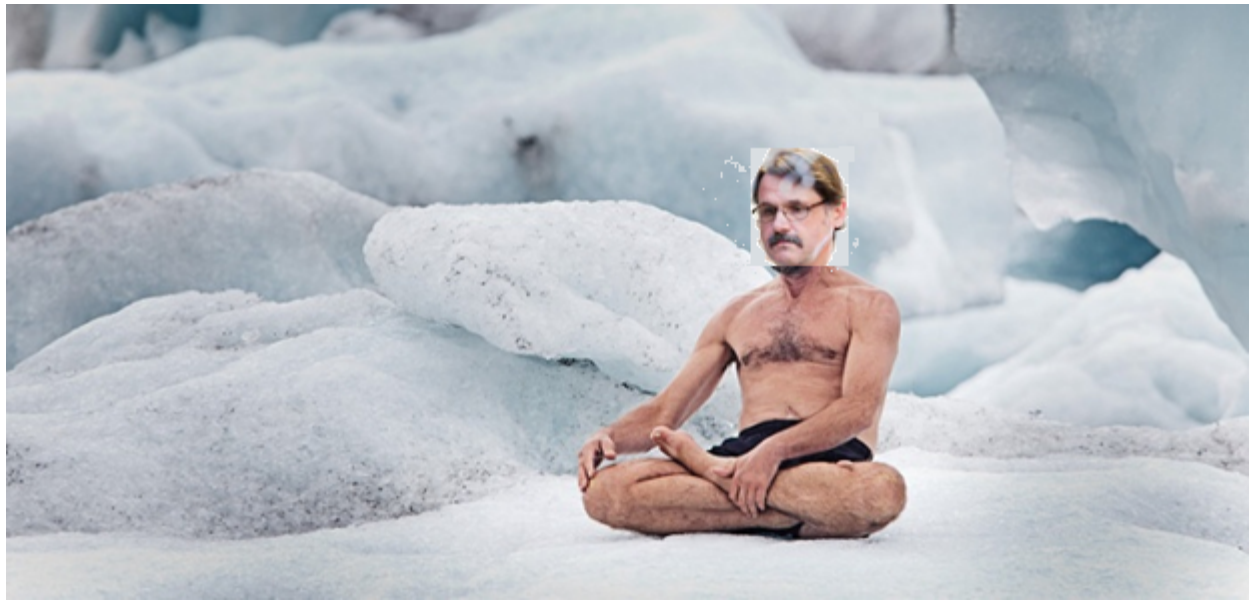
Prolonged QT interval in a symptomatic 55 years old man professional Lorry drivers

Dear Andrés, I would like to hear your opinion about this patient. If you like, you can forward it to colleagues.
The patient is treated in another hospital, but I was asked to give my opinion. I am not sure about if we can recommend him to continue as a lorry driver, but he owns a small company and it is of course problematic if he has to stop driving.

Kind regards

Nikus Kjell M.D.
“The ice Man” from Finland

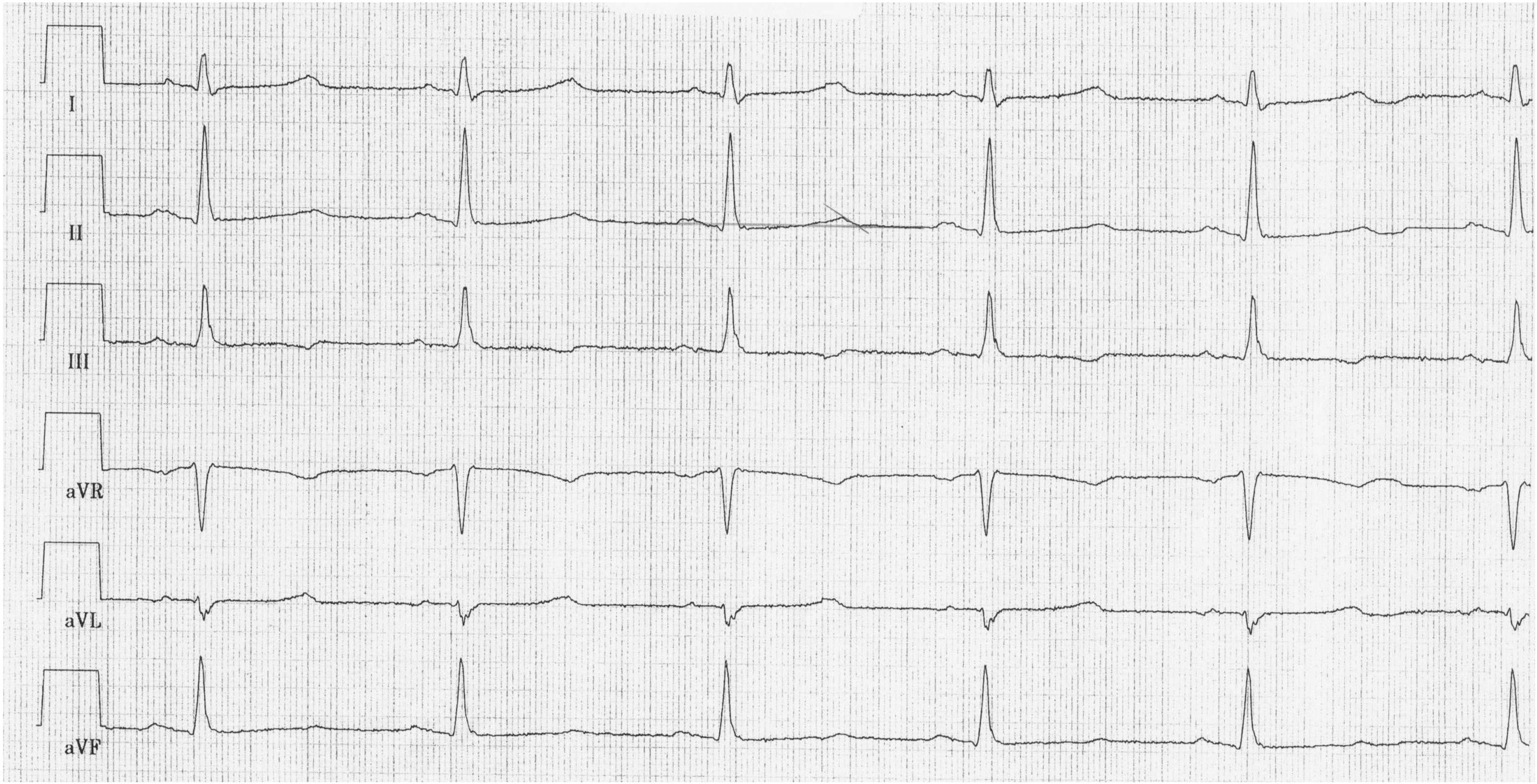


No family history of unexplained sudden death
No symptoms of coronary artery disease
No symptoms related to physical exercise
No suspicion of secondary prolonged QT
Two episodes of palpitations within one year, self-measured heart rate then 194 bpm
One unexplained syncope
    Stood up from a chair and lost his consciousness
    Suturated for wound in the face
12- Lead ECG: I have measured from a couple of ECGs and QTC was >500 ms except in one recording
Normal Echocardiography
Stress test: exercise tolerance better than normal (max. load 275W, heart rate 178 bpm), QT shortened during the stress test (no absolute values available) A few short SVT episodes. No signs of ischemiaGenetic analysis for LQTS negative (16 different genes)
Holter: 943 supraventricular ectopic beats. SVT max. 207/min, duration 14 sec. During night maximal QT 610/min at heart rate 50
Genetic analysis for LQTS negative (16 different genes)

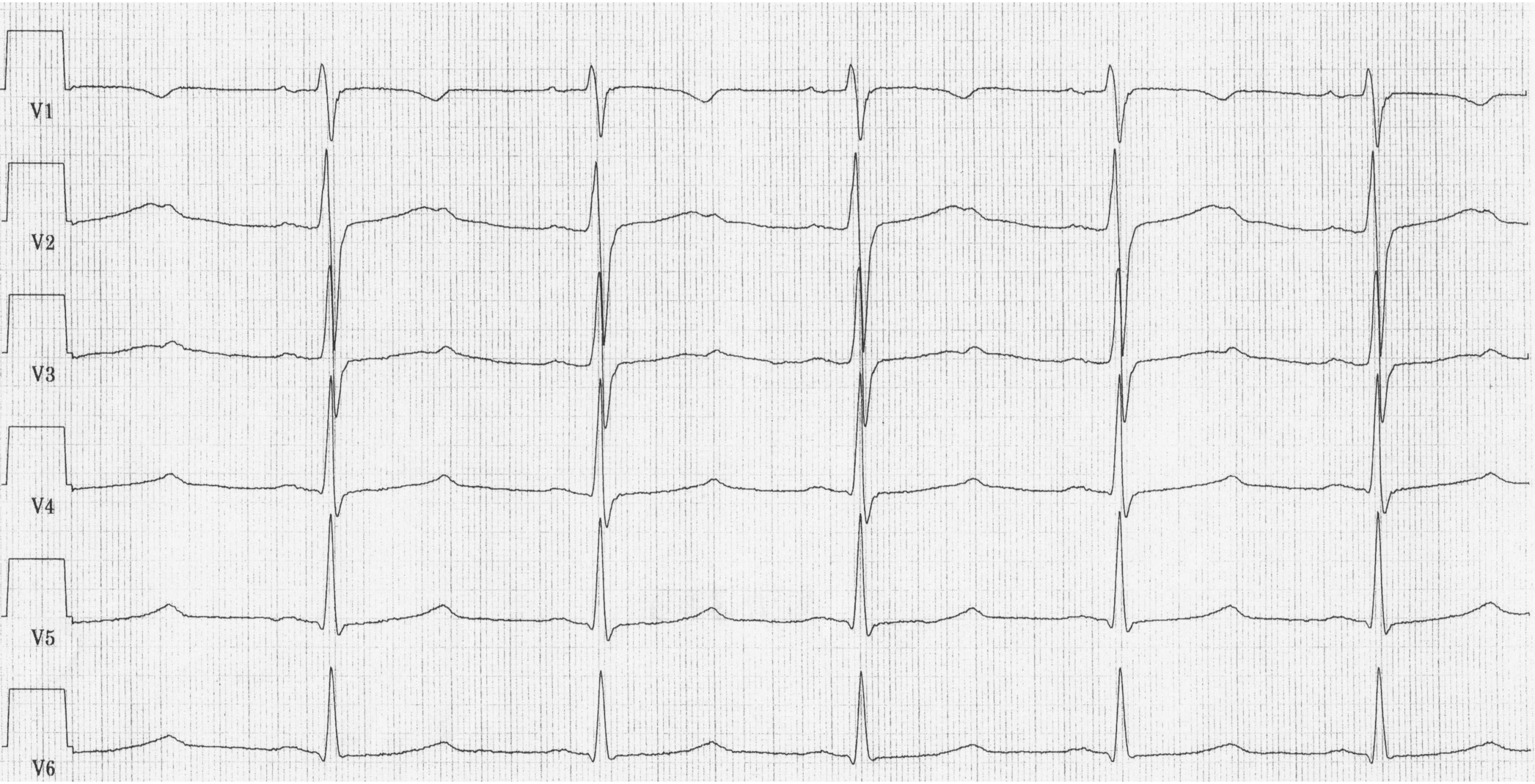
Problems/questions

- Prolonged QT interval: phenotype?
- One syncope – orthostatic?
- Paroxysmal SVT → EP study?
- Genetic analysis negative: New mutation?
- Recently put on β-blocker
- Professional driver's license acceptable?

