October 16 - 18
14th EDITION 2015

MY CONFLICTS OF INTEREST ARE

Honoraria from St. Jude,Medtronic,Boston Scienific,Biotronik for lectures

Drug induced Torsades

First described by Seltzer and Wray in 1964 as explanation for Quinidine syncope

Dessertenne first described Torsades de points in 1966

Acquired Long QT Syndromes

Drugs:

Antiarrhythmics (1A, III)
Phenothiazines, antidepressants.
Antibiotics: erythromycin, ketoconazole, pentamidine
Antihistamines: astemizole Seldane

Metabolic:

Low K, Mg, Ca.
Hypothyroidism

Toxins:

Liquid protein diet
Chinese herbs.
Organophosphates

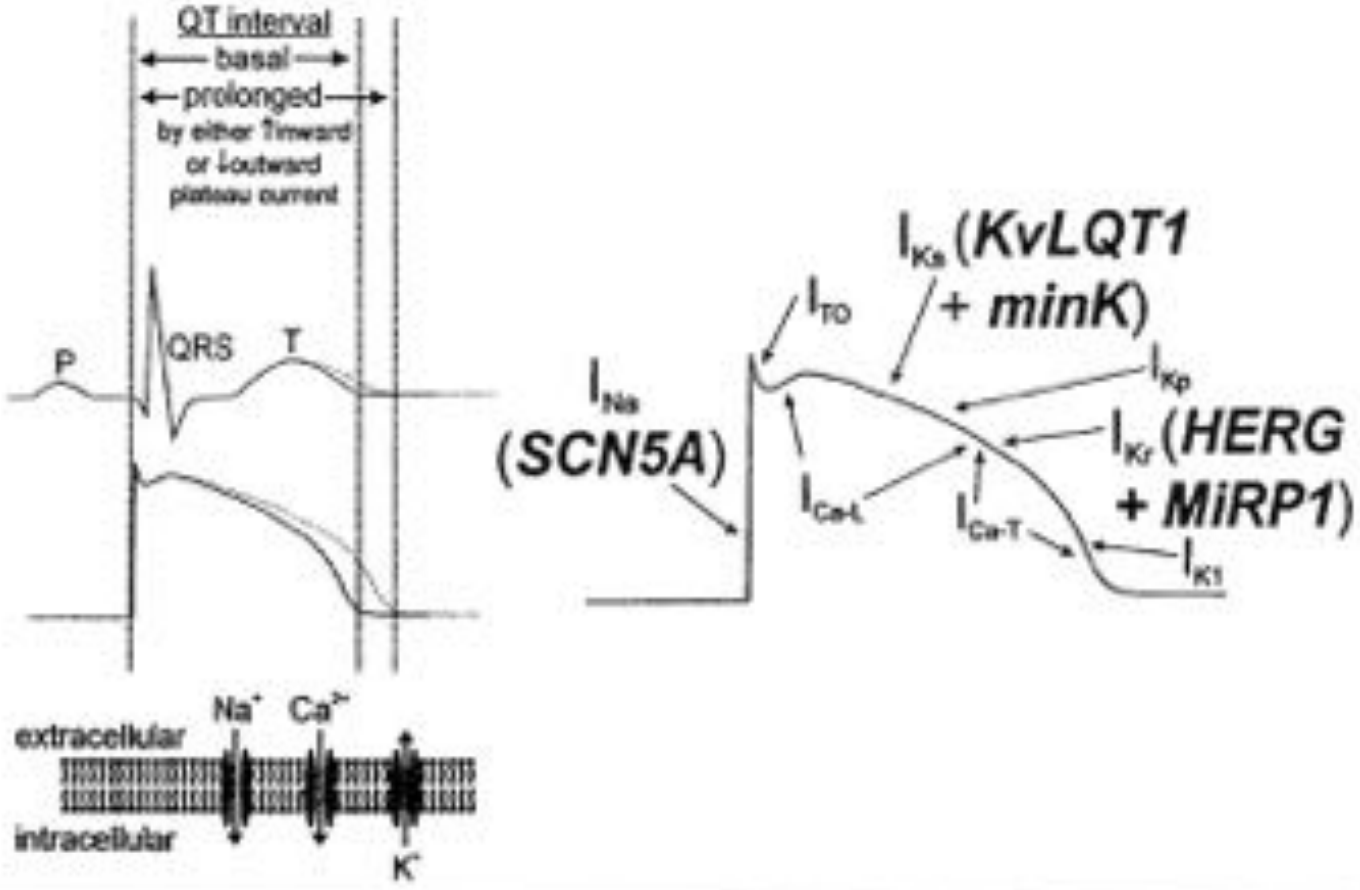
Bradyarrhythmias

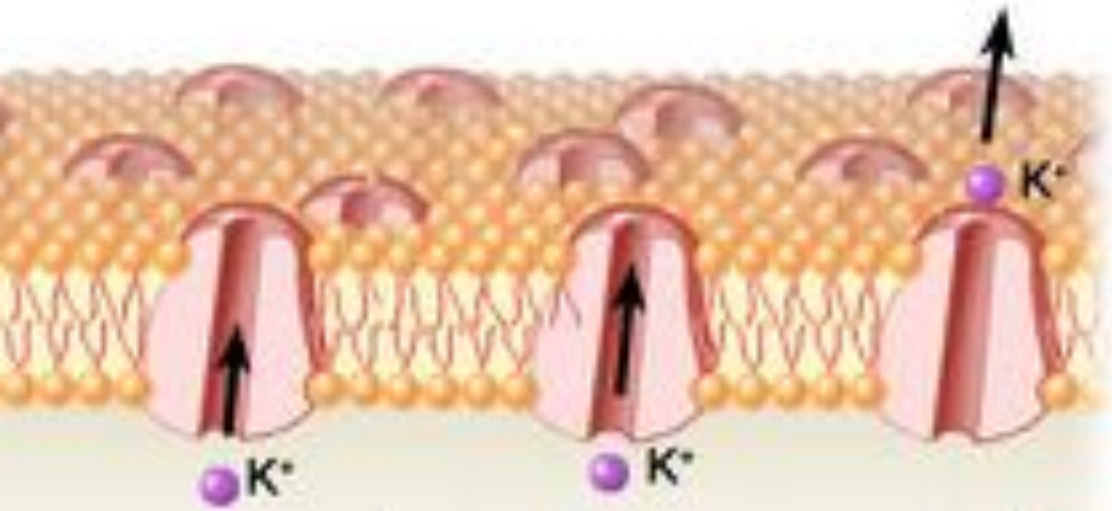
Intracranial disease

Myocardial ischemia

Neck Surgery

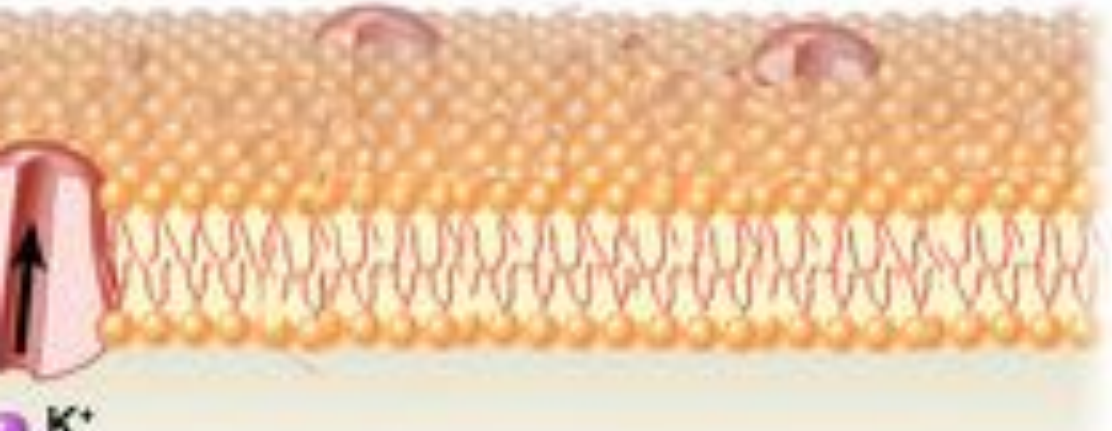
Ion Currents and Repolarization





Normal K^+ Channels

Normal

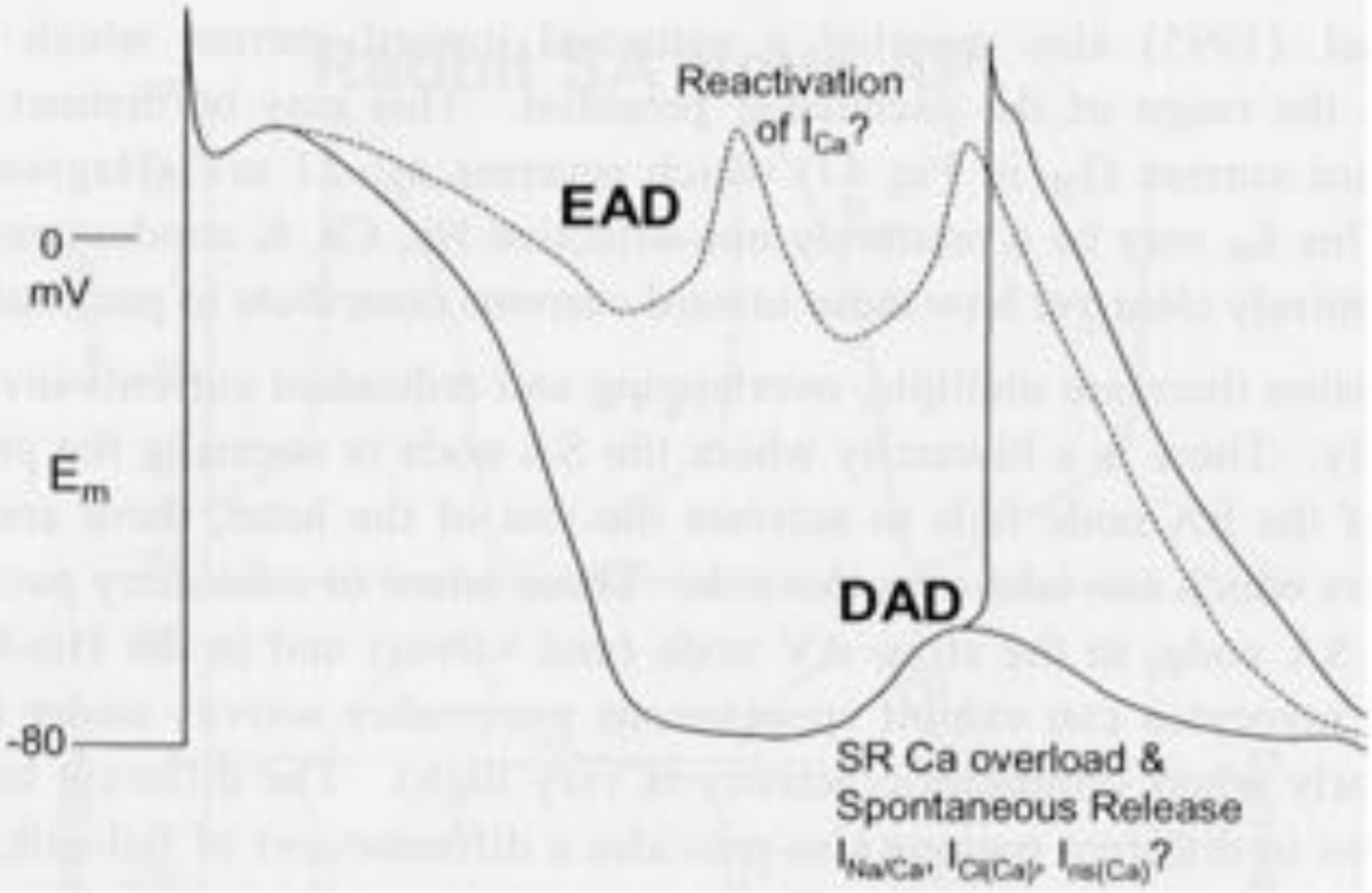


ene defect

lack of K^+ Channels

Long QT

D.M. Bers Cardiac E-C Coupling



Mechanism of drug –induced torsades 2

Late Na current is key to the rate adaptation of ventricular repolarization

For example, with large late Na current there is longer APD (QT) at slower rates.

