grillo, MD
Raffaella Bloise, MD

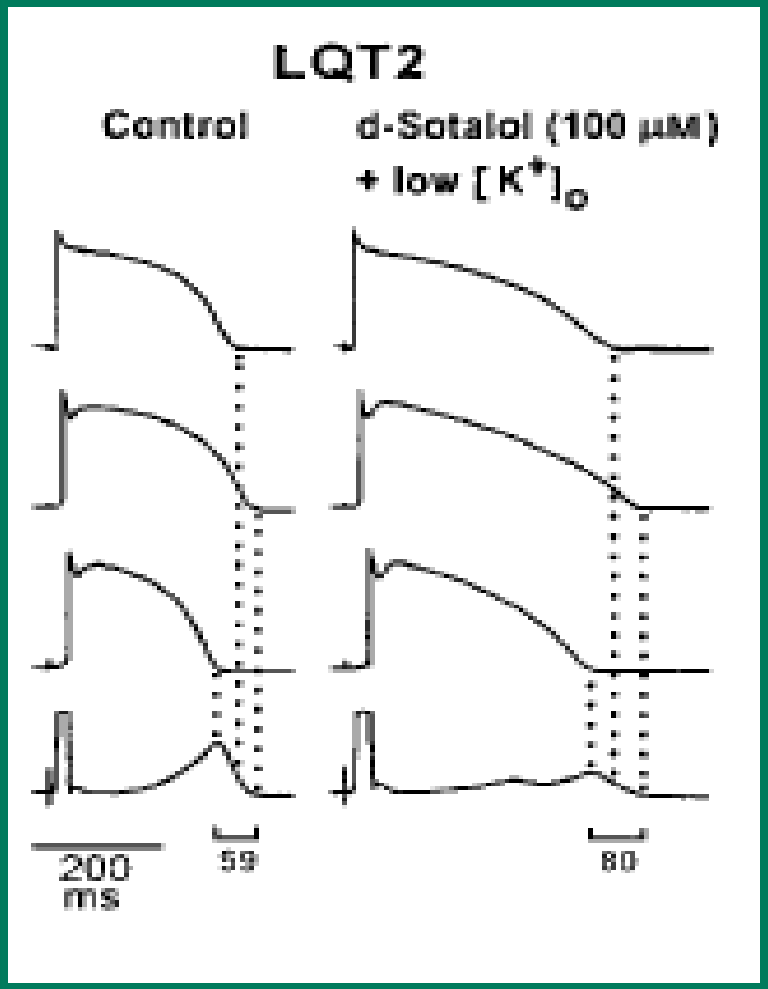
Context Data on the efficacy of β-blockers in the 3 most common genetic lon syndrome (LQTS) loci are limited.

Objective To describe and assess outcome in a large systematically genotyped p lation of β-blocker–treated LQTS patients.

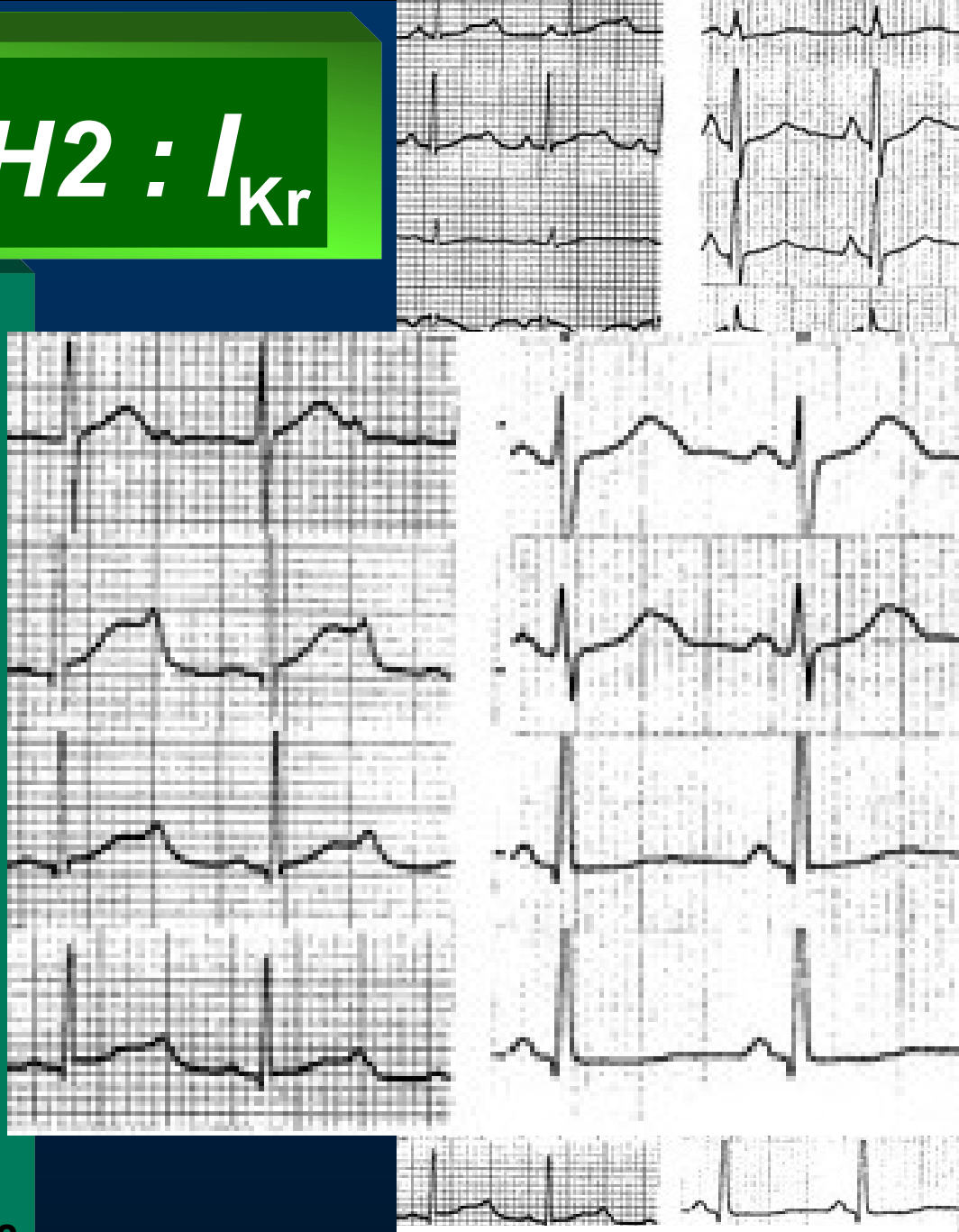
Design, Setting, and Patients Consecutive LQTS-genotyped patients (n= in Italy treated with β-blockers for an average of 5 years.



LQT2: *KCNH2* : I_{Kr}



Yan, Antzelevitch, *Circulation* 1998



Zhang, *Circulation 2000*

LQT2: I_{Kr}

Arrhythmia triggers:

Stress = Rest.

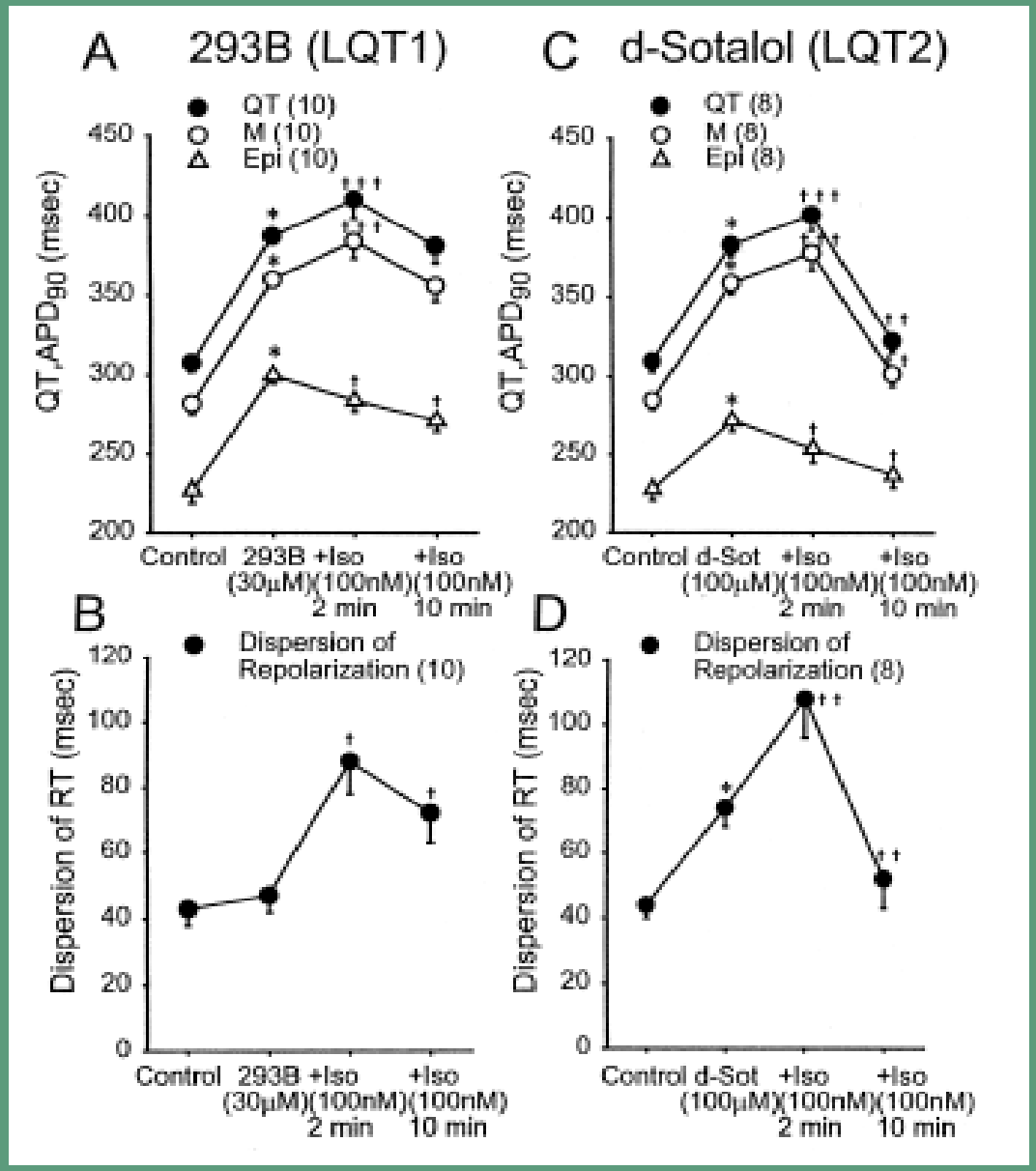
Sudden noise.

Post-partum.

Schwartz, *Circulation* 2001.

Wilde *JACC* 1999.

Ackerman, *Heart Rhythm* 2004



Shimizu & Antzelevitch, *JACC* 2000

LQT2: I_{Kr}

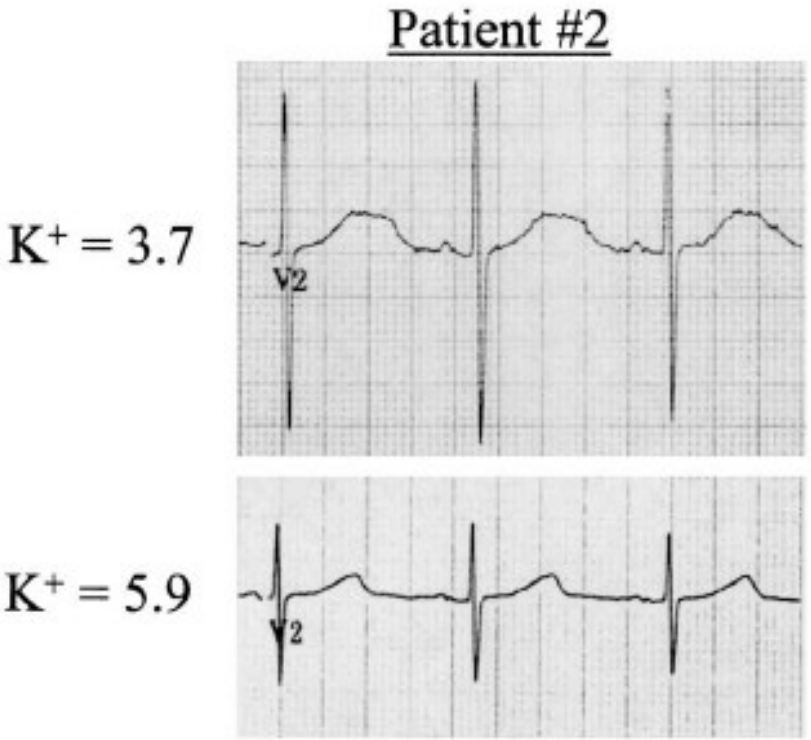
Vol. 42, No. 10, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/j.jacc.2003.07.006

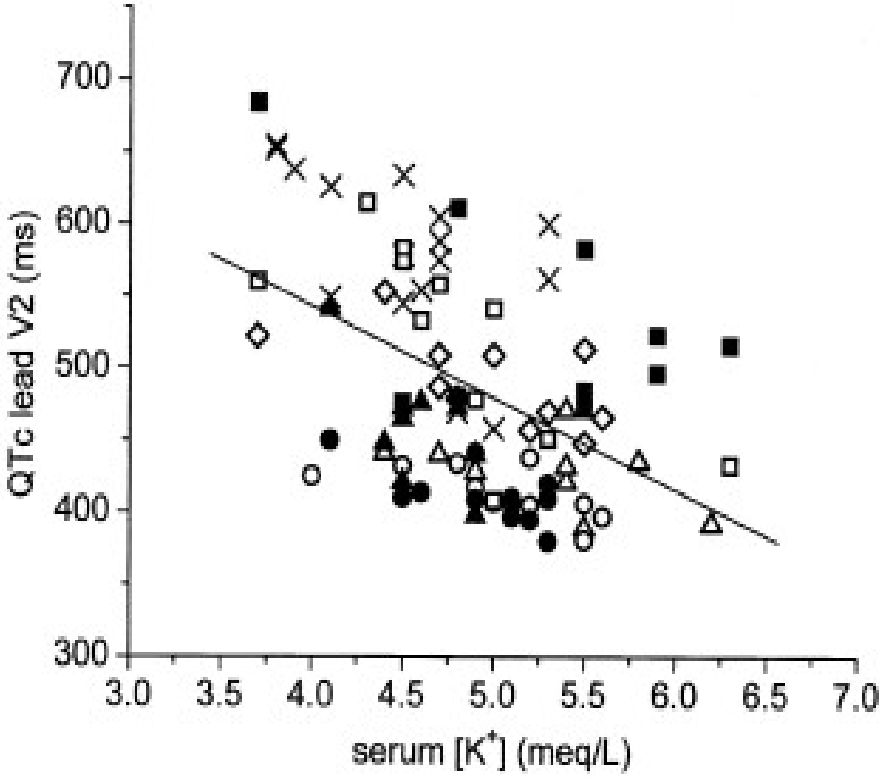
A New Oral Therapy for Long QT Syndrome

Long-Term Oral Potassium Improves Repolarization in Patients With *HERG* Mutations

JACC 2003

Susan P. Etheridge, MD, FACC,* Steven J. Compton, MD, FACC,† Martin Tristani-Firouzi, MD,* Jay W. Mason, MD, FACC‡

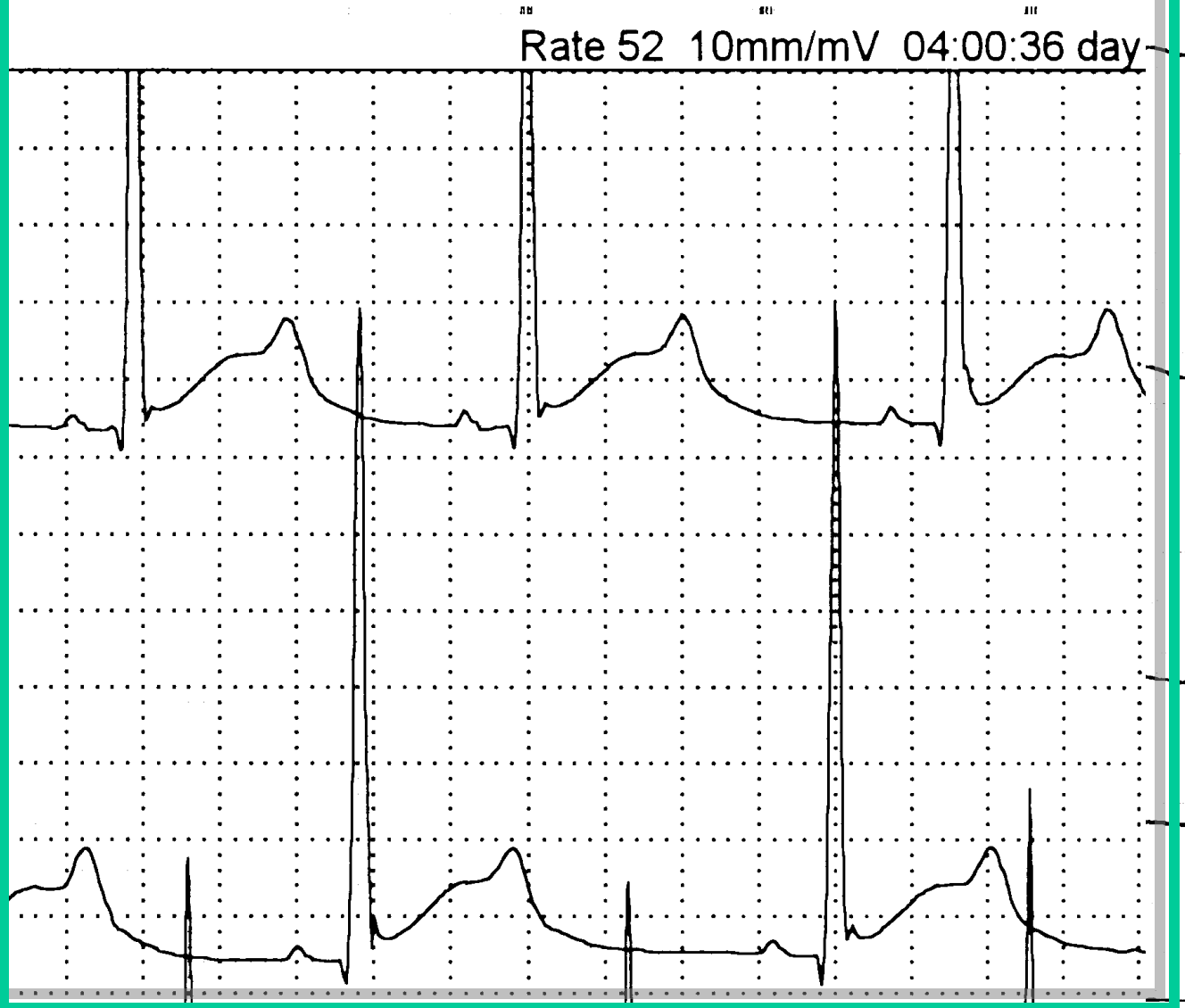




Saul Viskin 2002

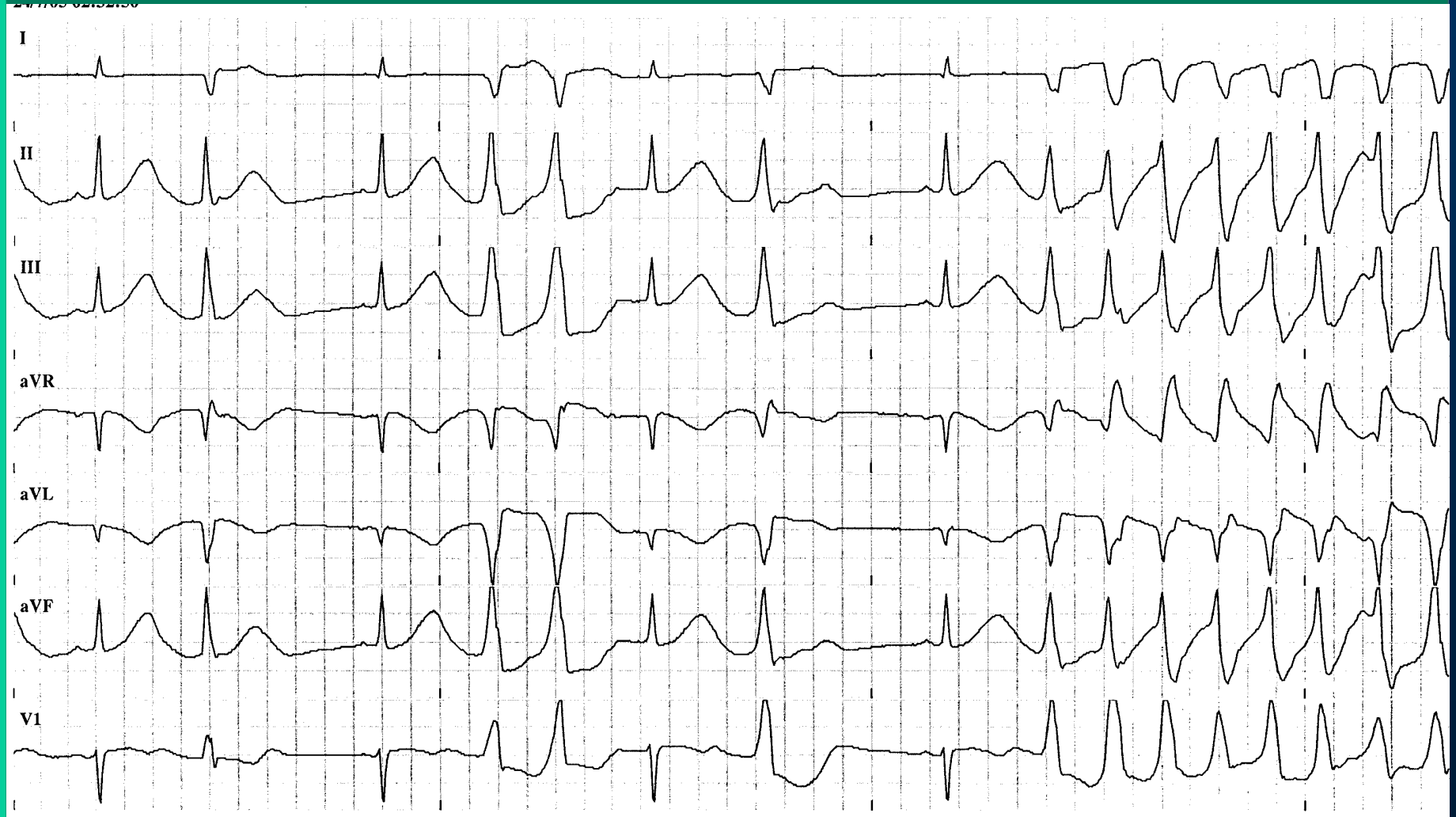
LQT2: I_{Kr}

The same LQT2 carrier during sleep



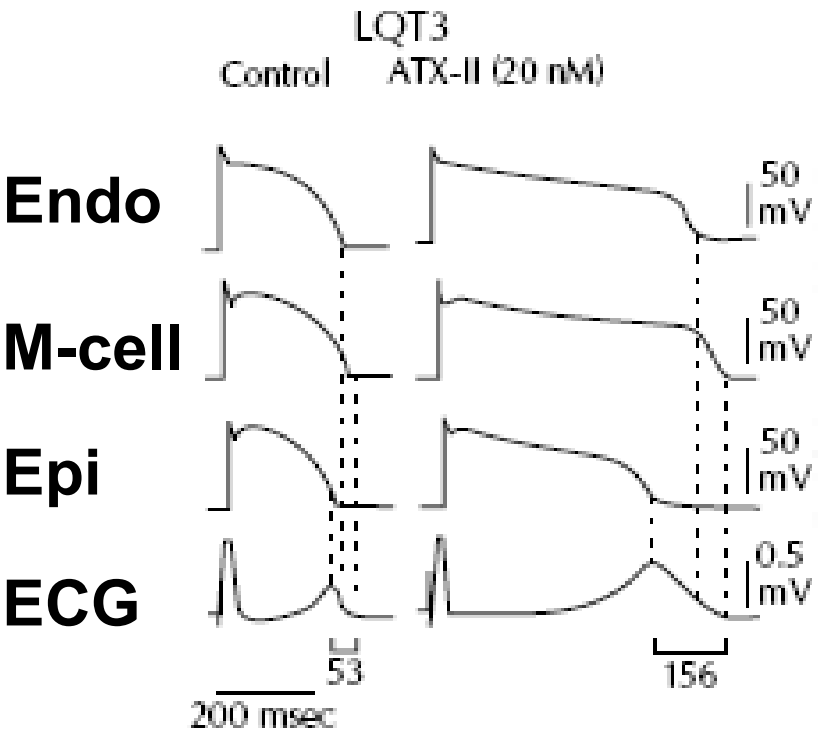
LQT2: I_{Kr}

Pause-dependent torsade de pointes: 19-year post-partum woman with LQT2.

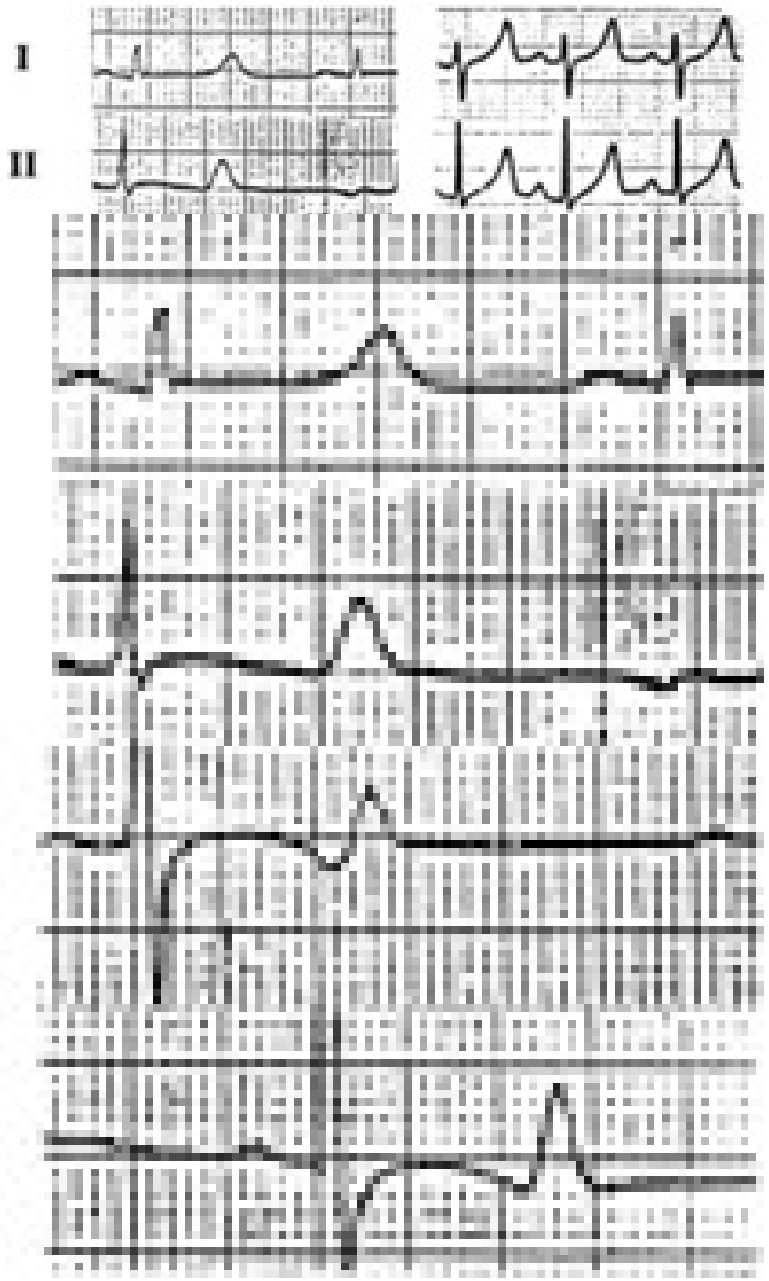


Sami Viskin 2002

LQT3: *SCN5A* :



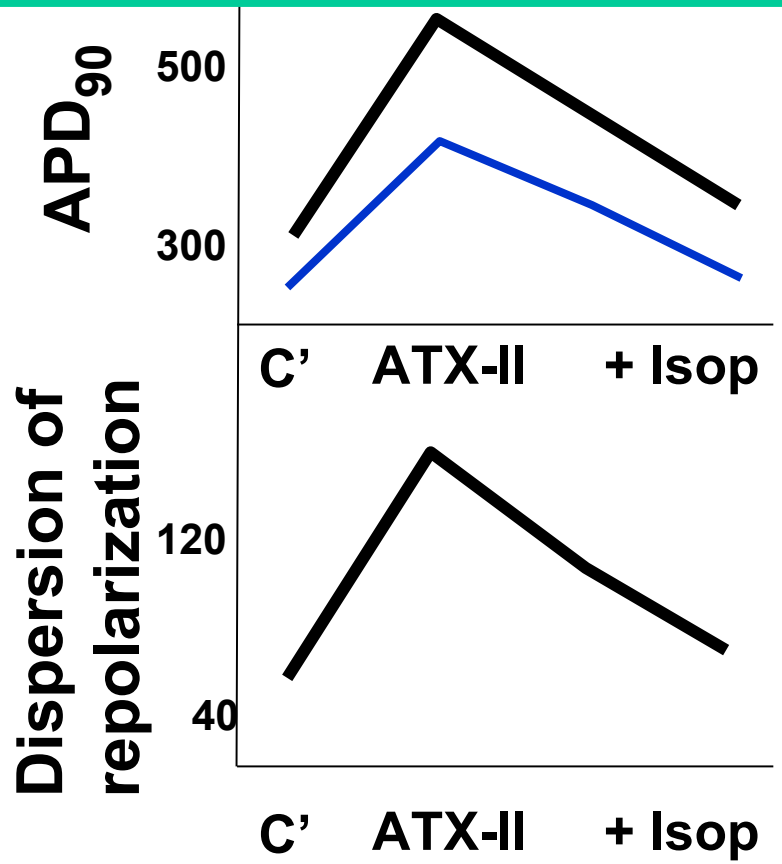
Yan, Antzelevitch, *Circulation* 1998



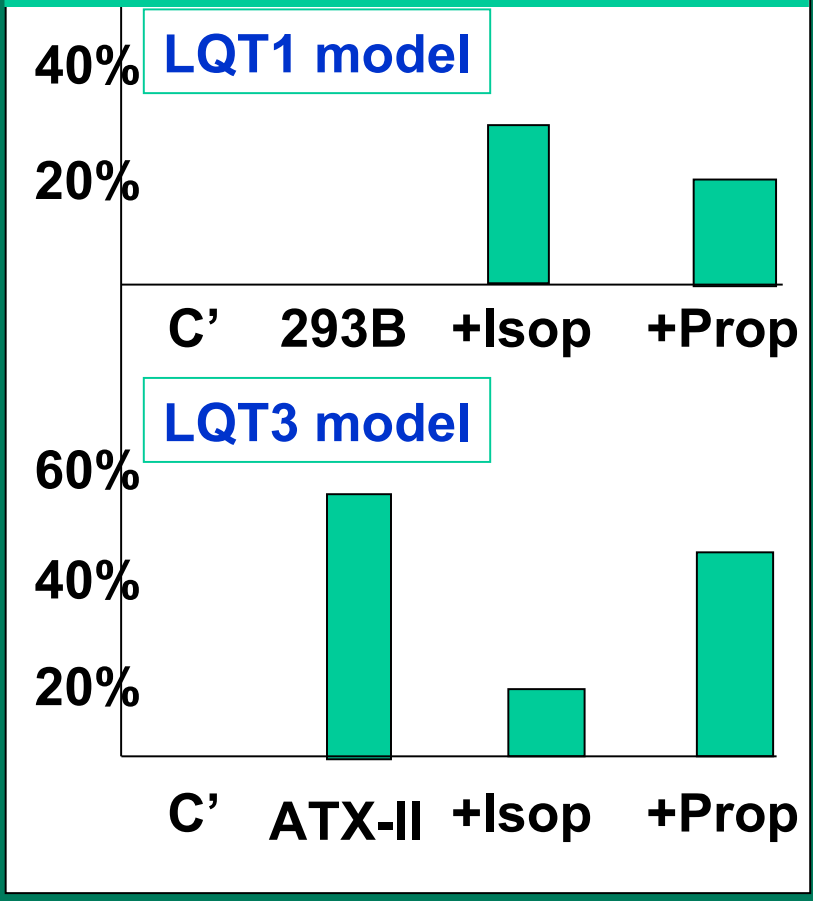
Zhang, *Circulation 2000*

LQT3: *SCN5A* : I_{Na}

Dispersion of repolarization in the wedge model.

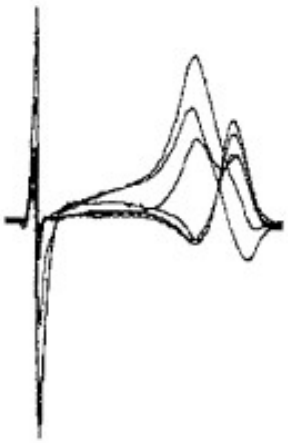


Spontaneous TdP in the wedge model.

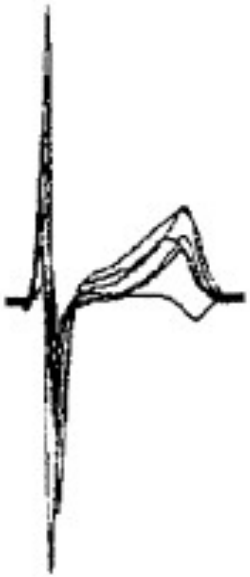


LQT3: *SCN5A* : I_{Na}

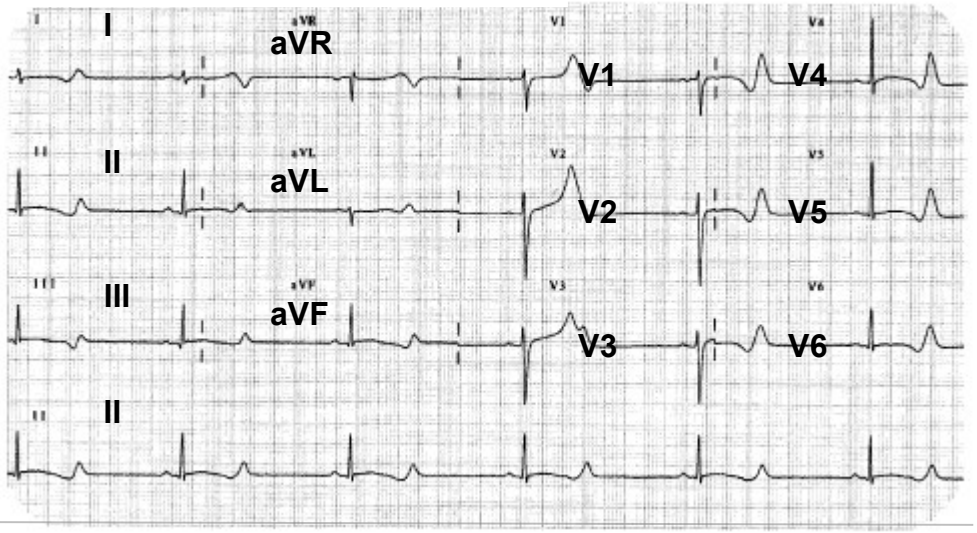
Baseline



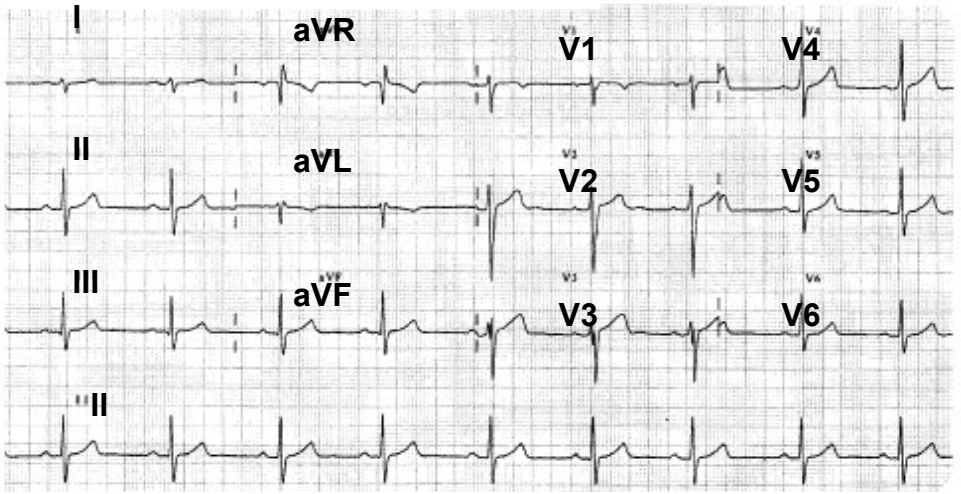
Flecainide



LQT3 baseline

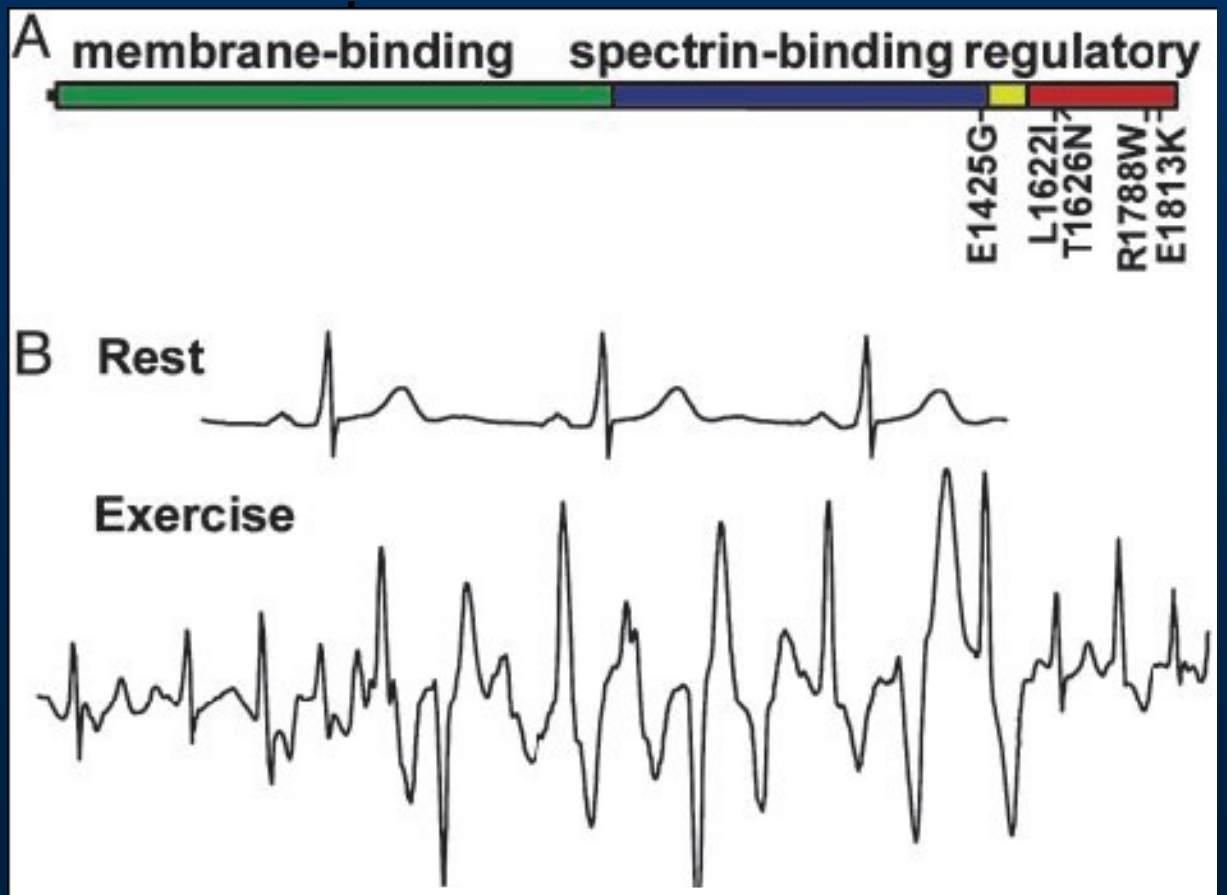


LQT3 flecainide



Benhorin, *Circulation* 2000

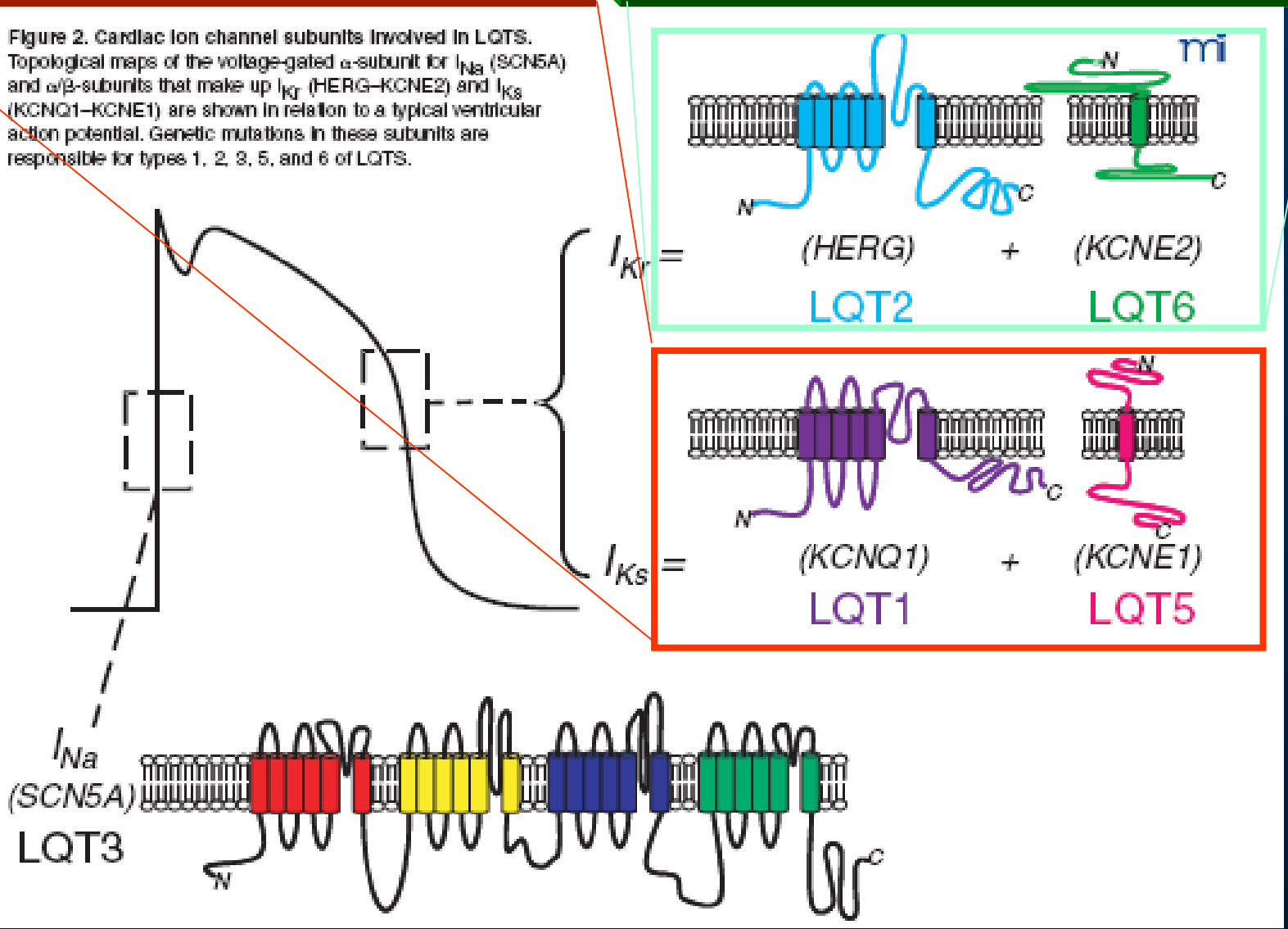
LQT4: *Ank2:* Membrane adaptor protein Ankyrin-B



Mohler, *Proc Nat Acad Sci* 2004.

LQT5: *KCNE1 : ß-*I_{Ks}

LQT6: *KCNE2 : ß-*I_{Kr}



Sami Viskin 2002

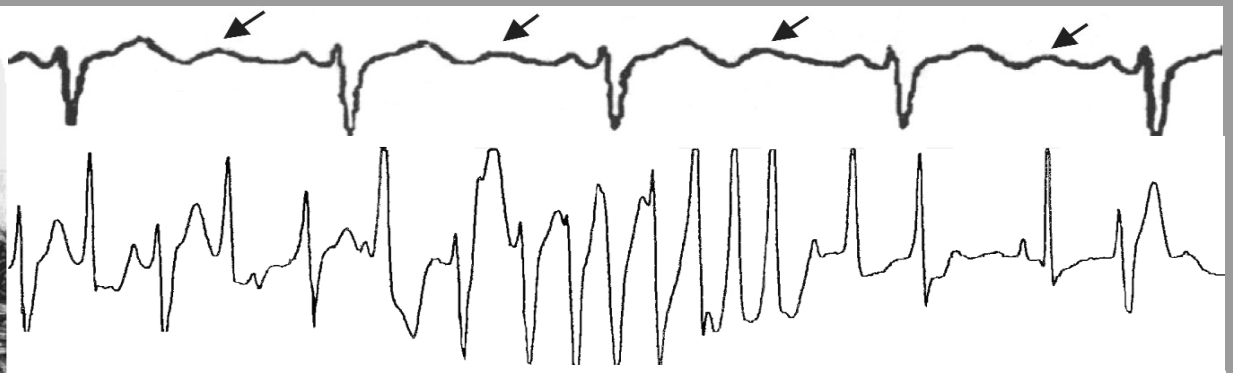
LQT7:*KCNJ2 :* Kir2.1 Inward rectifier : I_{K1}

Andersen syndrome:

Acta Paediatr Scand 1971

Intermittent muscular weakness,
Extrasystoles
Developmental abnormalities.

Canun, *Am J Hum Gen* 1999.

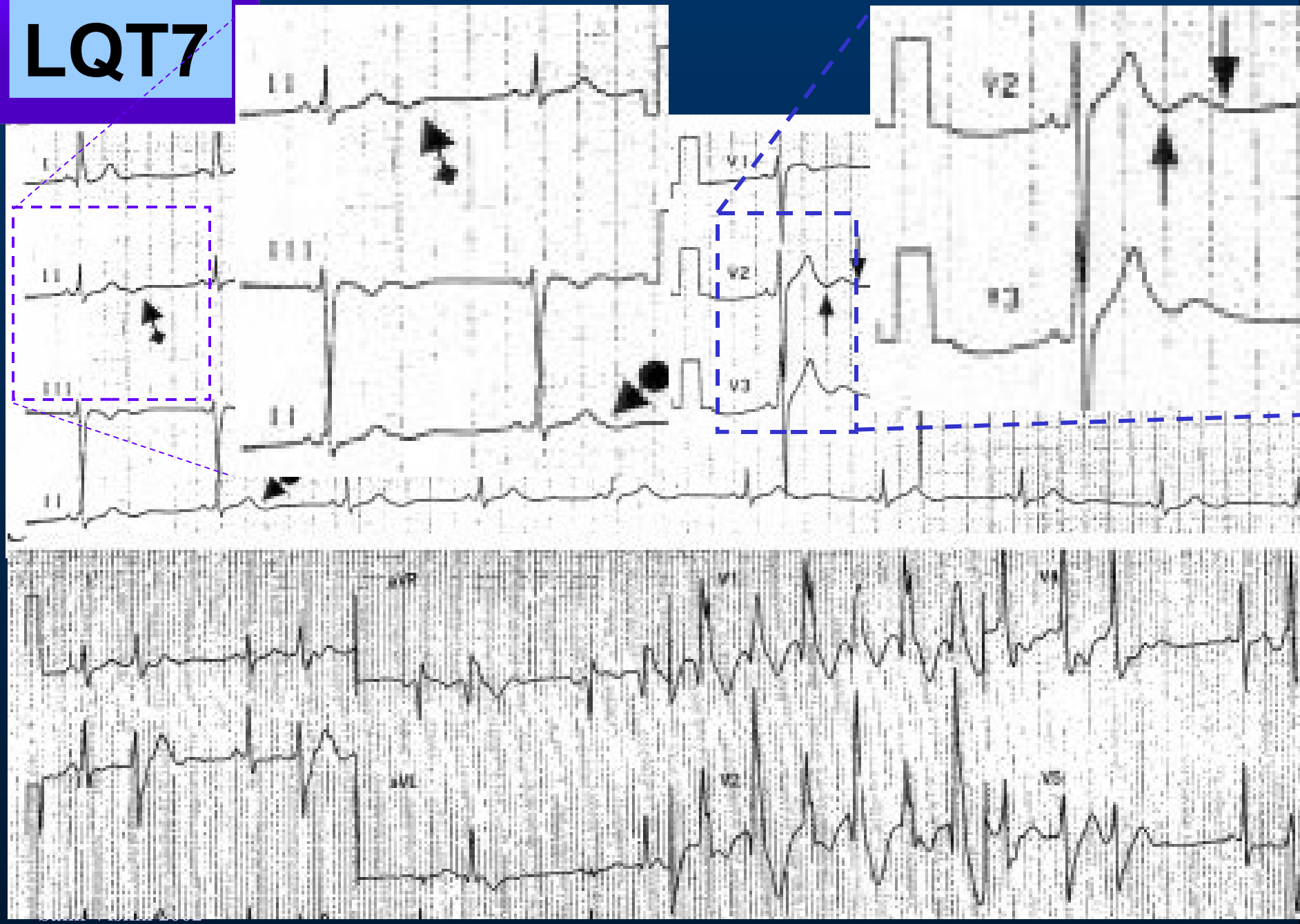


96 patients: *Tristani-Firouzi, JCI 2002.*

- **Periodic paralysis = 50%**
- **Dysmorphic features = 74%.**
- **Cardiac symptoms = 11%**

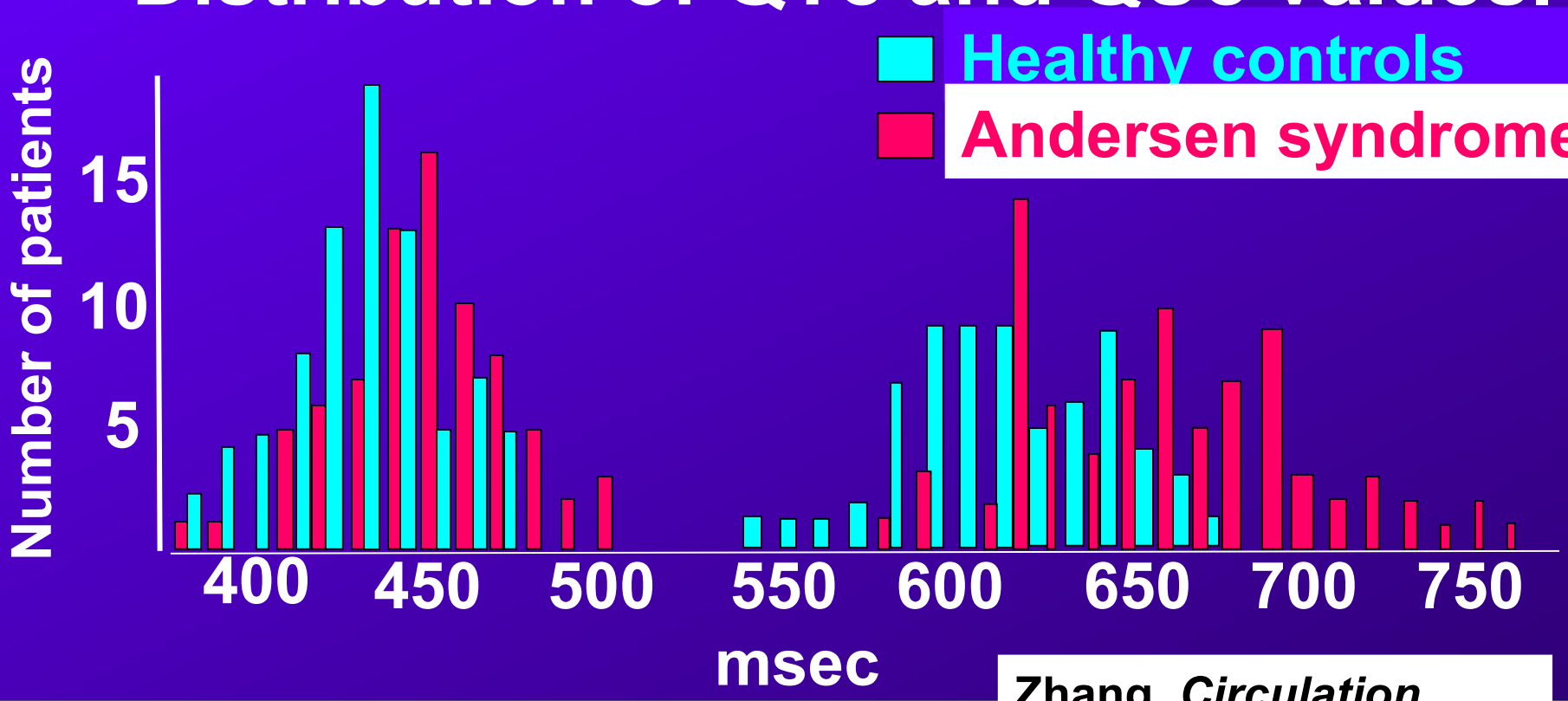
Zhang *Circulation* 2005

LQT7



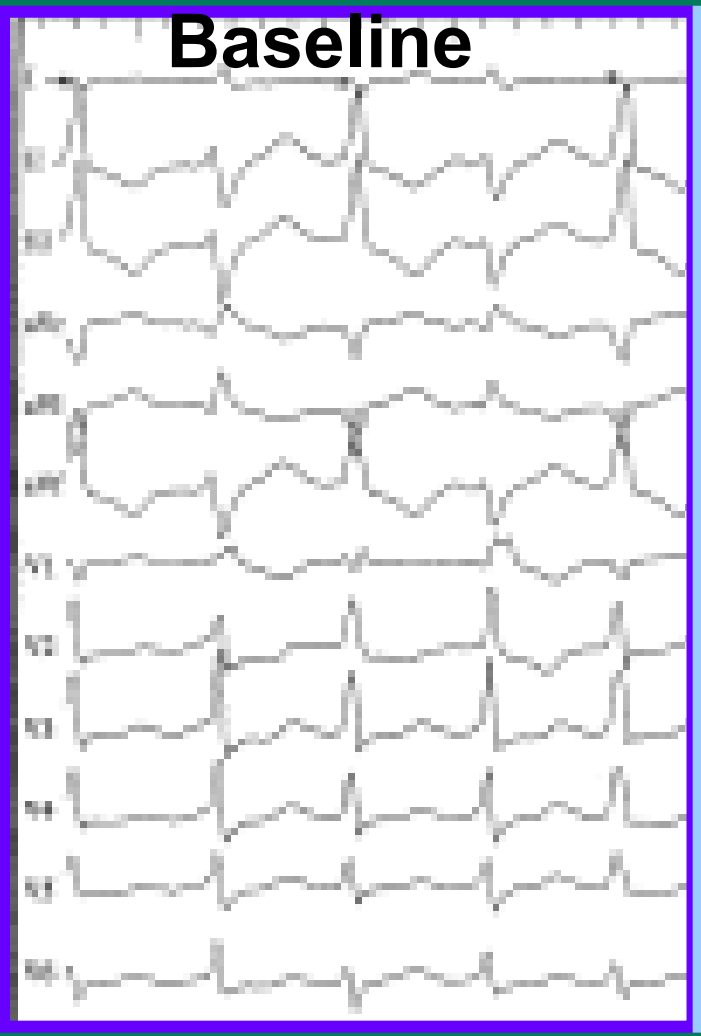
LQT7

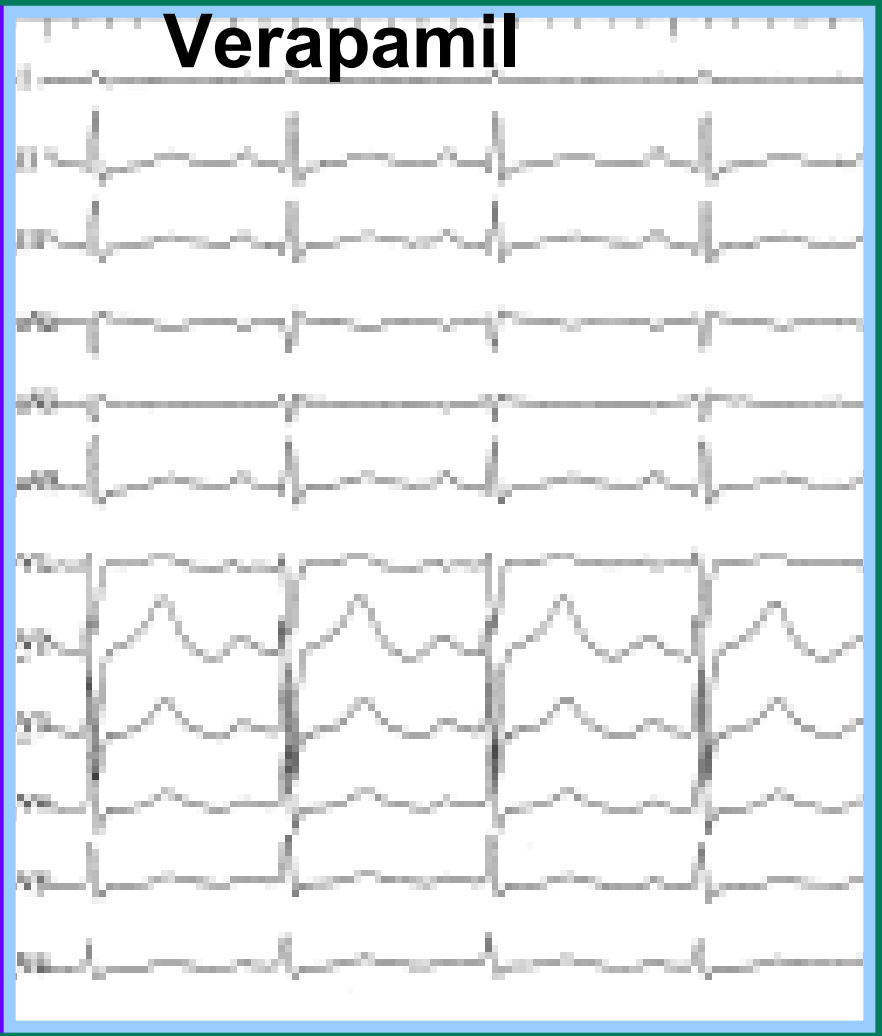
Distribution of QTc and QUc values.



Zhang, *Circulation* 2000

LQT7

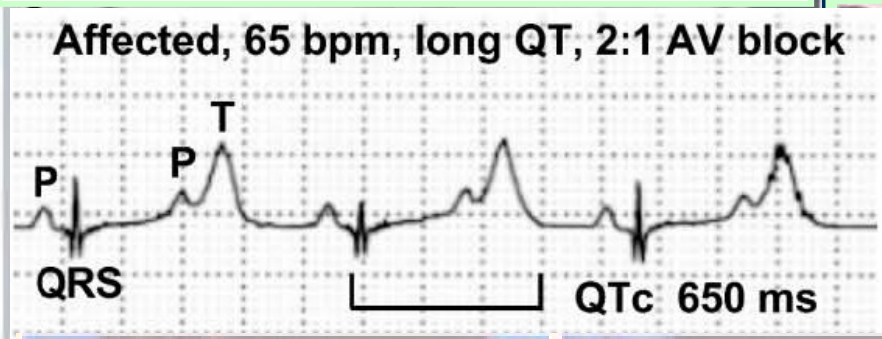


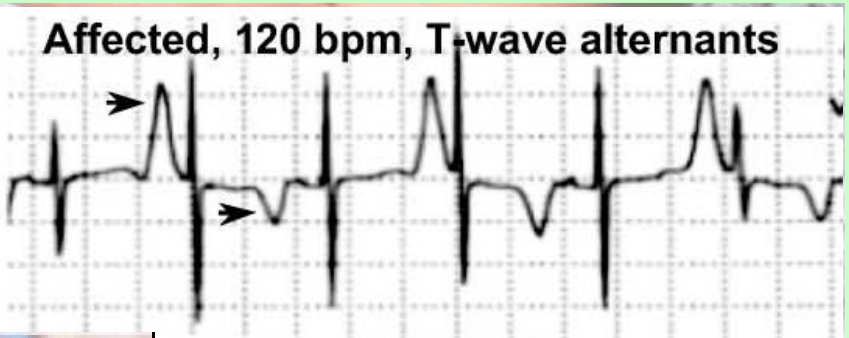


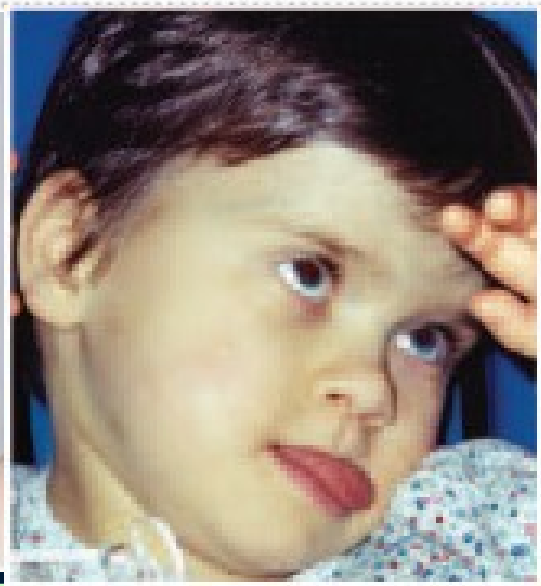
LQT8: $Ca_v1.2$: L-type Ca-channel.

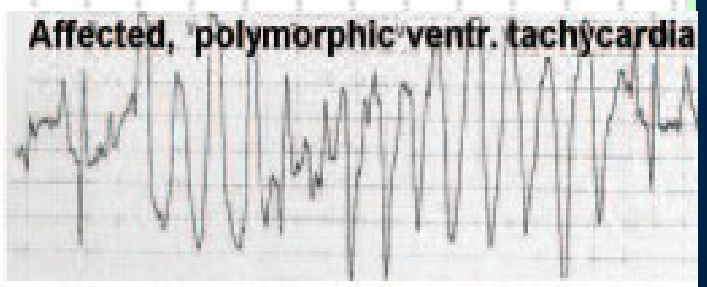
Timothy syndrome:

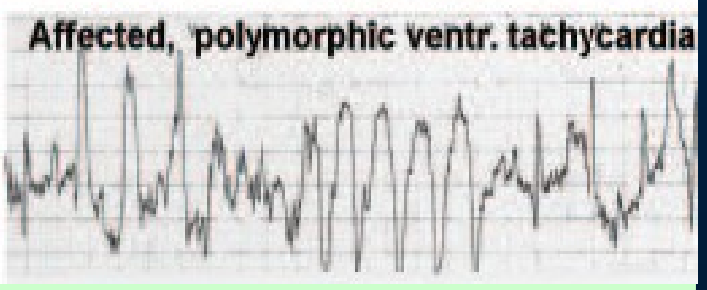
Long QT + syndactyly.