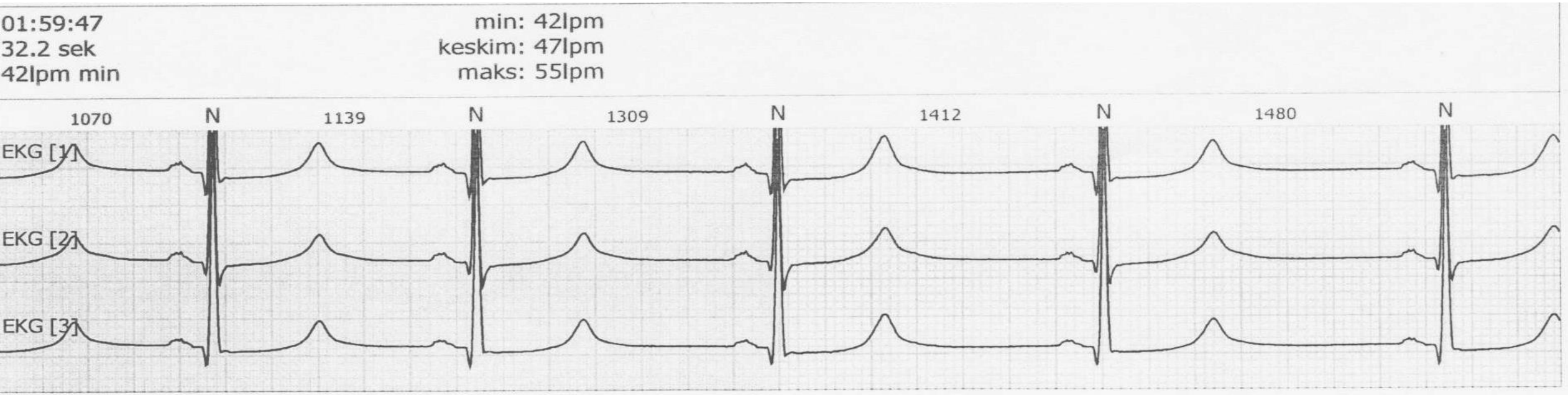
50 mm/sec!!. QTc ~525 ms



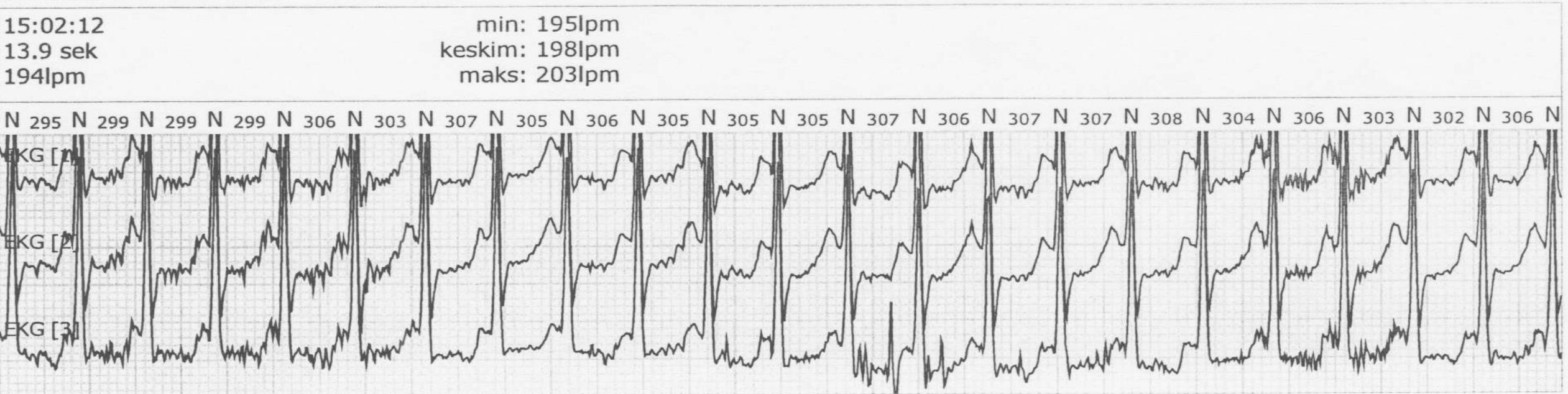
50 mm/sec!!. QTc ~525 ms



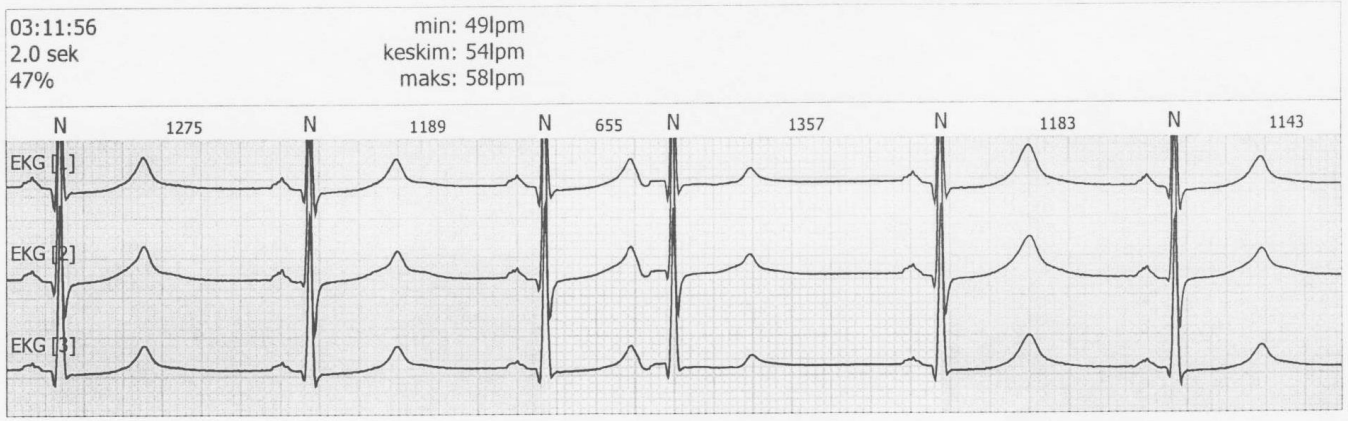
Holter

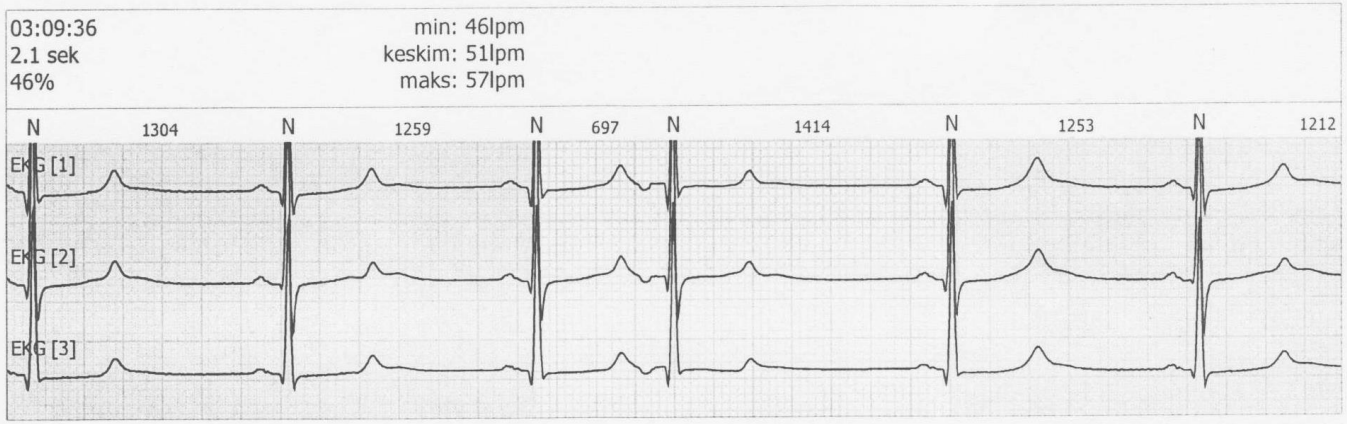


Paroksysmaalinen eteistakykardia [25 mm/s 10 mm/mV] Quantity: **2**

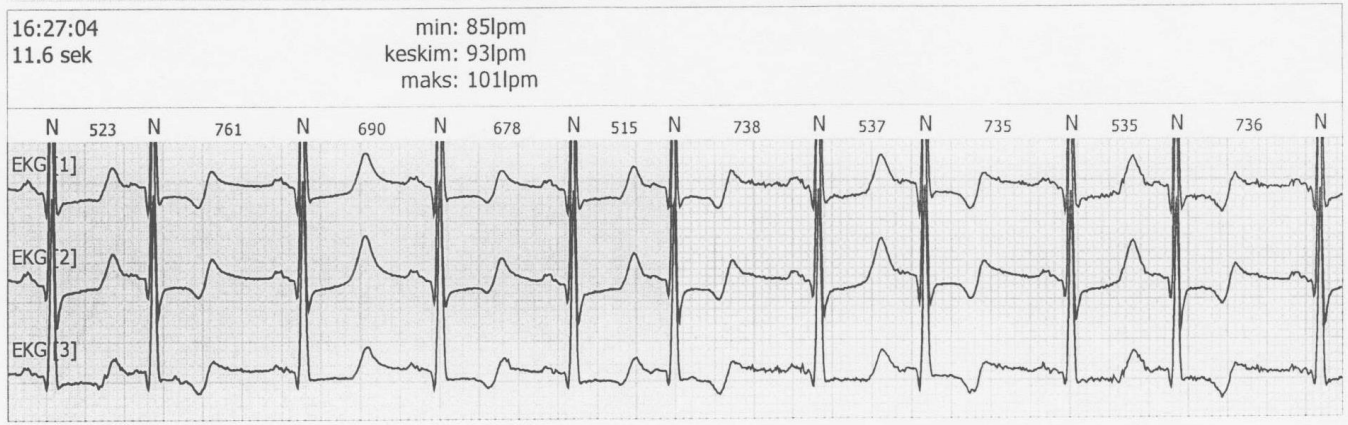


Holter





Epäsäännöllinen sinusrytmi [25 mm/s 10 mm/mV] Quantity: **21**



Colleagues opinions

Hello Andrés,

Looks very much like a SCN5A mutation. However, for a de novo mutation I would have expected a more severe phenotype.

I have the same patient (younger but with a SCN5a mutation, QTc 590 msec) and I authorized him to be hired as a fire fighter.

What about the ECG of the parents or siblings, children ?

Best,

Philippe Chevalier M.Ph.D. Chef du seeervice de Rythmologie GHE, Chu Claude Bernard University- Lyon France.