Increased APD of any cause will serve to amplify late Na current by slowing inactivation and lead to prolongation of the Tp-e interval (measure of TDR)

JACC Journals

From: Mexiletine Prevents Recurrent Torsades de Pointes in Acquired Long QT Syndrome Refractory to Conventional Measures

JACCCEP. 2015;1(4):315-322. doi:10.1016/j.jacep.2015.05.008

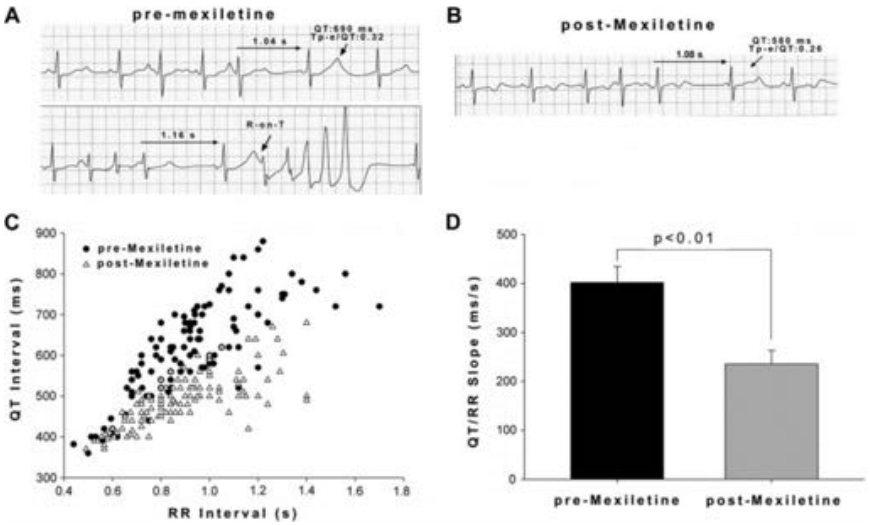
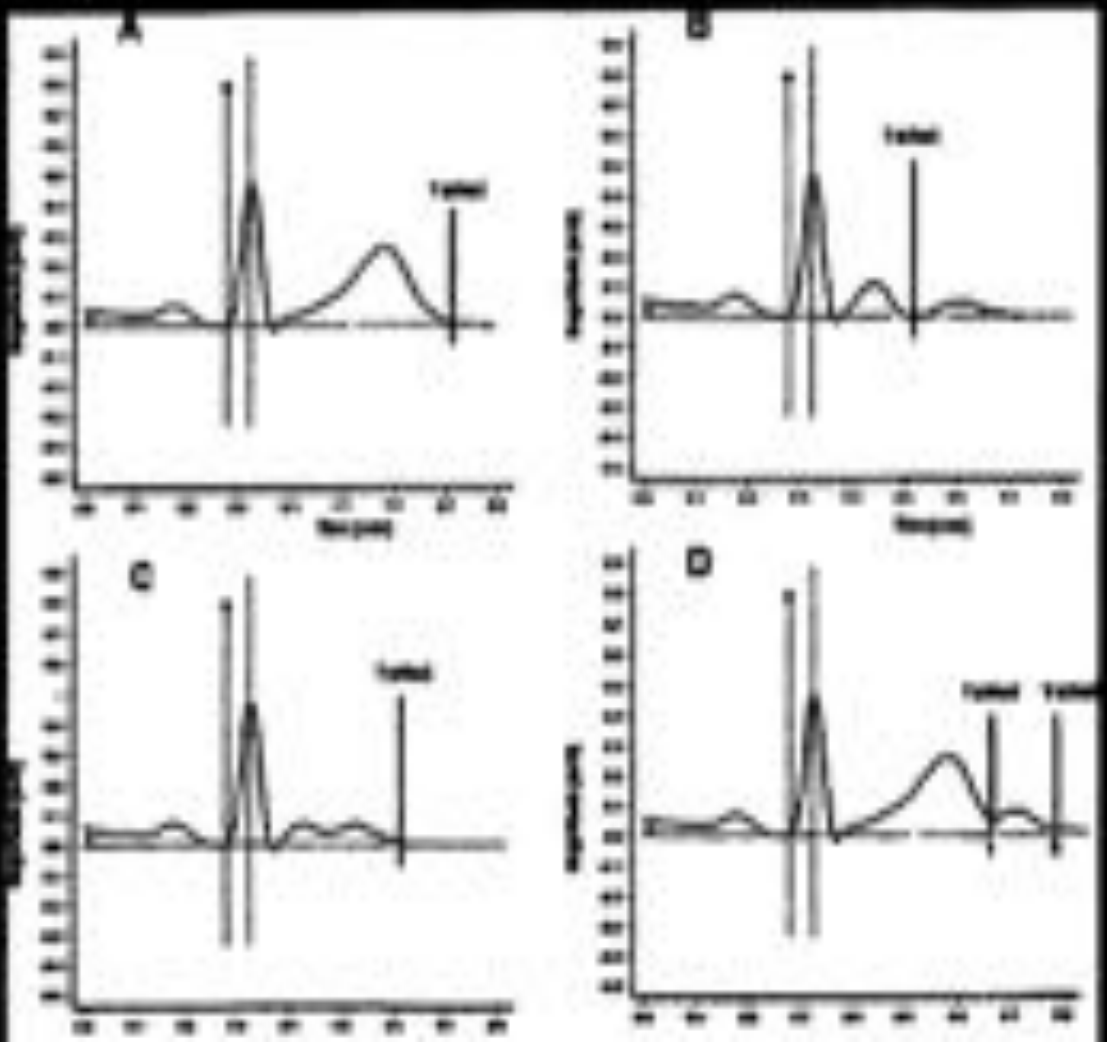


Figure Legend:

Effect of Mexiletine on Pause-Dependent QT Prolongation and QT-RR Slope

Pause-dependent QT exacerbation with large T-waves before the use of mexiletine (A) and its resolution after mexiletine (B). (C) Plots displaying the change in QT intervals across different RR intervals in 8 patients, before (solid circles) and after (open triangles) mexiletine. (D) Bar chart illustration of the change in mean QT-RR slopes of 8 patients before and after mexiletine use.

Measuring the QT Interval with T Waves of Differing Morphology

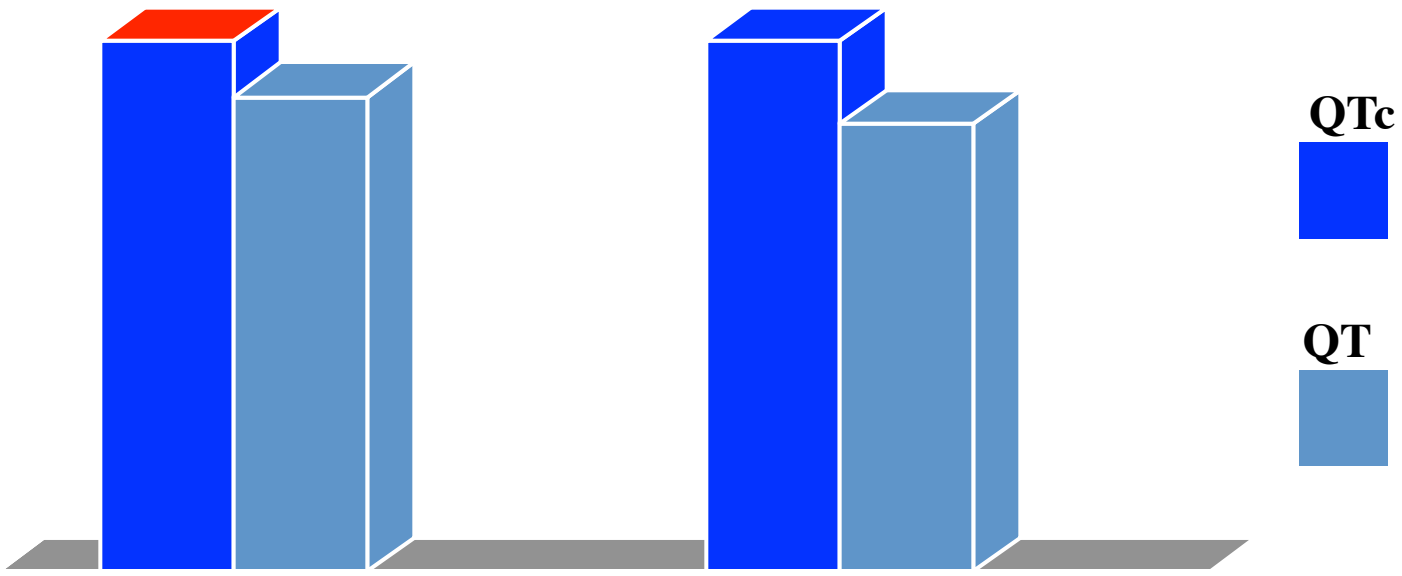


Normal QTc Interval - Criteria

QTc (msec)	Male	Female
Normal	<430	<450
Borderline	431-450	451-470
Prolonged	>450	>470

QT Intervals in Drug Induced TdP

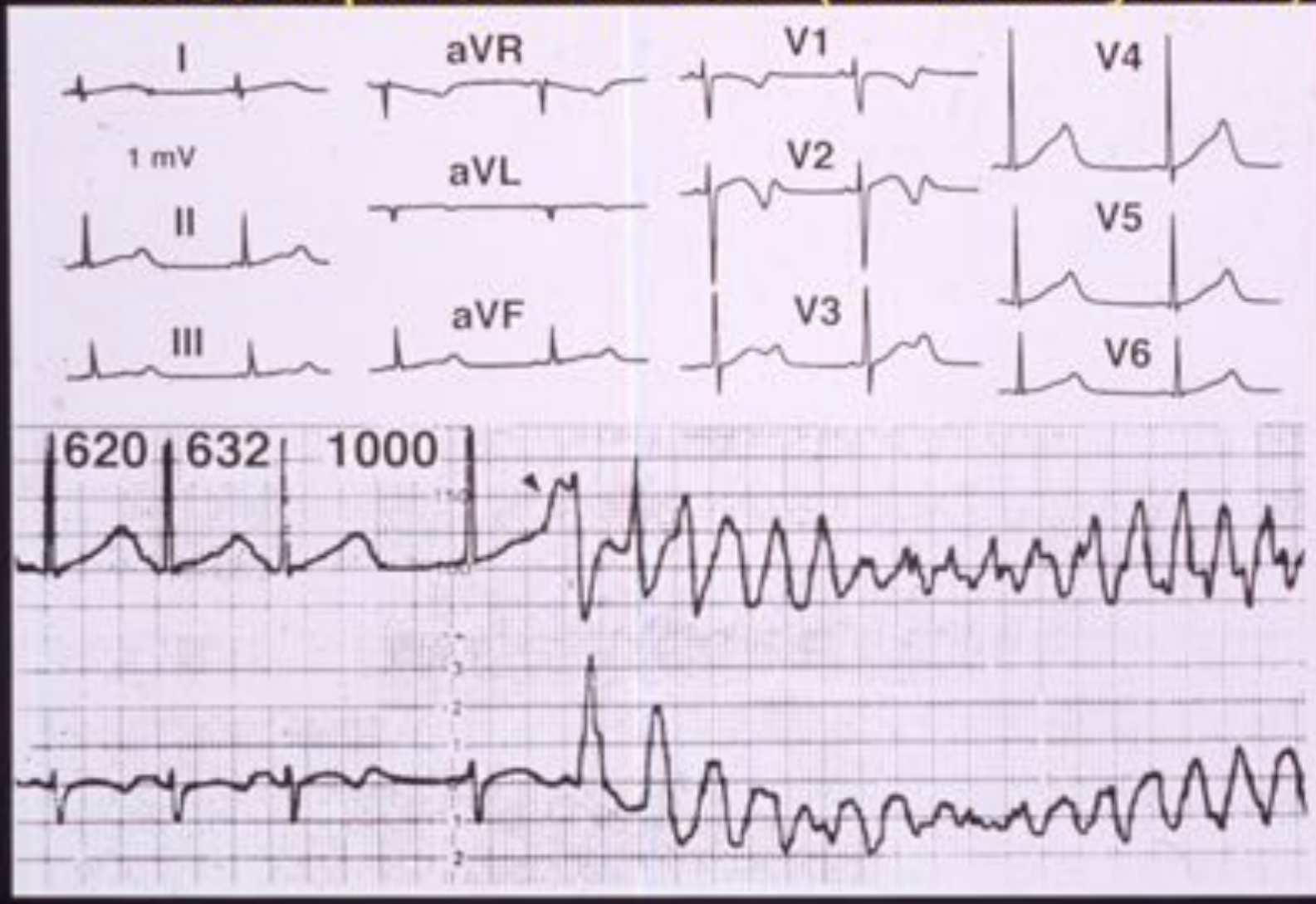
Percent of Patients with QTc or QT> 500 msec (%)