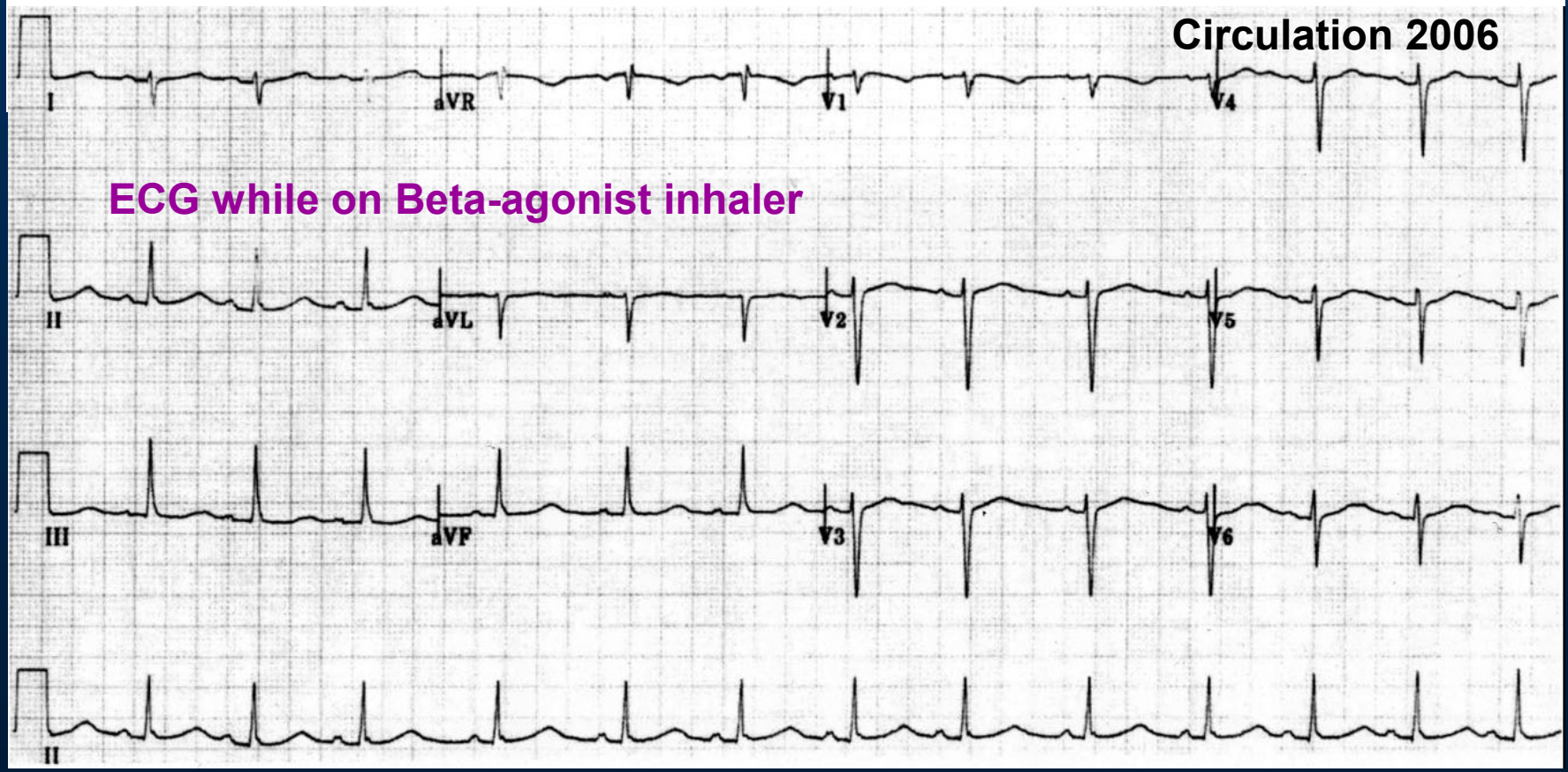




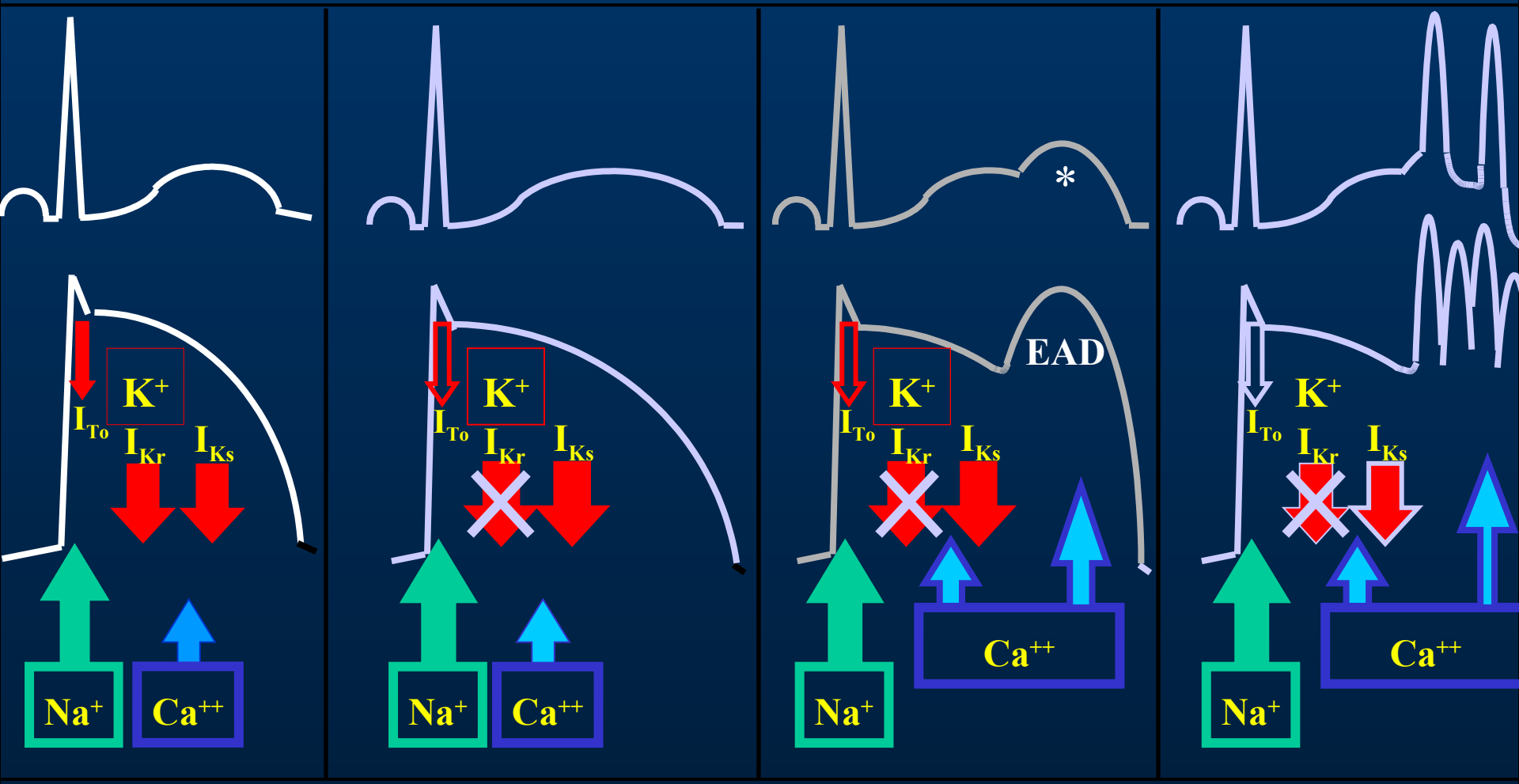
Heart malformation, immune deficiency, autism

Mutant Caveolin-3 Induces Persistent Late Sodium Current and Is Associated With Long-QT Syndrome

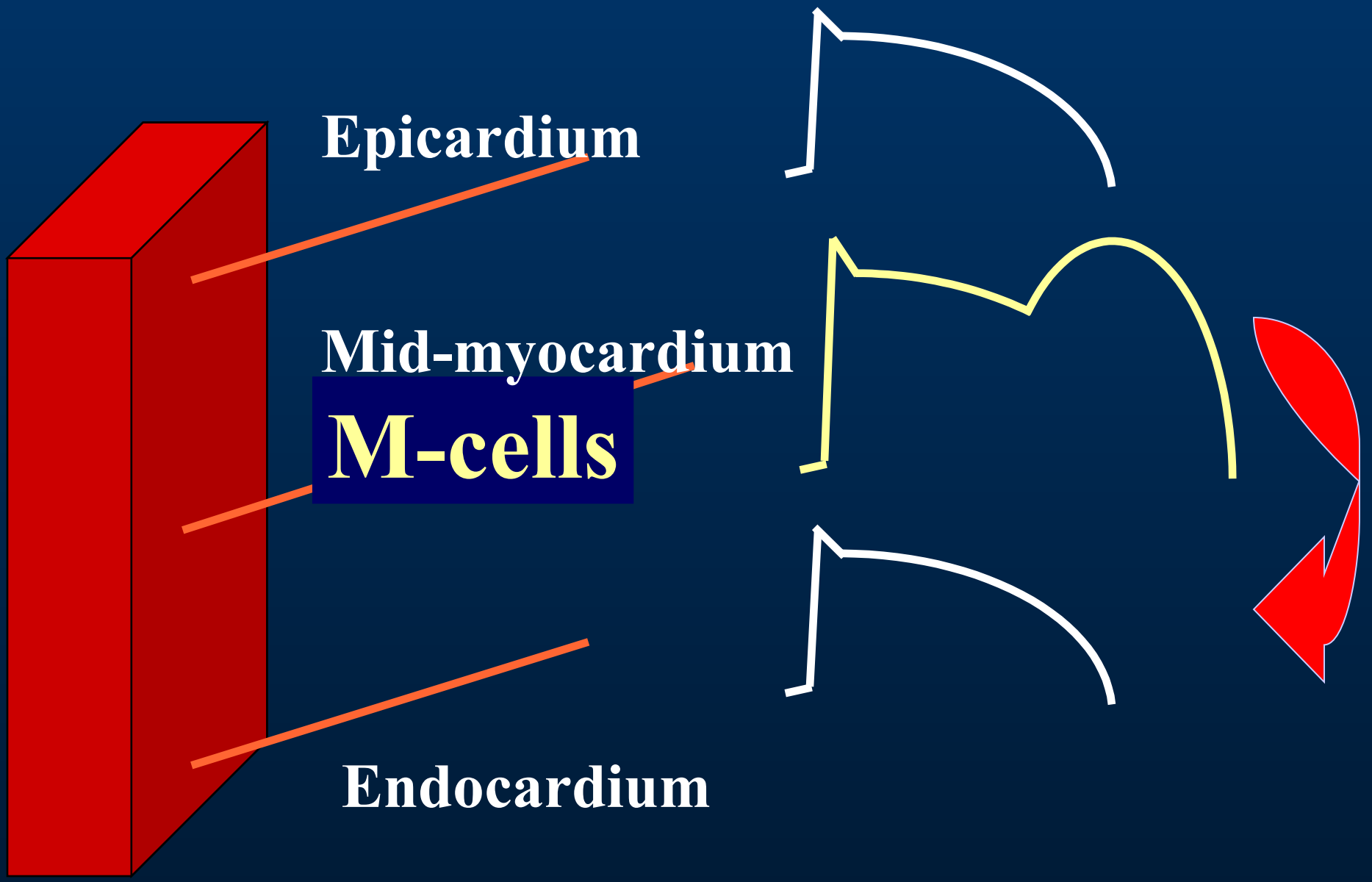
Matteo Vatta, PhD*; Michael J. Ackerman, MD, PhD*; Bin Ye, PhD; Jonathan C. Makielski, MD; Enoh E. Ughanze, MD; Erica W. Taylor, BS; David J. Tester, BS; Ravi C. Balijepalli, PhD; Jason D. Foell, BS; Zhaohui Li, PhD; Timothy J. Kamp, MD, PhD; Jeffrey A. Towbin, MD



Sami Viskin 2002



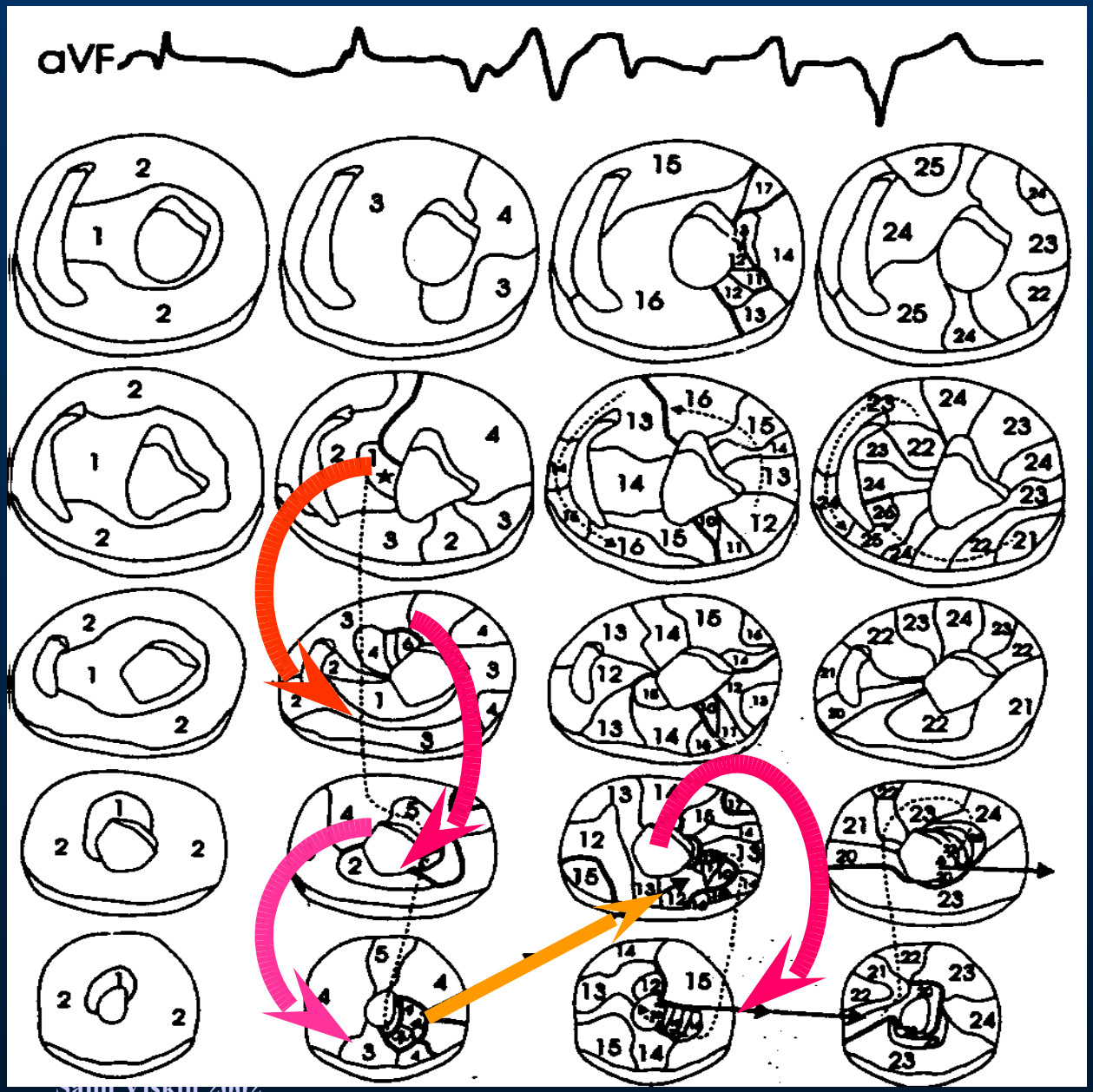
Viskin. *Harrison ONLINE* 2000



Sami Viskin 2002

Antzelevitch, *J Am Coll Cardiol* 1994

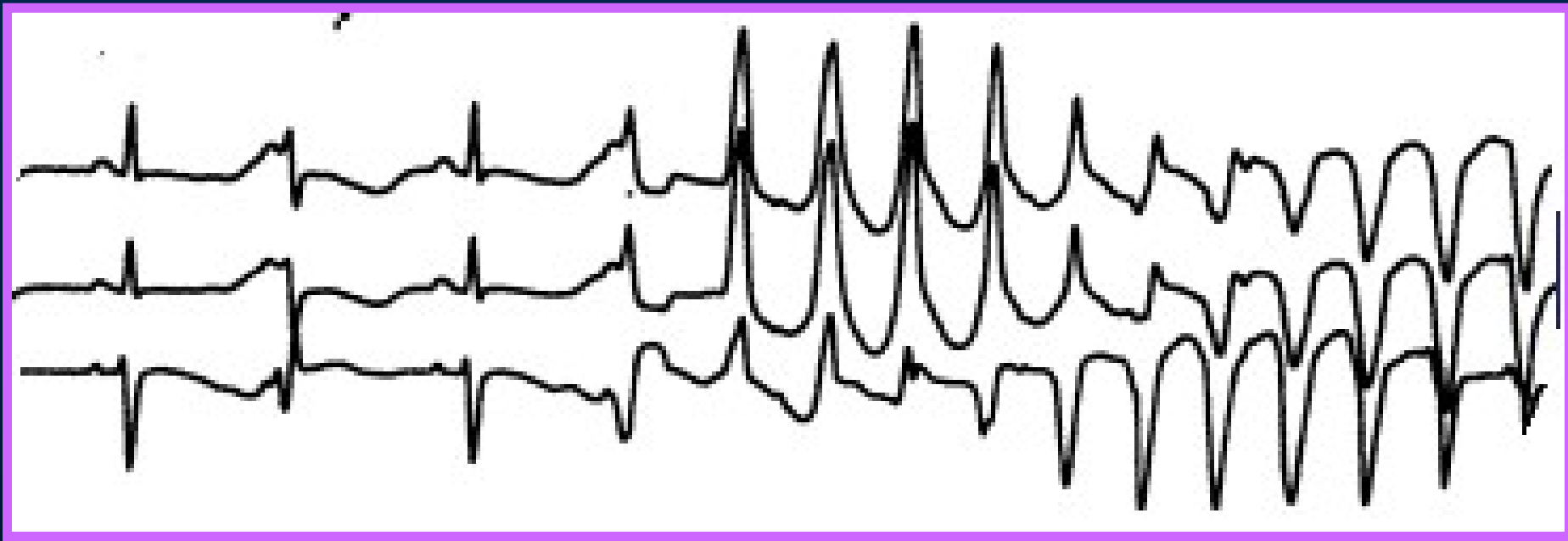
Three-dimensional mapping of torsade de pointes



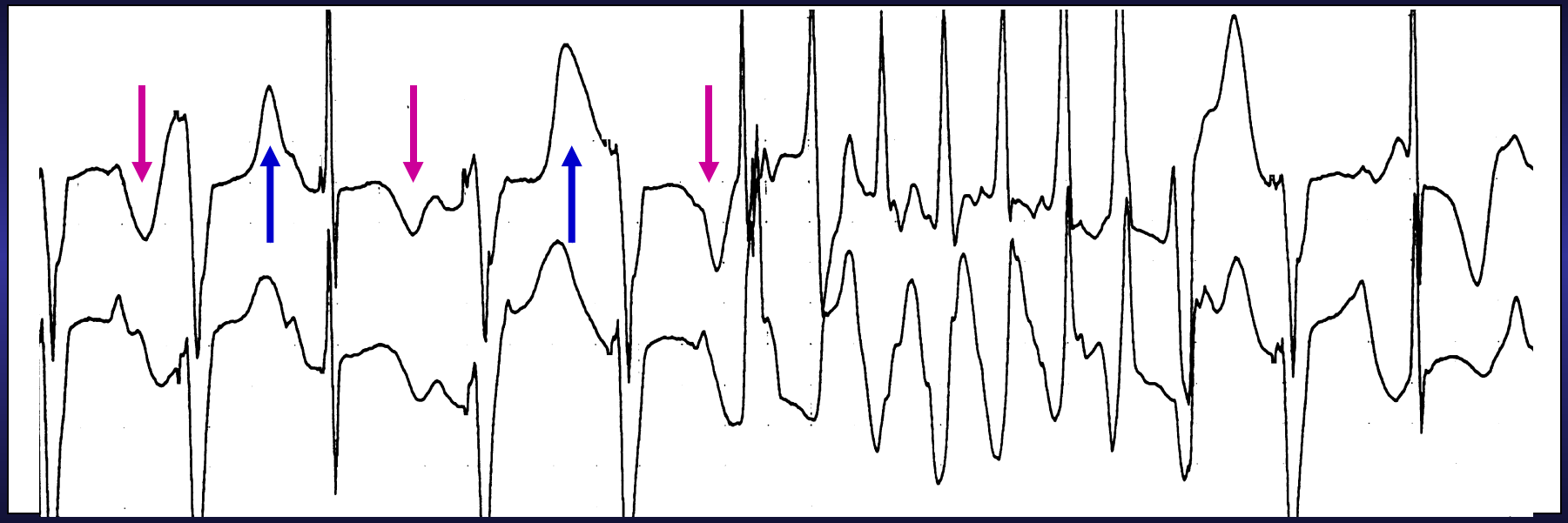
El-Sherif,
Circulation 1997

The congenital long QT syndromes

Torsade de pointes



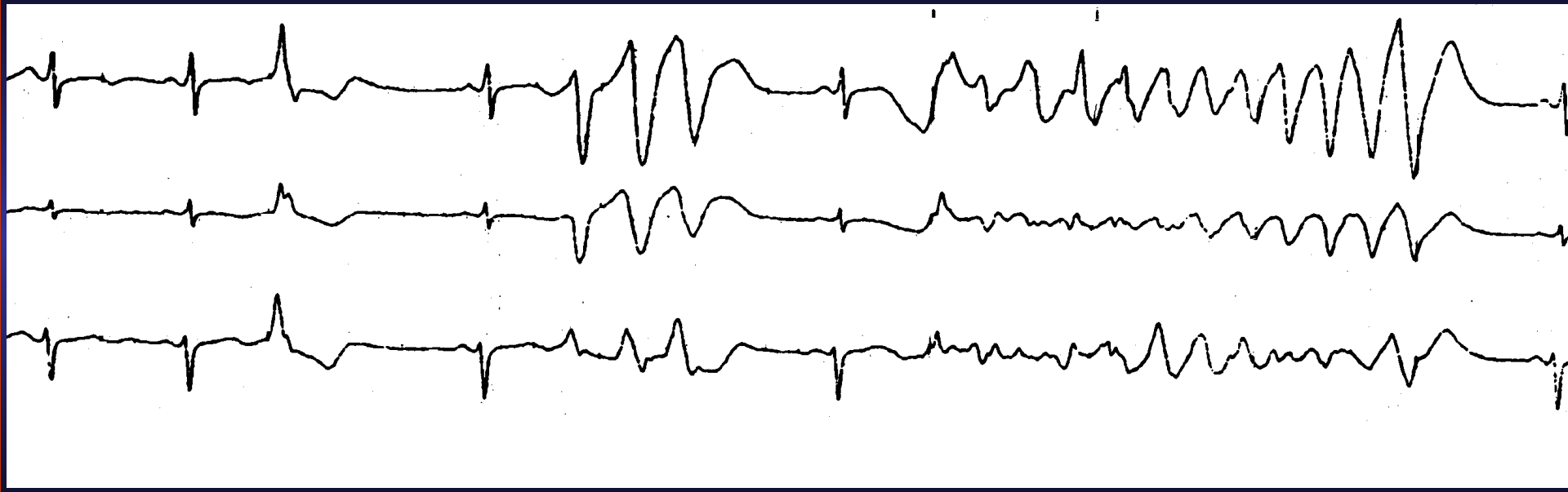
Adrenergic-dependent torsade de pointes



Adrenergic-dependent torsade de pointes

Sam

Pause-dependent torsade de pointes

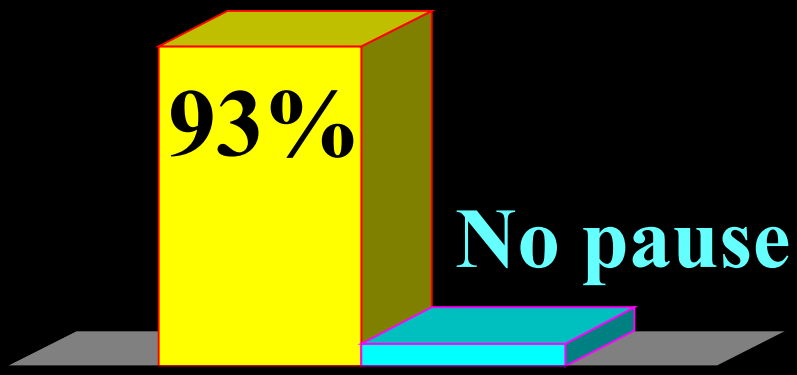


Sami Viskin 2002

Viskin, *Heart* 2000

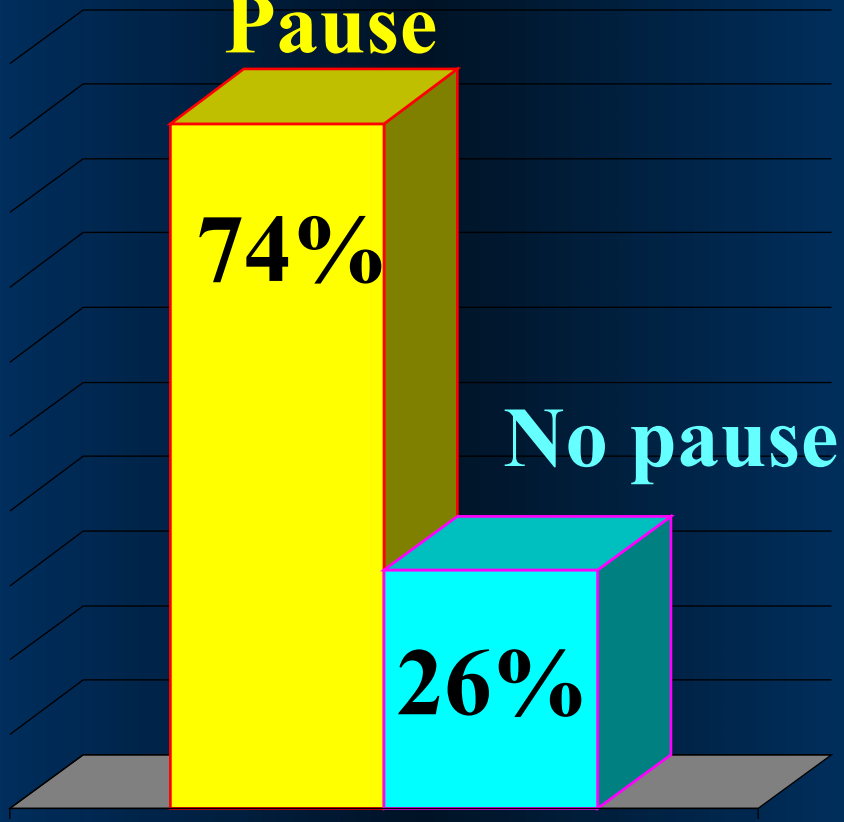
Evidence supporting the importance of pause-induced torsade de pointes (TdP).

15 consecutive patients with documented TdP

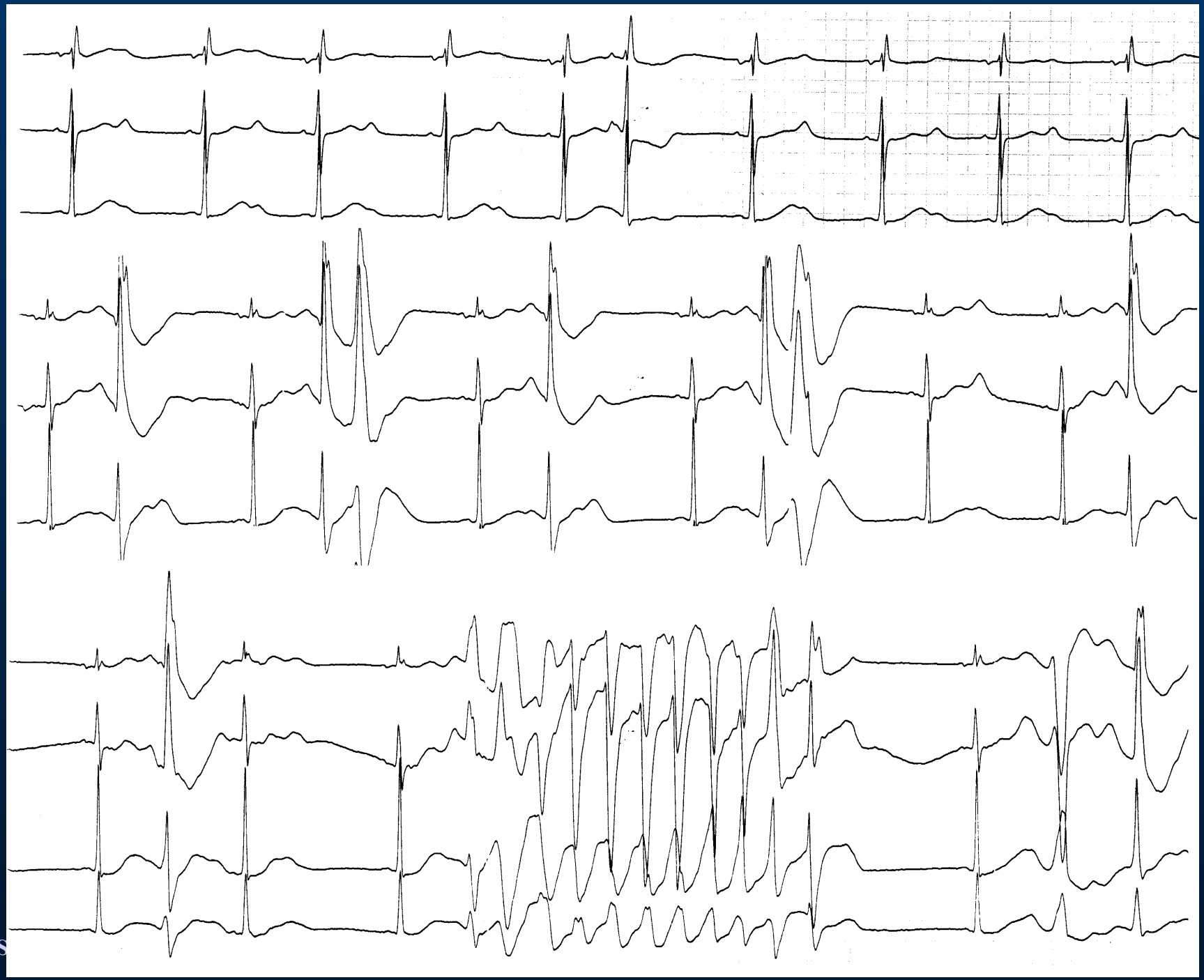


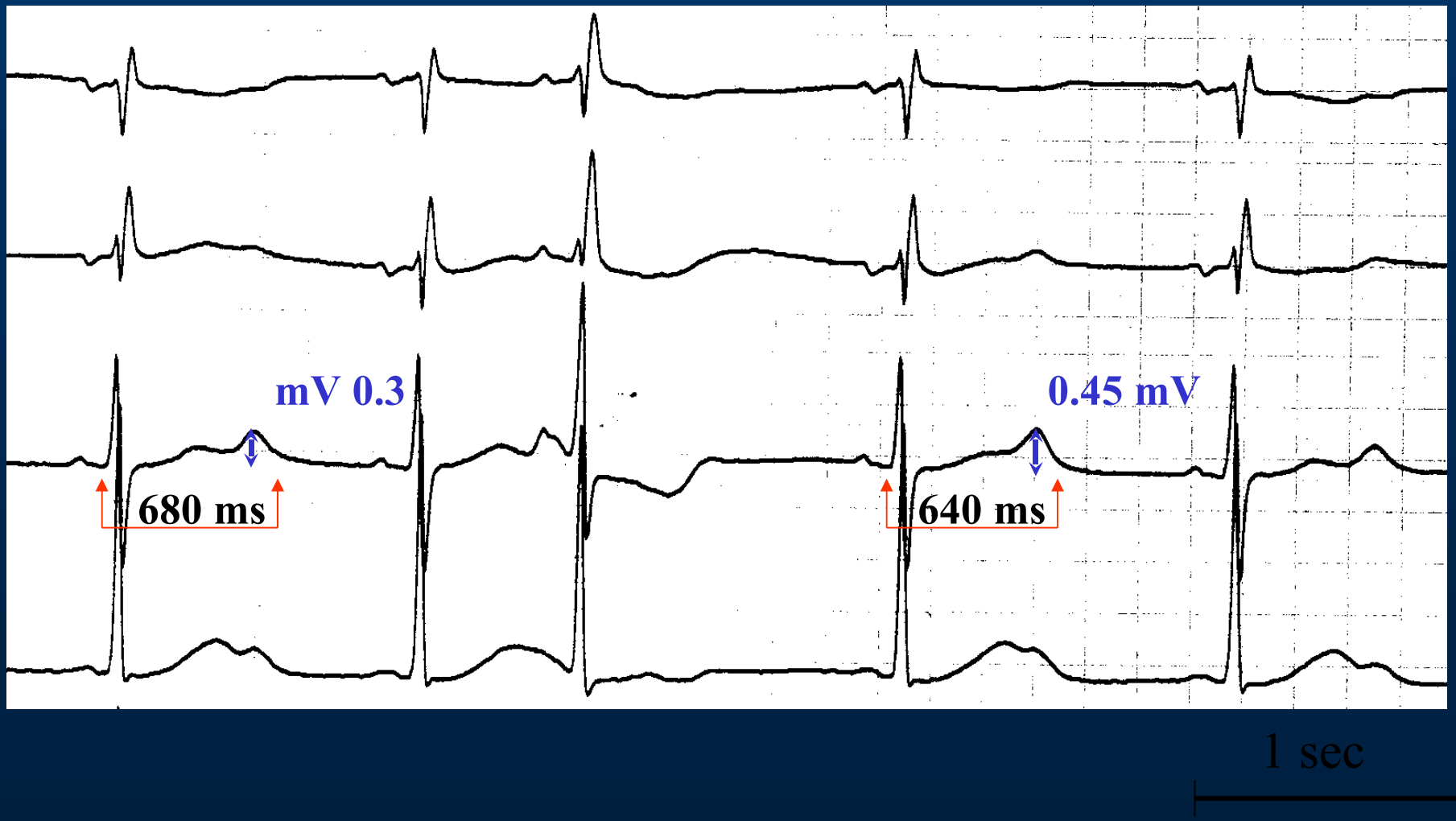
Viskin, *JACC* 1996

62 published published illustrations of TdP



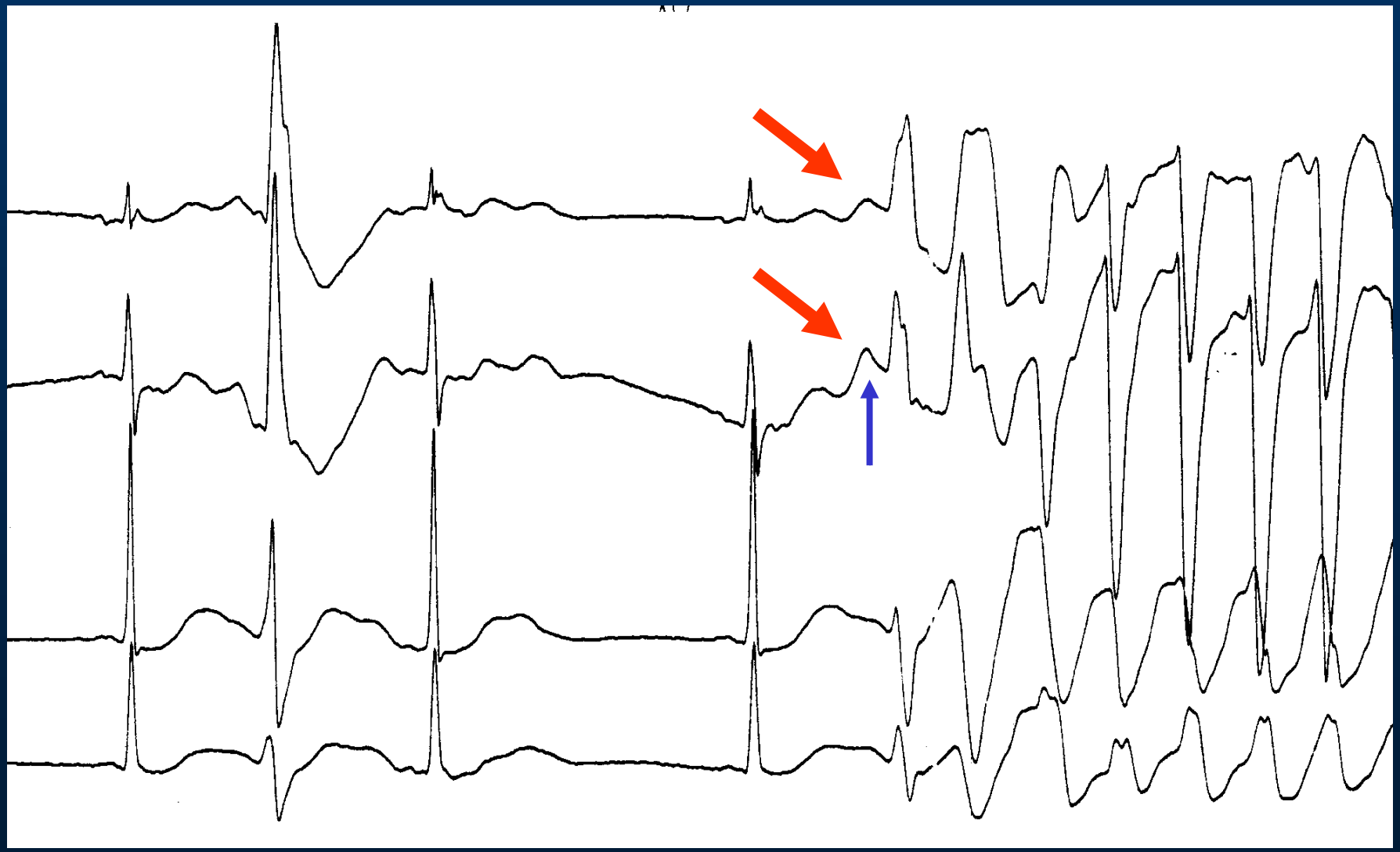
Viskin, *Heart* 2000





Sami Viskin 2002

Sami Viskin 2002



Sami Viskin 2002

JACC Vol. 20, No. 6
November 15, 1992:1391–6

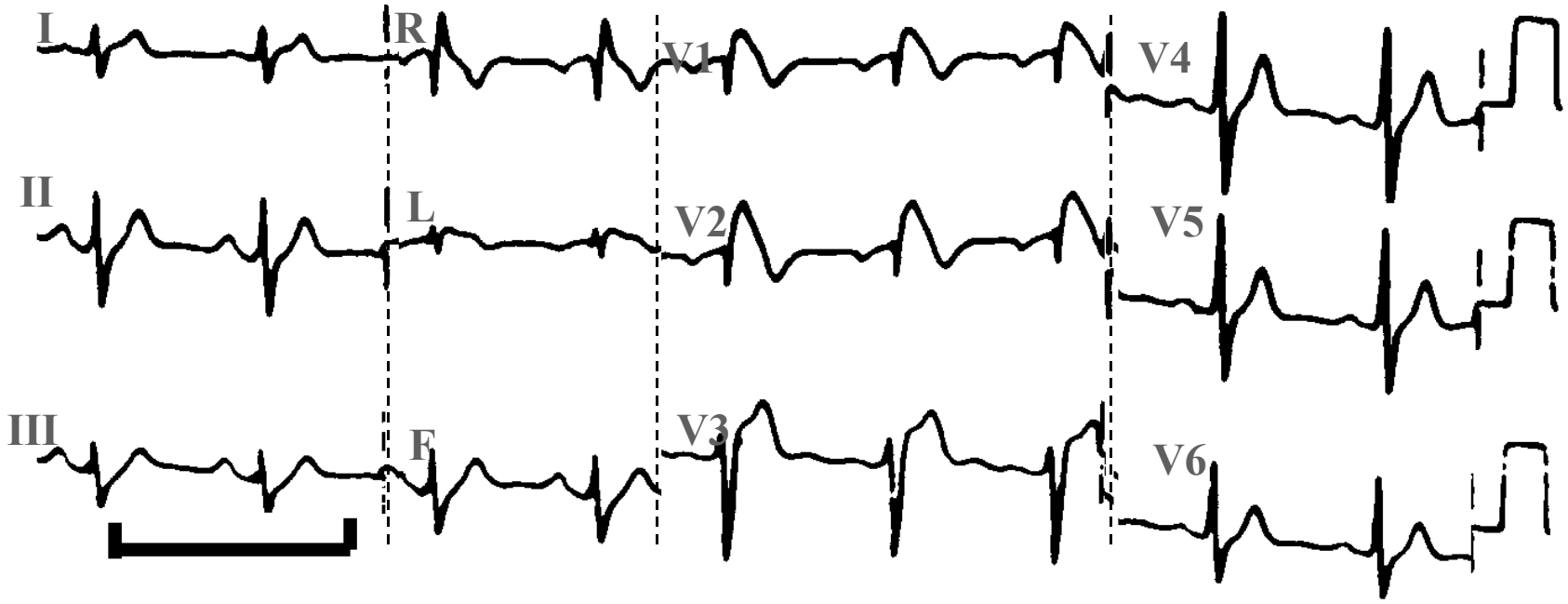
Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death: A Distinct Clinical and Electrocardiographic Syndrome

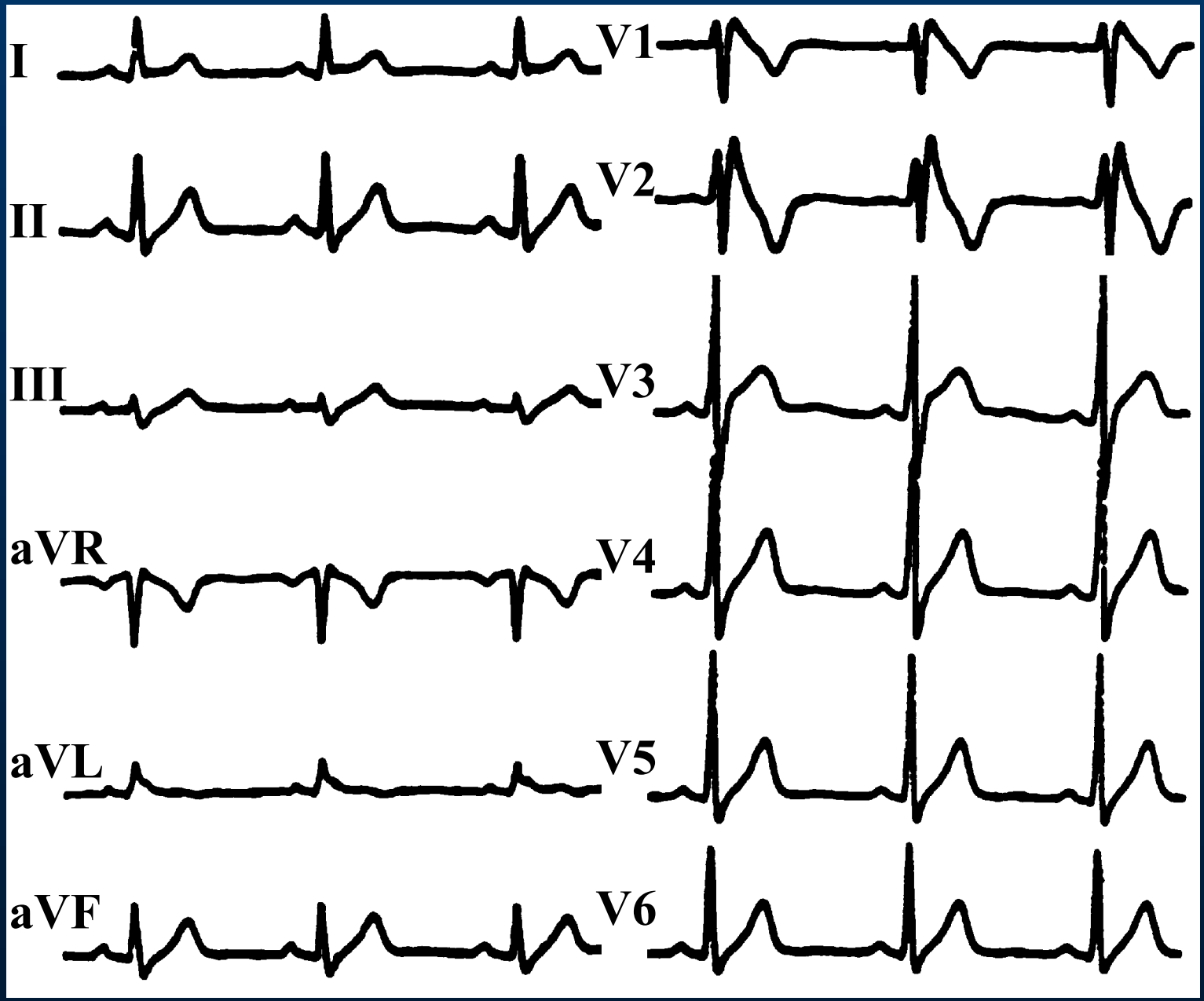
A Multicenter Report

PEDRO BRUGADA, MD, JOSEP BRUGADA, MD*†

Aalst, Belgium and Barcelona, Spain

Objectives. The objectives of this study were to present data on eight patients with recurrent episodes of aborted sudden death whom ventricular biopsies were performed. The arrhythmia leading to (aborted) sudden death was a rapid polymorphic





Sami Viskin 2002

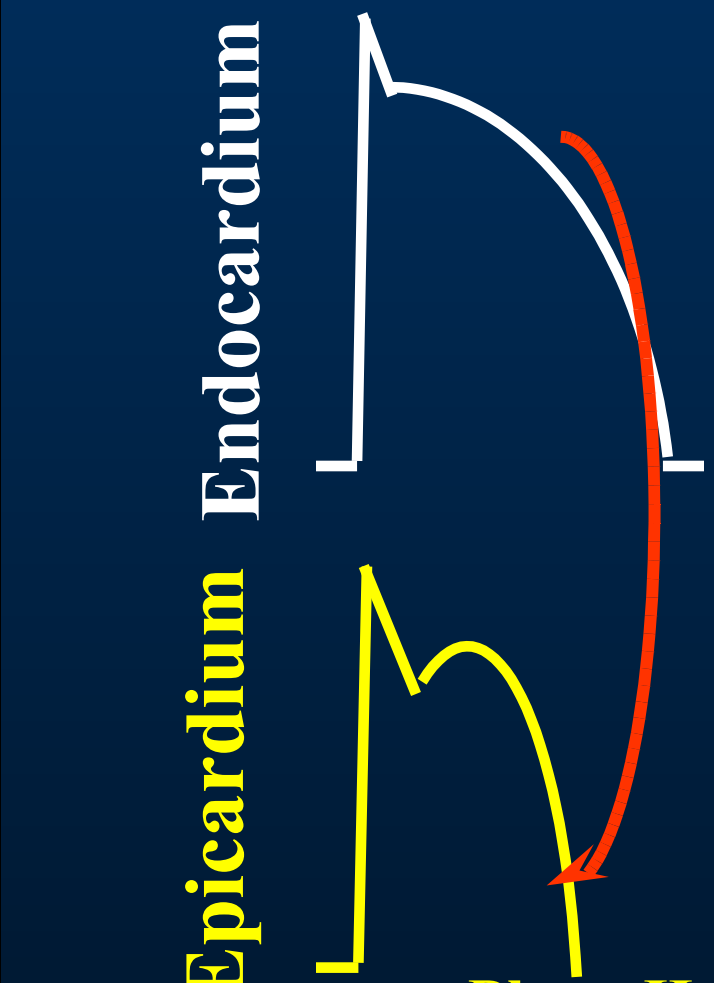
Viskin. When you only live twice. *N Engl J Med 1995.*

Brugada Syndrome

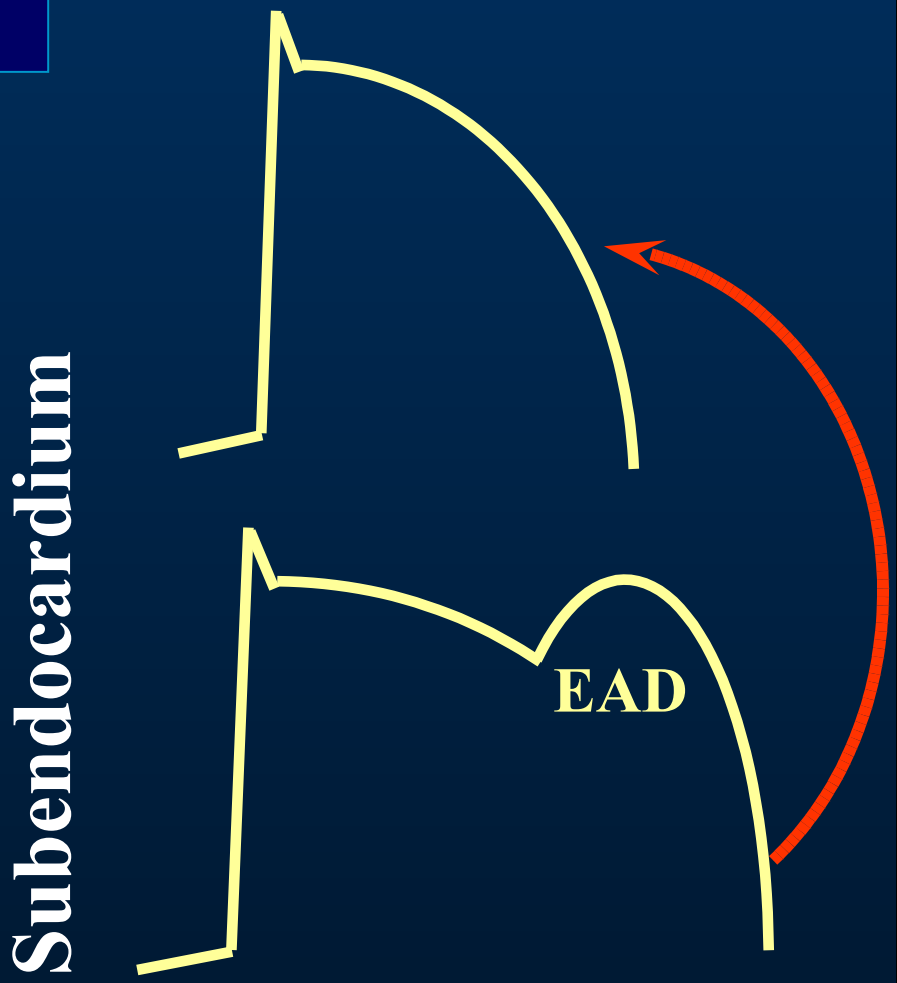
LQT3

Na+

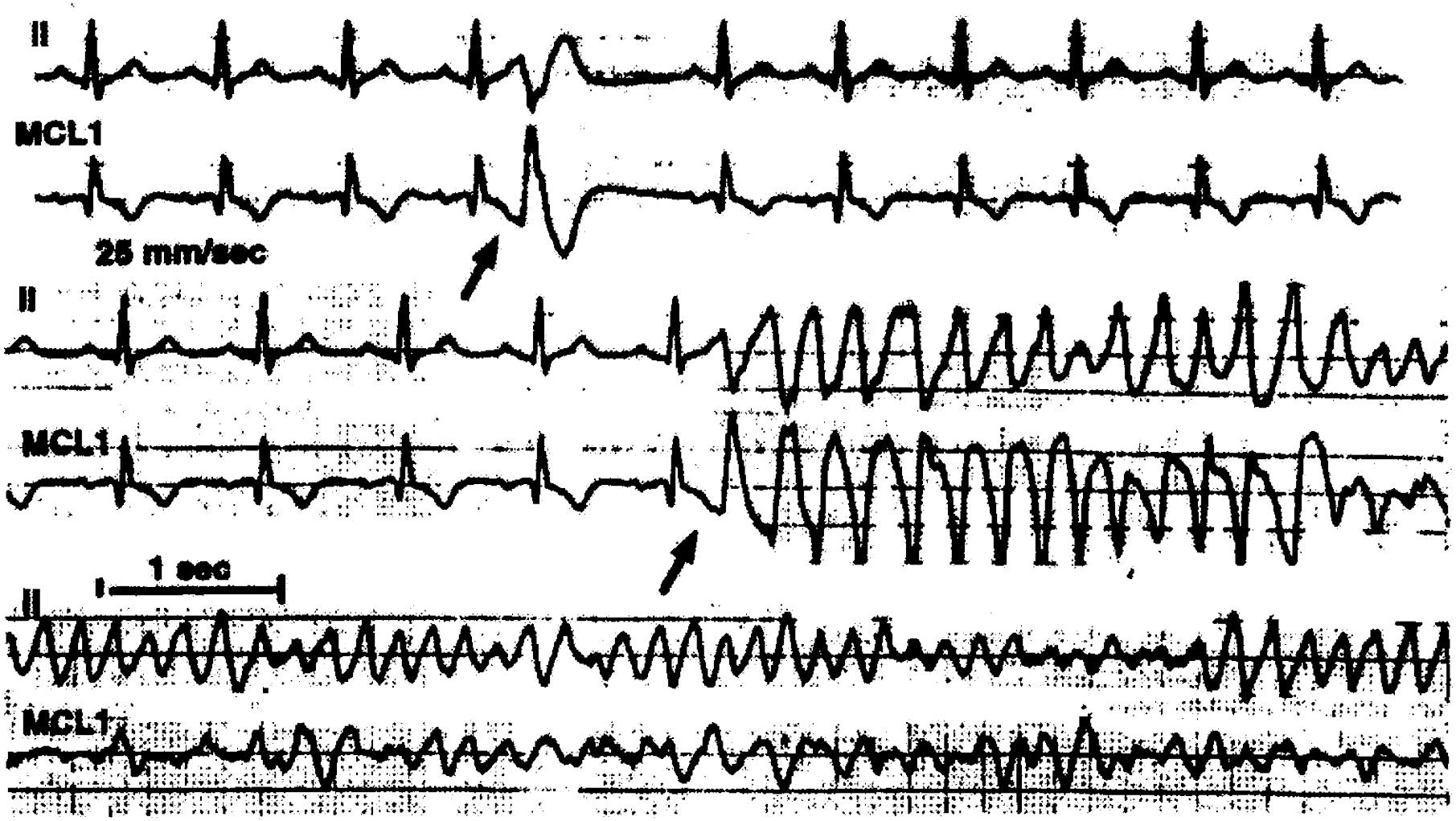
Normal



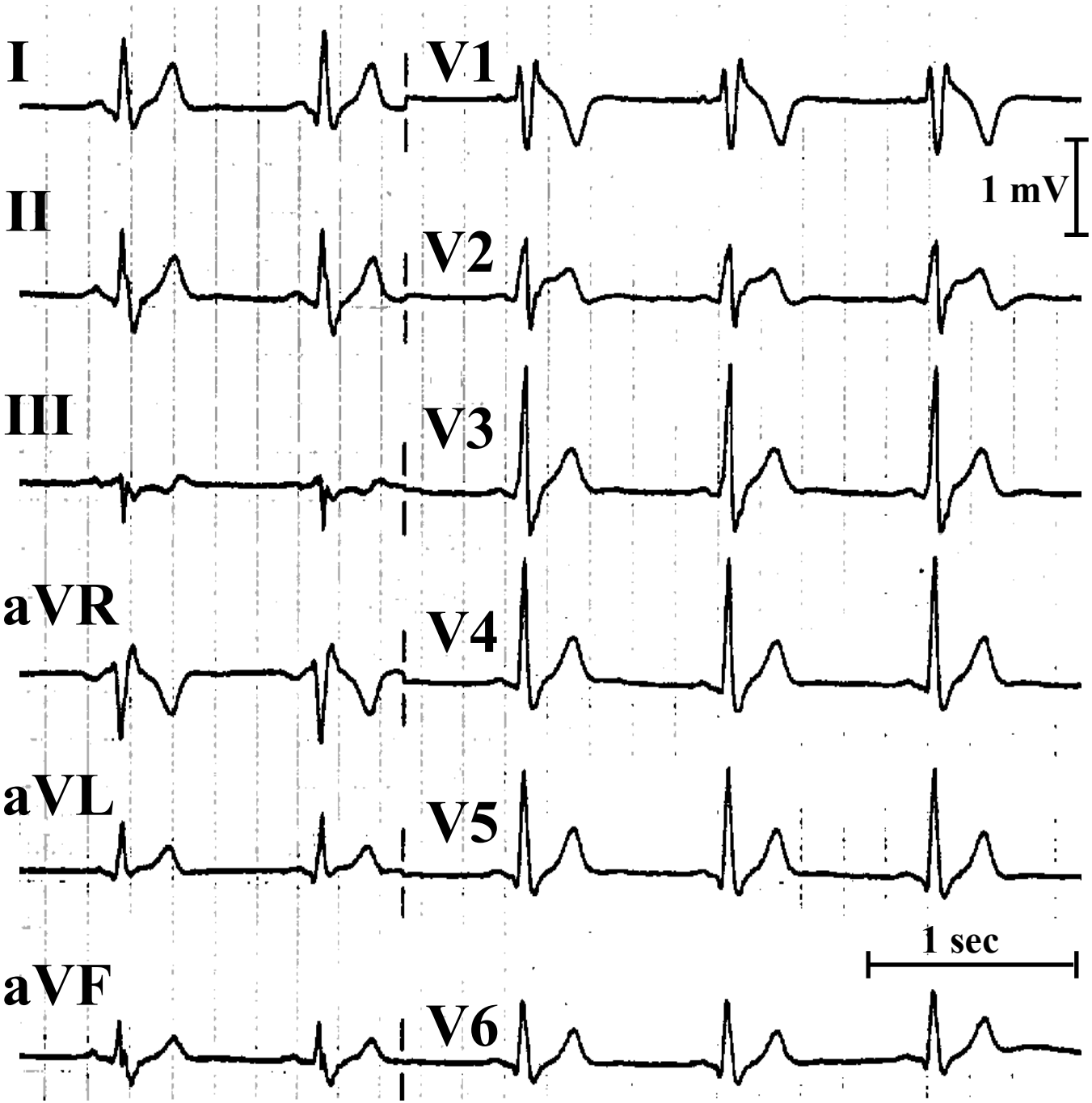
Phase II reentry



Phase III reentry

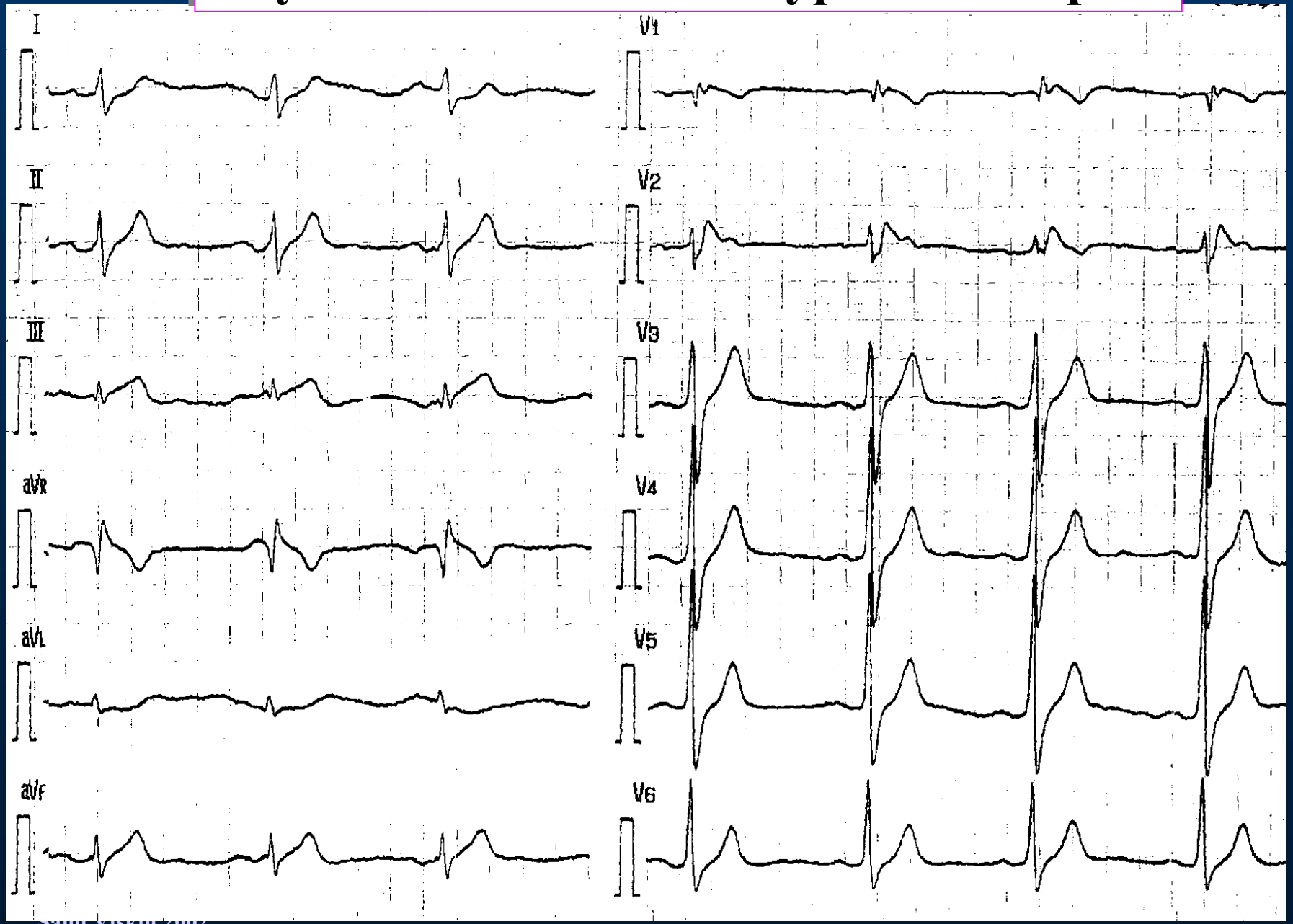


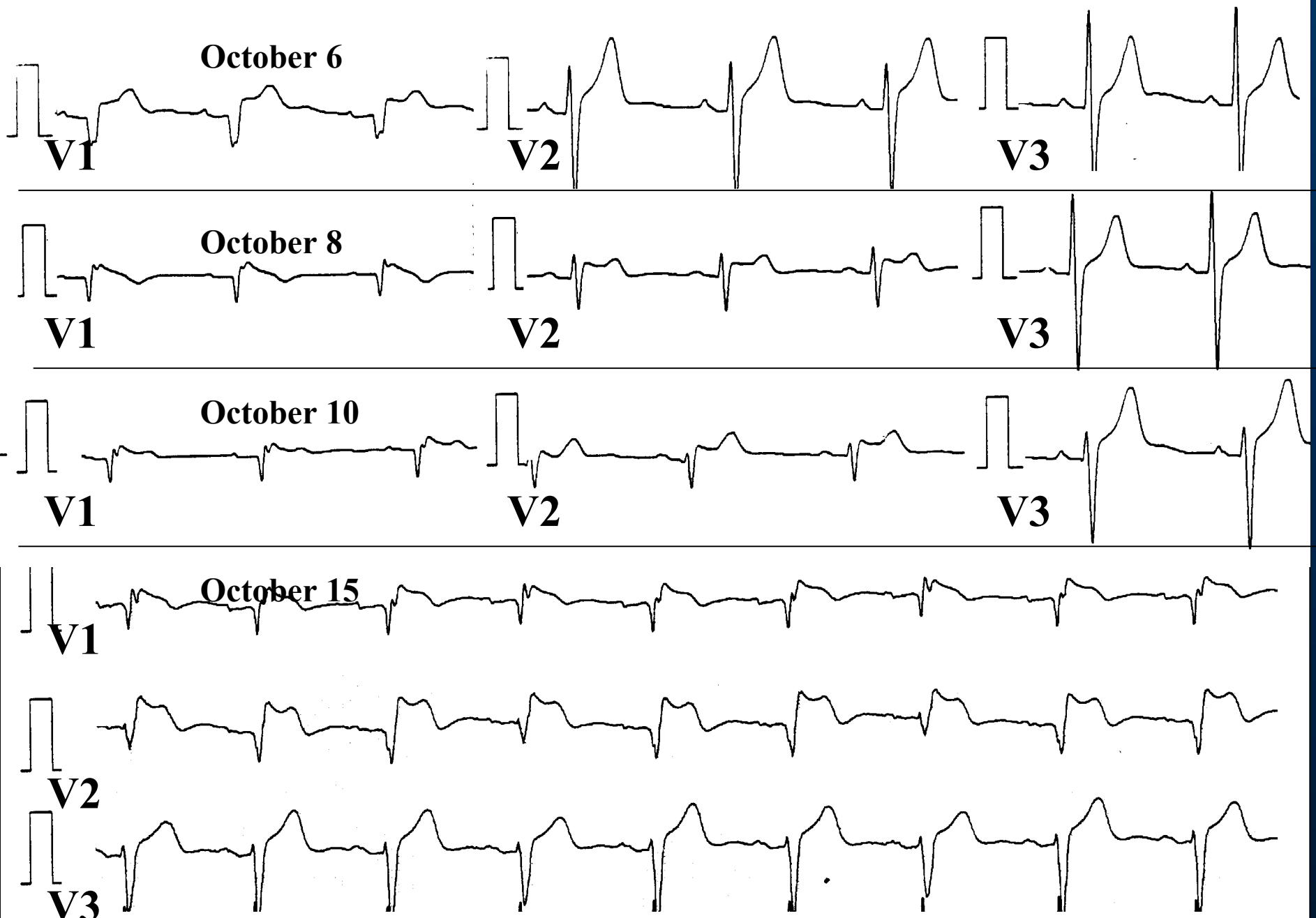
Viskin, *J Cardiovasc Electrophysiol* 1997


