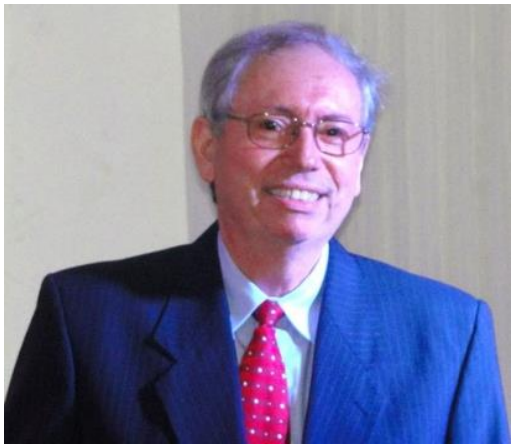
Symptomatic hereditary Long QT Syndrome in middle-age woman



https://ekgvcg.wordpress.com/

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Português: Reporte de caso

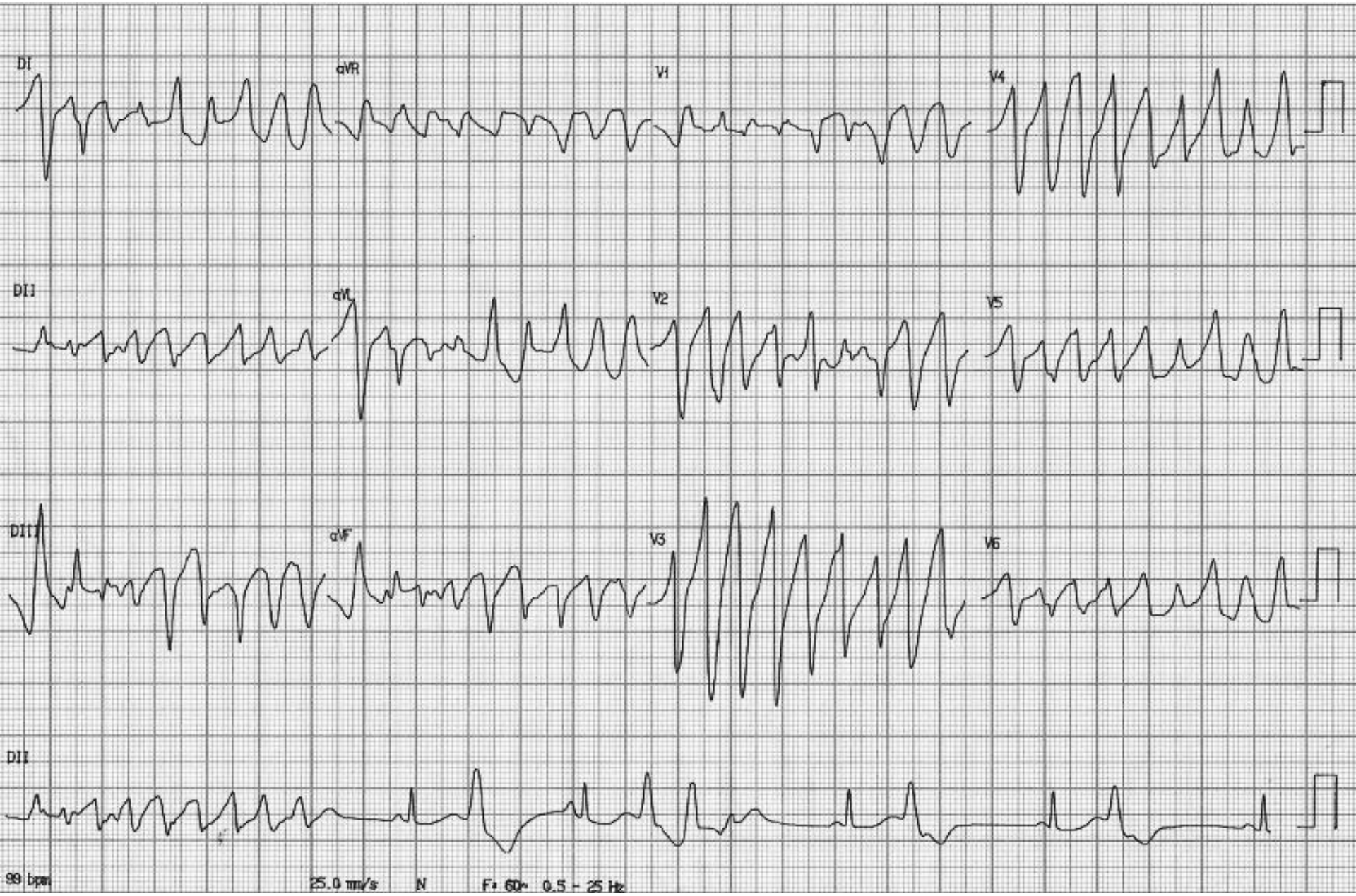
Mulher Caucasiana, de 37 anos com recente episodio de morte súbita abortada por evento de Torsades de Pointes (TdP) que degenerou em fibrilação ventricular (ECG-1) ou FV sem prévia TdP (II longo).
História prévia de síncope precedida de palpitações taquicárdicas.
Historia familiar positiva de morte súbita em familiar de primeiro grau (um primo morreu subitamente ainda jovem). Em uso de propranolol.
Sem cardiopata estrutural aparente.
Eletrólitos normais.
Foi solicitado ECG e teste genético no probando e familiares.
Perguntas:

1) **Qual o diagnóstico do ECG1, ECG-2 e II longo?**
2) **Qual é a abordagem adequada?**

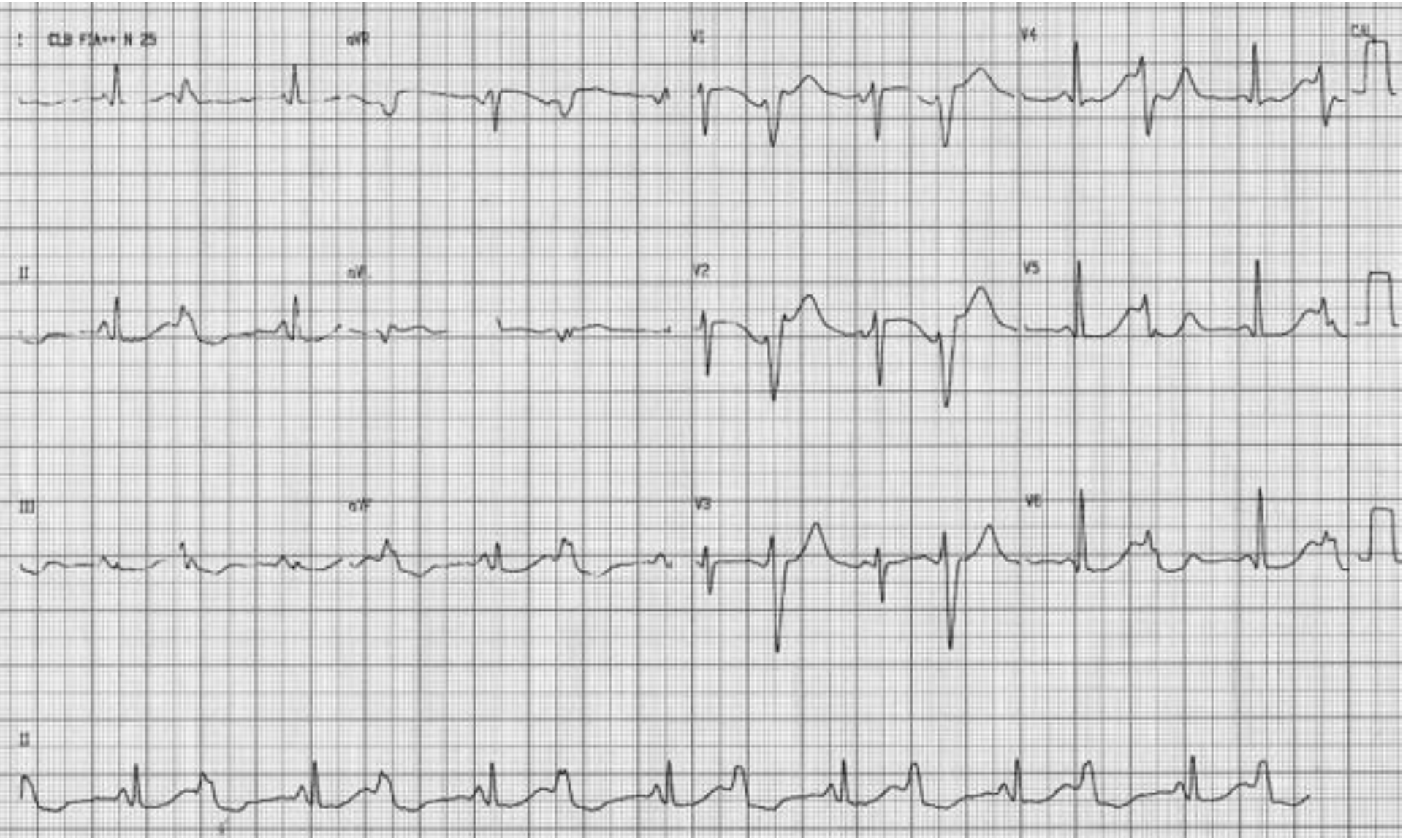
Case Report

Caucasian woman, 37 years old with recent episode of aborted sudden cardiac death by Torsades de Pointes (TdP) event that degenerated into ventricular fibrillation (ECG-1) or direct FV without previous TdP (II long).
Previous history of syncope preceded by palpitations.
Positive family history of sudden cardiac death in first degree relative (a cousin died suddenly at a young age). She is in regular use of propranolol.
No apparent structural heart disease.
Electrolytes: normal.
We requested ECG and genetic testing to the proband and family members.
Questions:
What is ECG-1, ECG-2 and long II lead diagnosis?
What is the appropriate approach?

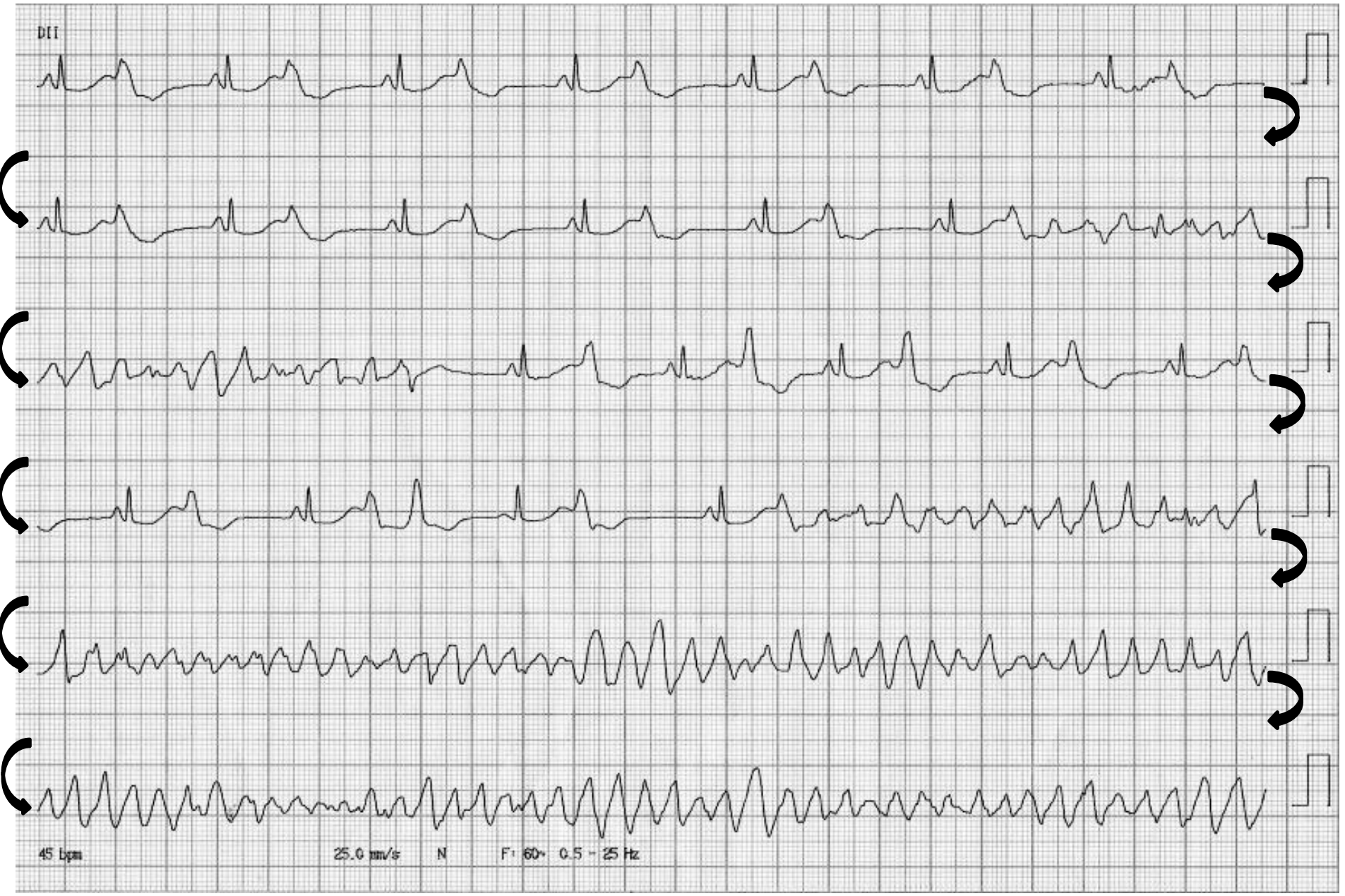
ECG-1 at admission



ECG-2 - 12 lead ECG



ECG II long continuous



Colleagues opinions

For those who like eponyms, the bigeminy is also known as "particular bigeminy of Dessertenne" for the French physician who first described torsades de pointes.

Great tracings!
Cordial saludo, Sergio Pinskis MD

Answer from Andrés to Sergio
Dear Sergio effectively. Francois Dessertene was born in 1917. In 1943, he became an intern, and in 1948 an Asssitant Professor of Medicine. He worked at the Hôpital Lariboisère in Paris and was the assistant to Prof. Bouvrain and later to Prof. Slama. In 1966 (**Dessetenne 1966**), in his pionnerign work (publishied in *Arch des Mal du Coeur*), he described a variety of polymorphic VT characterized by two variable foci, which expained the twisted peaks. This particular aspect is now described using the French term "torsade de pointes", Dessertenne's tachycardia or TdP. Dessertene clearly made the distinction between TdP and ventricular tachycardia, although TdP may turn into ventricula tachycardia. TdP are typically characterized by an ECG pattern of polymorphous but organized electrical activity of ventricular origin that occurs in the setting of a long QT interval, long-coupled bigeminy, and has specific precipitating causes and therapeutic responses. TdP can result from congenital (adrenergic dependent) and acquired (pause dependent) factors and may have similar cardiac substrates with different precipitating events. TdP shows unique electrocardiographic features of a special VT . Since this description, TdP has become increasingly recognized as a common and important clinical syndrome. When originally described, it seemed possible to separate torsades de pointes from other forms of VT. However, increasing data indicate that the electrocardiographic features of the TdP are insufficient to make an accurate diagnosis in all cases. In fact, practically none of the various elements of the initial description remain as absolutely sensitive and specific diagnostic markers for TdP. This similarity with other VTs has led some authors to question the validity of maintaining TdP as a unique arrhythmia, completely separated from other forms of polymorphic VTs(Leenhardt 1992)
Andrés.

Spanish
Interesantísimo caso!!! Qué bien documentado está.
ECG1 impresiona TV polimorfa (no parece TdP),
ECG 2 EV monomorfas, la pregunta es si no están emergiendo de una onda U, Evaluar si no presenta síndrome de Andersen Tawil (analizar características físicas y neurológica).
ECG 3 es una FV.
Conducta: CDI, si fuera Andersen-Tawil, se podría administrar flecainida.
Veremos lo que dicen los maestros de este foro. saludos.
Oscar Pellizón MD, Rosario, Argentina

English
Very interesting case!!! Very well documented.
ECG1 seems to show polymorphic VT (it doesn't seem to be TdP).
ECG2 monomorphic PVC. The question is if they are emerging from a U wave. Evaluate if she does not have Andersen Tawil syndrome (analyze physical and neurological features).
ECG3 is VF.
Management: ICD, if it was Andersen-Tawil, flecainide could be administered.
Let's see what the experts in the forum say. Regards.
Oscar Pellizón MD, Rosario, Argentina

Portuguese: Prezado Oscar, a Síndrome de Andersen-Tawill (ATS) é uma canalopatia autossômica dominante de baixa penetrância que afeta o canal de potássio retificador interno inward rectifier em fase 3 e 4 caracterizada por paralisia periódica flácida, anormalidades esqueléticas faciais características (hipertelorismo, implantação baixa das orelhas, micrognatia, clinodactilia do quinto dedo e sindactilia) associada a arritmias cardíacas secundárias ao intervalo QT prolongado seguido de onda U proeminente. Classificada dentro da síndrome do QT longo congênito como a forma LQT7. Cerca de 80-90% dos pacientes apresentam mutação no cromossomo 17 (locus 17q23-q24.2) no gene KCNJ2 o qual codifica a proteína kir2.1. Prolongamento do intervalo QT é observado em aproximadamente 50% dos casos e em 80% apresentam arritmias ventriculares. A taquicardia ventricular e **bidirecional** como a taquicardia ventricular polimórfica catecolaminérgica e aquela da intoxicação digitálica. Pode ser vista em cerca de 30% dos casos. O tratamento de escolha é com betabloqueadores de longa meia vida. O uso de marca-passo e cardiodesfibriladores implantável está indicado na profilaxia secundária de morte súbita ou falha do tratamento com betabloaqueadores. A paciente apresentada não apresenta nada da triada mencionada. Andrés.

Answer to Dr. Pellizón

English: Dear Oscar,

The Andersen-Tawill syndrome (ATS) is an autosomal dominant channelopathy of low penetrance, affecting the inward rectifier potassium channel in phases 3 and 4, characterized by periodical flaccid paralysis, characteristic facial skeletal anomalies (hypertelorism, low-set ears, micrognathia, clinodactyly of the fifth finger and syndactyly) associated to cardiac arrhythmias, secondary to long QT interval, followed by prominent U wave. Classified within congenital LQTS as LQT7. Close to 80-90% of the patients presented mutation in chromosome 17 (locus 17q23-q24.2) in gene KCNJ2, which encodes the kir2.1 protein. QT interval prolongation is observed in around 50% of the cases and 80% presented ventricular arrhythmias. The ventricular tachycardia is **bidirectional**, as the polymorphic catecholaminergic ventricular tachycardia and that by digitalis intoxication. It could be seen in near 30% of the cases. The treatment of choice is with beta blockers with a long half life. Pacemakers and ICD are indicated as secondary prophylaxis of sudden cardiac death or failure of treatment with beta blockers.