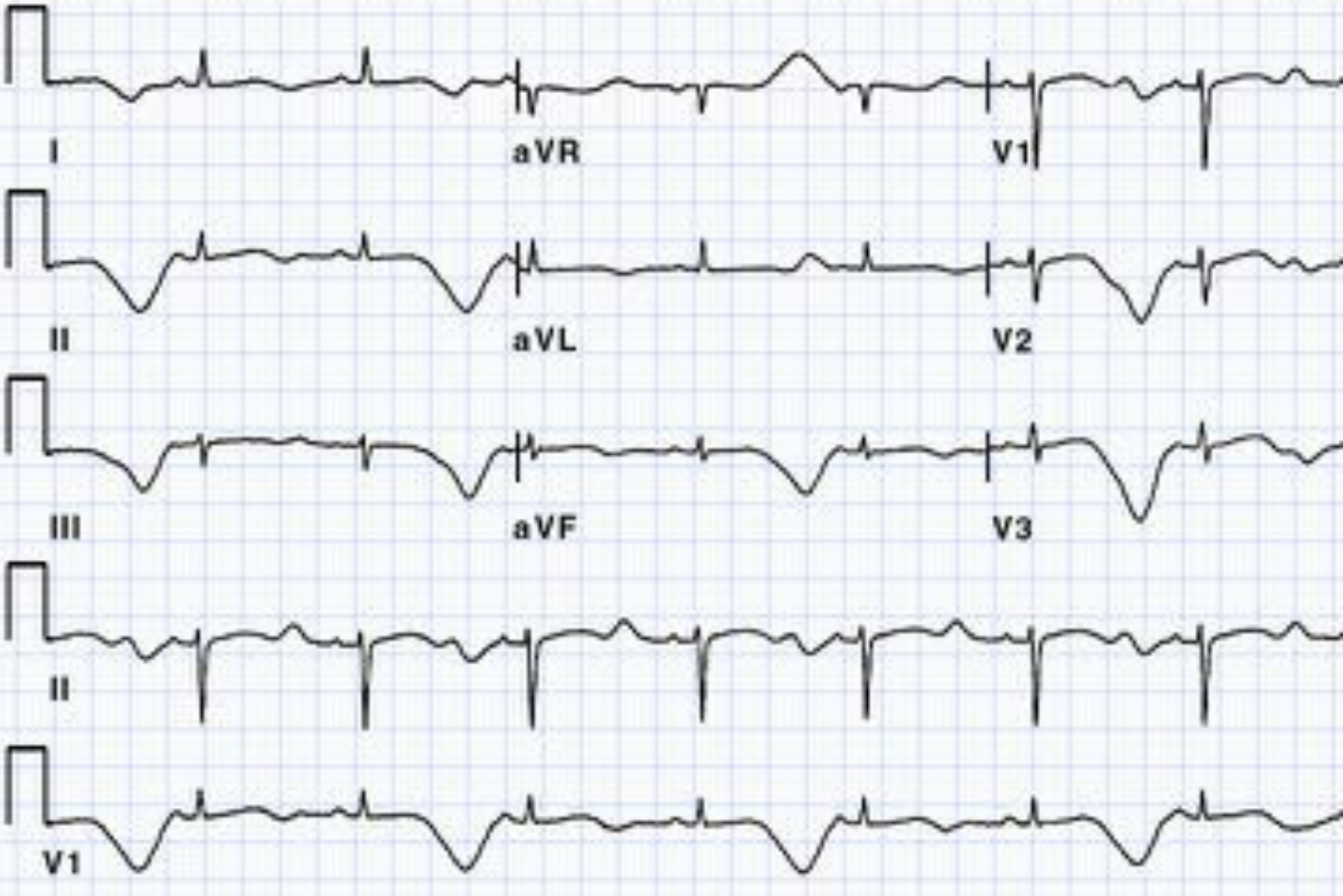
(N= 332) (N=189)

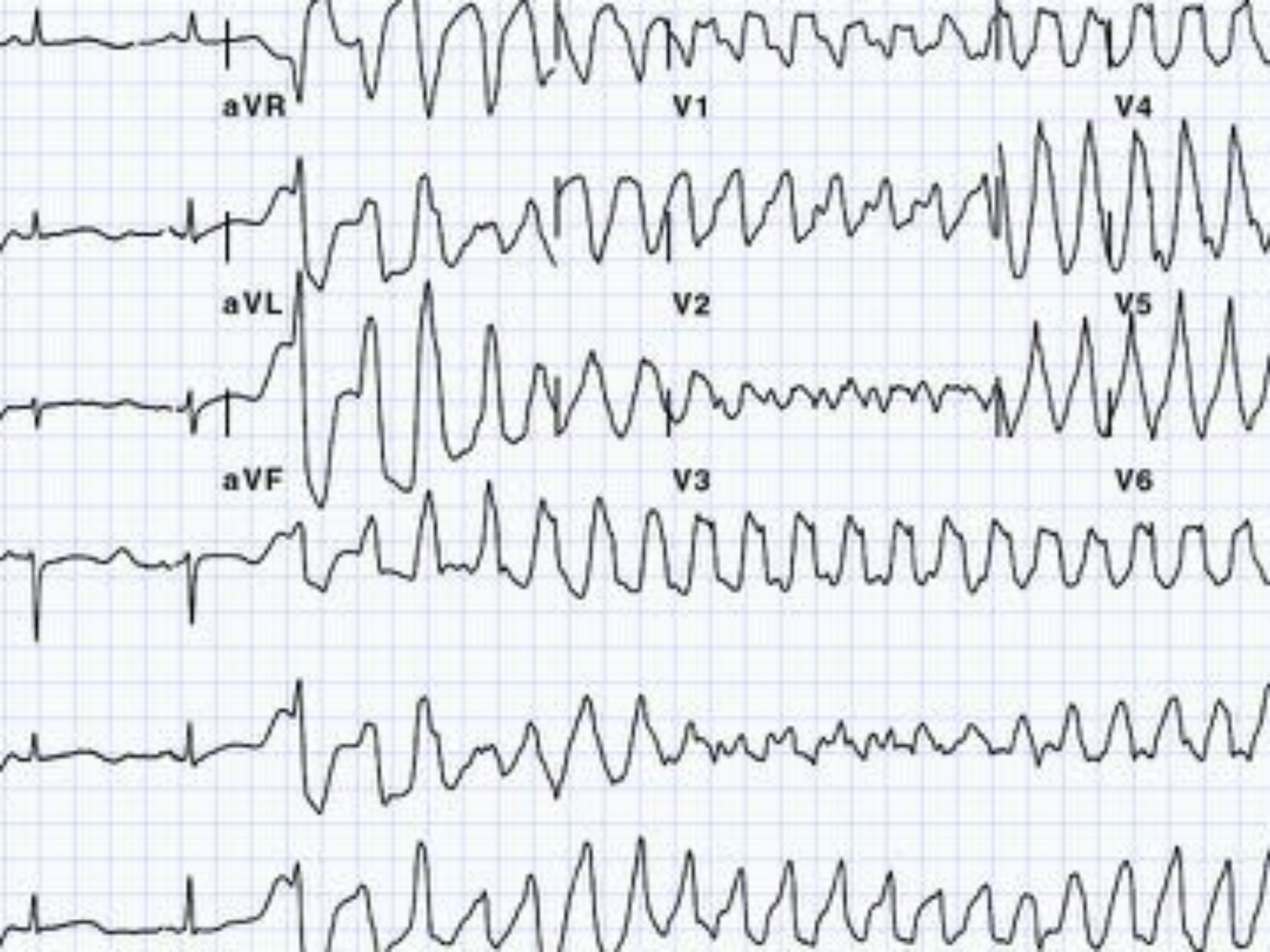
Makkar et al *JAMA* 1993; 270: 2590-2597.
Bednar & Ruskin (personal communication)

Pause dependent torsade (sinus arrhythmia)



Long QT Syndrome



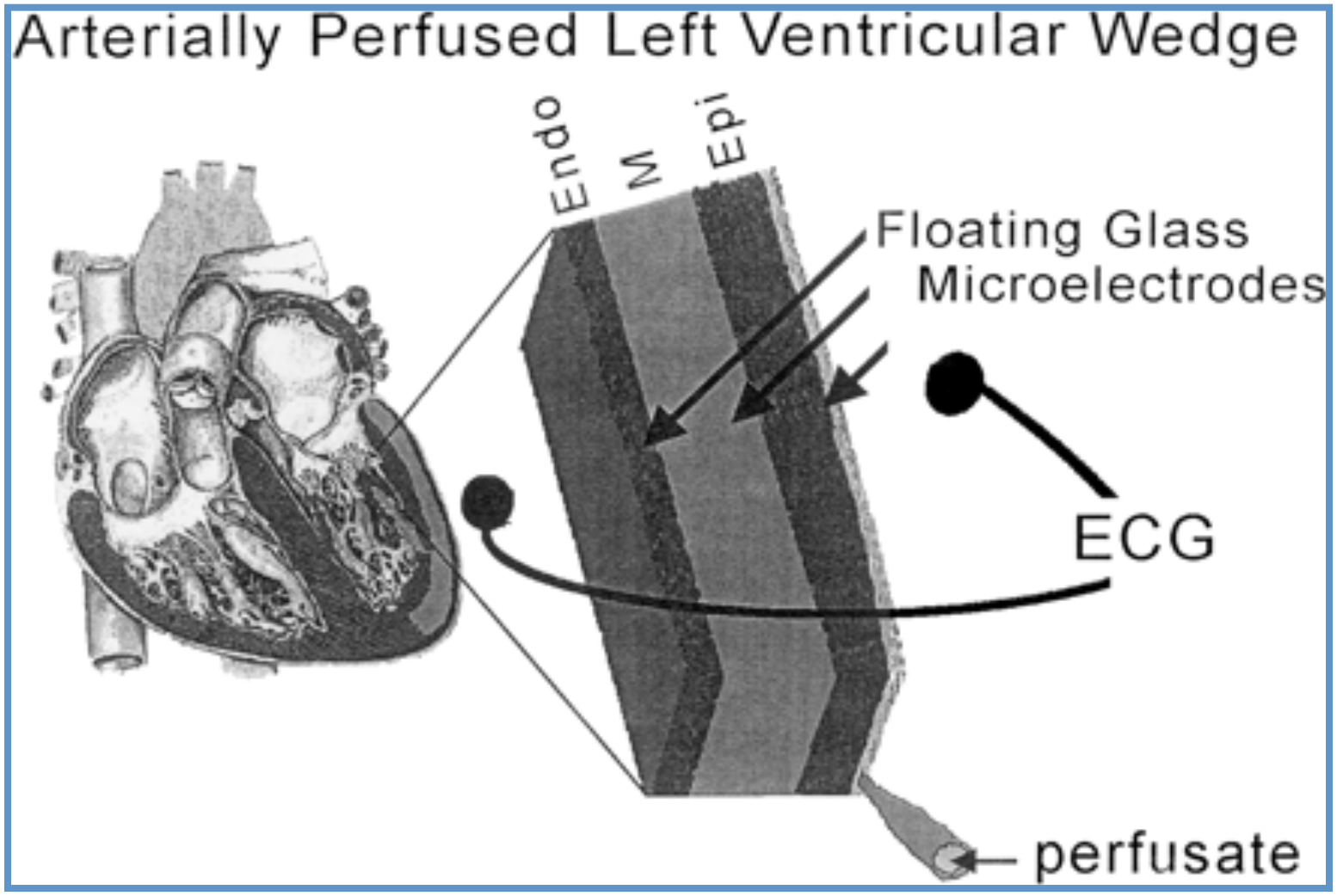

aVR
V1
V4
aVL
V2
V5
aVF
V3
V6

Mechanisms Of Drug - Induced QT Prolongation and Tdp

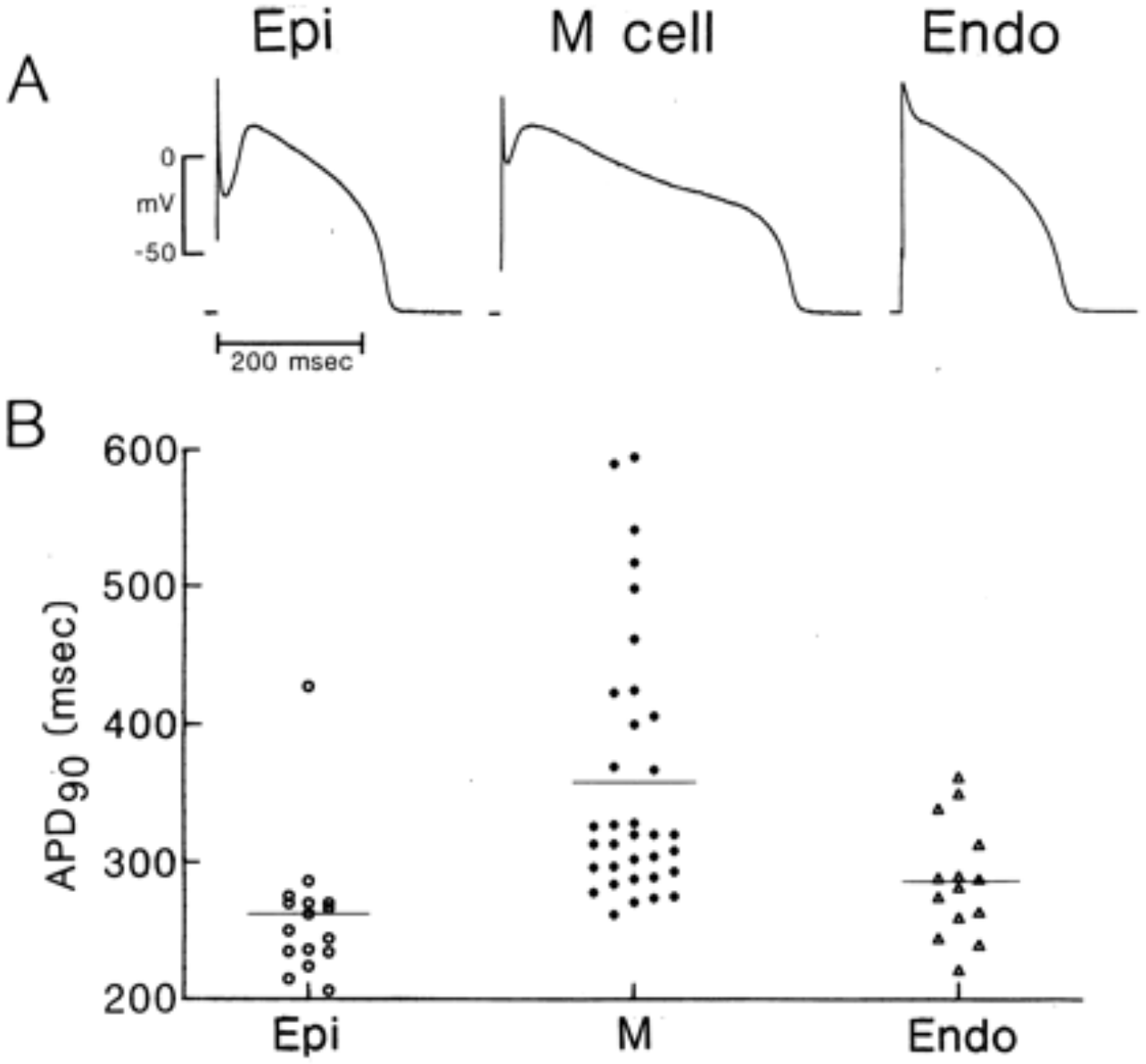
- Block of repolarizing K^+ currents
- Stimulation of $I_{Ca\text{-}I}$
- Stimulation of I_{Na}