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

Gerberg

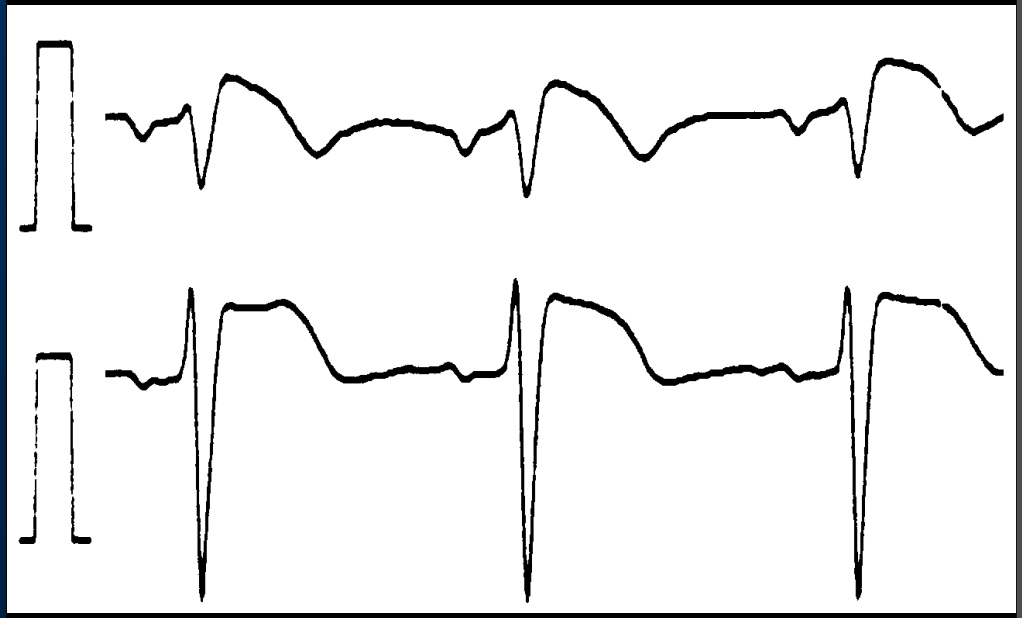
22 years-old male with atypical chest pain




October 6
V1
V2
V3
October 8
V1
V2
V3
October 10
V1
V2
V3
October 15
V1
V2
V3

Prevalence of the Brugada sign in idiopathic VF and in healthy controls

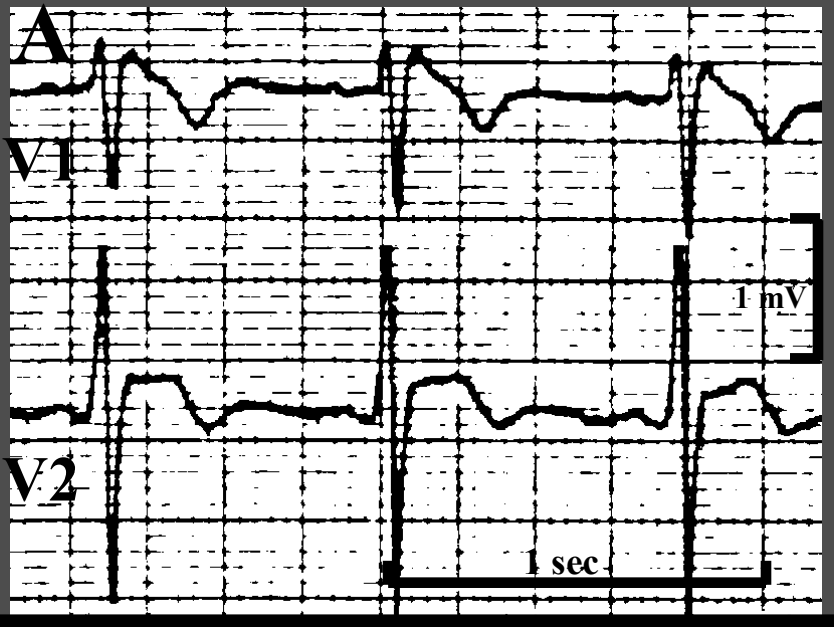
Major Brugada sign



Idiopathic VF 15%

Control 0 (95% C.I. <0.5%)

Minor Brugada sign

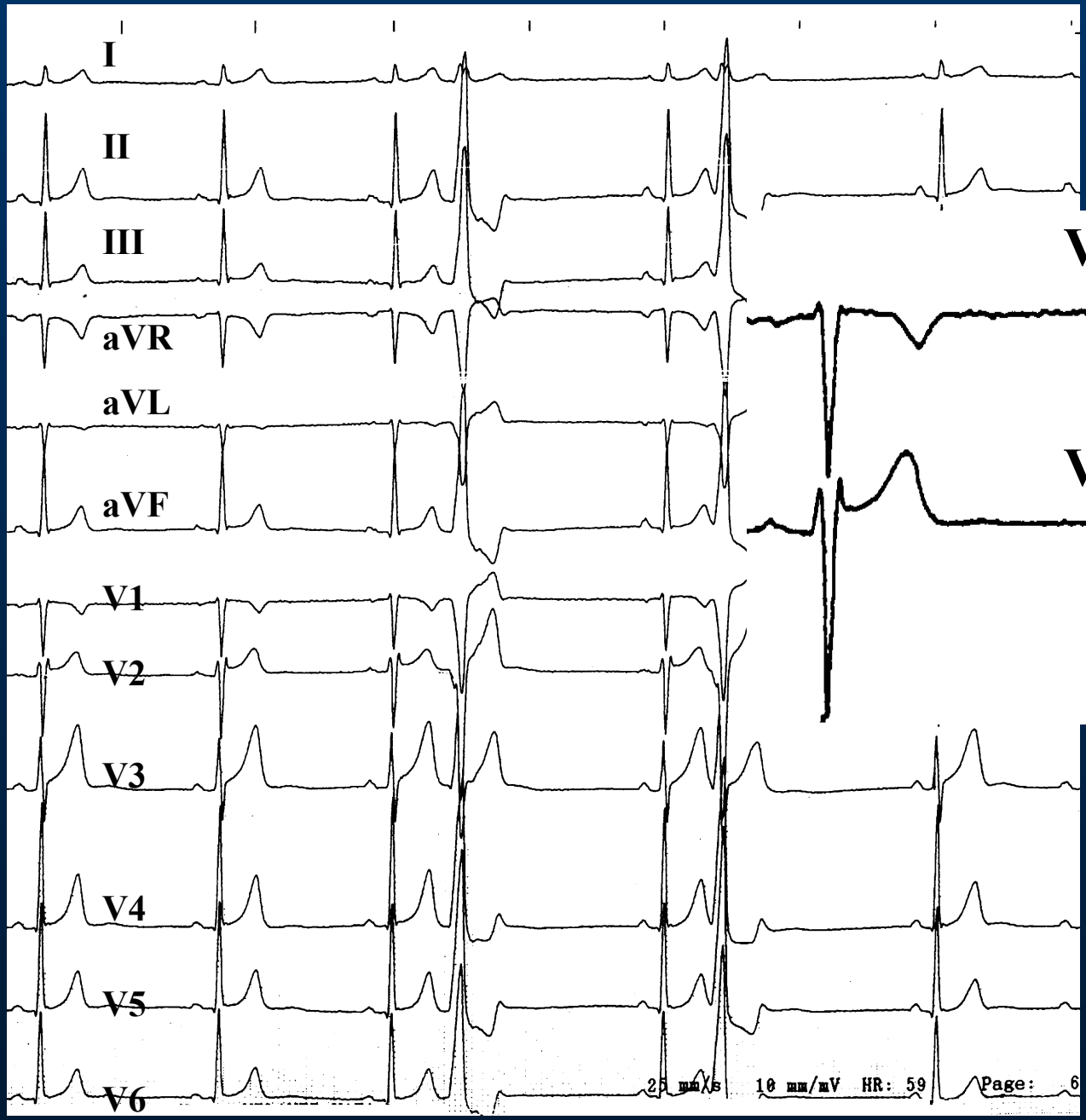


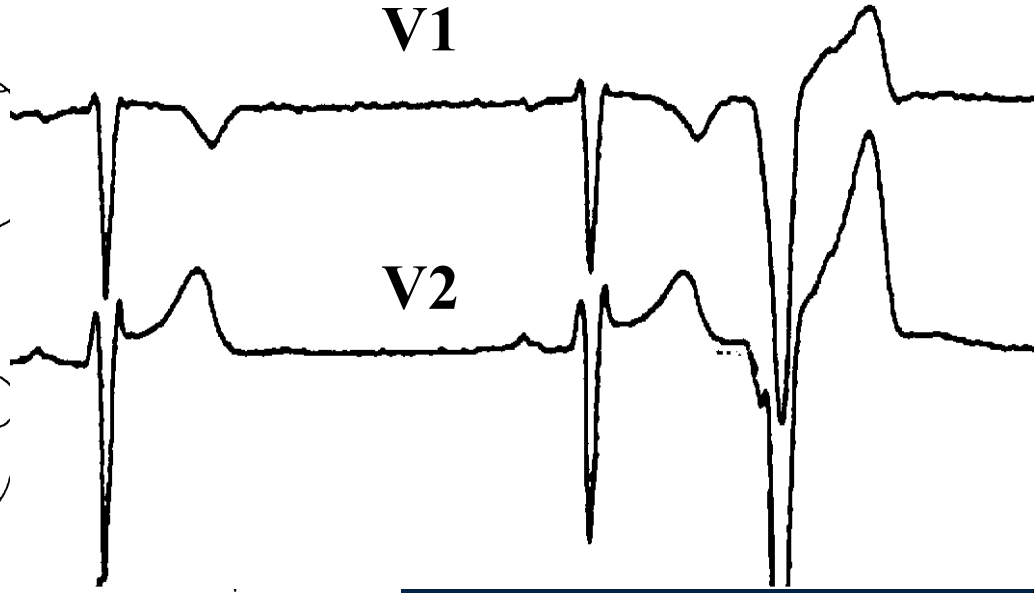
Idiopathic VF 5%

Control 1%

Sami Viskin 2002

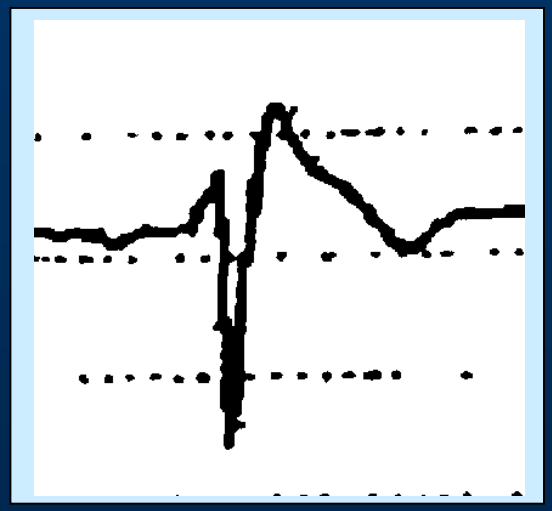
Viskin, *Heart* 2000

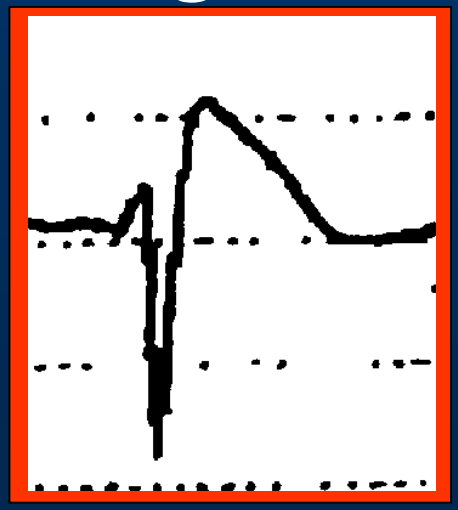




Sami Viskin 2002

Prevalence of the Brugada sign (cont.)



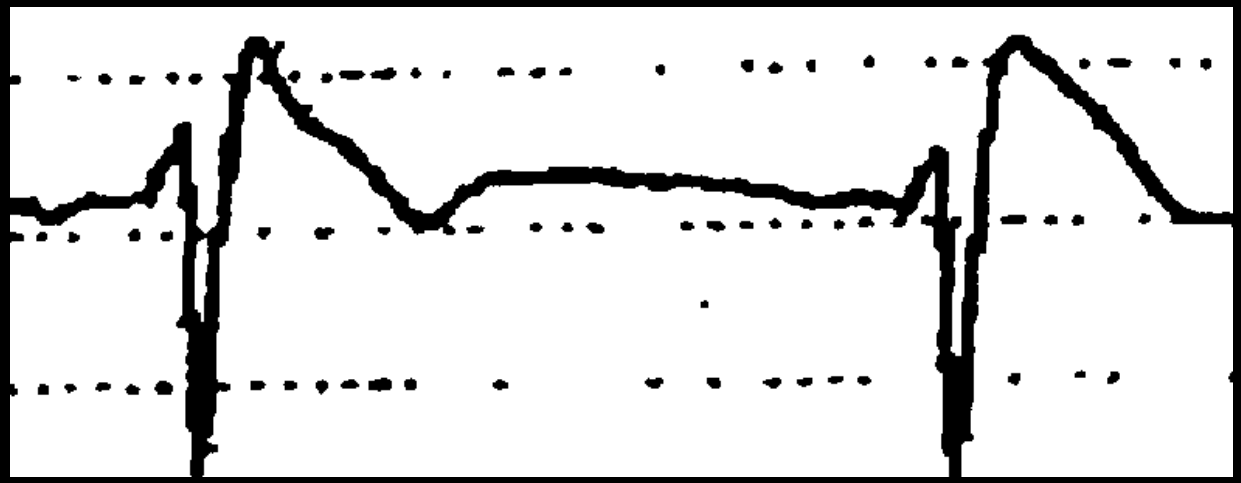


Saddle back pattern:

the common thing?

Coved pattern:

the real thing?



Electrophysiologic studies in Brugada syndrome?

…please, don't confuse me with the facts!

Sami Viskin, M.D.
Tel Aviv Medical Center, Israel.

Heart Rhythm Society
Restoring the Rhythm of Life

Heart Rhythm 2007
28th Annual Scientific Sessions
May 9-12, 2007 • Denver, CO USA

Heart Rhythm Society

Restoring the Rhythm of Life

Heart Rhythm 2007

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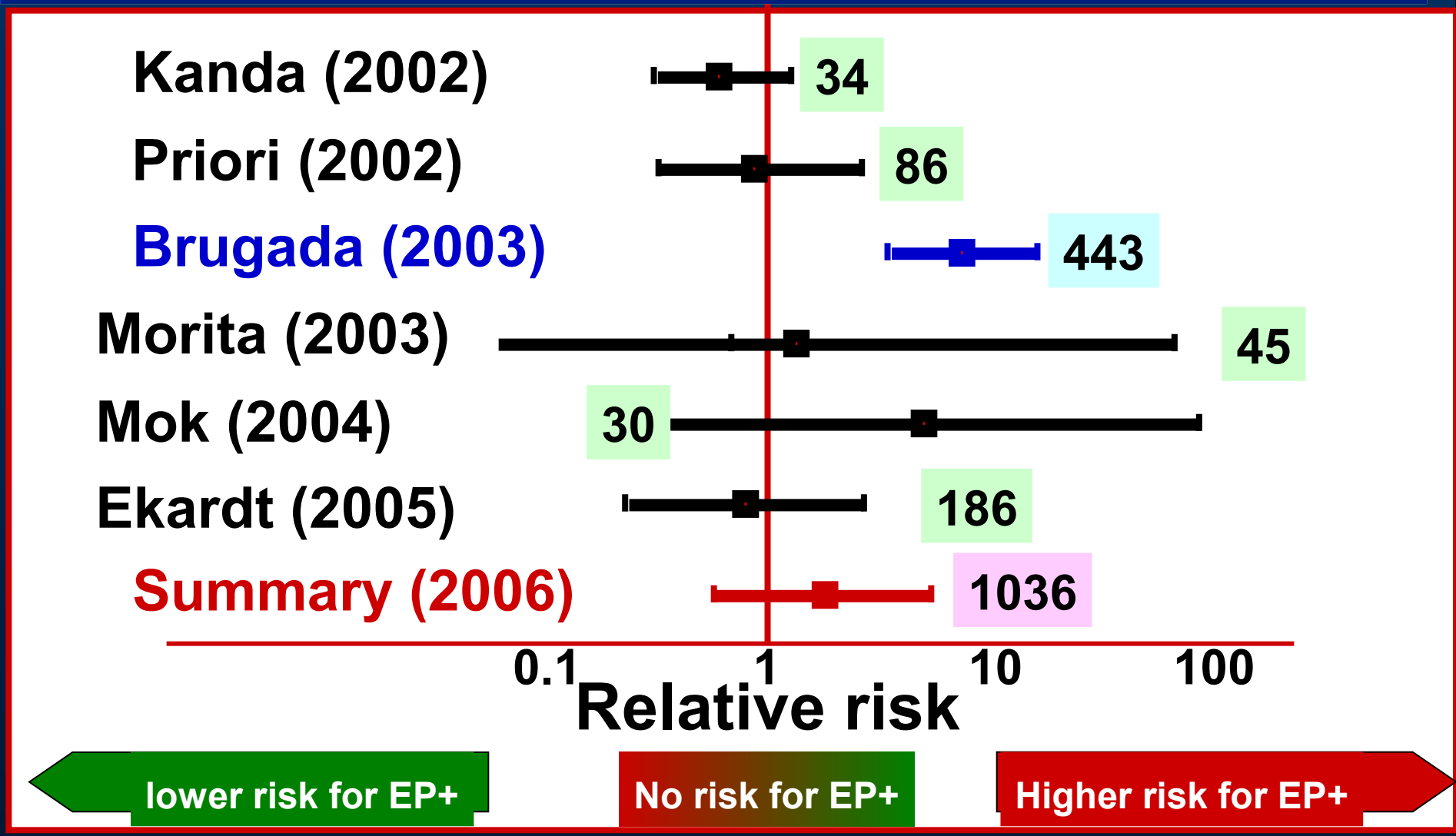
Sami Viskin, M.D.

Tel Aviv Medical Center, Israel.

Conflicts of interest

Relative risk of arrhythmic events in patients with Brugada ECG and positive EPS



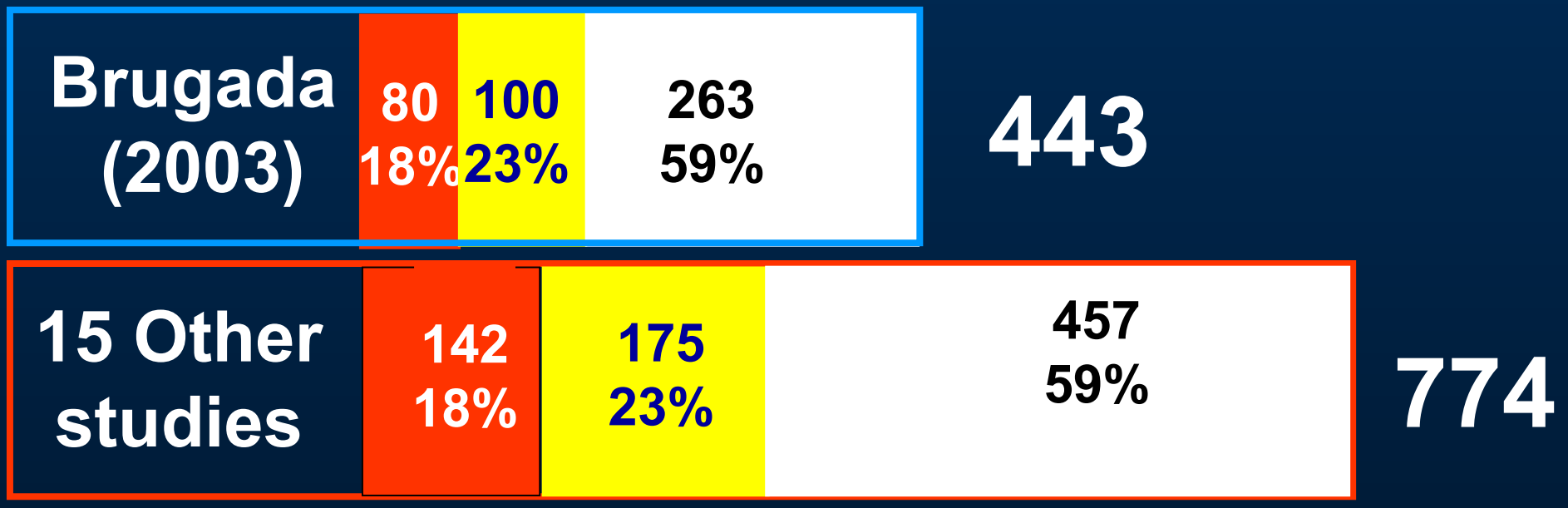
Sami Viskin 2002

Gehi: Risk stratification in Brugada syndrome, a *Meta-Analysis.* JCE 2006

Role of Programmed Ventricular Stimulation in Patients with Brugada Syndrome. A Meta-Analysis of Worldwide Published Data.

M. Paul, J. Gerss, E. Schulze-Bahr, T. Wichter, C. Vahlhaus, A.A.M. Wilde, G. Breithardt, L. Eckardt. *Eur Heart J* 2007 (In Press).

Number of patients with Brugada syndrome who underwent EPS



Role of Programmed Ventricular Stimulation in Patients with Brugada Syndrome. A Meta-Analysis of Worldwide Published Data.

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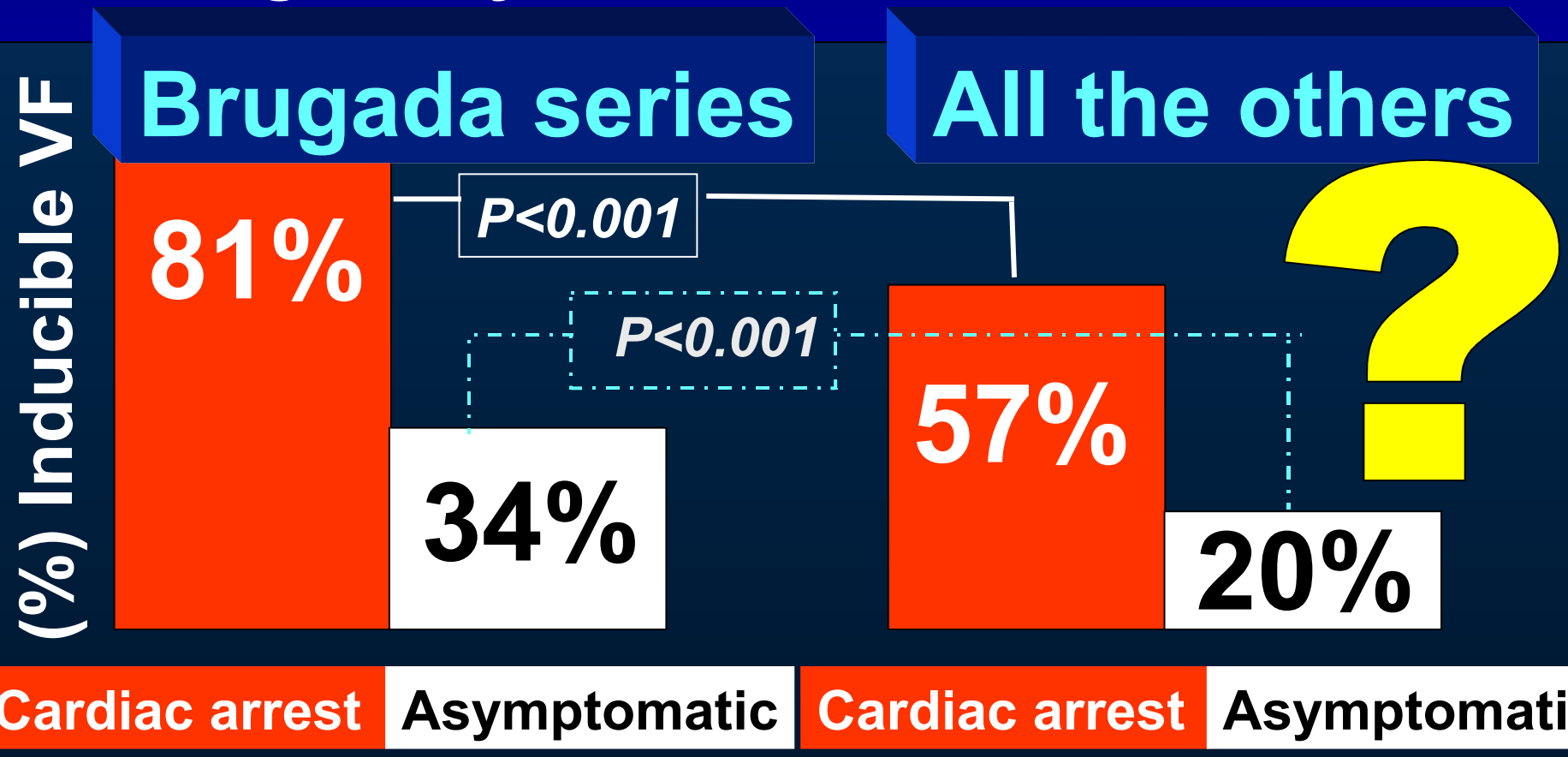
What percentage of patients with Brugada syndrome have inducible VF ?



Higher inducibility rates in the *Brugada Series:*

1. Sicker patients?
2. Aggressive EP protocol?
   - More pacing sites?
   - More extrastimuli?
   - Shorter coupling intervals?

Sami Viskin 2002

Patients included in different series of Brugada syndrome*: Same but different?.*

	Brugada *(2003)* *n= 443*	Bordachar (2004) *n*= 59	Priori (2002) *n*= 200	Eckardt (2005) *n*= 212
Male	77%	75%	76%	72%
Type I ECG	*71%*	*83%*	*51%*	*59%*
Months	31 ±41	34 ±13	34 ±44	40 ±50
% with events	14%	5%	7%	4%

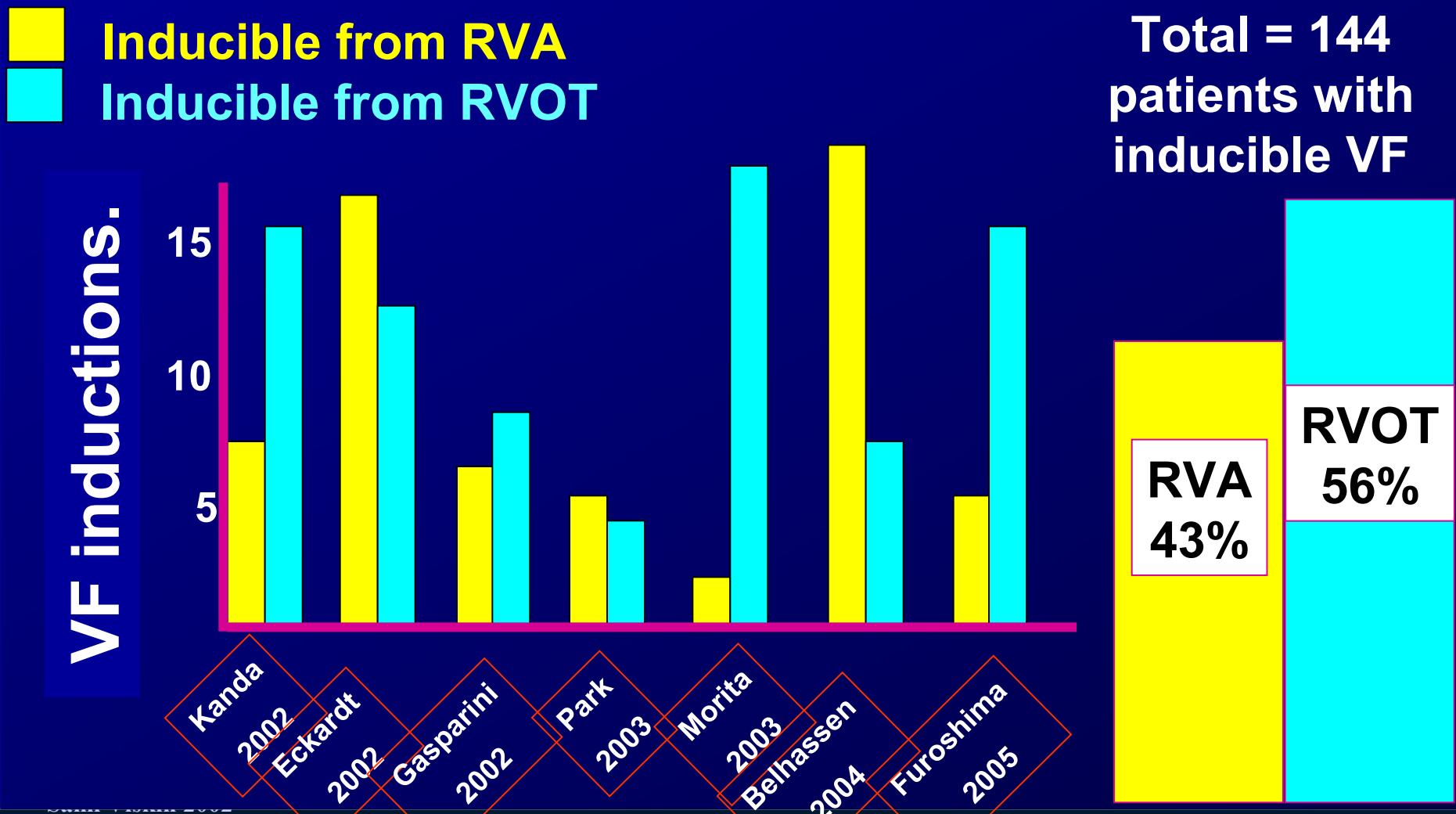
Higher inducibility rates in the *Brugada Series: Not due to aggressive EPS protocol.*

	Brugada series	Other studies
Pacing Sites	RVA only	RVA + RVOT
Extrastimuli	3	3
Minimal coupling interval	200 ms	≤200 ms

Sami Viskin 2002

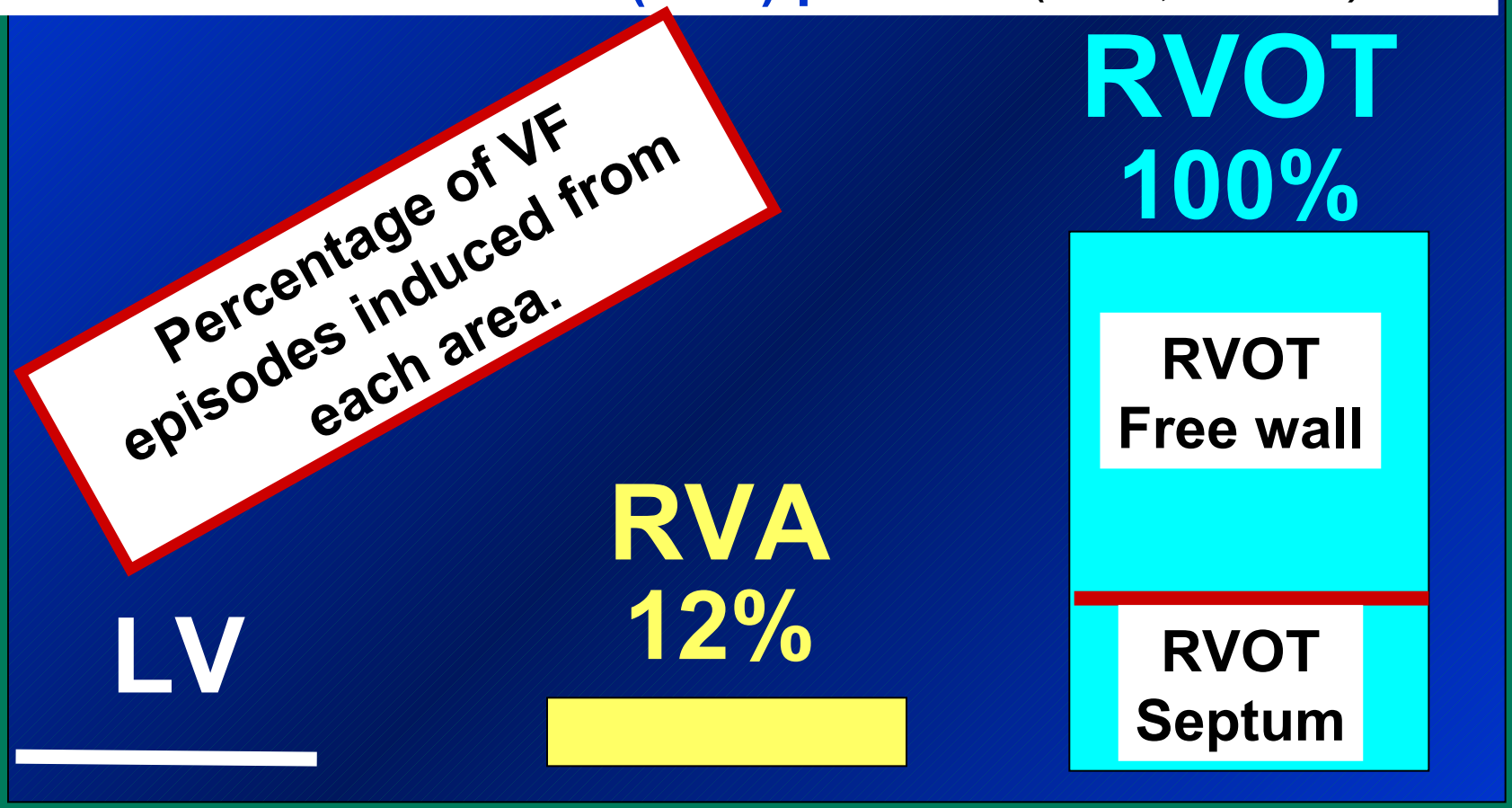
Eckardt (Eur Heart J 2002): 66% of VF episodes in Brugada were induced with CI < 200 msec

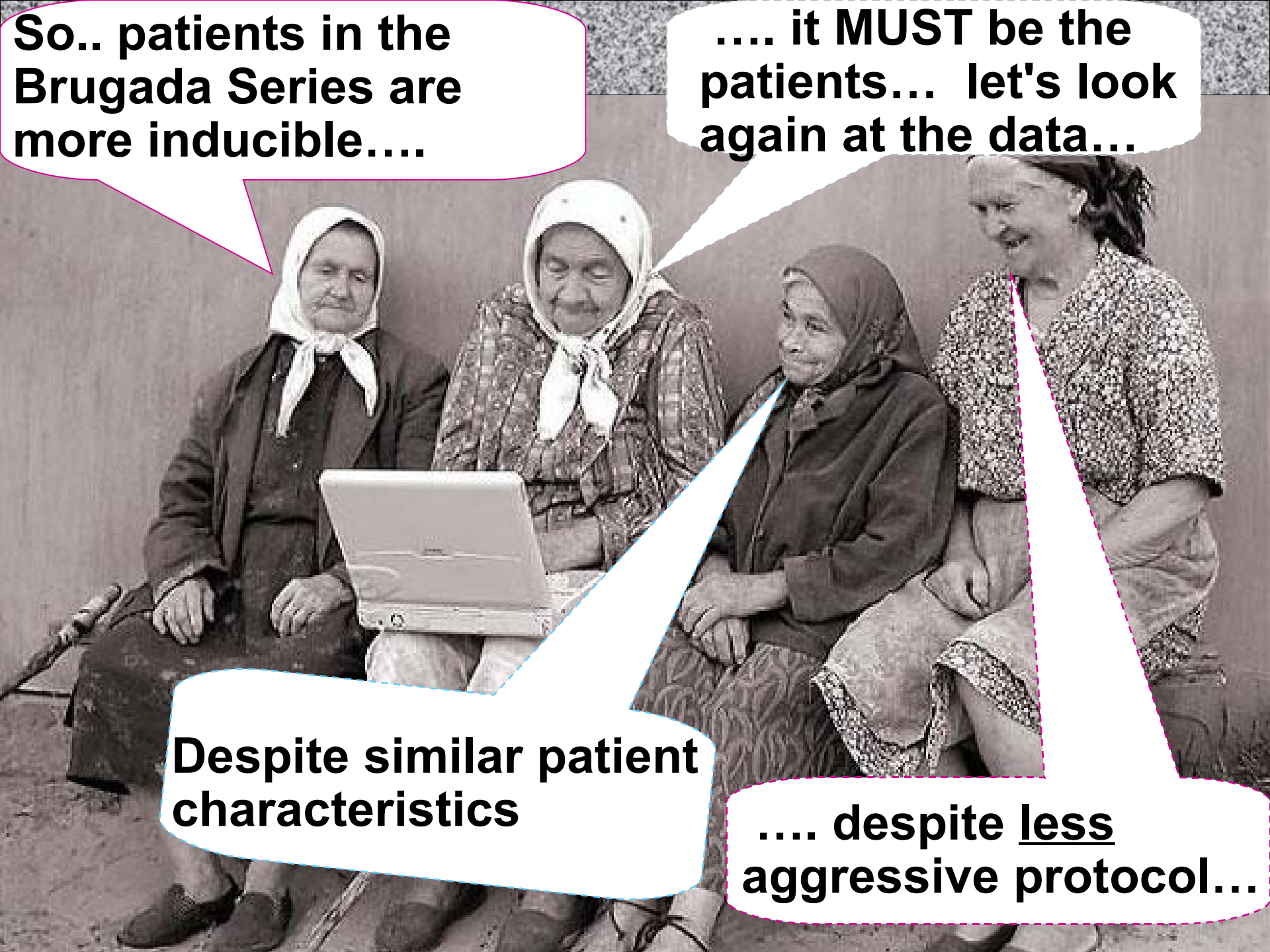
Contribution of the RVOT (right ventricular outflow tract) to inducibility of VF.



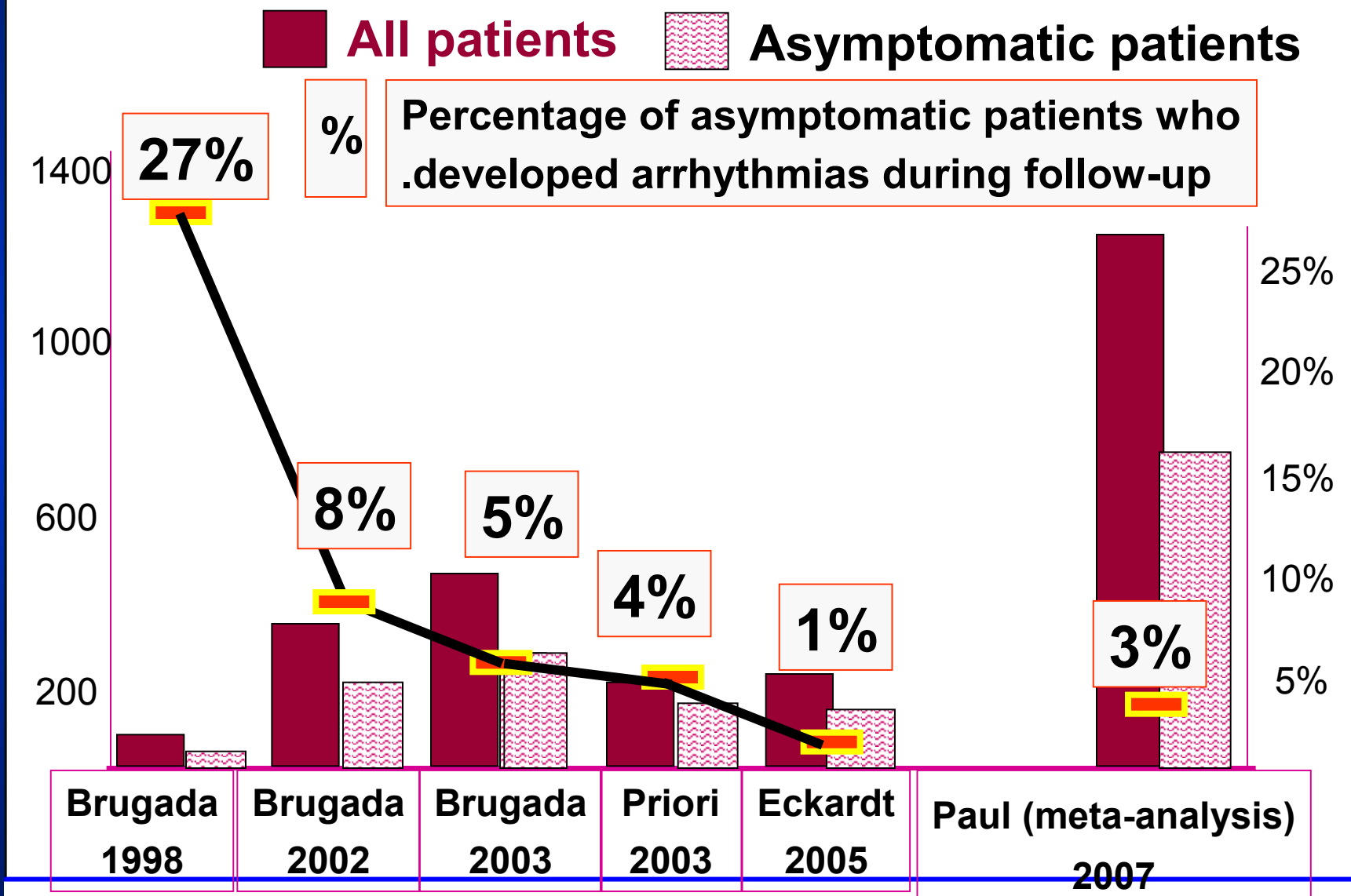
Site-Specific Arrhythmogenesis in Patients with Brugada Syndrome

45 patients with Brugada syndrome (all type I) ECG.
All patients underwent EP-stimulation at all sites.
Inducible VF in 17 (38%) patients (Morita, JCE *2003*).



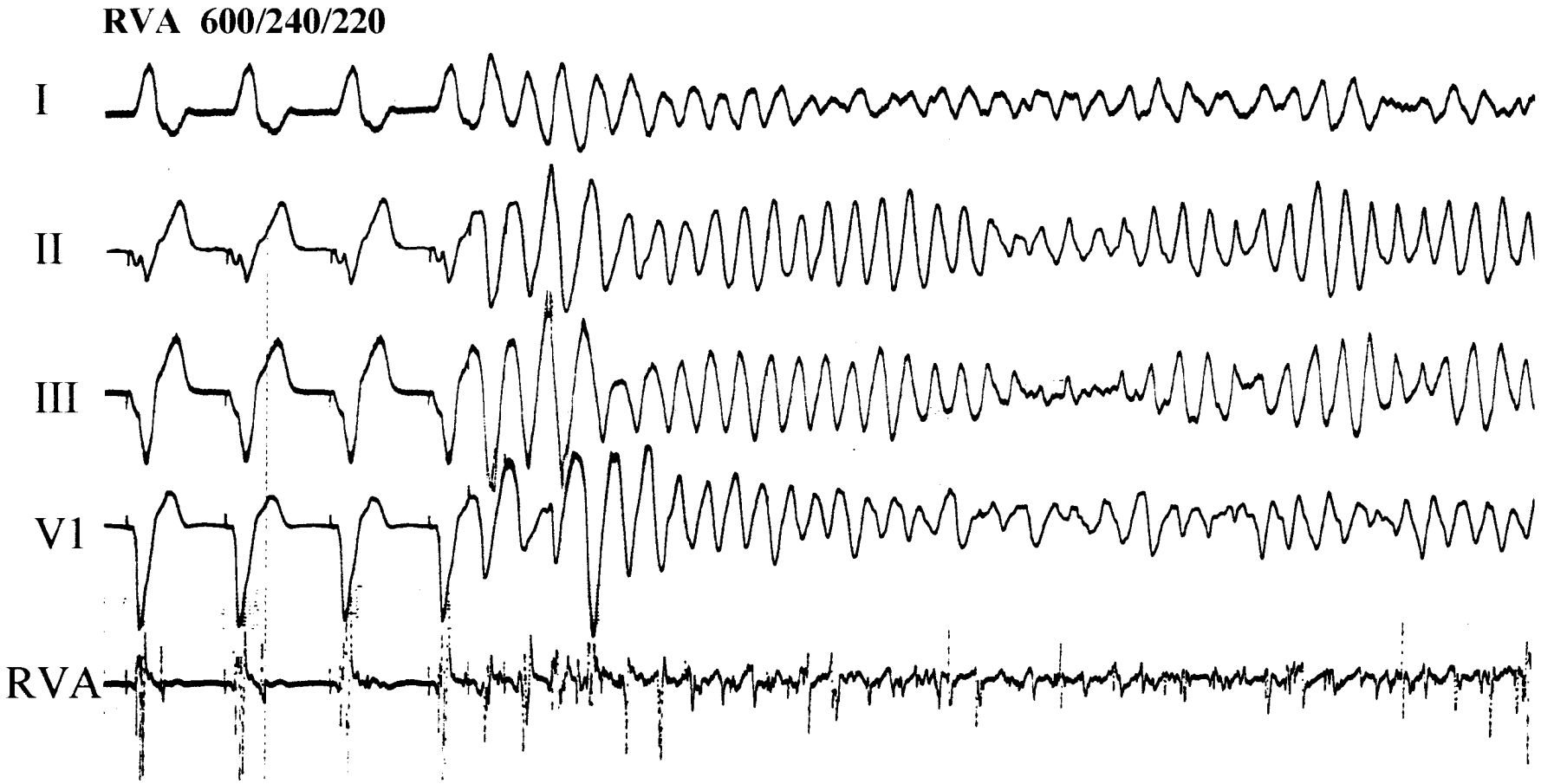

So.. patients in the Brugada Series are more inducible….
…. it MUST be the patients… let's look again at the data…
Despite similar patient characteristics
…. despite less aggressive protocol…

Asymptomatic Brugada patients in different publications.



A Meta-Analysis of Worldwide Published Data. M. Paul. *Eur Heart J* 2007 (In Press).

What is the role of EPS in *asymptomatic* patients with Brugada syndrome ???



Induction of VF with 2 extrastimuli:

Results of a Ventricular Stimulation Protocol Using a Maximum of 4 Premature Stimuli in Patients Without Documented or Suspected Ventricular Arrhythmias

PEDRO BRUGADA, MD, HOSHIAR ABDOLLAH, MD, BILL HEDDLE, MB, BS, and HEIN J. J. WELLENS, MD

Is this normal ?

10% = 5/52 had inducible VF.

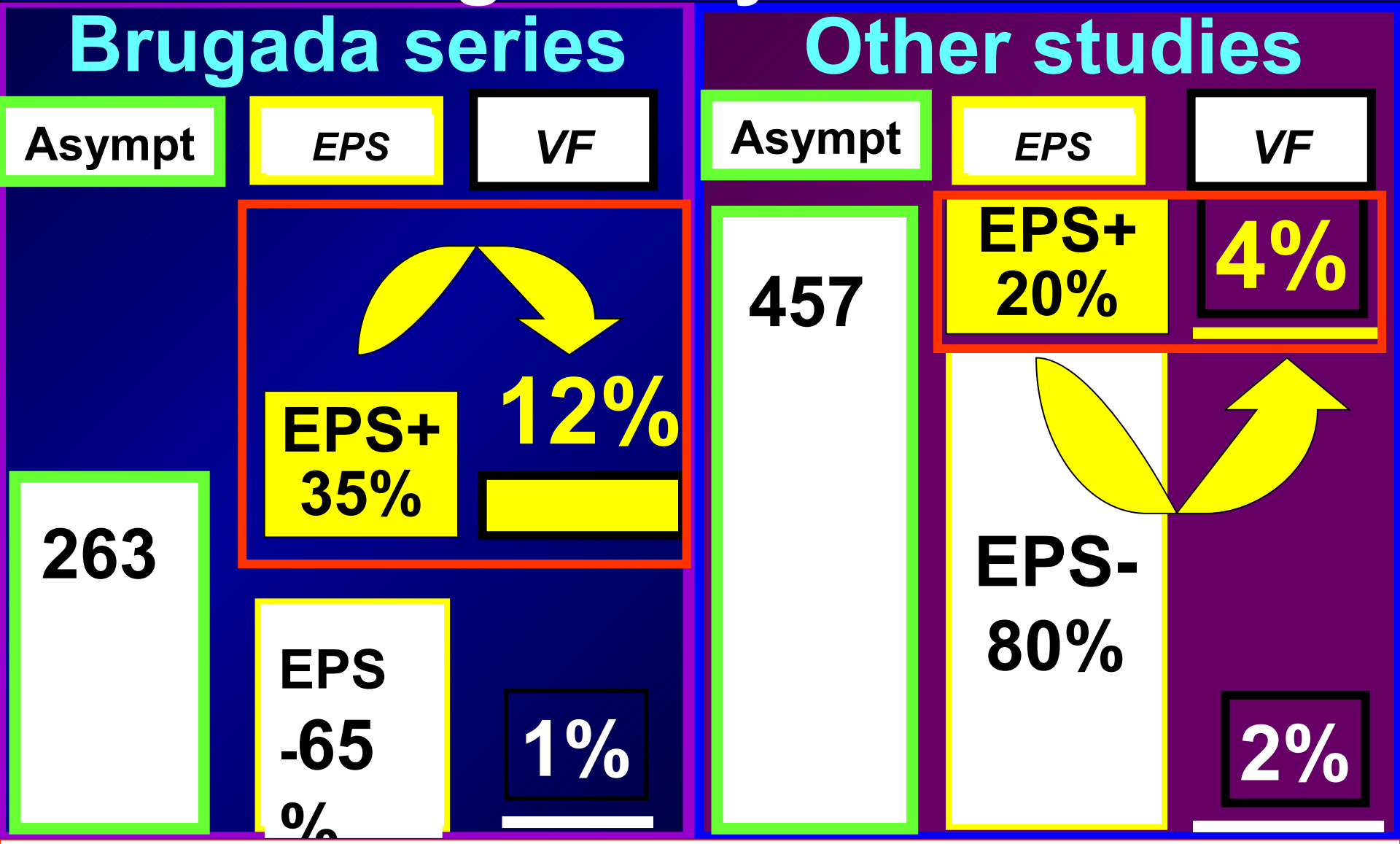
…in 24/54 = <u>46%</u> the protocol was stopped because polymorphic VT was induced !

52 patients without ventricular arrhythmias:

- **Stimulation *only at the RVA.***
- ***Only one basic cycle length.***
- ***No minimal coupling interval.***

Am J Cardiol 1983

Value of EPS in Asymptomatic Brugada Syndrome



Asymptomatic patients with inducible VF =198 patients from 8 studies.

Conclusions:

	Brugada Series	Other Series
Induction of VF at EPS	High	Low
Spontaneous VF	High	Low
Predictive value of EPS	High	Poor

Sami Viskin 2002

Conclusions:

We need more data.

We need uniform reporting.

We need longer follow-up.

What to do in the meantime?

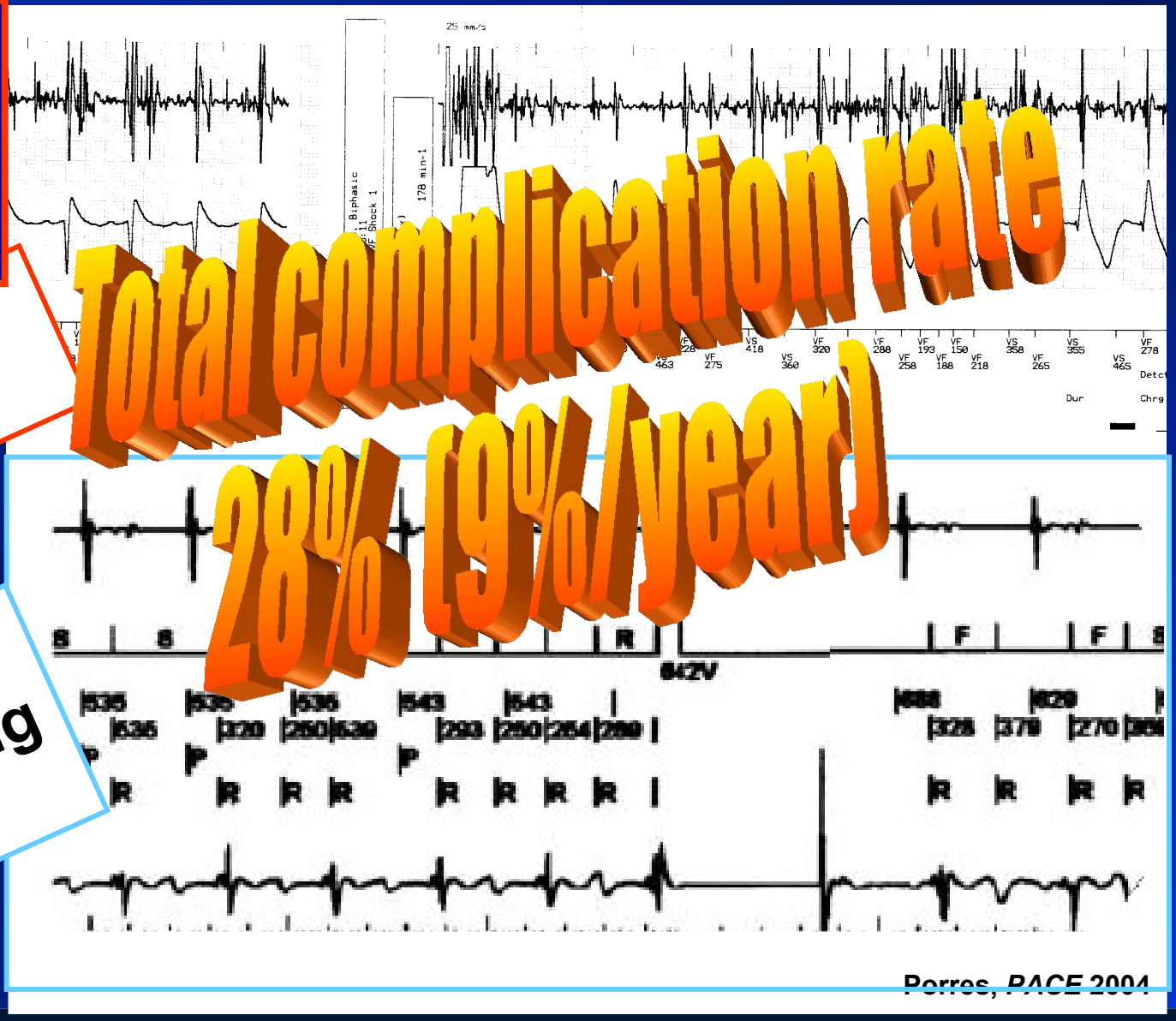
Sacher,
Circulation 2006:

High incidence of adverse events from ICD in Brugada syndrome.

Inappropriate shock
20%
4 shocks/patient

"Noise"
8%

T-wave oversensing
5%

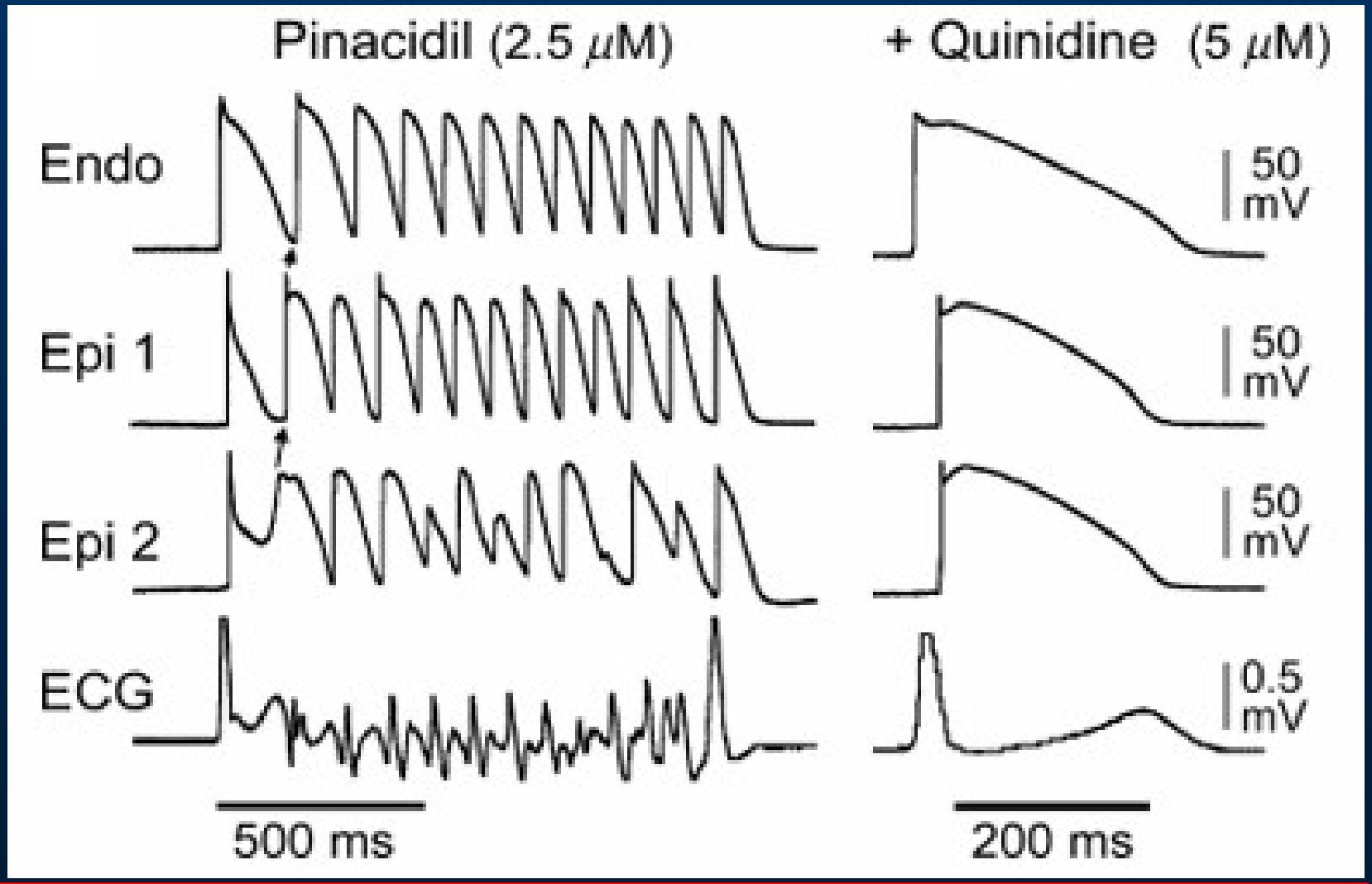


What to do in the meantime?

- Stop the flecainide test.
- Wait for the extra-cardiac ICD.
- Recommend the Home-EAD.
- Consider quinidine therapy.

why quinidine?