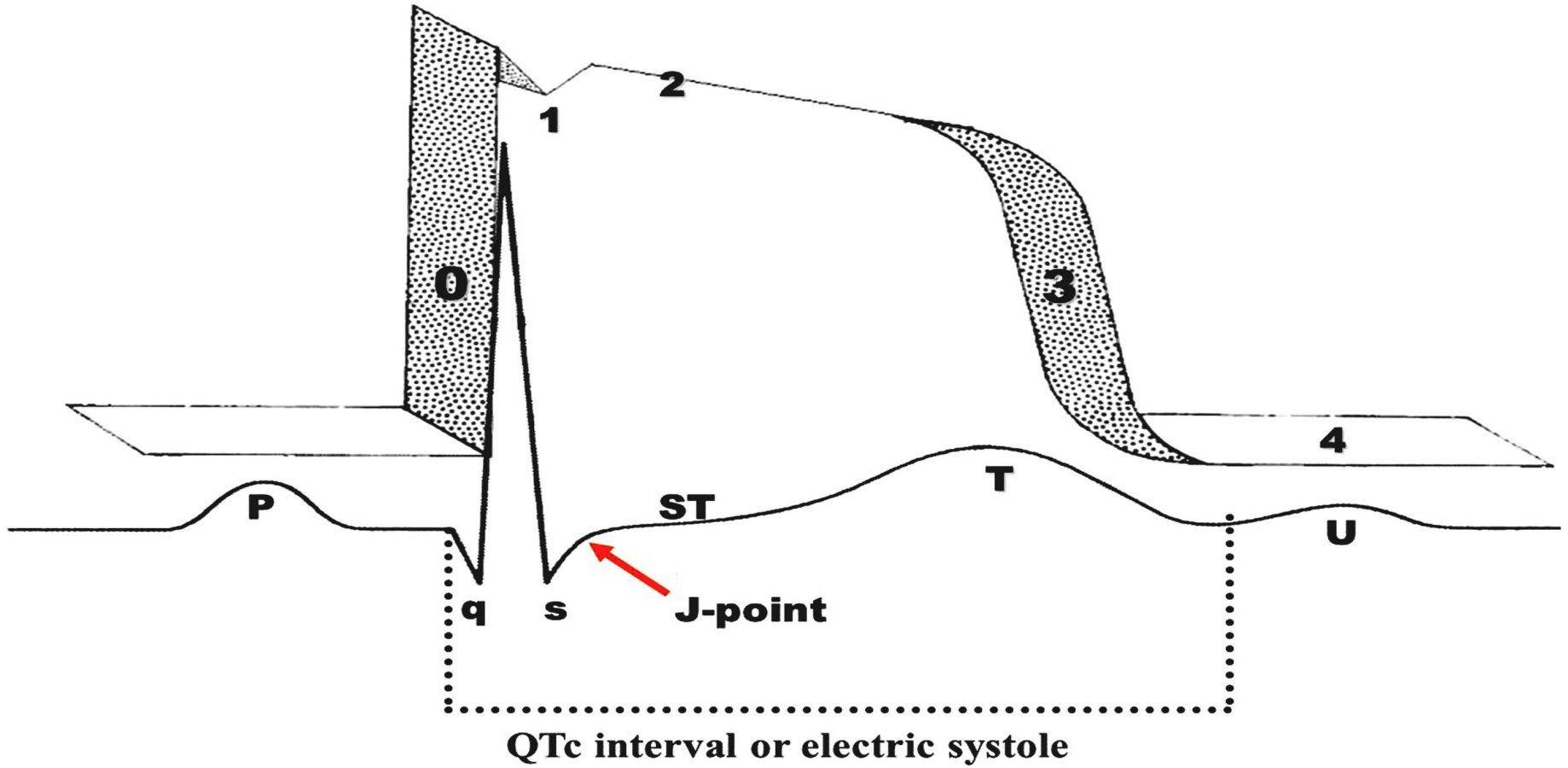
chevalier@chu-lyon.fr

Dear Andrés
Interesting case with high clinical impact.

This is a patient with long QT interval, that was discovered at the age of 55 years. A detailed analysis of his ECG, the QT interval lasts 525 ms (according to the slide). The QT interval dispersion is around 80 ms in the precordial leads. A positive fact in this patient is the shortening of the QT during exercise test. Note that during Holter monitoring the QT interval is long only during bradycardias, when the heart rate is around 80 bpm, these interval shortens.
It would be very interesting to obtain some information about the patient's height and weight (body mass index) or some information about his metabolic status. Usually lorry driver are obese, take drugs to prevent sleep. Both conditions can increase QT interval. Actually QT interval prolongation can be a marker for this metabolic condition.
The patient has a supraventricular tachycardia on Holter whose mechanism is not clear as there is a lot of noise in the baseline that precludes a better assessment of the tachycardia mechanism. I do not think necessary electrophysiological study only to evaluate the tachycardia. A better ECG tracing can help the diagnosis and to treat the patient. Atrial tachycardia is a very commom finding during Holter in patient at that age.
The patient has a past history of fainting that looks like neuromediated syncope based on clinical history.
The beta blocker may be a treatment option if the patient has symptoms. My only advice would be to avoid any kind of drugs that can prolong the QT further. If there is any sign of metabolic syndrome it should be treated.
We must remember that QT interval of 525 ms is still within a tolerable range for this interval for males, mainly for those without past history of arrhythmic episodes. A spontaneous variability of 76 ms up to 100 ms during Holter monitoring has been previously demonstrated (Am J Cardiol 1991; 67:774; JACC 1996; 27:76) and can be expected in this condition, according to the literature.
The long QT interval in this patient was an incidental finding when the patient underwent a medical evaluation. In my opinion has only prolonged QT interval without the "disease" properly (only the phenotype) or it is a marker of other metabolic condition.
Would have no trouble leaving this patient keep driving.
Best regards
Dalmo Moreira

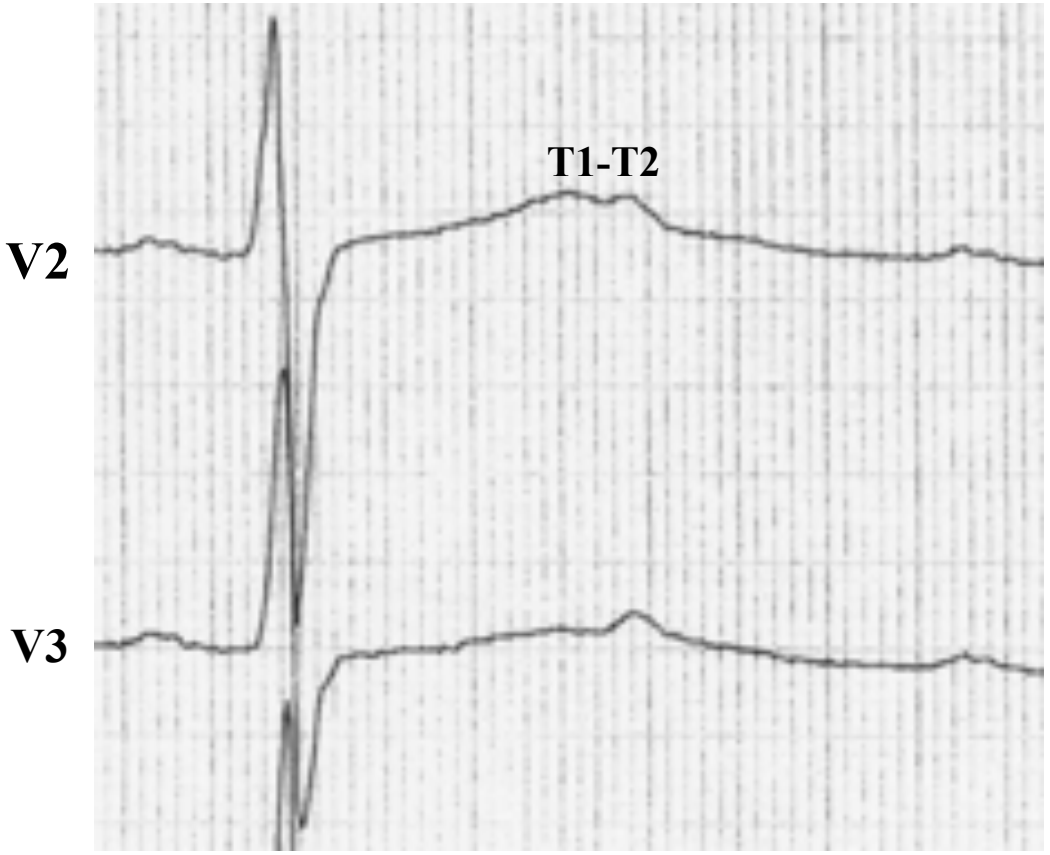
Final comments

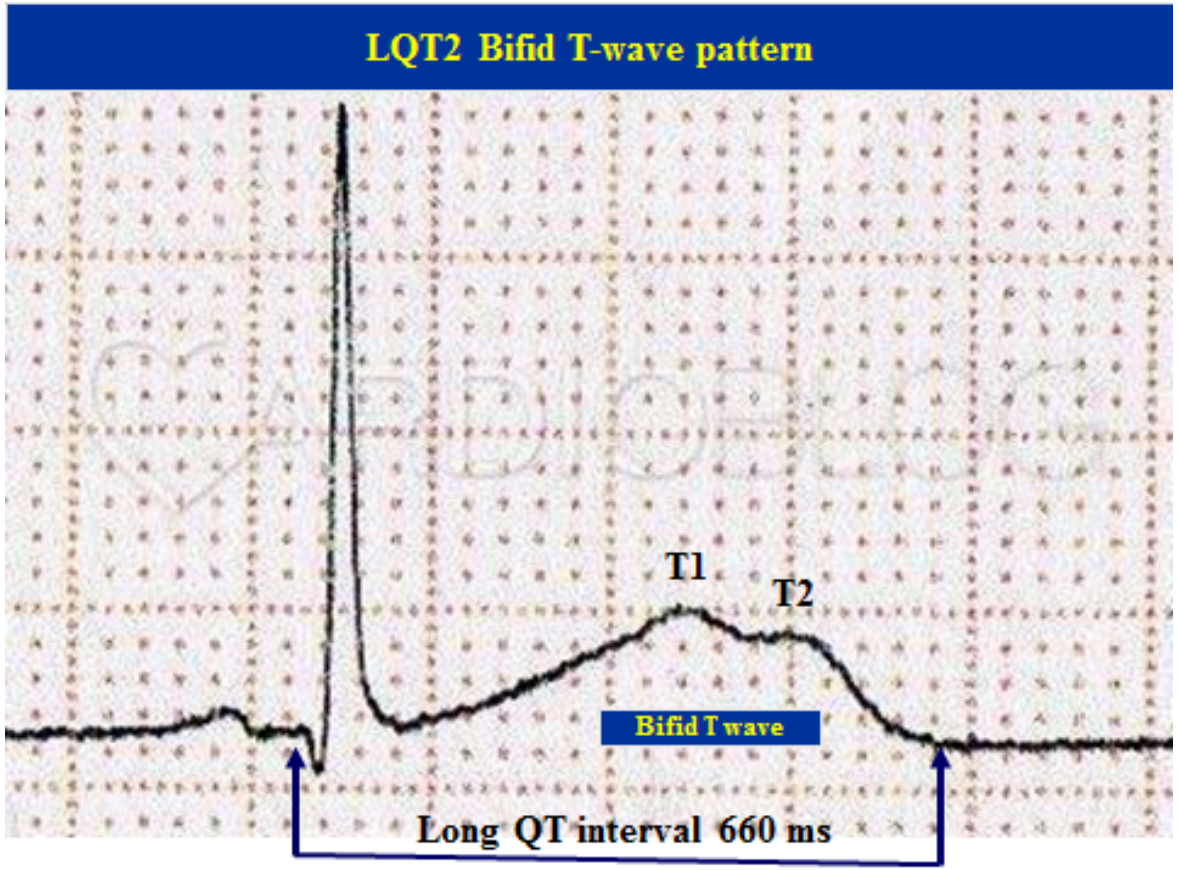
By Andrés Ricardo Pérez-Riera



Representation of minimal and maximal normal values of QTc interval and its correlation with monophasic action potential.
QTc values < 330 ms are considered short QT interval. Values of QTc > 450 ms are considered long QT intervals. Normal values of QTc are between 350 to 440 ms or 446 + - 15%.