This patient does not present any of the mentioned triad. Andrés.

Dear Andres,

Thanks for sharing a challenging and high risk case.

I wish an accurate QT measurement could be obtained from ECG tracings showing frequent PVCs in bigeminy and TdPs/VF. Having a family Hx of SD, being symptomatic and on beta-blocks, I assume her physicians may have the baseline ECG tracings showing consecutive QRS in sinus rhythm. If so QT measurement should be done there before establishing a solid Dx of inherited LQTS. Family ECG screening is also helpful.

My major concern is the frequent "R-on-T" PVCs (single foci, RV origin?), which may be the major trigger of TdP/VF. If those bigeminy PVCs had something to do with pre-exciting pathway, EP docs will know what to do next.

Looking forward to learning more from LQTS and EP experts from this forum.

Sincerely yours,

Li Zhang

Estimado Andrés,

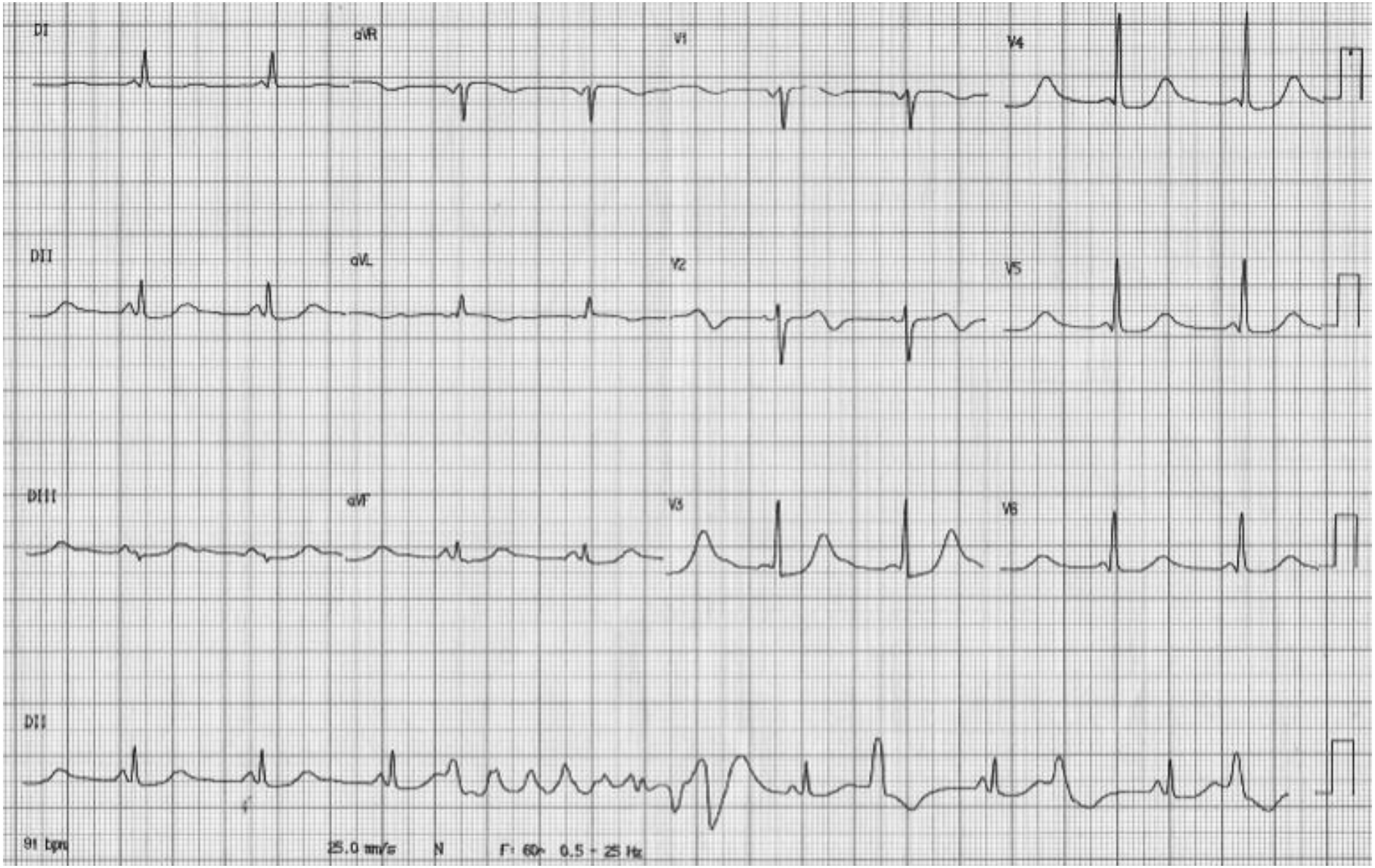
Gracias por compartir un caso difícil y de alto riesgo.

Seria fundamental tener una medición exacta del intervalo QT lo cual podría obtenerse a partir de trazados anteriores. Tenerlos seria ideal. El ECG muestra extrasístoles bigeminadas constantes y frecuentes (que no permiten en ningún momento hacer la medición del intervalo QT) asociadas a TdP/FV. Pregunto si sus médicos no tendrían registros basales del ECG que muestren QRS consecutivos en ritmo sinusal. La medición del intervalo QT no puede hacerse, lo que seria necesario para establecer un sólido diagnóstico de SQTL heredado. El estudio electrocardiográfico de los familiares podría ser de mucha utilidad. Mi principal preocupación son las extrasístoles frecuentes con fenómeno de "R-sobre-T" (foco de origen en el VD?) que pueden ser las principales responsables desencadenante de las TdP / FV. Si estas extrasístoles bigemininadas tienen algo que ver con una vía de pre-excitación, lo podría documentar un estudio electrofisiológico (EEP) que debería hacerse a continuación. Esperemos aprender más de SQTL de los expertos en EP de este foro.

Sinceramente,

Li

Dear Dr. Li Zhant this ECG allows us to measure the QT / QTc interval, because differently from the previous, it has not constant sustain bigeminy.
Andrés



Dear Andres and dear friends, I just got to check email, sorry for the delay. From the ECG tracing provided today, the QT interval is clearly prolonged: QTc 480 ms in lead II, and 550 ms in V2 and V4, T-U merging in V3, excluding U the QTc in V3 is 540 ms. Since the image is not in high quality, my measurement could be a little off. Plus a family Hx of premature SD the diagnosis of inherited LQTS can be established. You are correct Andres, the ECG pattern is atypical. Family ECG screening is absolutely needed to identify additional gene carriers and to compare the ECG patterns. I'm willing to help if considered. I suspect that she may have two mutations or a new gene mutation. In either one this case is highly publishable after obtained positive genetic testing results. If obtained no known LQTS-causing mutations identified in commercial labs, I would suggest to collaborate with a high quality and accountable research Lab for new gene hunting by exonome sequencing. Just name a few Labs for references: Dr. Dan Hu's Lab at Masonic Medical Research Lab can do it free of charge. hudan0716@hotmail.com; So does Dr. Tintelen's lab Dr. p.vantintelen@amc.uva.nl or Dr. Ackerman's Lab ackerman.michael@mayo.edu. Abnormal T wave morphology and disparity of ventricular repolarization in this case: I do not like the T wave look showing on this tracing! It is symmetric with a prolonged Tpeak-Tend interval. As indicated above, the QTc dispersion is also very large suggesting increased dispersion of ventricular repolarization transmurally and globally. This patient also has a pre-exciting pathway showing as a super short PR interval (80 ms in leads I, V4-6). Since there is no delta wave, I assume the pathway connected to the higher section of the ventricular conduction system. In summary this patient has two conditions, the pre-exciting (fast pathway conduction) and LQTS (delayed repolarization). Such combination is very rare and appears to be a bad combination as what has developed. TdP/VF may be triggered activities, the bigeminy PVCs may be a re-entry mechanism. Dr. Charlie Antzelevitch is much more insightful. The LQTS and EP experts in your forum may offer their suggestions in terms of the treatment strategies. Two arrhythmia Pros I would recommend are Dr. Ganxin Yan and Dr. Peter Kowey. Last week I got to review a case of frequent short coupling PVC induced VF. That patient had VF storm (>100 VFs in 2-3 days) and required repeated cardioversion). His physicians finally got VF eliminated. If needed I will be happy to connect them with you to see how they handed their case successfully.

Anyway, I hope this patient will get treated wisely safely. Sincerely yours,

Li Zhang MD

My dear friends: I personally do not see anything atypical about this case of long QT syndrome. The PR is most likely an incidental finding that has nothing to do with her disease. The QT is very long. A very important teaching point is that one should never measure the QT interval during ventricular bigeminy because the ventricular extra systole originating from the T-wave is HIDING the end of the T-waves and is therefore hiding the end of the QT. However, in this case, if one looks at lead V4 of ECG #2one can see that the T-wave was rising to the sky when it was interrupted by the extra systole. This extra systole represents an early after-depolarization (EAD) arising from the T-wave. The fact that the arrhythmias in this female are pause dependent suggests that the underlying etiology is LQT2 (unless receiving QT prolonging medications) (references 1 and 2). There is nothing unusual about the fact that the ventricular extrasystoles are of the same morphology all the time, suggesting an outflow tract origin. Because long QT syndrome is a channelopathy affecting the entire heart, one expects to see arrhythmias originating from many different areas. However, we showed some years ago (reference 3) that in the long QT syndrome the FIRST ectopic beat of torsade de pointes and the EAD-related ectopic beats originate preferentially from the outflow tract. This is interesting because the outflow tract is also a preferential site of origin for the beat initiating polymorphic arrhythmias not only in Brugada syndrome (where this fact is accepted and understood) but also in CPVT (reference 4).
Treatment: Higher doses of beta-blockers, IV magnesium at this point, potassium supplements to keep the K levels <4.5 and ICD with dual chamber pacing programmed to pace the atrium at 80/min.

Hope this helps
Sami Viskin

References:

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2. Birati EY, Belhassen B, Bardai A, Wilde AA, Viskin S. The site of origin of torsade de pointes. *Heart*. 2011;97:1650-16
3. Sumitomo N, Harada K, Nagashima M, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. *Heart*. 2003;89:66-70.

Estimado Sami: muchísimas gracias por tu clara explicación. Es siempre estimulante tener la opinión de un colega de conocimiento tan profundo del tema como usted. Tu comentas que nada de atípico encuentras en este trazado, y que el intervalo PR corto es una concomitancia fortuita, no obstante, debes concordar conmigo que no es una cosa común o usual en el LQTS encontrar un intervalo PR corto con QRS estrecho (sin onda delta) lo que asociado a la taquiarritmia podría interpretarse como un Long Ganong Levine. En el presente caso si algunos componentes de la familia muestran PR corto asociado a intervalo QT prolongado sugiere que esta asociación puede no ser randómica, casual o aleatoria y que eventualmente pueda tener un componente genético. Para testar esta hipótesis debemos realizar ECGs y estudio genético en los familiares del probando, Tanto la duración del intervalo PR cuanto la del complejo QRS y del intervalo QT están influenciados por determinantes genéticas (**Silva 20015**). Este reciente estudio cooperativo del departamento de epidemióloga genética da Universidad Erasmus de Róterdam Holanda, de la de Leiden y de la del Rosario Colombia realizaron una coorte del "genome-wide association studies"). El primer objetivo del presente estudio fue utilizar una cohorte grande, basada en las familias, no comprobada sobre la base del fenotipo, para estimar la heredabilidad de unos varios parámetros electrocardiográficos para evaluar la proporción de heredabilidad explicado por variantes genéticas identificadas previamente por el estudio del genoma completo GWAS. Los autores identificaron un gran número de genes relacionados con la variabilidad de los principales parámetros del ECG, como la duración del intervalo PR, del complejo QRS y del intervalo QT. Este estudio demostró que, a pesar de los GWAS explican apenas una parte de la variabilidad del rasgo electrocardiográfico, una gran cantidad de heredabilidad queda por explicar, es la así llamada "heredabilidad perdida". La inclusión de estudios en GWAS de otros fenotipos ECG aumentó aún más la cantidad de intervalos PR explicados por heredabilidad, lo que sugiere claramente que el estudo completo del genoma GWAS los factores genéticos influencian en la duración del PR, a pesar que hasta la fecha de no alcanza gran importancia genómica en términos de la duración del PR. El aumento de tamaño de las muestras del genoma completo GWAS, en busca de la identificación de variantes menos comunes ocasiona propensión a aumentar la parte explicable de heredabilidad del rasgo ECG.
Andrés.

English

Answer to Dr. Sami Viskin:

Dear Sami: thank you for your clear explanation. It is always exciting to have an opinion from a colleague with profound knowledge on the subject as you. You comment that you find nothing unusual on these ECGs, and that the short PR interval observed is a fortuitous happening; however, you must agree with me that it is not common or usual to find LQTS associated with short PR interval and narrow QRS (without delta wave) and tachyarrhythmia: Long Ganong Levine? In this case, if some family members show short PR associated to long QT, it suggests that this association may not be random, and that it may possibly have a genetic component. To test this hypothesis we should perform ECGs and genetic screening on the families of the proband. Both the PR interval duration and that of the QRS complex and the QT interval are influenced by genetic determinants (**Silva 20015**). This recent cooperative study of the Department on Genetic Epidemiology from the Erasmus University Rotterdam, the Netherlands, the Leiden University and the Universidad del Rosario, Colombia, studied a cohort of the genome-wide association studies (GWAS). The first goal of this study was to evaluate a large cohort based on families, not verified on the phenotype basis, to estimate heritability of several ECG parameters to asses the rate of heritability, explained by previously identified genetic variants in the complete GWAS genome. The authors identified a large number of genes related to the variability of the main ECG parameters, and the PR interval, QRS complex and QT interval duration. This study showed that in spite of the GWAS explaining only a part of the ECG trait variability, a large amount of heritability remains to be explained; the so-called missing heritability. The inclusion of studies in the GWAS of other ECG phenotypes further increased the number of PR intervals explained by heritability, clearly suggesting that in the complete GWAS genome study, genetic factors influence PR duration, although to this date it does not reach a great genomic significance in terms of PR duration. An increase in the size of the samples of the complete GWAS genome, looking for the identification of less common variants, causes a tendency to increasing the explainable part of heritability of ECG traits.

Andrés.

Looks like classic Long QT with bigeminal rhythm likely due to EAD driven PVC (see Wilde JACC) which deteriorates into torsades. For acute management since electrolytes have been corrected consider overdrive atrial pacing, Mg infusions and increase beta blocker dose. Also consider use of late Na blockers (i.e. Mexilitine or Ranolazine. Long term consider AICD avoidance of drugs that prolong QT and and aggressively replace loss of body fluids.

Spanish

Parece un sindrome de QT prolongado clásico ocasionado por actividad gatillada precoz "early after depolarization" (Ver Wilde JACC) que degenera en TdP.

Para el manoseo agudo: marcapaso atrial, infusion de Mg y aumento de la dosis del beta bloqueador . Tambien considerar los bloqueantes tardios de sodio como mexiletine o ranolazina.

Para tratamiento de largo plazo: abolir farmacos que prolonguen el QT, considerar CDI y tratamiento de eventuales perdidas de liquidos corporales.

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Professor Andrés Ricardo Perez Riera M.D.Ph.D. I want to make a historical emend with respect to polymorphic ventricular tachycardia (PVT) This term was coined in 1979 by Sclarovsky et al(1).
We studied 34 cases of PVT of the QRS complexes with changing RR intervals and a HR of 150 to 300 beats/min, termed PVT were described. The factors involved in the appearance of this arrhythmia were the administration of antiarrhythmic drugs: quinidine, procainamide, ajmaline, antianginal prenylamine and antidepressant thioridazine. 21 patients were treated for PVCs, 3 for chronic recurrent VT, six for atrial flutter and AF, three for angina pain and one patient for mental depression. All patients except one had a drug-induced prolonged QTc interval before the appearance of PVT. Most of the patients with this arrhythmia were considered to have severe myocardial disease. Lidocaine and electric cardioversion were administered to all patients, but were effective only in 7 patients whose tachycardia occurred in short, single episodes. The most effective treatment was temporary ventricular pacing at rates ranging from 100 to 140 beats/min. IV isoproterenol proved to be successful in another 10 cases Patients with severe myocardial involvement receiving antiarrhythmic drugs for PVCs, especially the multiform variety, are at high risk for the development of PVT.
Samuel Sclarovsky MD Israel

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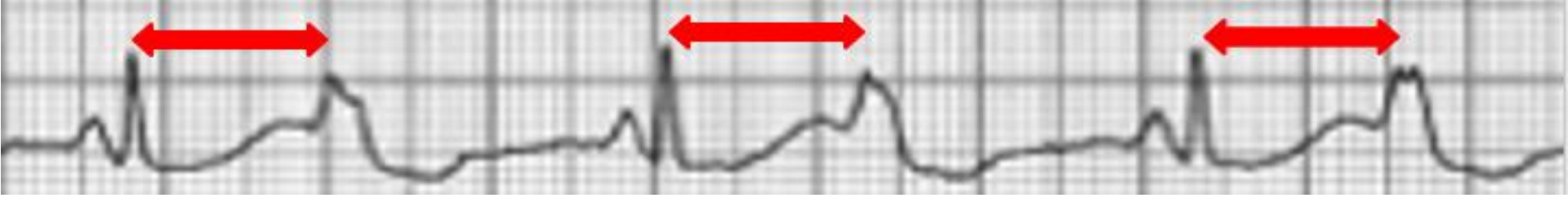
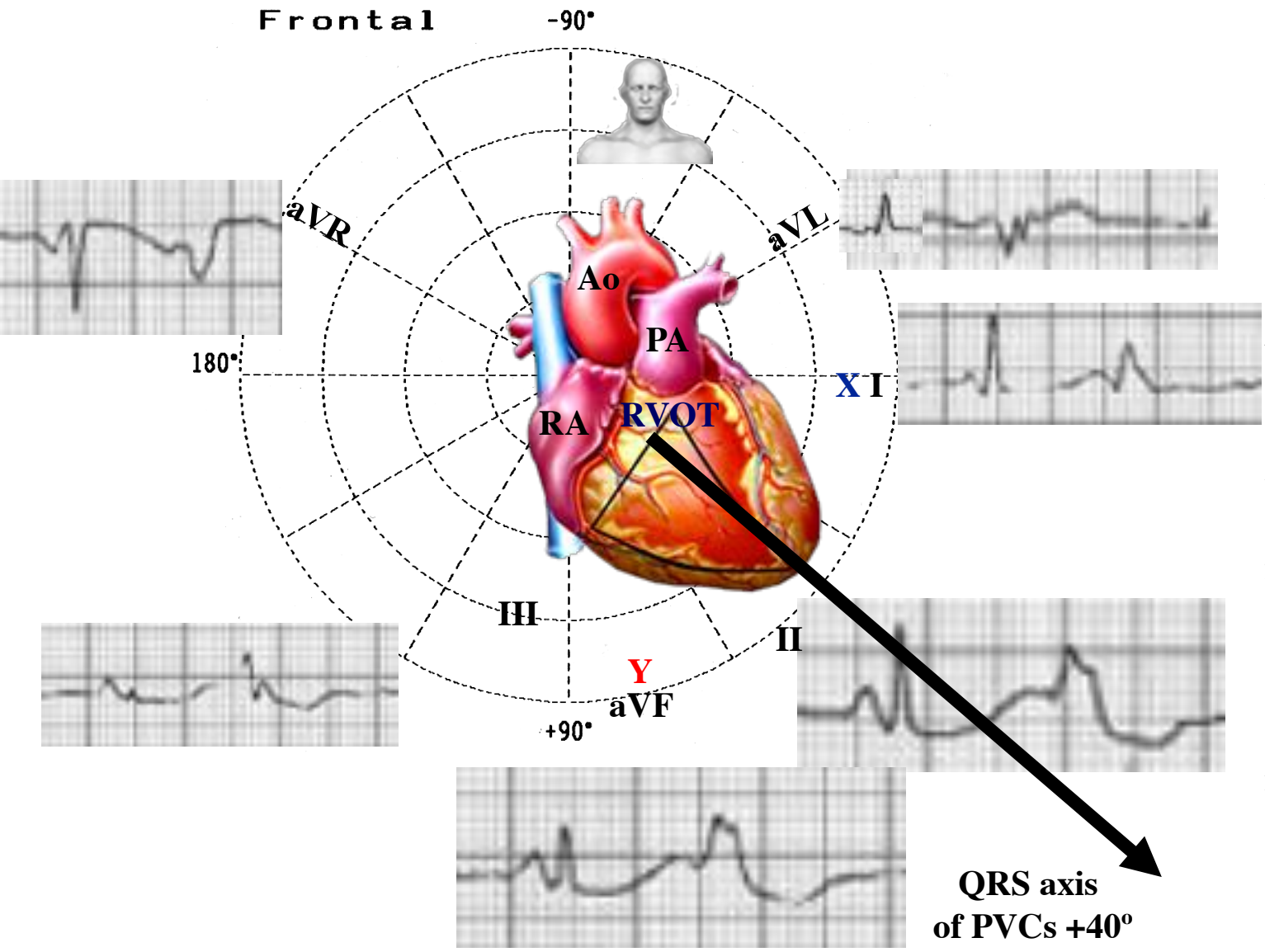
Samuel Sclarovsky Israel