Quinidine works well in the web-preparation:

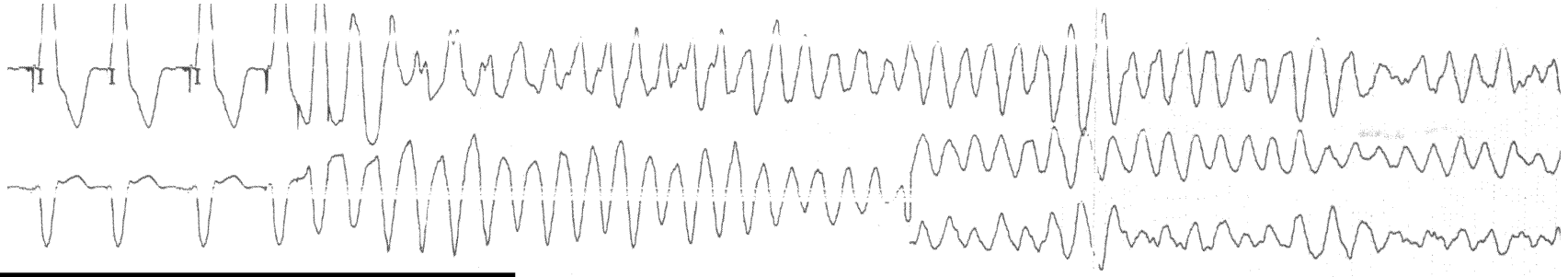


Prevention of phase-2 reentry by quinidine in the model of Brugada syndrome (Yan, Antzelevitch 2006)

Quinidine works well in EP-laboratory:

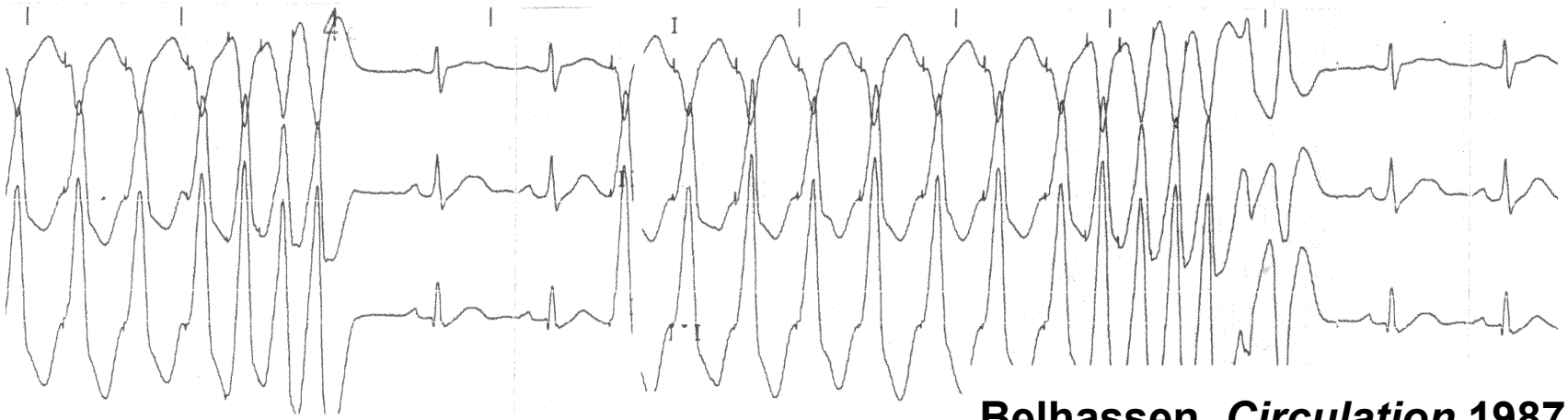
Baseline:

Induction of VF with 2 extrastimuli



Quinidine 1.5 g/day:

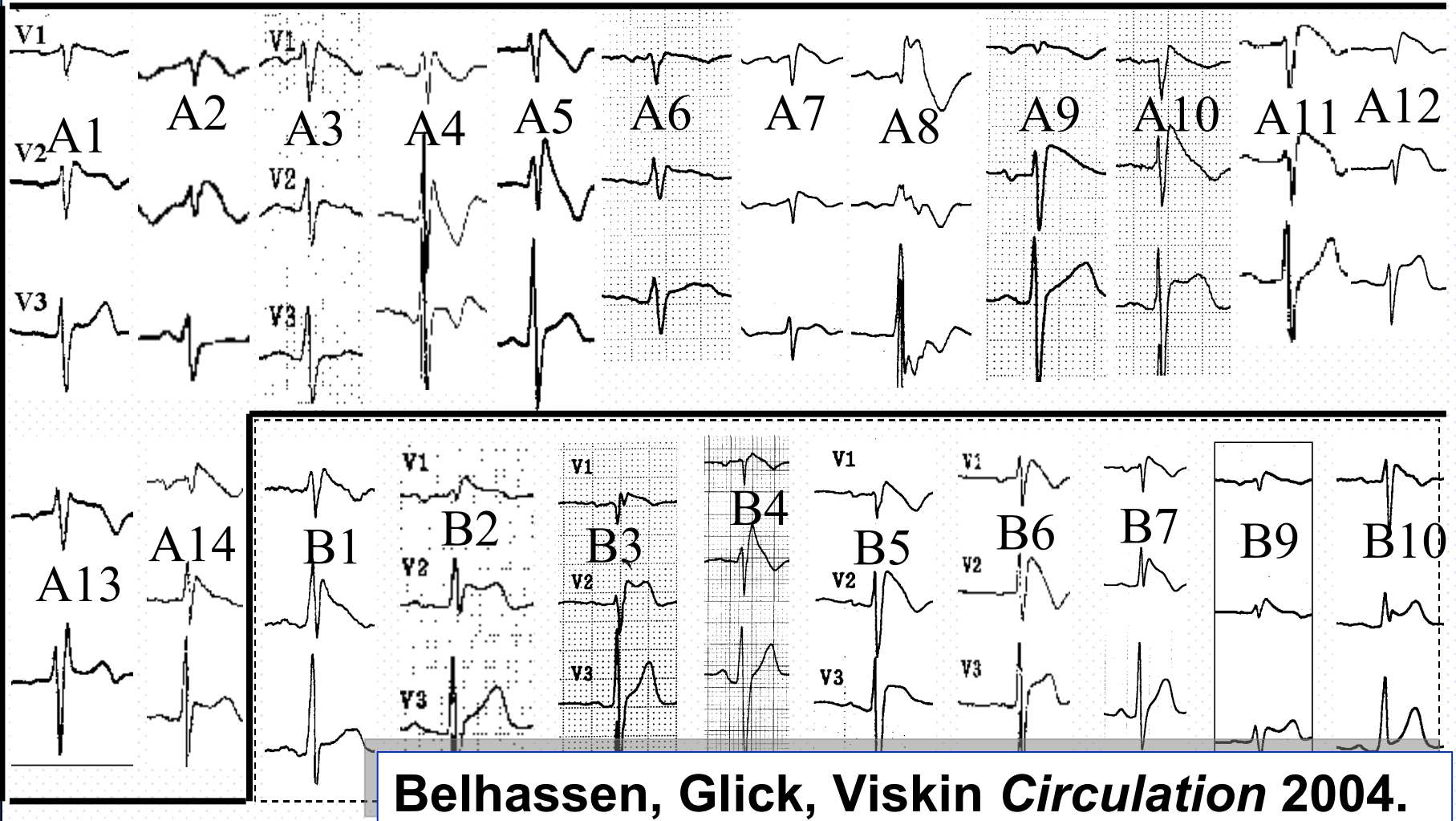
No inducible arrhythmias with 4 extrastimuli



Belhassen, *Circulation* 1987

Quinidine works well in the real world:

Efficacy of Quinidine in High-Risk Patients with Brugada Syndrome



Belhassen, Glick, Viskin *Circulation* 2004.

	Total	Symptomatic	Asymptomatic
	38	15*	23*
Baseline EPS			
VF	25	15	10
EPS on QND			
Negative	22	13 (87%)	9 (90%)
Long term Quinidine	19	11	8
F-U: Years	4.6 ± 5.6	6.8 ± 6.4	1.7 ± 1.6
VF	0	0	0

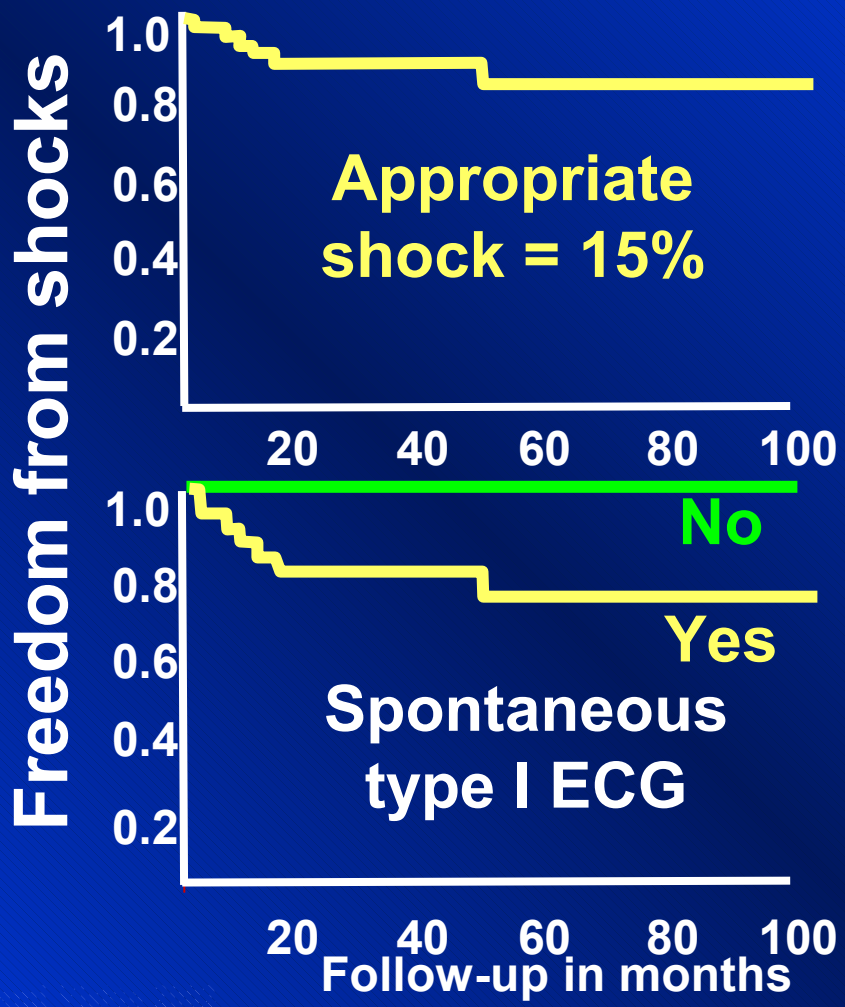
Expected VF by 3 years (Brugada JCE 2003): 54%, 23% and 12% for patients presenting with cardiac, syncope or asymptomatic with inducible VF, respectively.

Long-term follow-up of primary prophylactic implantable cardioverter-defibrillator therapy in Brugada syndrome

Andrea Sarkozy[1*], Tim Boussy[1], Georgios Kourgiannides[1], Gian-Battista Chierchia[1], Sergio Richter[1], Tom De Potter[1], Peter Geelen[1], Francis Wellens[2], Marieke Dingena Spreeuwenberg[3], and Pedro Brugada[1]

European Heart Journal

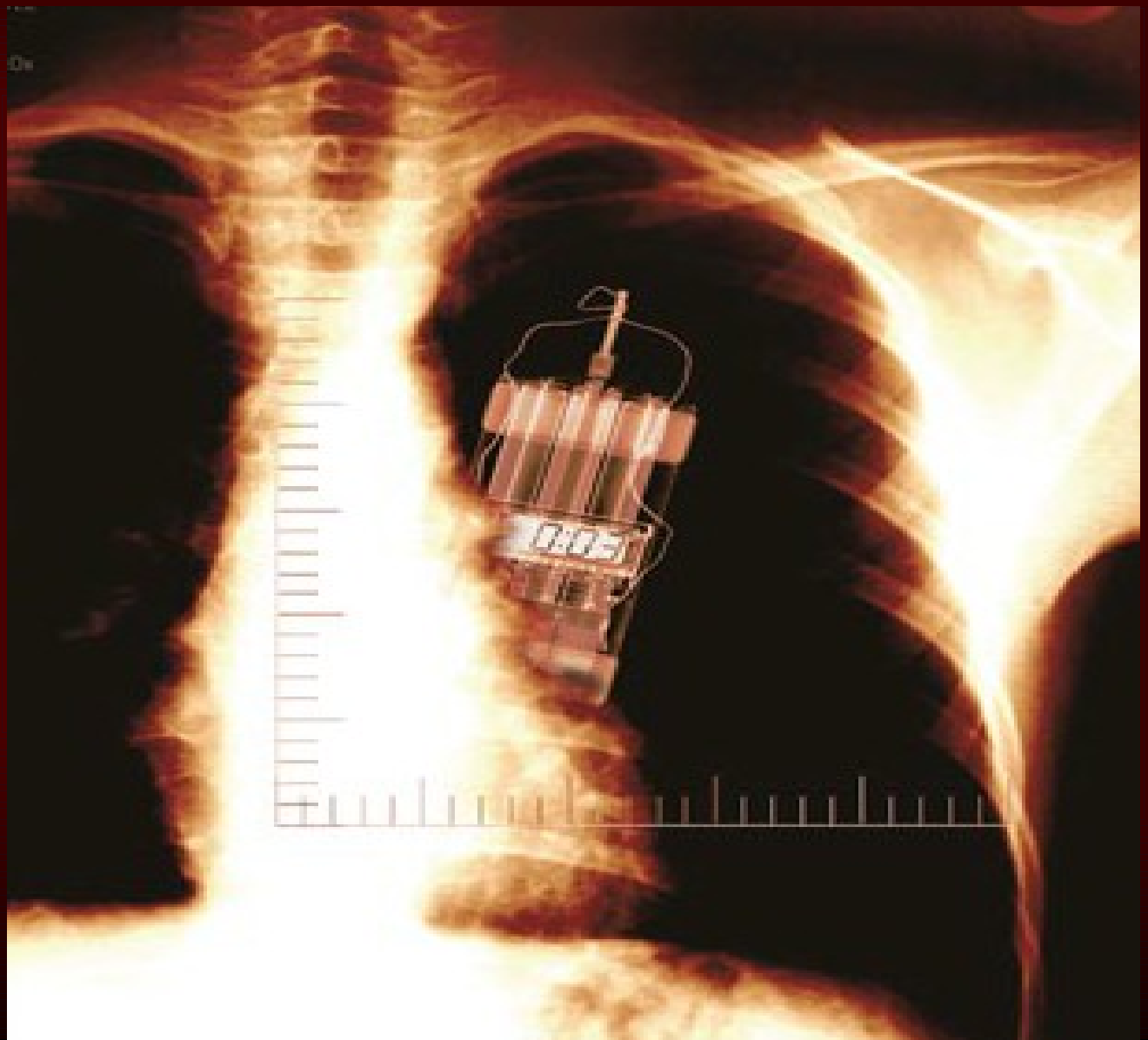
Appropriate shocks



Inappropriate shocks

60 patients with ICD (13 excluded) 47 ICD

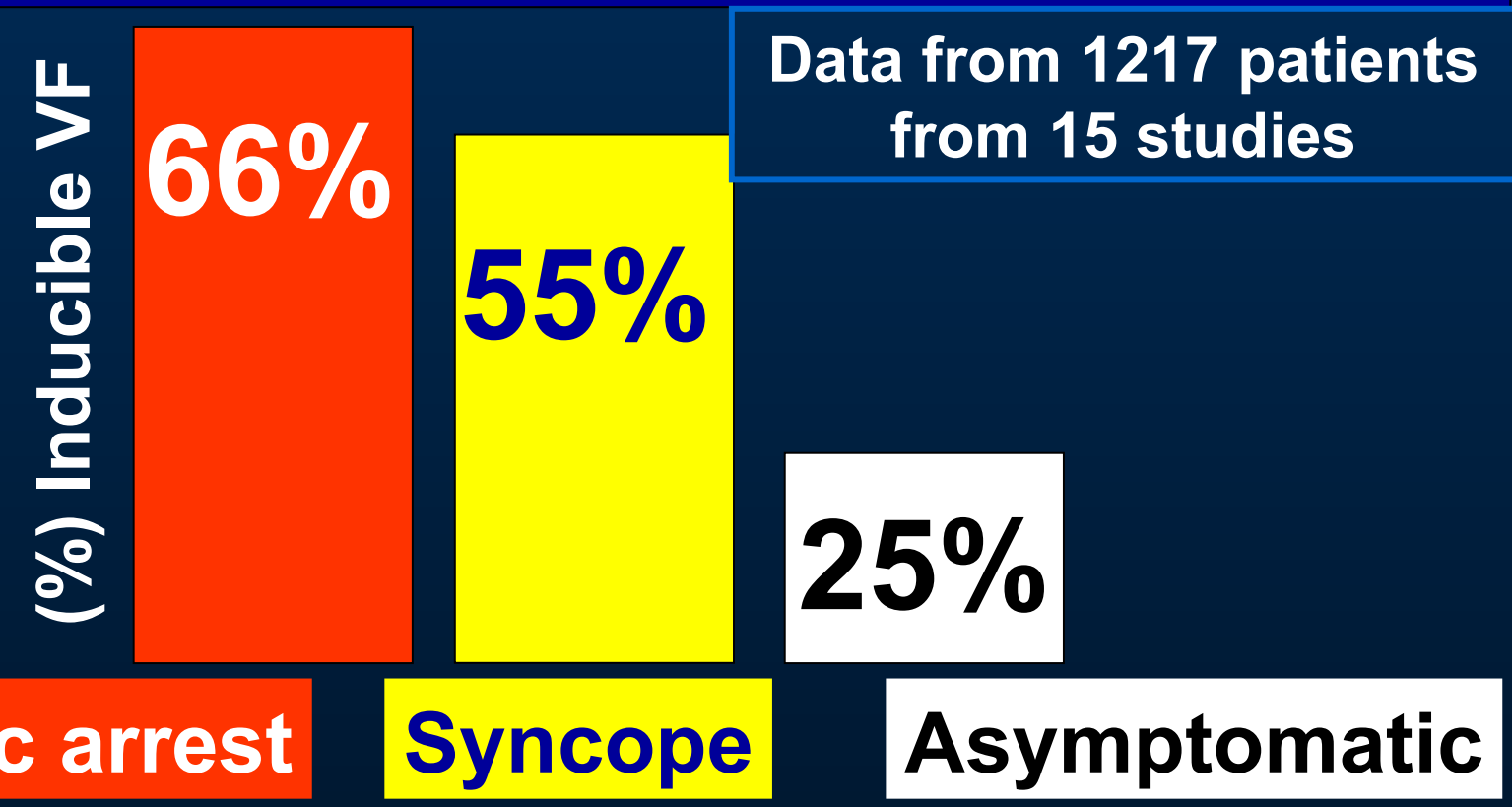
Asymptomatic Brugada syndrome… a cardiac ticking bomb?



Role of Programmed Ventricular Stimulation in Patients with Brugada Syndrome. A Meta-Analysis of Worldwide Published Data.

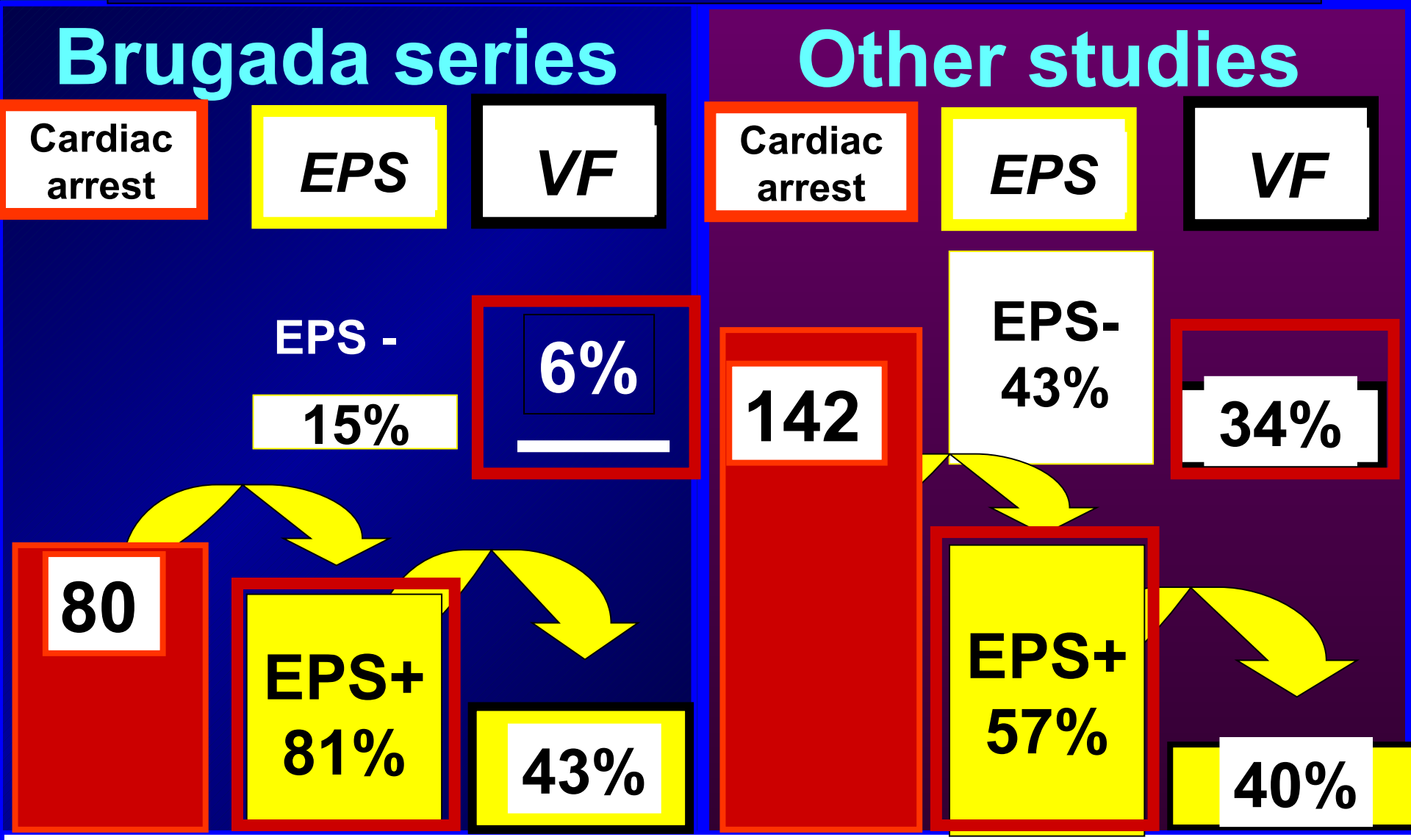
M. Paul, J. Gerss, E. Schulze-Bahr, T. Wichter, C. Vahlhaus, A.A.M. Wilde, G. Breithardt, L. Eckardt. *Eur Heart J* 2007 (In Press).

What percentage of patients with Brugada syndrome have inducible VF ?



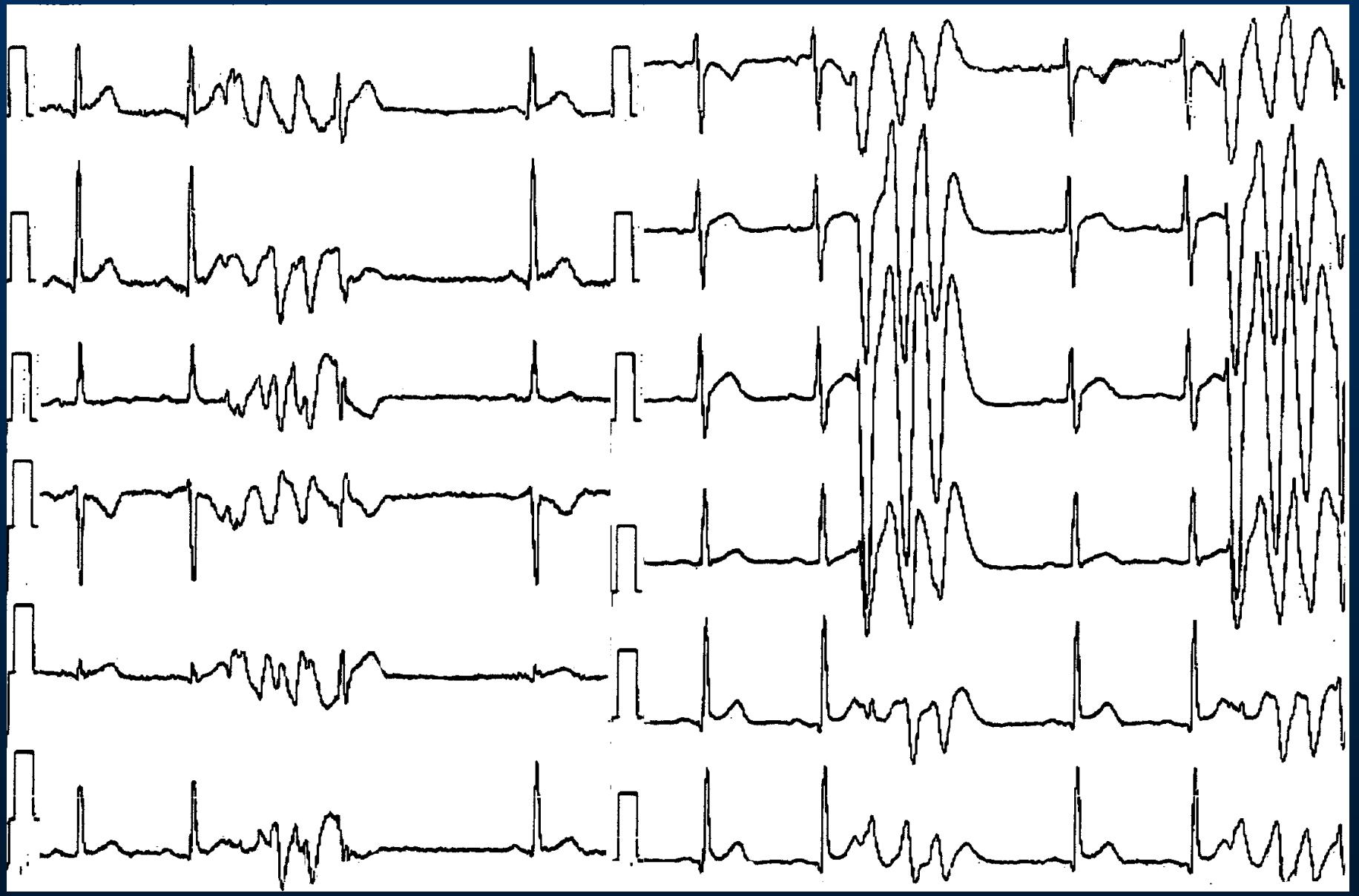
Data from 1217 patients from 15 studies

Value of EPS in patients with Brugada Syndrome and history of cardiac arrest



Meta-Analysis of Worldwide Published Data. M. Paul. *Eur Heart J* 2007 (In Press).

Idiopathic VF is *not* a diagnosis by exclusion.
This *is* idiopathic VF



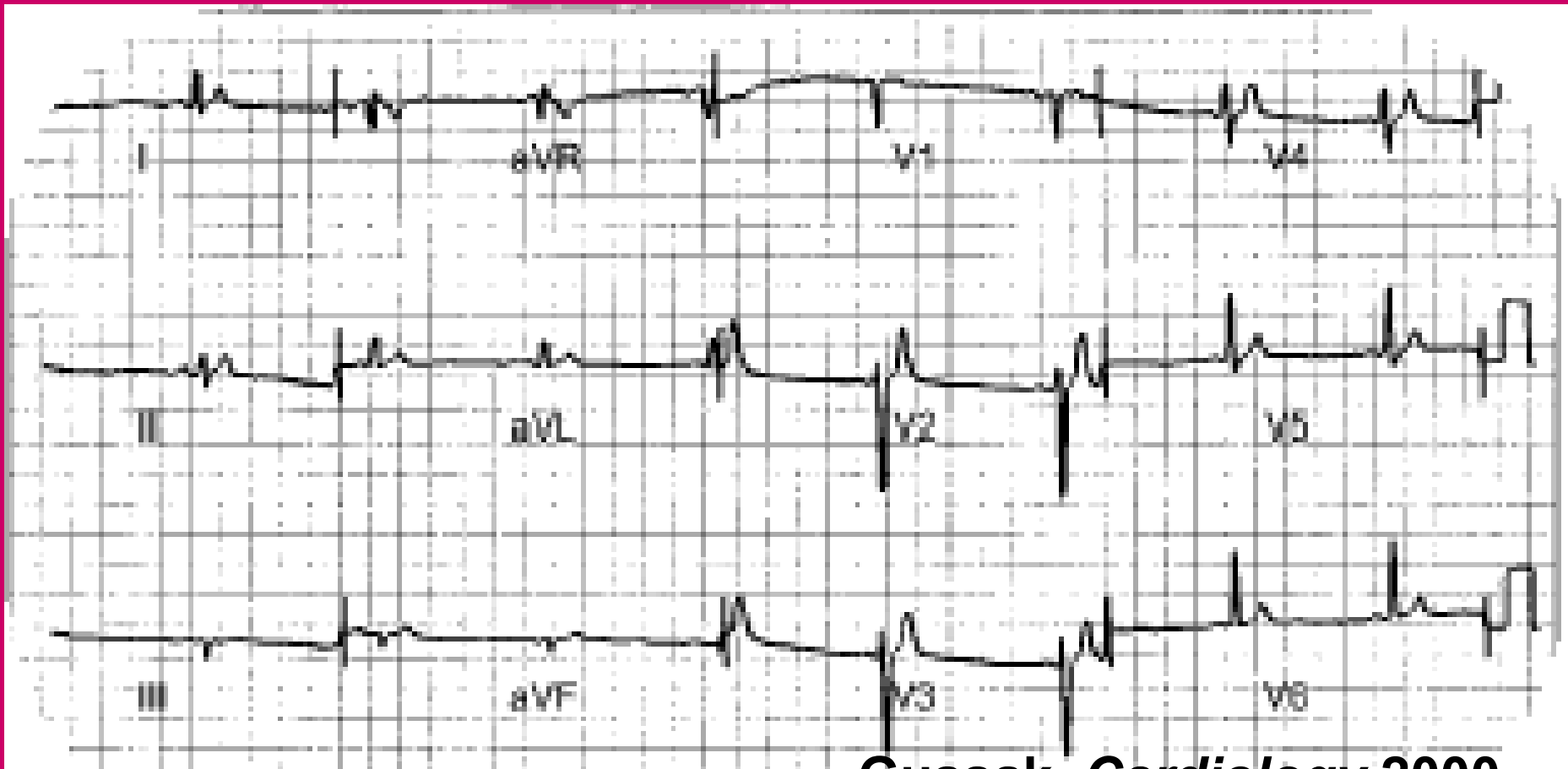
Arrhythmias, Electrophysiology and Electrocardiography

CARDIOLOGY

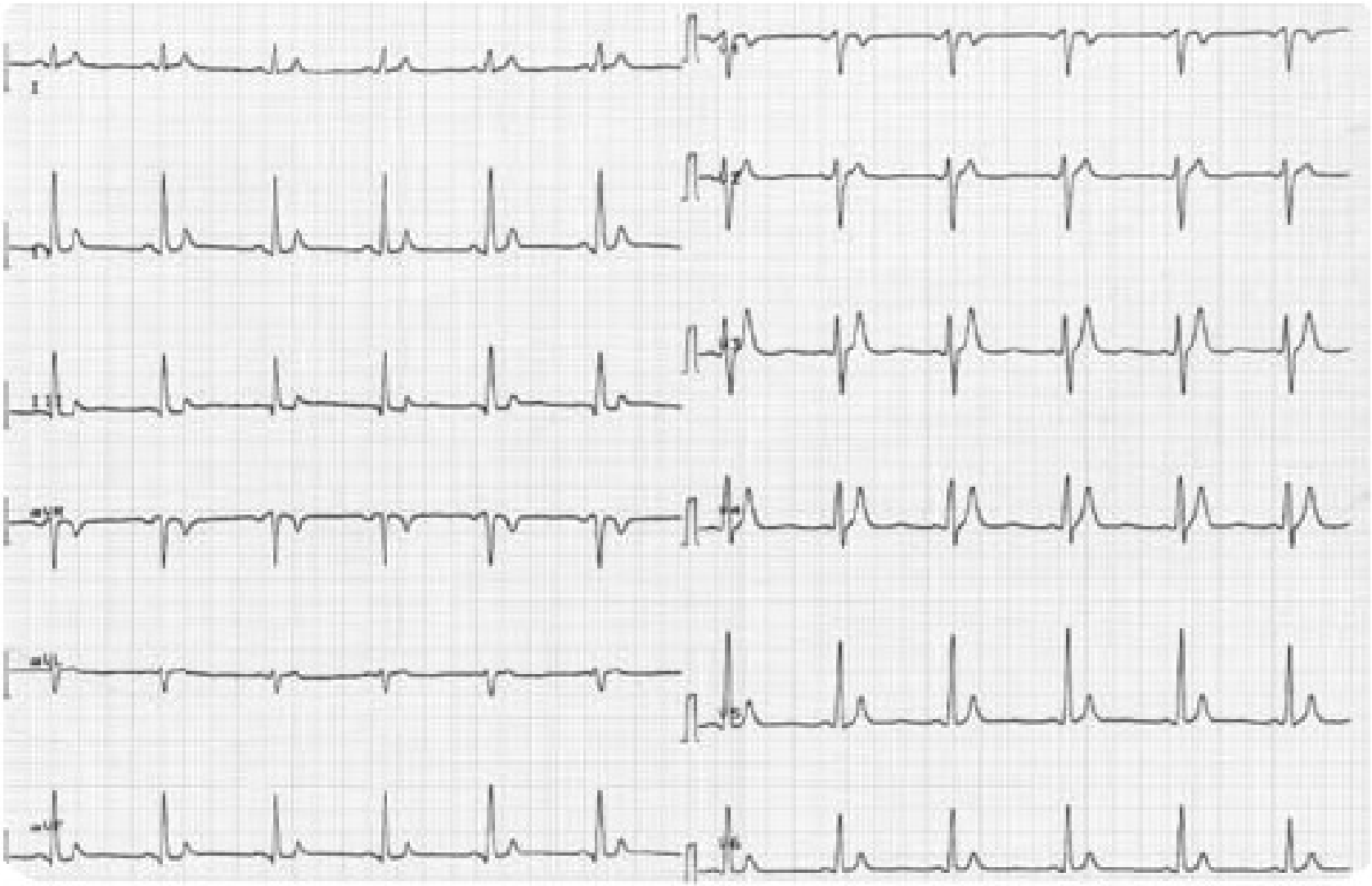
Cardiology 2000;94:99–102

Received: May 22, 2000
Accepted after revision: August 3, 2000

Idiopathic Short QT Interval: A New Clinical Syndrome?



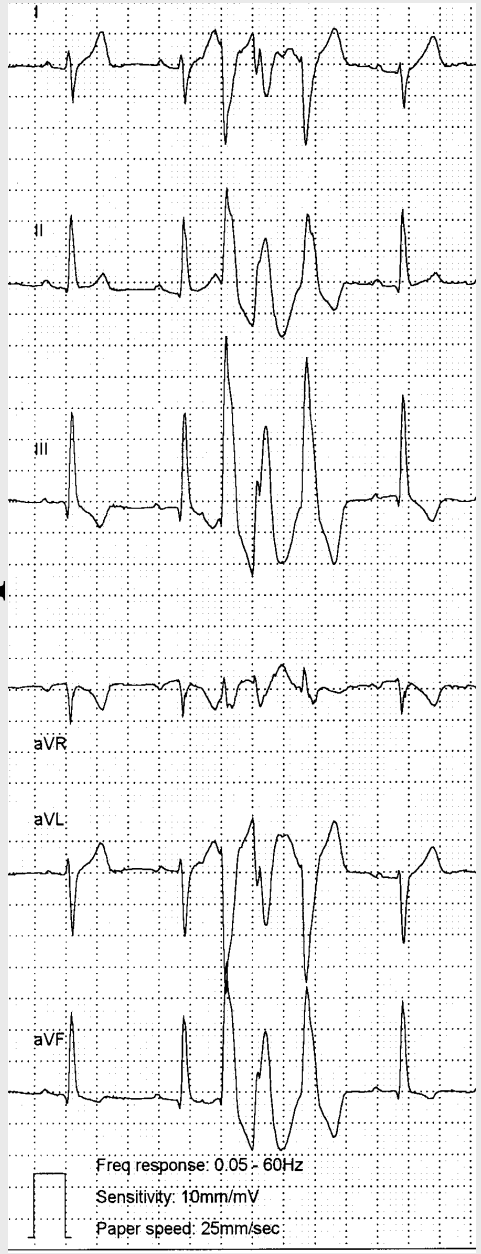
Gussak, *Cardiology* 2000.



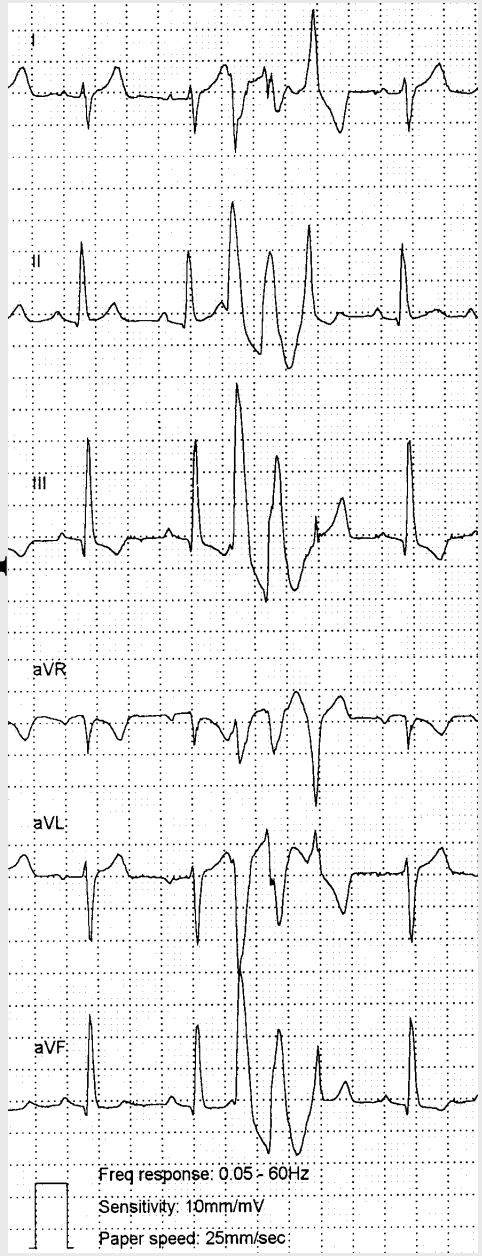
Wolpert, *J Cardiovasc Electrophysiol* 2005

Onset of polymorphic VT in idiopathic VF: Always the same

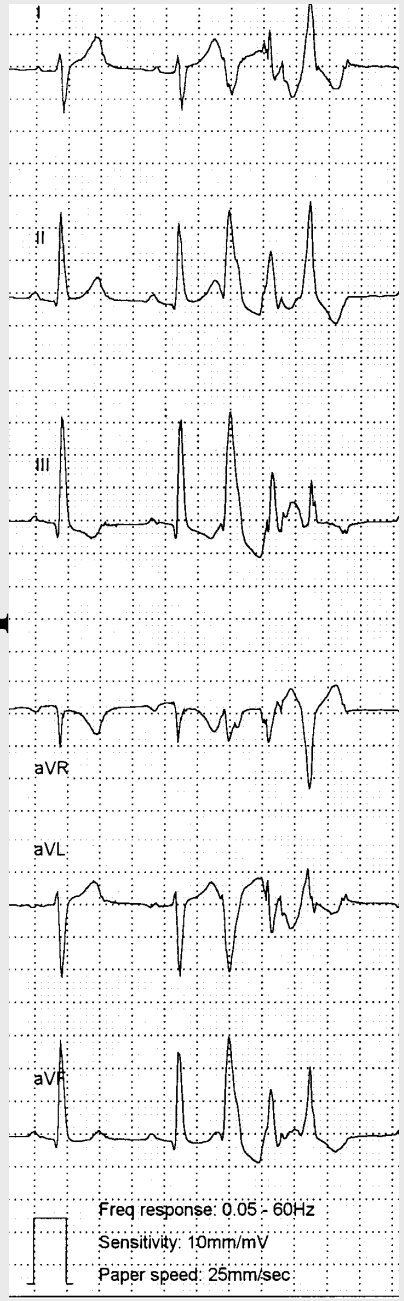
First episode



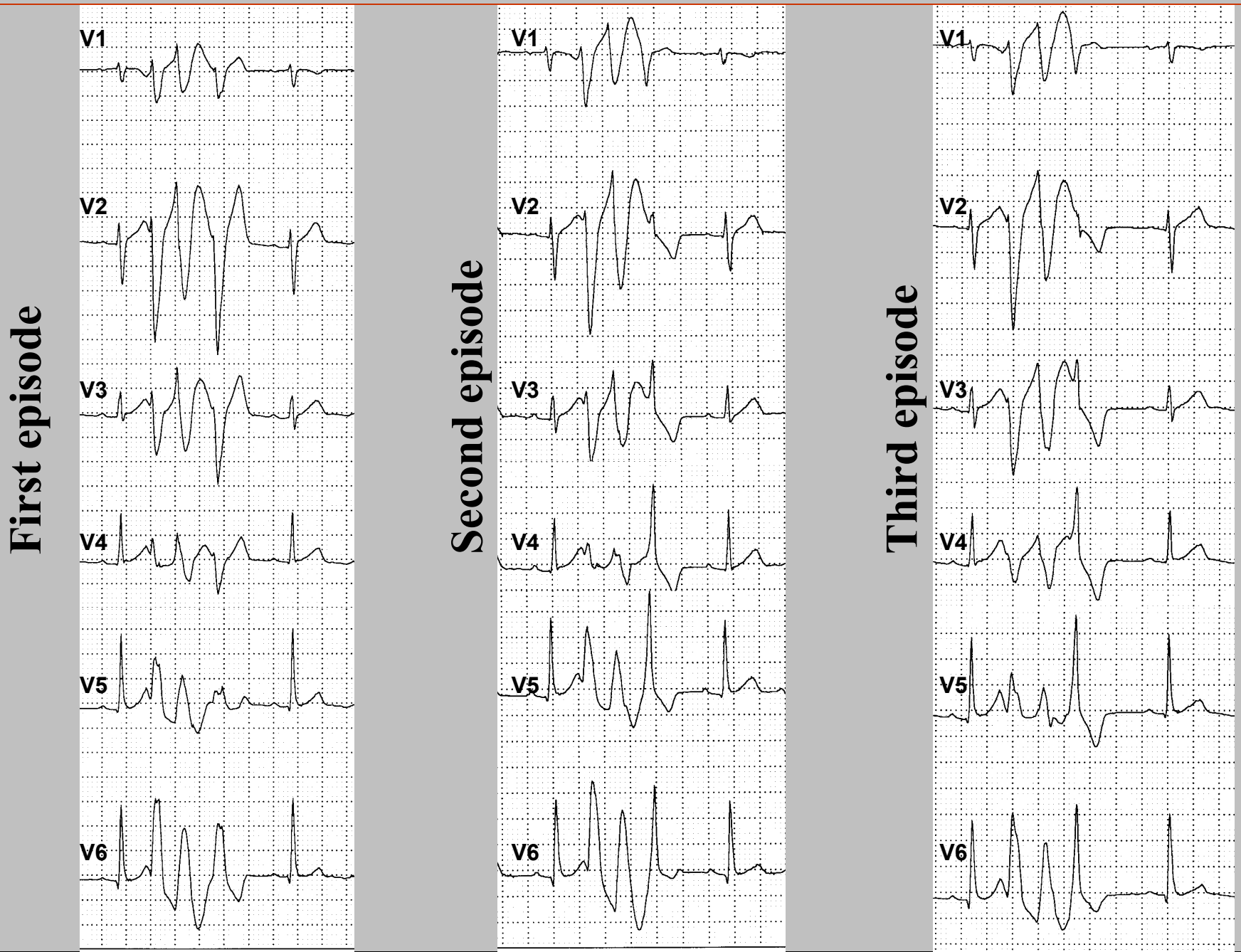
Second episode



Third episode

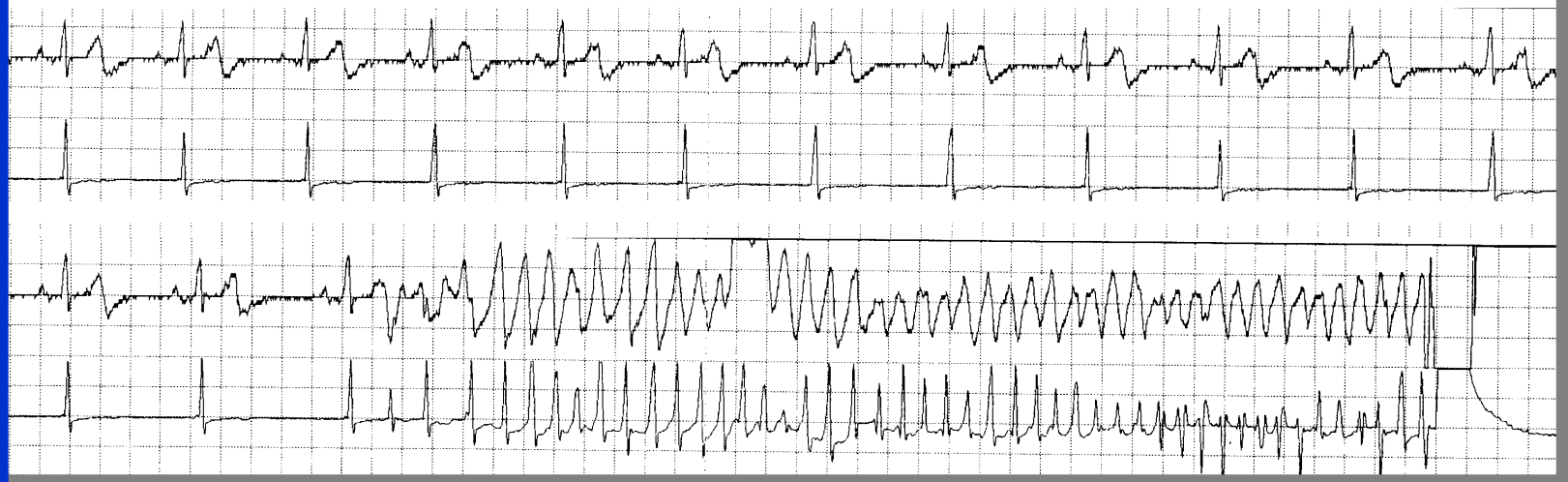


Onset of polymorphic VT in idiopathic VF: Always the same



Onset of VF in idiopathic VF: Always the same

First episode.

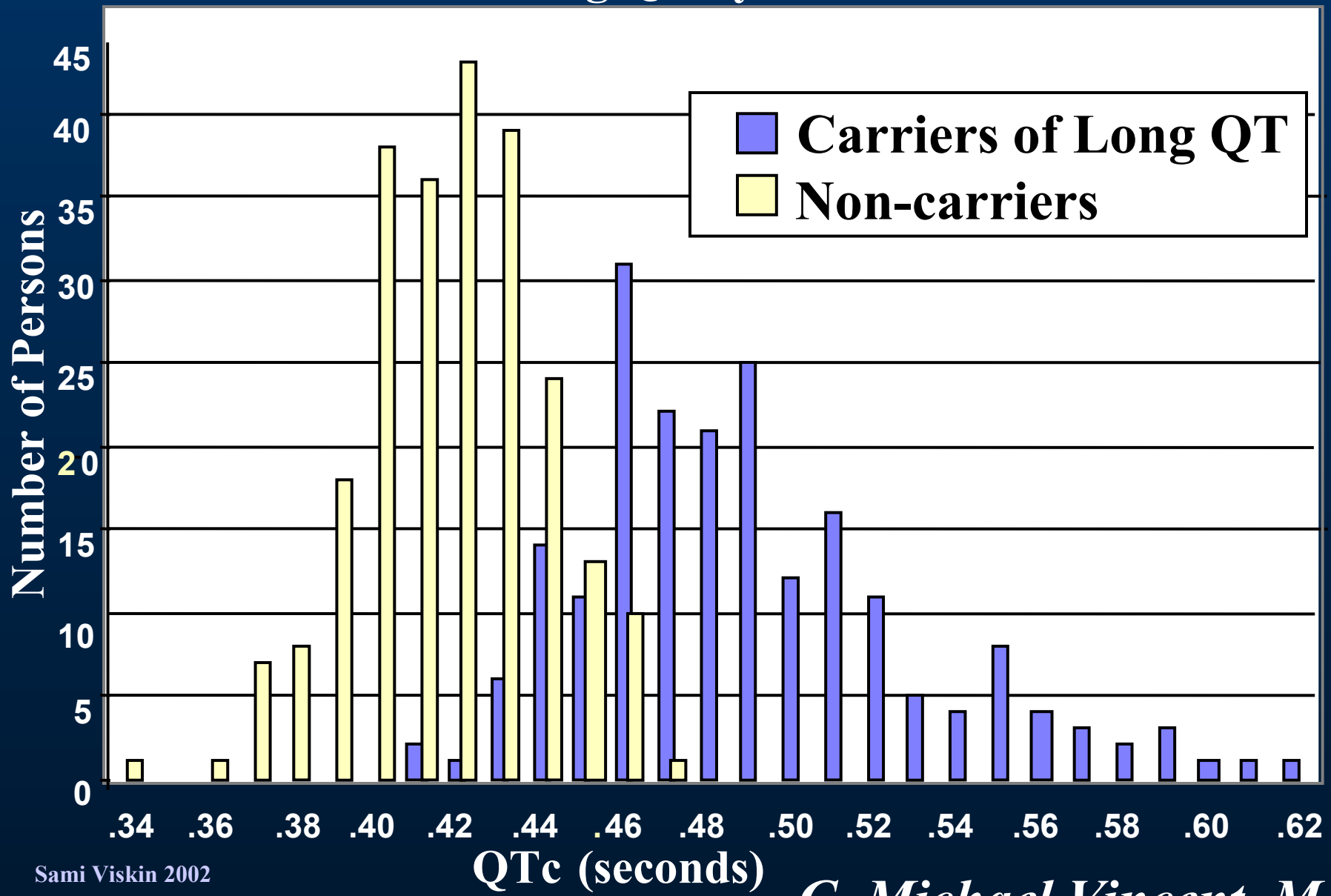


Second episode.

2003

Distribution of QTc Values

208 Gene Carriers of Long QT Syndrome and Non-Carriers.

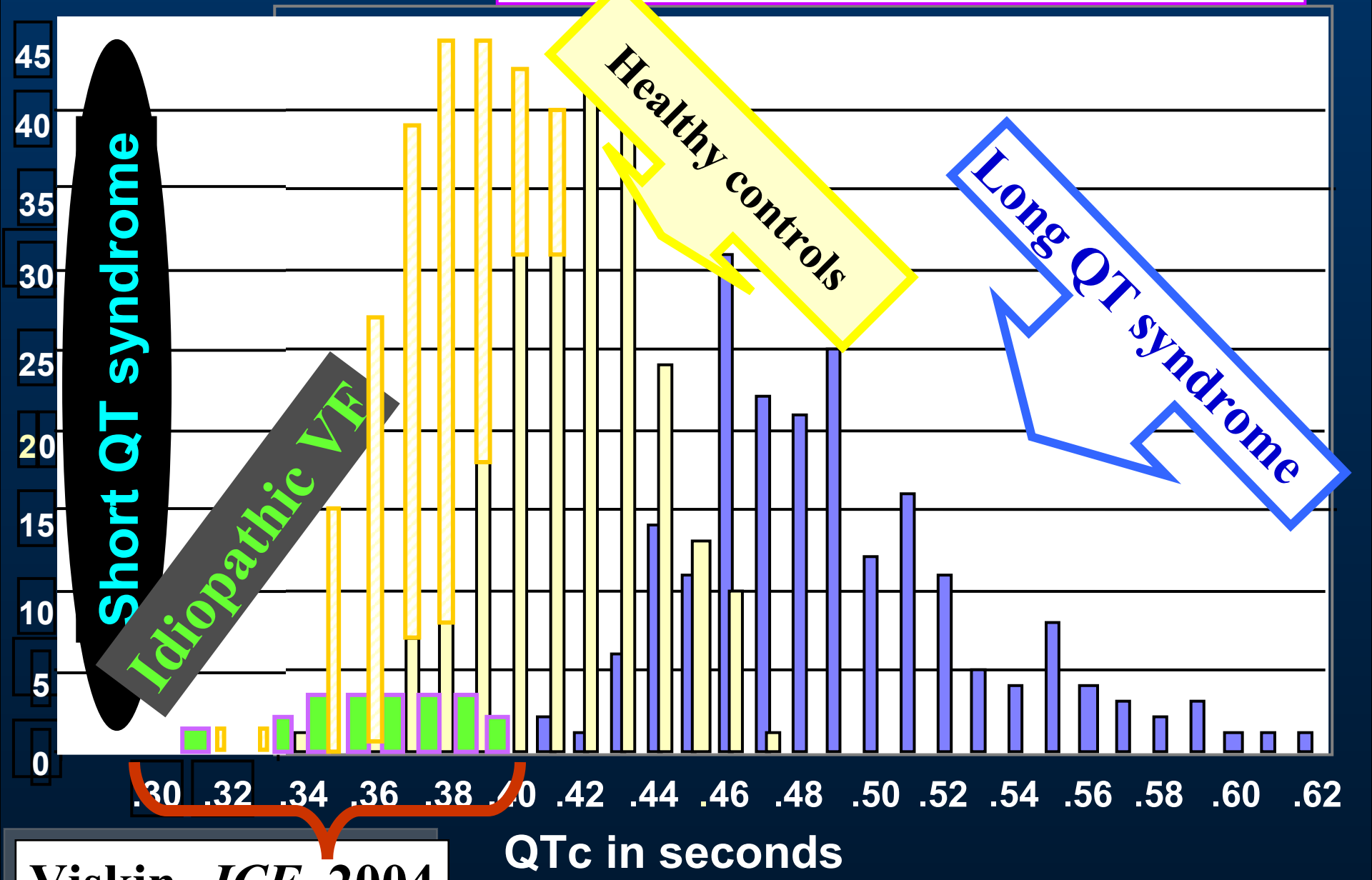


Sami Viskin 2002

G. Michael Vincent, M.D.

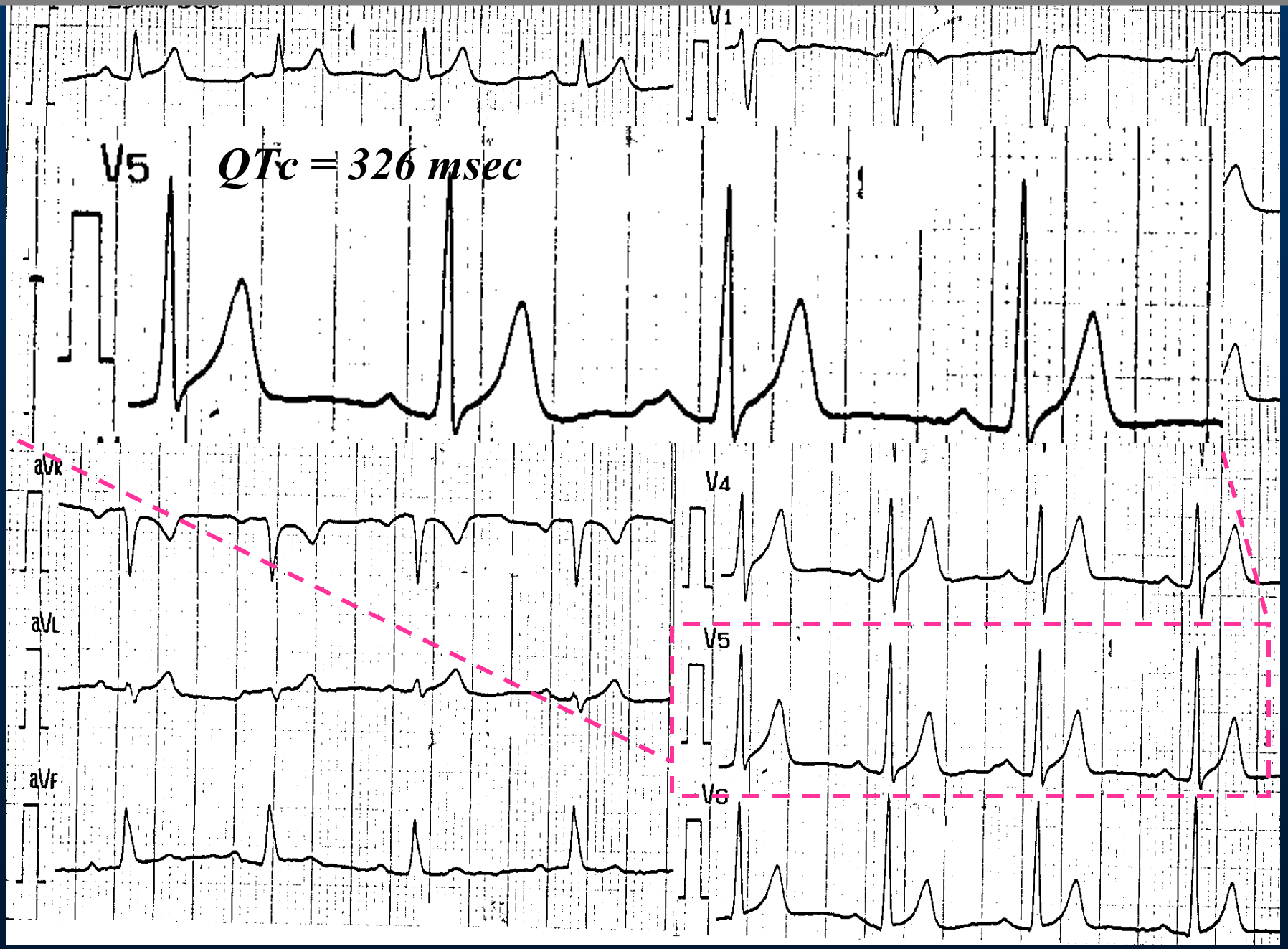
Present study

Data of Michael G. Vincent on Carriers and Non-Carriers of Long QT syndrome



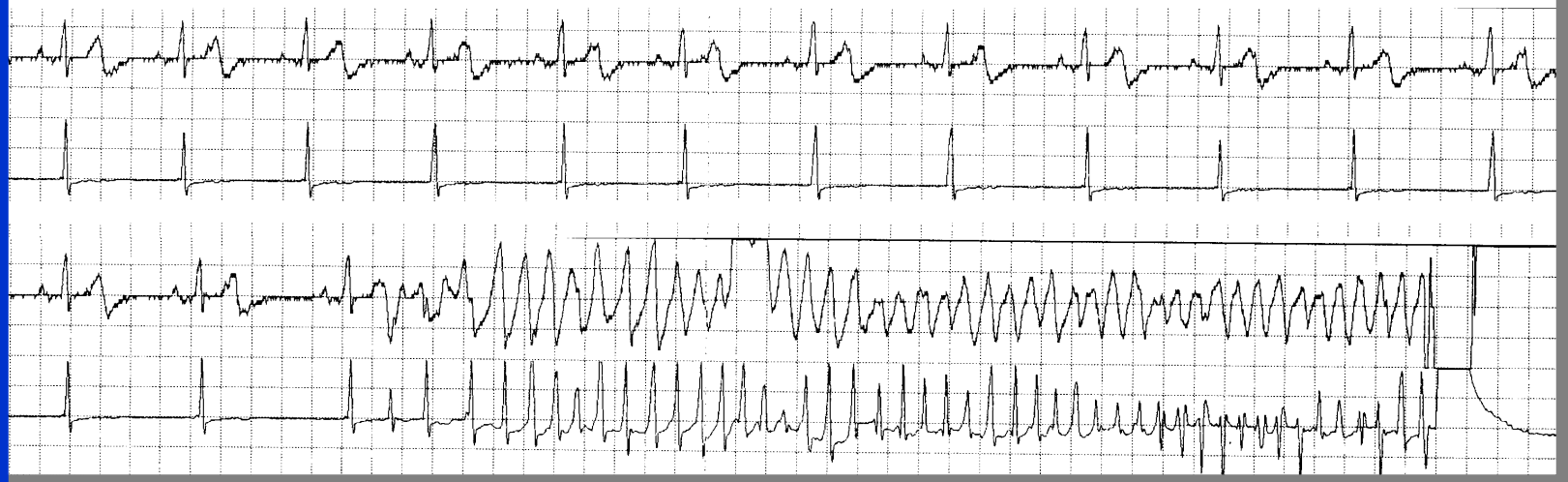
Viskin, *JCE* 2004

Idiopathic VF: Male 19 years, QTc = 326 msec (310 – 349 msec)

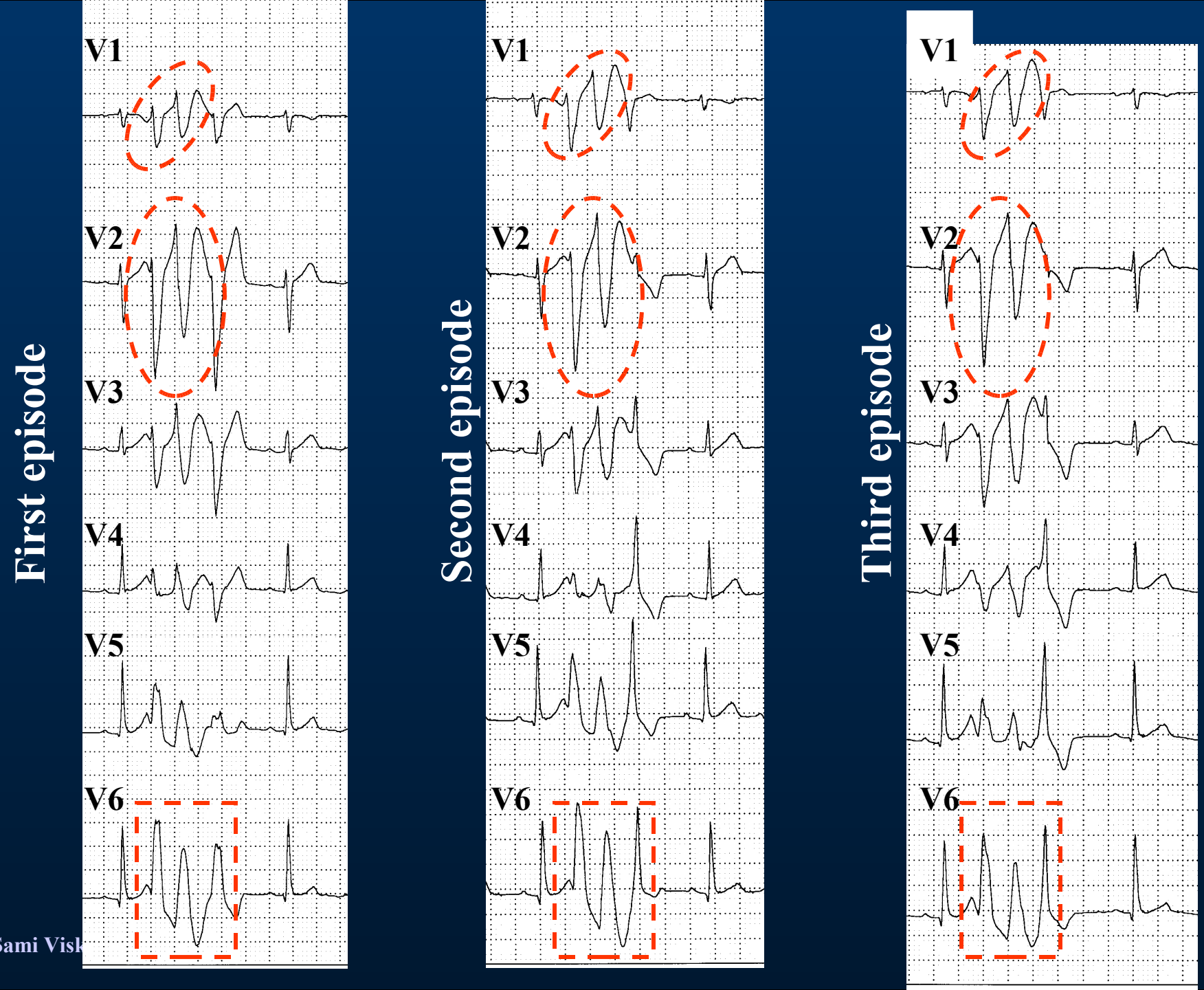


Onset of VF in idiopathic VF: Always the same

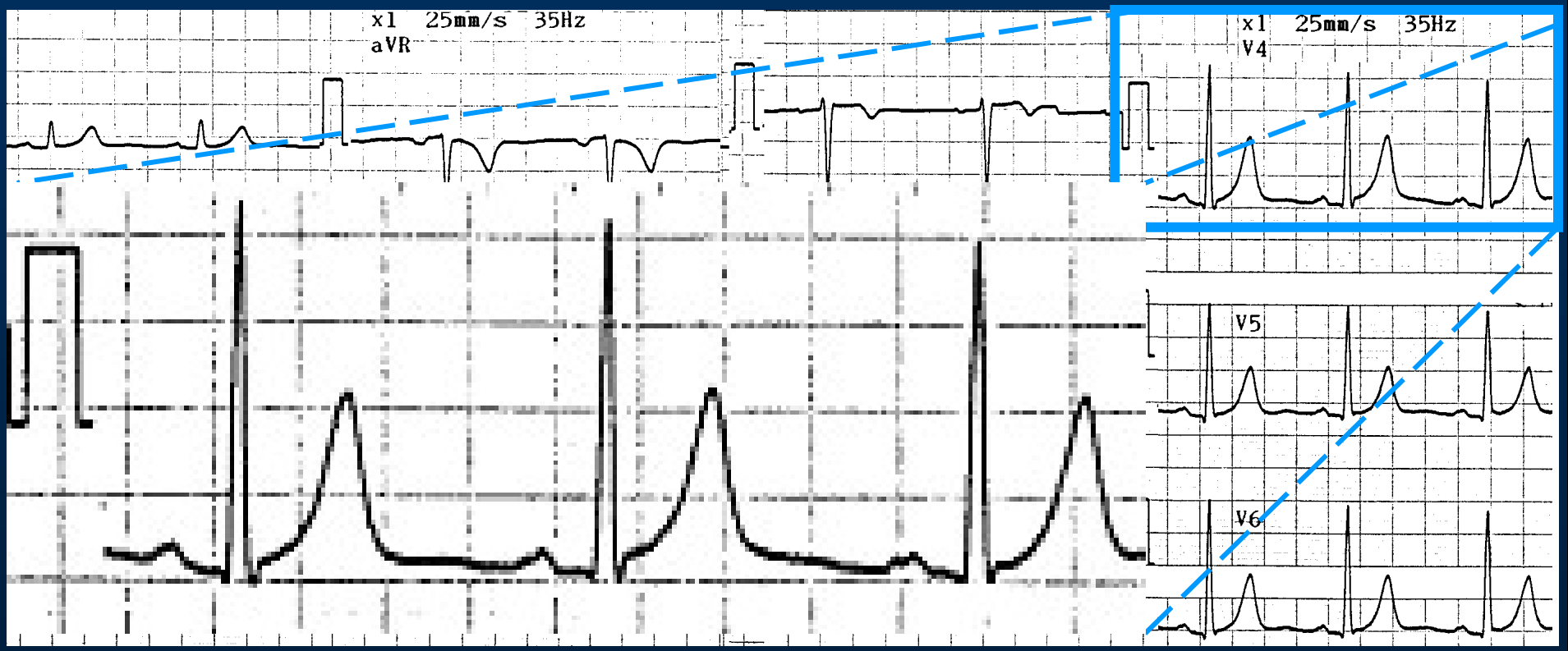
First episode.