Bimodal or notched T waves(The present case): Type 2 LQTS phenotype





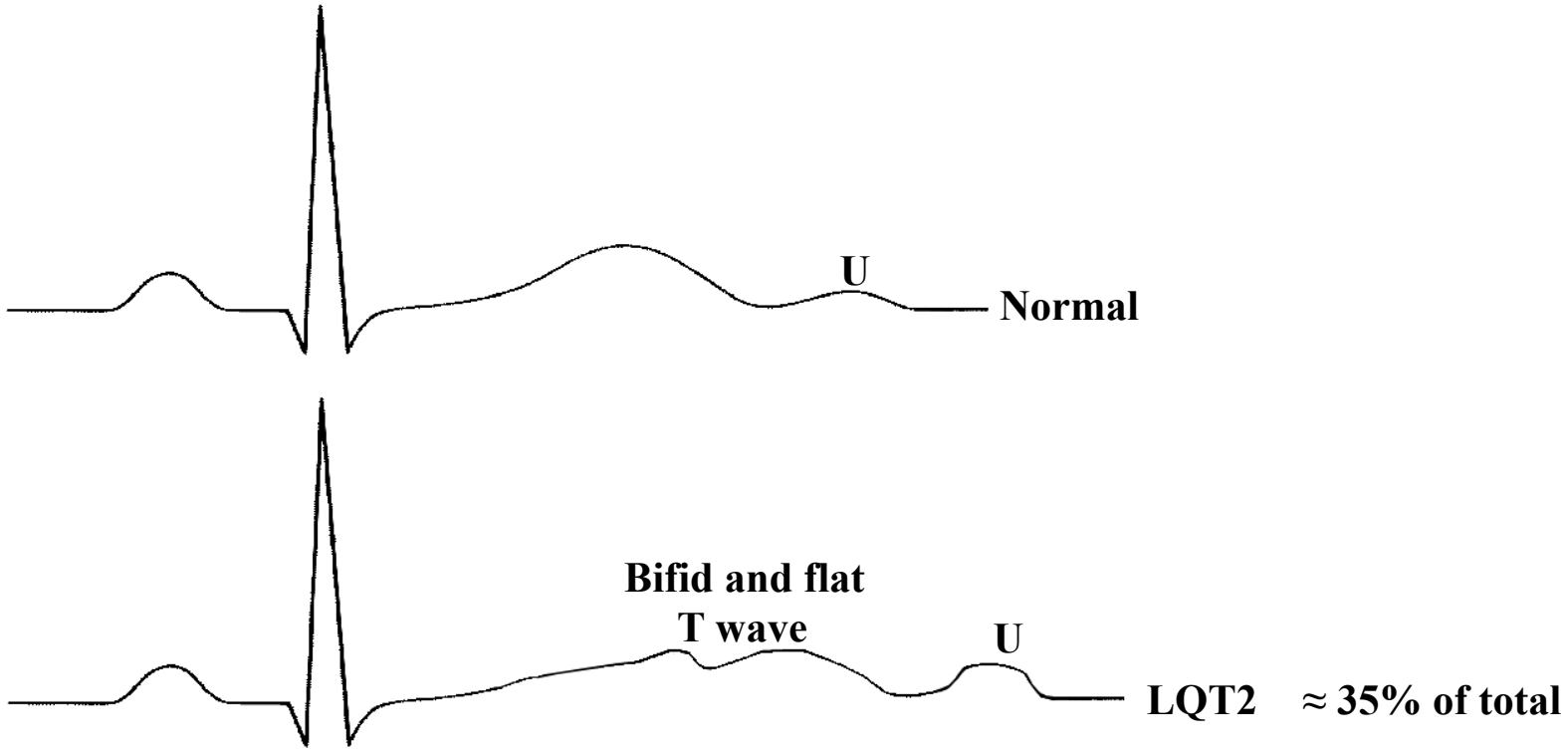
Bimodal or notched T waves may be distinguished from the T-U interval: the second apex of bimodal T wave (T2) is at a distance from the first one (T1) < 150 ms; the T1-U interval is > 150 ms ([1-2]). The second apex of bimodal T wave (T2) is at a distance < 150 ms from the first module (T1): The T1-U interval is always > 150 ms.

1. Lepeschkin E.: Physiologic basic of the U wave. In Advances in Electrocardiography. Edited by Schlant RC, and Hurst JW. New York, Grune & Stratton 1972;pp 431-447.
2. Lepeschkin, E.:The U wave of the electrocardiogram. Mod Concepts Cardiovasc Dis 1969;38:39.

Differentiation between bimodal or notched T waves in T-U interval.

Characteristics of HERG LQT2 variant/phenotype.

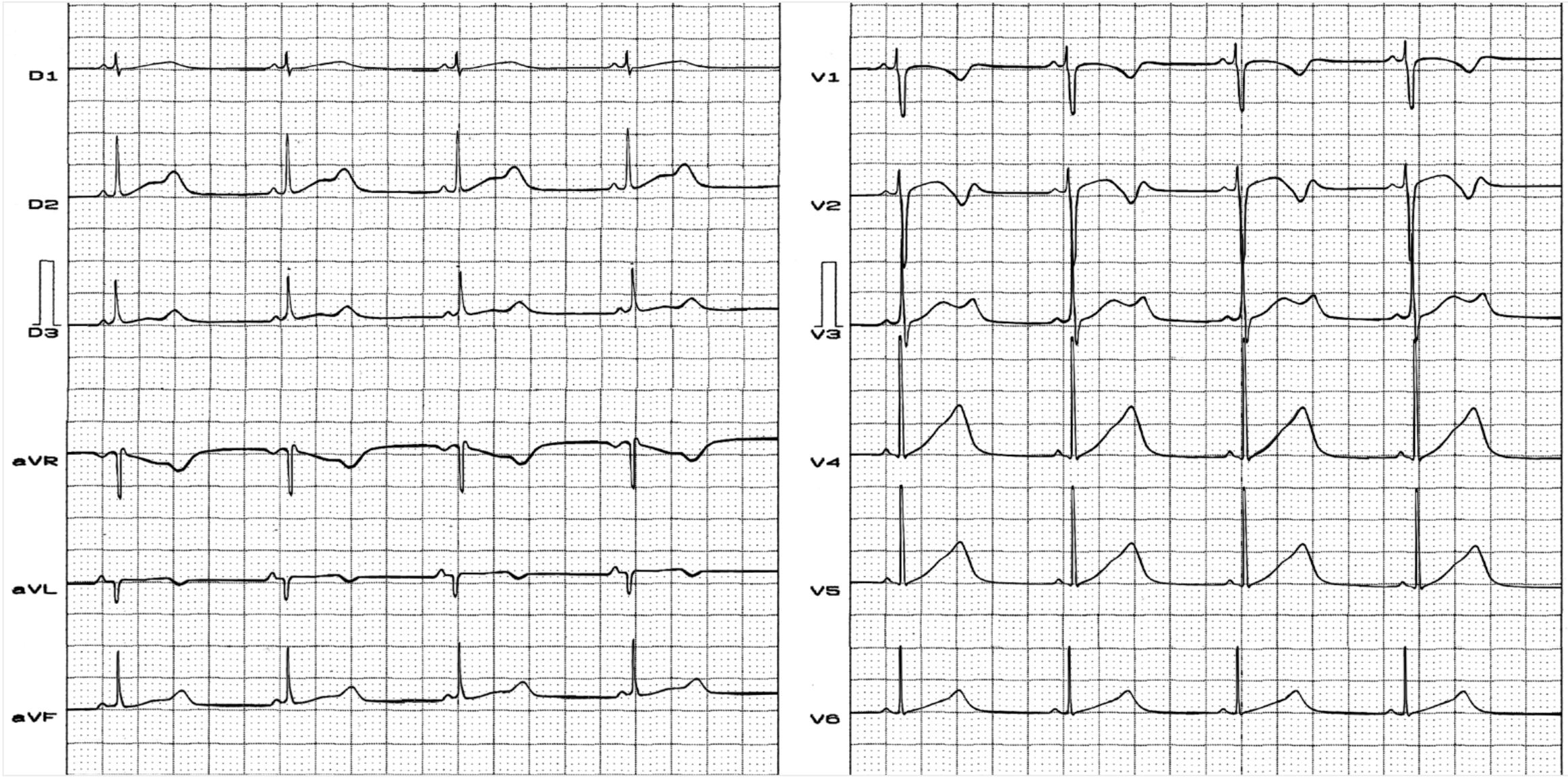
Events triggers: Emotion or stress and noises: LQT2 Auditory arousal



LQT2: ***OMIN 152437. Mutation: alpha subunit of the rapid delayed rectifier potassium channel (hERG = MiRP1) Current through this channel is known as I_{Kr}. This phenotype is also probably caused by a reduction in repolarizing current.***

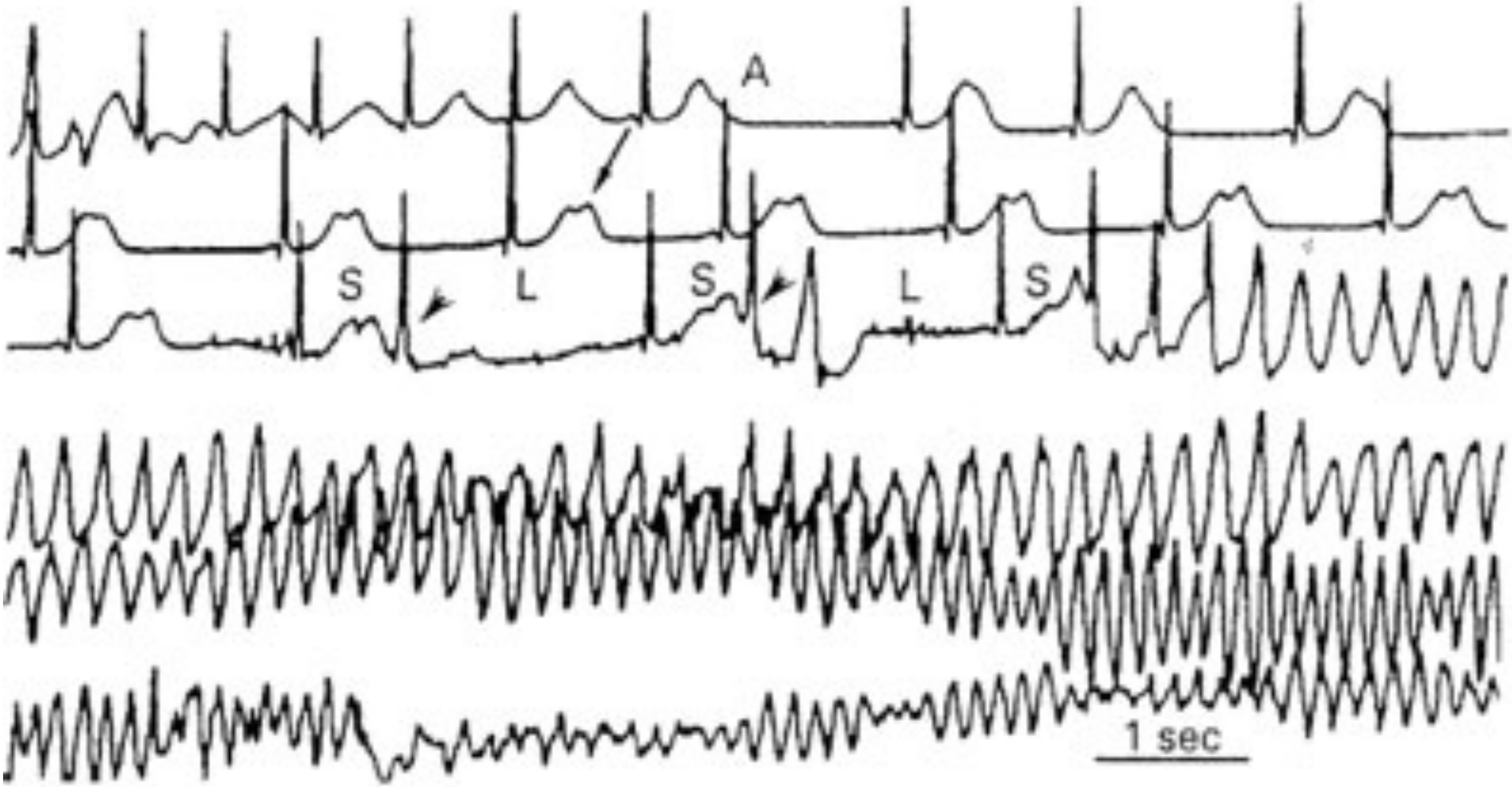
Location	Phenotype	Phenotype MIM number	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
7q36.1	{Long QT syndrome 2, acquired, susceptibility to}	613688	3	KCNH2	152427
7q36.1	Long QT syndrome 2	613688	3	KCNH2	152427
12p11.1	{Long QT syndrome, acquired, reduced susceptibility to}	613688	3	ALG10	603313

Name: D.S.F**Age:** 11 years old **Sex:** Fem. **Weight:** 38 kg**Height:** 1.45 m**Race:** white**Date:** 09/18/2001 **Medication in use:** Propanol 240 mg.