Final conclusions by
Andrés Ricardo Pérez-Riera, Raimundo Barbosa-Barros & Luiz Carlos de Abreu



The coupling interval or the period of time between the **normal heart beat and the PVCs have fixed coupling (400ms), coupling interval with R on T phenomenon a cardiac** event in which the ventricular stimulus causes premature depolarization of cells that have not completely repolarized. The constant interval between the sinus beat and PVC suggests a reentrant etiology rather than spontaneous automaticity of the ventricle (**Langendorf 1955**). However, in patients with prolonged QT/QTc interval, the rule of bigeminy may be caused by premature ventricular complexes (PVCs) due to early afterdepolarizations (EADs) (**Lerma 2007**). It is noted on the ECG as a ventricular depolarization falling somewhere within a The R-on T phenomenon may result in VT or VF. PVCs arising from the RVOT on right ventricle because have a LBBB pattern with inferior axis. PVCs occur in repeating bigeminy patterns. Bigeminy is a descriptive term' of cardiac irregularity refers to a continuous alternation of short and long cardiac cycles, corresponding to the phenomenon of pulsus bigeminus diagnosed at the bedside on palpation of the radial pulse. Such a grouping of PVCs may be the result of a number of different mechanisms involving a disturbance of impulse formation or impulse conduction, or a combination of both. In the presence of irregular ventricular beating the appearance of PVCs with fixed coupling, their continuation in the form of bigeminy, and the termination of the latter, all tend to depend on the duration of the cycle of the beat to which the PVC is coupled. Lengthening of the ventricular cycle favors the appearance of PVCs. The term "rule of bigeminy" is proposed as a short designation of this phenomenon. An adequate explanation of this "rule of bigeminy" can be based on the concept of a re-entry mechanism. Conversely, the existence of such a rule lends strong support to the view that re-entry is the mechanism responsible for PVCs with fixed coupling. Whenever there is a rapid and irregular response to supraventricular impulses--in AF in particular--a beat terminating a short cycle subsequent to a long one tends to exhibit a bizarre contour and QRS prolongation, caused by aberrant ventricular conduction. Criteria are presented for the differential diagnosis between such aberrant supraventricular beats and PVCs.

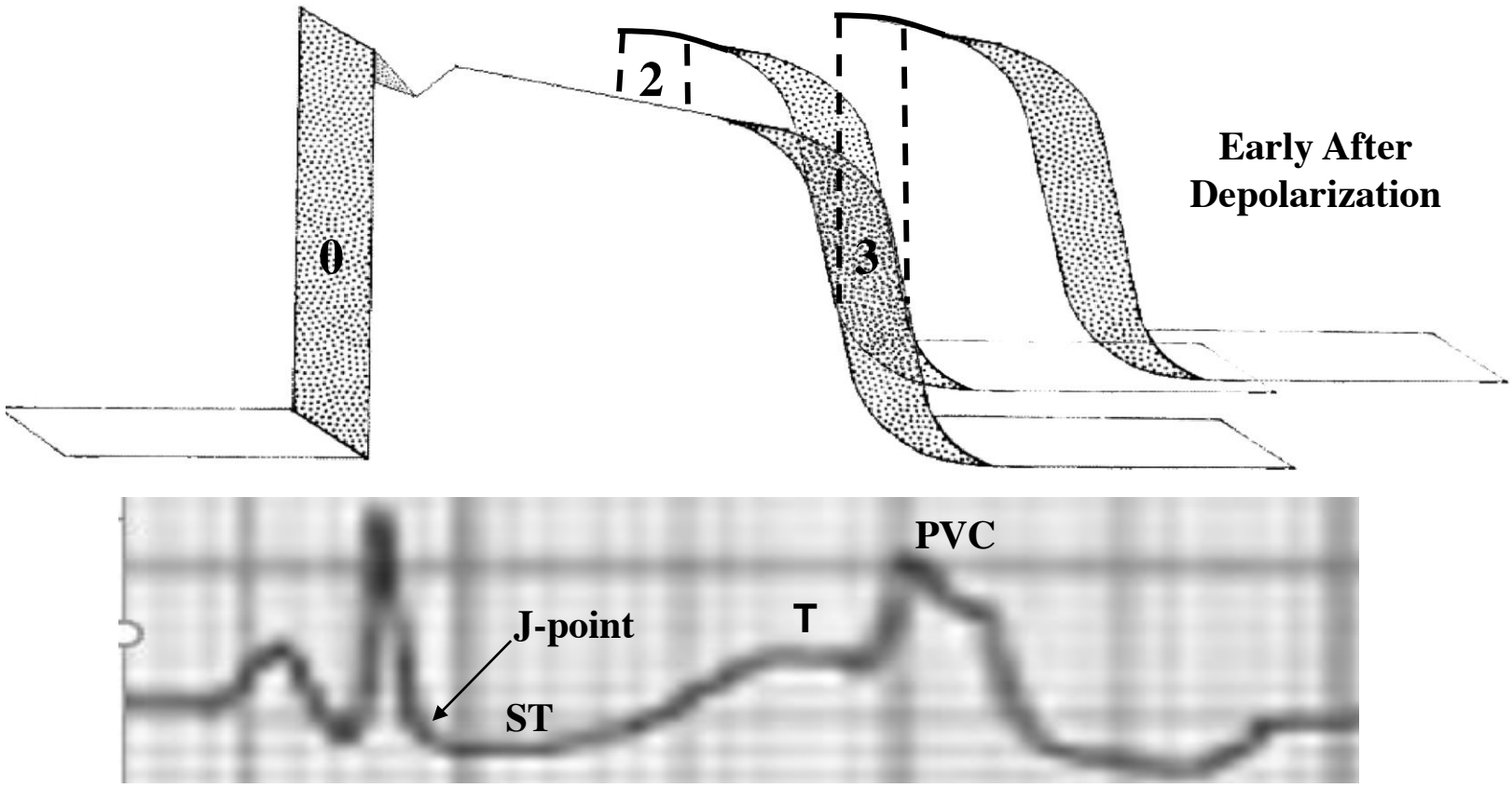
Monomorphic PVCs originates in the RVOT(infundibulum)



The majority of episodes of TdP (56%) and most QT-related PVCs (70%) originated from the outflow tract. There are no correlation between site of origin and the etiology of LQTS or the QT duration. On a given patient, multiple episodes of TdP tended to originate from the same area and the site of origin of QT-related PVCs correlated with the site of origin of TdP.

In the present case the monomorphic bigeminy PVCs have LBBB pattern wit inferior axis in the FP: positive PVC complexes in inferior leads and negative in aVR. In this case, PVCs axis is located at +40º, thus indicating origin in the RVOT.

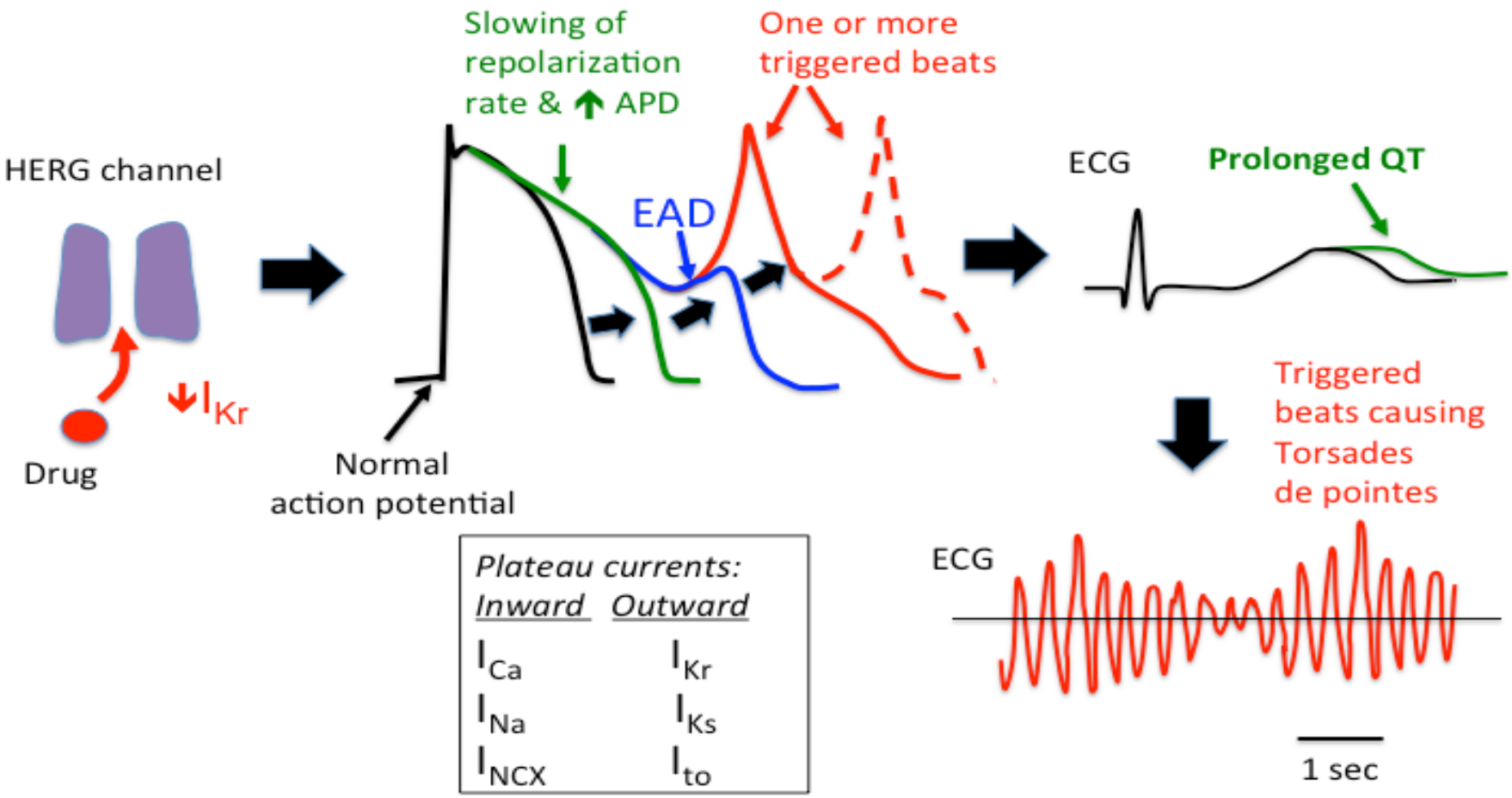
Mechanism of the PVCs: Early after depolarization (EAD) triggered activity



EAD-related Premature Ventricular Contraction

Early Triggered Activity: it is the one that depends on the oscillations of the AP that occur before repolarization is fulfilled at the end of phase 2 and phase 3 (see next slide). They are divided into: 1) Of phase 2: A) Oscillations that occur when in the plateau, dome or phase 2 by increase in inward Ca^{2+} by the slow $I_{Ca\text{-}L}$ channel. PVCs during self-perpetuating ventricular bigeminy ("rule of bigeminy") in LQRSs may be due to EADs. B. There is an additional and persistent inflow of the sodium cation in phase 2 or AP plateau. This is observed in LQT3. This explains the increase in ST segment duration in ECG. QT interval prolongation at the expense of ST segment prolongation.

Mechanism of EAD's

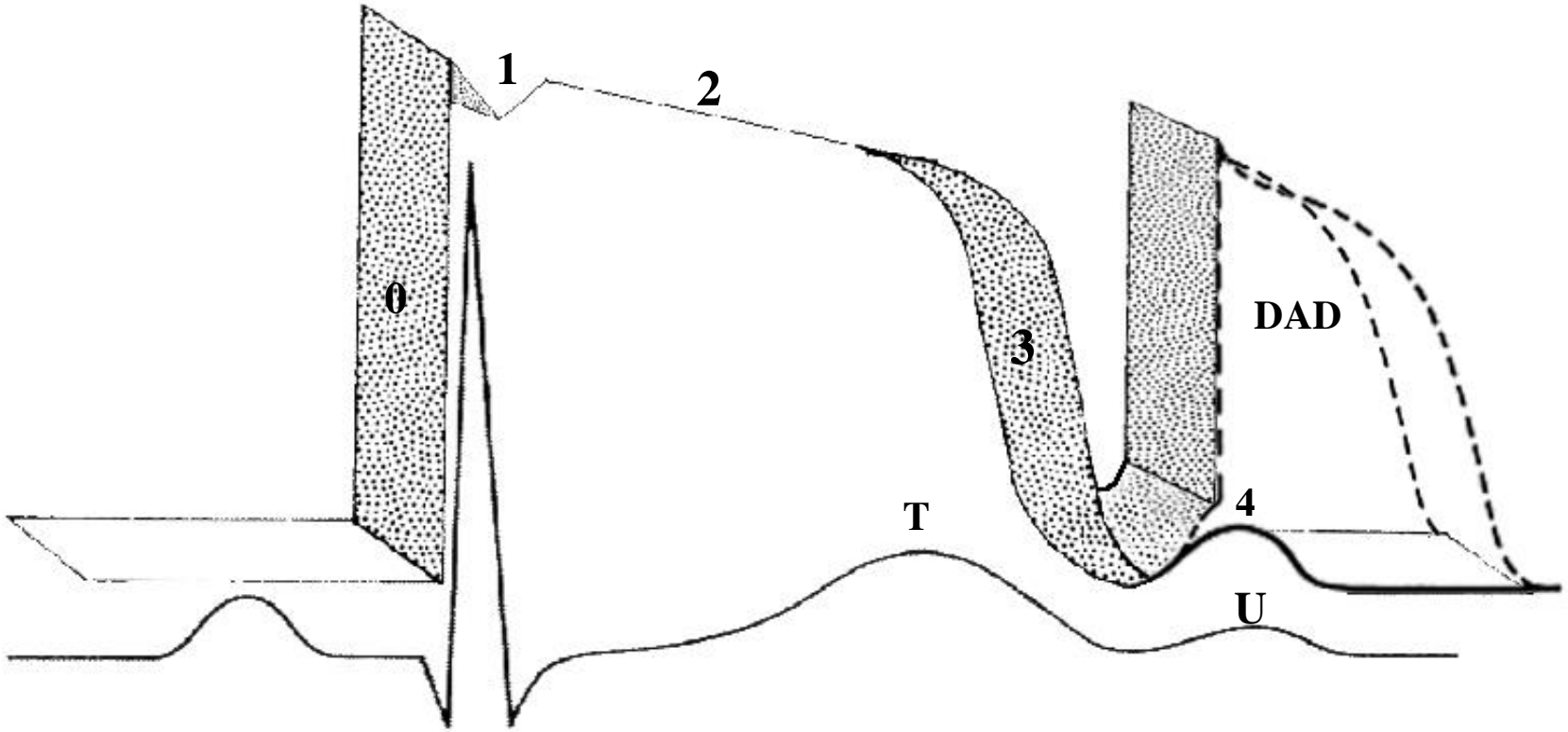


Mechanism of EAD formation & initiation of TdP. Drug-induced blockade of the HERG channel reduces I_{Kr} amplitude, which in turn reduces net outward current during the plateau, and prolongation of the ventricular APD and QT interval in the ECG (green). If net inward currents during phase 3 become larger than outward currents, this can form an EAD (blue). These changes are typically heterogeneous and can create a substrate for producing triggered beats in multiple locations, resulting in a multifocal ventricular tachycardia (**Kannankeril 2010**).

Triggered activity: After depolarizations triggered by a preceding impulse can lead to premature activation if the threshold is reached, and this can cause a PVC. Triggered beats are considered to be due to after-depolarizations triggered by the preceding AP. Afterdepolarization can occur either during (EADs) or after (late DADs) completion of repolarization. EADs commonly are responsible for bradycardia associated PVCs, but they also can be present with ischemia and electrolyte disturbances. Additionally, these are often seen in patients with ventricular arrhythmias due to digoxin toxicity and reperfusion therapy after MI. EADs are an important cause of lethal ventricular arrhythmias in LQTSs and HF, but the mechanisms by which EADs at the cellular scale cause arrhythmias such as PVT. EADs in intact cardiac tissue were described as a form of triggered activity (**Cranefield 1975**). Subsequently, EADs were implicated as the primary mechanism promoting arrhythmias in acquired and congenital LQTS, including TdP, PVT and VF. The strong association leaves little doubt that EADs at the myocyte level cause these arrhythmias at the myocardial tissue level. Five critical questions are: 1) What are the key dynamical mechanisms that cause EADs to form when repolarization reserve is reduced?; 2) Since myocytes in intact tissue are well-coupled to their neighbors, how does the tendency of an individual myocyte to develop an EAD overcome the repolarizing influence of adjacent myocytes without EADs? - or, phrased differently, how do EADs develop synchronously in a critically large enough mass of coupled myocytes to overcome the local source-sink mismatch, so that an overt EAD can trigger a PVC? .3) If EADs are focal, what is the basis of the shifting QRS electrical axis during PVT and TdP, which implies that the foci must continuously shift their location?. 4) Why have mapping experiments provided evidence suggesting with both focal and reentrant mechanisms of PVT and TdP? 5) If EADs preferentially occur during bradycardia, how do they cause triggered activity at fast heart rates?