Mechanism of Torsades de Pointes

- Early afterdepolarizations
- Transmural reentry



Yan & Antzelevitch Circulation. 1998;98:1921-1927



Yan & Antzelevitch Circulation. 1998;98:1928-1936

Torsades de Pointes

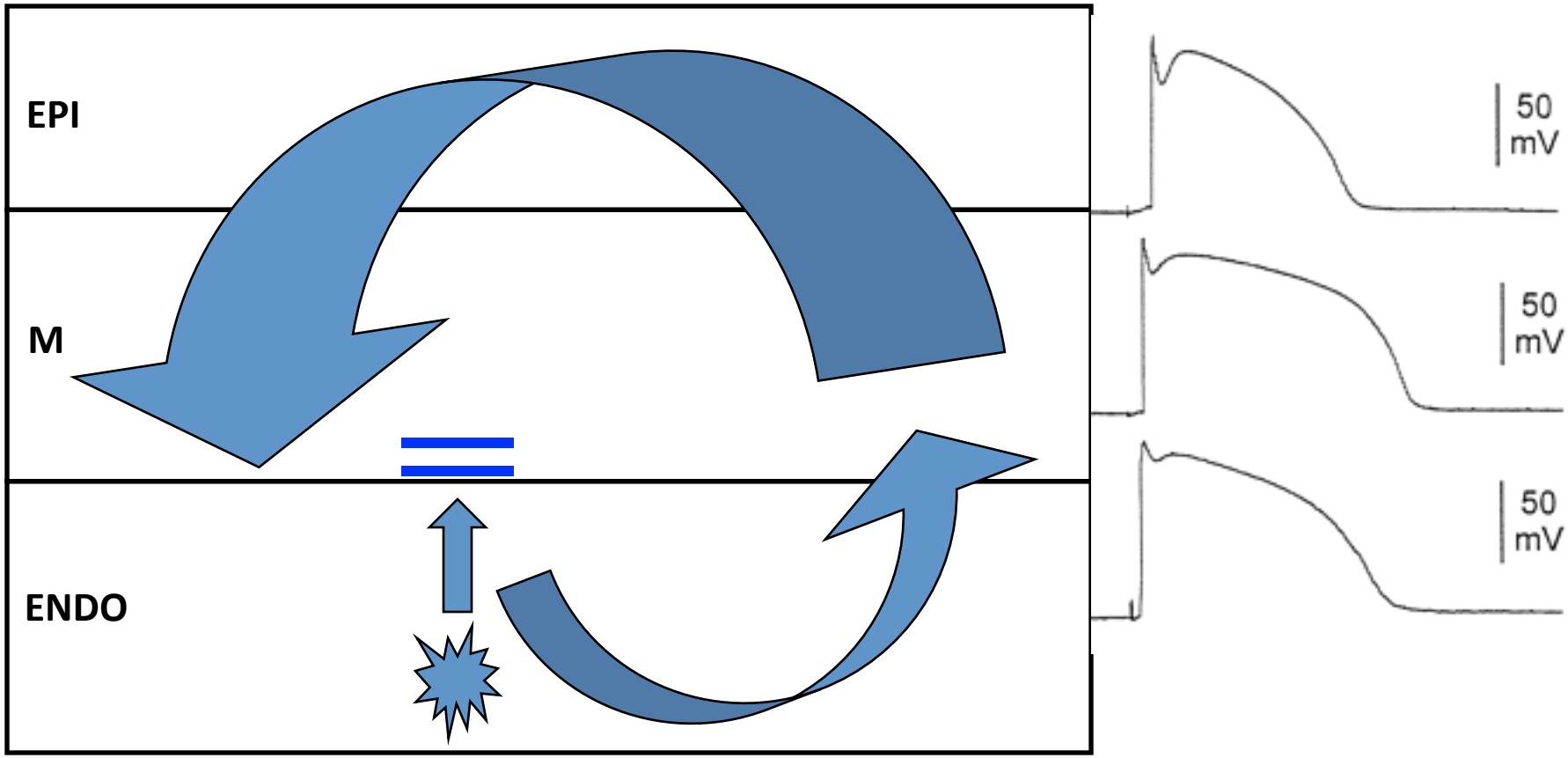
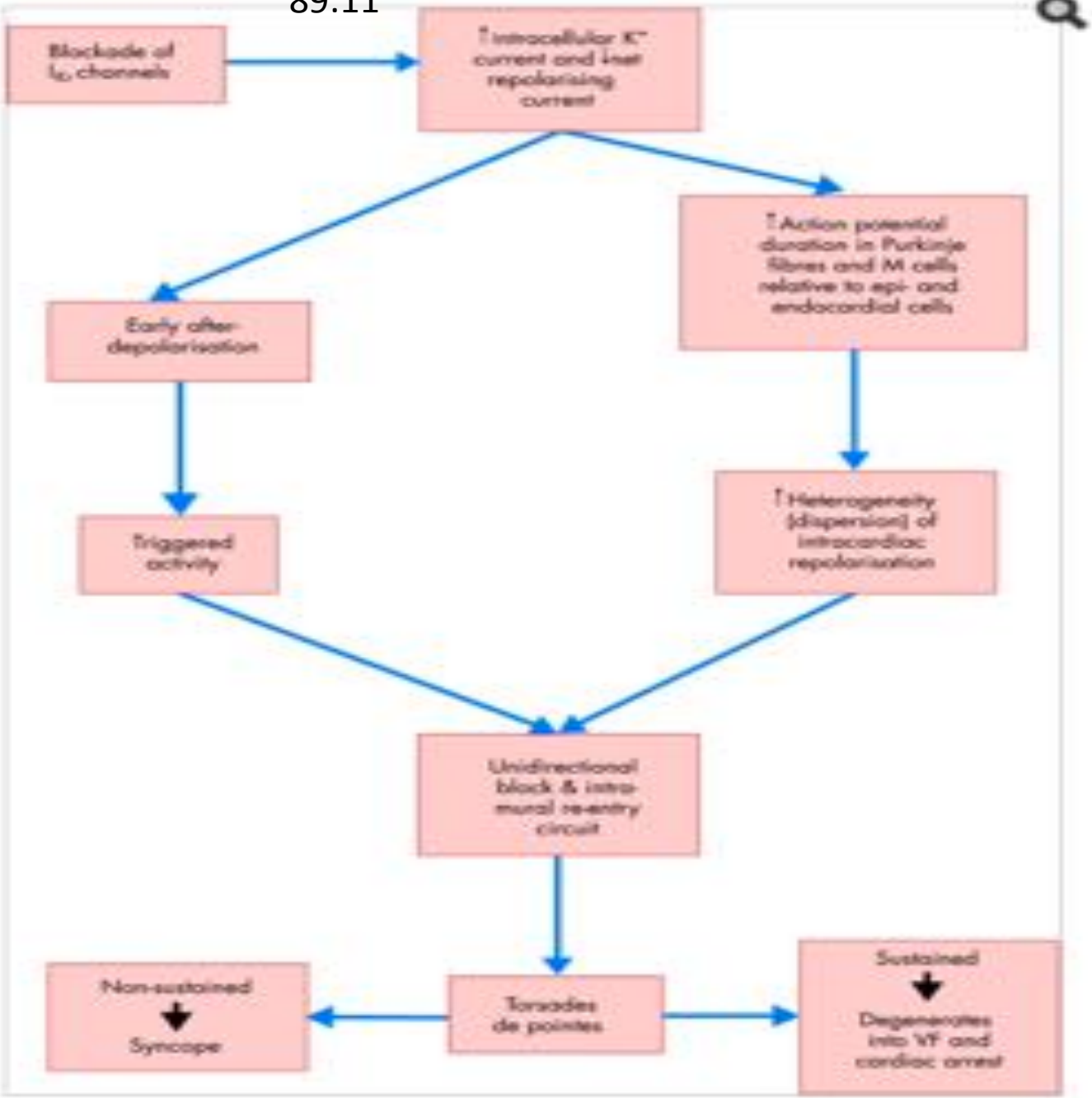