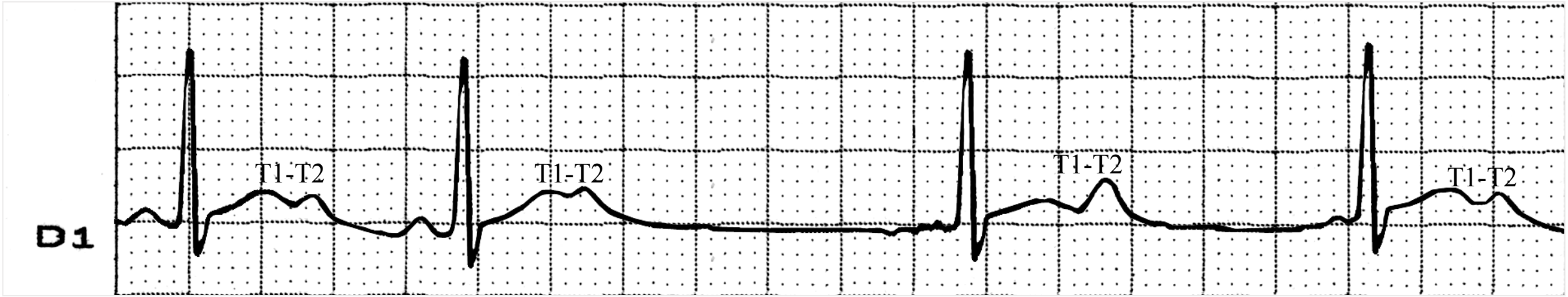


Clinical Diagnosis: heredofamilial long QT syndrome without deafness. Tracing performed moments after episode of syncope. Marked increase of T-U wave is observed.

ECG Diagnosis: sinus rhythm, HR: 63 bpm, long QT interval 500 ms (normal maximal value: 430 ms); very evident prominent U waves in II and V3.


A
S
L
S
L
S
1 sec

Bimodal T wave(T_1-T_2) Pseudo-U wave dependent on Bradyarrhythmic pause



Prominent U wave that increases voltage in pauses.

1. **Roden DM, et al. Inherited long QT syndromes: a paradigm for understanding arrhythmogenesis. J Cardiovasc Electrophysiol. 1999;10:1664-1683.**

Mapping Jiang et al. (1) found linkage to D7S483 at chromosome 7q35-q36 in 9 families with the LQTS; the combined lod score was 19.41 at theta = 0.001.

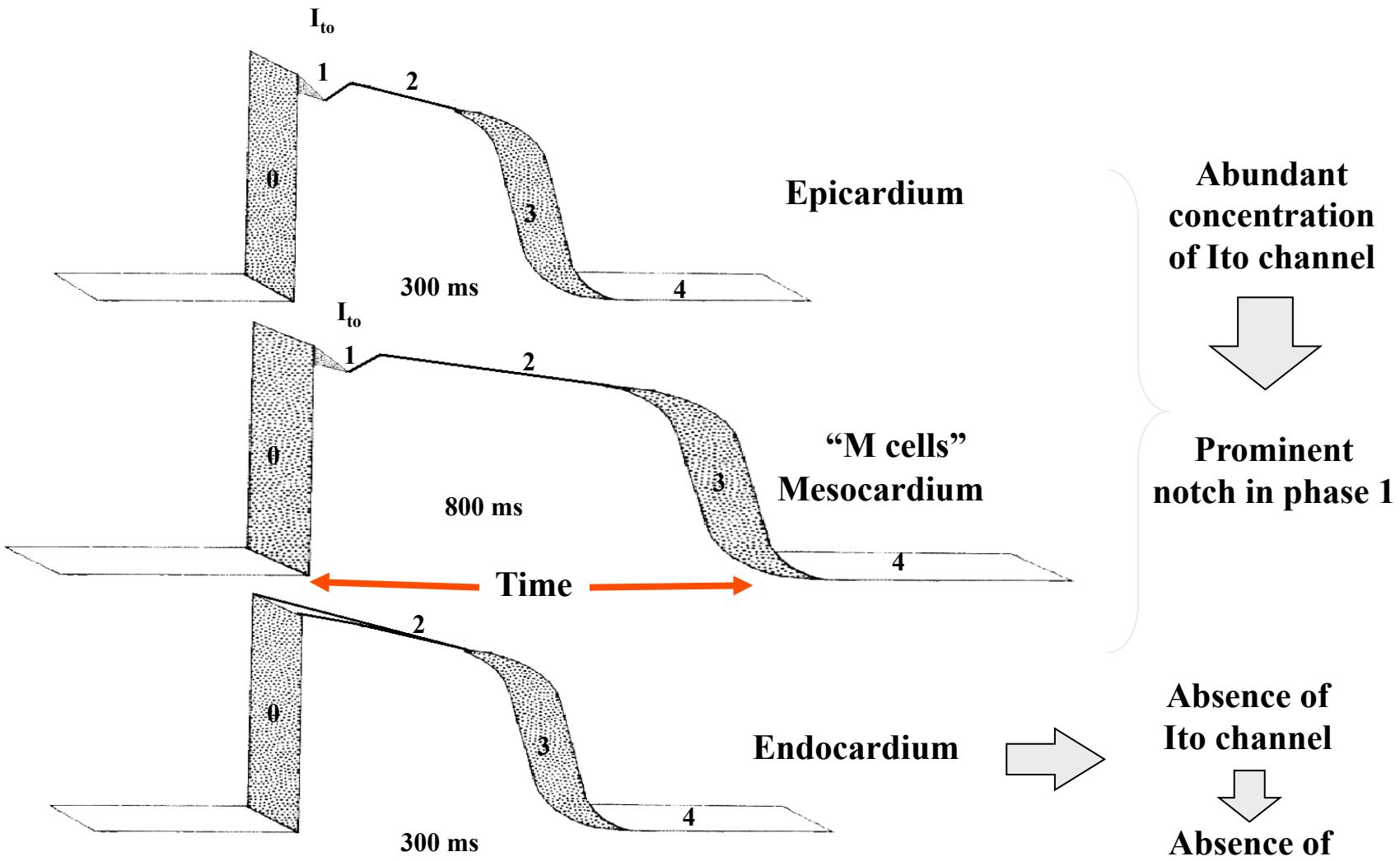
Curran et al. (2) showed that the KCNH2 gene mapped to the same YAC as D7S505, a polymorphic marker tightly linked to LQT2. They found no recombination events using linkage analysis with polymorphisms within KCNH2 for linkage studies of chromosome 7-linked LQT

Pathogenesis Curran et al noted that 2 hypotheses for LQT had previously been proposed. One suggested that a predominance of left autonomic innervation caused abnormal cardiac repolarization and arrhythmias. This hypothesis was supported by the finding that arrhythmias can be induced in dogs by removal of the right stellate ganglion. In addition, anecdotal evidence suggested that some LQT patients are effectively treated by β-adrenergic blocking agents and by left stellate ganglionectomy. The second hypothesis for LQT-related arrhythmias suggested that mutations in cardiac-specific ion channel genes (or genes that modulate cardiac ion channels) cause delayed myocellular repolarization. Delayed myocellular repolarization could promote reactivation of L-type Ca(2+) channels, resulting in secondary depolarizations. These secondary depolarizations are the likely cellular mechanism of torsade de pointes arrhythmias. This hypothesis is supported by the observation that pharmacologic block of potassium channels can induce QT prolongation and repolarization-related arrhythmias in human and animal models. The discovery that one form of LQT results from mutations in a cardiac potassium channel gene supported the myocellular hypothesis.

In a surrogate model of LQT2, Akar et al. (3) investigated a mechanism by which dysfunction at the molecular level may provide the electrical substrate for the life-threatening arrhythmia TdP. The authors used the novel approach of transmural optical imaging in a canine wedge preparation to determine the spatial organization of repolarization and arrhythmogenesis. They demonstrated islands of midmyocardial cells (M cells) with increased refractoriness, producing transmural gradients of repolarization that were directly responsible for conduction block and self-sustained intramural reentrant circuits(Phase 2 reentry) . These data highlighted a central role for M cells in the development of reentrant TdP in LQT2.