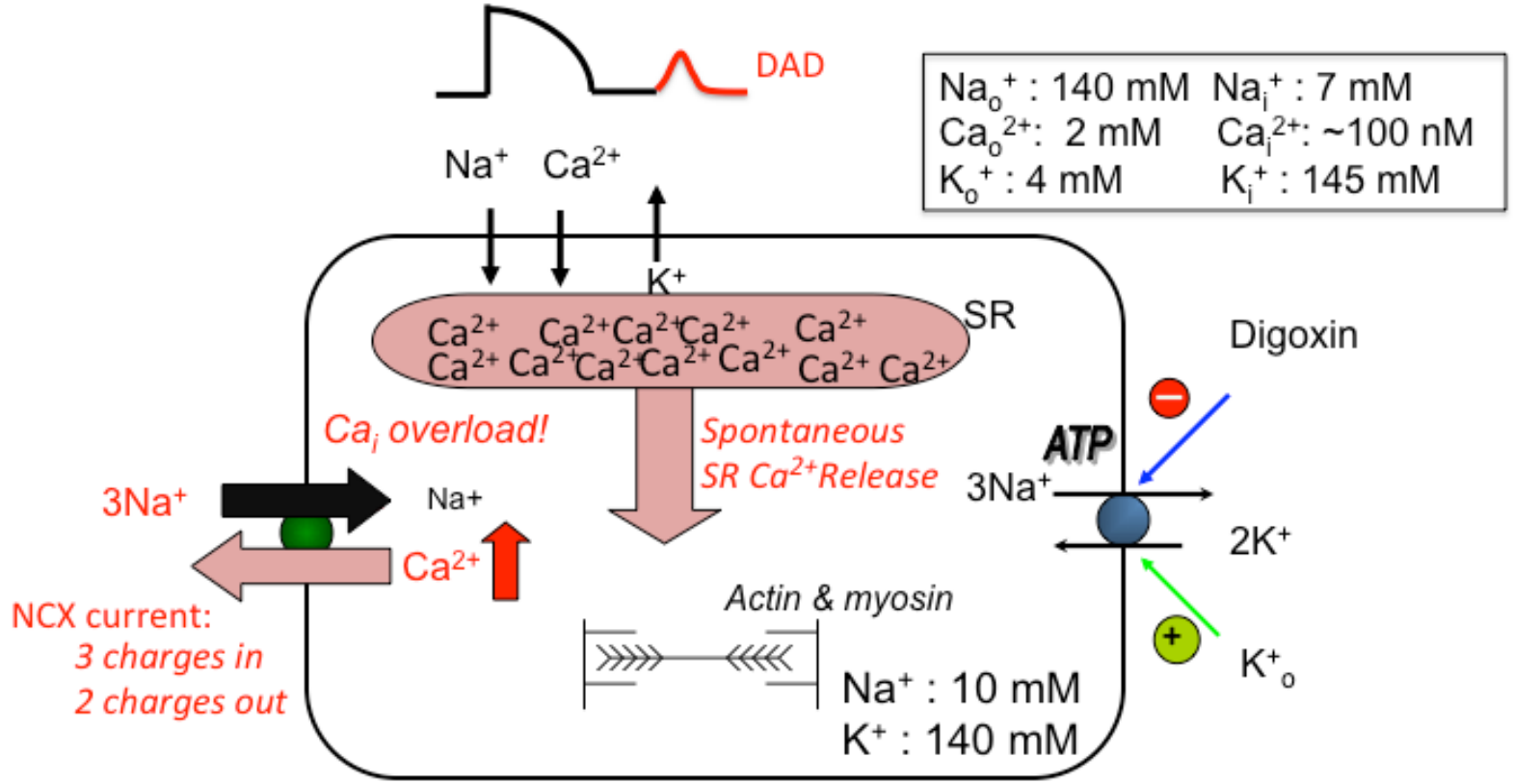
Delayed afterdepolarizations(DADs) begin during phase 4, after repolarization is completed but before another AP would normally occur via the normal conduction systems of the heart. They are due to elevated cytosolic Ca^{2+} concentrations, classically seen with digoxin toxicity. The overload of the sarcoplasmic reticulum may cause spontaneous Ca^{2+} release after repolarization, causing the released Ca^{2+} to exit the cell through the $3Na^{+}/Ca^{2+}$-exchanger. This results in a net depolarizing current. See next slide.

Concept of Delayed After Depolarization (DAD)



Concept: they are oscillations of the membrane potential that occur after having completed phase 3 of AP or in phase 4. When they reach the limit, they trigger a new AP. They are observed in high rates (tachycardia-dependent). Their mechanism is caused by the opening of the $I_{NS.}$ channel, sensitive to intracellular Ca^{2+} concentration. Clinical causes of DAD: ischemia and reperfusion, digitalis intoxication: atrial, junctional, fascicular and ventricular tachycardia, adrenergic stress: catecholamine-dependent VT, hypercalcemia, multifocal or chaotic atrial tachycardia: multiple foci with triggered automaticity by delayed after potentials in phase 4, originated by: increase of circulating catecholamine's, hypoxia, increase of CO^2, hypopotassemia, hypomagnesemia, etc, idiopathic VT of the right and left ventricular outflow tract (RVOT and LVOT) and Catecolaminergic Polymorphic VT (CPVT). DAD's are known to occur under conditions of intracellular calcium overload . DAD's are also increased in amplitude by increases in heart rate (opposite to the behavior of EAD's).

Mechanism for DAD's



The cellular mechanism underlying the formation of DADs. Excessive inhibition of the Na/K pump by digoxin, or high catecholamine levels can result in a situation of intracellular calcium overload. Under these conditions, most of the increase in intracellular calcium will be pumped into the sarcoplasmic reticulum. However, when calcium levels within the SR become too large, a spontaneous release of Ca from the SR occurs (perhaps as a self-protection mechanism). This results in activation of the Na/Ca exchange current. Efflux of one calcium ion in exchange for 3 sodium ions results in membrane depolarization during the diastolic interval. This is observed as a Delayed After Depolarization. DAD amplitude can reach threshold for producing an action potential if the depolarizing current is strong enough. High heart rates increase Ca uptake, resulting in a larger release of SR calcium, and an increased DAD amplitude. Hence the incidence and magnitude of DADs is enhanced at high heart rates (opposite to EADs, which are enhanced by slow heart rates).

Other ECG features in the present case

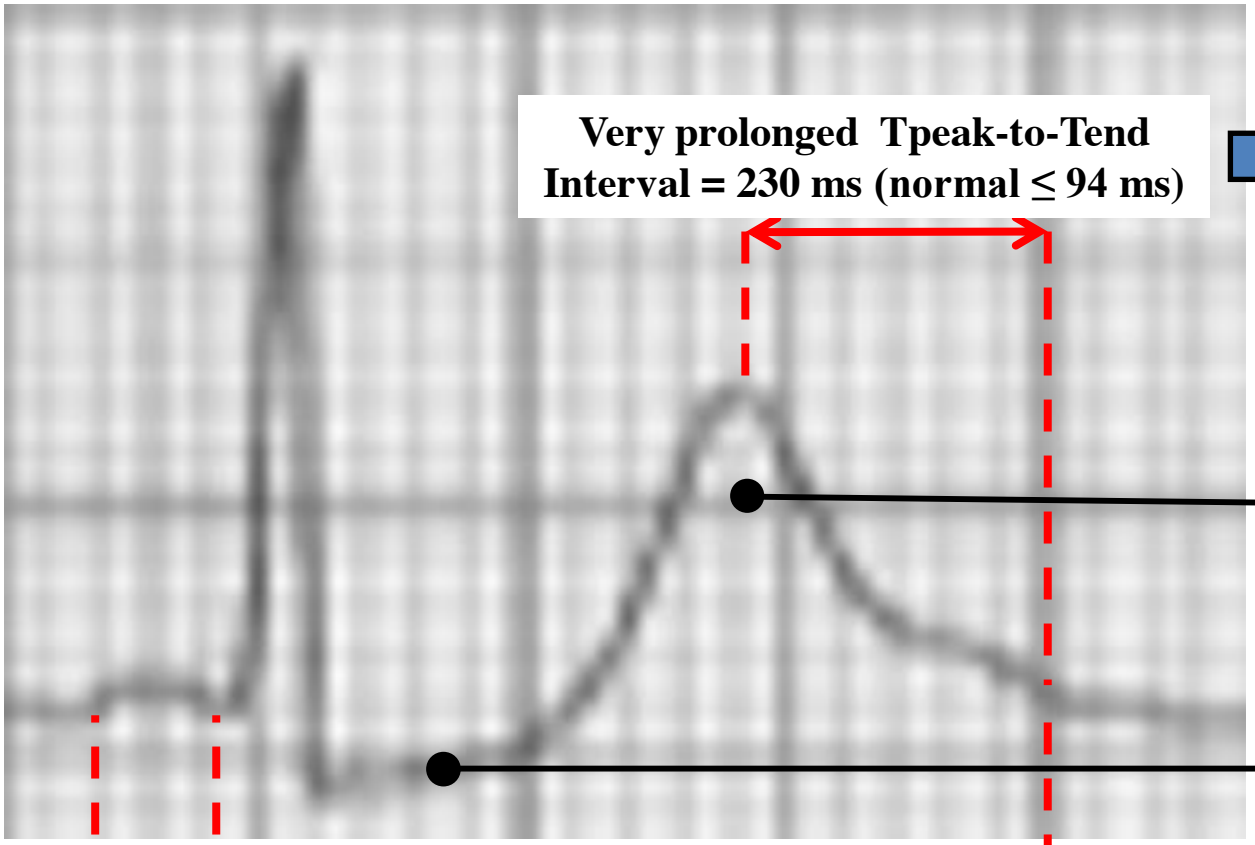
Short PR interval with normal QRS duration

In 1952, Lown, Ganong and Levine (**Lown 1952**) described a syndrome of short PR interval, normal QRS complexes and paroxysmal tachycardia. There has been considerable controversy in regard to the mechanism of the short PR interval and the tachyarrhythmias types associated with this syndrome.

A short PR interval has been described in the following scenarios:

- Tricuspid Atresia: Relatively short PR interval is observed un 50% of cases in TA (**Guller 1969**).
- Chronic obstructive pulmonary disease (COPD) (**Katz 1956**).
- Acute myocardial infarction (**Mathew 1973**).
- Hyperthyroidism.
- Cushing's disease (**Lown 1955**).
- Glycogen storage disease (Pompe's disease) (**Ehlers 1962**).
- Abbreviated atrioventricular conduction noted in children and young adults, ectopic impulse formation (atria, coronary sinus or AV junction).
- Erroneous measurement utilizing only one or two electrocardiographic leads (**Castellanos 1982**).
- Pheochromocytoma (**Surawicz 1977**): Electrophysiological studies demonstrated the presence of enhanced AV nodal conduction. After resection of this tumor, the PR interval returned to normal (**Huang 1984**).

The present case lead V3



Very prolonged Tpeak-to-Tend Interval = 230 ms (normal ≤ 94 ms)

Transmural dispersion of repolarization

Typical wide-based T-waves with a large amplitude suggesting LQT1 variant

ST segment depression: Zhang et al (**Zhang 2000**) described 10 different ST-T patterns in first 3 genotypes of the syndrome (4 in LQT1, 4 in LQT2, and 2 in LQT3), and these patterns were present in the majority of genotyped LQTS patients.

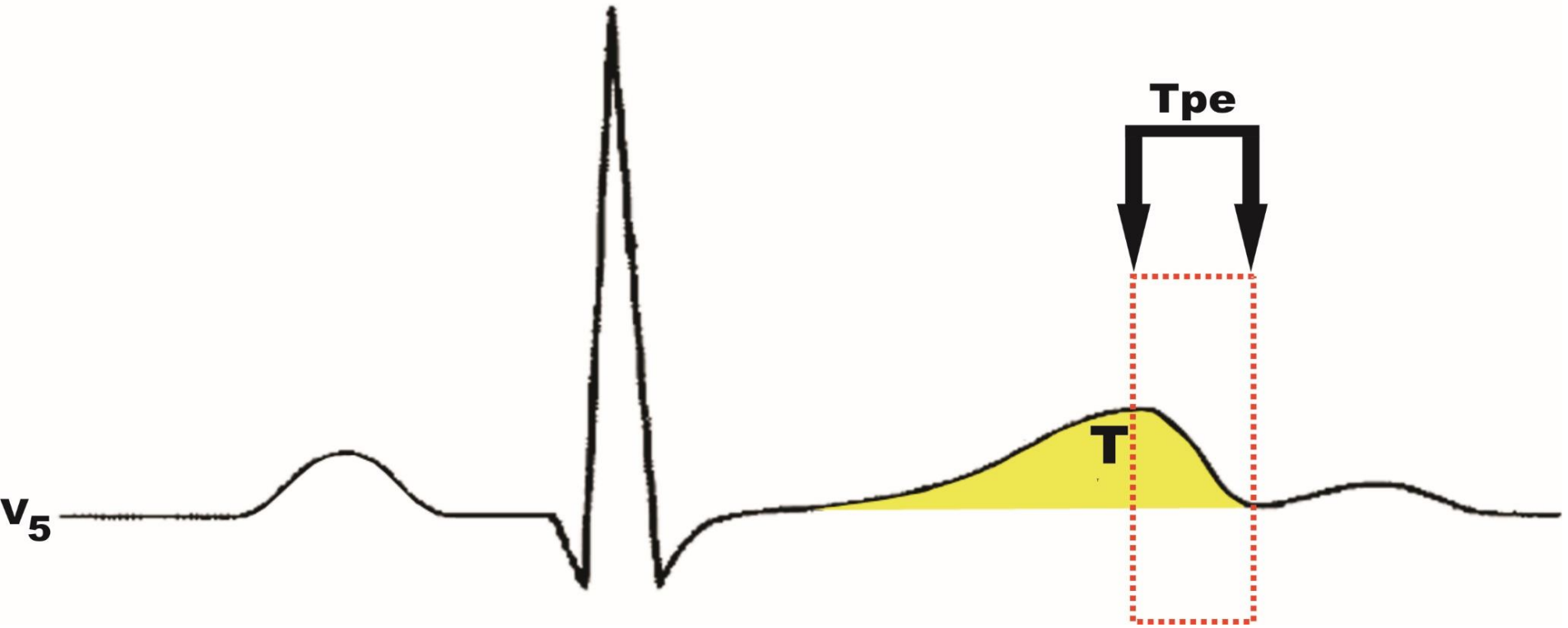
Very prolonged QT interval = 620 ms

Short PR interval: 90 ms

Broad-based prolonged high T waves suggesting LQT1 variant. T amplitude is generally quite small in the chromosome 7 genotype (LQT2); and T duration is particularly long in the chromosome 11 genotype (LQT1), such as this patient (**Moss 1995**). In our opinion, probably this a LQT1 variant.

Second Mechanism for TdP - Dispersion of Repolarization: $T_{peak} - T_{end}$ interval prolongation and $T_{peak} - T_{end}$ dispersion

The normal value of Tpeak/Tend interval (Tpe) is 94 ms in men and 92 in women when measured in the V_5 lead. Tpe prolongation to values ≥120 ms is associated to a greater number of events in patients carriers of BrS



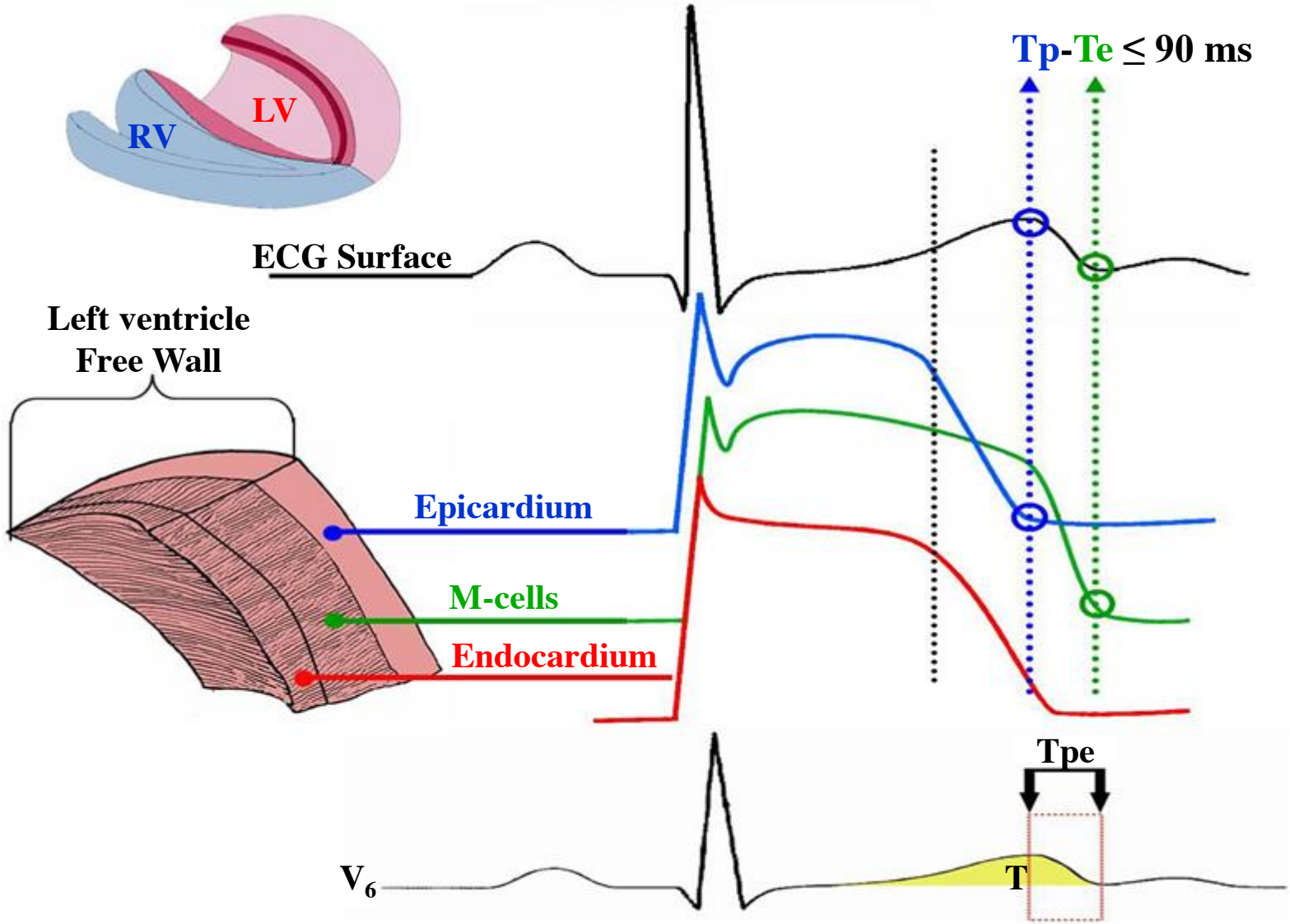
Interval elapsed from the apex to the end of T wave (Tpeak-Tend interval or Tpe). Tpe may correspond to transmural dispersion of repolarization and consequently, the amplification of this interval is associated to malignant ventricular arrhythmias.