Figure 2

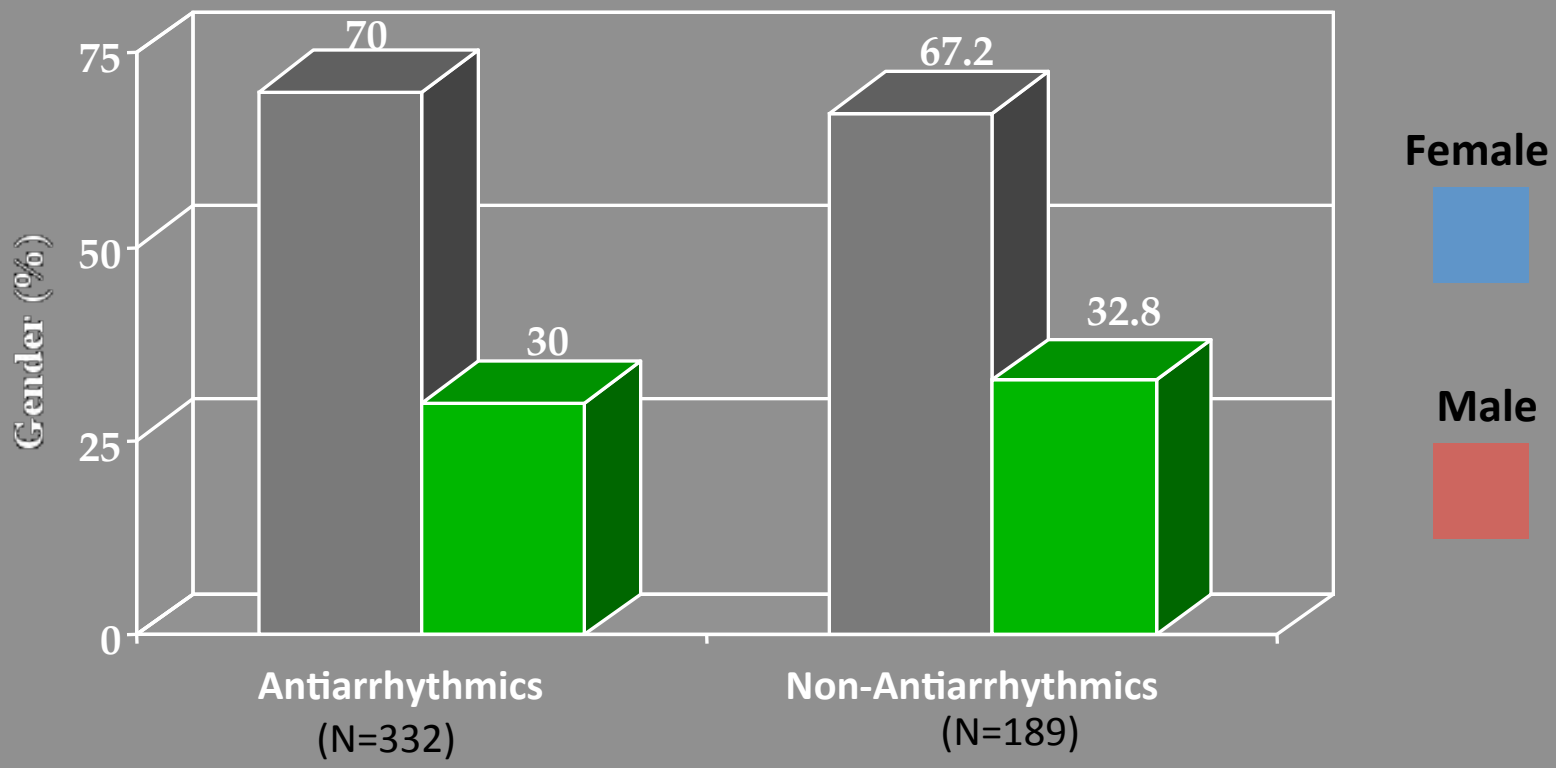
Heart 89:11



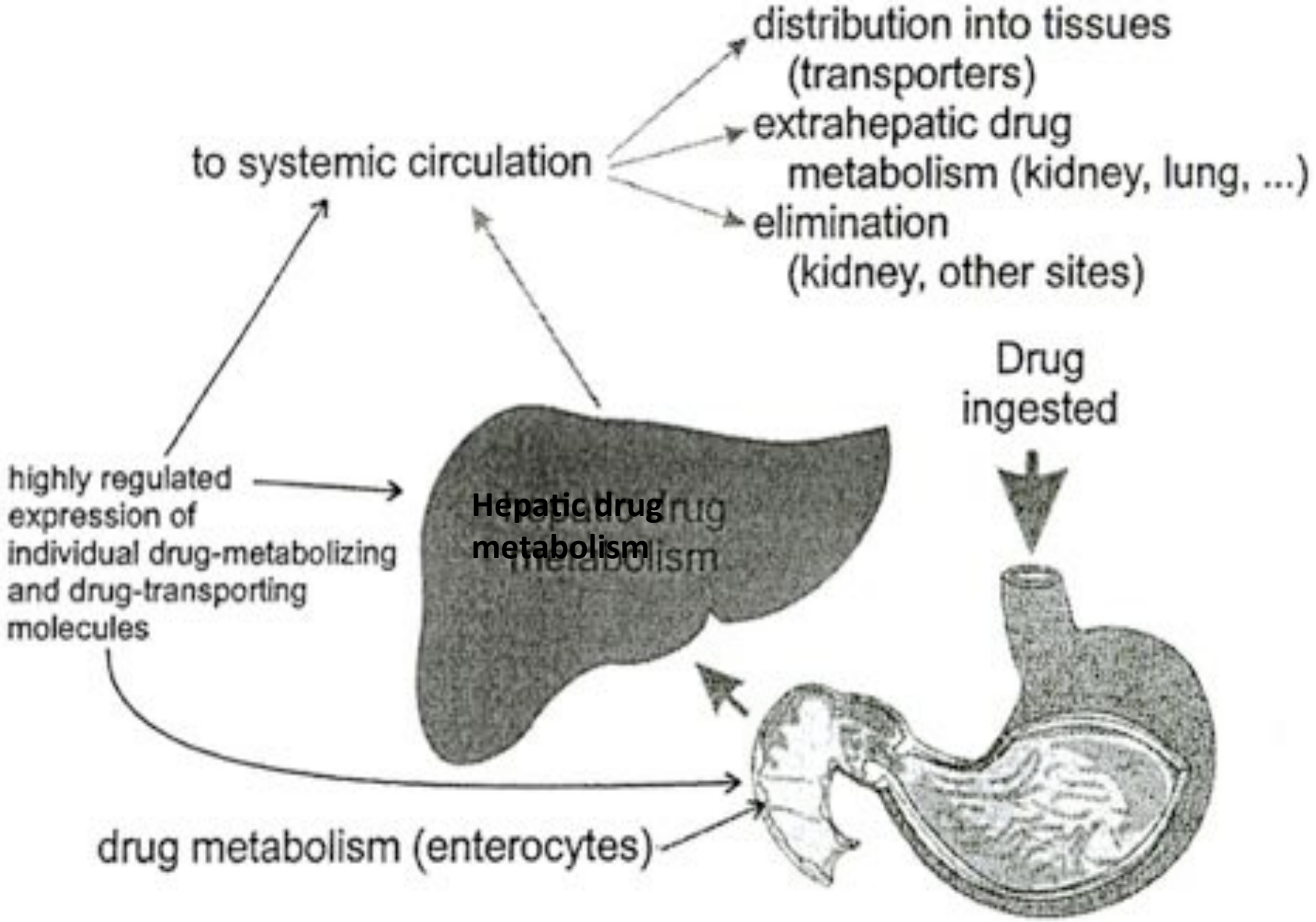
TdP: Multiple-Hit Hypothesis

- Drug exposure (IKr blocker)
- Second risk factor
  - Bradycardia
  - Hypokalemia
  - Female gender
  - Metabolic inhibitor
  - Other QT prolonging drugs
  - Underlying heart disease (CHF, LVH, AF)
  - Genetic polymorphism (IKr or IKs)
  - Cardiac Memory

Drug-Induced TdP - Gender Distribution



Makkar et al *JAMA* 1993; 270: 2590-2597.
Bednar & Ruskin (personal communication)

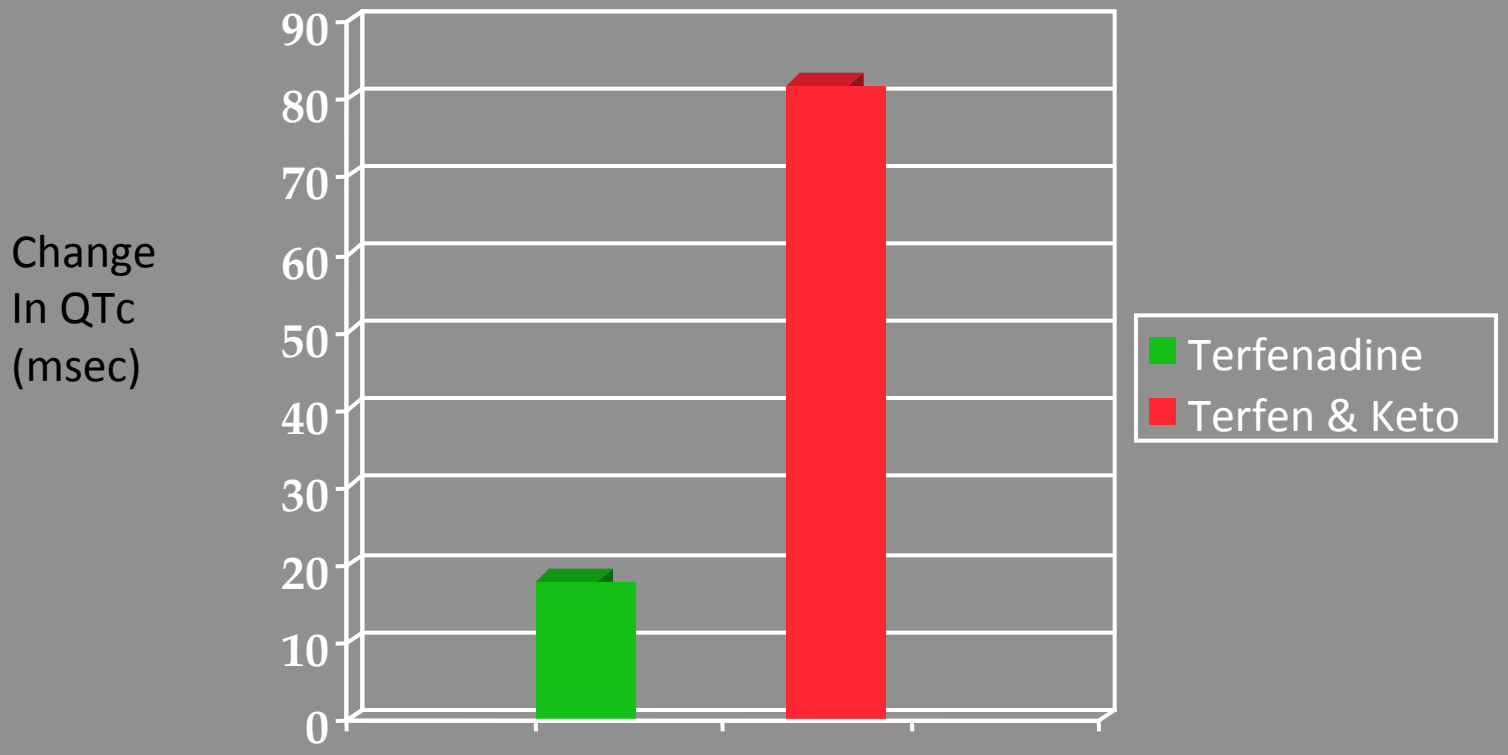


Roden, D. Cardiac Electrophysiology
(Zipes & Jalife) Ch XIV WB Saunders 2000

CYP450 3A4 Inhibitors

- Amiodarone
- Cimetidine
- Fluoxetine
- Grapefruit juice
- Protease inhibitors
- Ketoconazole; itraconazole
- Macrolide antibiotics (not Azithromycin)
- Nefazadone

QTc Changes with Terfenadine
Effect of CYP3A4 Inhibition with Ketoconazole



Drug Induced Torsades de Pointes

Drug	EP Effects	Metabolic Liability
Terfenadine	IKr blocker	3A4 substrate
Cisapride	IKr blocker	3A4 substrate
Mibefradil	IKr blocker	3A4 inhibitor
Erythromycin	IKr blocker	3A4 inhibitor
Astemizole	IKr blocker	3A4 substrate
Dofetilide	IKr blocker	Renal excretion
Sotalol	IKr blocker	Renal excretion

Conclusions - DNA variants in the coding regions of congenital long-QT disease genes predisposing to aLQTS can be identified in ≈ 10% to 15% of affected subjects, predominantly in genes encoding ancillary subunits.

Yang et al Circulation105:1943

Table 1

Heart Yang and Camm 89:1363 2003

Twenty most commonly reported drugs associated with torsades de pointes (TdP) between 1983 and 1999[3]

Drug	TdP (n)	Fatal (n)	Total (n)	TdP/total (%)
Sotalol	130	1	2758	4.71
Cisapride	97	6	6489	1.49
Amiodarone	47	1	13725	0.34
Erythromycin	44	2	24776	0.18
Ibutilide	43	1	173	24.86
Terfenadine	41	1	10047	0.41
Quinidine	33	2	7353	0.45
Clarithromycin	33	0	17448	0.19
Haloperidol	21	6	15431	0.14
Fluoxetine	20	1	70929	0.03
Digoxin	19	0	18925	0.10
Procainamide	19	0	5867	0.32
Terodiline	19	0	2248	0.85
Fluconazole	17	0	5613	0.30
Disopyramide	16	1	3378	0.47
Bepridil	15	0	384	3.91

Torsades due to Antiarrhythmic agents

- Quinidine will induce Tdp at low or normal serum levels higher levels block Na current and is thought to be protective.
- Most class 3 agents show linear relationship between drug dose and QTc as well as reverse use dependency.(Dofetilide,Sotalol,Ibutilide)
- Amiodarone seldom produces Tdp absent reverse use dependency as well as decreased transmural difference in refractoriness

Treatment of Drug induced Torsades 2015

Withdraw offending agent

Replenish potassium and correct other aggravating factors

IV Mg and Mg infusion if necessary

Cardiac Pacing (Isoproterenol)

Mexiletine

JACC Journals

From: Mexiletine Prevents Recurrent Torsades de Pointes in Acquired Long QT Syndrome Refractory to Conventional Measures

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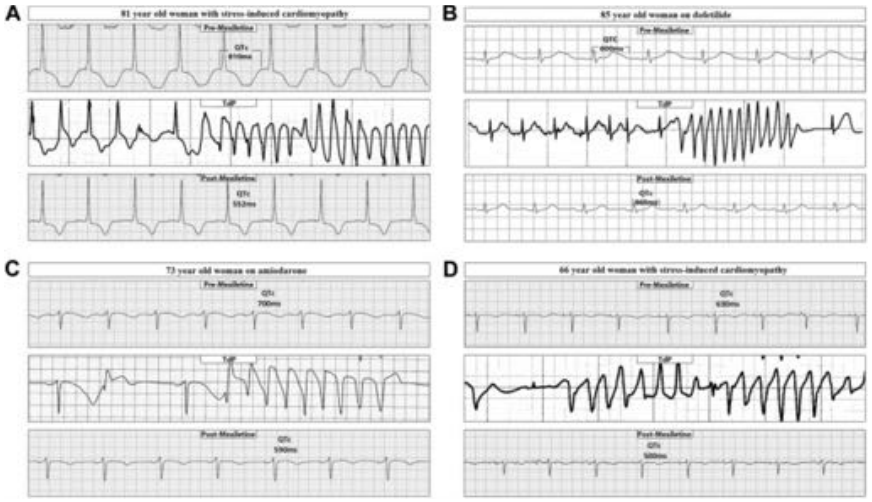


Figure Legend:

Effect of Mexiletine on QT Interval and TdP

Electrocardiogram (ECG) strips of 4 cases displaying long QT pre-mexiletine, followed by torsade de pointes (TdP), and post-mexiletine ECG strips. In case A, the post-mexiletine ECG was recorded 24 h after the first dose and after a total of 400 mg. In case B, it was recorded 15 h after the first dose and after a total of 300 mg. In case C, the post-mexiletine ECG was recorded 25 h after the first dose and after 600 mg of mexiletine. In case D, the post-mexiletine ECG was recorded 23 h after the first dose and after a total of 600 mg. Note that all 4 episodes of TdP occurred following a long-short interval.

Badri et al JACC EP 1:315 2015

Background

Long QT interval can predispose to TdP and is therefore associated with significant mortality. Currently, there is no available pharmacotherapy to target directly the ionic basis of most LQTS for the acute termination of TdP. Earlier evidence highlighted the role of $I_{Na\text{-}L}$ in the pathophysiology of long QT and TdP, particularly in patients with congenital LQTS.

Methods

Twelve patients with TdP caused by acquired LQTS were treated with mexiletine after failure of conventional treatment including discontinuation of QT-prolonging drugs, intravenous administration of magnesium, and correction of serum electrolyte abnormalities.

Results

No recurrence of TdP occurred within 2 h after initiation of treatment with mexiletine in all 12 patients. Macro T-wave alternans accompanied by QT prolongation, an electrocardiographic precursor of TdP that was seen in 3 patients, was also abolished by mexiletine. Treatment with mexiletine shortened the QTc interval from 599 ± 27 ms to 514 ± 16 ms ($p = 0.001$). The interval from the peak to the end of the T-wave ($T_{p\text{-}e}$ interval) decreased from 145 ± 18 ms to 106 ± 9 ms ($p = 0.005$). The $T_{p\text{-}e}$/QT ratio decreased from 0.27 ± 0.02 to 0.23 ± 0.018 ($p = 0.01$). Mexiletine had no significant effect on QRS complex duration.