Second episode.


First episode
V1
V2
V3
V4
V5
V6
Second episode
V1
V2
V3
V4
V5
V6
Third episode
V1
V2
V3
V4
V5
V6

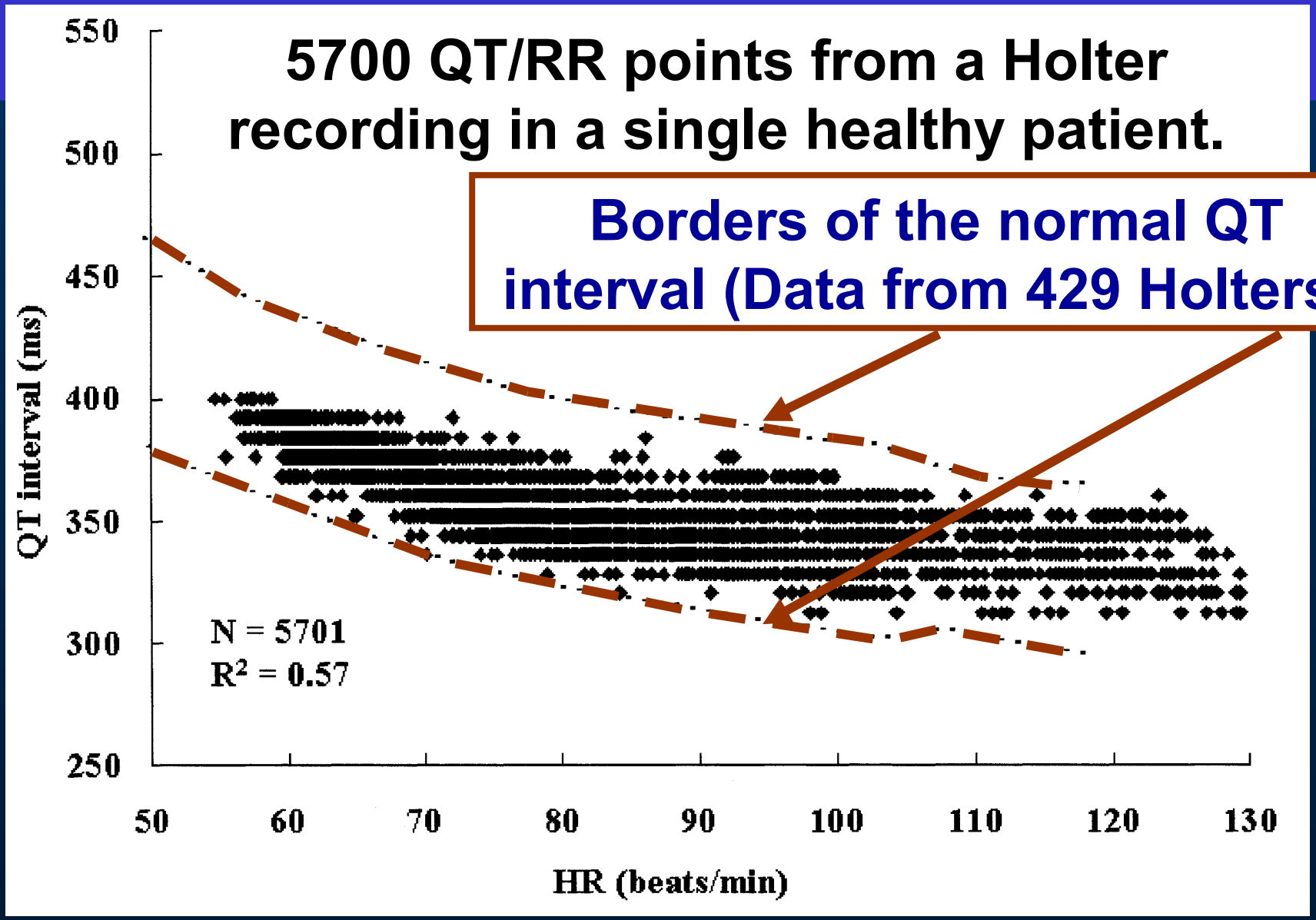
Relatively short QT in a healthy control.



R-R = 910 – 980 msec; QT = 360- 370 msec; QTc =364 – 377 msec

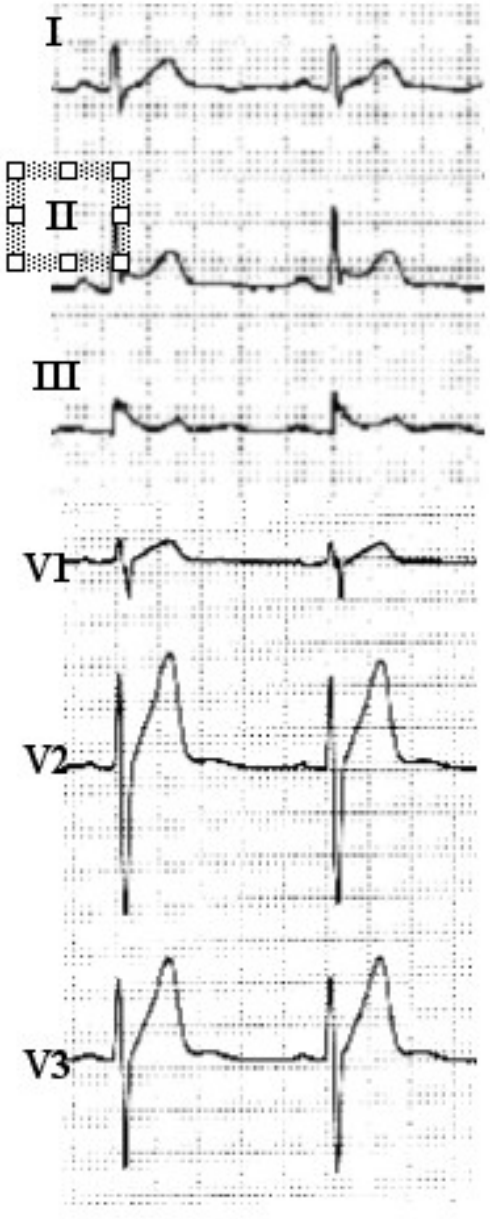
Sami Viskin 2002

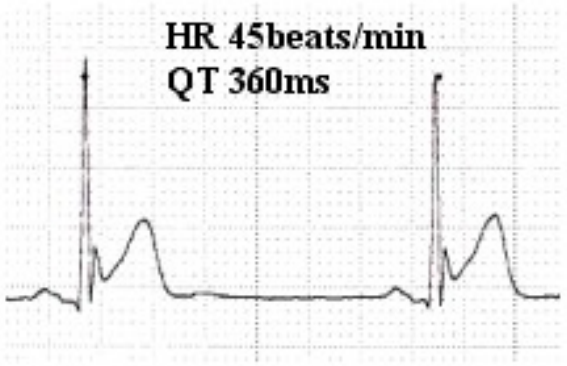
QT interval at different heart rates

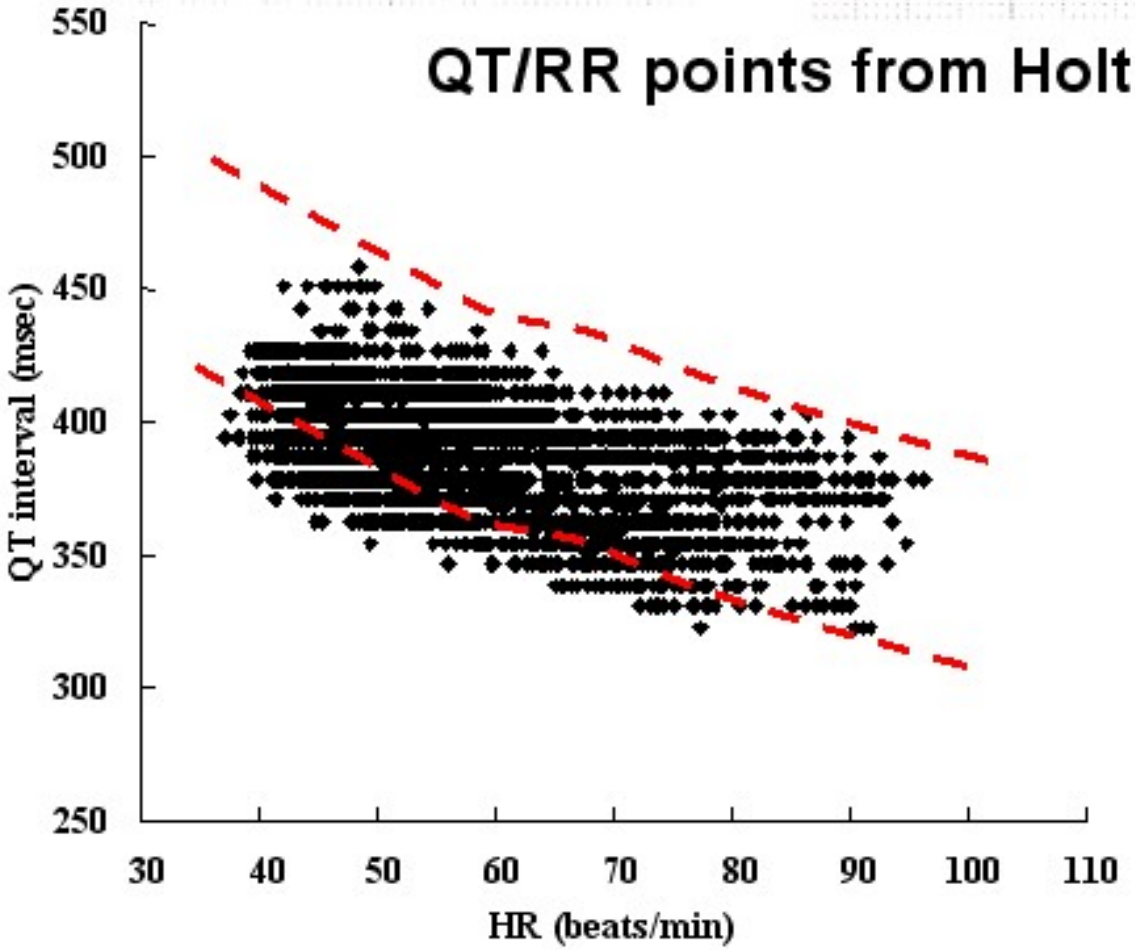


Sugao, Fujiki. *Heart* 2005.

Male, 33 years old.
Idiopathic VF



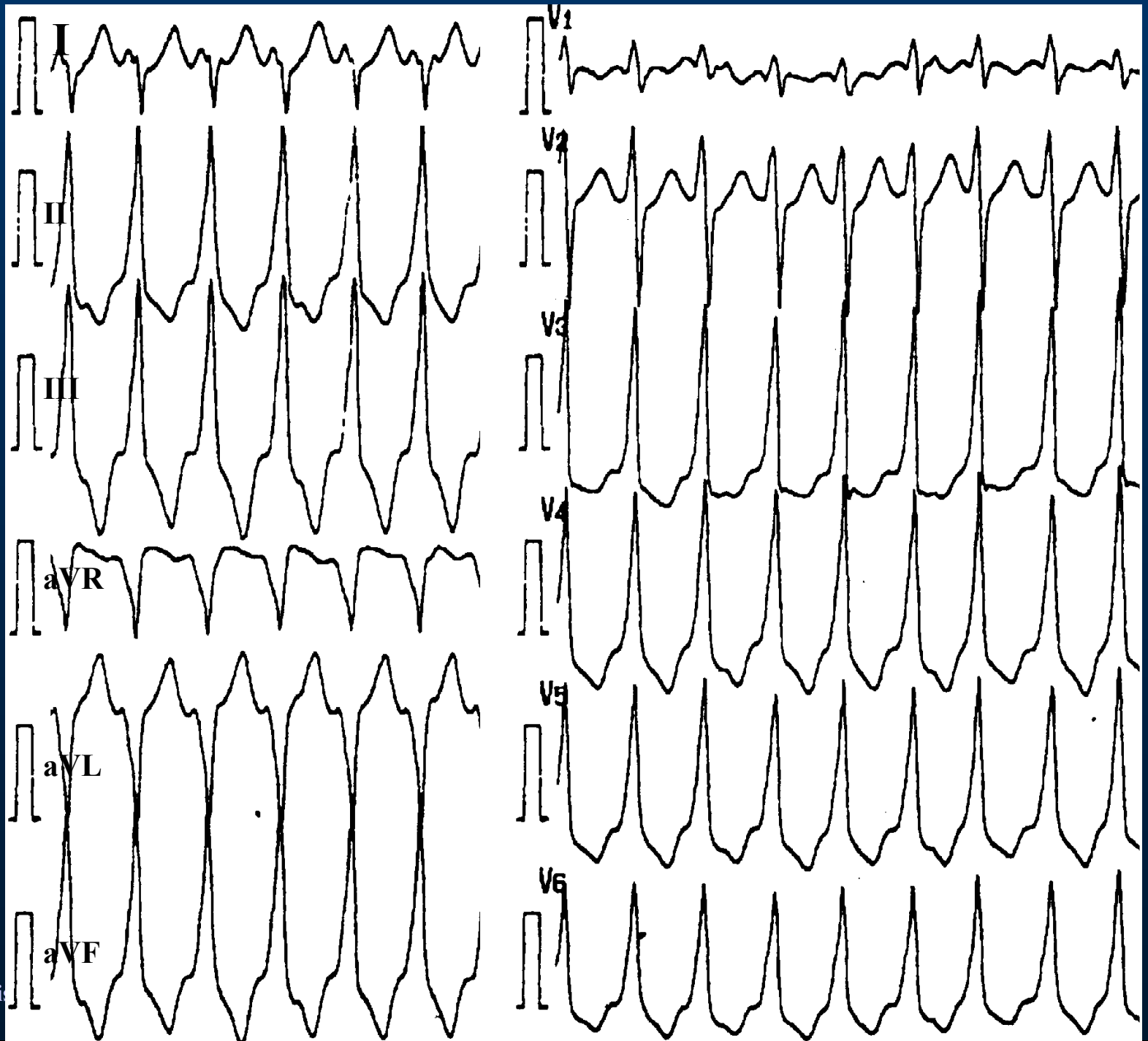


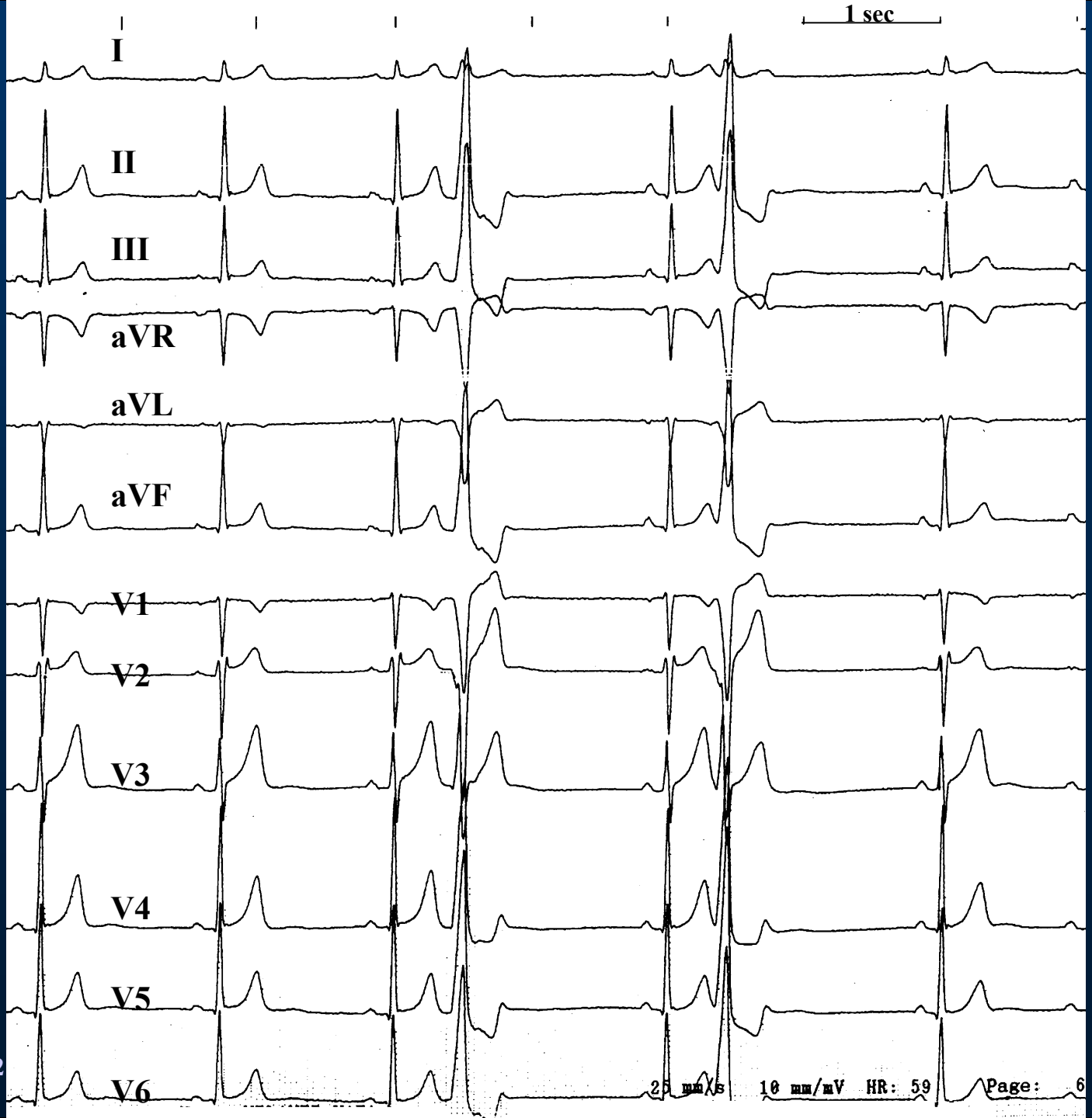


Akira Fujiki, personal communication, 2005.

The evolving etceteras...

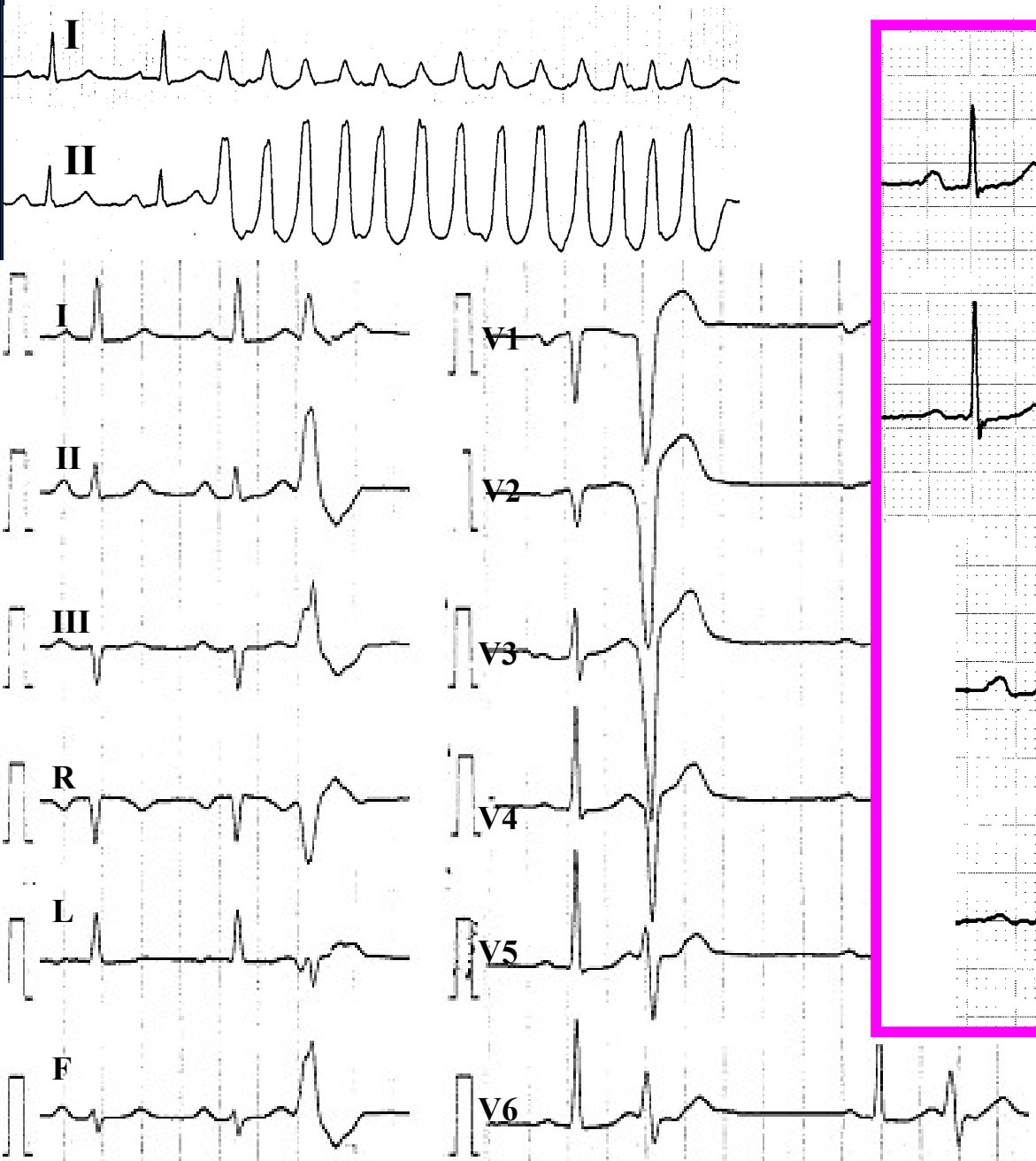
Sami Viskin 2002

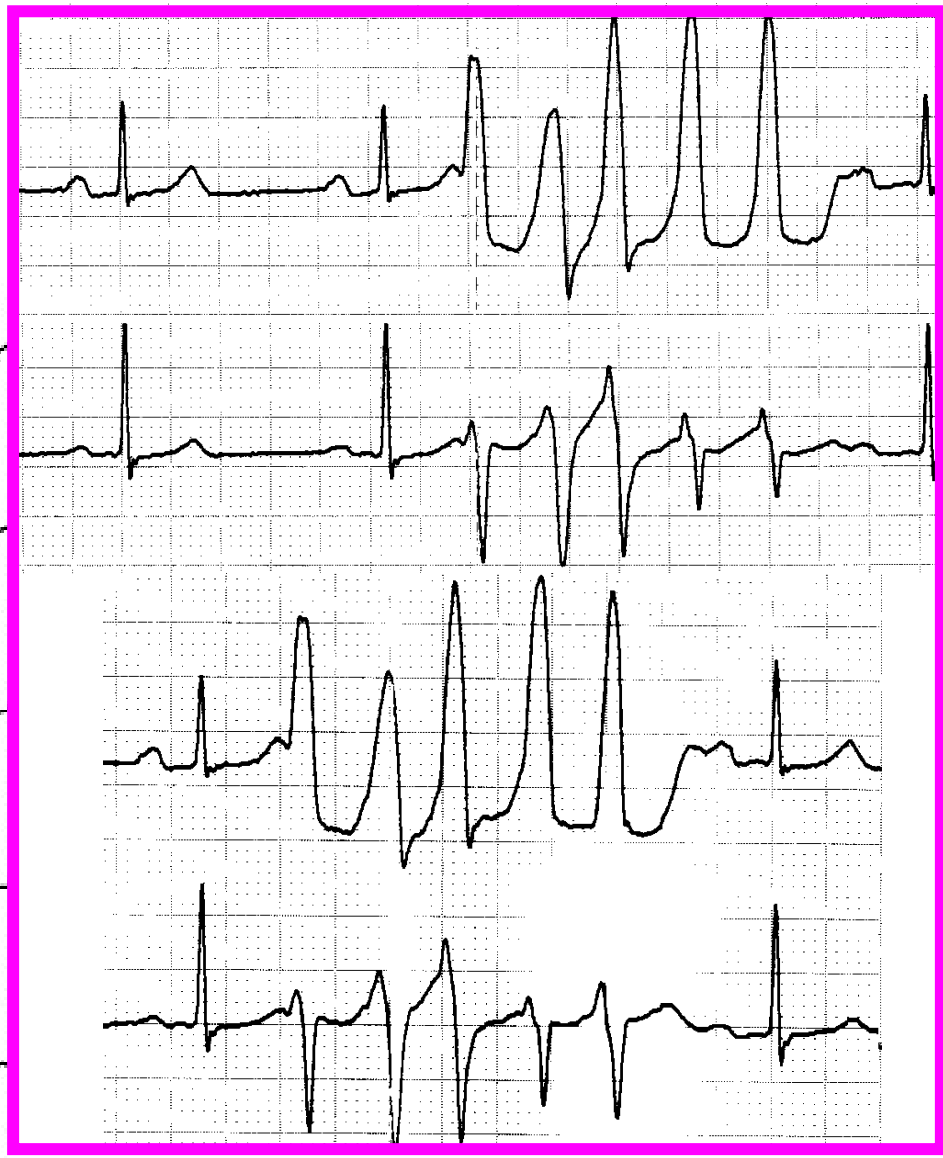

I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6



Sami Viskin 2002

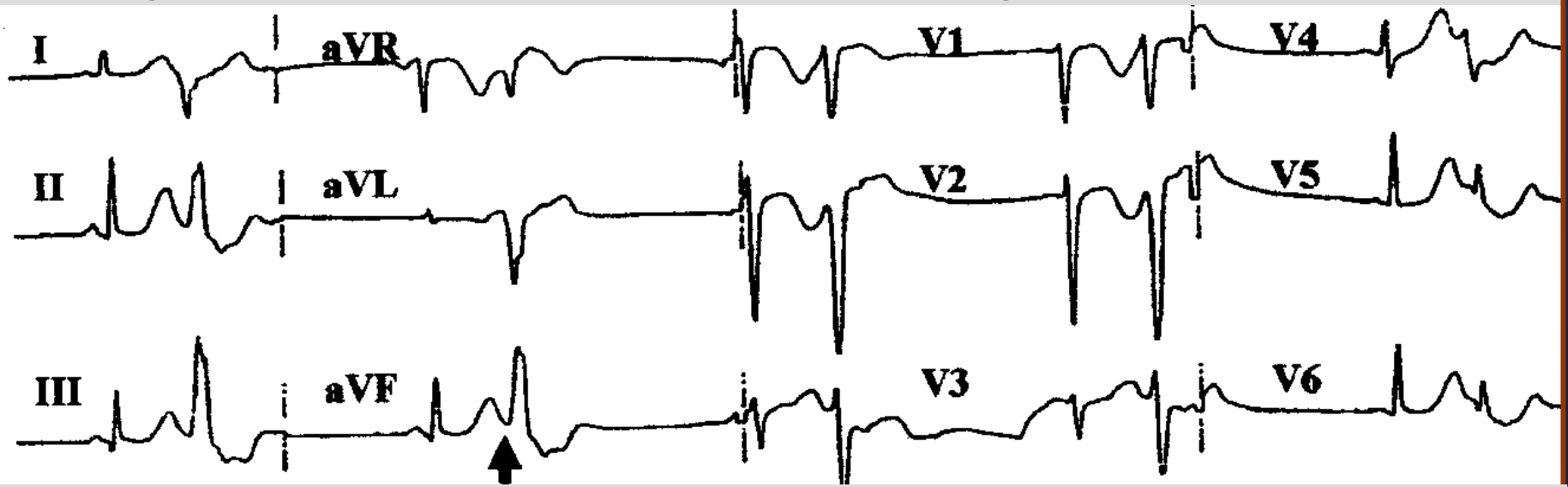
The “short-coupled variant” of RVOT-VT



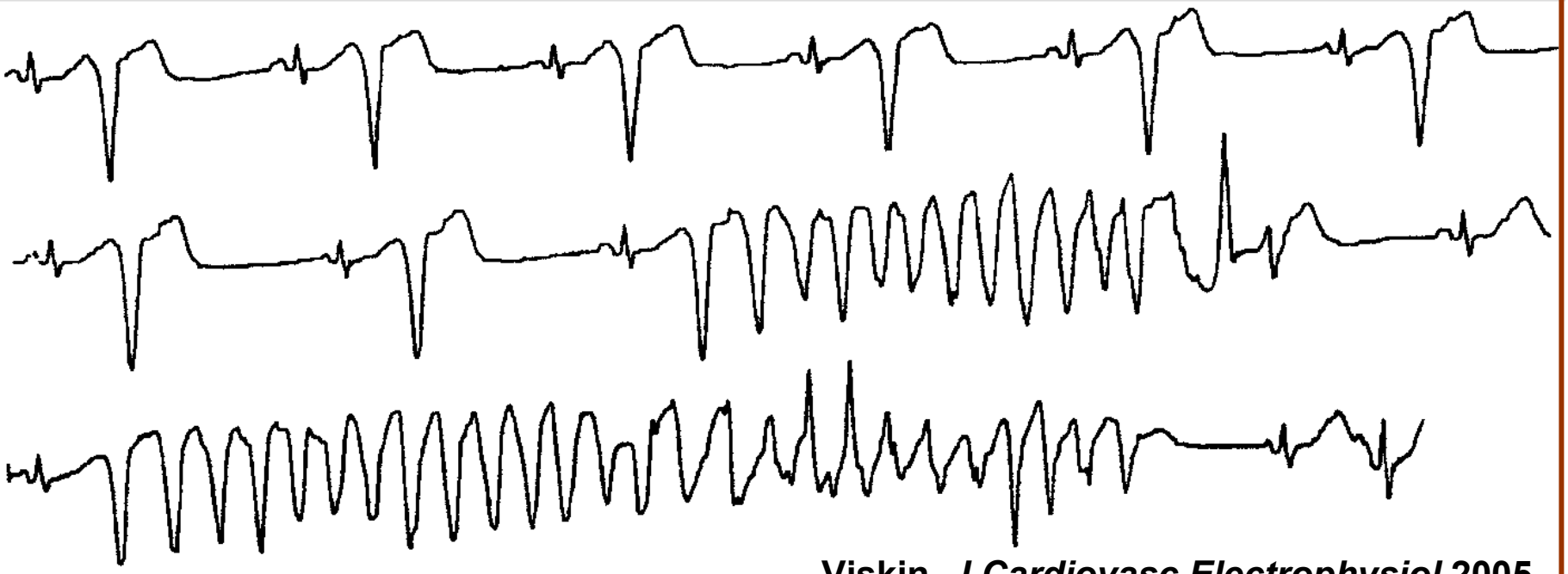


Viskin, *JCE 2005.*

A 47 years-old woman had this for 15 years…….

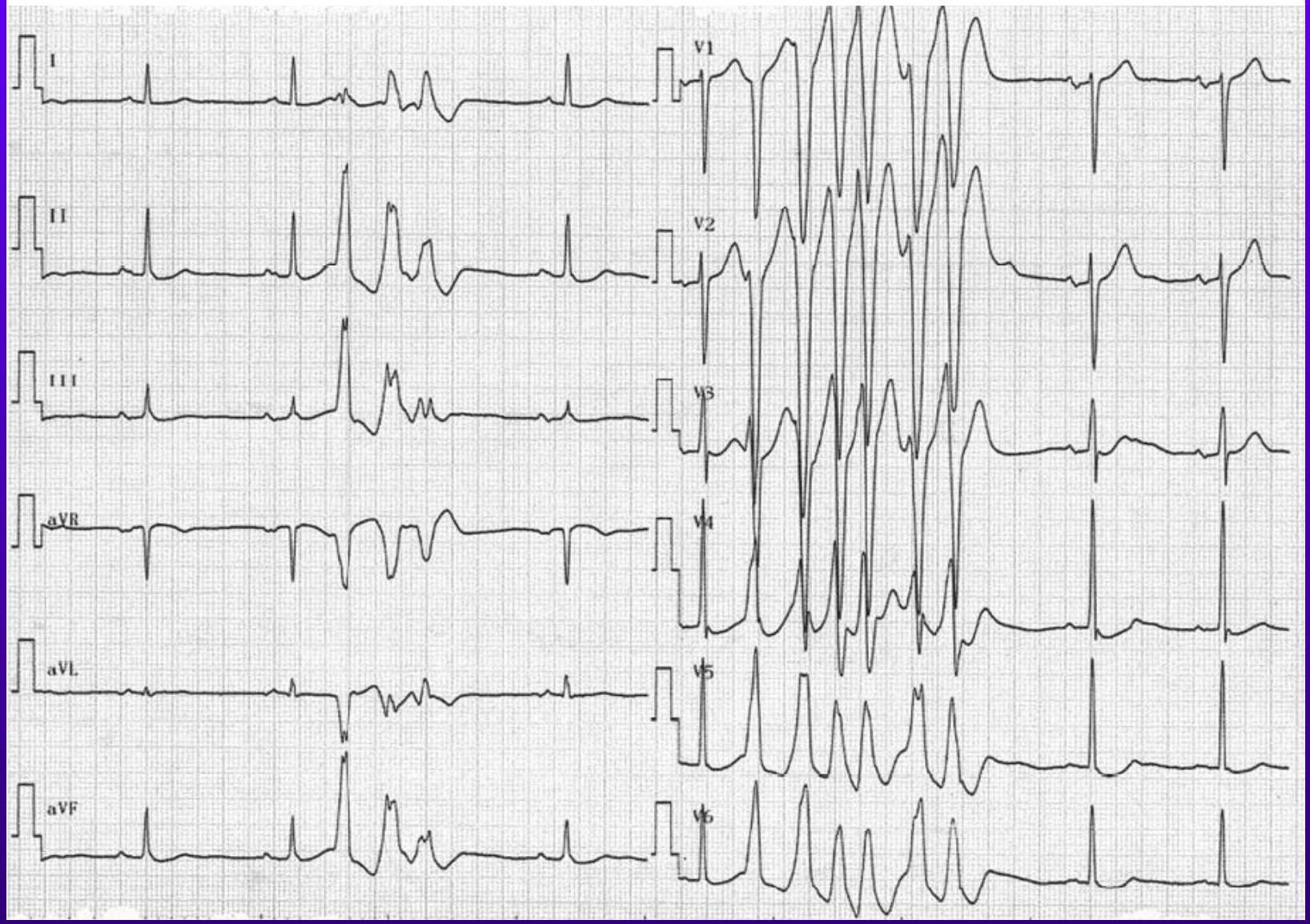


….and then had this:



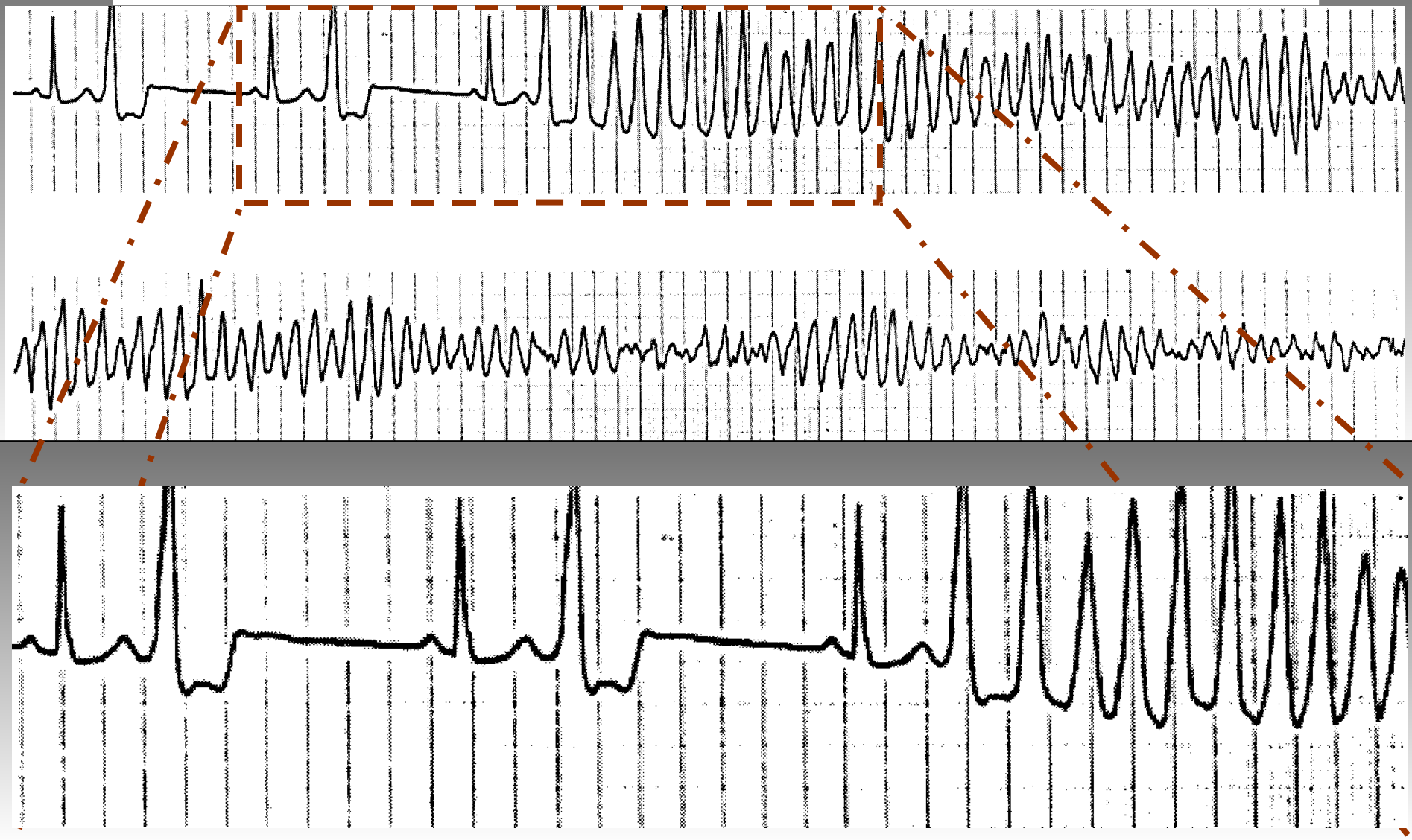
Viskin, *J Cardiovasc Electrophysiol* 2005

Malignant Polymorphic VT originating from the RVOT *(n*=16 out of 101 RVOT referred for RF ablation).



Noda, Shimizu, et.al. *JACC*. 2005

Malignant Polymorphic VT originating from the RVOT.

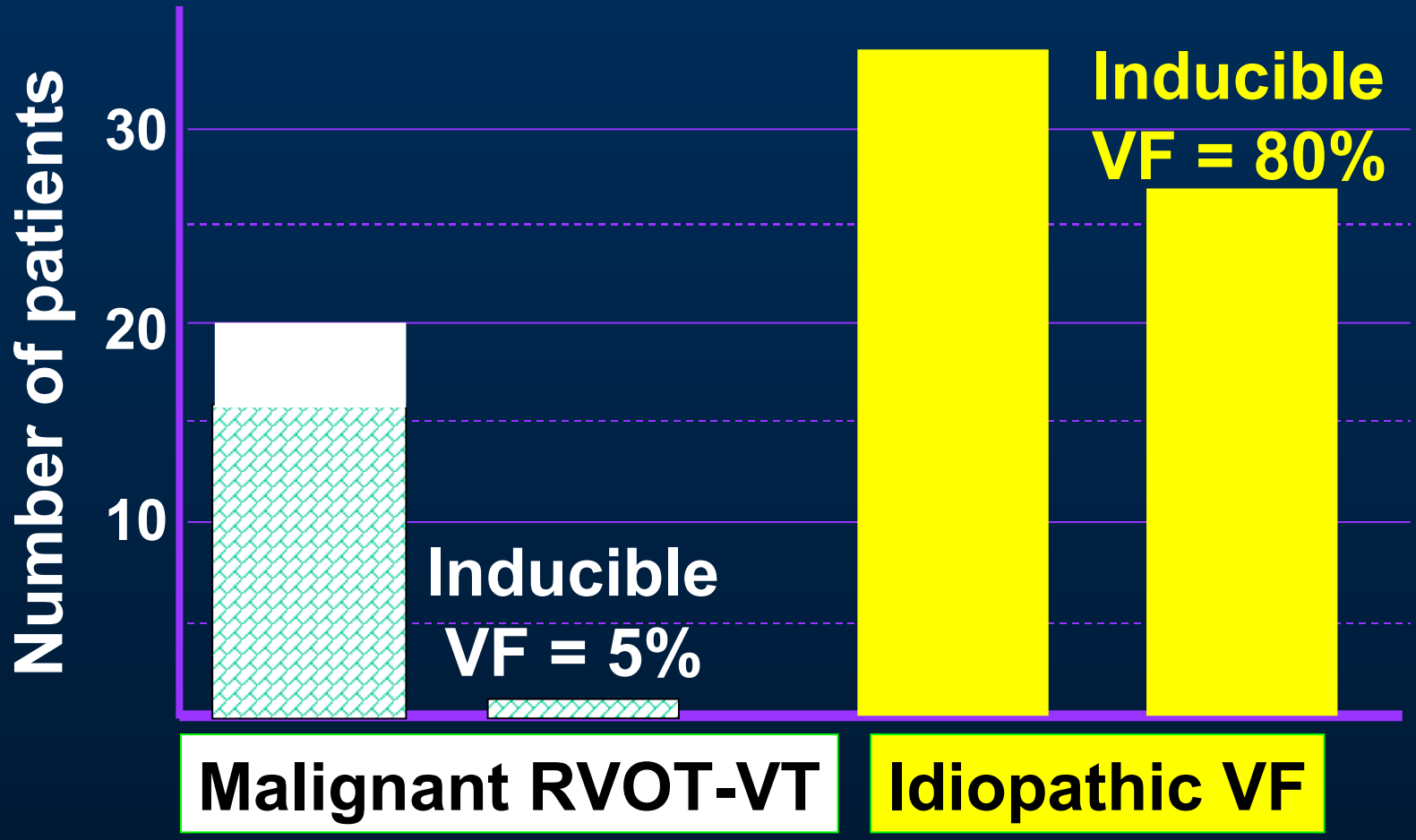


Sami Viskin 2002

Noda, Shimizu, et.al. *JACC*. 2005

How different is the Malignant RVOT-VT from Idiopathic VF ?

How many have inducible VF at EPS?



Noda, Shimizu, *JACC 2005*

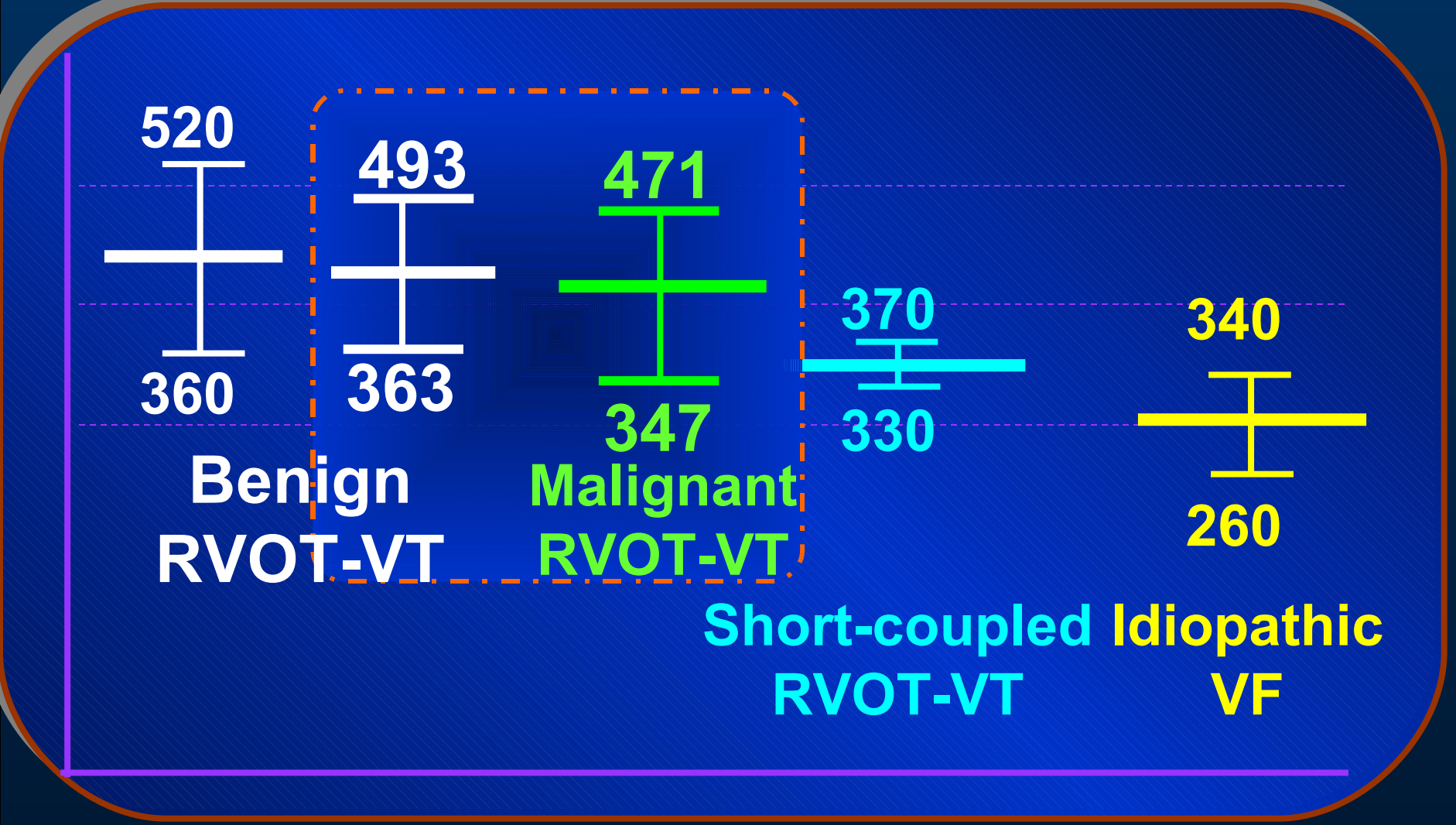
Belhassen, Viskin, *JCE 1999*

How different is the Malignant RVOT-VT from Idiopathic Monomorphic VT ?

	Benign RVOT *(n=16)*	Malignant RVOT *(n=85)*	*P value*
Gender	71%	66%	*NS*
Age	43 ± 14	39 ± 10	*NS*
Symptoms duration	80 ± 100 months	80 ± 100 months	*NS*
Syncope	18%	69%	*0.001*

Noda, Shimizu, et.al. *JACC*. 2005

Coupling interval of the ventricular extrasystoles (Mean ± S.D. in msec.)



Sami Viskin 2002

Noda, Shimizu, *JACC* 2005

Viskin, *JCE* 2005

Primary electrical disease:

Long QT syndromes.

CPVT.

Brugada syndrome

Emerging Syndromes

Benign RVOT-VT

Malignant RVOT-VT

Idiopathic VF

Short QT Syndrome

Short-coupled RVOT-VT


Thank you
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Is idiopathic ventricular fibrillation a *short QT* syndrome?

Sami Viskin, David Zeltser, Maya Ish-Shalom, Amos Katz, Michael Glikson, Dan Justo, Dorit Tekes-Manova and Bernard Belhassen.

Tel Aviv Sourasky-Medical Center, Tel Hashomer Sheba Medical Center and Sackler-School of Medicine, Tel Aviv University; Soroka University Medical Center and Ben-Gurion University and the Staff Periodic Examination Center, Israeli Defense Forces, Israel.

Presenter Disclosure Information

Consultant to Guidant

NASPE Heart Rhythm Society

1992

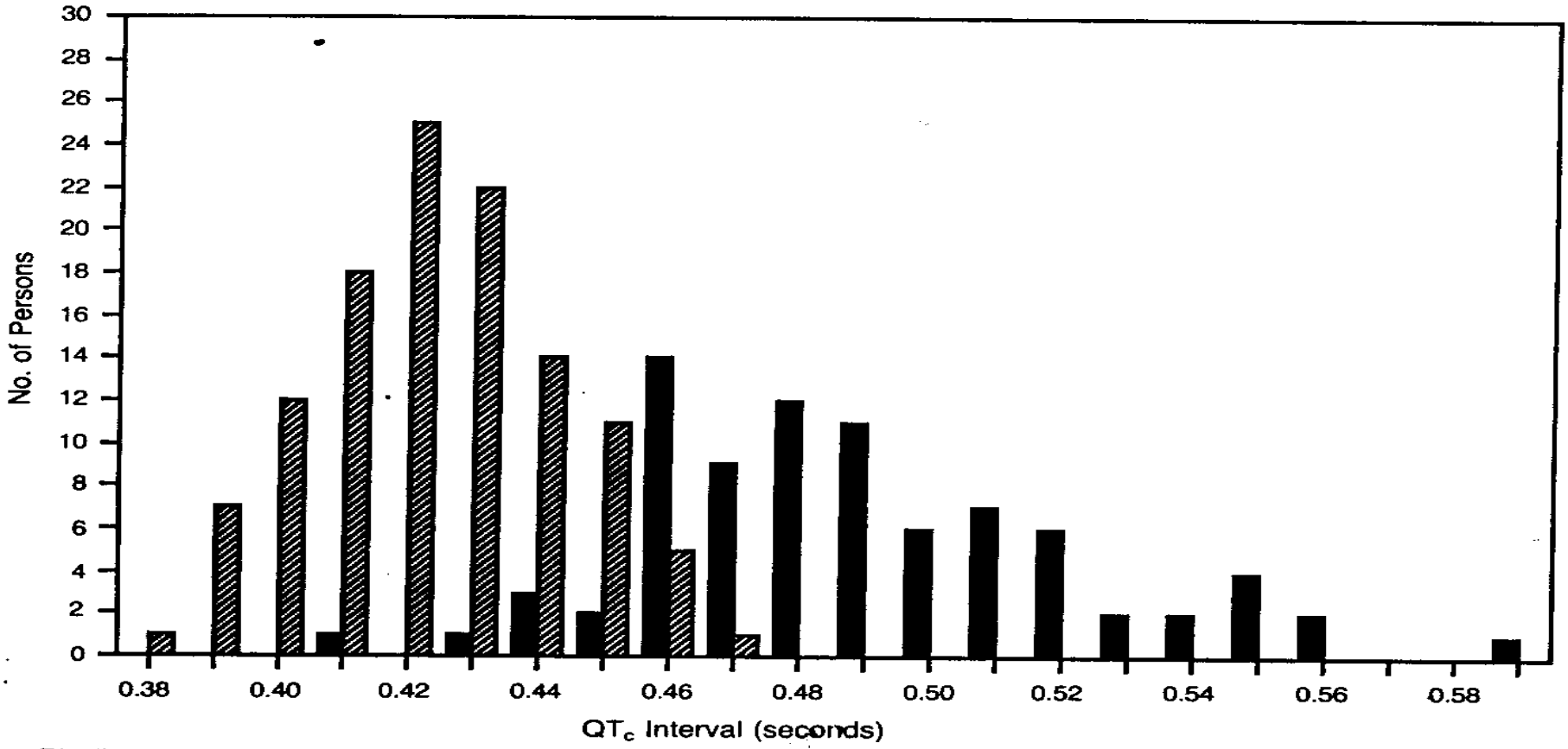
THE NEW ENGLAND JOURNAL OF MEDICINE

THE SPECTRUM OF SYMPTOMS AND QT INTERVALS IN CARRIERS OF THE GENE FOR THE LONG-QT SYNDROME

G. MICHAEL VINCENT, M.D., KATHERINE W. TIMOTHY, B.S., MARK LEPPERT, PH.D., AND MARK KEATING, M.D.

Abstract *Background.* The familial long-QT syndrome is characterized by a prolonged QT interval on the electro-

QT_c intervals of the gene carriers ranged from 0.41 to 0.59 second (mean, 0.49). By contrast, the QT intervals of the

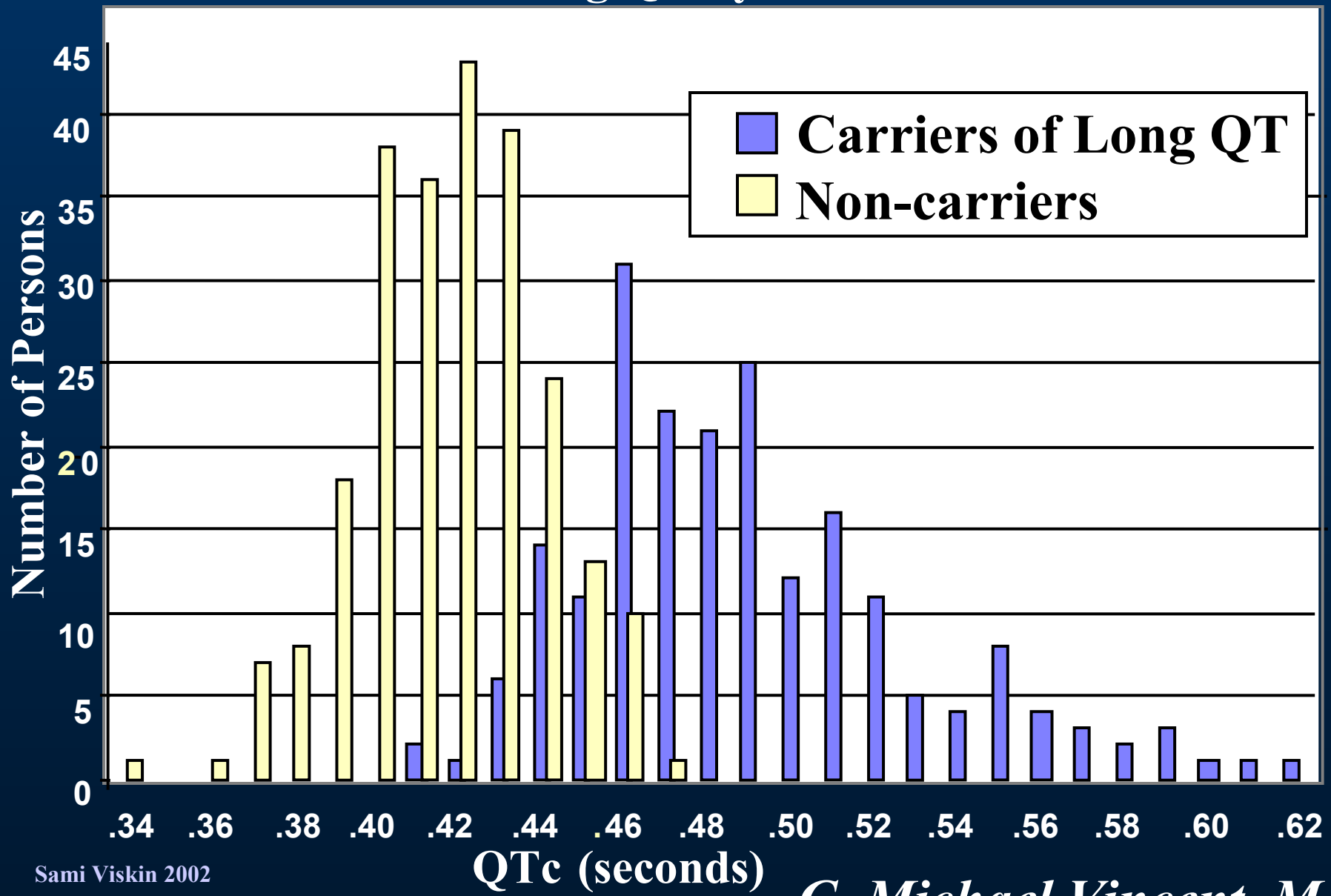


Distribution of QT_c Intervals among Carriers (Solid Bars) and Noncarriers (Hatched Bars) of the Long-QT Gene in All Three Kindreds Studied.