Prolongation of T peak/Tend interval (Tpe)

Another possible substrate for the development of ventricular tachyarrhythmias in channelopaties may be a significant transmural dispersion of the repolarization due to a heterogeneous abbreviation of the action potential duration. Normally T peak/Tend interval is 94 ms in men and 92 in women when measured in the V5 lead. In SQTS this parameter is prolonged > 92ms in women and > 94ms in men with the measurement in V5. In SQT1 patients the T waves in the precordial leads, appear often tall, narrow and symmetrical, with a relatively prolonged Tpeak-Tend interval (**Gaita 2003**).

Heterogeneity in action potential duration results in a myocardium that is more vulnerable to reentrant excitation, a second likely cause of TdP. Ventricular cells in the middle of the ventricular wall (M cells) have an action potential duration that prolongs disproportionately compared to other cell types in response to a slowing of heart rate and/or the presence of drugs that prolong the APD (**Anzelevitch & Burashnikov 2011**). M cells have also been found to be sensitized to the effects of APD-prolonging drugs (e.g. blockers of I_{Kr}) due to a larger expression of both an inward plateau Na current and a Na-Ca exchange current, as well as a smaller slow potassium current (I_{Ks}) compared to other ventricular myocytes (**Anzelevitch & Burashnikov 2011**). Hypokalemia would also increase the effect of APD-prolonging drugs.

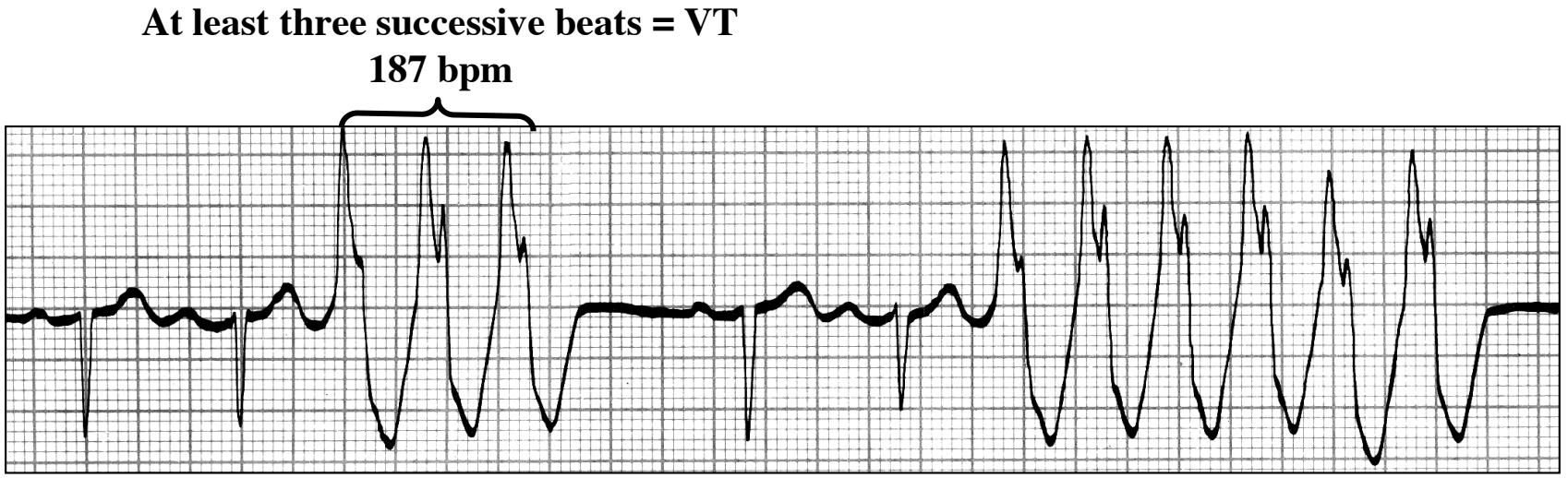
Proposed mechanism for TdP. Slowing of the HR in the presence of an APD-prolonging drug can enhance the normal **transmural dispersion of repolarization** that normally exists between mid-myocardial cells (M cells) and epicardial or endocardial cells (**Antzelevitch & Fish 2001**). Cells from the mid-wall region have a longer APD compared to endocardial or epicardial cells, and greater sensitivity to the effects of APD-prolonging drugs. Under the combination of such drugs and slowing of the HR, the M cell APD widens disproportionately, resulting in an abnormally large dispersion of APD values between regions (as indicated by the width between the two vertical lines). A dispersion of repolarization can induce a spread of current from the depolarized M cell region to the epicardial region that has regained its excitability (**Antzelevitch & Burashnikov 2011**). The source for depolarization can be either the L-type Ca current, Na-Ca exchange current (I-NCX), or a late plateau Na current. Heterogeneous changes in APD dispersion can produce multiple sites of re-excitation and induction of a multifocal VT or TdP. See next slide.



Experimental observations suggest several hypotheses about the mechanism responsible for TdP. TdP is proposed to arise from PVC due to triggered activity, especially EAD and to be perpetuated by a re-entrant mechanism as a result of the increased dispersion of repolarization (**Roden 1996; El-Sherif 1999**).

Ventricular Tachycardia (VT)

Concept: it is a term applied to ≥ 3 consecutive QRS complexes at a HR faster than 120 bpm (some experts use a cutoff rate of ≥ 100 bpm for VT) originates under the bifurcation of the His bundle, or ventricular muscle. In another words, from the lower pumping chambers of the heart (ventricles). In VT, the ventricles beat at a rapid rate, typically from 100-120 to 300 bpm, and are no longer coordinated with the atria.



Note: the inferior limit of 100 bpm, provided by some authors, would exclude Accelerated Ventricular Rhythm (AVR) or "slow VT" and some parasystolic VT.

No absolute electrocardiographic criteria exist for establishing the presence of VT. However, several factors suggest VT, including the following:

- Rate >120 bpm (usually 150-200)
- Wide QRS complexes (>140 ms)
- Presence of atrioventricular (AV) dissociation:
  - ➢Fusion beats
  - ➢Capture beats.

- **No sustained VT, NS-VT, VT runs, or transitory:** more than three consecutive ventricular depolarizations with a rate above 100 bpm and with a duration lower than 30 seconds. VT terminates spontaneously within 30s. Non-sustained VT is defined as a run of VT of less than 30 seconds duration.
- **Sustained VT (S-VT):** is defined as continuous VT lasting for >30s or that requires and intervention for termination (such cardioversion) 70% present prior infarction: or with hemodynamic involvement. Duration > 30 seconds or when they cause symptoms that made their interruption mandatory. While non-sustained ventricular tachycardia is a frequently observed dysrhythmia, sustained, monomorphic ventricular tachycardia is uncommon in the emergency department (ED) setting due to aggressive treatment of myocardial ischemia. When sustained VT causes signs or symptoms of diminished perfusion, emergent treatment is necessary.
- **Incessant VT:** when it occurs for more than 50% of the time in 24 hs Holter, it is paroxysmal (abrupt onset and end) and rate in general lower than the supraventricular ones. This variety, particularly if it presents a high rate, may lead to tachycardiomyopathy.

By underlying substrate

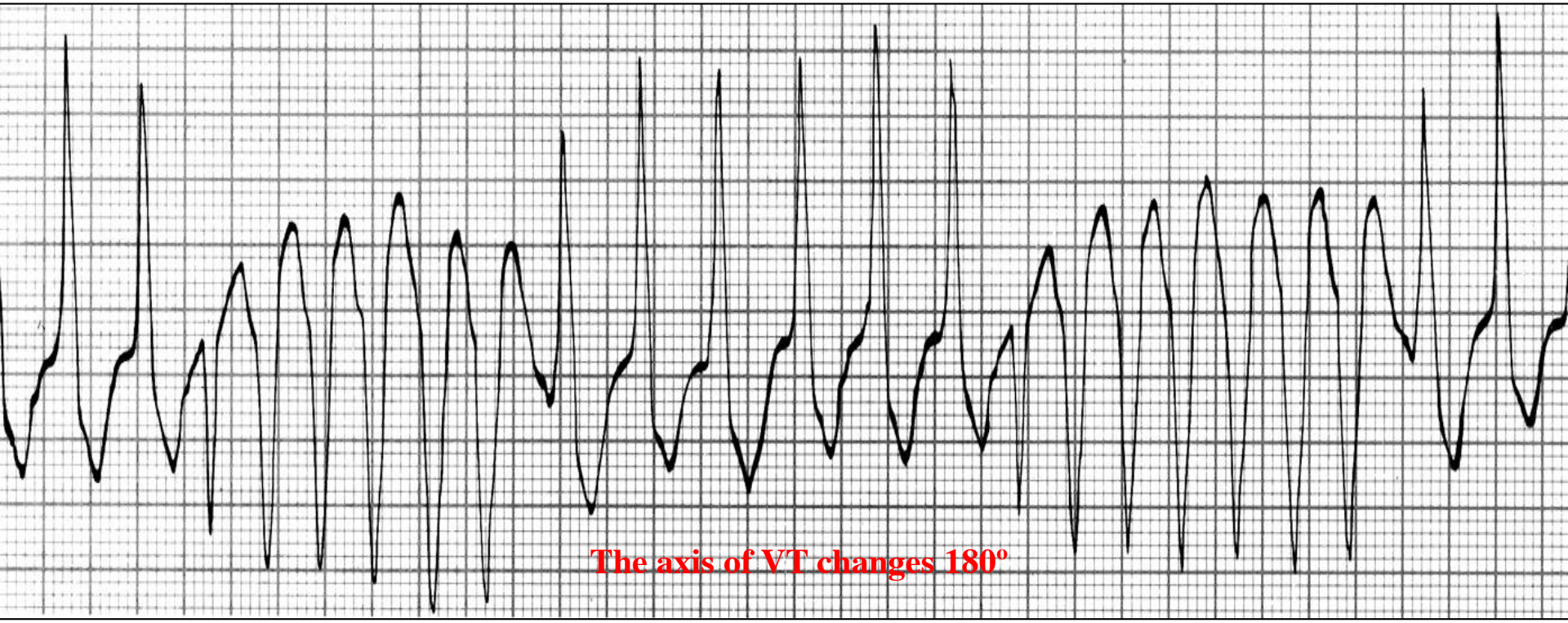
- With Structural Heart Disease
- No Structural Heart Disease
  - Monomorphic
  - Polymorphic: a) with long QT or TdP b) with normal QT interval or true QT.

VT classification according to QRS morphologies

- **Monomorphic VT:** has a similar QRS configuration from beat to beat. originating from a single focus with identical QRS complexes. Monomorphic VT results from a single abnormal focus or reentrant pathway and has regular, identical-appearing QRS complexes. Some variability in QRS morphology at initiations is not uncommon, followed by stabilization of the QRS morphology. RBBB and LBBB-like VT configurations are terms used to described the dominant deflection in V1, with a dominant R wave described as "RBBB-like" and dominant S wave as "LBBB-like" configuration (**Miller 1988**). While virtually all VT or PVCs with "RBBB-like" pattern arise in the LV only, VTs or PVCs with "LBBB-like" morphology can arise in either the LV or the RV. In the presence of prior infarction, VTs with "LBBB-like" pattern virtually always arise on or adjacent to the LV septum. In patients without structural heart disease, QRS complexes tend to be smooth and tall. With scarring of any etiology, the QRS complexes have lower amplitudes and are broader. Notching of the QRS is a sign of scar. QS complexes, other than in aVR, suggest the wave front is moving away form the recording site, but does not necessarily mean scar/infarct; however, qR or QR complexes in anatomically adjacent sites typically is a sign of infarction. Patients without structural heart disease usually exhibit a single-VT morphology, while in patient with significant structural heart disease multiple VTs are common (**Josephson 1988; 2008**).
- **Multiple monomorphic VT:** refers to more than one morphologically distinct monomorphic VT, occurring as different episodes or induced and different times. The induction or observation of multiple monomorphic QRS complex VTs at baseline electrophysiologic study predicted failure of subsequent serial electrophysiologic study - guided antiarrhythmic drug therapy (**Mitrani 1993**). This usually occurs in patients with significant scars (e.g., prior infarct, cardiomyopathy.).
- **Polymorphic, polymorphous VT or atypical VT:** Polymorphic or polymorphous VT (PVT) is recognized by a continuously changing QRS configuration form beat to beat, indicating a changing ventricular activation sequence and may precede development of VT. This may occur as part of the congenital long QT syndrome or acquired forms which are usually consequence of drug and /or electrolyte abnormalities (torsade de pointes: TdP) or other channelopathies, or may be because of

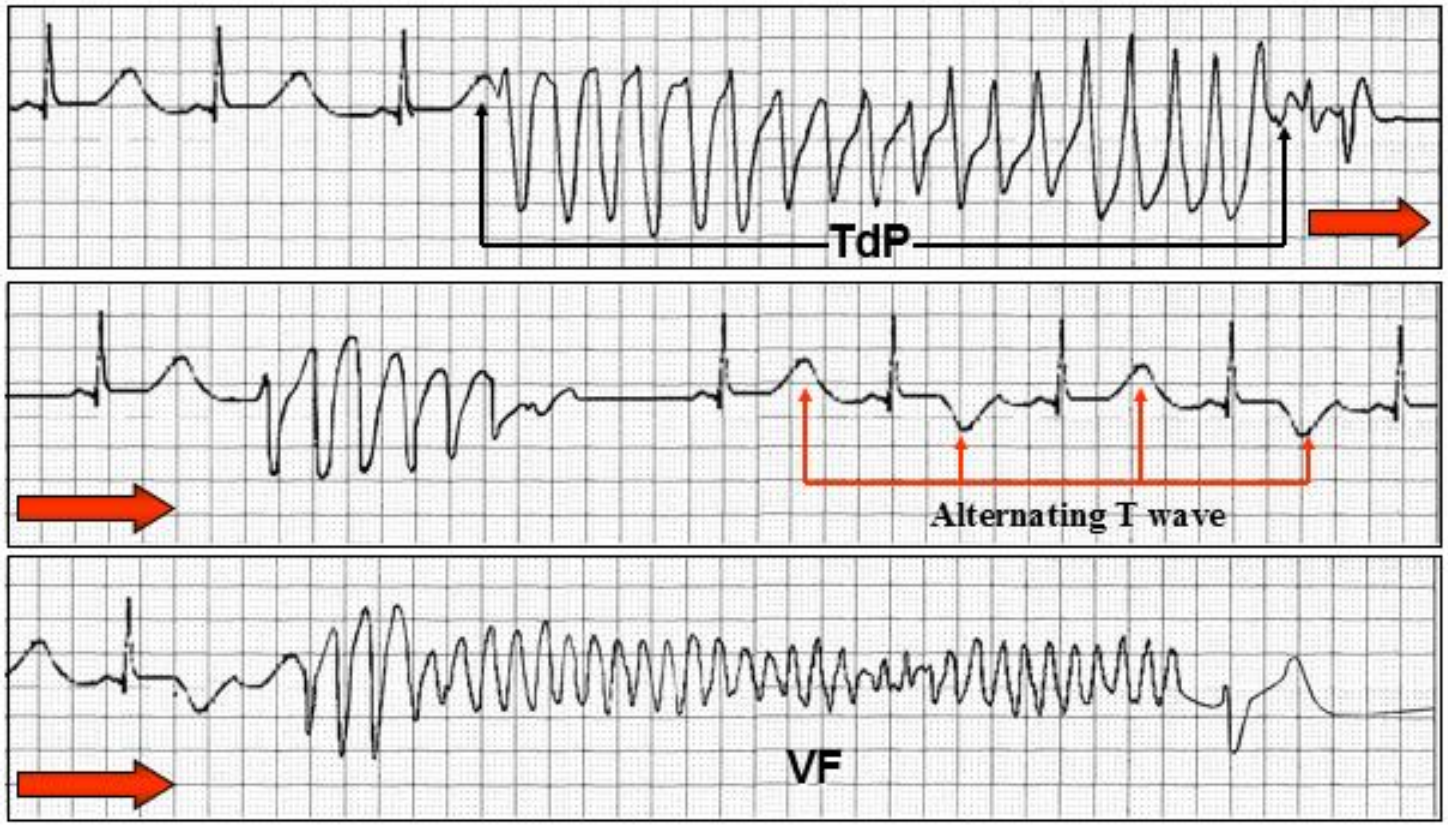
reentry in a patient with structural heart disease. The “polymorphic” nature does not define an arrhythmia mechanism. In the TdP the coupling of the initial PVC is belatedly or telediastolic, the heart rate is high (from 200 to 250 bpm) and characteristically the axis of VT changes suddenly 180º.

TdP: Rotation of the QRS apex along the baseline - “swinging pattern” or “twisting appearance”



Characteristics of Torsade de pointes (TdP)

- They are polymorphic VT with congenital, inherited or heredo-familial origin, or acquired by severe bradyarrhythmia, hypopotassemia or effect of drugs.
- They are polymorphic or atypical VT, i.e. they present a variable morphological pattern of QRS, and its end is usually spontaneous and rarely degenerates into VF. Figure below shows a continuous lead made in a 6-year-old child, carrier of congenital long QT syndrome, where a very prolonged QT interval is observed (670 ms) and episode of TdP that degenerates into VF after the presence of macrovolt T-wave alternans, the presence of which constitutes an ominous marker of arrhythmia.