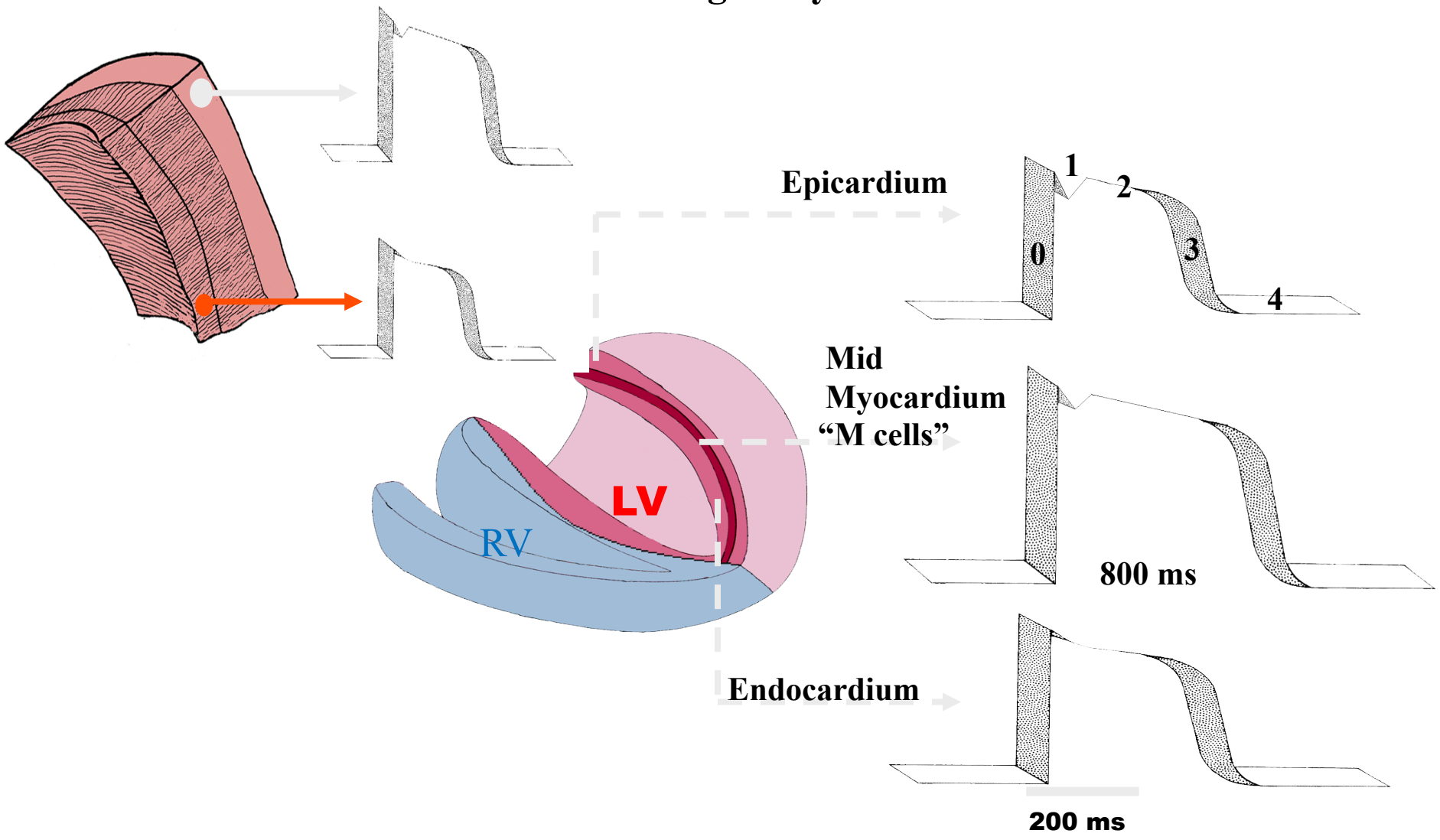
1. **Jiang C, et al. Two long QT syndrome loci map to chromosomes 3 and 7 with evidence for further heterogeneity. Nature Genet. 8: 141-147, 1994.**
2. **Curran ME, et al.. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 80: 795-803, 1995.**
3. **Akar FG. Unique topographical distribution of M cells underlies reentrant mechanism of torsade de pointes in the long-QT syndrome. Circulation 105: 1247-1253, 2002.**

Epicardium, mesocardium and endocardium: heterogeneity in ventricular wall thickness

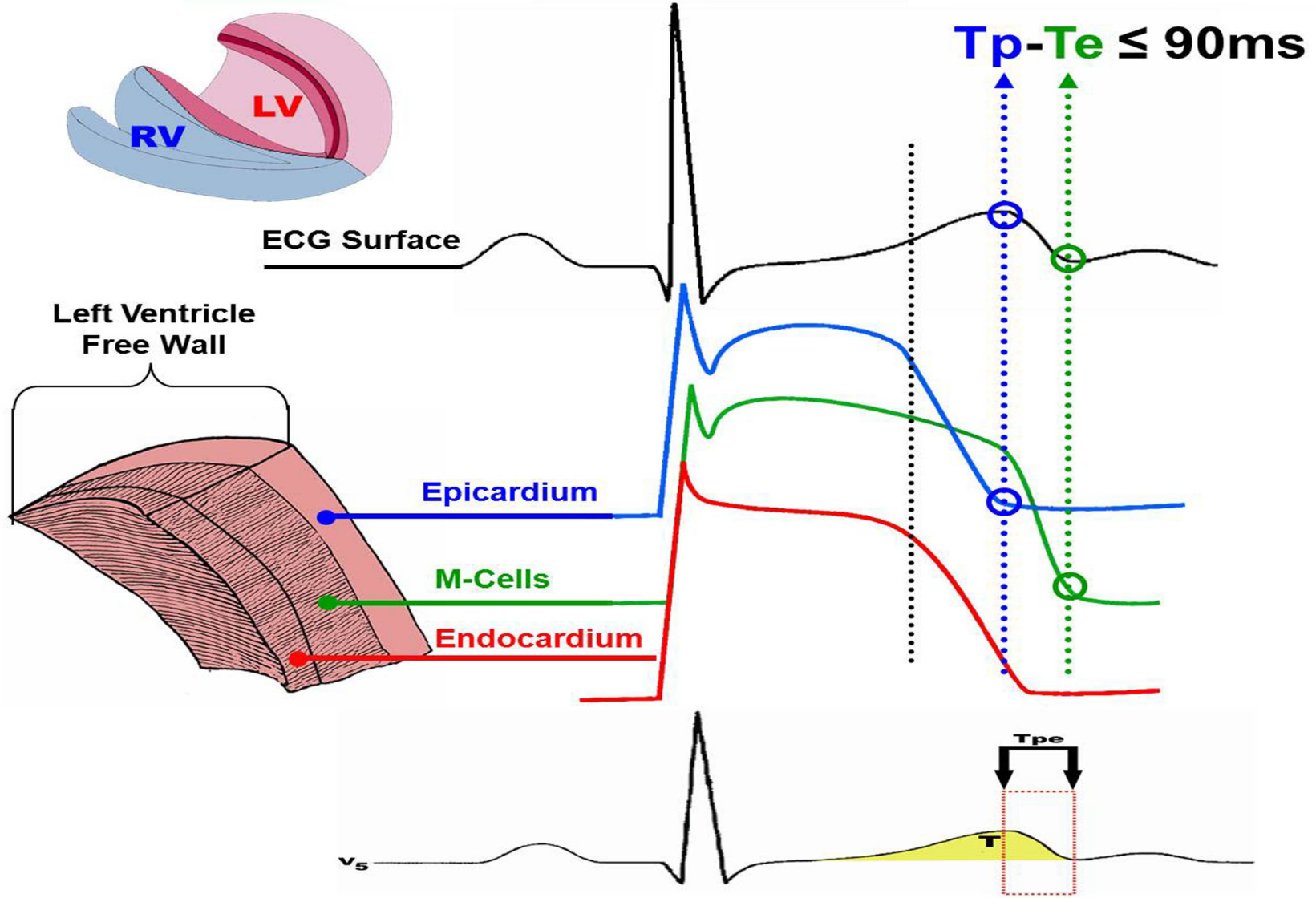


Outline of action potential in ventricular wall thickness. Differences in epi, meso and endocardium action potential profile and duration. The heterogeneous character of action potential is clearly observed in the 3 areas.

Action potential of ventricular contractile cells in wall thickness: epicardium, mesocardium and endocardium: heterogeneity

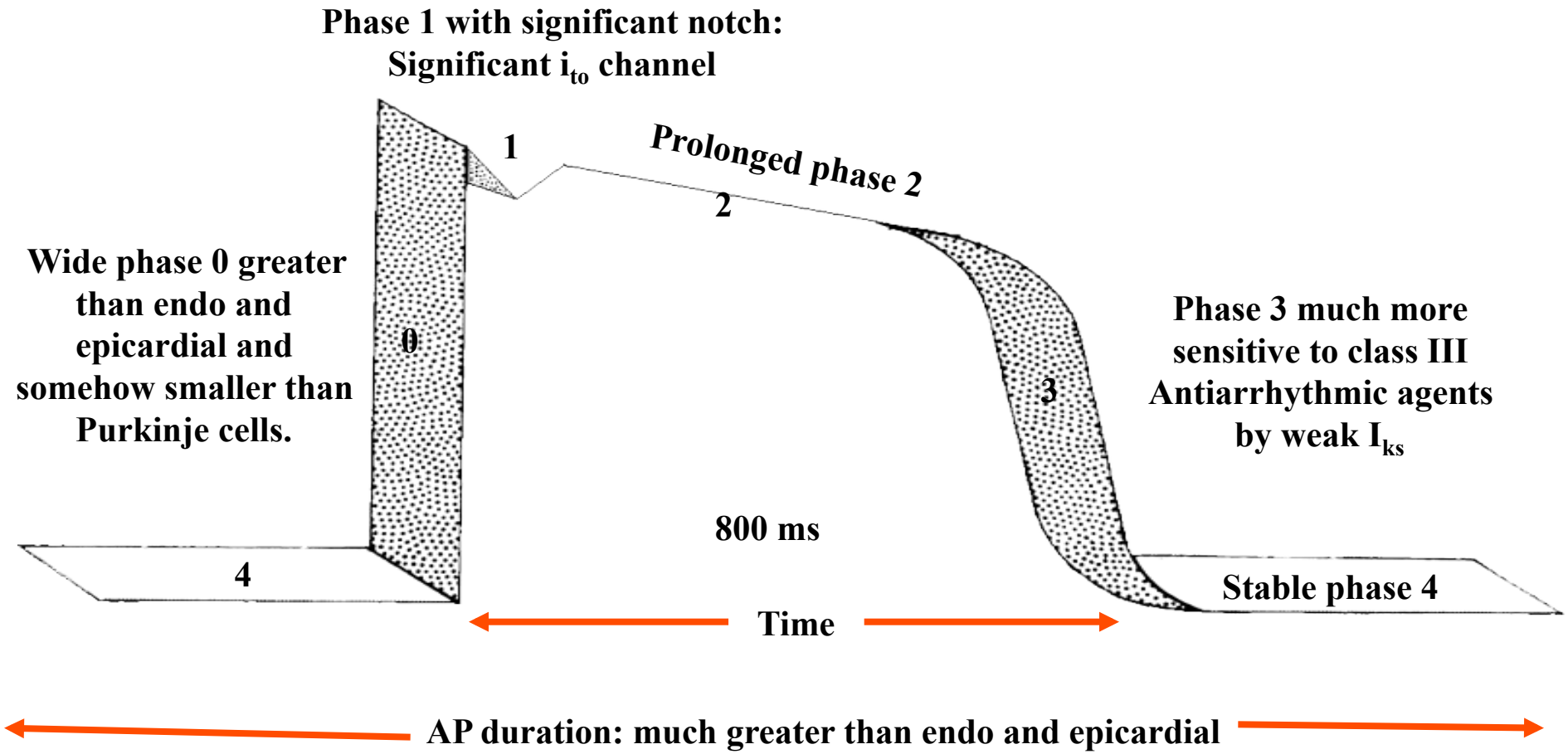


Outline of action potential in ventricular wall thickness. Differences in epi, mid and endocardium action potential profile and duration. The heterogeneous character of action potential is clearly observed in the 3 areas.



Representation of the Tpeak/Tend interval (Tpe).This is the interval elapsed from the apex to the end of T wave (Tpeak-Tend interval or Tpe). Tpe may correspond to transmural dispersion of repolarization and consequently, the amplification of this interval is associated to malignant ventricular arrhythmias. The normal value of Tpeak/Tend interval (Tpe) is 94 ms in men and 92 in women when measured in the V5 lead. In congenital SQTS this parameter is > 92ms in women and > 94ms in men (measurement in V5).

Characteristics of action potential of “M” cells of the ventricular mid-myocardium



Features of M cells action potential, essential in electrogenesis of long QT syndromes.