2003

Distribution of QTc Values

208 Gene Carriers of Long QT Syndrome and Non-Carriers.



Sami Viskin 2002

G. Michael Vincent, M.D.

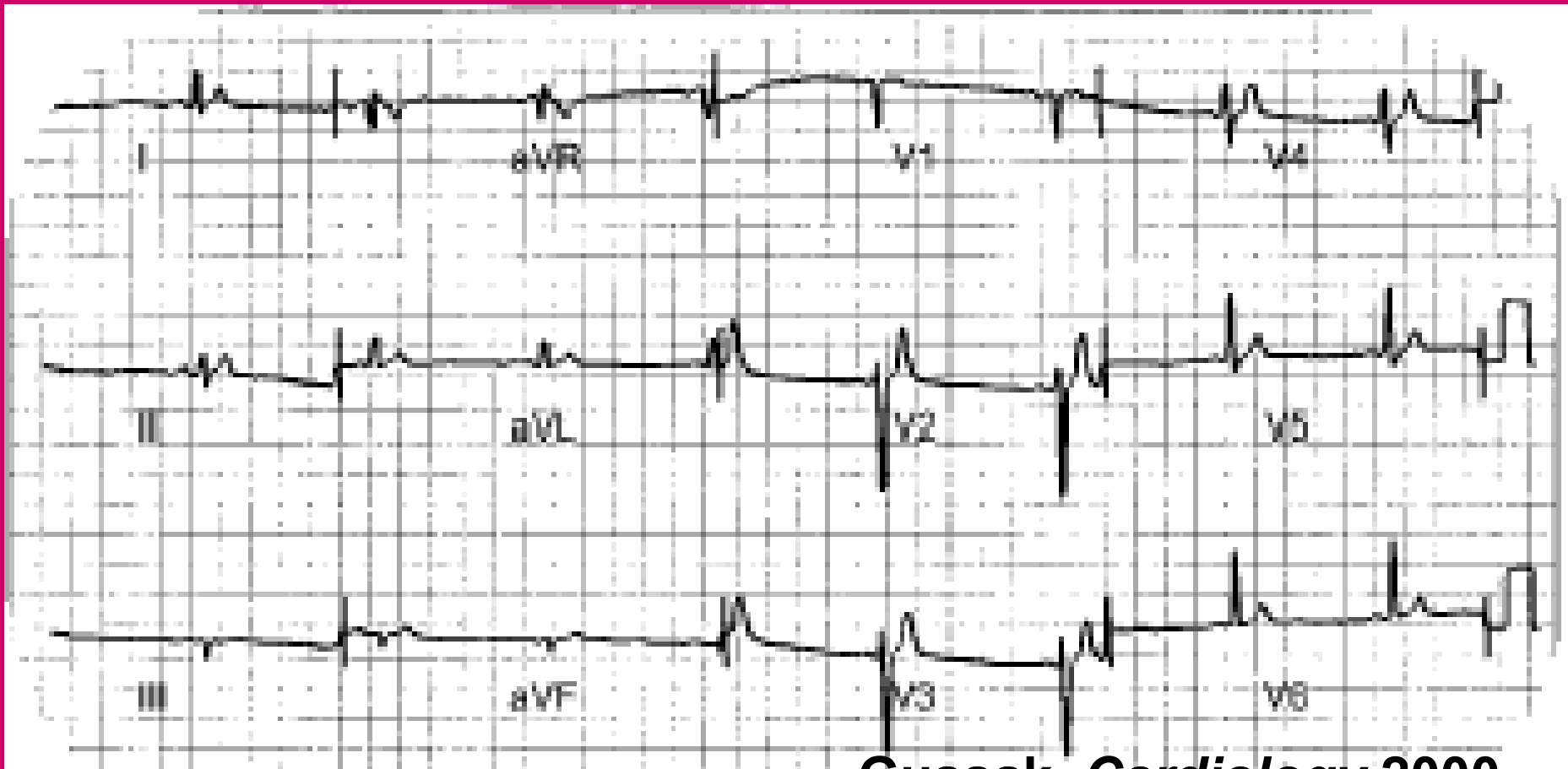
Arrhythmias, Electrophysiology and Electrocardiography

CARDIOLOGY

Cardiology 2000;94:99–102

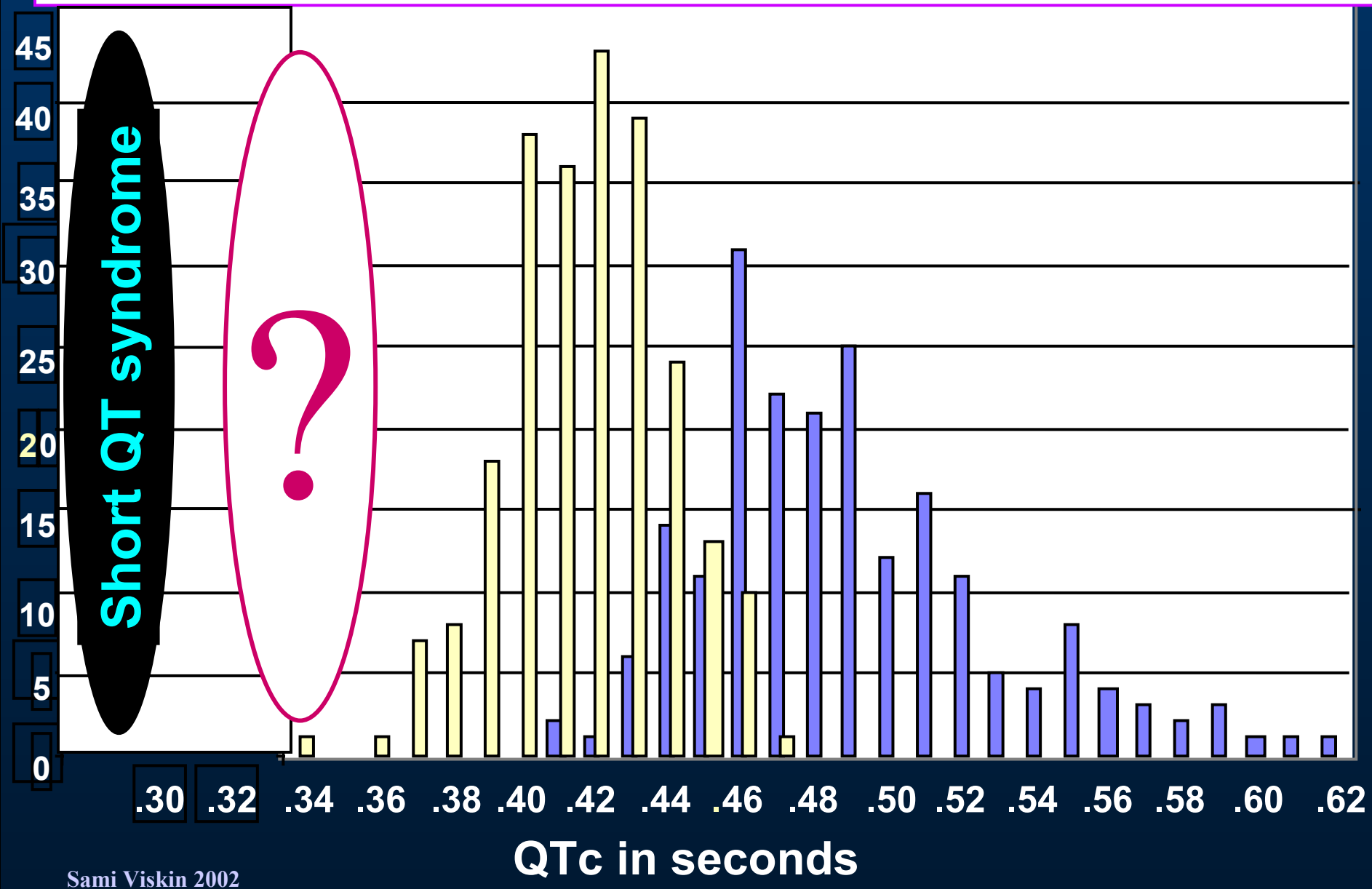
Received: May 22, 2000
Accepted after revision: August 3, 2000

Idiopathic Short QT Interval: A New Clinical Syndrome?



Gussak, *Cardiology* 2000.

Data of Michael G. Vincent on Carriers and Non-Carriers of Long QT syndrome



Sami Viskin 2002

Aim of study

Do patients with idiopathic VF have QT intervals that are "shorter than normal"?

Why patients with idiopathic VF?

- **Similarities between *short QT syndrome* and idiopathic VF.**
- **Holter study (Fujiki, *JCE 2004*): Insufficient QT prolongation at slow heart rates in idiopathic VF.**

Methods

- **28 patients with idiopathic VF (17 M+11 F)**
  - ***Exclusion:*** **Brugada sign.**
    Antiarrhythmic drugs
- **270 healthy controls (167 M+103 F).**

- **Blinded QT assessment by 3 investigators.**
- **Vincent's methodology:**
  - **3 QT – RR intervals averaged (lead II).**
  - **End of the T = Point of maximal change as it merges with baseline.**
- **QT measurement at *slow* heart rate favored.**

Definition of "short QT":

QTc ≤ 360 msec for males
QTc ≤ 370 msec for females

Definition of "very short QT":

QTc ≤ 300 msec.

Results.

	Idiopathic VF 28 patients		Control 270 patients	
Males	17 (61%)		167 (62%)	
Age	37 ± 15		36 ± 11	
	Males	*Females*	*Males*	*Females*
R-R	924 ± 182	787 ± 134	914 ± 151	843 ± 124
QTc	371 ± 22	411 ± 29	385 ± 19	401 ± 24

Results.

Mean QTc

Healthy males	385 ± 19 msec
Idiopathic VF males	22 ± 371

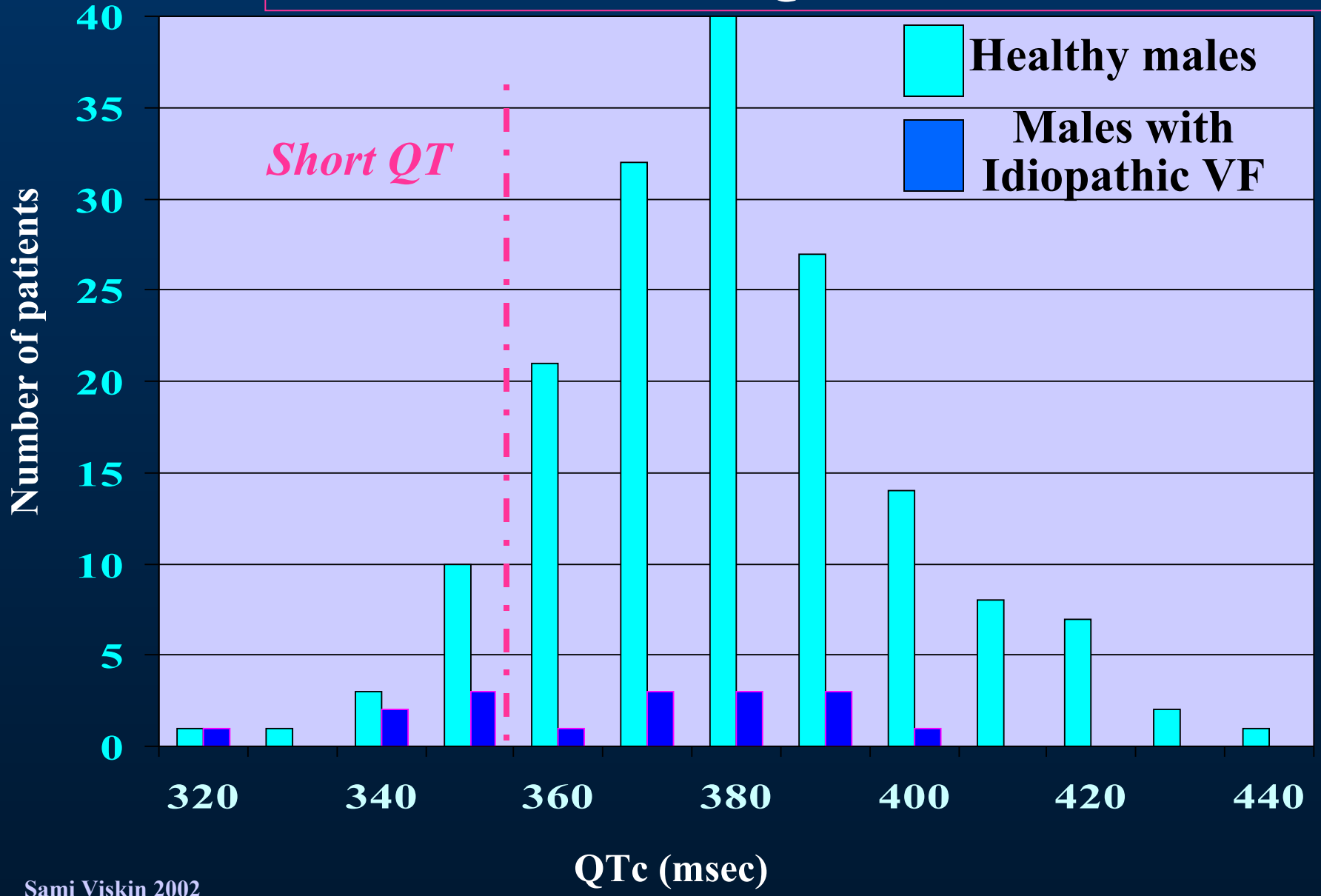
$p = 0.034$

Proportion of patients with *short QT*

Healthy males		Idiopathic VF males
9%	$p = 0.003$	35%

Results.

Distribution of QTc values in males.



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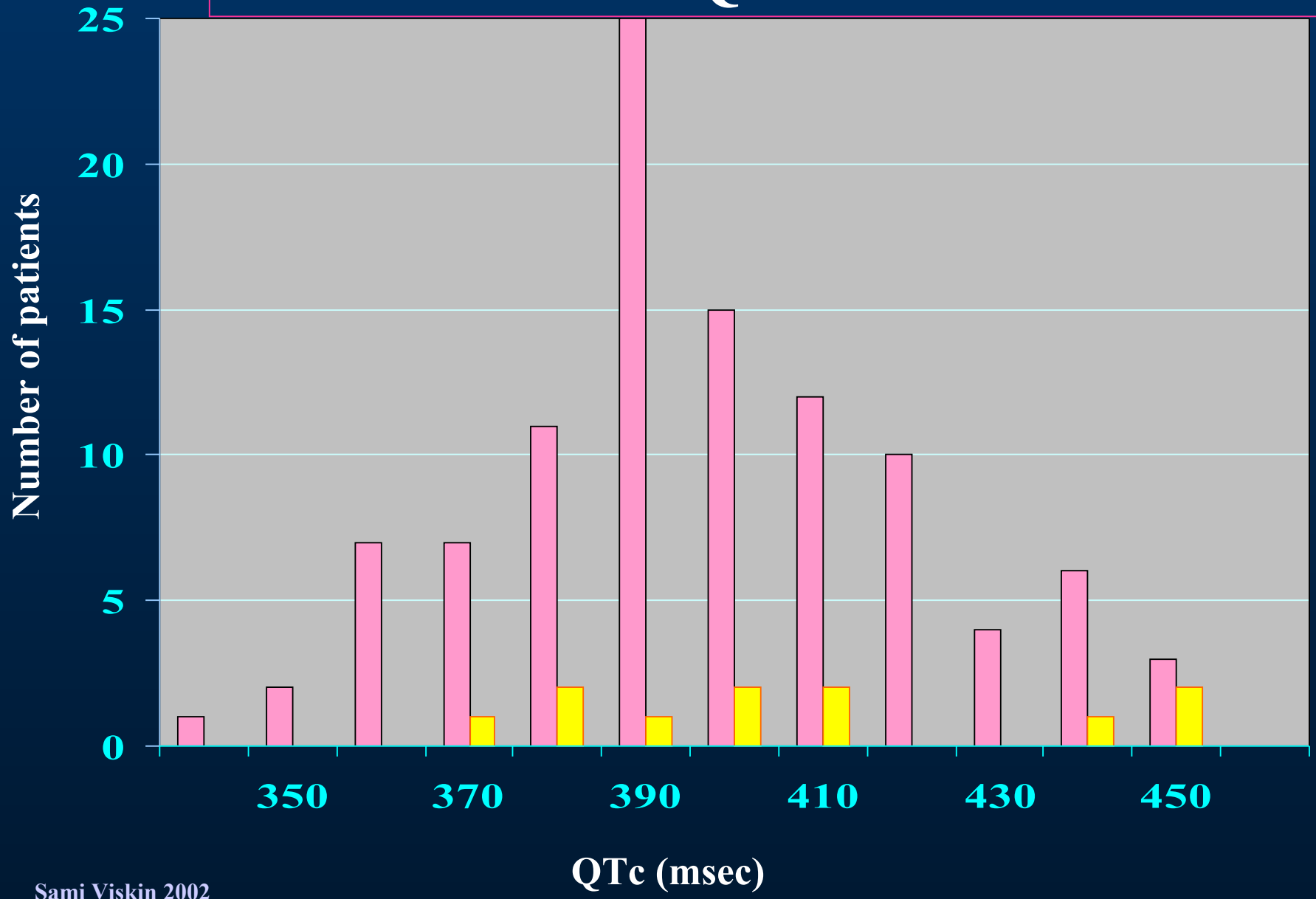
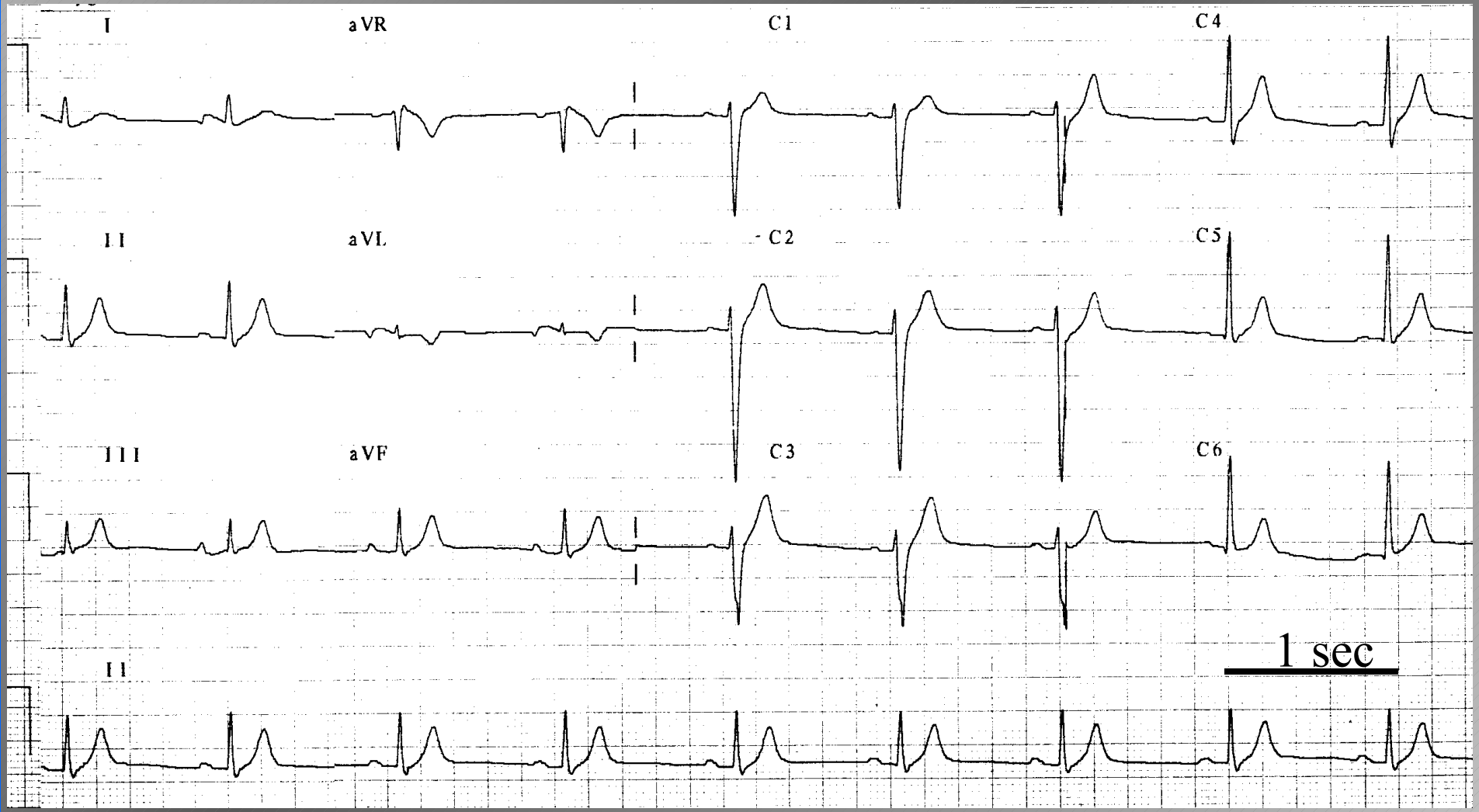
Results.

Distribution of QTc values in females.



Idiopathic VF: Male, 28 years

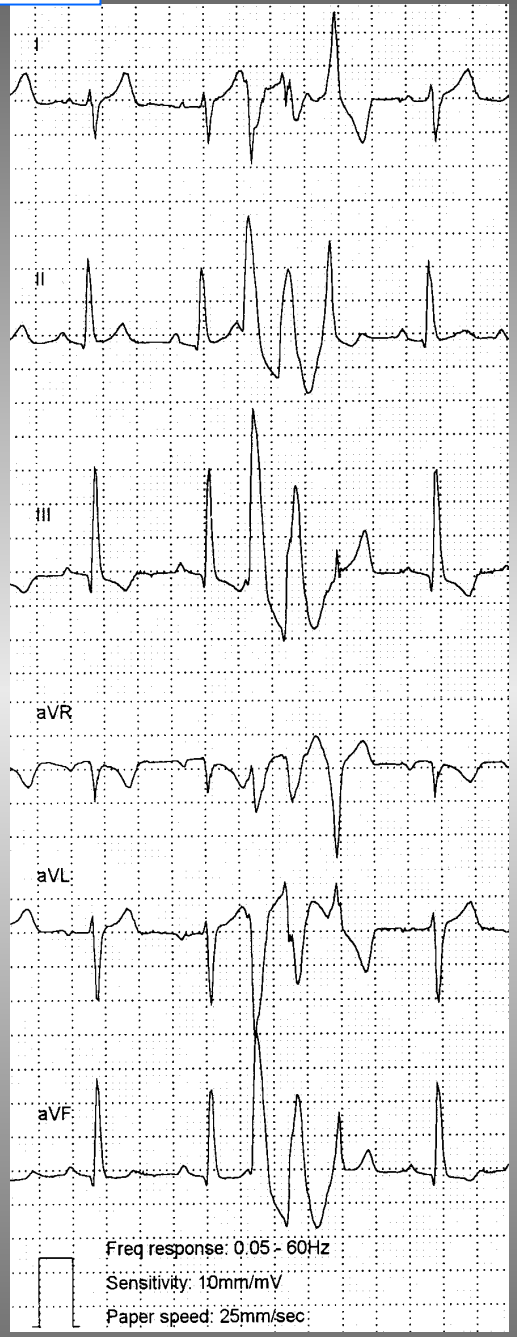
QTc = 326 msec (310 – 349 msec)



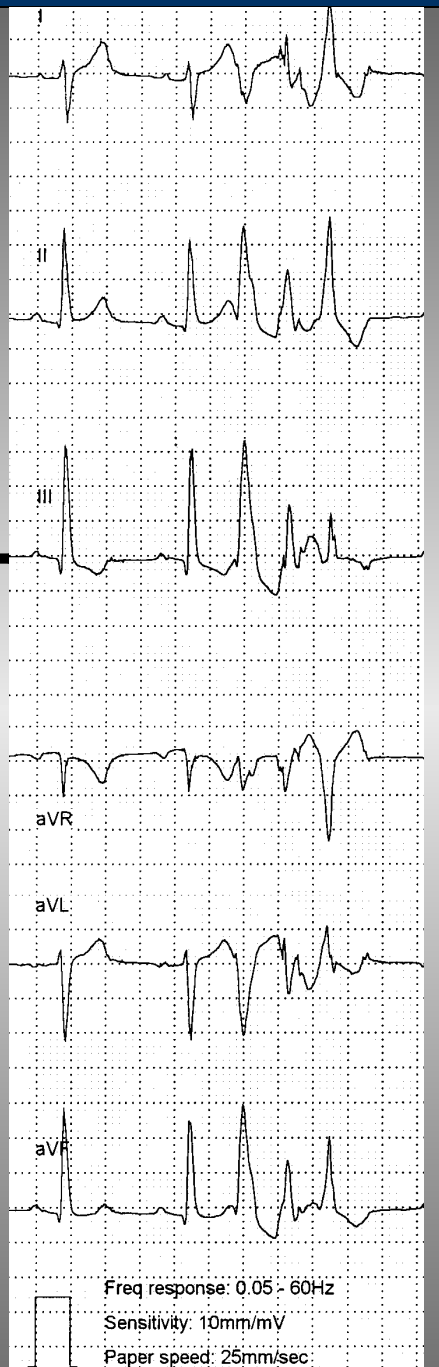
Idiopathic VF: Male, 19 years.

First episode

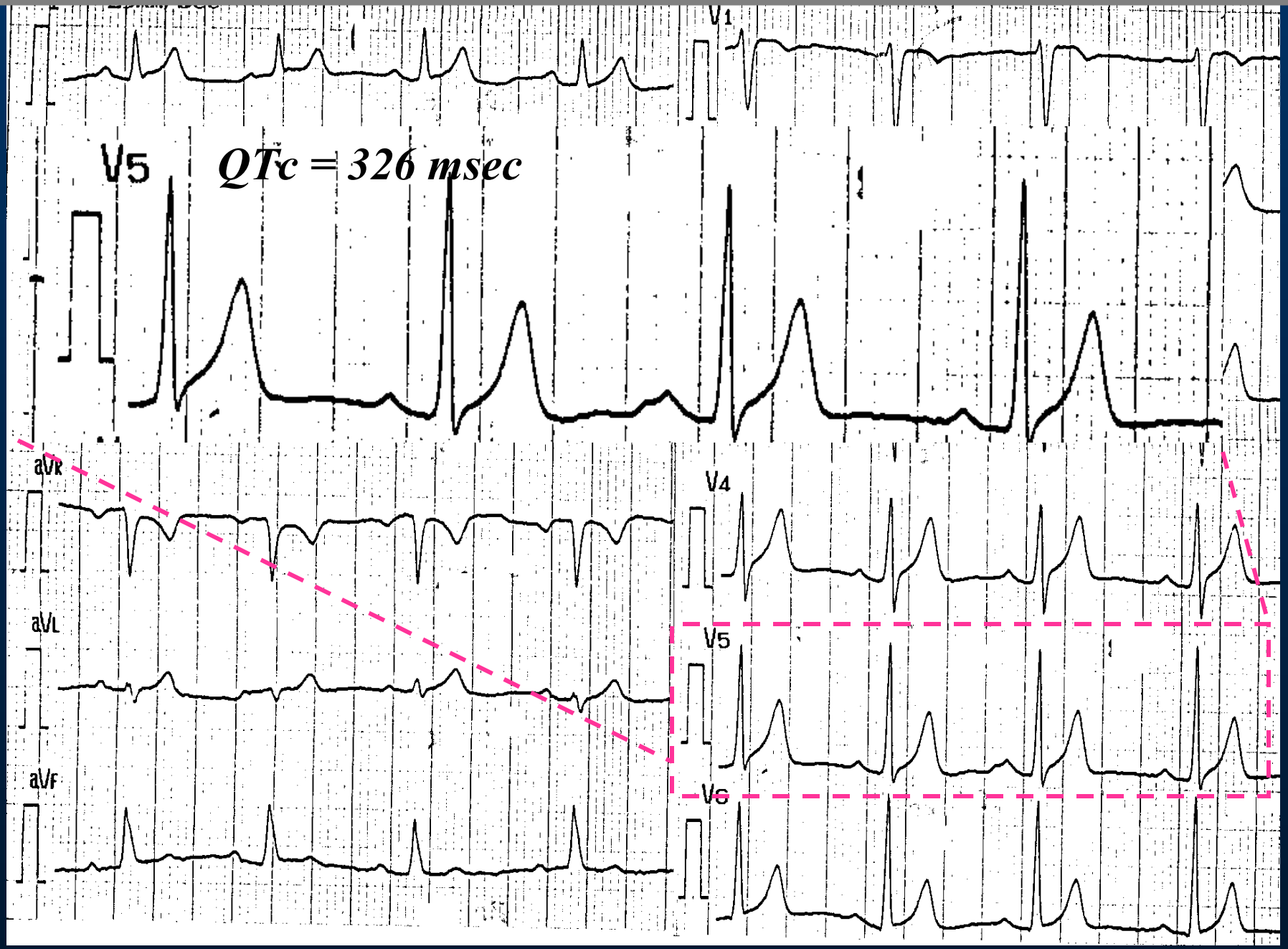
Second episode



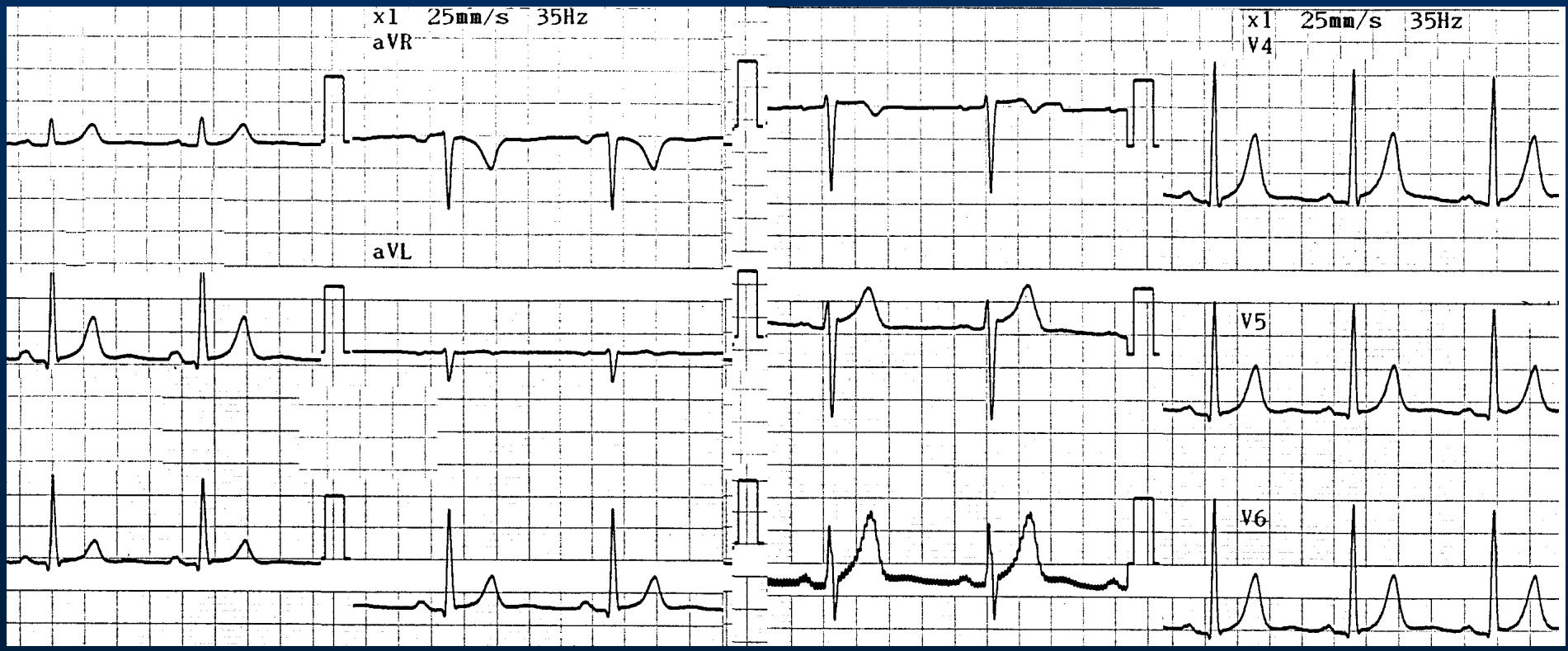
Third episode



Idiopathic VF: Male 19 years, QTc = 326 msec (310 – 349 msec)



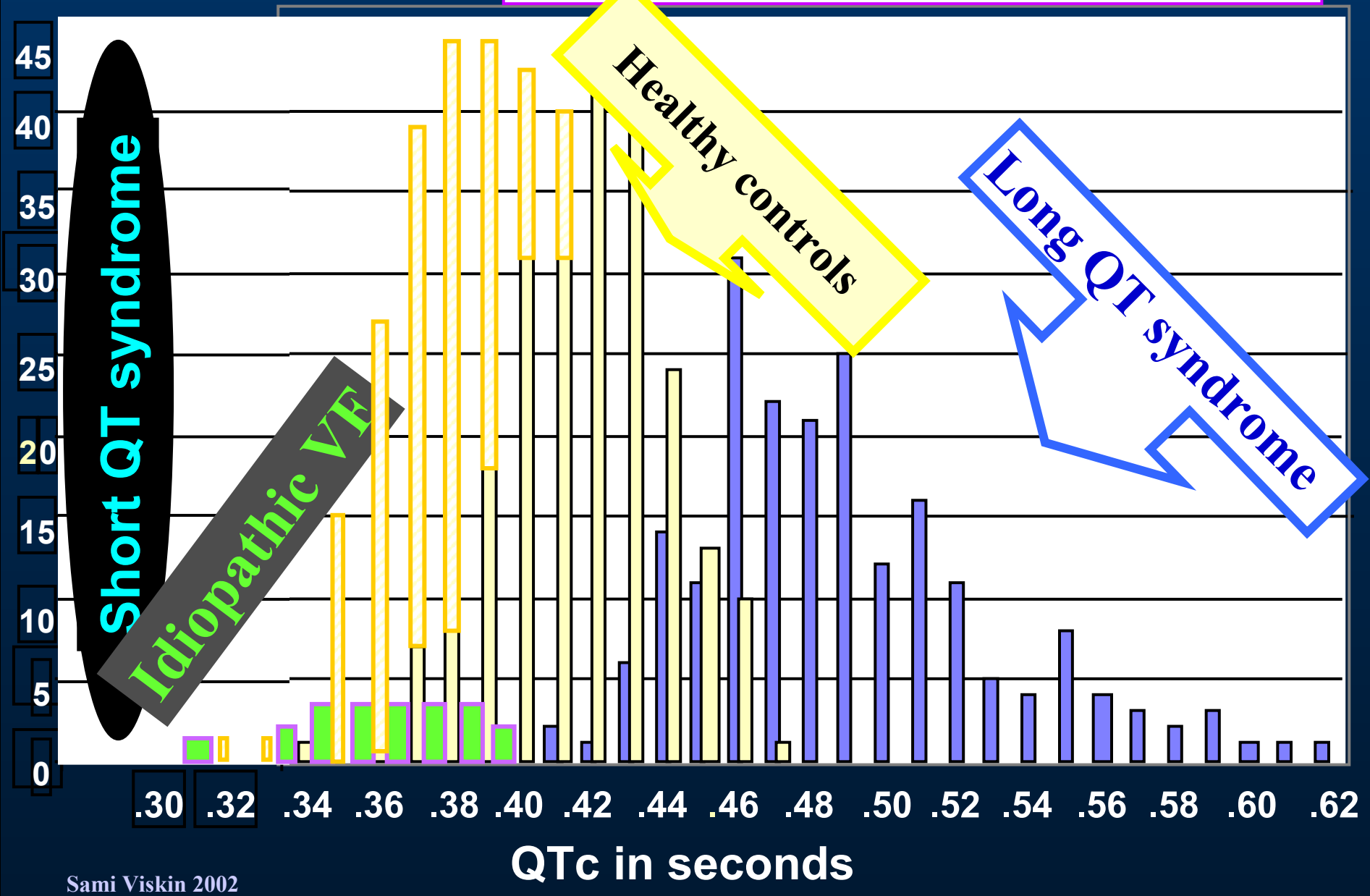
Relatively short QT in a <u>healthy</u> (or so we hope) control.



R-R = 910 – 980 msec; QT = 360- 370 msec; QTc =364 – 377 msec

Present study

Data of Michael G. Vincent on Carriers and Non-Carriers of Long QT syndrome



Sami Viskin 2002

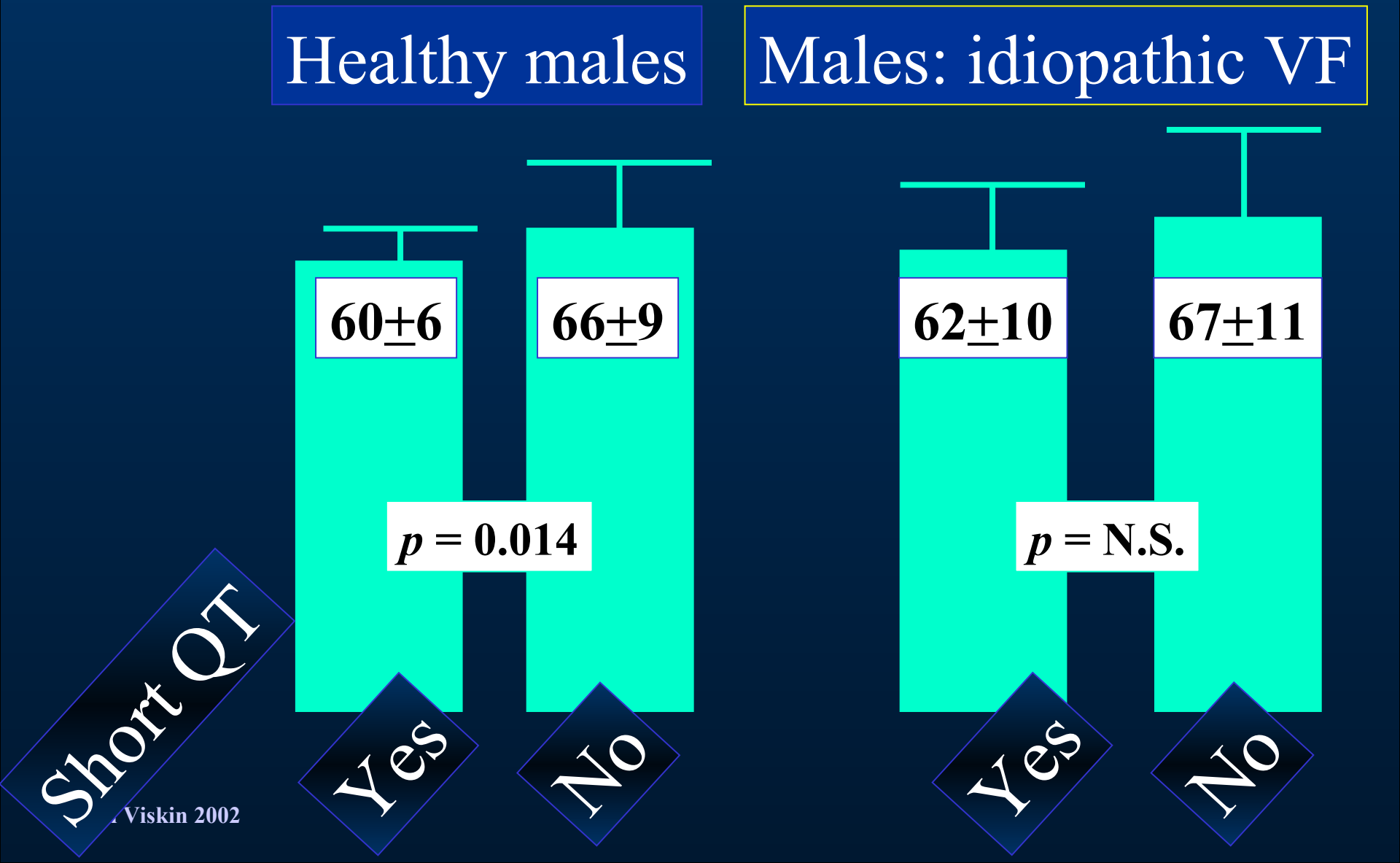
Clinical implications

~~Normal QT = QT that is not prolonged.~~

QTc = 300 – 360 msec may entail arrhythmic risk

Further studies are needed to define when is a short QT interval “too short.”

Heart rate for males with and without short QT



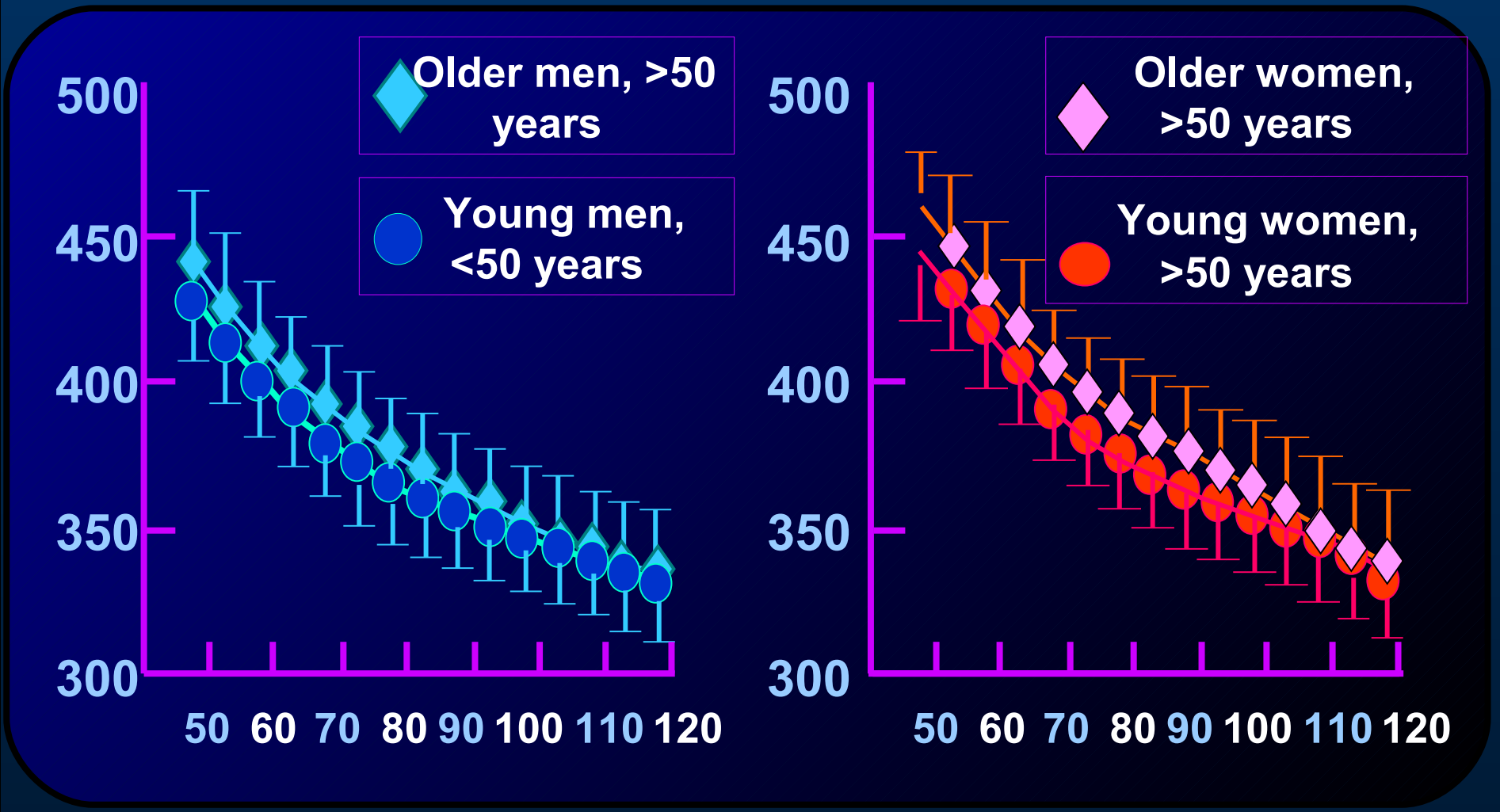
Multivariate analysis:

Among males, the association between a "short QT" and a history of VF was independent from the heart rate ($p = 0.0046$)

Relative risk for male patients with "short QT" for having a history of VF was 5.45 (95% CI 1.7 – 17.6)

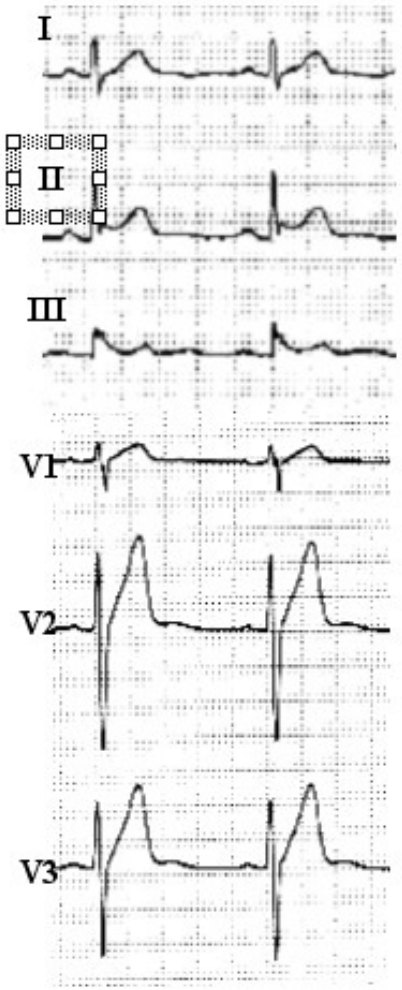
QT interval at different heart rates.

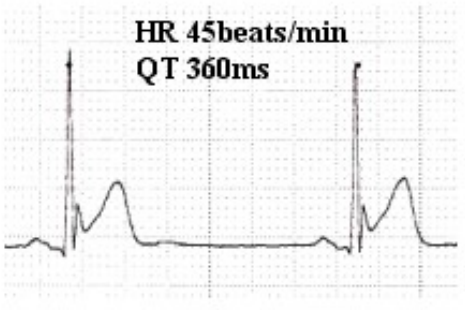
Data from 422 healthy men and women.

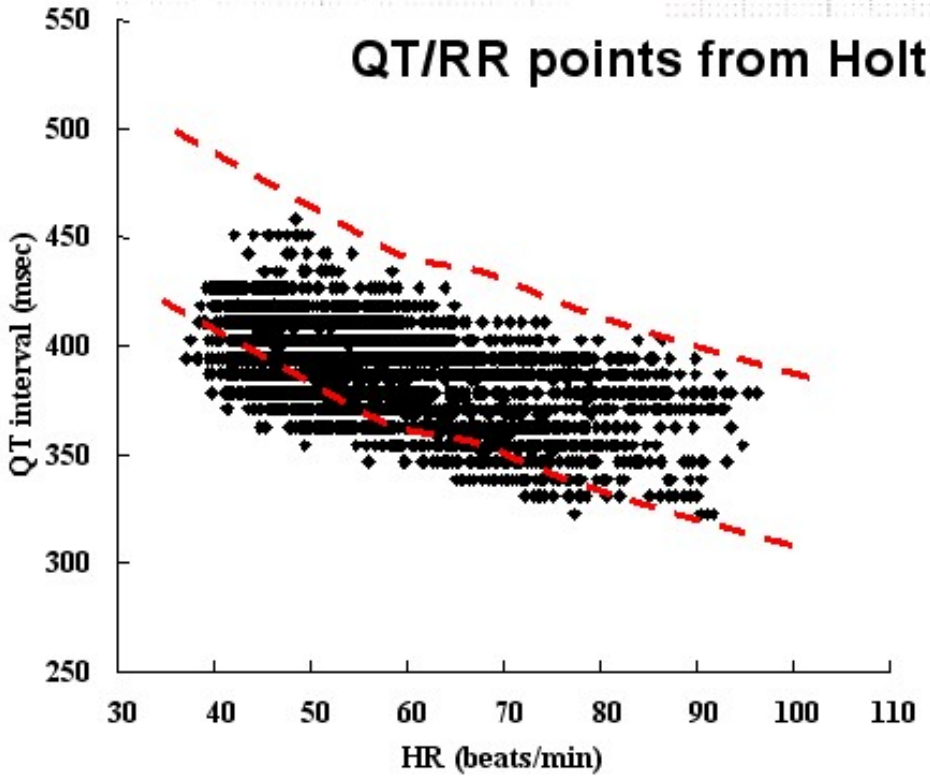


Sugao, *Heart* 2005

Male, 33 years old.
Idiopathic VF

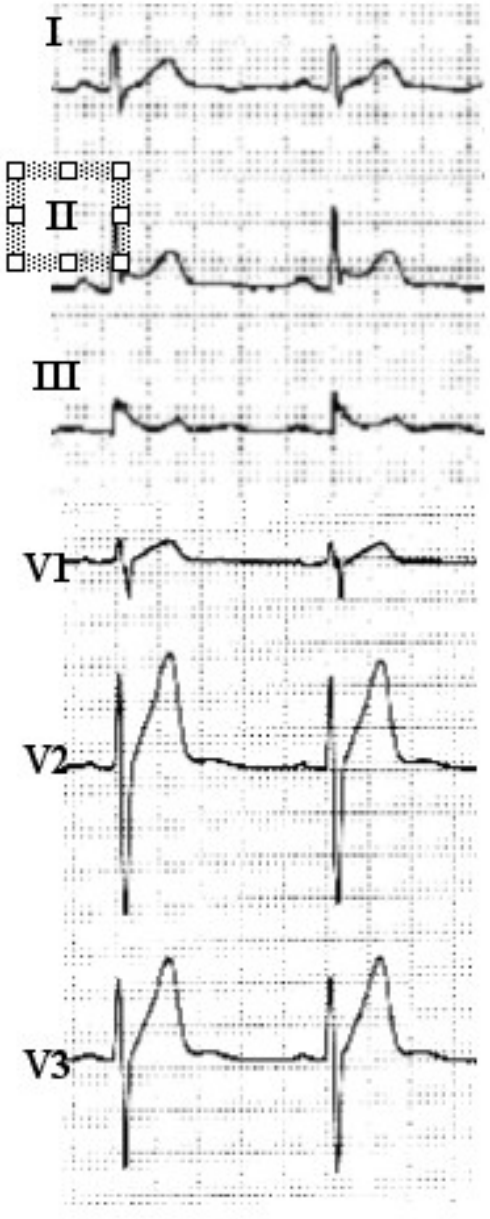


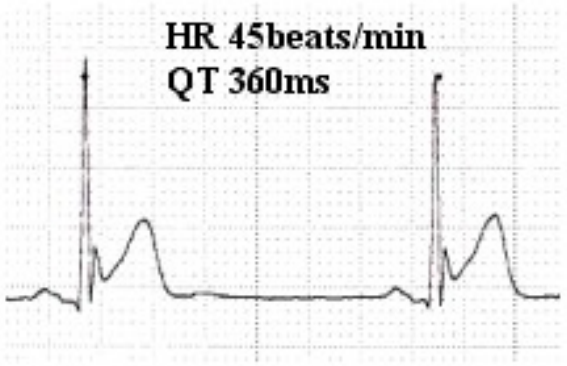


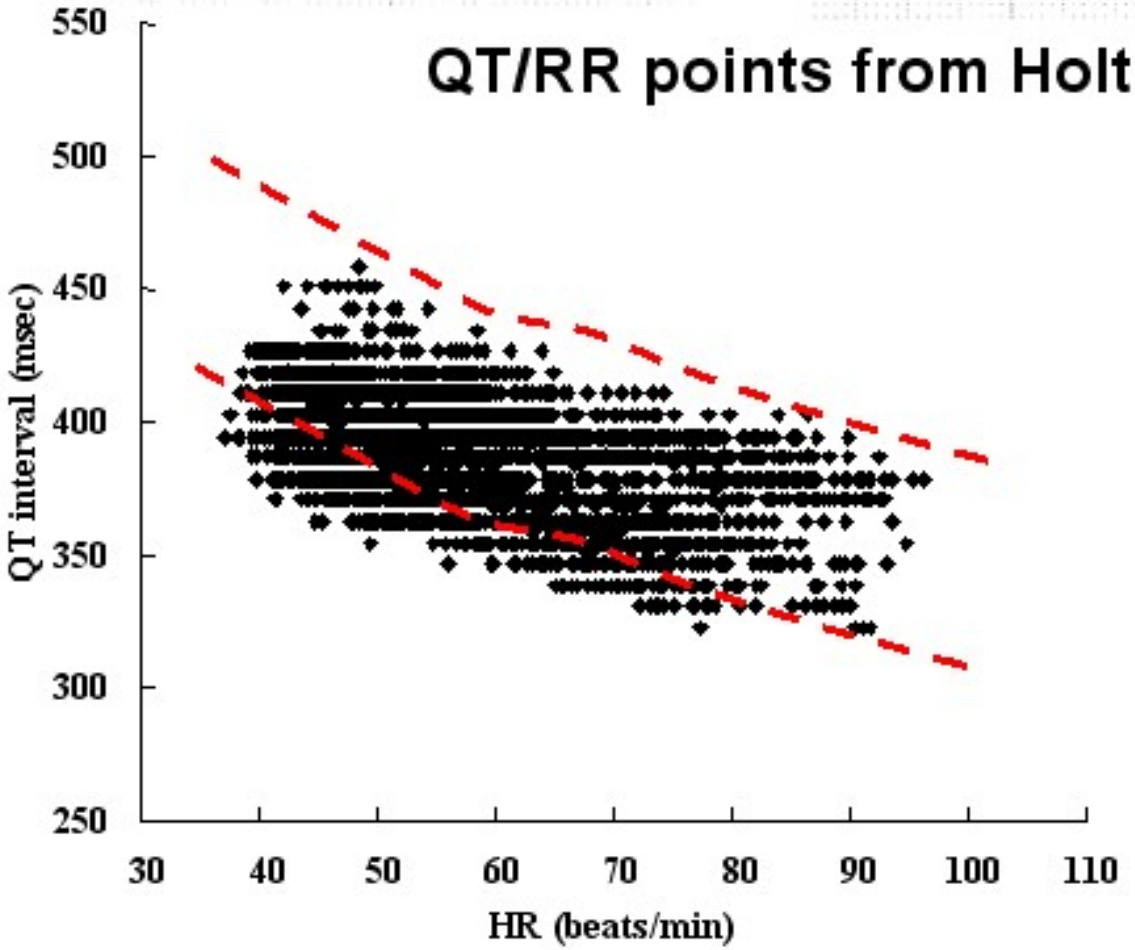


Akira Fujiki, personal communication, 2005.

Male, 33 years old.
Idiopathic VF







Akira Fujiki, personal communication, 2005.

Sami Viskin 2002

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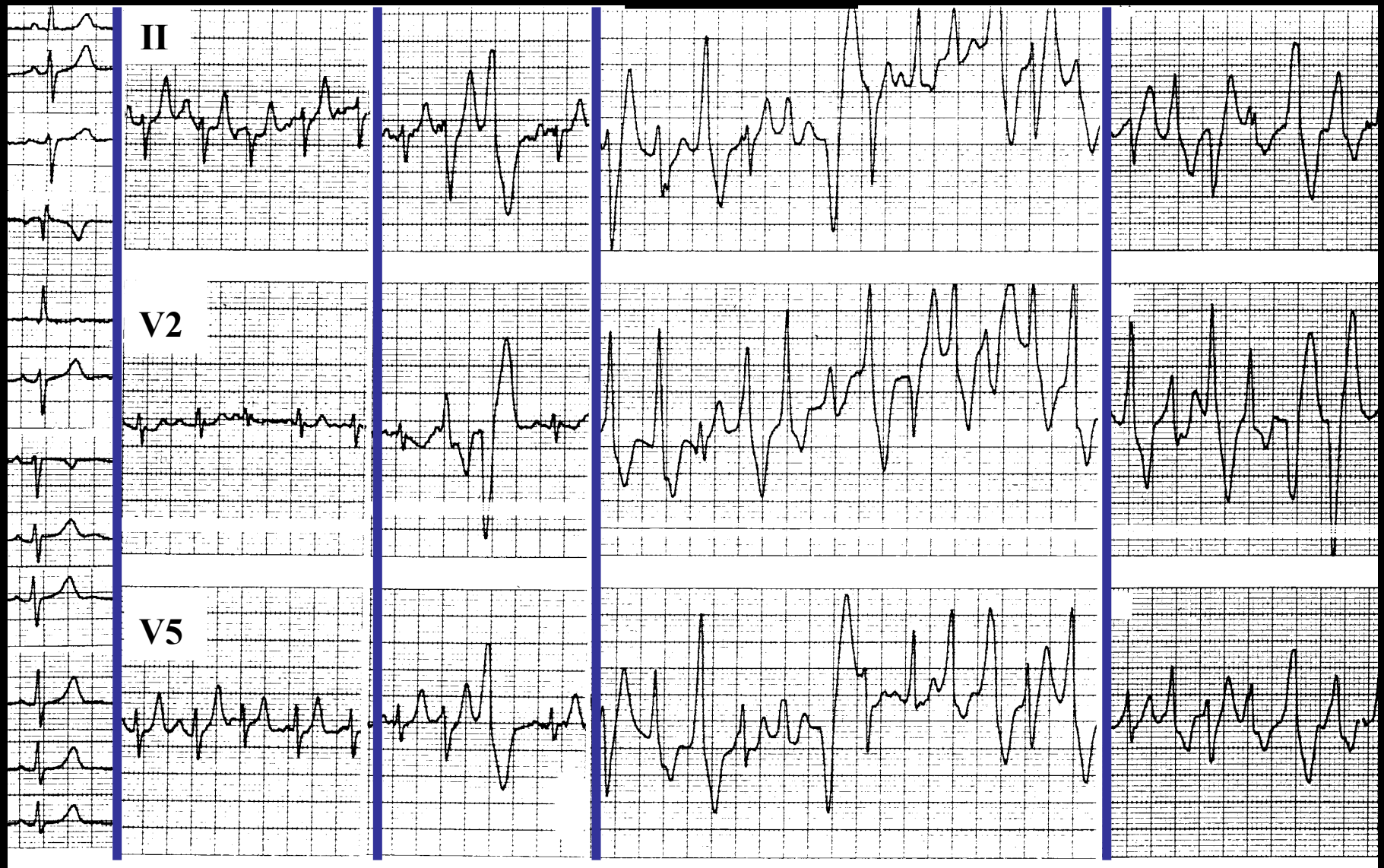
Catecholamine sensitive polymorphic VT

Rest

Exercise

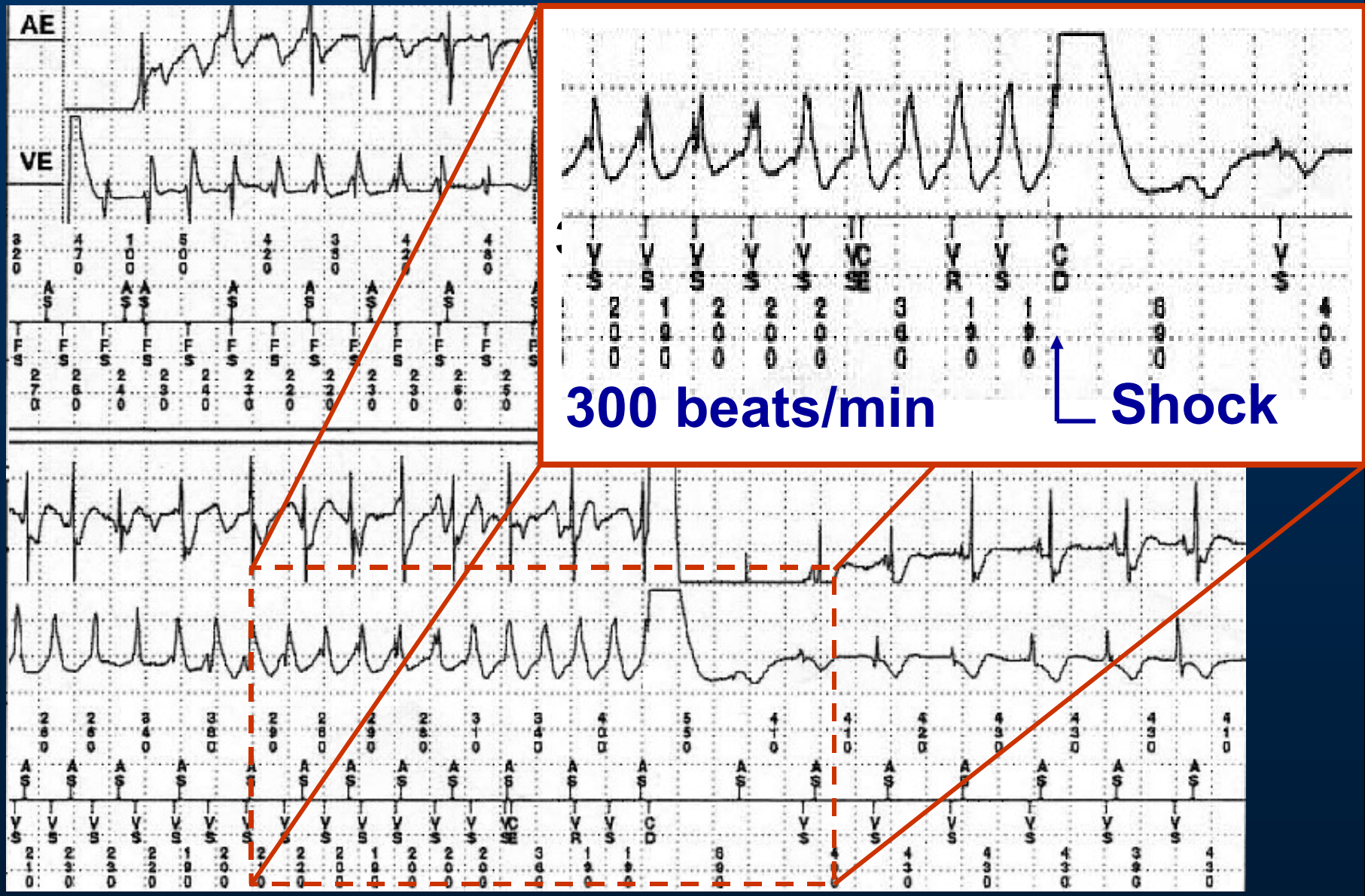


Sami Viskin 2002

Viskin, *Prog Cardiovasc Dis* 1998

Sami Viskin 2002

Appropriate ICD shock during syncope. KCNJ2 mutation.



Chun, *Heart Rhythm* 2004.

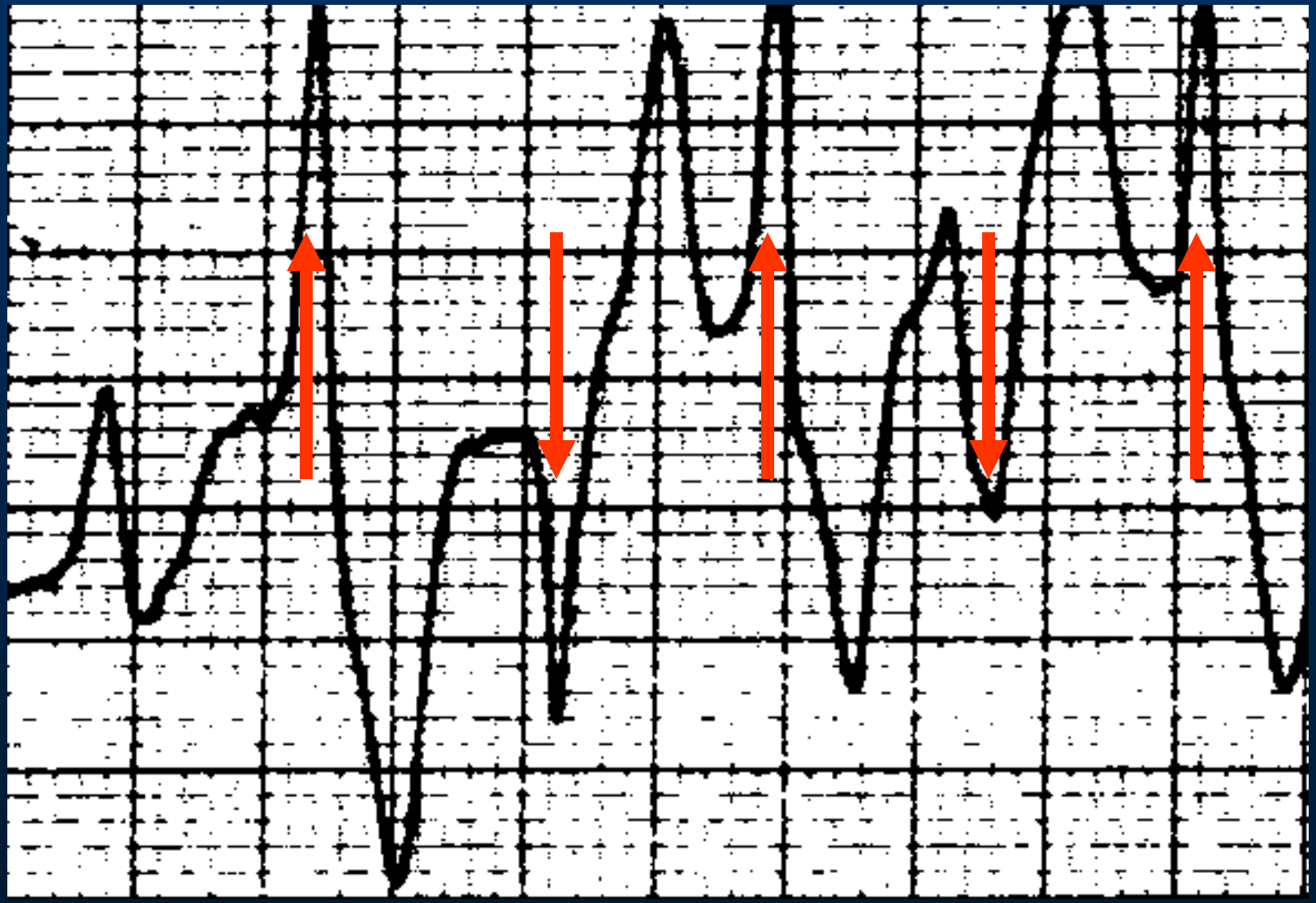
Chun, *Heart Rhythm* 2004.