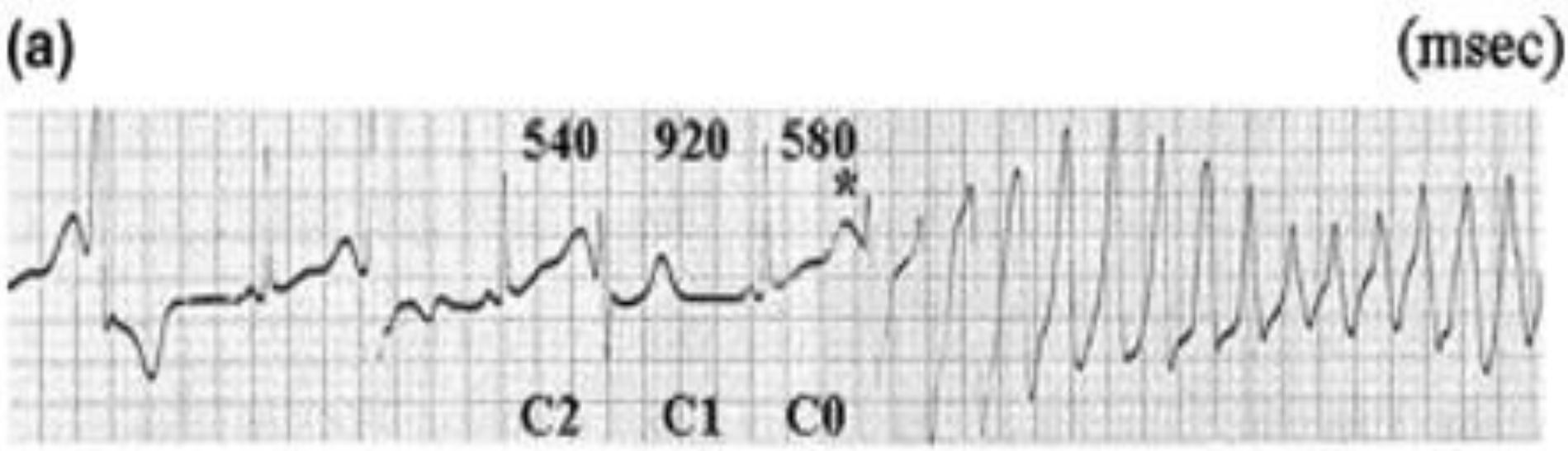
Very prolonged QT interval (670 ms), TdP run, macrovolt T-wave alternans and degeneration into ventricular fibrillation.

- TdP is defined as a PVT consisting of more than five consecutive beats during which the peaks of QRS complexes twisted above and below the isoelectric line.(**Locati 1995**)

Classification of the initiation mode of TdP (Noda 2004)

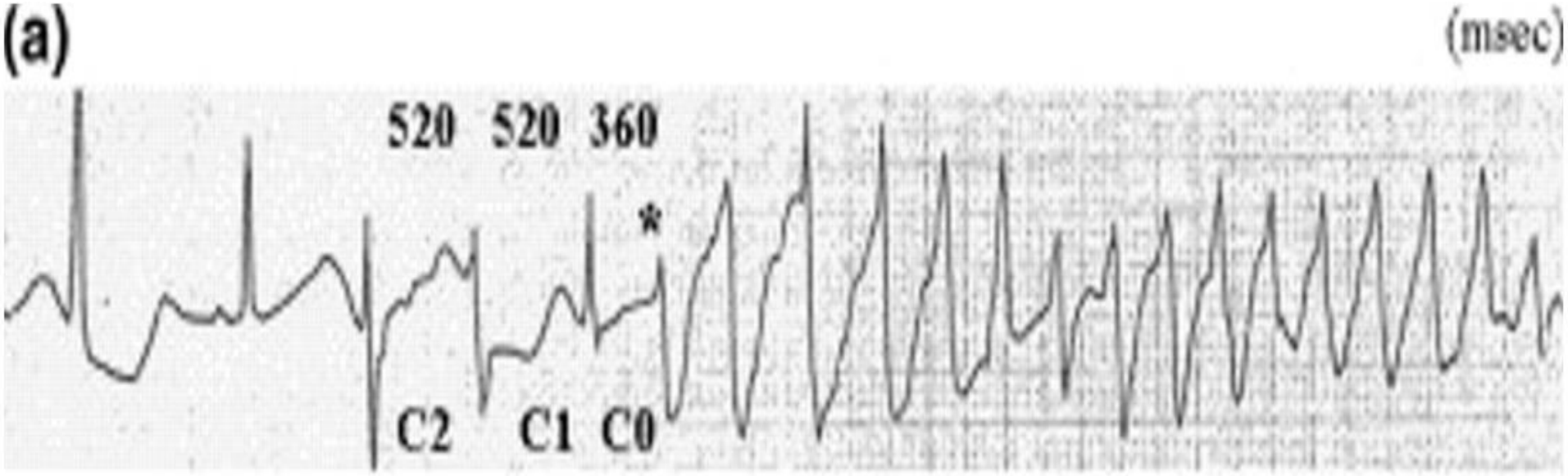
The initiating mode of TdP was classified into three different patterns:

I. An SLS pattern, an "increased sinus rate" (ISR) pattern and a "changed depolarization" (CD) pattern. The SLS pattern is defined as one or more short–long cardiac cycles followed by an initiating short-coupled PVC, and the relationship between the three consecutive preceding RR intervals was $C_1 > C_2$ and C_0. (a) shows that a PVC led to a post-PVC pause (C_1=920 ms), which changed the QTU of the following beat and culminated in TdP. The preceding RR intervals of TdP fulfilled the criteria of C_1 (920 ms)>C_2 (540 ms) and C_0 (580 ms).



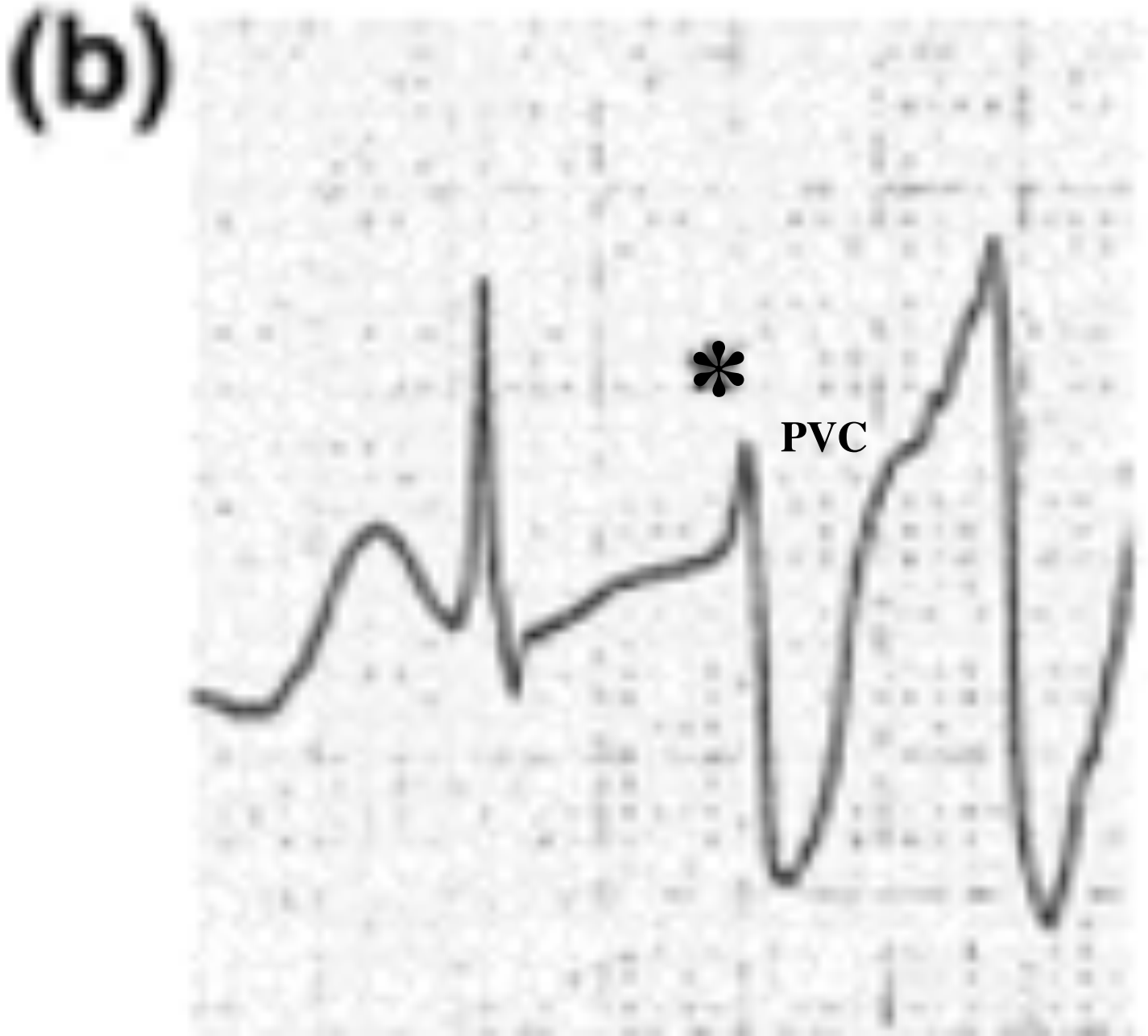
II. The ISR pattern is defined as a gradual increase in the sinus rate with or without T-wave alternans, and the relationship between the preceding RR intervals is $C_2 \geq C_1 \geq C_0$.

(a) illustrates a gradual increase in the sinus rate with T-wave alternans resulting in TdP. The preceding RR intervals of TdP fulfilled the criteria for C_2 (520 ms) ≥ C_1 (520 ms) ≥ C_0 (360 ms).

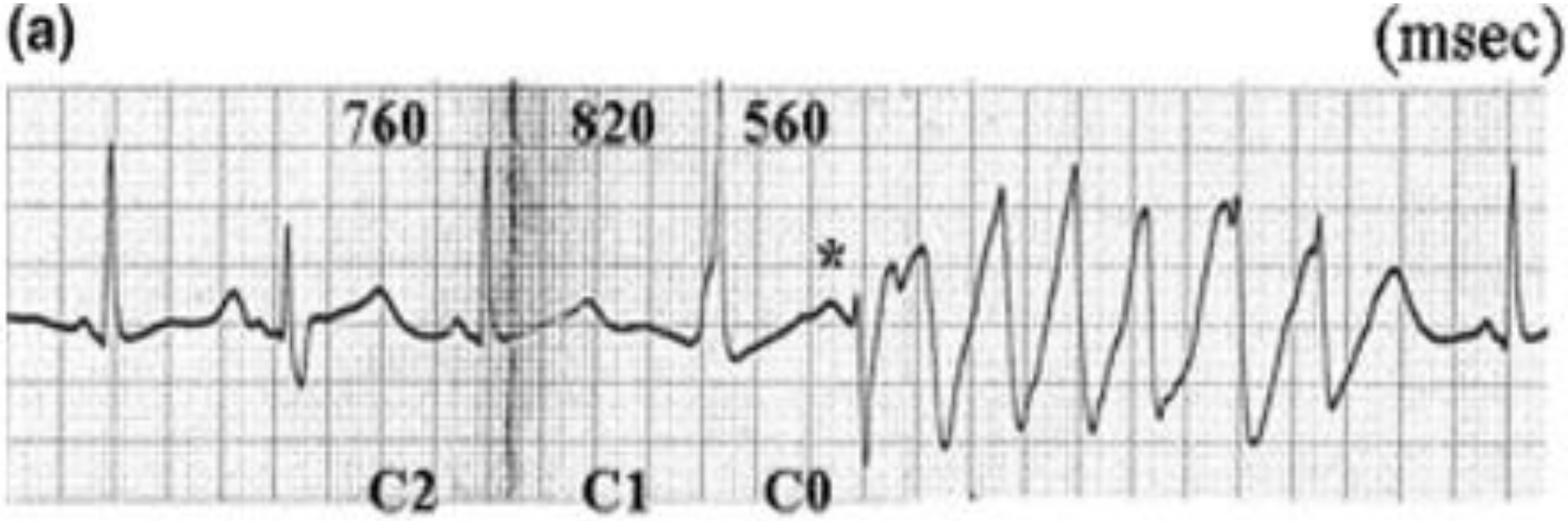


The "Increased sinus rate" (ISR) pattern as an initiating mode of TdP. (a) The monitoring electrocardiogram indicates that TdP is induced by a gradual increase in the sinus rate with T-wave alternans, and that the relationship between the preceding RR intervals fulfills the criteria for C2 (520 ms) ≥ C1 (520 ms) ≥ C0 (360 ms).

(b) The initiating PVC occurs before the T-wave peak (*) of the last beat before the onset of TdP.

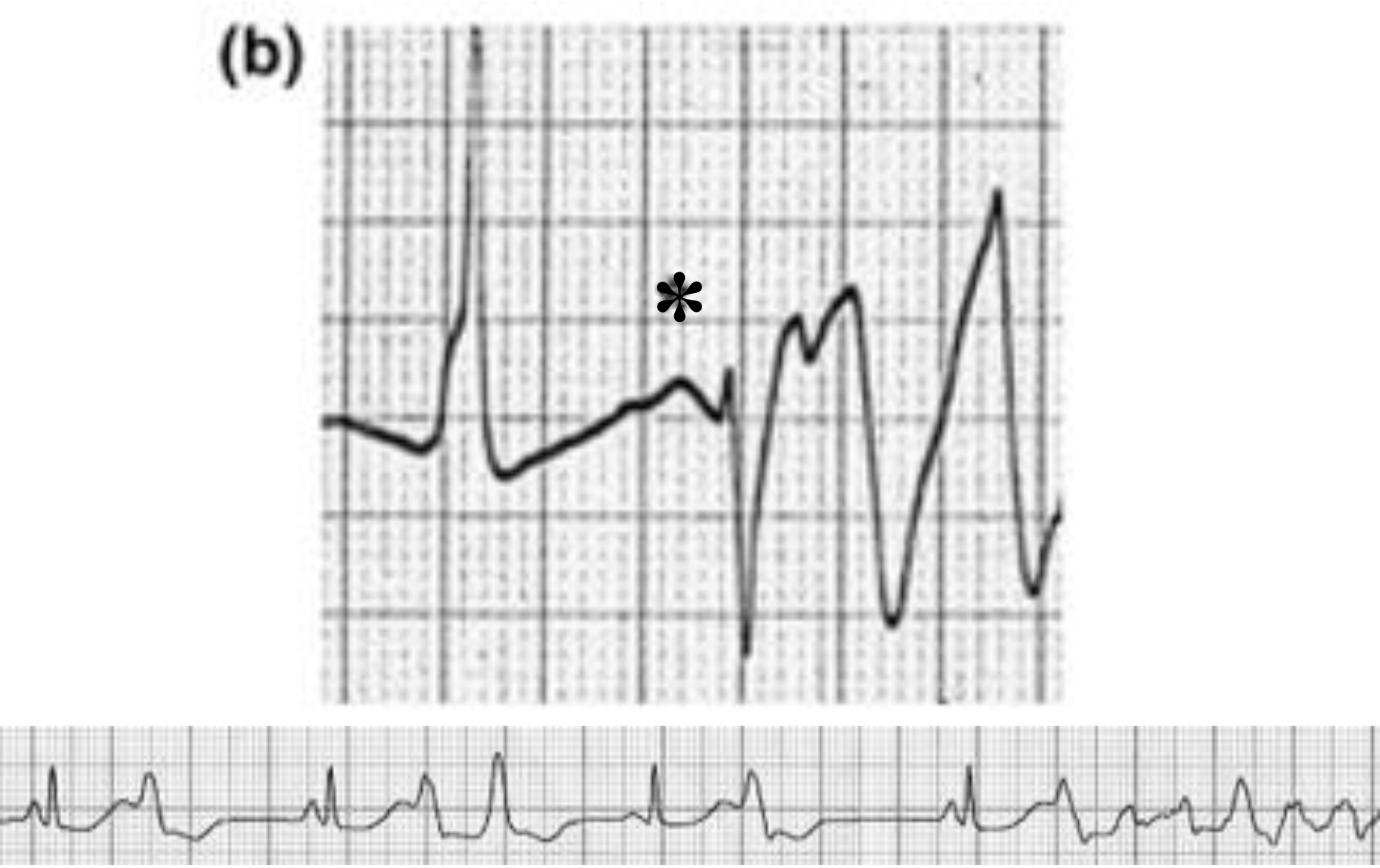


III. The "changed depolarization" CD pattern was defined as a sudden long-coupled PVC or fusion beat followed by a short-coupled PVC, and the relationship between the preceding RR intervals was $C_1 \geq C_2 > C_0$. This pattern was different from the SLS pattern, in that the last beat before the onset of TdP was PVC or a fusion beat, and resulted in a change of repolarization (QT interval) of the last beat.(a) represents a sudden long-coupled PVC as the last preceding beat of TdP, resulting in marked QT prolongation and subsequent TdP. The preceding RR intervals of TdP fulfilled the criteria for C_1 (820 ms)$\geq C_2$ (760 ms)$> C_0$ (560 ms).



The "changed depolarization" (CD) pattern as an initiating mode of TdP.
(a) The monitoring electrocardiogram shows that TdP is induced by a sudden long-coupled PVC followed by a short-coupled PVC. The relationship between the 3 consecutive preceding RR intervals fulfills the criteria for C_1 (820 ms) $\geq C_2$ (760 ms)$> C_0$ (560 ms).

(b) The initiating PVC appears after the T-wave peak of the last beat before the onset of TdP.



The present case: monomorphic PVCs with LBBB pattern with inferior axis that appear after the T-wave peak

- Base rhythm is slow, and the events are bradycardia-dependent (acquired) or triggered by strain: adrenergic-dependent (congenital).
- Presenting a possible disappearance of the event with increase in heart rate.
- Initial PVC coupling is long or telediastolic; however, as QT is prolonged there is R-on-T phenomenon.
- Presenting high heart rate between 150-300 bpm (generally, 200-250 bpm).
- Presenting QRS axis rotation around the baseline of approximately 180°.
- The efficient therapeutic measures depend on whether the cause is congenital or acquired (**Odero 2010**).
- Abnormal, giant T-U waves separate TdP initiation in LQTS patients from PVCs in other heart disease and from other PVCs in LQTS patients. EADs initiate TdP and, if present, may help to identify an imminent risk for TdP. (**Kirchhof 2009**)

TdP should be differentiated from polymorphic ventricular tachycardia without prolonged QT interval. Table below shows the main differences between both.