Conclusions

$I_{Na\text{-}L}$ blockade with mexiletine may be an effective treatment approach to terminate refractory TdP from several acquired causes of LQTS.

Potential beneficial effects of late Na blockade

- Decreased QT in animal models of pronged QT
- Shown to be effective in patients with LQT3
- Mexiletine,Flecainide and Ranolazine have been shown to decrease the QT in pts with LQT3 but latter 2 also block Ikr (also true of Verapamil)
- Experimental drug (Gilead) pure late Na channel blocker

Cardiac memory mimicking myocardial ischaemia

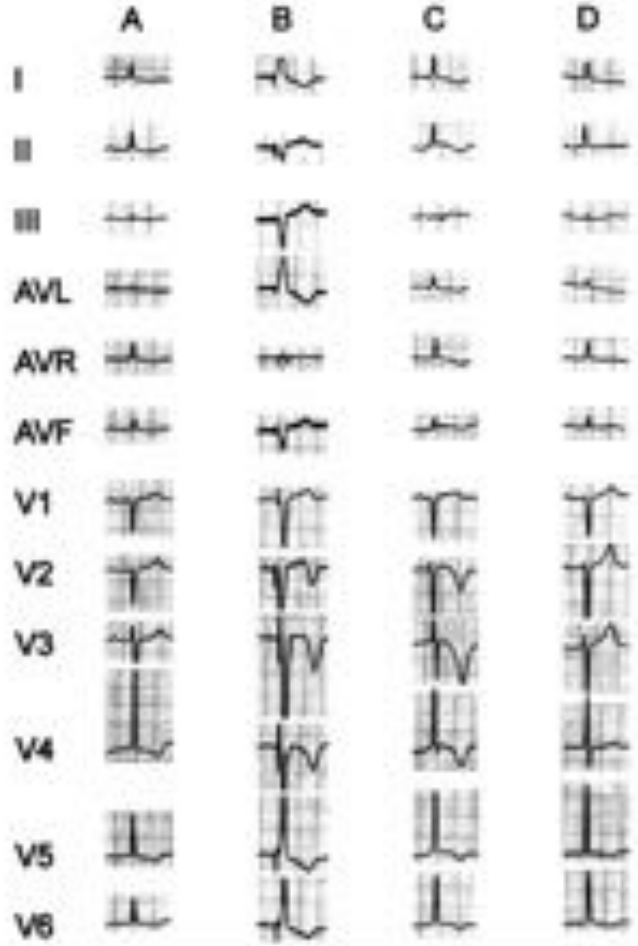


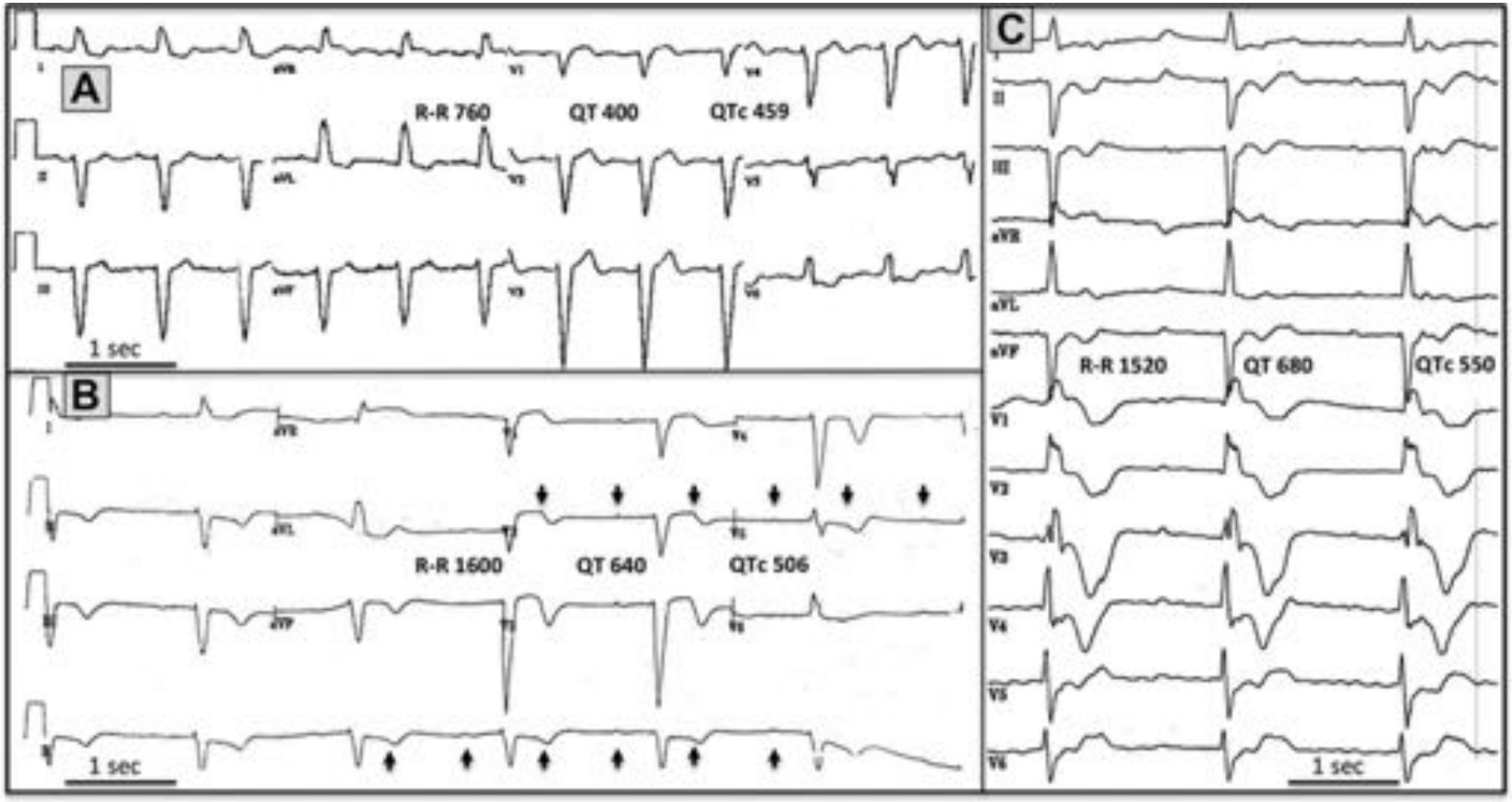
Figure 1

Twelve-lead ECGs from patient with sick sinus syndrome. A, sinus rhythm and nonspecific lateral repolarization abnormalities before pacemaker implantation; B, ventricular pacing one day after pacemaker implantation; C, new T wave inversions with intrinsic ventricular rhythm two days after pacemaker implantation; D, resolution of T wave inversion three days after pacemaker implantation

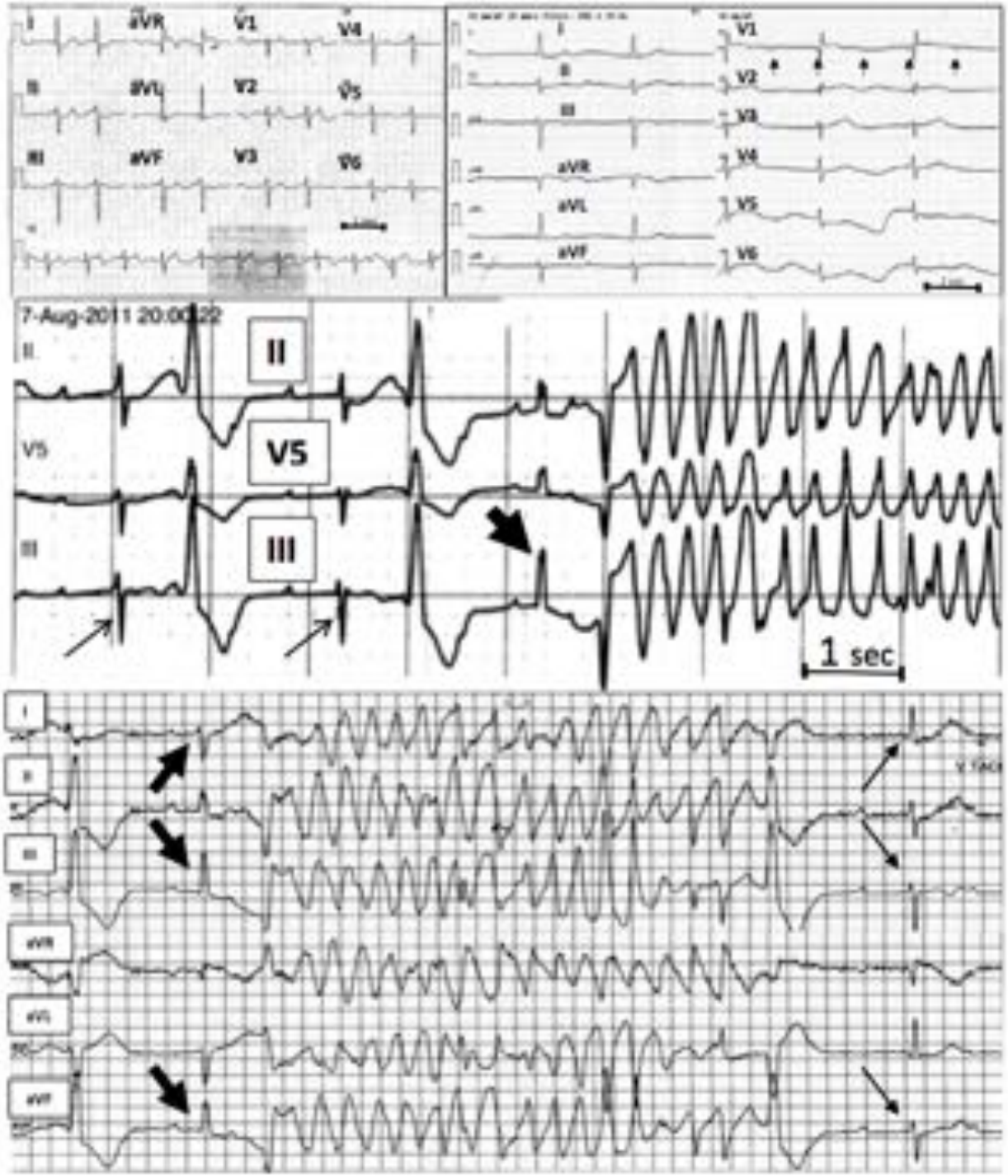
Long QT syndrome complicating atrio-ventricular block: The proarrhythmic role of cardiac memory.

[1]Raphael Rosso*, M.D., [1]Arnon Adler*, M.D., [2]Boris Strasberg, M.D., [3]Milton E. Guevara-Valdivia, M.D., [4]Riyaz Somani, M.D., [4]Adrian Baranchuk, M.D., [1]Amir Halkin, M.D., [5]Manlio F. Márquez, M.D., [6]Thomas Oliver, M.D., [6]Melvin Scheinman, M.D., [1]Arie Steinvil, M.D., Bernard [1]Belhassen, M.D., [7]Mark Kazatsker, M.D., [8]Amos Katz and [1]Sami Viskin, M.D.

Effects of QRS morphology change during atrioventricular block (AVB).



Raphael Rosso et al. Circ Arrhythm Electrophysiol. 2014;7:1129-1135

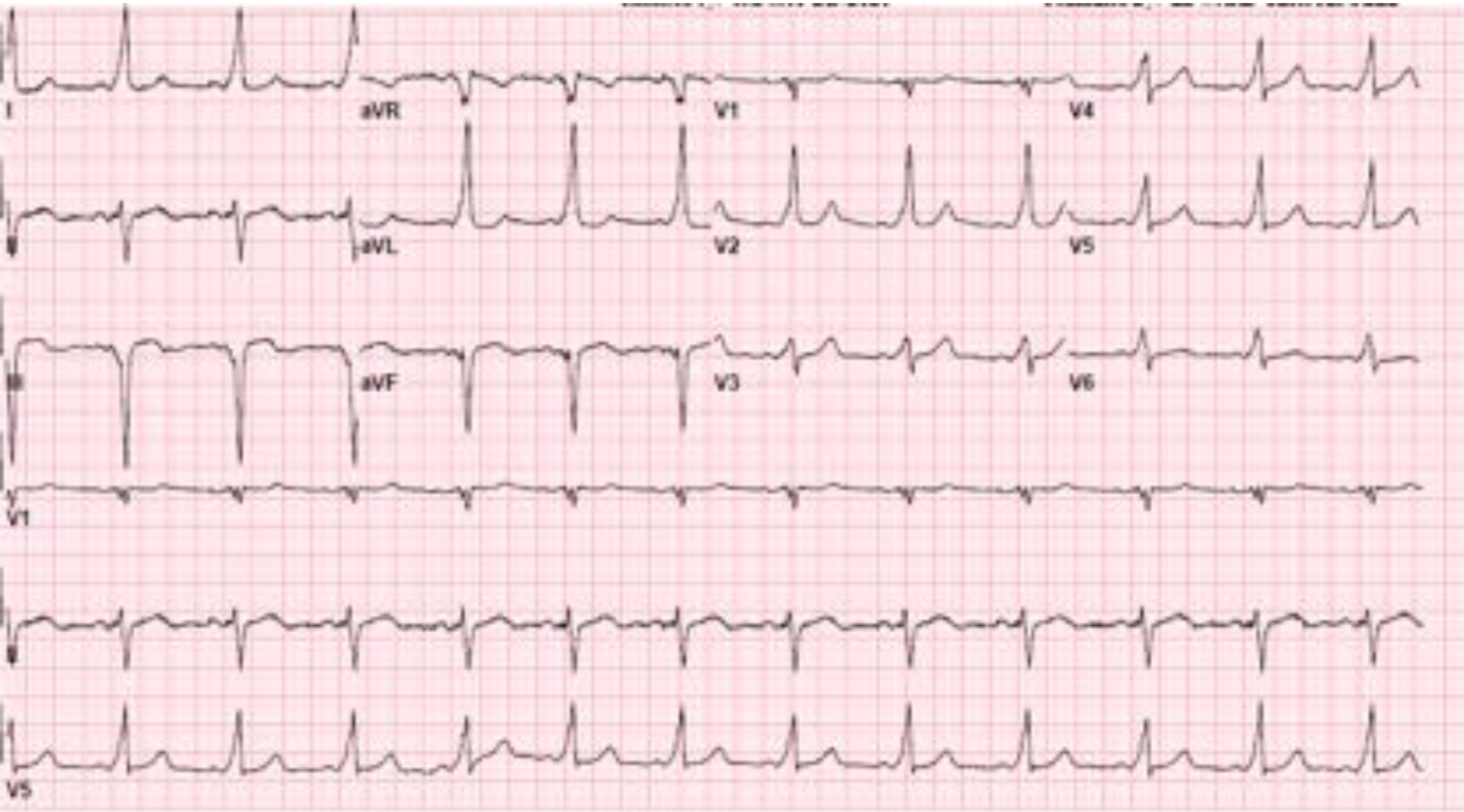

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
V5
III
1 sec

QT Prolongation During Therapeutic Hypothermia of Sudden Cardiac Arrest Patients Does Not Cause Predisposition to Ventricular Arrhythmias