Sami Viskin 2002

Sami Viskin 2002

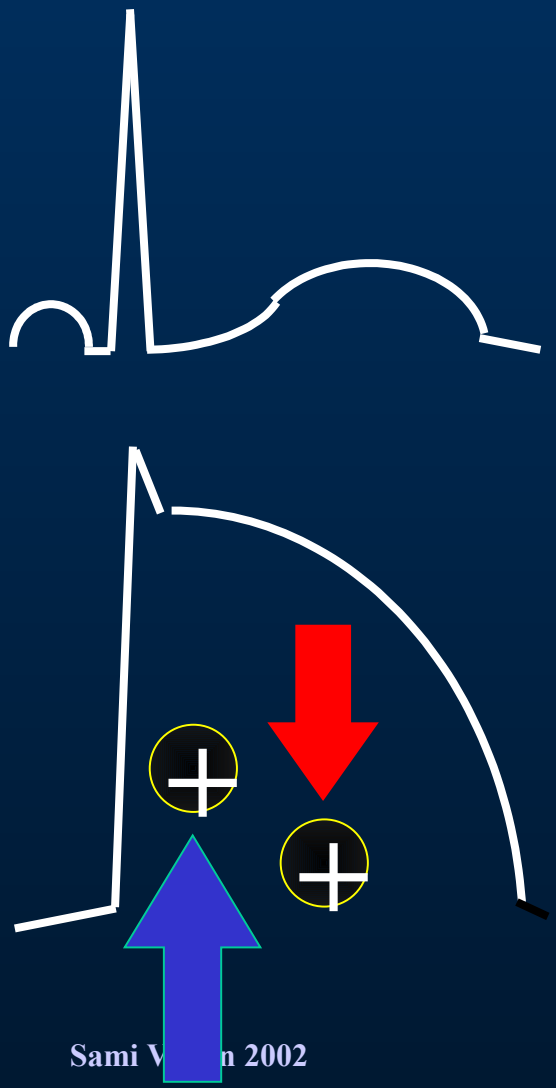
Sami Viskin 2002

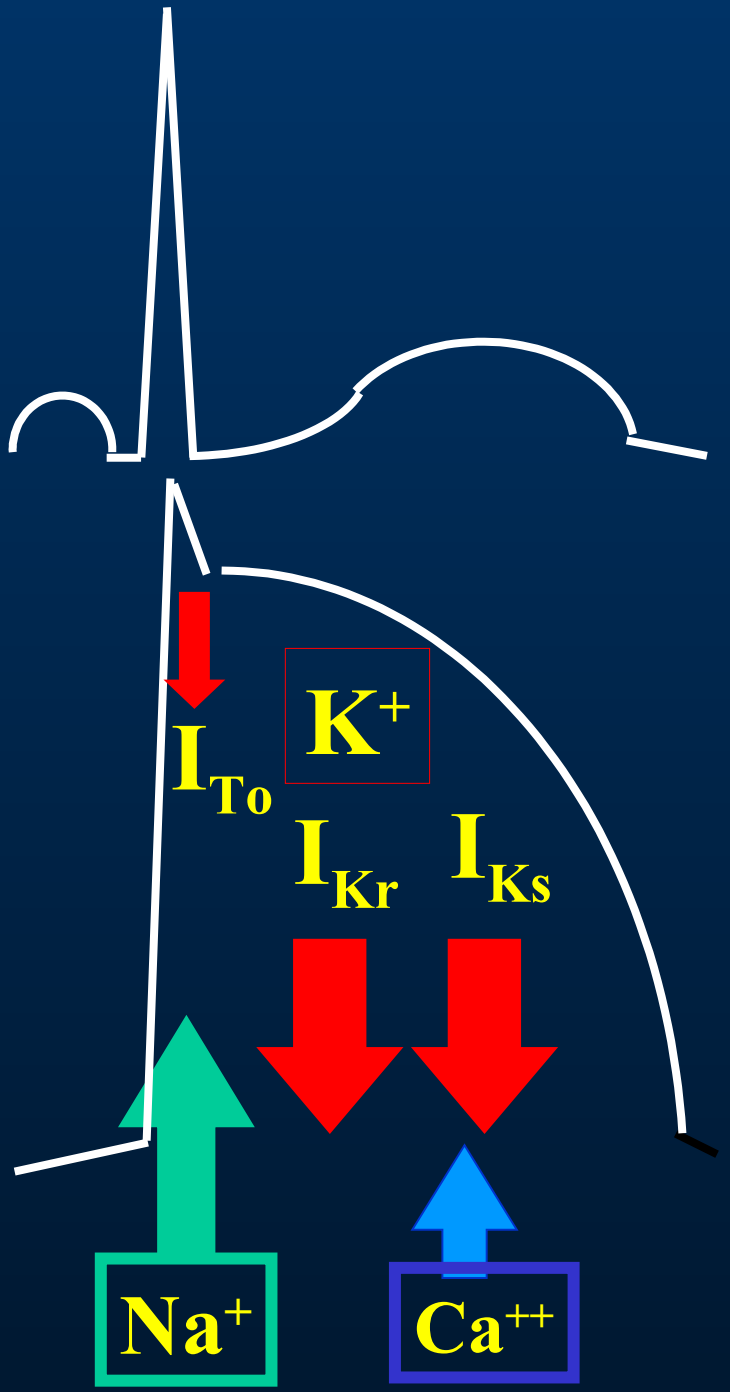
Bidirectional tachycardia in catecholaminergic VT

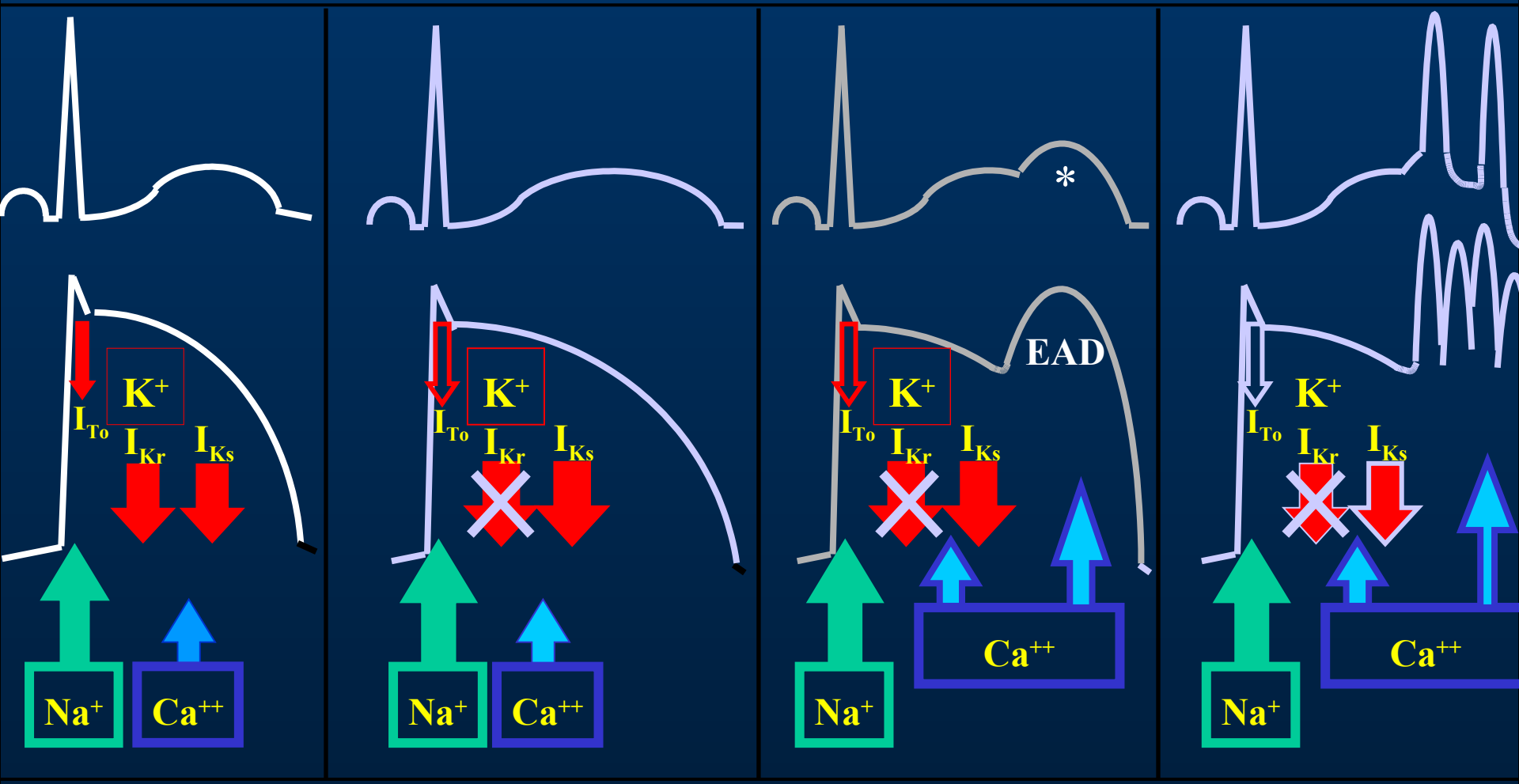


Sami Viskin 2002

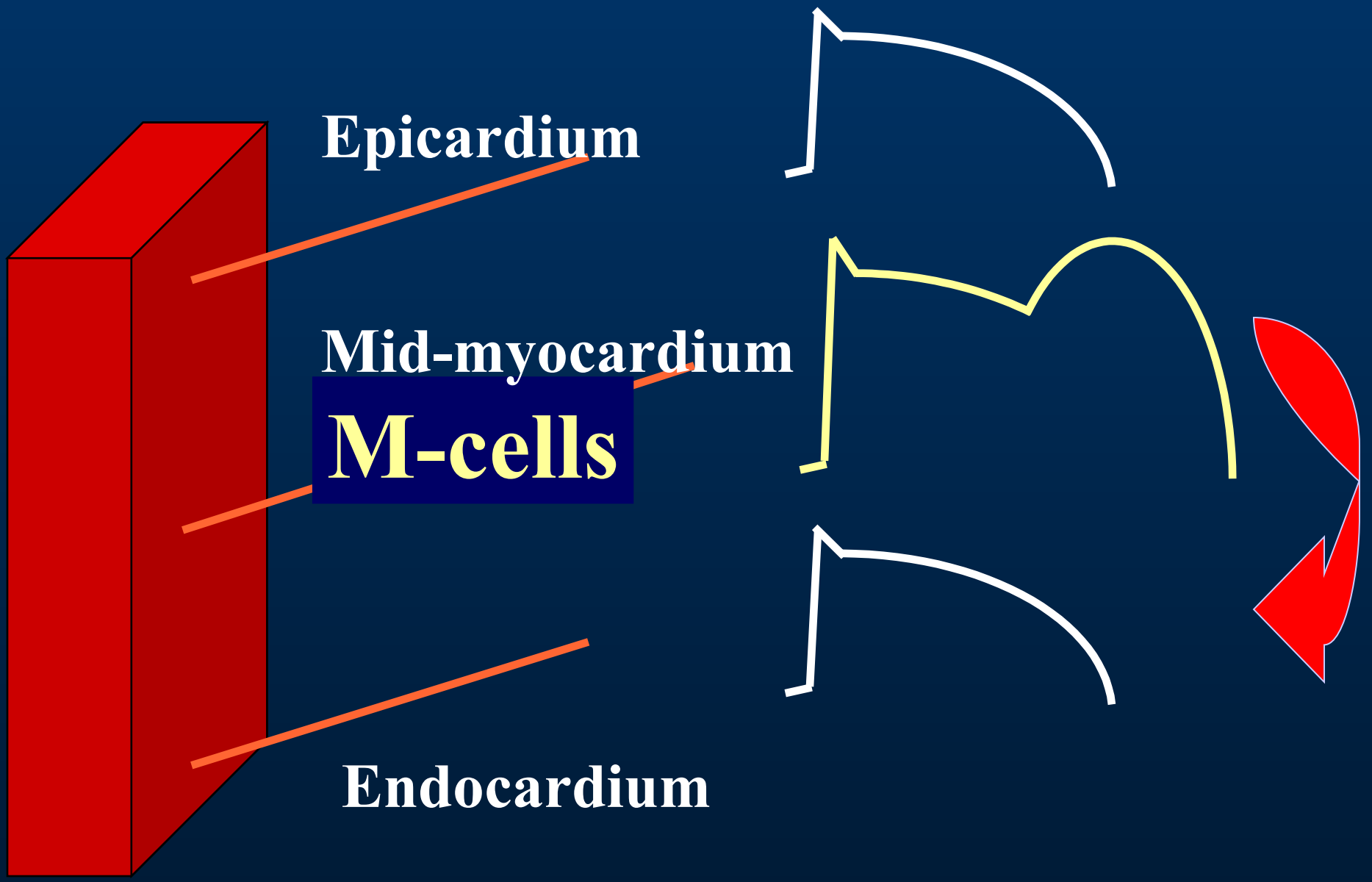
The long QT syndromes







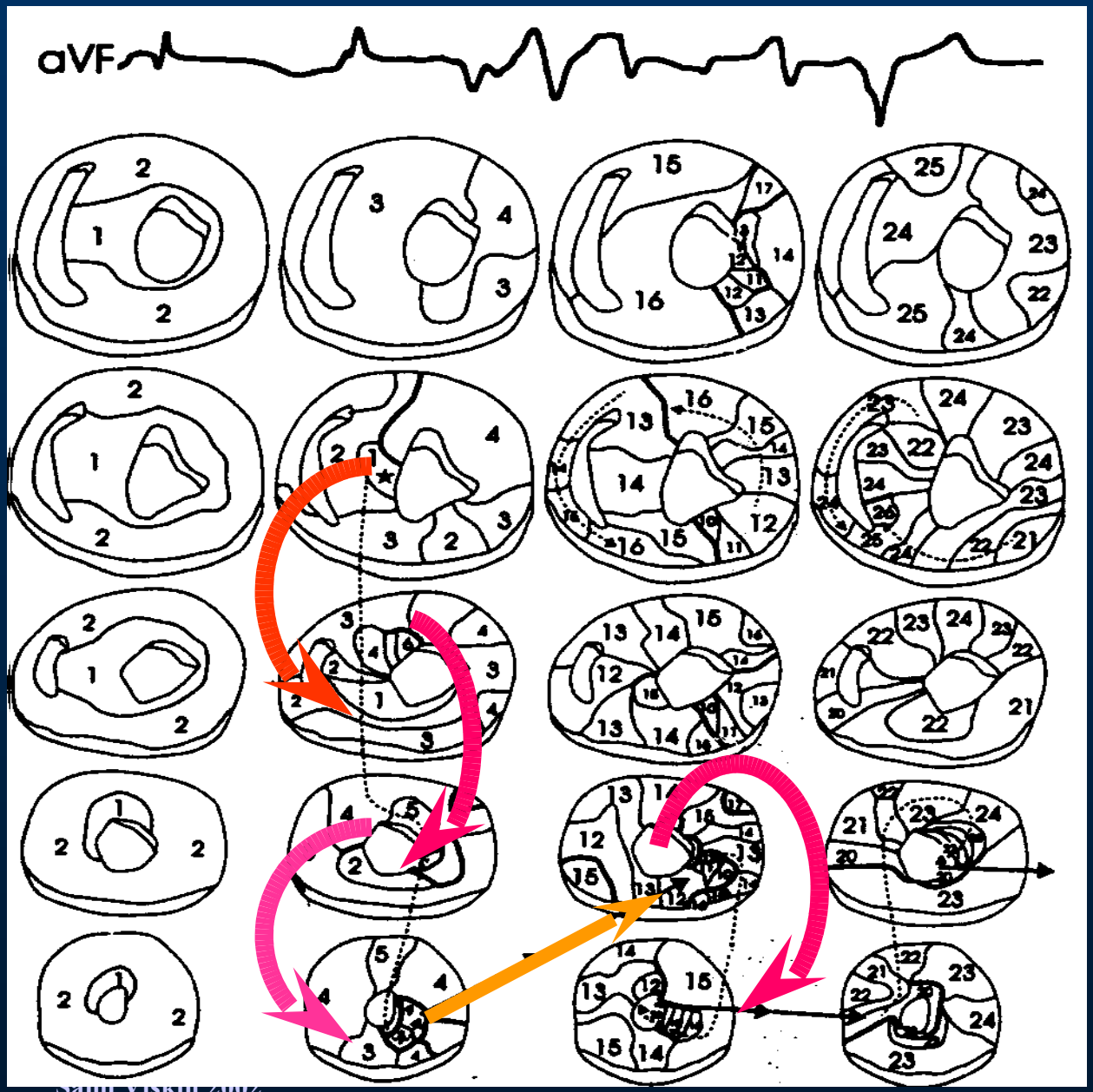
Viskin & Roden. *Harrison ONLINE* 2000



Sami Viskin 2002

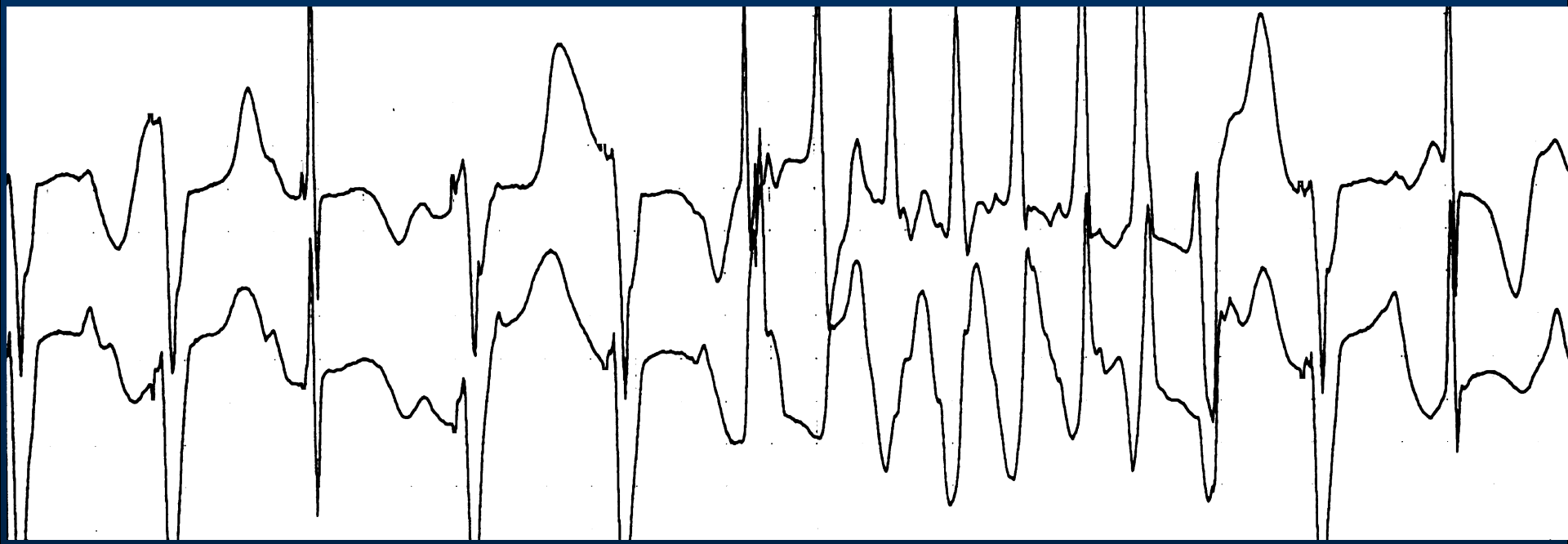
Antzelevitch, *J Am Coll Cardiol* 1994

Three-dimensional mapping of torsade de pointes

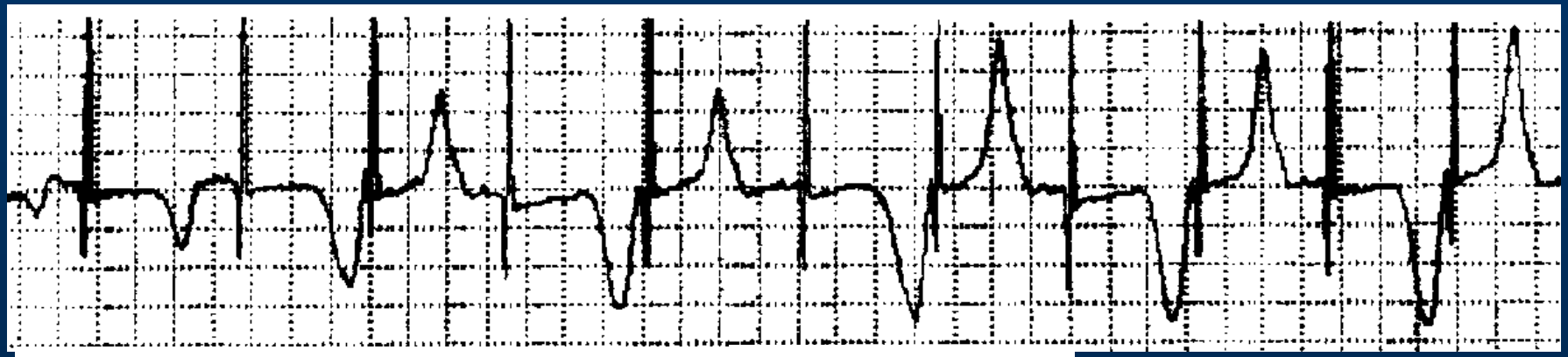


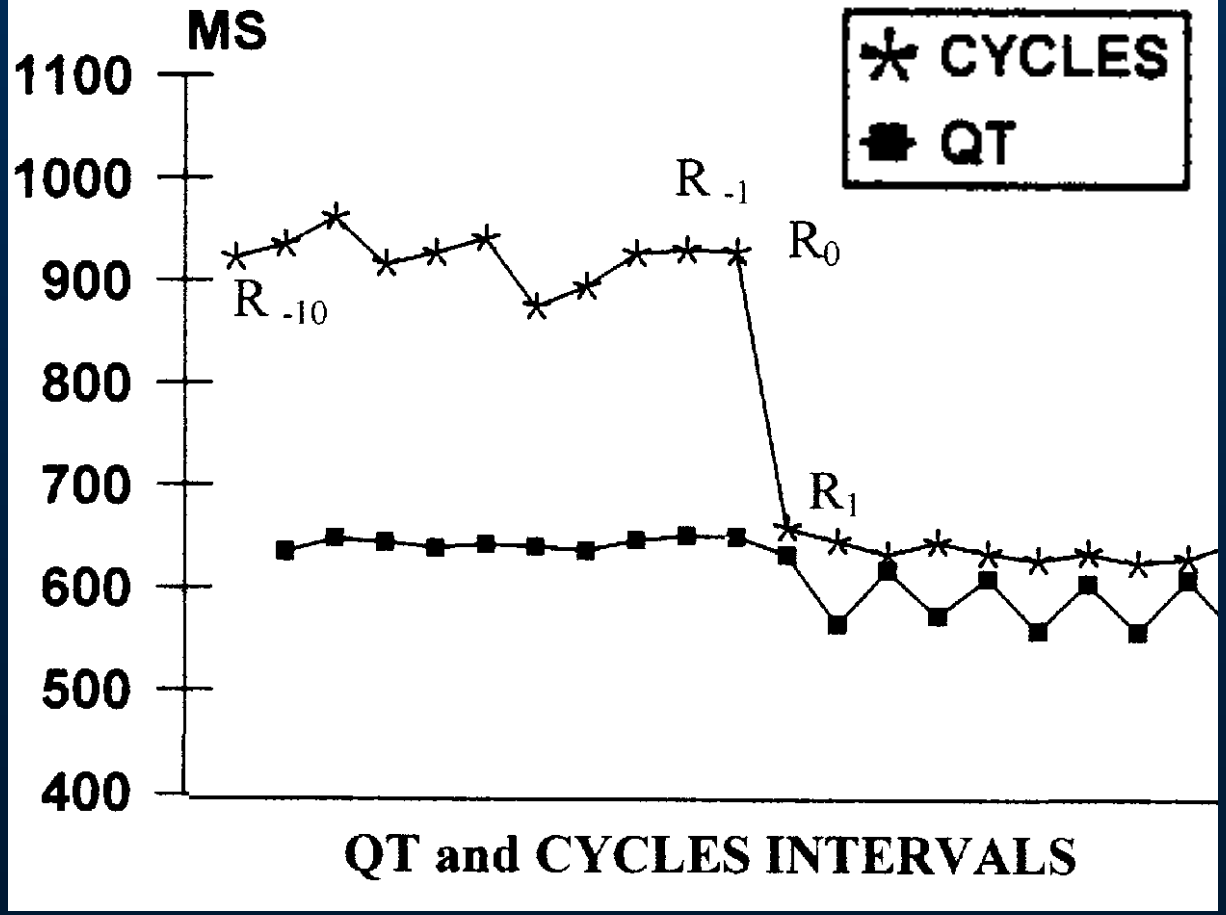
El-Sherif,
Circulation 1997

Adrenergic-dependent torsade de pointes



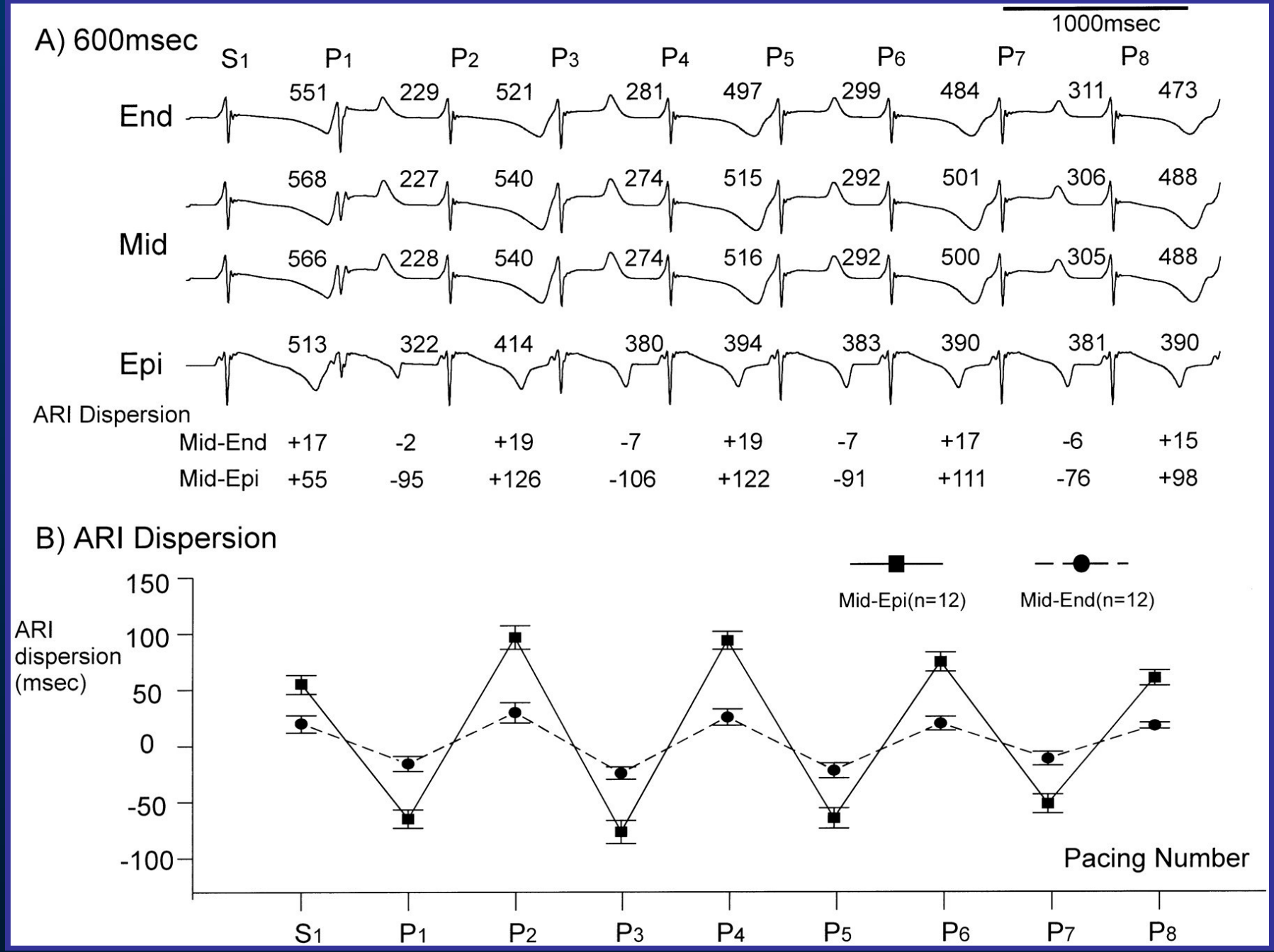
Sami Viskin 2002





T wave alternans (45% of patients with LQTS).

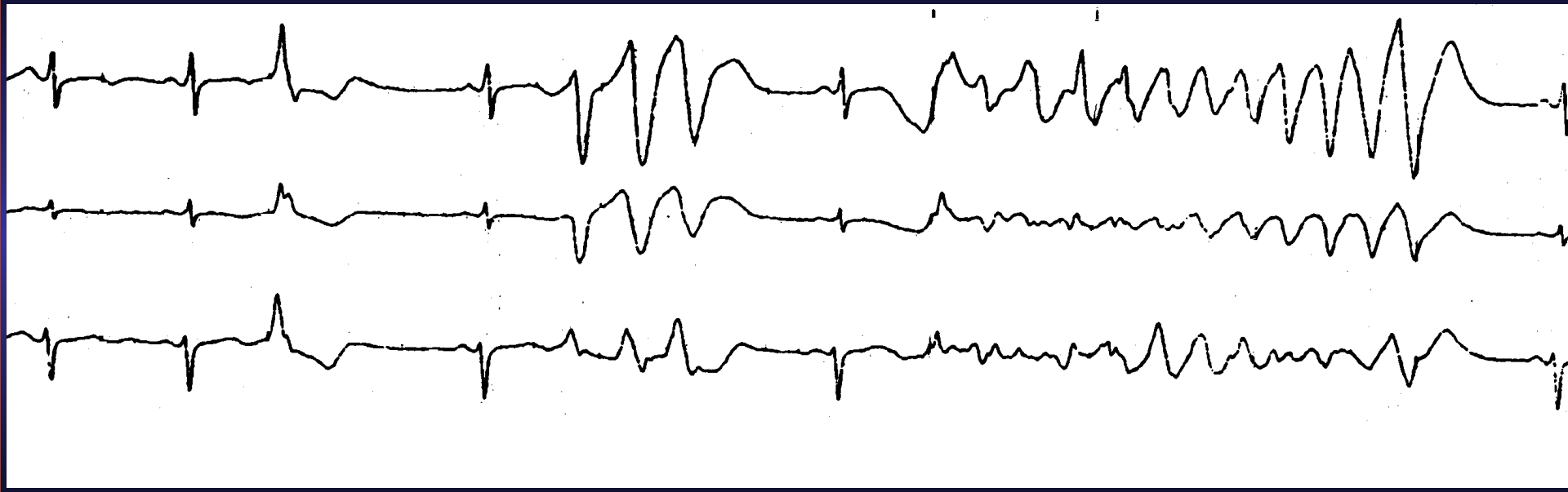
F.E.S. Cruz Filho
***JACC* 2000**



Sami Viskin 2002

Chinushi, *Circ Res* 1998.

Pause-dependent torsade de pointes



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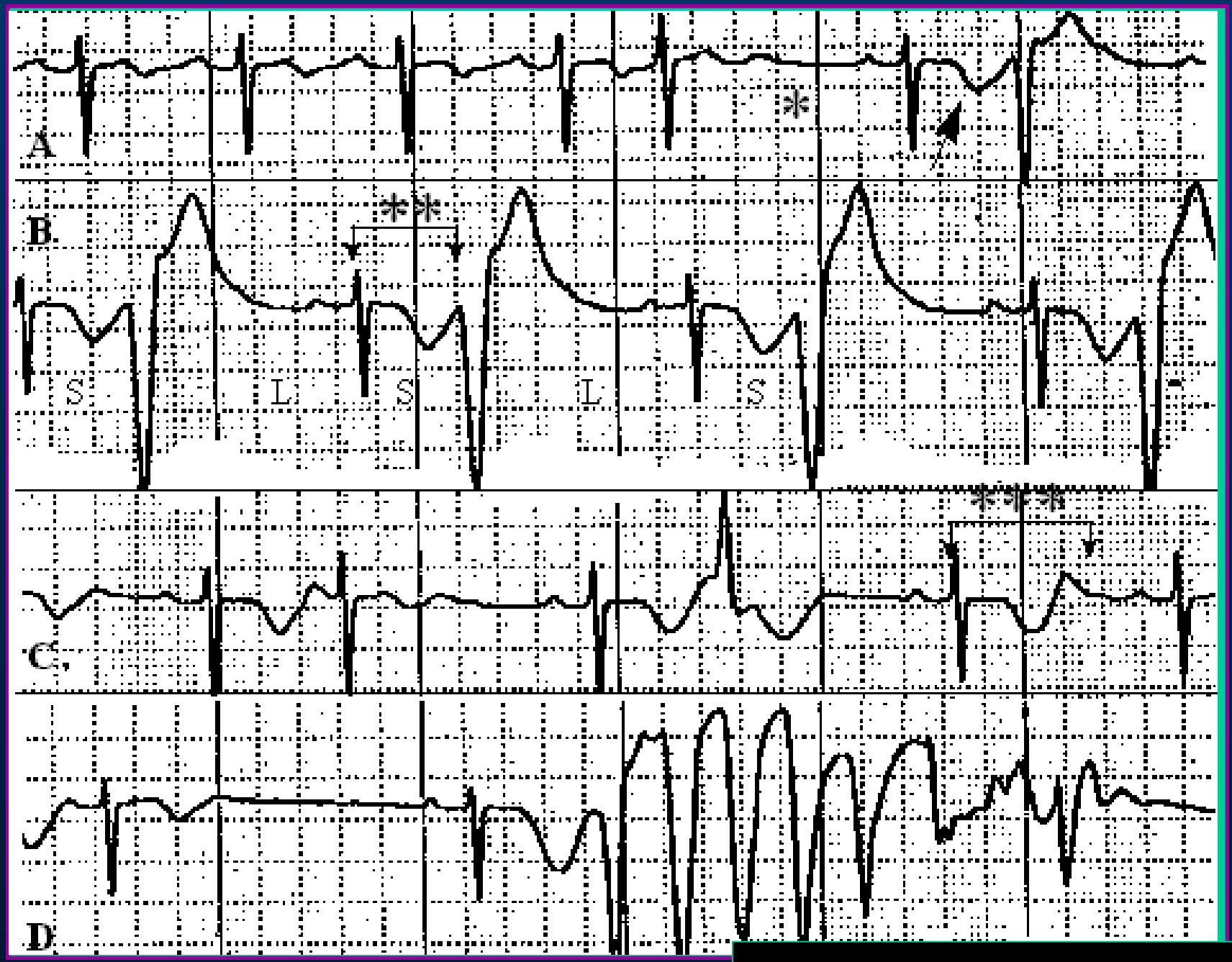
Viskin, *Heart* 2000



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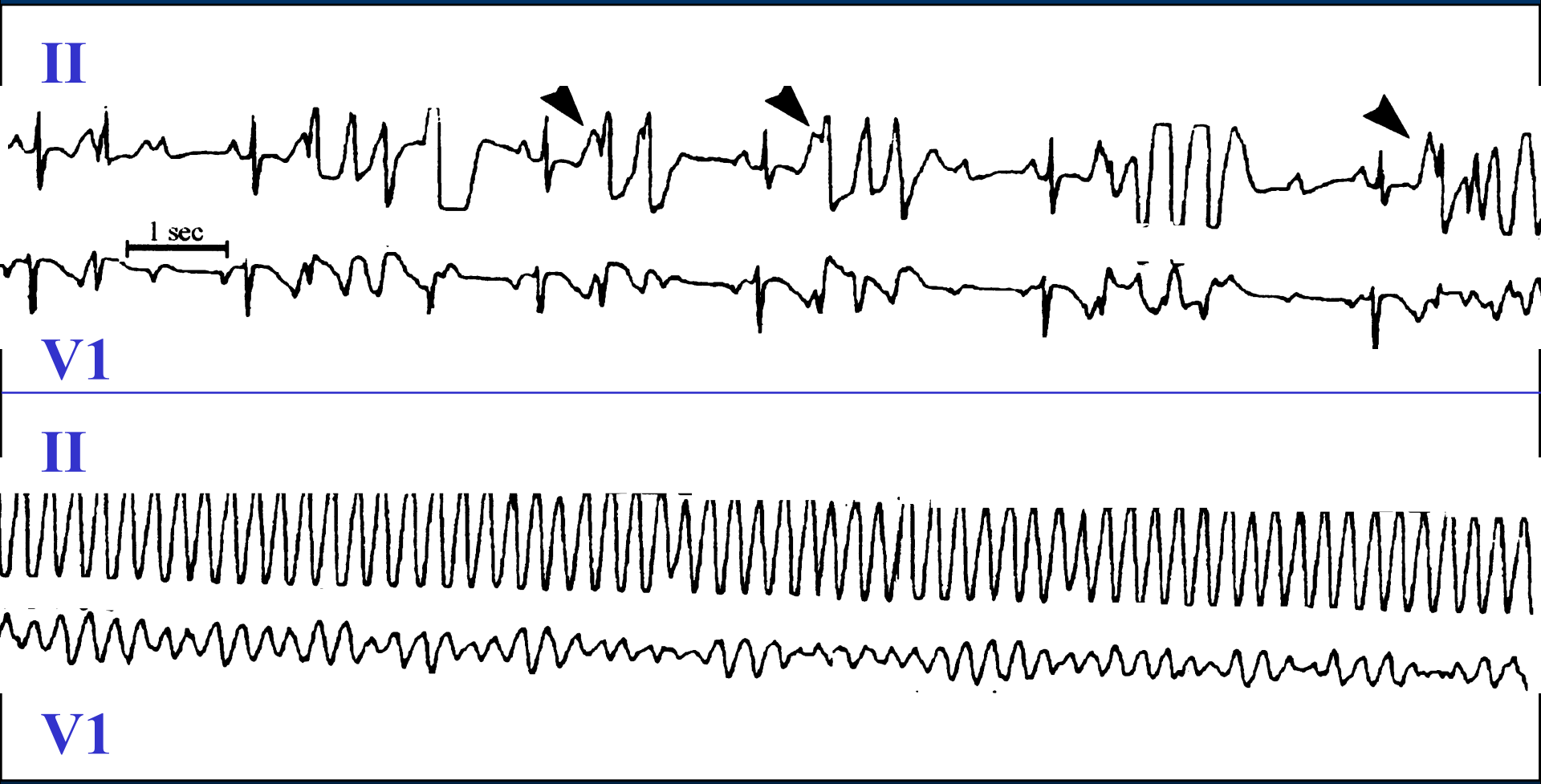
Viskin, *Lancet 1999*



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Viskin, *Lancet 1999*

Ventricular arrhythmias in patients with organic heart disease

Myocardial infarction

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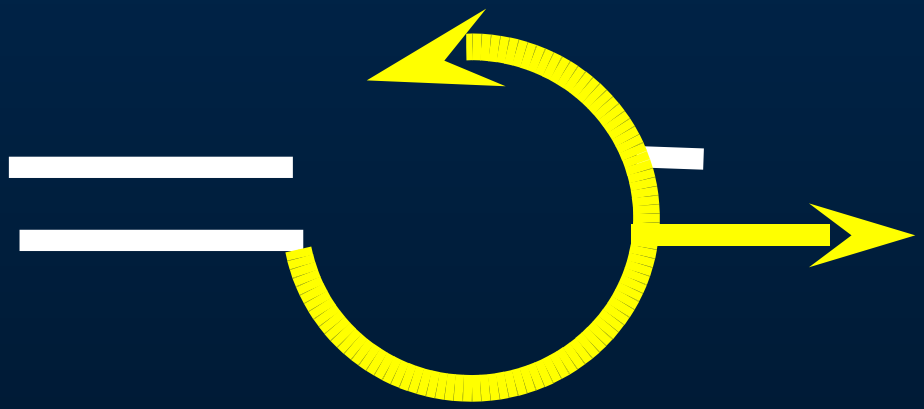
Reentry: basic requirements.

1. Two pathways.

2. Unidirectional block.

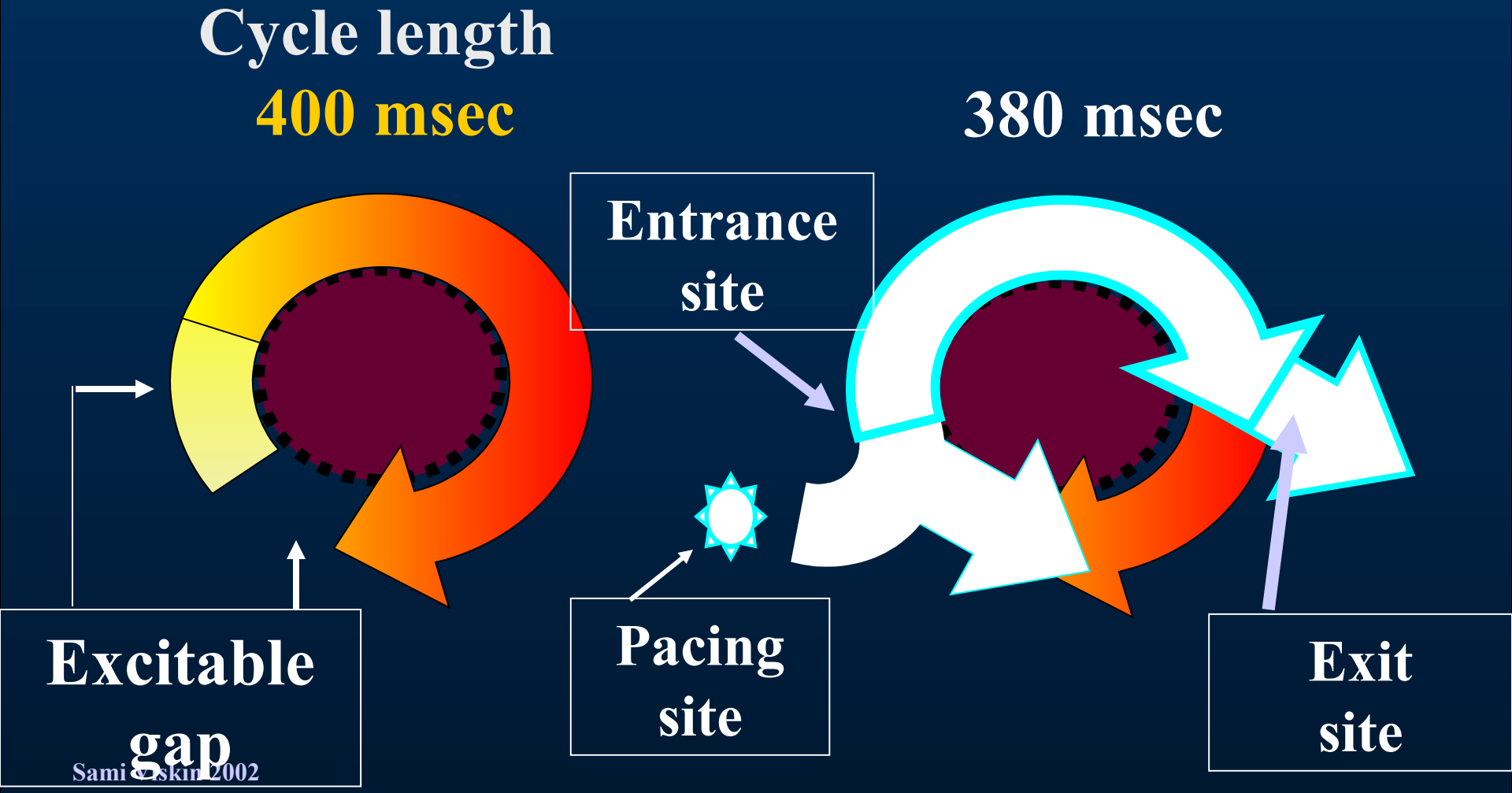
3. Slow conduction.



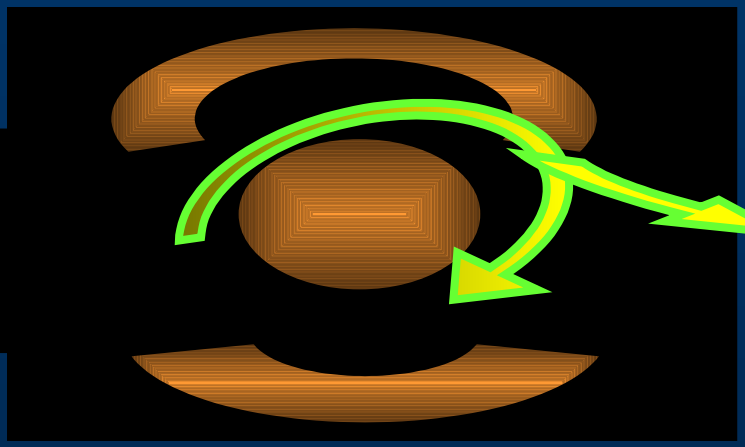
4. Reentry.

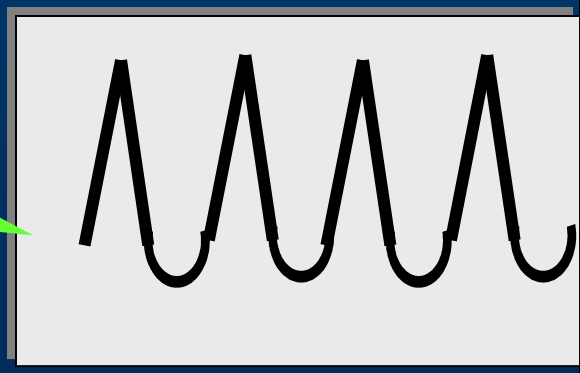
Characteristics of arrhythmias due to reentry.

1. Induction by programmed stimulation.
2. Entrainment.



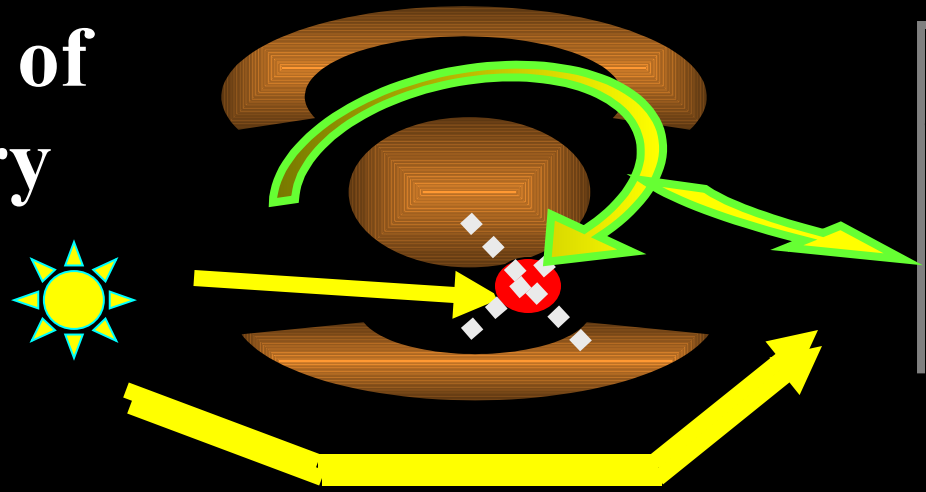
Arrhythmia due to reentry

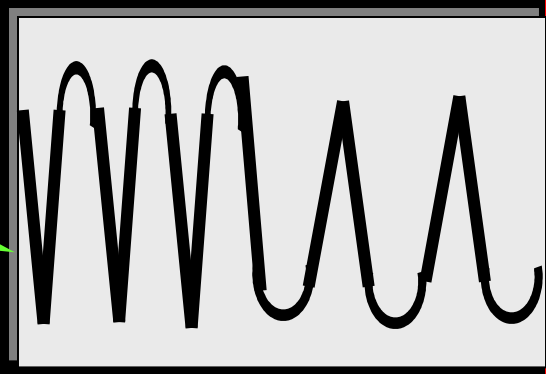




Entrainment with fusion (manifest entrainment)

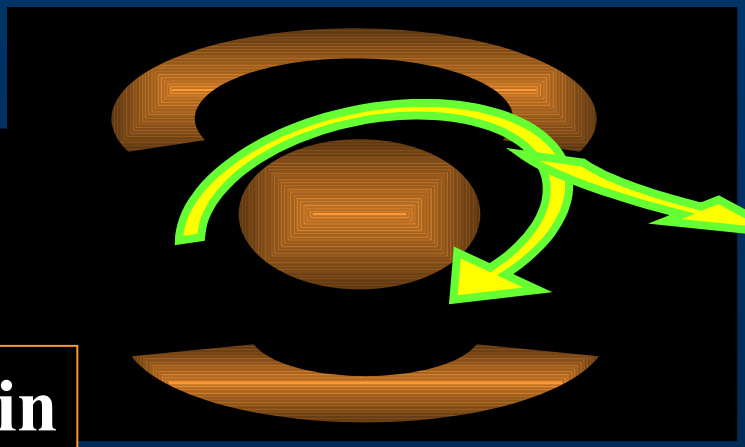
Pacing out of the reentry circuit

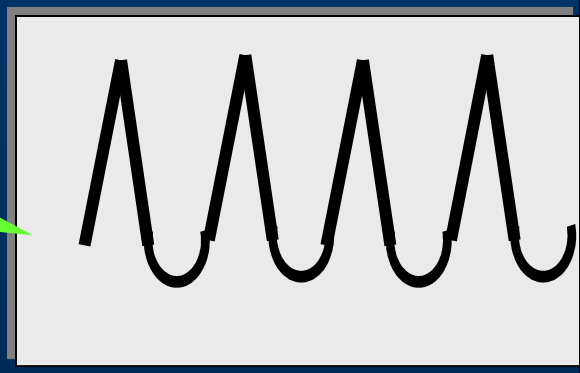




Arrhythmia due to reentry

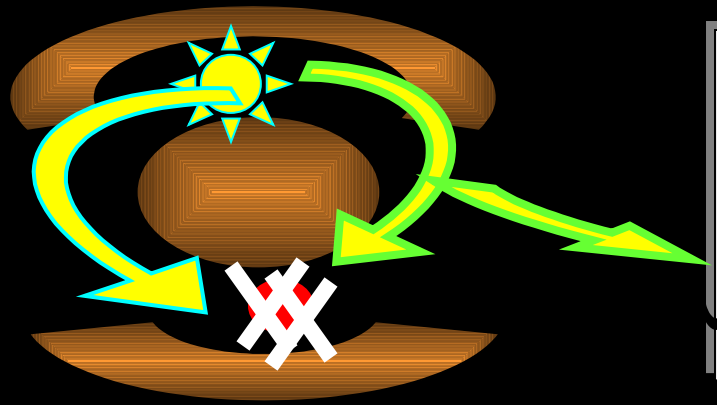
Rate 190 beats/min

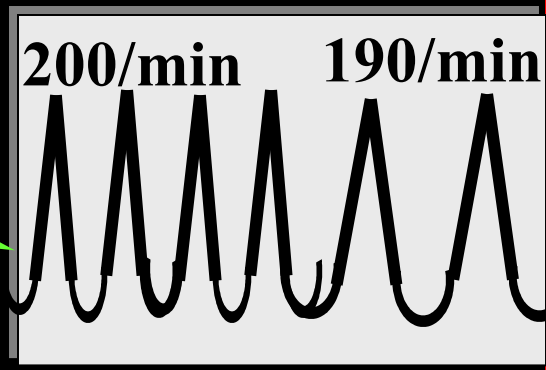




Concealed entrainment

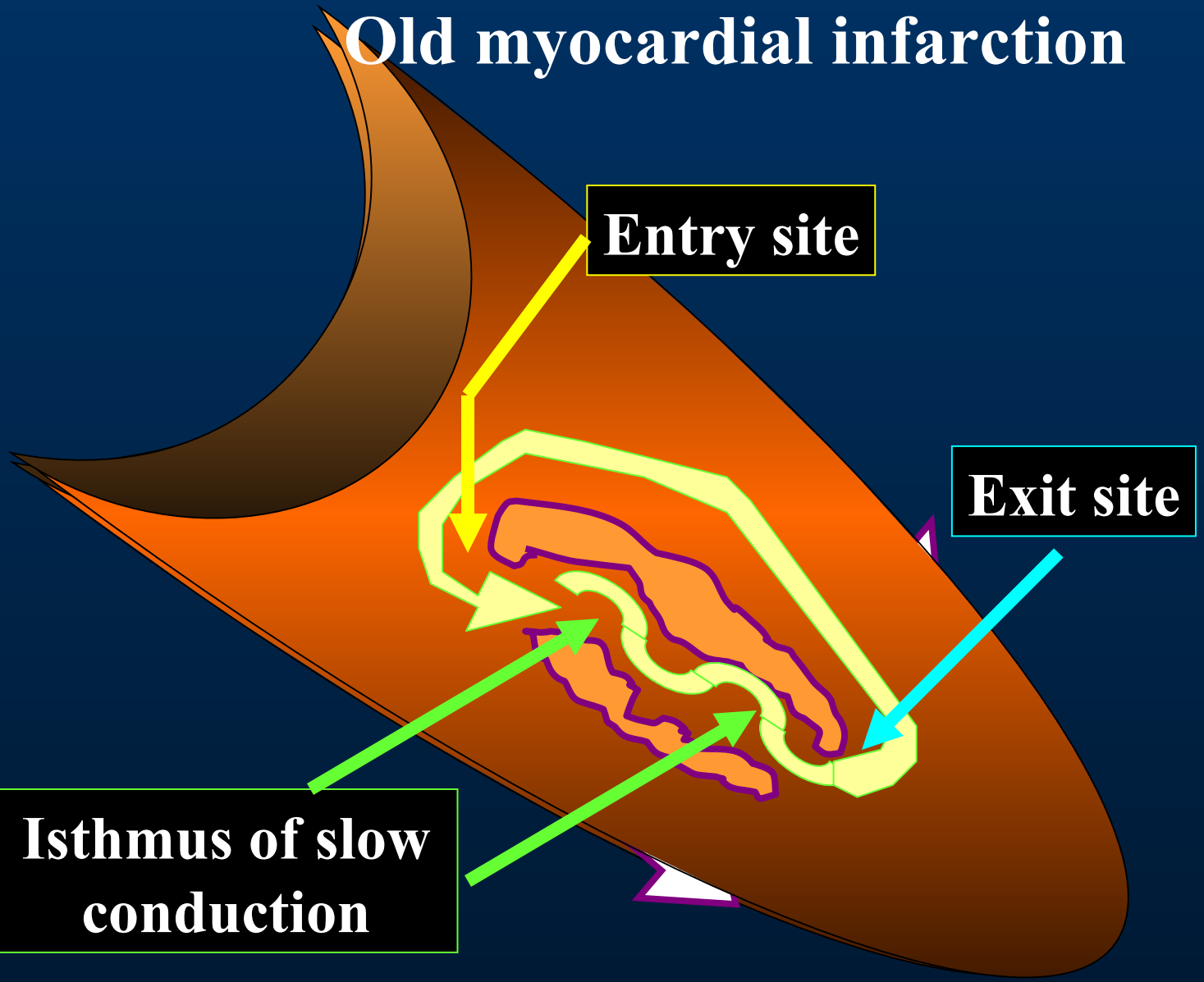
Pacing <u>within</u> the reentry circuit

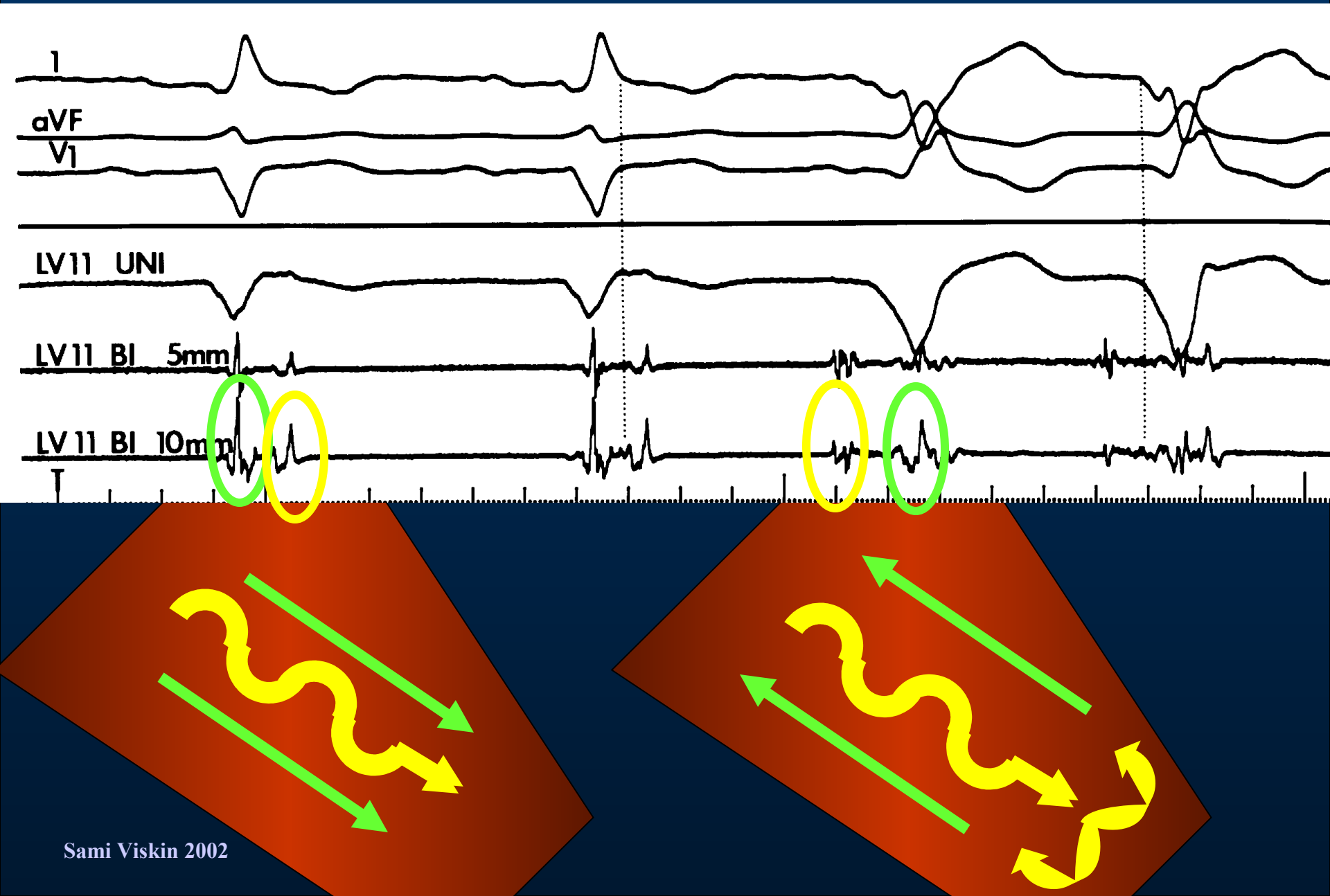




Pacing at 200 beats/min

Monomorphic VT in patients with heart disease. Old myocardial infarction





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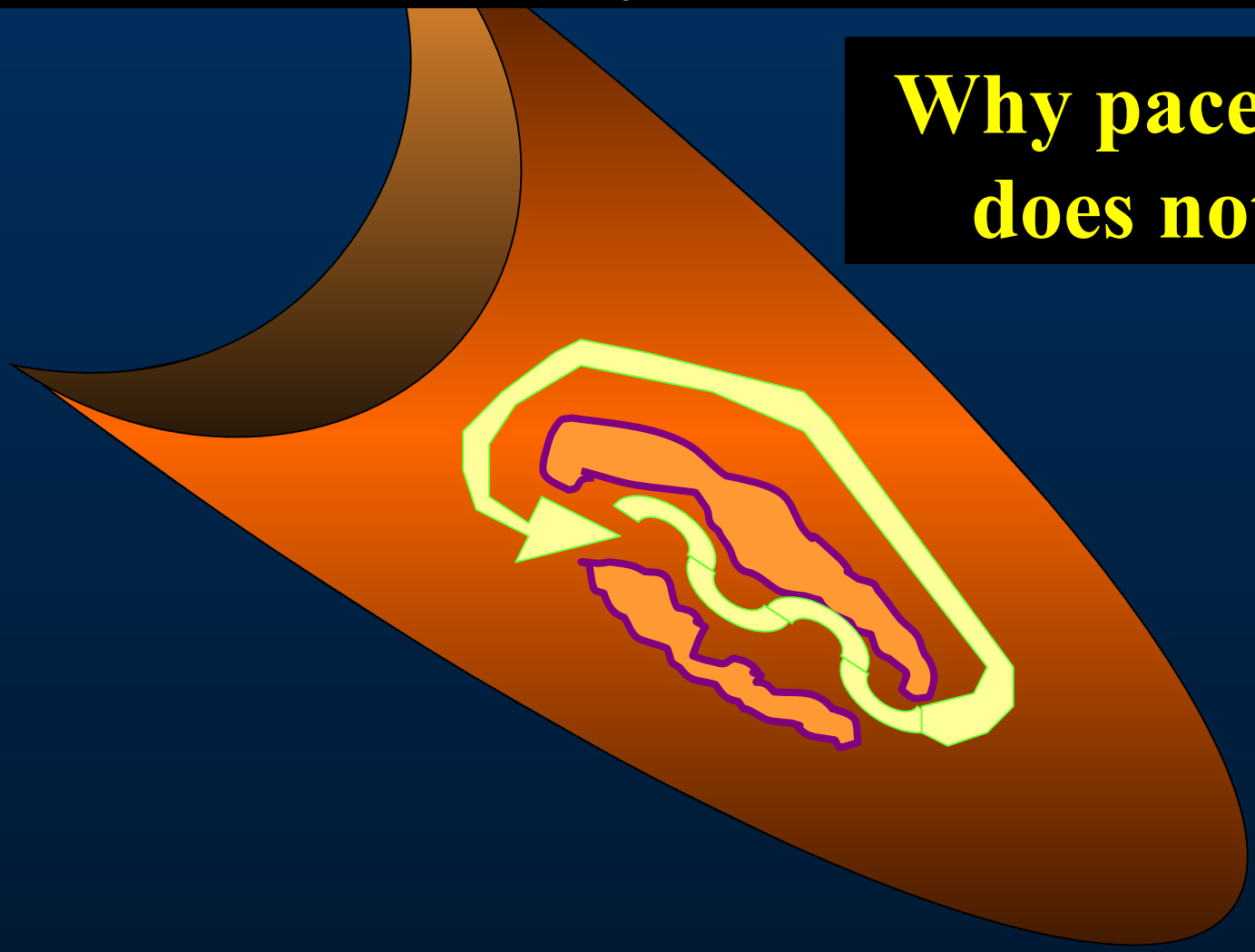
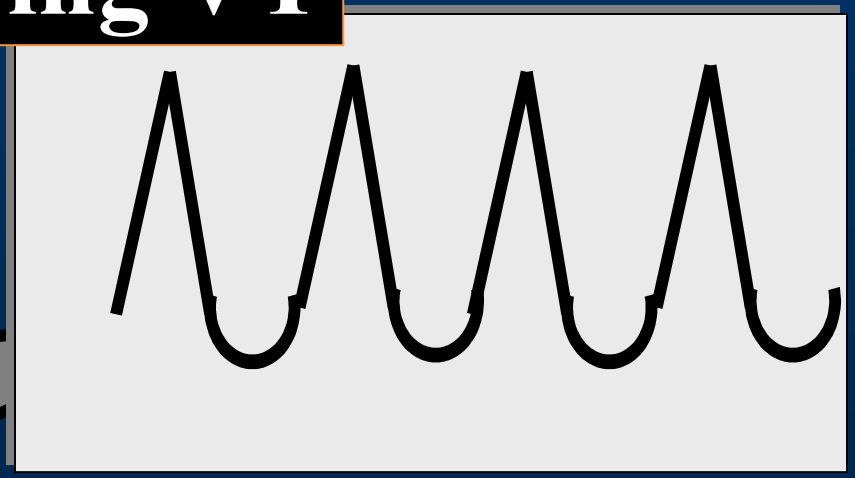
Mapping of monomorphic VT in patients with old myocardial infarction

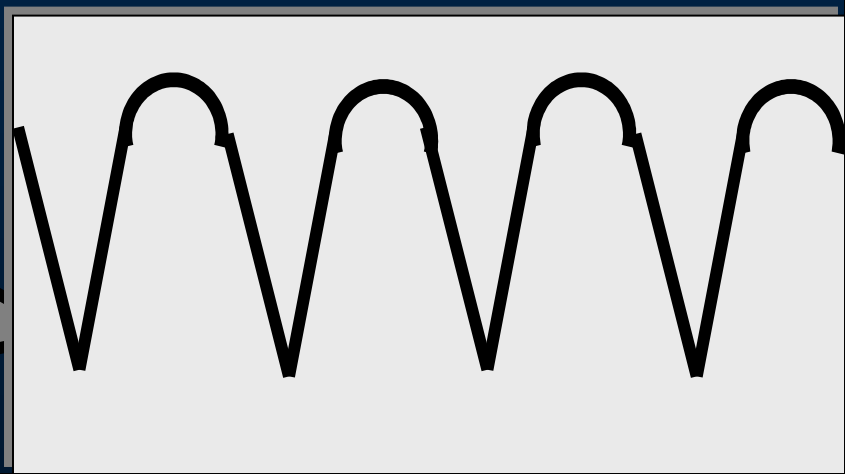


Why pace mapping does not work?