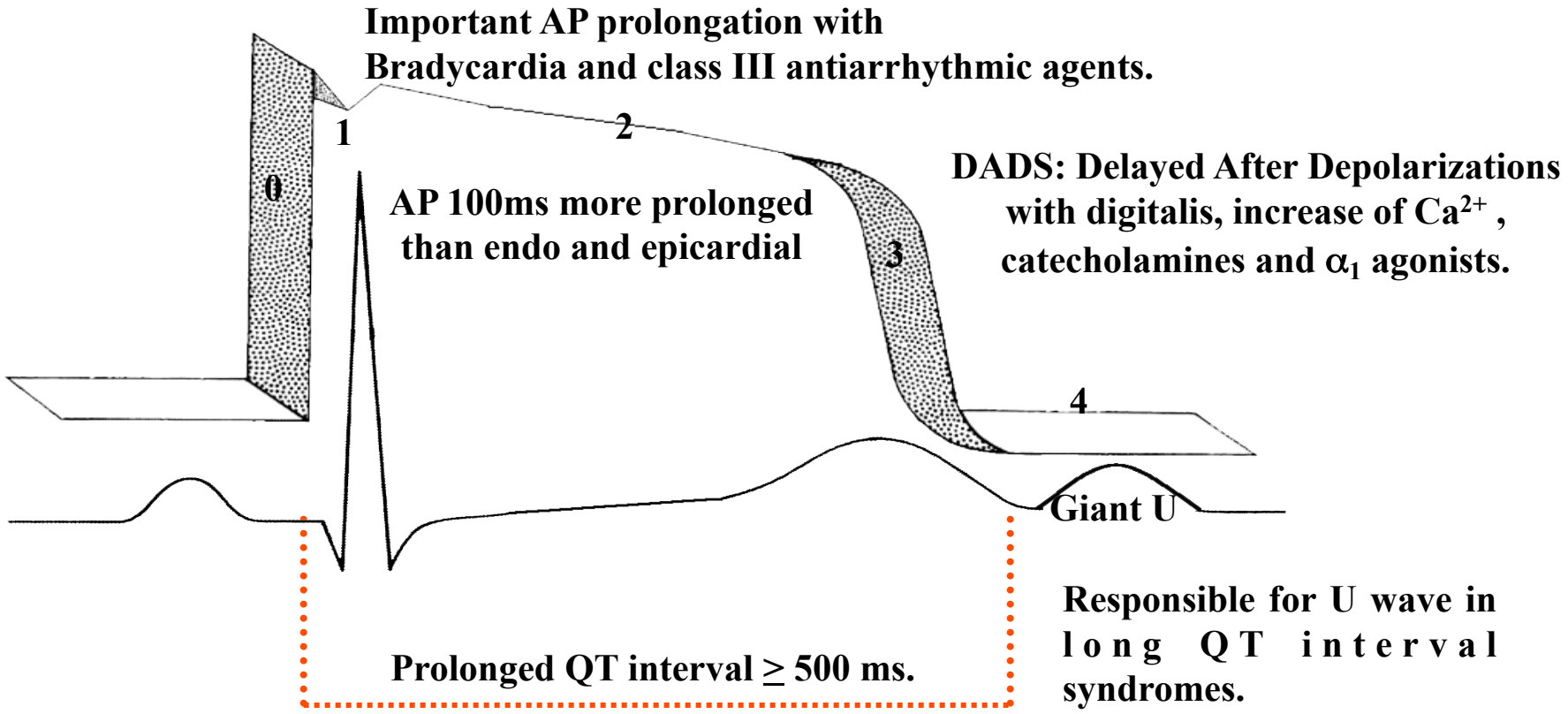
Characteristics of "M" cells

1) **Location:** central or mid-myocardium; deep epicardial portion of LV lateral and anterior wall, and throughout the RV outflow tract.
2) **Histology:** cannot be differentiated from endocardial and epicardial cells.
3) **Action Potential:** more prolonged: $\geq$ 800 ms, phase 0 wider than endocardial and epicardial cells, and smaller than Purkinje; phase 1 with significant notch by abundance of I_{to} channel; prolonged phase 2; phase 3 more sensitive to class III antiarrhythmic agents by having a weaker slow delayed outward rectifying potassium channel (I_{ks}) and phase 4 is stable (nonautomatic cell).
4) Responsible for QTc interval prolongation in LQTS.
5) Responsible for numerous alterations in T waves, known as "enigmatic" T waves, observed in LQTS.
6) Responsible for prominent U waves of LQTS (QU), decisive in the genesis of Torsade de Pointes (TdP).
7) Greater increase in AP duration during low heart rates (bradyarrythmia), before the use of class III antiarrhythmic agents (d-sotalol), quinidine, erythromycin, ATX-II, and anthopleurin A.
8) They are responsible for early after depolarizations (EADs) or in phase 3: bradycardia-dependent.
9) They are responsible for triggering TdP (subendocardial focus by "M" cells and Purkinje cells).
10) They are responsible for DADs (Delayed After Depolarizations) with digitalis, increase of Ca2+, catecholamines and α1 agonists. They induce changes in AP duration. In this aspect, they are different from epicardial and endocardial cells, and are similar to Purkinje. The ion substrate for these differences is caused by a weaker slow outward K+ channel at the end of AP phase 3 ("delayed rectifier current"): IKs that determines a more prolonged AP.

Summary of M cells features.

“M” cell action potential and ECG with long QT interval

EADs: Early After Depolarizations With Class III Antiarrhythmics Agents.



M cells action potential and ECG with long QT interval.

Roden et al.(1) reviewed the genetics of acquired LQTS and discussed the structural features of the HERG channel that render it more vulnerable to blockade by drugs: the presence of multiple aromatic residues oriented to face the permeation pore, which provide high-affinity binding sites for a wide range of compounds; and the absence of a pair of proline residues in the S6 helix that forms part of the pore, resulting in an unkinked S6 helix in the HERG channel that is hypothesized to increase access to the binding site

Itzhaki et al. (2) reported the development of a patient/disease-specific human induced pluripotent stem cell (iPSC) line from a patient with LQT2 that was due to an A614V missense mutation in the KCNH2 gene. The generated iPSCs were coaxed to differentiate into the cardiac lineage. Detailed whole-cell patch-clamp and extracellular multielectrode recordings revealed significant prolongation of the APD in LQTS human iPSC-derived cardiomyocytes when compared to healthy control cells. Voltage-clamp studies confirmed that this APD prolongation stems from a significant reduction of the cardiac potassium current I(Kr). Importantly, LQTS-derived cells also showed marked arrhythmogenicity, characterized by EADs and triggered arrhythmias. Itzhaki et al. (2) then used the LQTS human iPSC-derived cardiac tissue model to evaluate the potency of existing and novel pharmacologic agents that may either aggravate (potassium-channel blockers) or ameliorate (calcium-channel blockers, K(ATP)-channel openers, and late sodium-channel blockers) the disease phenotype. These authors concluded that their study illustrated the ability of human iPSC technology to model the abnormal functional phenotype of an inherited cardiac disorder and to identify potential new therapeutic agents.

Inheritance: Although inheritance of the LQTS is autosomal dominant, female predominance has often been observed and has sometimes been attributed to an increased susceptibility to cardiac arrhythmias in women. Imboden et al. (3) demonstrated distortion in the transmission of the mutant alleles in both LQT1 and LQT2. They investigated the distribution of mutant alleles in 484 nuclear families with LQT1 and 169 nuclear families with LQT2, all with fully genotyped offspring. Classic mendelian inheritance ratios were not observed in the offspring of either female carriers of LQT1 or male and female carriers of LQT2. Among the 1,534 descendants, the proportion of genetically affected offspring was significantly greater than that expected according to mendelian inheritance: 870 were carriers of a mutation (57%), and 664 were noncarriers (43%). Among the 870 carriers, the allele for the LQTS was transmitted more often to female offspring (55%) than to male offspring (45%). Increased maternal transmission of the LQTS mutation to daughters was also observed, possibly contributing to the excess of female patients with autosomal dominant LQTS.

1. **Roden DM., et al.. Genetics of acquired long QT syndrome. J. Clin. Invest. 115: 2025-2032, 2005.**
2. **Itzhaki I. et al. Modelling the long QT syndrome with induced pluripotent stem cells. Nature 471: 225-229, 2011.**
3. **Imboden M, et al. Female predominance and transmission distortion in the long-QT syndrome. New Eng. J. Med. 355: 2744-2751, 2006.**

Clinical Management: Defective protein trafficking is a possible consequence of gene mutation. Trafficking-defective mutant HERG proteins are characterized by a reduced delayed rectifier potassium current and give rise to LQT2. High-affinity HERG channel-blocking drugs can result in pharmacologic rescue of this current. Rajamani et al. (1) studied the electrophysiologic consequences of pharmacologic mutant HERG blockade using 2 blocking agents. One compound, fexofenadine, rescued the electrophysiologic defect without complete channel blockade, suggesting that this might be a useful treatment for some LQT2 patients.

Molecular genetic: Currant et al (2) performed single-strand conformation polymorphism and DNA sequence analyses and detected HERG mutations in 6 LQT families, including 2 intragenic deletions, 1 splice-donor mutation, and 3 missense mutations. In 1 kindred, the mutation arose de novo. Northern blot analyses showed that HERG is highly expressed in the heart. The data were interpreted as indicating that mutation in the HERG gene is responsible for LQT2.

Zhou et al. (3) used electrophysiologic, biochemical, and immunohistochemical methods to study the molecular mechanisms of HERG channel dysfunction caused by LQT2 mutations. They found that some mutations, e.g., tyr611 to his and val822 to met caused defects in biosynthetic processing of HERG channels with the protein retained in the endoplasmic reticulum. Other mutations, e.g., ile593 to arg and gly628 to ser, were processed similarly to wildtype HERG protein, but these mutations did not produce functional channels. In contrast, the thr474-to-ile mutation expressed HERG current but with altered gating properties. These findings suggested that the loss of HERG channel function in LQT2 mutations is caused by multiple mechanisms including abnormal channel processing, the generation of nonfunctional channels, and altered channel gating.

Priori et al (4) identified 9 families, each with a 'sporadic' case of LQTS, i.e., only the proband was diagnosed clinically as being affected by LQTS. 6 probands were symptomatic for syncope, 2 were asymptomatic with QT prolongation found on routine examination, and 1 was asymptomatic but showed QT prolongation when examined following her brother's SCD while swimming. 5 had mutations in HERG (4 missense, 1 nonsense) and 4 had missense mutations in KCNQ1. 4 of the mutations were de novo; in the remaining families at least 1 silent gene carrier was found, allowing estimation of penetrance at 25%. This contrasted greatly with the prevailing view that LQTS gene mutations may have penetrances of 90% or more. This study highlighted the importance of detecting such silent gene carriers since they are at risk of developing TdP if exposed to drugs that block potassium channels. Further, the authors stated, carrier status cannot be reliably excluded on clinical grounds alone.

1. Rajamani S, et al. Pharmacological rescue of human K+ channel long-QT2 mutations. Circulation 105: 2830-2835, 2002.
2. Curran M.E, et al.. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 80: 795-803, 1995.
3. Zhou Z, et al. HERG channel dysfunction in human long QT syndrome: intracellular transport and functional defects. J. Biol. Chem. 273: 21061-21066, 1998
4. Priori et al. Genetic and molecular basis of cardiac arrhythmias: impact on clinical management. Parts I and II. Circulation 99: 518-528, 1999.