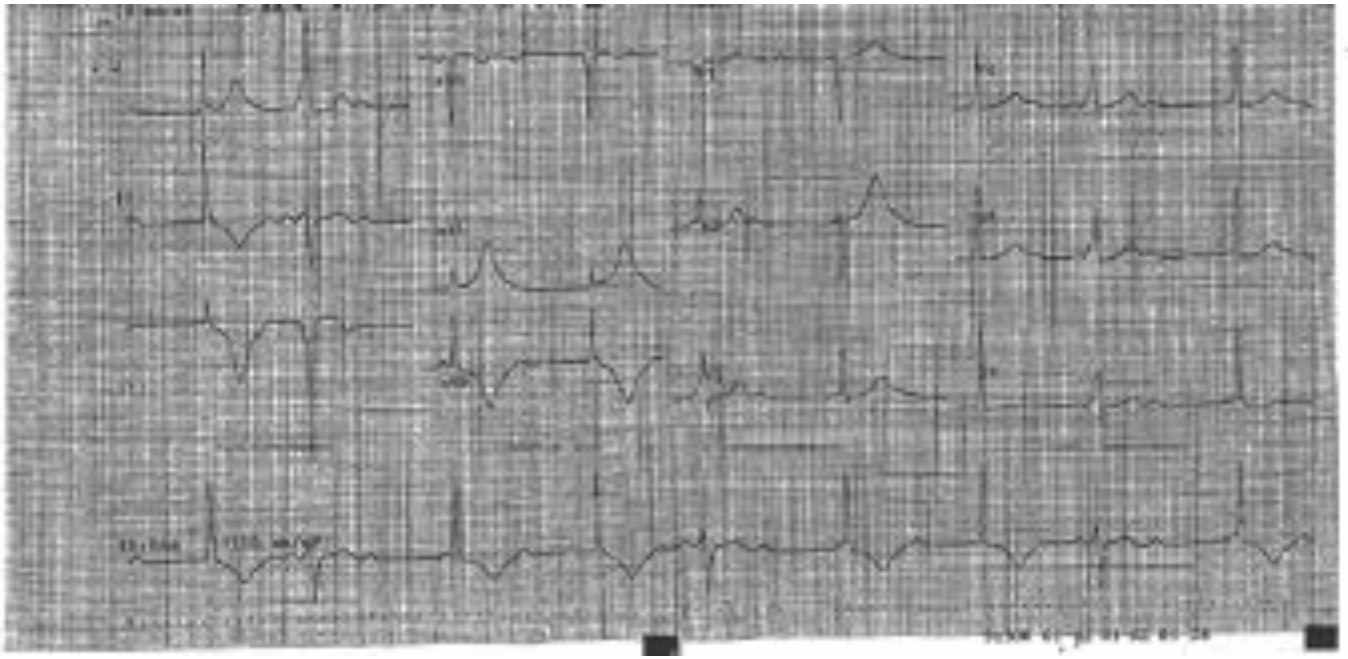
DAVID N. GACHOKA, MD, MUJEEB SHEIKH, MD, YOUSEF AL AHWEL, MD, BLAIR P. GRUBB, MD, FACC, JEFFREY HAMMERSLEY, MD, SADIK KHUDER, PhD and YOUSUF KANJWAL, MD, FACC

University of Toledo Medical Center, Electrophysiology Section, Division of Cardiology, Department of Medicine, University of Toledo, College of Medicine, Toledo, OH

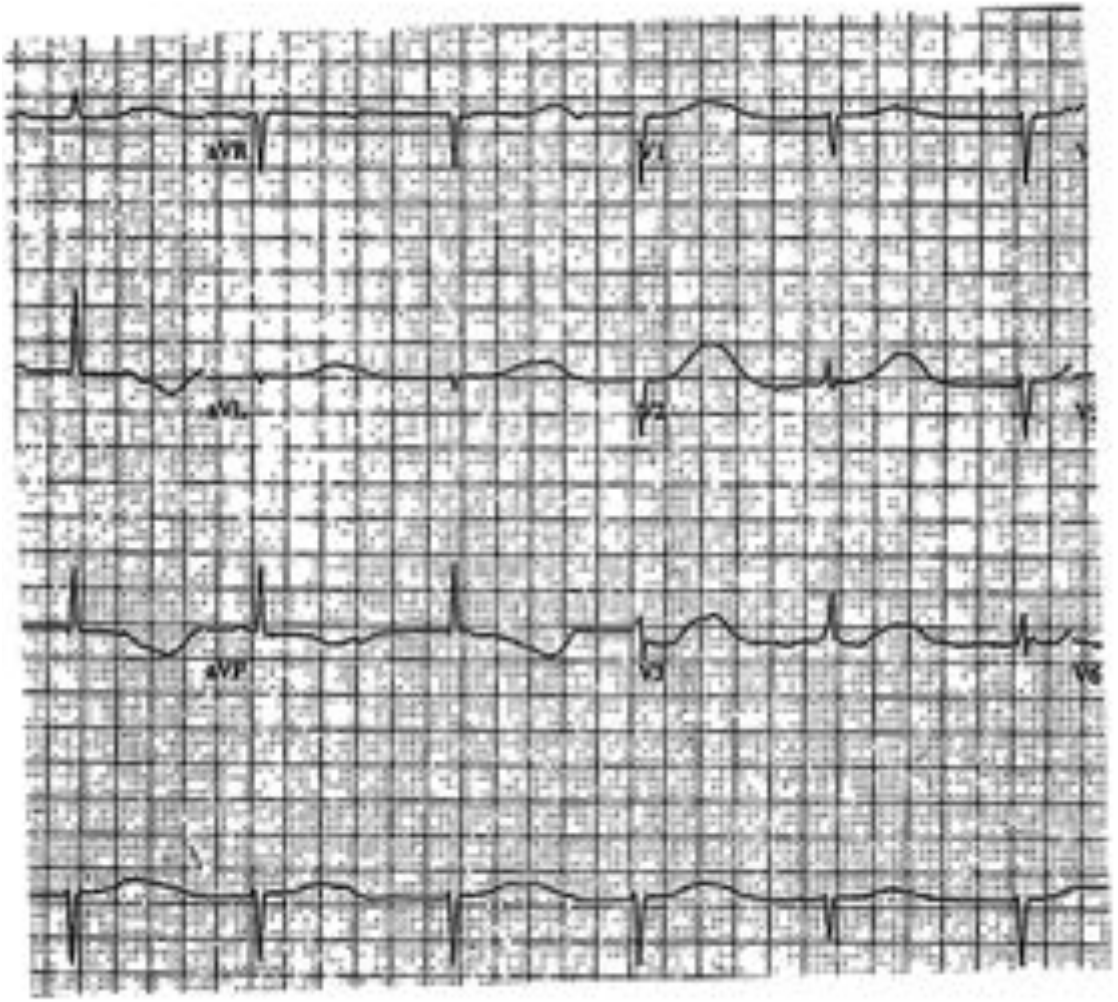
35 year old presents with cardiac arrest