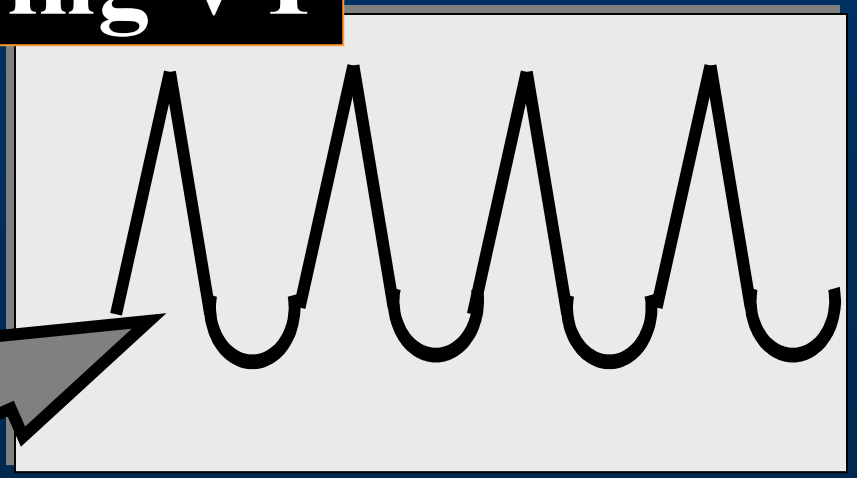
ECG during VT



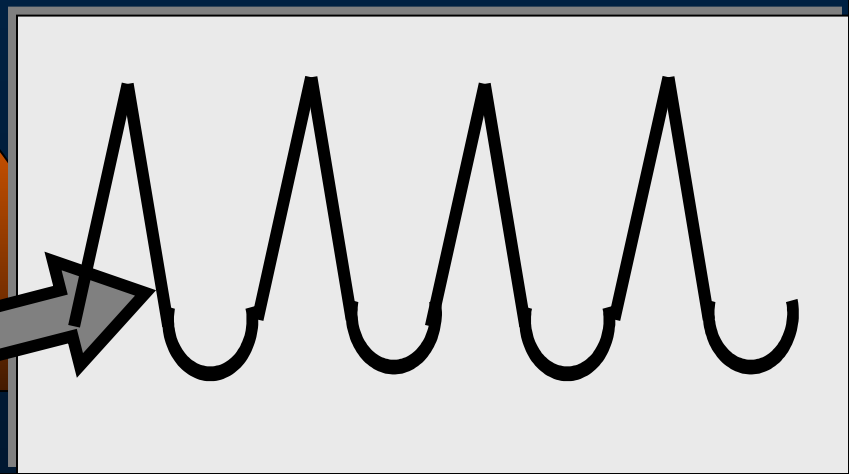
ECG during pacing



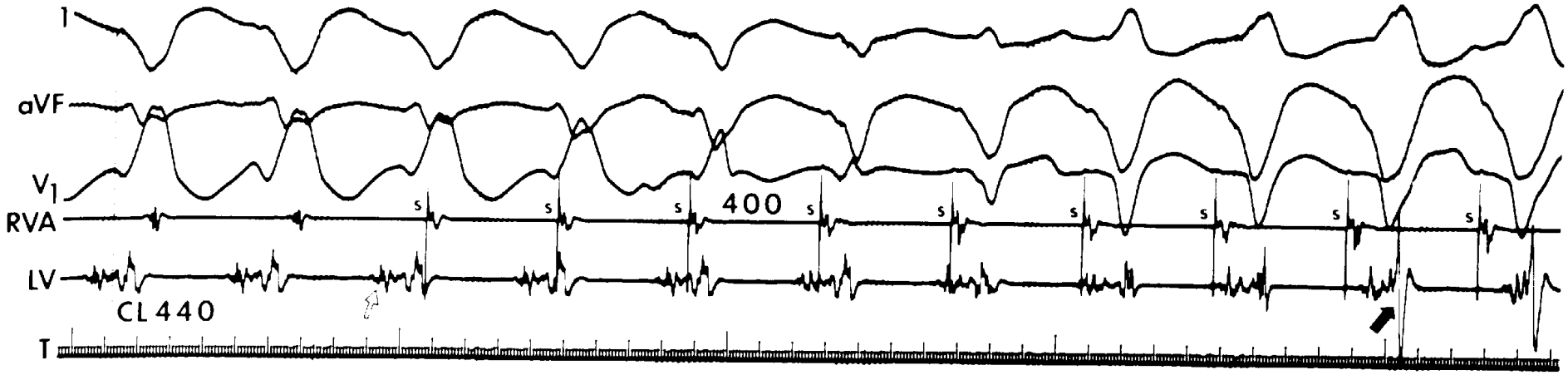
ECG during VT



Pacing during VT



Manifest entrainment (entrainment with fusion): pacing outside of the VT circuit



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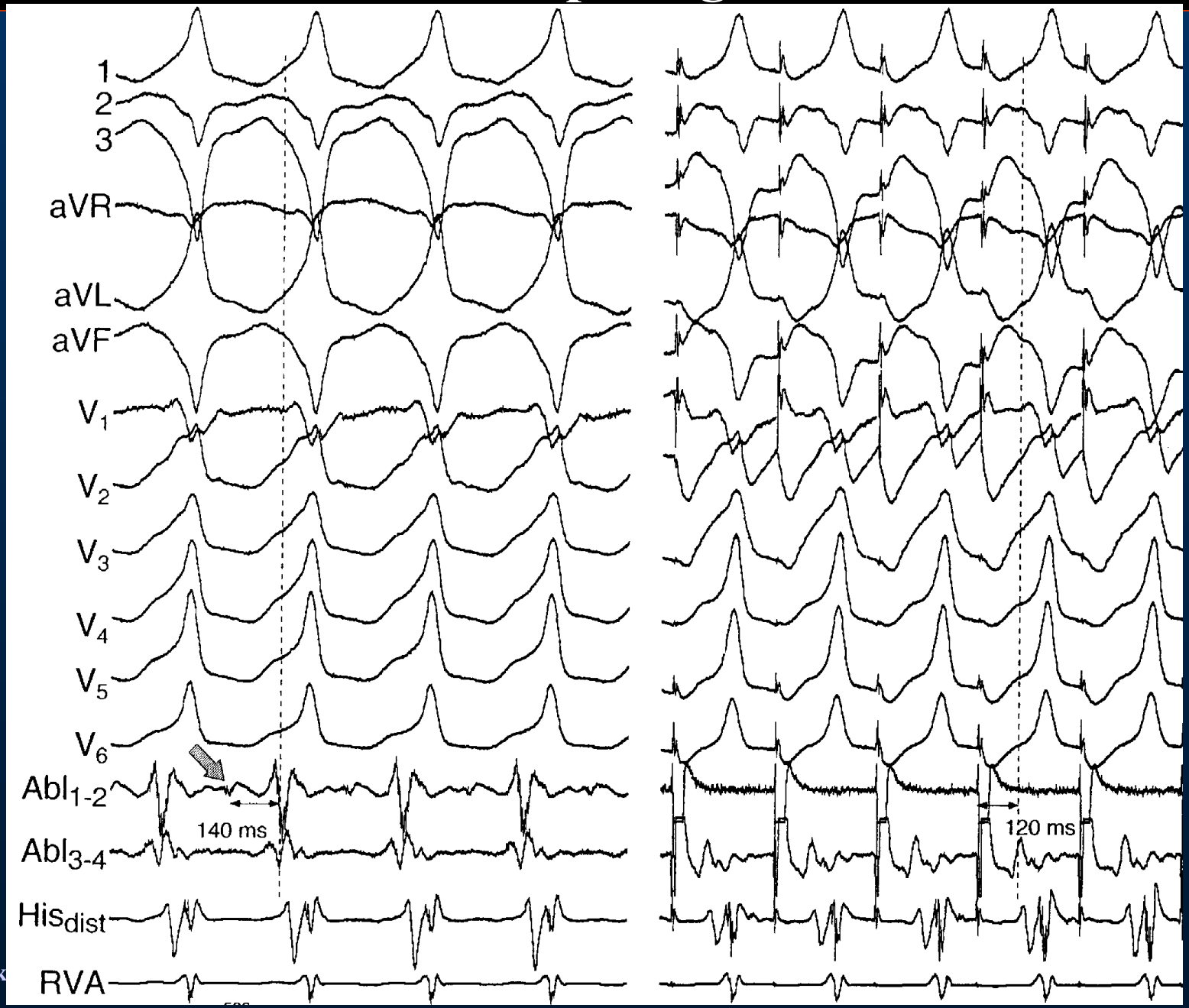
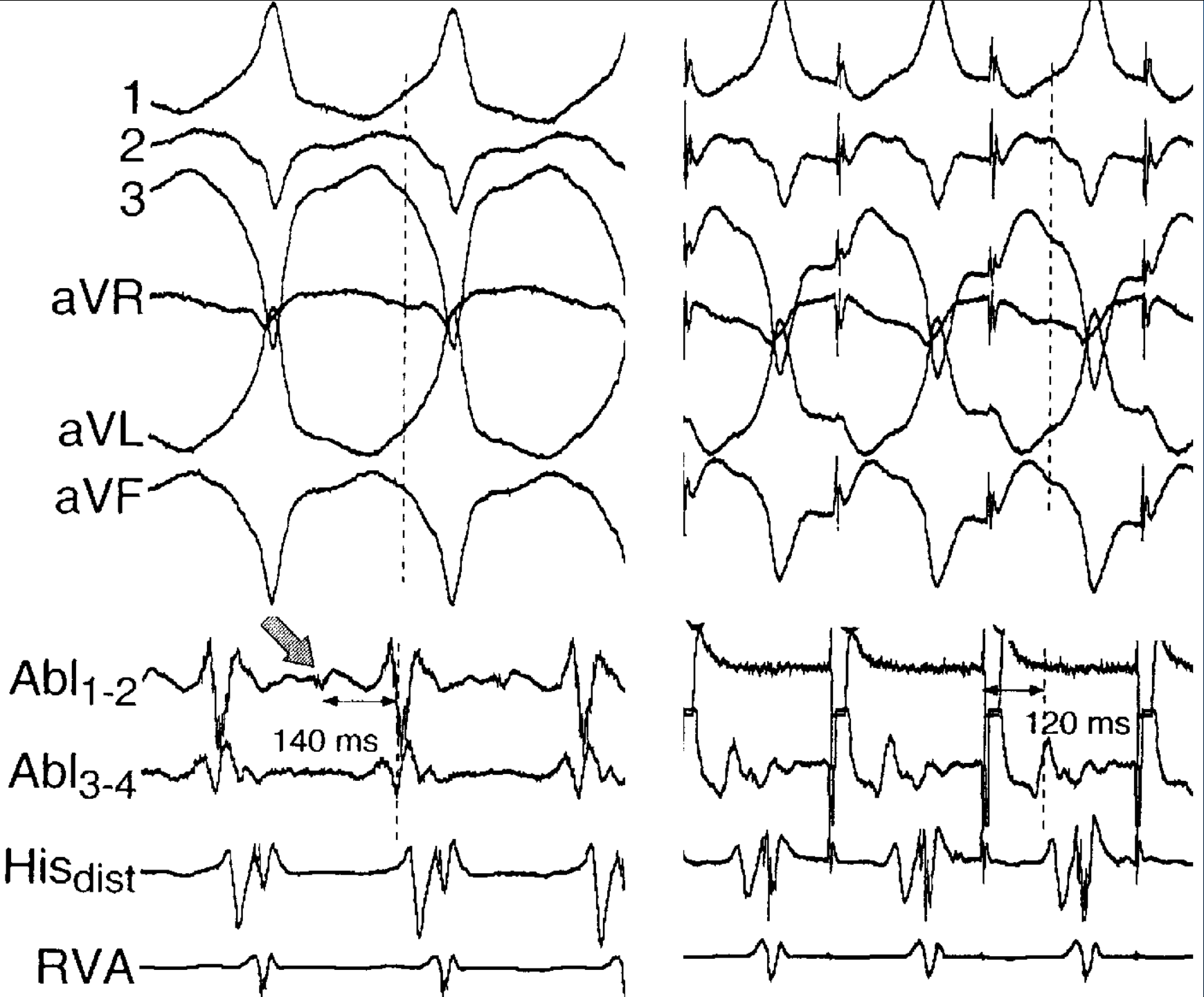
Concealed entrainment: pacing within the VT circuit




1
2
3
aVR
aVL
aVF
Abl1-2
Abl3-4
140 ms
120 ms
HisDist
RVA

Mapping for ablation in VT after myocardial infarction

1. During sinus rhythm.
- Identify areas of slow conduction:
  - Late potentials.
    - Long spike-QRS intervals

2. During ventricular tachycardia.
- Identify areas of slow conduction:
  - Mid-diastolic potentials.

3. During VT entrainment.
- Concealed entrainment
  - Spike-QRS = MDP-QRS
    - PPI = VT cycle length

Mapping and ablation of poorly tolerated VT.

1. Slow VT rate with drugs.

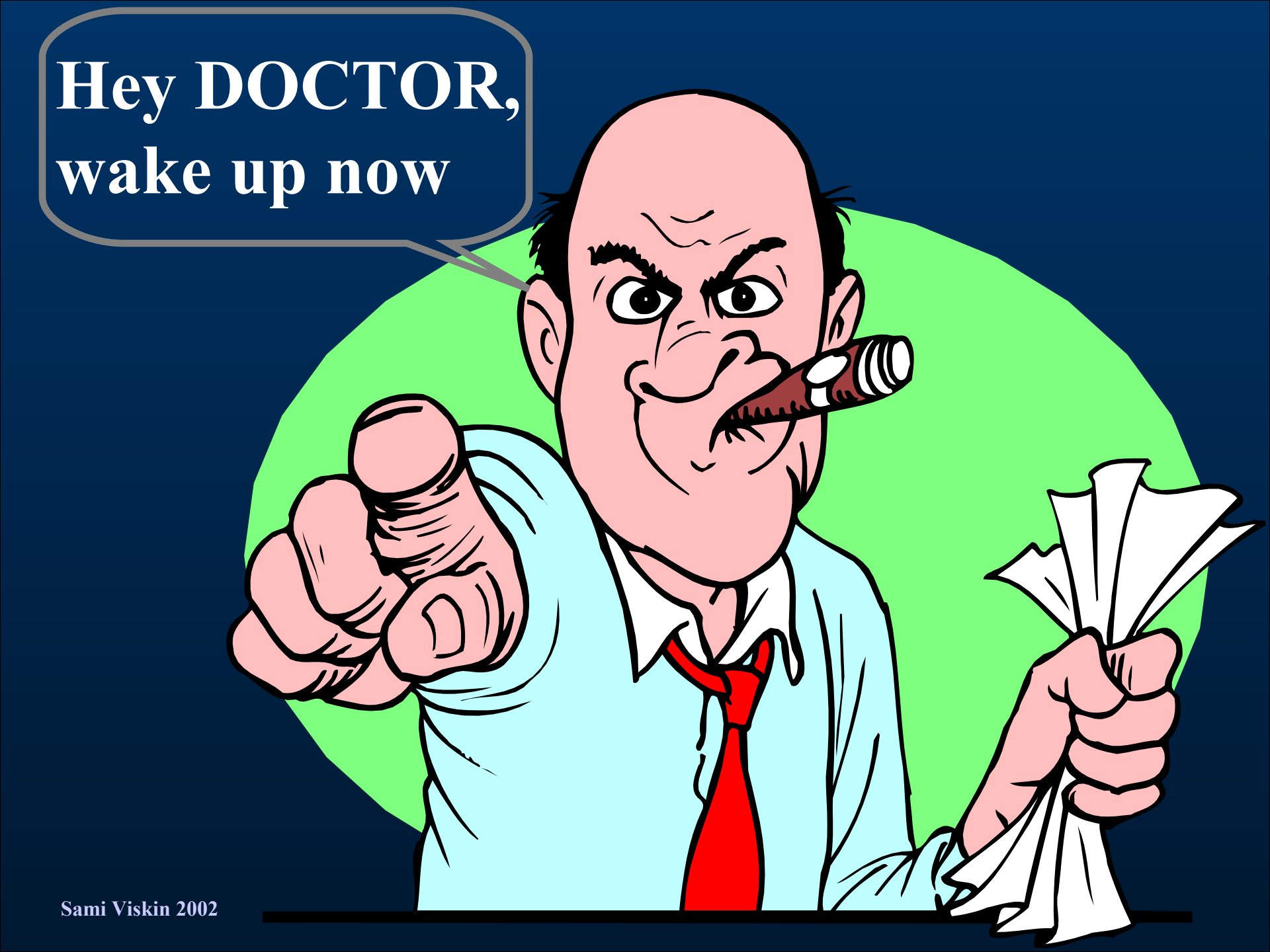
2. Mapping with non-contact electrodes.

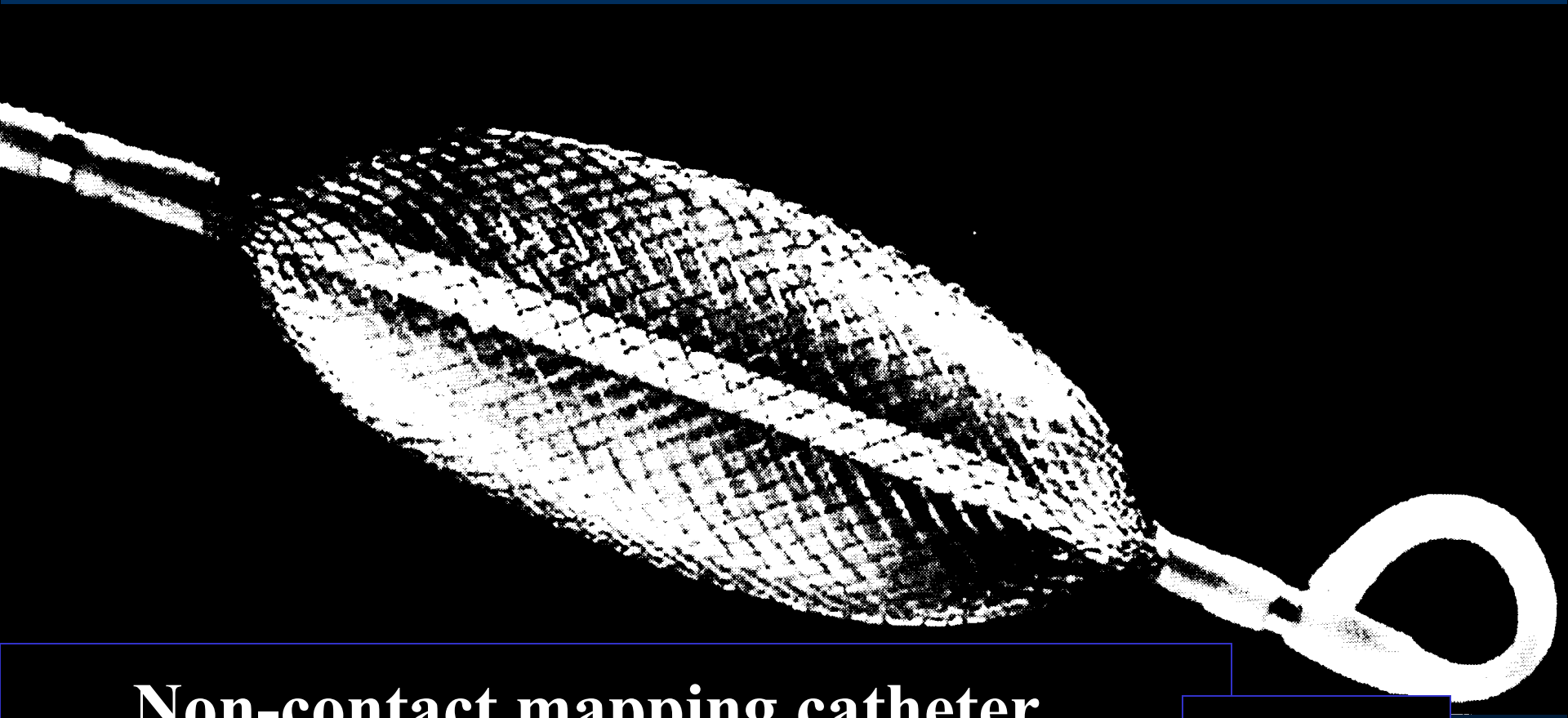
3. Mapping in sinus rhythm:
   - Locate abnormal areas (low voltage, fractionated electrograms).
   - Long pace to QRS intervals.
   - Pace mapping QRS similar to VT

- **Well-tolerated, verapamil sensitive, sustained monomorphic VT (not catecholamine sensitive) – RBBB pattern with left axis, rate 210/min – with no evidence of organic heart disease.**

- **Asymptomatic non-sustained (12 QRS, 180/min) monomorphic VT (single lead recording) in a patient with old myocardial infarction (LVEF 20%).**

- **Out-of-hospital cardiac arrest due to sustained monomorphic VT deteriorating to VF in a patient with non-ischemic dilated cardiomyopathy.**


Hey DOCTOR,
wake up now
Sami Viskin 2002



Non-contact mapping catheter

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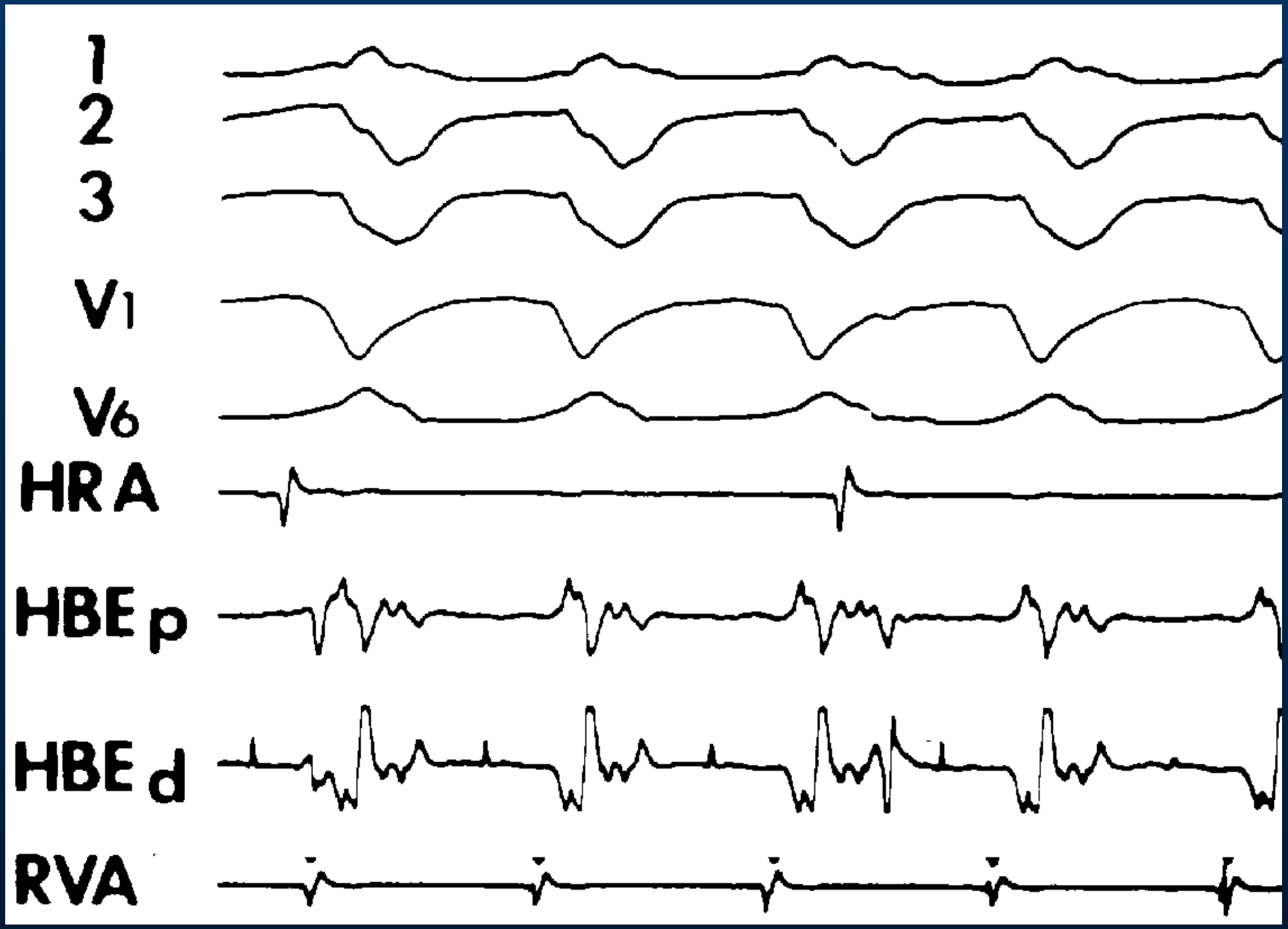

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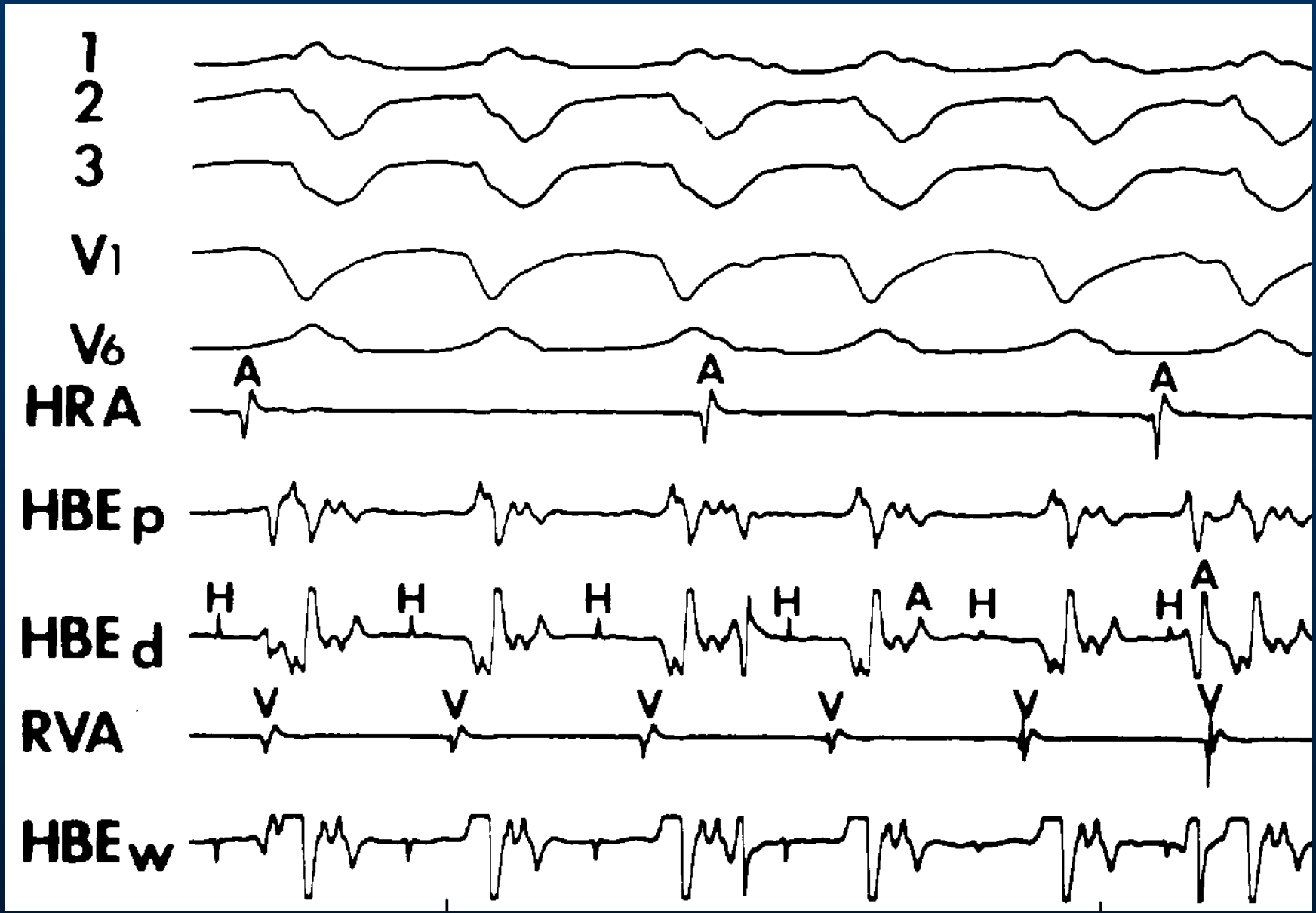

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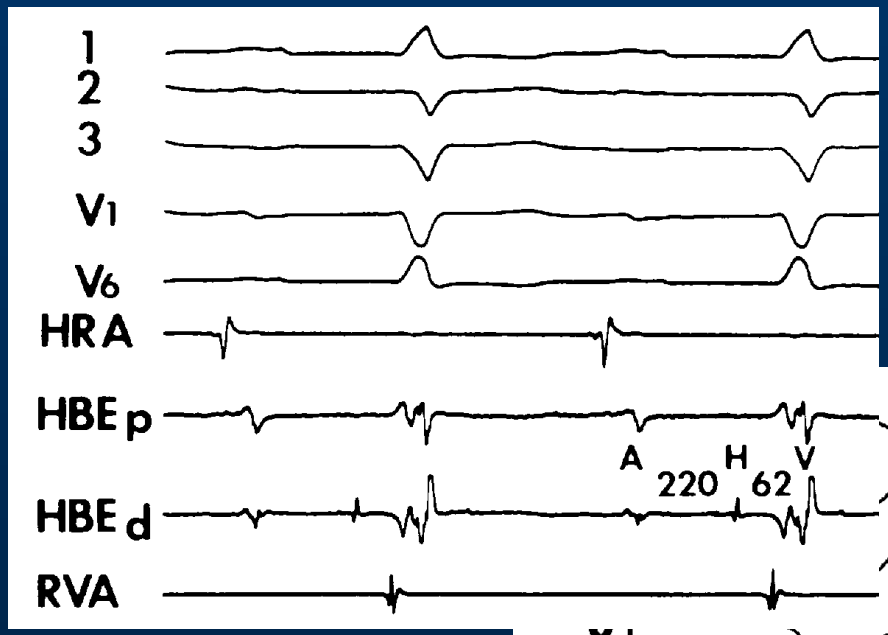

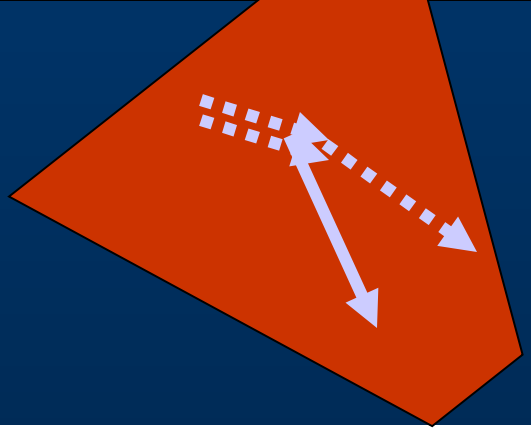

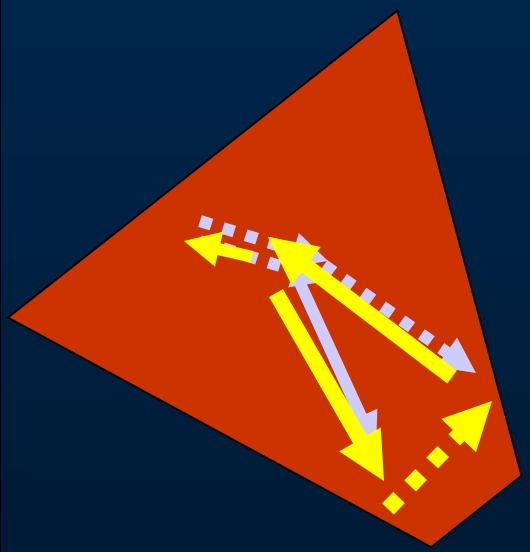

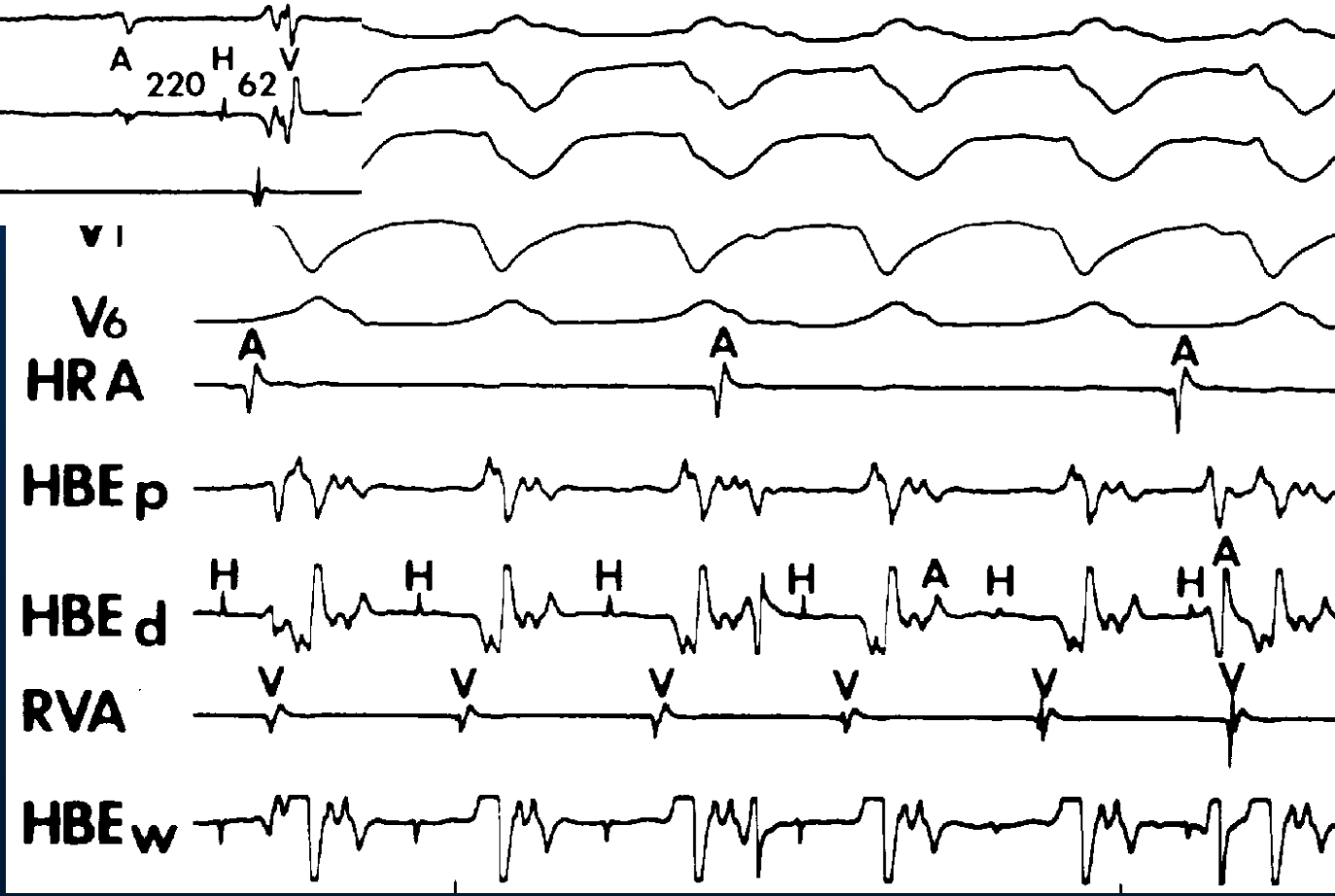

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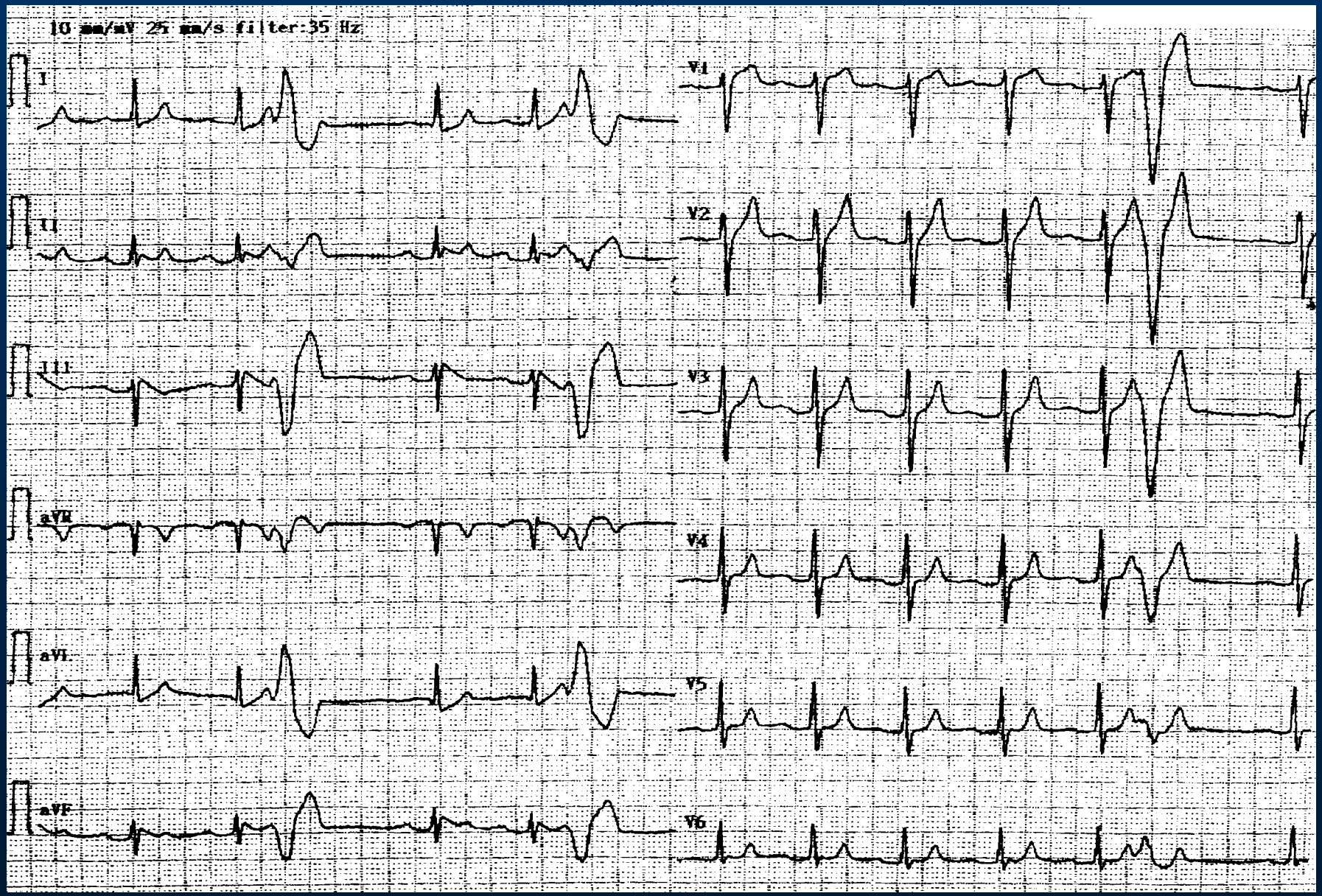
23-9-2002 Naharya



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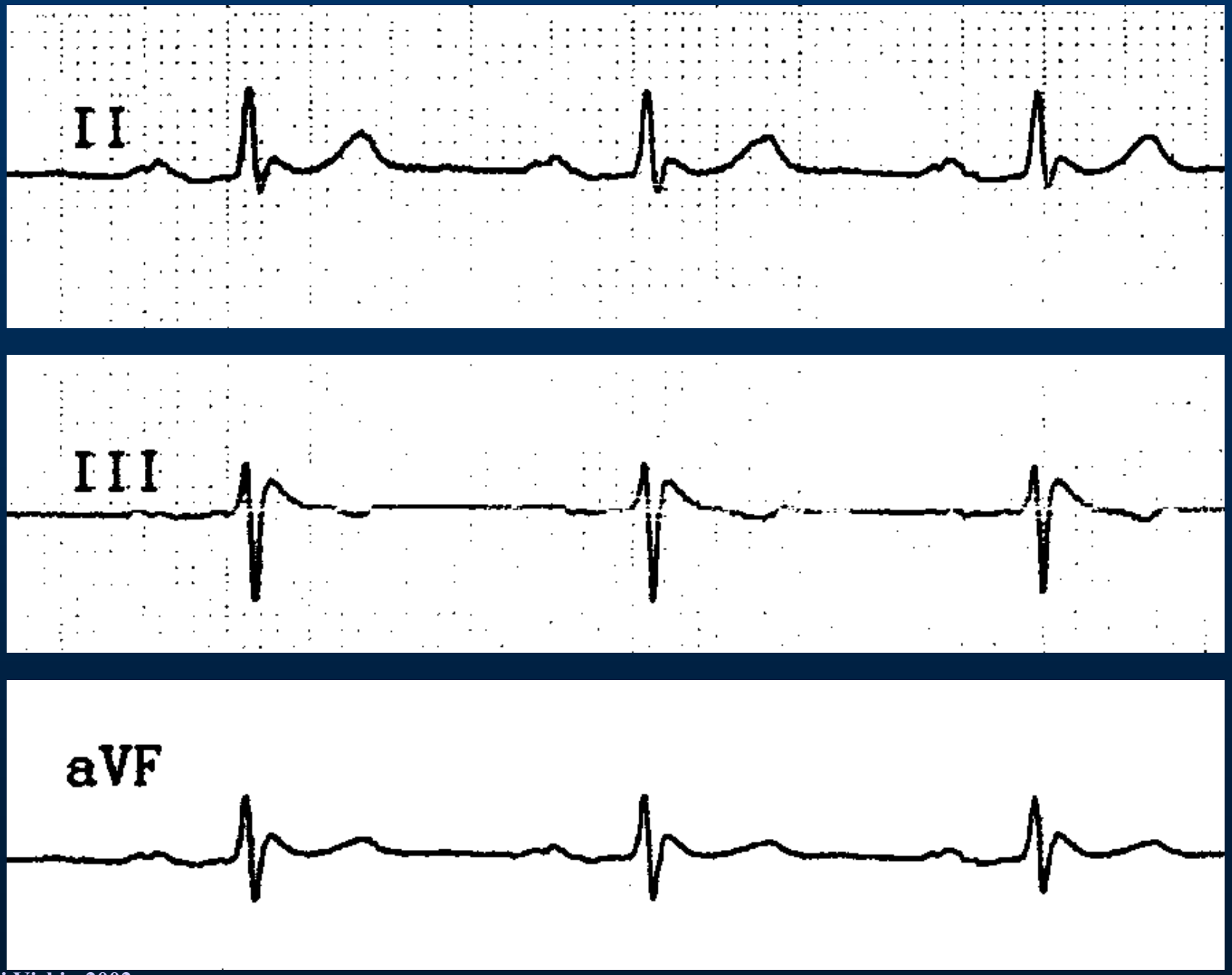
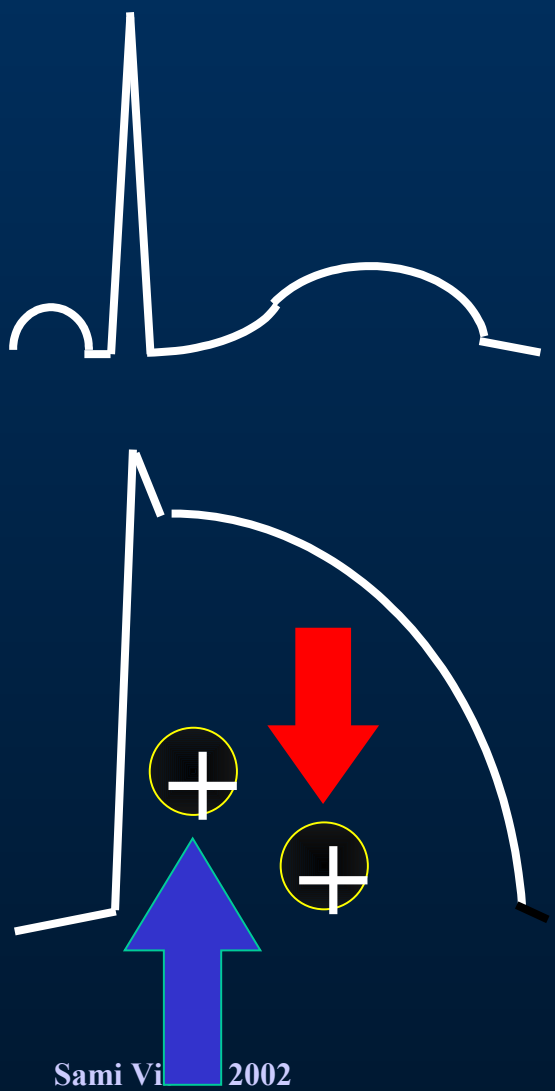
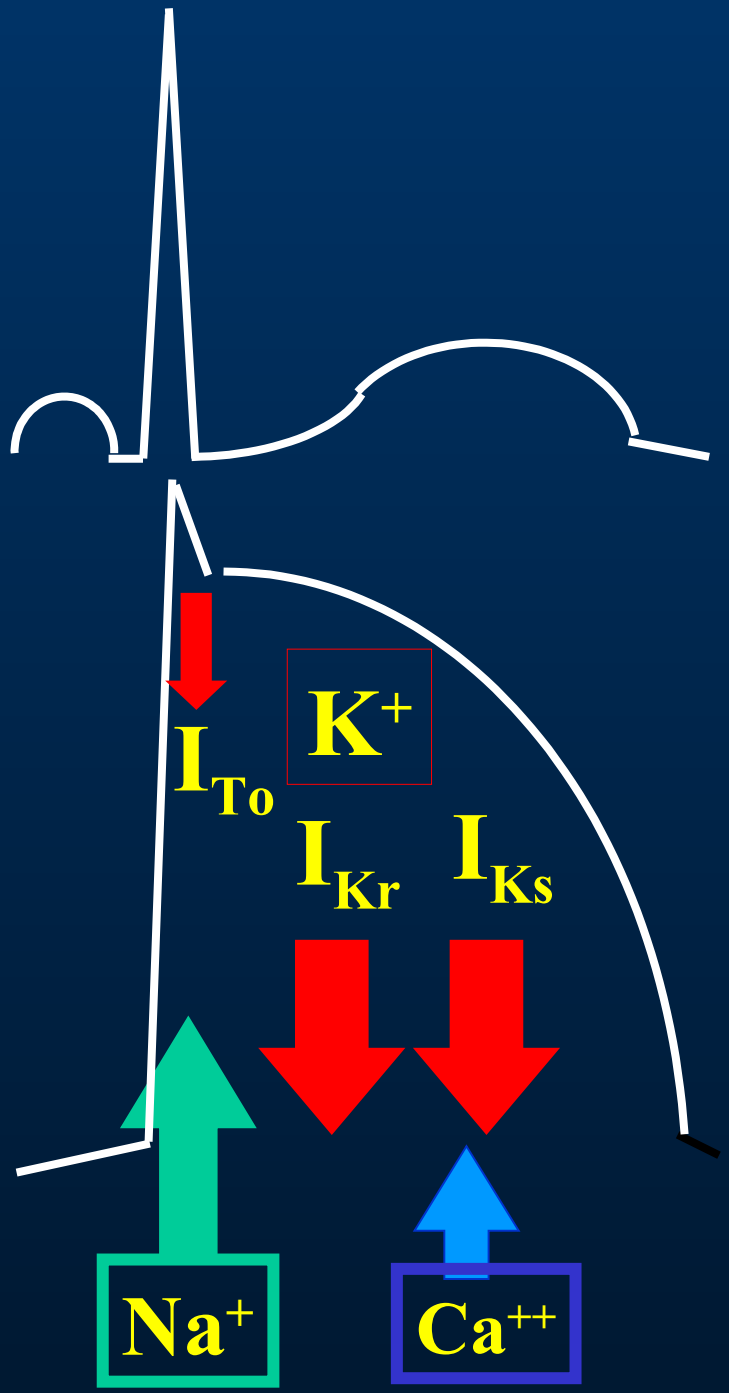
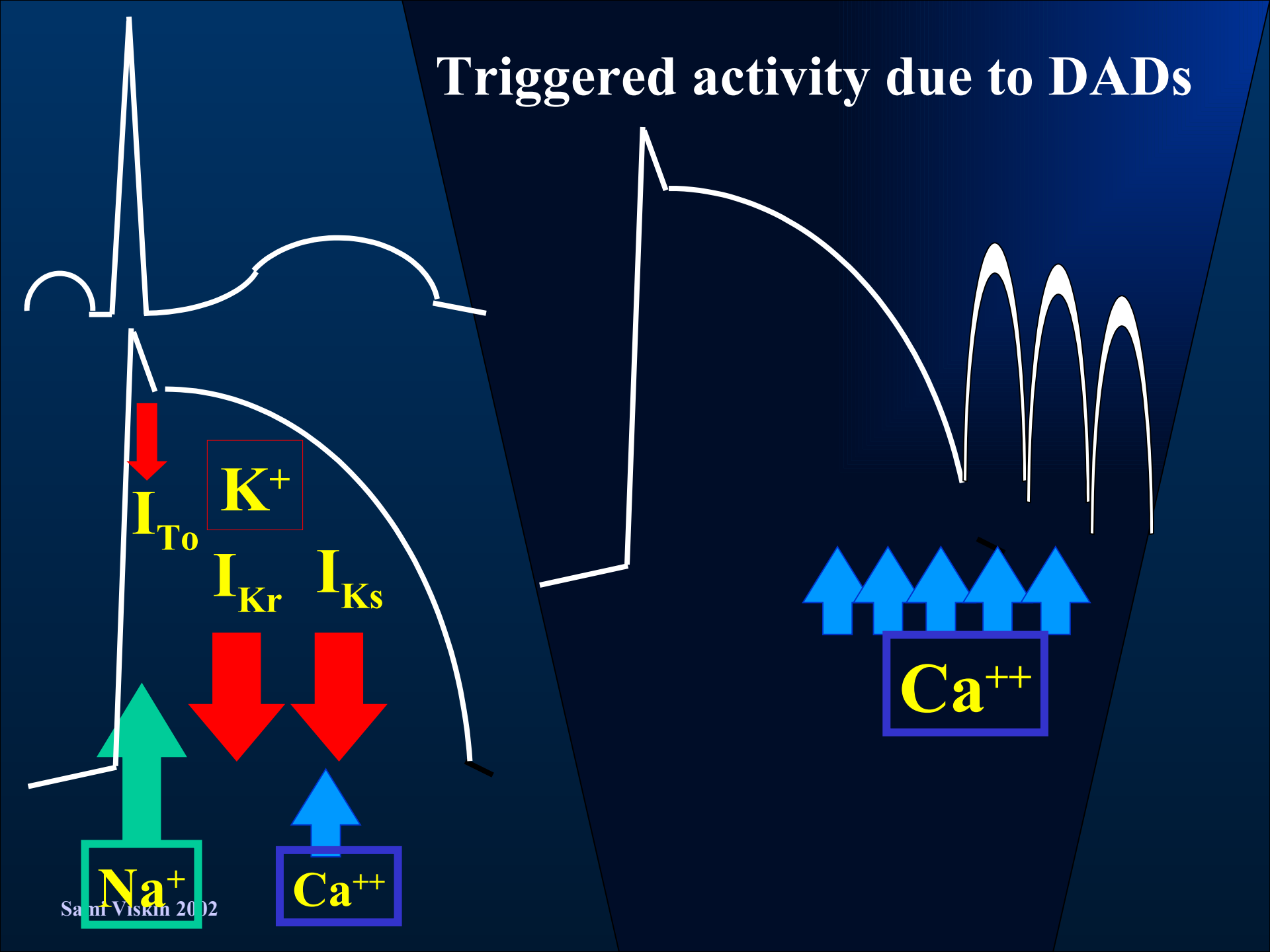
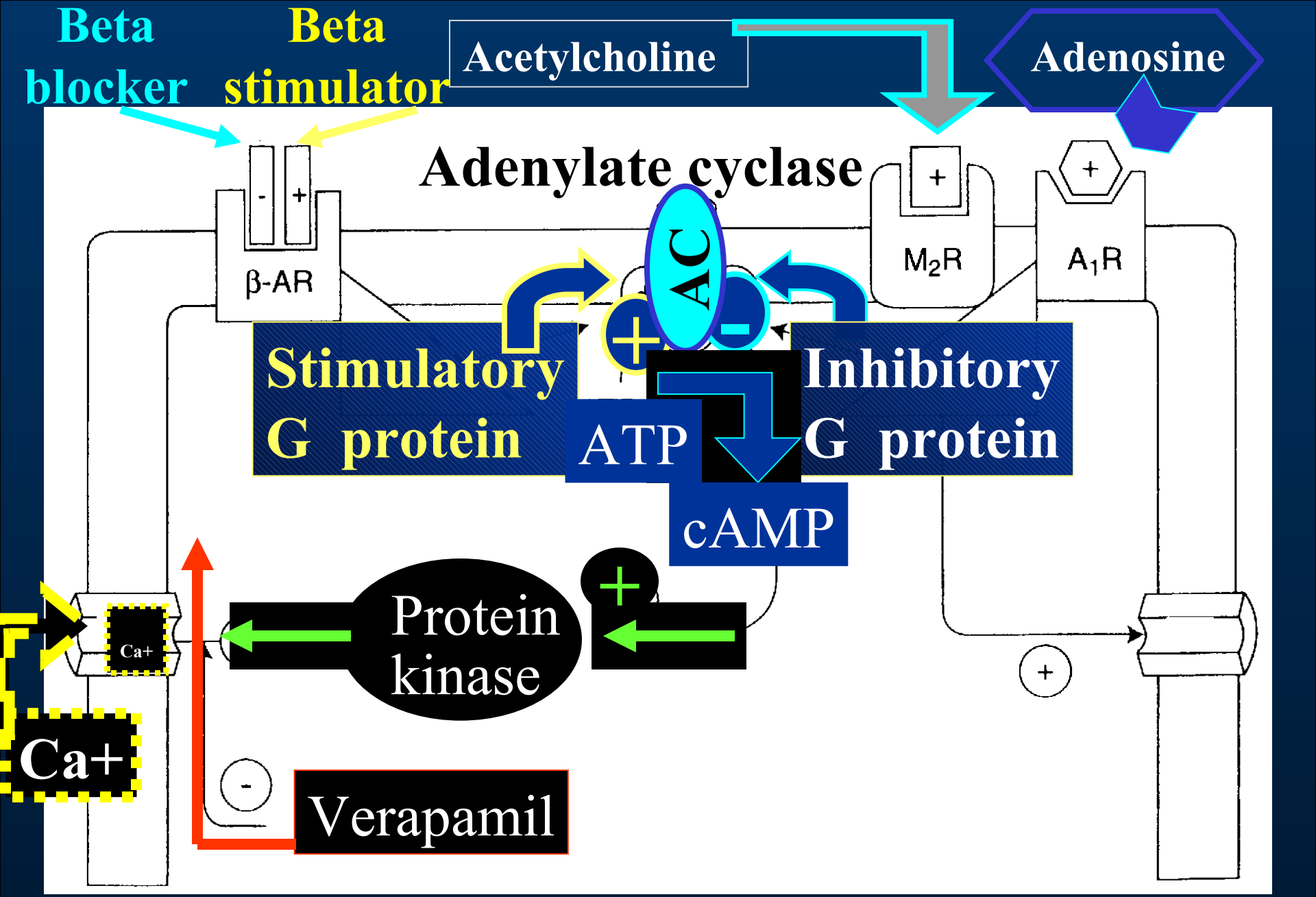



Sami Vi 2002


I_{To}
K^+
I_{Kr}
I_{Ks}
Na^+
Ca^{++}

Triggered activity due to DADs

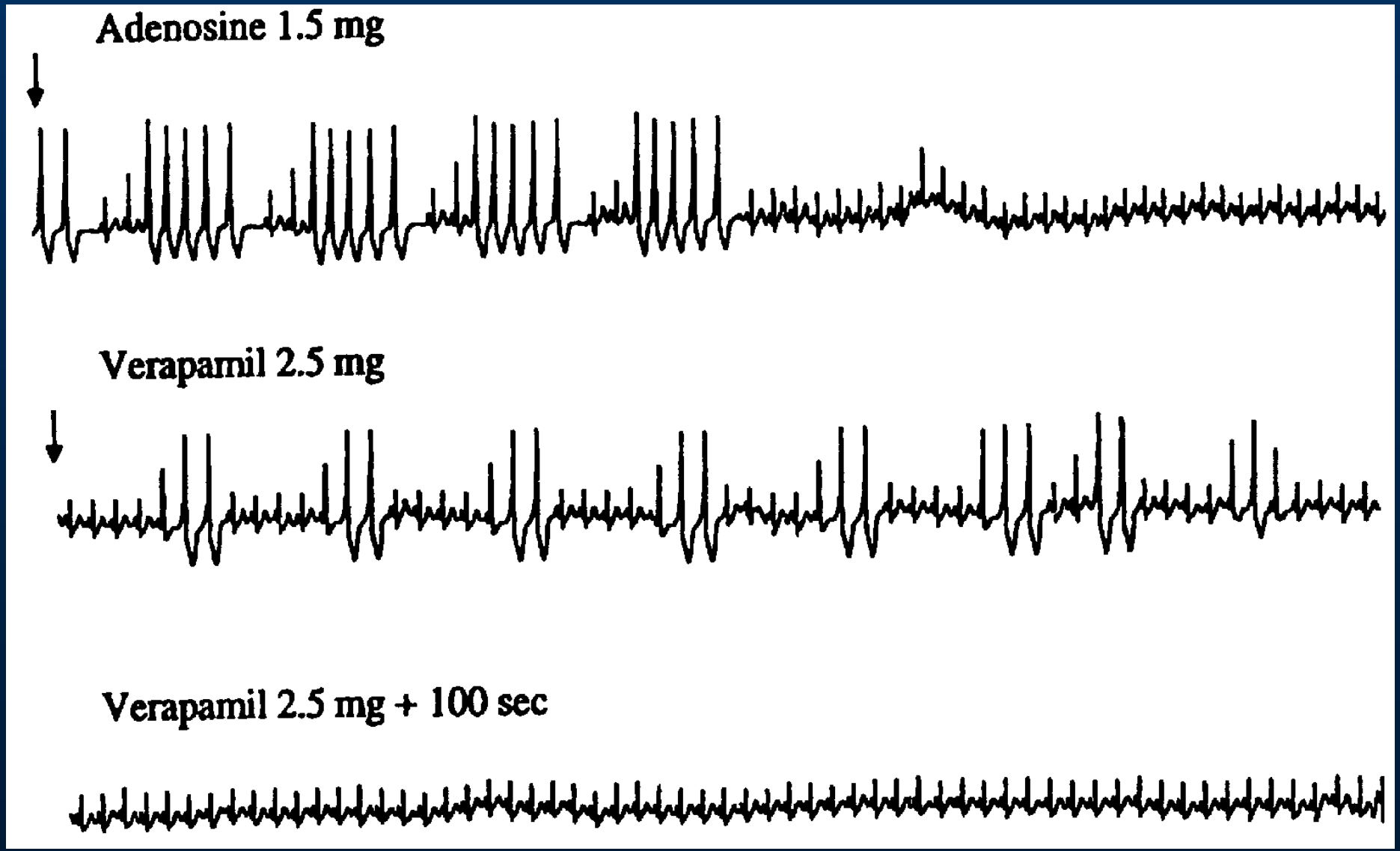




Lerman, *Circulation* 1995;92:421

Lerman, *Cardiol Clin* 2000;18:265

Incessant repetitive non-sustained monomorphic VT
Response to adenosine and to verapamil.



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Lerman, *Circulation* 19995