	Torsade de Pointes (TdP)	Polymorphic VT (PVT) with normal QT interval
Related to bradyarrhythmia	Yes	No
Pauses prior to the event	Yes	No
Associated to electrolytic disorders	Frequent	No
First extrasystole coupling	Late or telediastolic	Short or early
QTc	Prolonged	Normal or close
U wave	Frequent and of great voltage	Absent or of normal voltage

Management of the present case

During the acute events short term management: Short-term management of TdP is the same in both acquired and congenital LQTS, except that β1-adrenergic stimulation may be tried in the acquired form but is contraindicated in the congenital LQTS. In an otherwise stable patient, DC cardioversion (CV) is kept as a last resort because TdP is paroxysmal in nature and is characterized by its frequent recurrences following CV. Although TdP frequently is self terminating, it may degenerate into VF such us the present case, which requires direct current (DC) defibrillation. Any offending agent should be withdrawn. Predisposing conditions such as hypokalemia, hypomagnesemia, and bradycardia should be identified and corrected. Magnesium is the drug of choice for suppressing EADs and terminating the arrhythmia (**Tzivoni 1988; Kurita 1993**). Magnesium achieves this by decreasing the influx of calcium, thus lowering the amplitude of EADs. Magnesium can be given at 1-2 g IV initially in 30-60 seconds, which then can be repeated in 5-15 minutes. Alternatively, a continuous infusion can be started at a rate of 3-10 mg/min. Magnesium is effective even in patients with normal magnesium levels. Because of the danger of hypermagnesemia (depression of neuromuscular function), the patient requires close monitoring. Some authorities recommend supplemental potassium to increase the potassium concentration to high normal, which increases the efflux of potassium from myocardial cells, thus causing rapid repolarization. - higher β-blocker dose. Also consider use of late Na blockers i.e. Mexilitine or Ranolazine. Mexiletine also may be helpful in suppressing TdP. In one study, it was used in patients with HIV who had acquired LQT interval and TdP. It effectively suppressed the TdP on a long-term basis (**Kocheril 1997**). Patients with congenital LQTS are thought to have an abnormality of sympathetic balance or tone TdP. If the patient experiences breakthrough TdP, a short-acting β-blocker, such as esmolol, can be tried. Isoproterenol is contraindicated in the congenital LQTS (adrenergic-dependent). Because of precautions, contraindications, and adverse effects associated with its use, this drug is used as an interim agent until overdrive atrial temporary pacing can be started. Based on the fact that the QT interval shortens with a faster HR, pacing can be effective in terminating TdP. It is effective in both forms of the LQTS because it facilitates the repolarizing potassium currents and prevents long pauses, suppressing EADs and decreasing the QT interval.

Atrial pacing is the preferred mode because it preserves the atrial contribution to ventricular filling and also results in a narrower QRS complex and hence a shorter QT. In patients with AV block, ventricular pacing can be used to suppress TdP. Pacing should be instituted at a HR of 90-110 bpm until the QT interval is normalized. Overdrive pacing may be necessary at a rate of up to 140 bpm to control the rhythm. The patient with TdP who is in extremis should be treated with electrical CV or defibrillation. Anecdotal reports cite successful conversion with phenytoin (Dilantin) and lidocaine. A few cases of successful conversion using phenytoin and overdrive pacing have been reported. If patient is unresponsive to conversion with phenytoin and overdrive pacing, attempt electrical cardioversion.

Long term management: consider AICD with dual chamber pacing at 80bpm avoidance of drugs that prolong QT and aggressively replace loss of body fluids.
β-adrenergic antagonists at maximally tolerated doses are used as a first-line long-term therapy in congenital LQTS. Propranolol is used most extensively, but other agents such as esmolol or nadolol (absent in Brazil) also can be used. β-blockers should be avoided in those congenital cases in which bradycardia is a prominent feature. β-blockers are contraindicated in acquired LQTS because bradycardia produced by these agents can precipitate TdP. Patients without syncope, ventricular tachyarrhythmia, or a family history of SCD can be observed without starting any treatment. Permanent pacing benefits patients who remain symptomatic despite receiving the maximally tolerated dose of β-blockers and can be used adjunctively with β-blockers. It decreases the QT interval by enhancing the repolarizing potassium currents and suppressing EADs.
High left thoracic sympathectomy, another antiadrenergic therapy, is effective in patients who remain refractory to β-blockade and pacing. Accidental ablation of ocular efferent sympathetic nerves may result in Horner syndrome. AICDs are useful in instances when TdP recurs despite treatment with β-blockers, pacing, and possibly left thoracic sympathectomy. β-blockers should be used along with AICDs because shock can further precipitate TdP by adrenergic stimulation. An AICD for refractory cases may often precede sympathectomy.

Considerations about Congenital Long QT Syndrome (LQTS)

Rare, heredo-familial, autosomal syndrome (there are sporadic, isolated, non-familial cases), genetically heterogeneous, caused by mutations in the encoding genes of the sarcolemmal potassium or sodium channels (channelopathies) causing dysfunction in them and thus, extending ventricular repolarization, which in turn predisposes the appearance of a special modality of polymorphic or malignant atypical ventricular tachycardia, known as Torsade de pointes (TdP) that may cause syncope or occasionally degenerate into VF and sudden cardiac death (SCD) (**Ackerman 1998; Viskin 1999**). Occasionally, the condition is diagnosed after a young relative presents SCD. In some individuals, the diagnosis is made when ECG shows prolonged QT interval.

A history of cardiac events is the most typical form of presentation. A family history of cardiac arrest and SCD, especially in young people, may suggest a familial, congenital form. The triggering of events depends on the genotype; thus, physical and emotional stress are triggering factors in the LQT1 and LQT2 variants (**Schwartz 2001; Ackerman 1999; Wilde 1999**). The main trigger in the LQT1 variant is swimming and exposition to cold water in the face. In the LQT2 variant, the main trigger is the presence of noise or auditory stimulus as, for instance, an unexpected clock alarm or phone ringing.

The LQT3 variant is triggered by an increase in vagal tone, a reason why the events predominate during sleep by nocturnal vagotonia.

A diagnostic clue could be found in the presence of sensorineural hearing loss, indicating a rare recessive form of Jervell and Lang-Nielsen syndrome (JLNS).

The acquired forms of LQTS could also have an underlying genetic component.

A careful analysis of the ventricular repolarization aspect may suggest with a high degree of certainty, the type of variant.

This syndrome may present a congenital origin, when mutations occur in the proteins that encode the ion sodium and potassium channels of the myocardial cells (**Ackerman 1997**), or acquired due to the use of drugs, electrolytic alterations or metabolic disorders (**Roden 2005**).

Congenital LQTS

Most are familial. The cardiac events (syncope, cardiorespiratory arrest, or sudden cardiac death), generally occur in young individuals without structural heart disease.

Prevalence: The frequency is unknown, but it seems to be a common cause of SCD and unexplained death children and young adults. It is certainly much more common than what was thought. It could be as frequent as 1 in 5,000 to 7,000. This means that one in 5,000-7,000 newborn babies have the disease. The Jervell, Lange-Nielsen form is rare, but the Romano-Ward variant is being recognized with an increasing frequency. In USA, the presence of long QT syndrome affects close to 50,000 people with up to 3,000 deaths per year. It is present in all races and ethnic groups, but its frequency is not the same in all races.

The autosomal dominant form is the most common one, known as Romano-Ward syndrome (**Kapa 2009**), and it presents a prevalence estimated initially around 1:25,000 babies born alive. The autosomal recessive forms associated to central deafness (Jervell and Lange-Nielsen syndrome) are much more rare (**Jervell 1957; Schwartz 2006**). The prevalence of recessive forms in children between 4 and 15 years in the countries of Wales and Ireland has been estimated between 1.6 and 6 per million. In Sweden and Norway, the recessive form of Jervell-Lange-Nielsen (JLNS MIM 220400) appears to have a relatively high prevalence in pre-teenagers; i.e. > 1:200,000 born alive (**Winbo 2012**). A study made in Caucasians yielded a first estimation of LQTS prevalence. Based on non-genotyped infants with QTc between 451 and 470 ms, a much higher prevalence has been estimated, that could be around 1:2,000 born alive. The molecular triage guided by ECG may identify most children with LQTS and unmask affected relatives, thus enabling efficient preventive measures (**Schwartz 2009; Giudicessi 2013**). This estimated prevalence coincides with the studies by Professor Ackerman's group. These authors studied non-genotyped babies that had QTc intervals between 451 and 470 ms, estimating a prevalence close to 1:2,000. About JLNS after its first description in Norway in 1957, it was confirmed that in no place there is a prevalence as high as in these countries, where a prevalence of at least 1:200,000 is estimated. The KCNQ1 and KCNE1 proteins coassemble in a potassium channel, and the mutations in any gene or in the KCNQ1 KCNE1 gene interrupt the production of endolymph in the cochlear vascular grooves causing central deafness. A mutation in the KCNQ1 gene appears to be the

main one in JLNS. Some heterozygous carriers of mutation in any JLNS gene may suffer QTc intervals increase and be symptomatic LQTS, with an accurate genotype-phenotype correlation that has not been established, which complicates genetic counseling and the evaluation of clinical risk in carriers.

The physical examination usually does not lead to diagnosis of LQTS; however, some children may present a lower heart rate than that expected for the age. The presence of congenital central deafness indicates the possibility of JLNS. The presence of skeletal deformations, cognitive and behavioral alterations, and muscular-skeletal problems with immunological dysfunction, may suggest LQT8 variant or Timothy syndrome. Hinterseer et al (**Hinterseer 2009**) discovered that the increase in short term QT interval variability in patients with symptomatic LQTS, could be a non-invasive additive marker, useful in the diagnostic triage to fill the gap while results from genetic tests are expected. This study is the first in humans to observe this association.

Genotypes: The following two tables show the dominant (Romano-Ward syndrome) and recessive genotypes (Jervell-Lange-Nielsen syndrome) identified until the present time. The LQT1 variants (60%), LQT2 (35%) and LQT3 (2%) together constitute 97% of all cases. To this moment, 13 genotypes have been identified in 50% to 80% of the patients clinically affected by congenital LQTS (**Shimizu 2014**).

Genotype-phenotype correlations have been investigated in the three main genotypes (LQT1, LQT2, and LQT3), resulting in a specific therapy according to the genotype. A more thorough analysis of each genotype has suggested the location of the mutation, and type or function-specific differences for each clinical phenotype between LQT1, LQT2 and possibly LQT3.

Genetic base of the autosomal dominant Romano-Ward syndrome

Type of LQT	Chromosomal locus	Genetic mutation	Affected ion channel
LQT1: 60% of cases	11p15.5	*KVLQT1* (*KCNQ1*) (heterozygote)	Slow outward potassium rectifier channel (I_{Ks})
LQT2: 35% of cases	7q35-36	*HERG*	Rapid outward potassium rectifier channel (I_{Kr})
LQT3: 2% of cases.	3p21-24	*SCN5A*	Rapid sodium channel (INa^+)
LQT4	4q25-27	?	?
LQT5	21q22.1-22.2	*KCNE1* (heterozygote) Jervell and Lange-Nielsen syndrome.	Slow outward potassium rectifier channel (I_{Ks})
LQT6	21q22.1-22.2	*MiRP1*	Rapid outward potassium rectifier channel (I_{Kr})
LQT7	17	KCNJ2	Associated to Andersen-Tawil syndrome (ATS1) (I_{K1})
LQT8 Timothy's Syndrome	12p13.3	CACNA1C Cav1.2	LTCC: L-type Calcium Channel
LQT9	3p25	CAV3	Late inward Na^+ current in phase 2
LQT10	11q23	SCN4B	Prolonged Na+ influx
LQT11	7q21-q22	AKAP9	I_{ks}
LQT12	22q11.2	SNTA1	I_{Na+}
LQT13	11q24	KCNJ5	I_{kACTH} I_{K1}

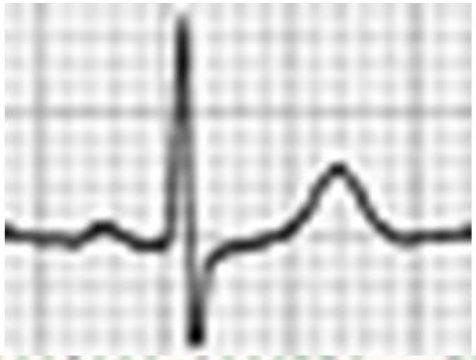
Genetic base of the autosomal recessive Jervell-Lange-Nielsen syndrome

Type of LQT	Chromosomal Locus	Genetic mutation	Affected ion channel
JLN1	11p15.5	KVLQT1 (KCNQ1) (homozygote)	Slow outward potassium rectifier channel (I_{Ks})
JLN2	21q22.1-22.2	KCNE1 (homozygote)	Slow outward potassium rectifier channel (I_{Ks})

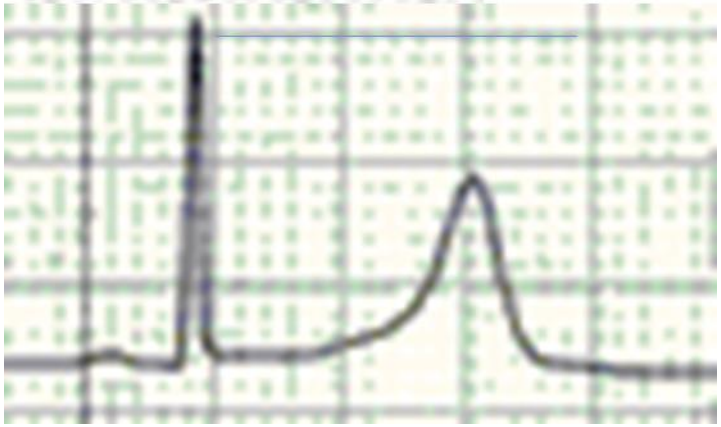
LQT1 - This variant affects the slow outward potassium current subsequent to a mutation in the short arm of chromosome 11 (**Keating 1991**). ECG is characterized by the presence of prolonged QT interval associated to a wide T wave with wide base. Moreover, this variant under infusion of low doses of epinephrine, presents a paradoxical increase of QT interval, unlike the LQT2 and LQT3 variants that tend to shorten QTc interval during this pharmacological test (**Ackerman 2002**). Thus, any sympathetic stimulus (physical or mental stress) extends QT interval and may generate ventricular arrhythmias more frequently than in the LQT2 and LQT3 variants (**Shimizu 2004**). Beta-adrenergic stimulation in the LQT1 variant causes an increase in transmural dispersion of the ventricular myocardium by unequal effect on the action potential duration in the ventricular wall thickness, conditioning an increase in the Tpeak-Tend or Tpe interval. In normal conditions, these values should not exceed 94 ms in men and 92 ms in women when measured in V5. All channelopathies have transmural dispersion of repolarization, considered the main arrhythmogenic factor. Most of the arrhythmic events in the LQT1 variant is triggered during a practice of physical exercises, particularly swimming. Consequently, they should be forbidden in the LQT1 variant. The beta adrenergic stimulus causes a greater dispersion of ventricular repolarization by shortening more intensely the transmembrane action potential (TAP) in subepicardial and subendocardial cells, and acting to a lesser extent in the M cells of the mid myocardium, which naturally possess a weaker Iks channel. LQT1 patients in 62%

of the cases present their events during exercise, and only 3% occur during sleep or rest. Ninety nine percent of patients that had events during swimming are LQT1. Auditory stimulus only triggered events in 2% of the patients with LQT1 (**Hebert 2002**). Chinese investigators showed that the LQT1 variant would have a mutation-dependent trigger. Thus, in the L191P mutation the events occur during sleep or when waking up, while the F275S, S277L mutations in the S5 and G306V transmembrane domain in the channel pore, are triggered by stress and exercise (**Lui 2002**).

Characteristics of LQT1 variant or kvLQT1 defect



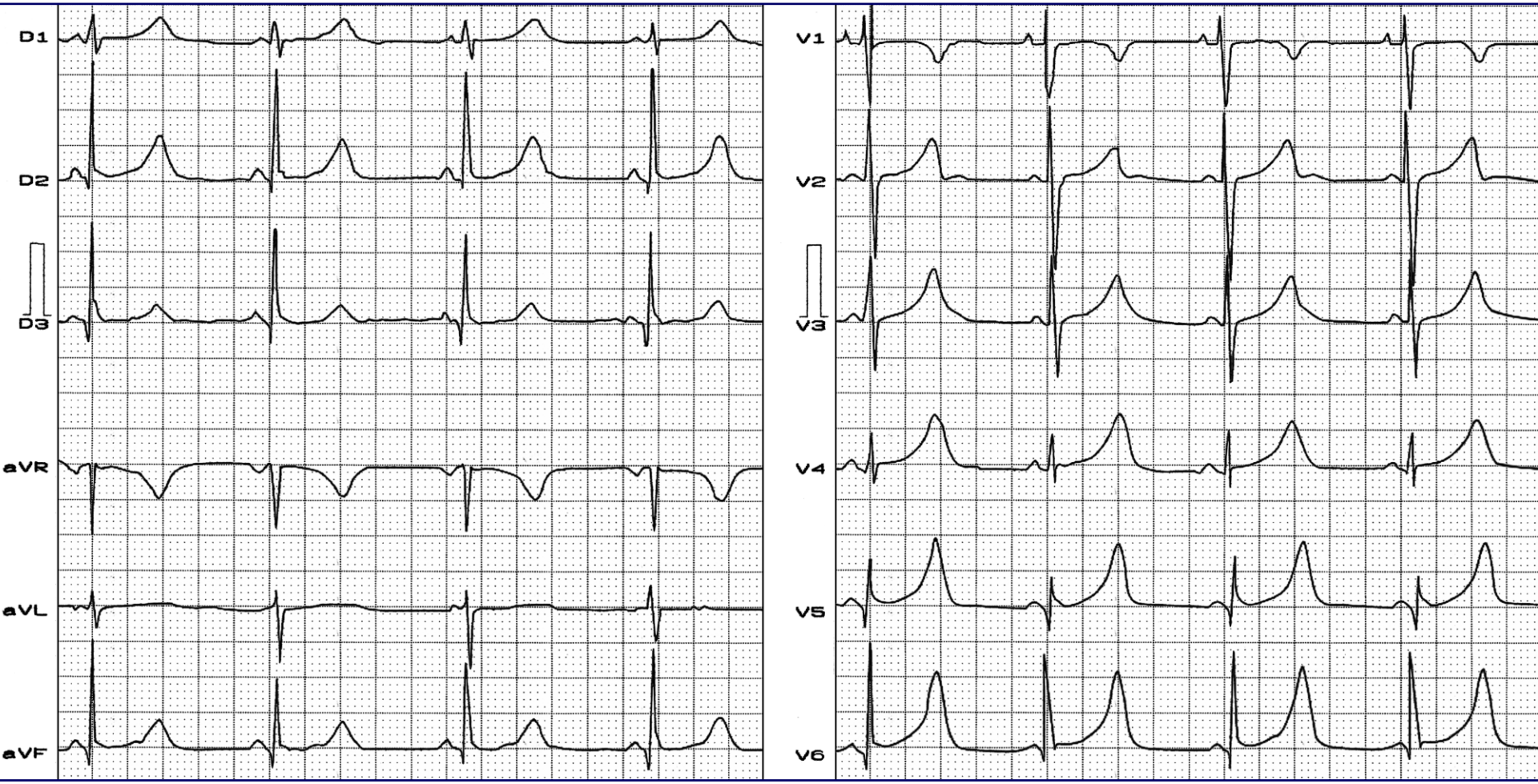
Normal (QT = 390 ms)



LQT1 60% of total

Events triggers: *Exercise*, *especially swimming*

- Broad-based prolonged T waves (QT = 580 ms).
- Moderate HR dependence of QT interval.
- Short arm of chromosome 11.
- Mutation: 11p15.5.
- Affected channel in TAP: I_{ks} delayed rectifier potassium current.
- Single variant with high % of events during exercise or swimming.



ECG from a patient with a type 1 LQTS (LQT1). Typical wide-based T-waves with a large amplitude are observed.