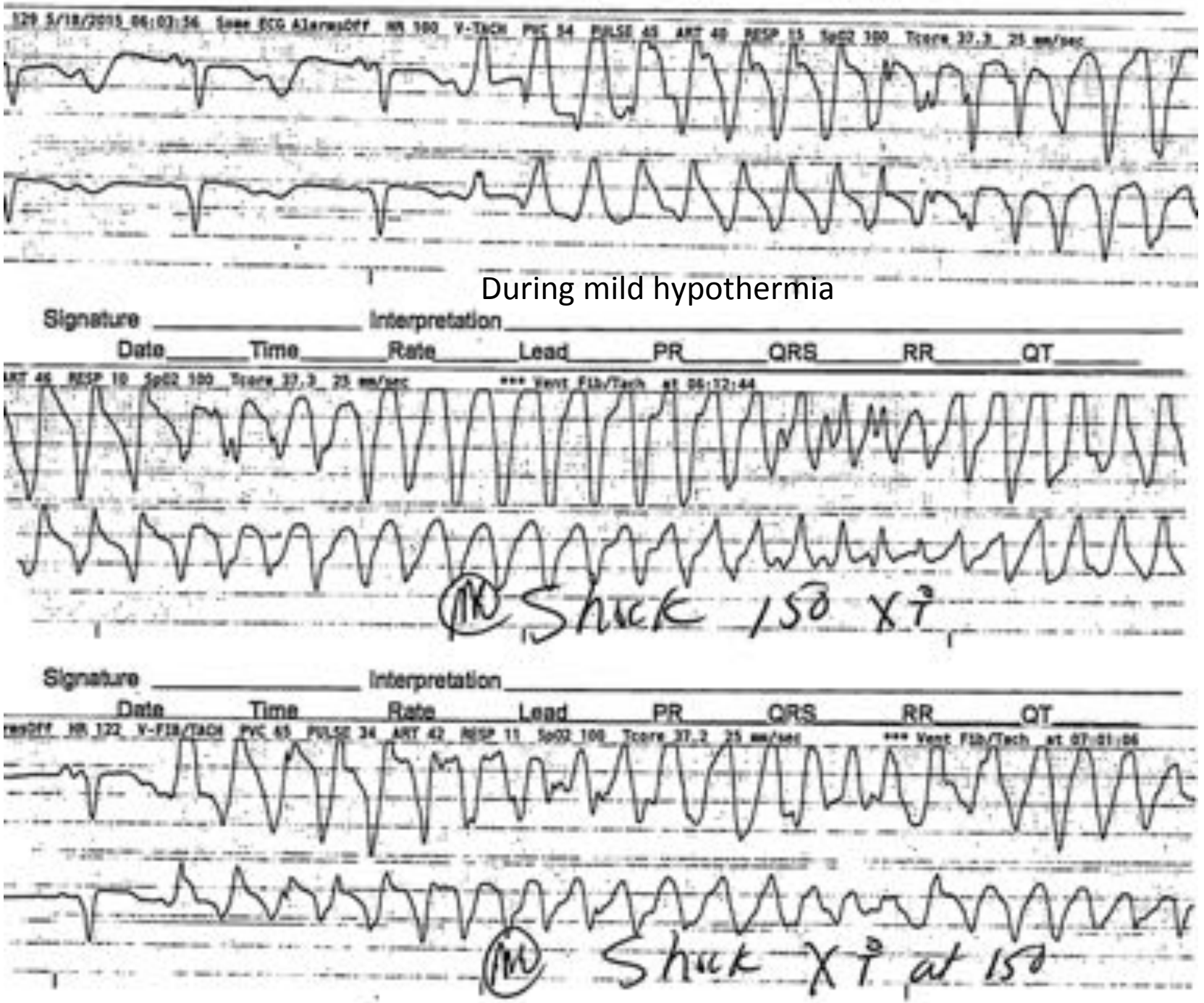


Routine ECG 1 day prior to cardiac arrest



Post arrest




During mild hypothermia
Signature
Interpretation
Date
Time
Rate
Lead
PR
QRS
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QT
Shock 150 X 3
Signature
Interpretation
Date
Time
Rate
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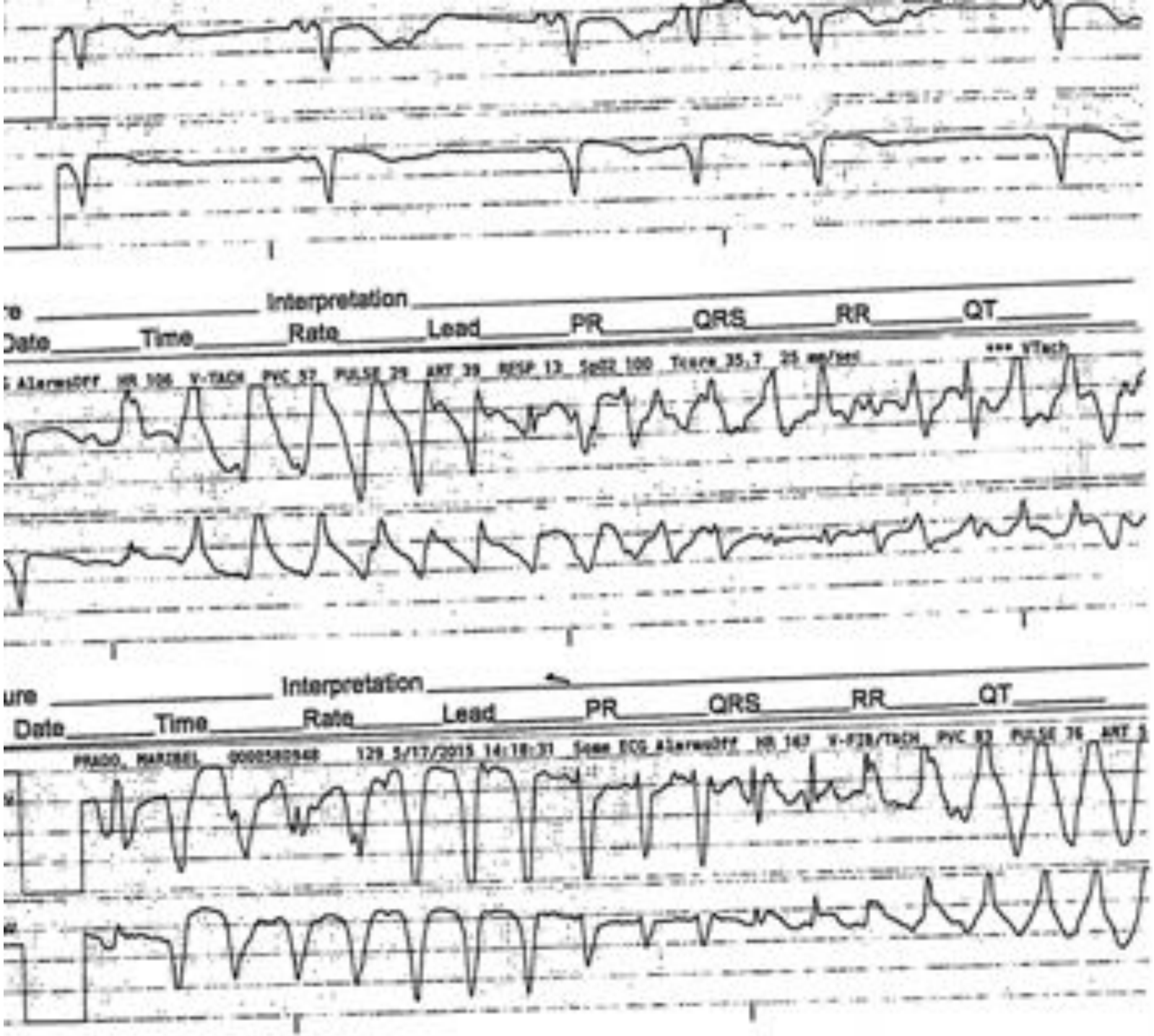
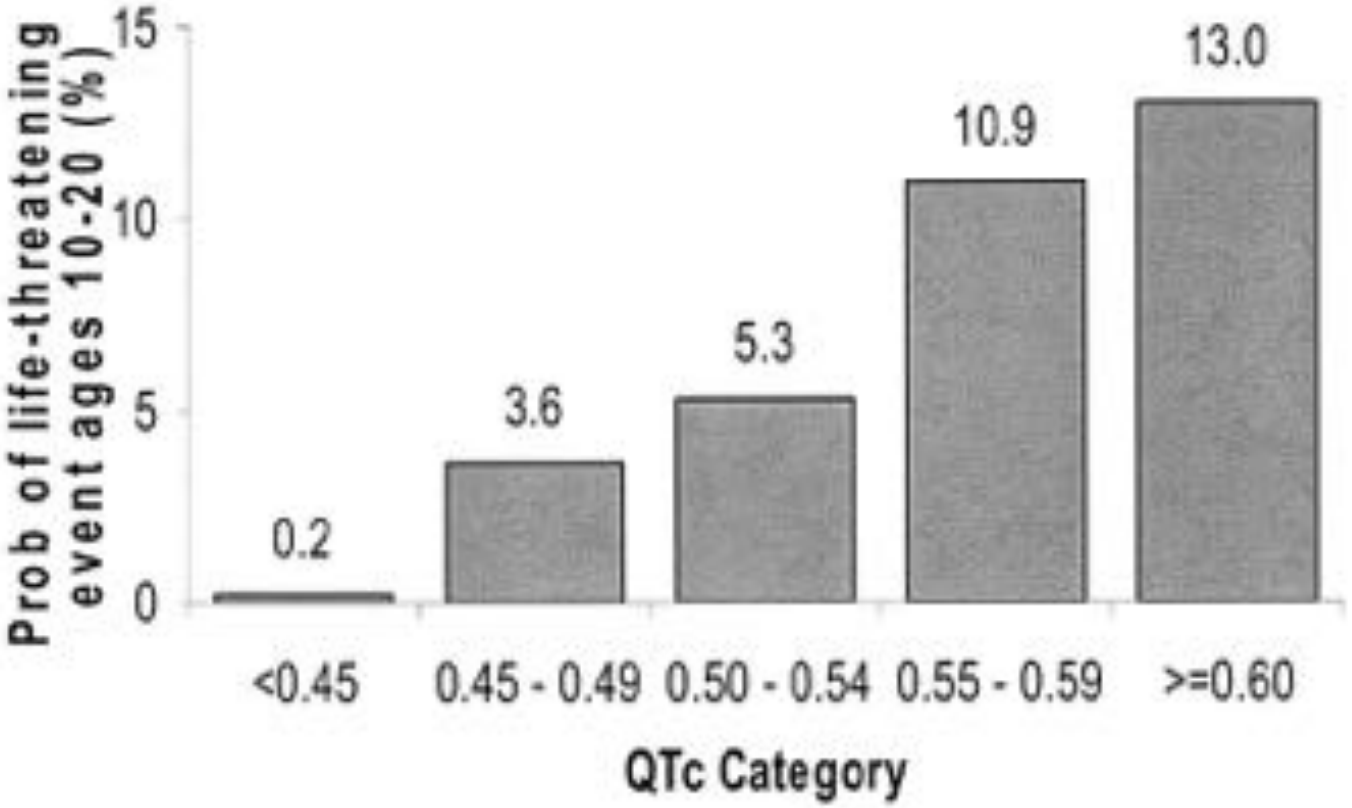
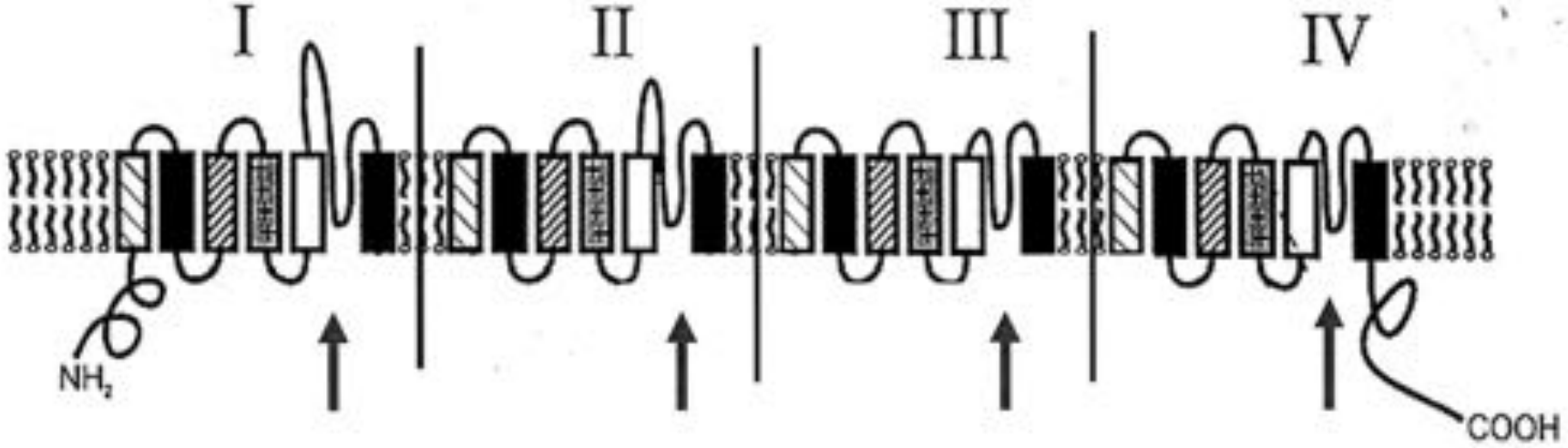
PR
QRS
RR
QT
Shock X 3 at 150


Interpretation
Date Time Rate Lead PR QRS RR QT
*** VTach
Interpretation
Date Time Rate Lead PR QRS RR QT



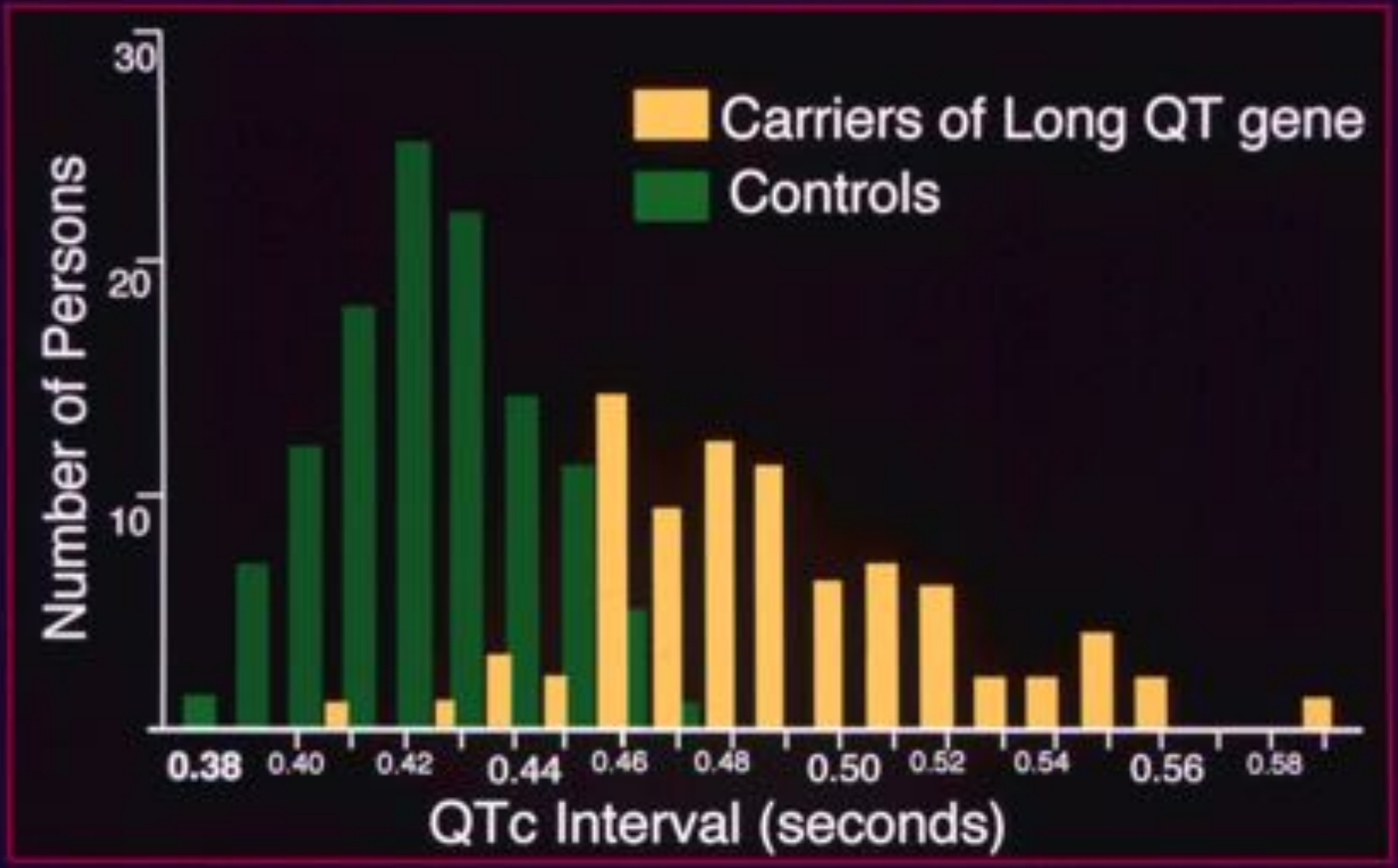
No. Events	5	60	31	23	17
No. Subjects	2936	1901	652	237	148

Moss, A



HERG Channel: tetramer of 4 identical subunits

QTc Intervals in Carriers of Long QT Gene and Controls.



Vincent. N Engl J Med 1992.

Congenital Long QT Syndrome: TU-Wave Alternance