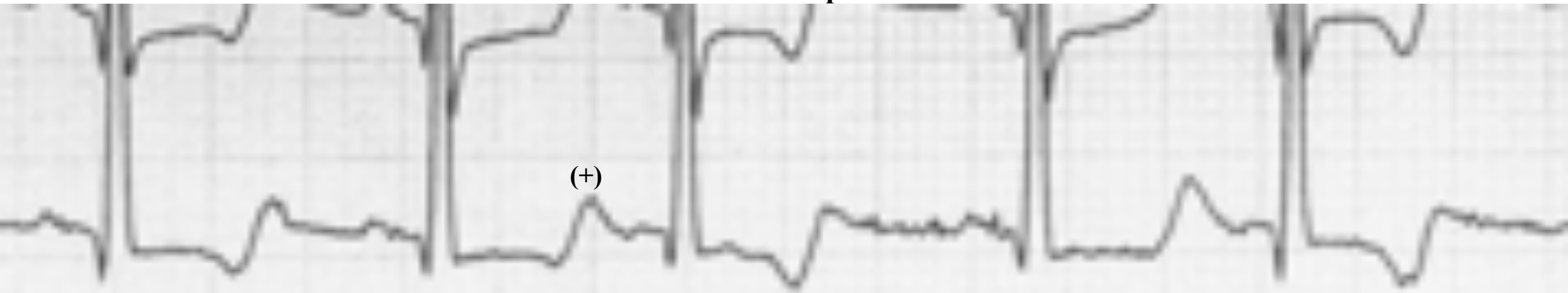
Susceptibility to Acquired LQT2: Although many commonly used drugs block I(Kr), in certain individuals drugs evoke a paradoxical life-threatening cardiac rhythm disturbance, known as acquired long QT syndrome. Although acquired LQTS is a leading cause of drug withdrawal according to the US Food and Drug Administration, DNA sequencing in patients with acquired LQTS revealed HERG mutations only in rare cases, suggesting that HERG modulators are often responsible. By using C. elegans,
Petersen et al. (1) developed in vivo behavior assays that identified candidate modulators of Unc103, the worm HERG ortholog. By using RNA interference methods, they showed that worm homologs of 2 HERG-interacting proteins, hyperkinetic and Kcr1, modify Unc103 function. In patients with drug-induced cardiac repolarization defects, sequencing of the KCR1 gene (ALG10) revealed an ile447-to-val substitution (I447V) that occurred at a reduced frequency relative to a matched control population, suggesting that I447V may confer reduced susceptibility to acquired LQTS. The clinical result was supported by in vitro studies of sensitivity of HERG to dofetilide by using coexpression of HERG with wildtype and I447V KCR1 cDNAs.

Genotype/Phenotype

Zareba et al. (2) determined the influence of genotype on phenotype of the LQTS; 112 persons had mutations at the LQT1 locus, 72 had mutations at the LQT2 , and 62 had mutations at the LQT3. The frequency of cardiac events (syncope, aborted cardiac arrest, or SCD) was highest with mutations at the LQT1 (63%) or the LQT2 (46%) than among subjects with LQT3mutation (18%). The cumulative mortality through the age of 40 among members of 3 groups of families studied was similar; however, the likelihood of dying during a cardiac event was significantly higher among families with mutations at the LQT3 (20%) than among those with mutations at the LQT1 (4%) or the LQT2 (4%).
Moss et al (3) investigated the clinical features and prognostic implications of mutations involving the pore and nonpore regions of the HERG channel in LQT2. 44 different mutations in this gene were identified in 201 subjects, with 14 localized to the pore region (amino acid residues 550 through 650). A total of 35 individuals had mutations in the pore region and 166 in nonpore regions. Those with pore mutations had a markedly increased risk for arrhythmia-associated cardiac events (syncope, cardiac arrest, or sudden death) compared with those with nonpore mutations.

1. **Petersen C I, et al. In vivo identification of genes that modify ether-a-go-go-related gene activity in Caenorhabditis elegans may also affect human cardiac arrhythmia. Proc. Nat. Acad. Sci. 101: 11773-11778, 2004.**
2. **Zareba W, et al. International Long-QT Syndrome Registry Research Group. Influence of the genotype on the clinical course of the long-QT syndrome. New Eng. J. Med. 339: 960-965, 1998.**
3. **Moss AJ.et al. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. Circulation 105: 794-799, 2002.**

The second Holter of this patient



Classic beat-to-beat T-wave macrovolt or macrosopic T wave alternans.

Macrovolt or macorscopic T-wave alternans is observed intermittently. This phenomenon entails electrical instability and constitutes a marker for non-homogeneous recovery in ventricular repolarization in ventricular wall thickness or appearance of tachyarrhythmias events with significant electrical and hemodynamic repercussion. T-wave alternans polarity is a characteristic of patients carriers of long QT syndrome (LQTS). Isolated T-wave alternans not related to tachycardia or premature contractions usually indicates advanced heart disease or severe electrolytic disorder. The following are possible causes for T-wave alternans: *Tachycardia; sudden changes in cycle length or HR; severe hyperkalemia by uremia; experimentally in hypocalcemia in dogs; severe myocardial impairment: cardiomyopathy; acute myocardial ischemia, especially in variant angina; after resuscitation; acute pulmonary embolism; after the administration of amiodarone , quinidine (1; 2) or pentamidine(3); congenital long QT syndromes of the Romano-Ward or Jerver-Lange-Nielsen types.* This flashlight shows that macrovolt T-wave alternans is a tell-tale of acute arrhythmogenic cardiac distress. It can be easily picked up with the bare eye. This exceptional clinical phenomenon formed the basis of the development of microvolt T-wave alternans as a risk stratifier for sudden arrhythmic cardiac death.

1. **Wegener FT, et al. Amiodarone-associated macroscopic T-wave alternans and torsade de pointes unmasking the inherited long QT síndrome. Europace 2008; 10: 112.**
2. **Grabowski M, et al. Drug-induced long-QT syndrome with macroscopic T-wave alternans.Circulation. 2004;110:459.**
3. **Kroll CR, et al. T wave alternans and Torsades de Pointes after the use of intravenous pentamidine.J Cardiovasc Electrophysiol. 2002:13.**

Cardiac ion channel mutational analysis is a category of genetic testing used in clinical practice for determining the status of long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome genes in blood, saliva, or tissue from patients and family members at risk for cardiac events such as syncope and sudden death. Such testing is most informative following careful phenotypic characterization. Individuals with ion channelopathies may benefit from prevention (avoidance of triggers and predisposing drugs) and treatment (e.g., beta blocker therapy, implantable cardioverter-defibrillator (ICD) placement) modalities.

Guidelines by independent groups

A 2007 consensus report by the U.S. National Heart, Lung, and Blood Institute and the Office of Rare Diseases on gene mutations affecting ion channel function concluded that genetic testing for LQTS must be combined with clinical evaluation, and noted lack of clarity in the proportion of SQTS cases that might be explained by the corresponding KCNH2, KCNJ2, and KCNQ1 genes(1). A 2011 HRS) / EHRA consensus statement further states that LQTS genetic testing is recommended for any asymptomatic patient with idiopathic (not attributable to QT prolonging disease states or conditions) QTc values > .480ms. (prepuberty) or > .500 ms. (adult), and may be considered for QTc values ≥ .460 and .480, respectively (2). (QTc = "HR- QTc interval," as per the Bazett formula (3.).

The Heart Rhythm UK Familial SDS Statement Development Group published in 2008 a position statement on genetic testing for SCD syndromes based on a comprehensive review of English language publications, grading of the evidence, and secondary review of the evidence by an external committee(4). The Group followed with a position statement on ICD placement for these conditions based on risk of SCD(5).

1. ***Lehnart SE,et al. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. Circulation. 2007 Nov 13;116(20):2325-45. Erratum in: Circulation. 2008 Aug 19;118(8):e132.***
2. ***Ackerman MJ,et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011 Aug;8(8):1308-39. PubMed PMID: 21787999.***
3. ***Moss AJ. Long QT Syndrome. JAMA. 2003 Apr 23-30;289(16):2041-4.***
4. ***Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group. Clinical indications for genetic testing in familial sudden cardiac death syndromes: an HRUK position statement. Heart. 2008 Apr;94(4):502-7.***
5. ***Garratt CJ, et al. Heart Rhythm UK Familial Sudden Cardiac Death Syndromes Statement Development Group. Heart Rhythm UK position statement on clinical indications for implantable cardioverter defibrillators in adult patients with familial sudden cardiac death syndromes. Europace. 2010 Aug;12(8):1156-75.***

The first position statement and the more recent HRS/EHRA report recommend genetic testing for all patients with a firm diagnosis of congenital LQTS and those with clinical features of CPVT (due to its severity, despite an acknowledged lower clinical sensitivity), but that expert clinical and family history assessment are needed when genetic testing is undertaken for borderline LQTS cases and known or suspected cases of BrS. Practice guidelines from the ACC/ AHA/ ESC(1) have noted an evolving role for genetic testing of LQTS in risk stratification and clinical decision making. Both independent reviews and professional society guidelines agree that genetic testing by itself is not recommended in making a diagnosis or prognosis for BrS, though it may be used to support clinical diagnosis, and early detection of at-risk relatives· (1;2;3).

Nikus mentioned that 12- Lead ECG: that QTC was >500 ms except in one recording. Statistical analyses of risk factors for cardiac events showed that the QTc >500 ms was a strong and significant predictor for cardiac events. Additionally, recent syncope (< 2 years in the past) was the predominant risk factor in affected adult (> 40 yo) subjects(5).

1. **Zipes DP, et al ; American College of Cardiology/American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006 Sep 5;114(10):e385-484.**
2. **Martini B, et al. Brugada by any other name? Eur Heart J. 2001 Oct;22(19):1835-6.**
3. **Wilde AA. Long QT syndrome: a double hit hurts more. Heart Rhythm. 2010 Oct;7(10):1419-20.**
4. **Takenaka K, et al. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long-QT syndrome. Circulation.**
5. **Goldenberg I, et al. Long-QT syndrome after age 40. 2003 Feb 18;107(6):838-44. Circulation. 2008 Apr 29;117(17):2192-201.**

Answer to the questions

- QT interval phenotype? Answer LQT2-Like pattern
- One syncope – orthostatic? No. This patient had T-wave macro-alternace This phenomenon entails electrical instability and constitutes a marker for non-homogeneous transmural recovery in ventricular repolarization in ventricular wall thickness or appearance of tachyarrhythmias events with significant electrical and hemodynamic repercussion.
- Paroxysmal SVT → EP study? Yes
- Genetic analysis negative: New mutation? Is possible
- Recently put on β-blocker: We agree.
- Professional driver's license acceptable?: No. Why? The risk that patients with life-threatening ventricular arrhythmias might pose if allowed to drive must be addressed. The principal factors that determine the magnitude of this risk are the likelihood that patients, once treated, will experience a recurrence of their arrhythmia, the likelihood that such a recurrence will impair consciousness sufficiently to interfere with their ability to operate a motor vehicle, the probability that such an event will result in an accident, and the probability that such an accident will result in death or injury to other road users or innocent bystanders. Special mention should be made of patients who have the LQTS, which is classified as acquired or congenital. The acquired forms are due either wholly or in part to reversible factors, such as drugs that prolong the QT interval or electrolyte abnormalities such as hypokalemia and hypomagnesemia. Most patients can be allowed to drive after correction of these reversible factors. The inherited disorders are associated with TdP, that can produce syncope mainly in presence of macro T-wave alternance. Arrhythmias and syncope occur most often during physical exertion or emotional stress. Treatment effectively prevents symptoms in the vast majority of patients, and symptoms decrease in frequency over time, particularly during the second to fourth decades. They are uncommon after the fourth decade. Drugs that prolong the QT interval should be avoided in these patients. Patients who have symptomatic LQTS should not have driving privileges, but patients with LQTS who are asymptomatic or who have a history of symptoms but are asymptomatic on treatment should receive driving privileges after a 6-month symptom-free interval. Individuals subject to loss of consciousness due to Stokes-Adams attacks or other cardiac arrhythmias may not be considered for any class of licence until the underlying cardiac condition has been corrected, and should be reviewed after one year. The individual with a single unexplained episode of loss of consciousness or awareness may be allowed to operate any motor vehicle provided the individual is investigated and the condition felt to be benign. The person who has suffered more than one syncope episode should not operate any motor vehicle until the cause of the episodes has been determined and successful corrective measures taken. A history of vasovagal syncope in adolescents is not felt to constitute a driving hazard.