LQT2

This variant is due to a chromosomal mutation affecting the HERG gene (human ether-a-go-go gene) that encodes the rectifying rapid outward potassium Ikr channel in phase 3 of cardiac action potential. In this variant, the arrhythmic events are triggered by noises (clock alarms), emotions or stress.

ECG is characterized by QT interval prolongation with bifid T wave and of low amplitude (T1-T2), with T1-T2 interval <150 ms (figures 9 and 10).

The authors from the Masonic Medical Research Laboratory in Utica, NY, USA, suggest that the "M" cells present in the mid myocardium have a repolarization time more prolonged than the endo and epicardial cells (comparable to Purkinje cells), and they could be responsible for congenital or acquired long QT syndrome. In long QT syndromes, a U wave would be caused by M cells in the mid myocardium (**Lazzara 1995**).

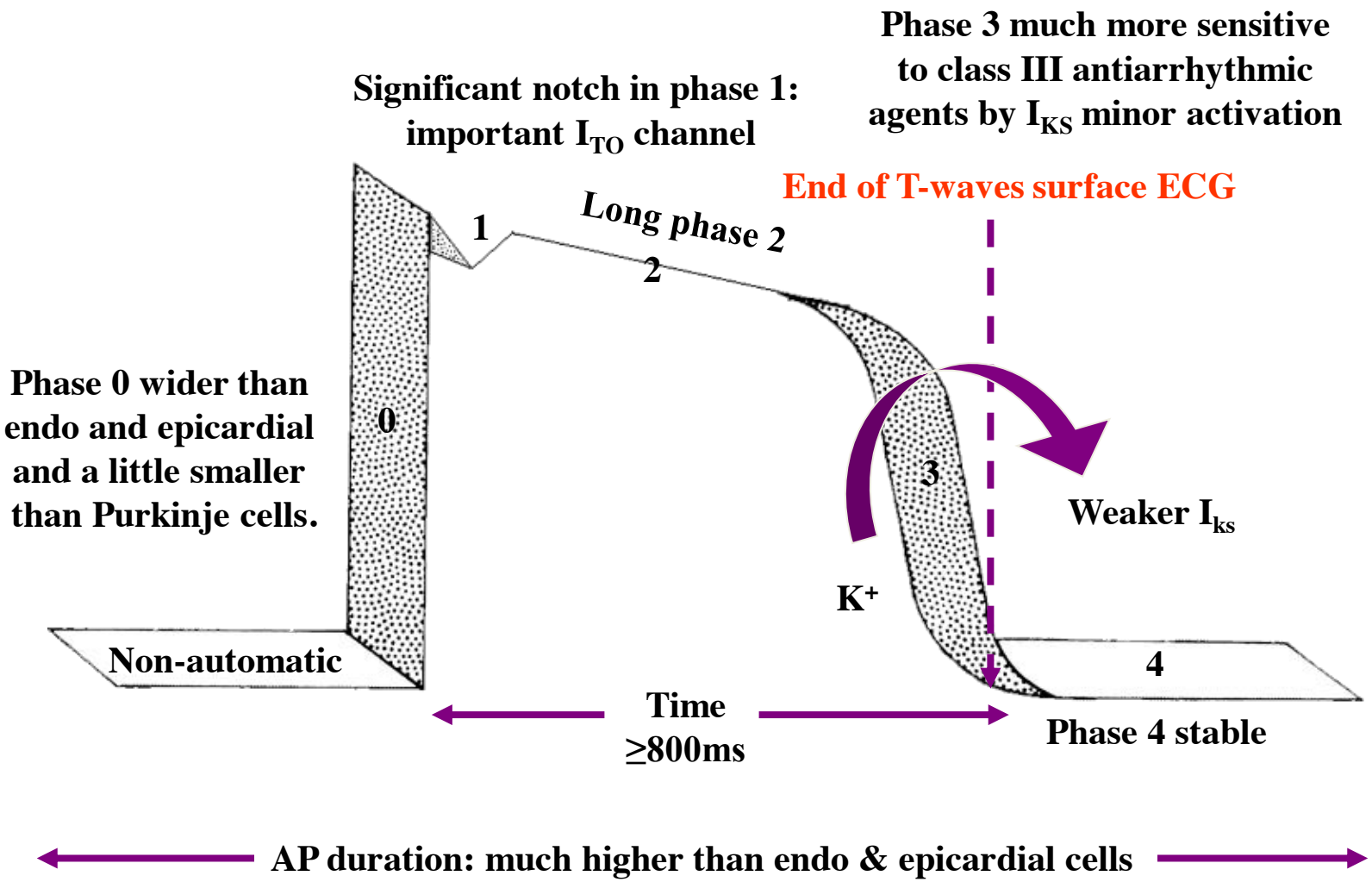
The electrophysiological features of M cells are summarized as follows:

I. **Phase 0** wider than in the endocardial and epicardial cells (greater dromotropism), and minimally less wide than Purkinje cells;
II. **Phase 2** long and in plateau similar to Purkinje cells;
III. **Phase 3** with weak (Iks) slow outward potassium channel and much more sensitive to class III antiarrhythmic agents, like amiodarone and sotalol;
IV. **Stable phase 4;** i.e. without diastolic depolarization or automatism (non-automatic cell);

M cells are responsible for transmural heterogeneity of ventricular wall repolarization, which may be estimated in surface ECG by the Qtpeak-Qtend interval.

Propranolol produces shortening better when compared to metoprolol and nadolol, in the LQT1 and LQT2 variants (**Chockalingam 2012**).

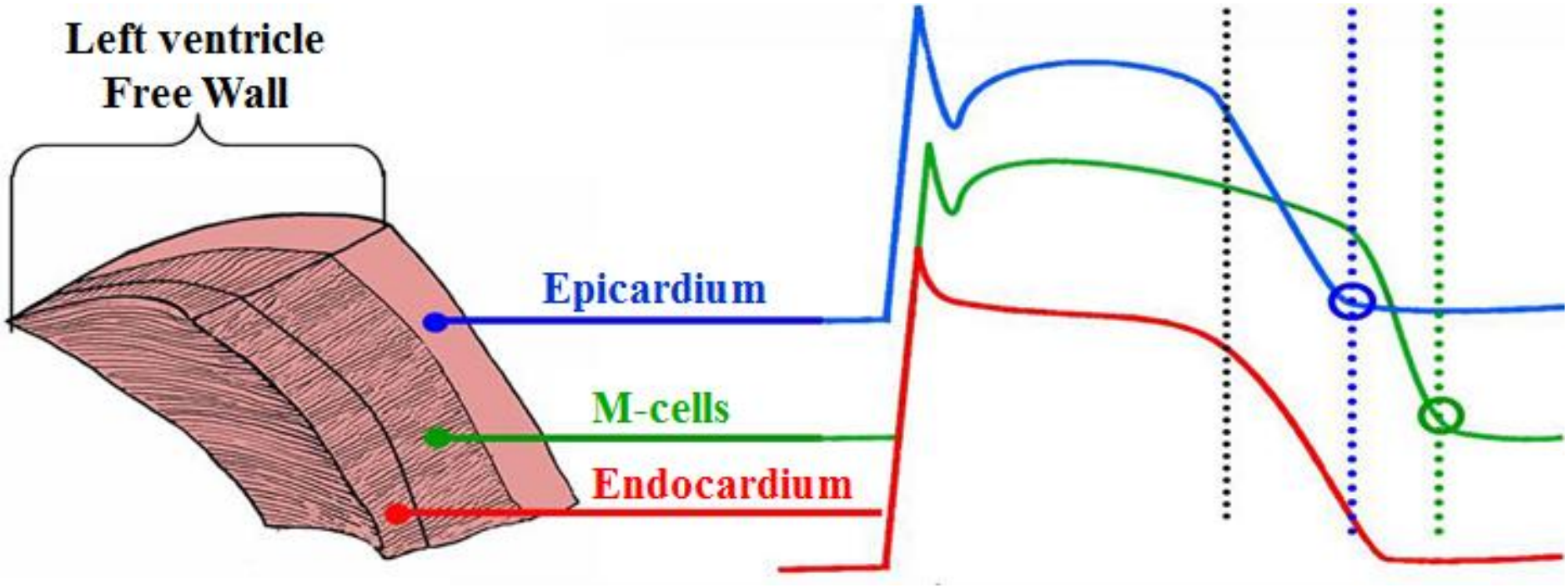
Characteristics of AP of "M" cells of ventricular mid-myocardium



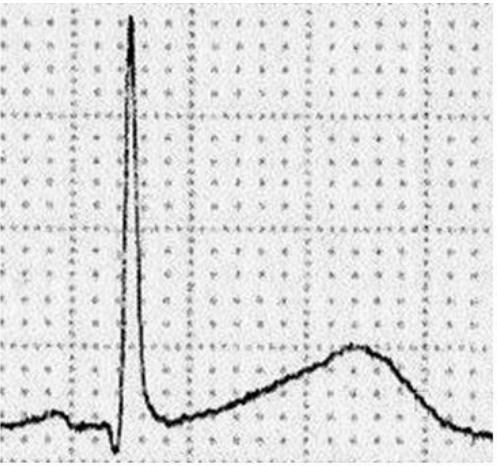
Characteristics of action potential of M cells. It is a fast and non-automatic fiber; therefore, we could say that it is a mixture between Purkinje cells and contractile ventricular myocardium. It is very sensitive to bradycardia and class III antiarrhythmic drugs, such as amiodarone and sotalol.

Electrophysiological characteristics of ventricular myocardial cells

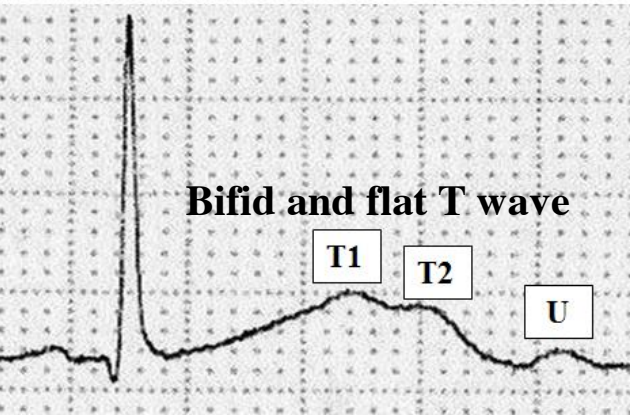
	Epicardium	Mid-myocardium: Transitional cells	Endocardium
AP duration	300ms	800ms	300ms
Phase 1: notch	I_{to} channel very abundant, responsible for prominent notch in phase 1.	Abundant I_{to} channel	I_{to} channel absent. There is no phase 1 with notch.



Characteristics of HERG LQT2 variant



Normal

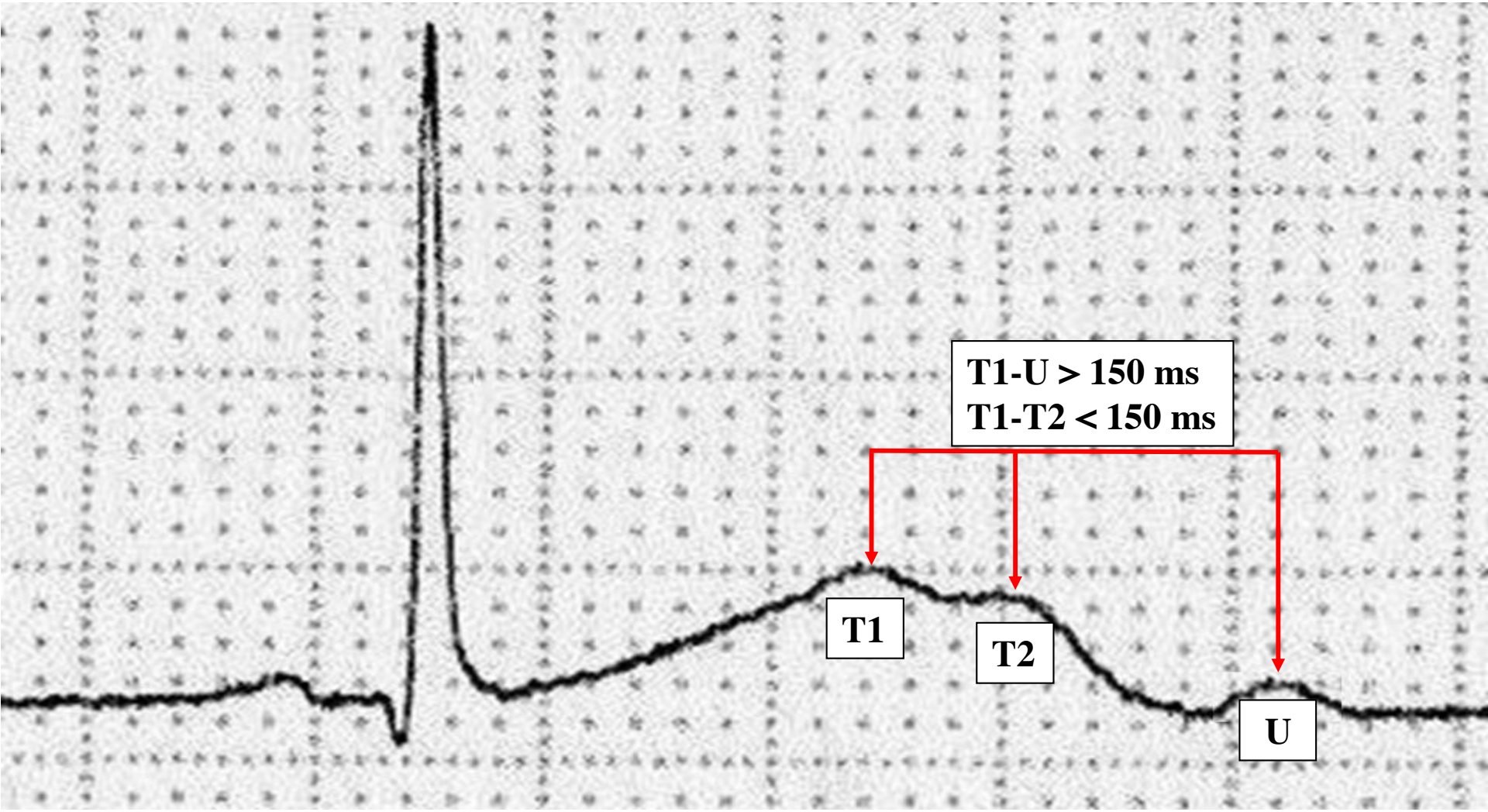


LQT2 ≈ 35% of total

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

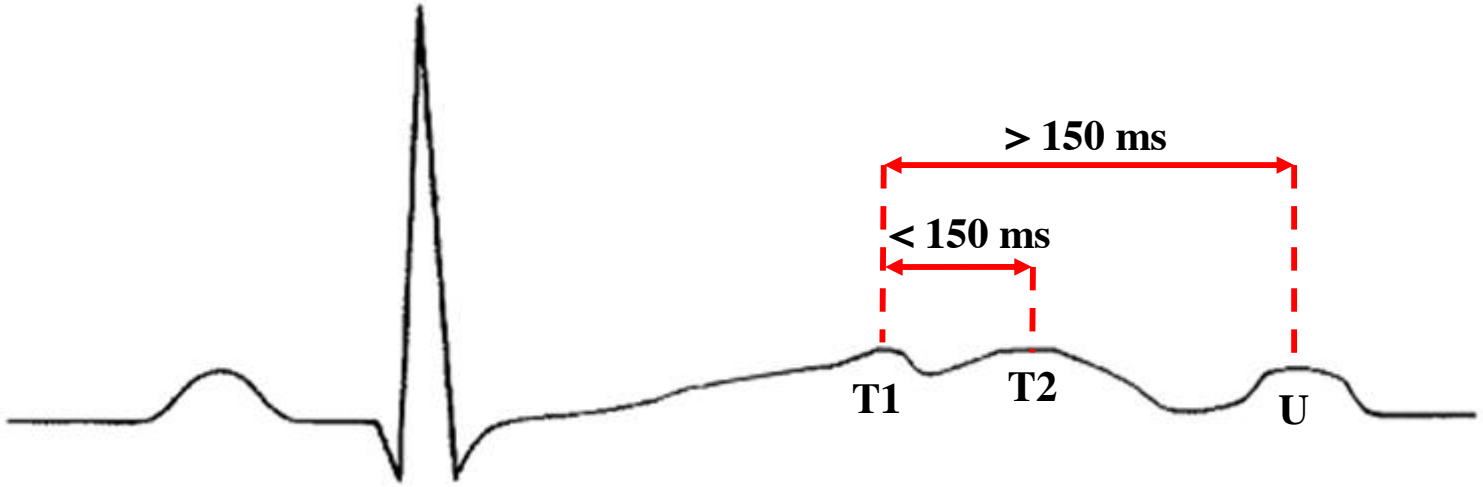
LQT2: ***OMIN 152437. Mutation: alpha subunit of the rapid delayed rectifier potassium channel (hERG = MiRP1) Current through this channel is known as I_{Kr}. This phenotype is also probably caused by a reduction in repolarizing current.***

Differentiation between bimodal T waves of LQT2 from T-U interval



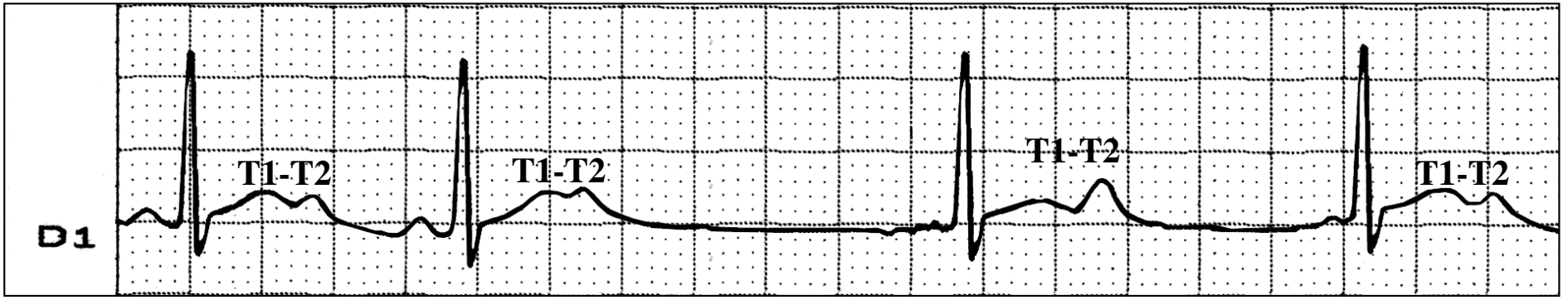
Characteristics of HERG LQT2 variant (Lepeschkin 1969-1972)

Differentiation of bimodal T waves characteristic of variant 2 of LQTS of T-U interval



The second apex of bimodal T wave (T2) is at a distance < 150 ms of the first module (T1). The T1-U interval is always > 150 ms.

Bimodal T wave (T1-T2 pseudo-U wave dependent on bradyarrhythmic pause (Roden 1999)

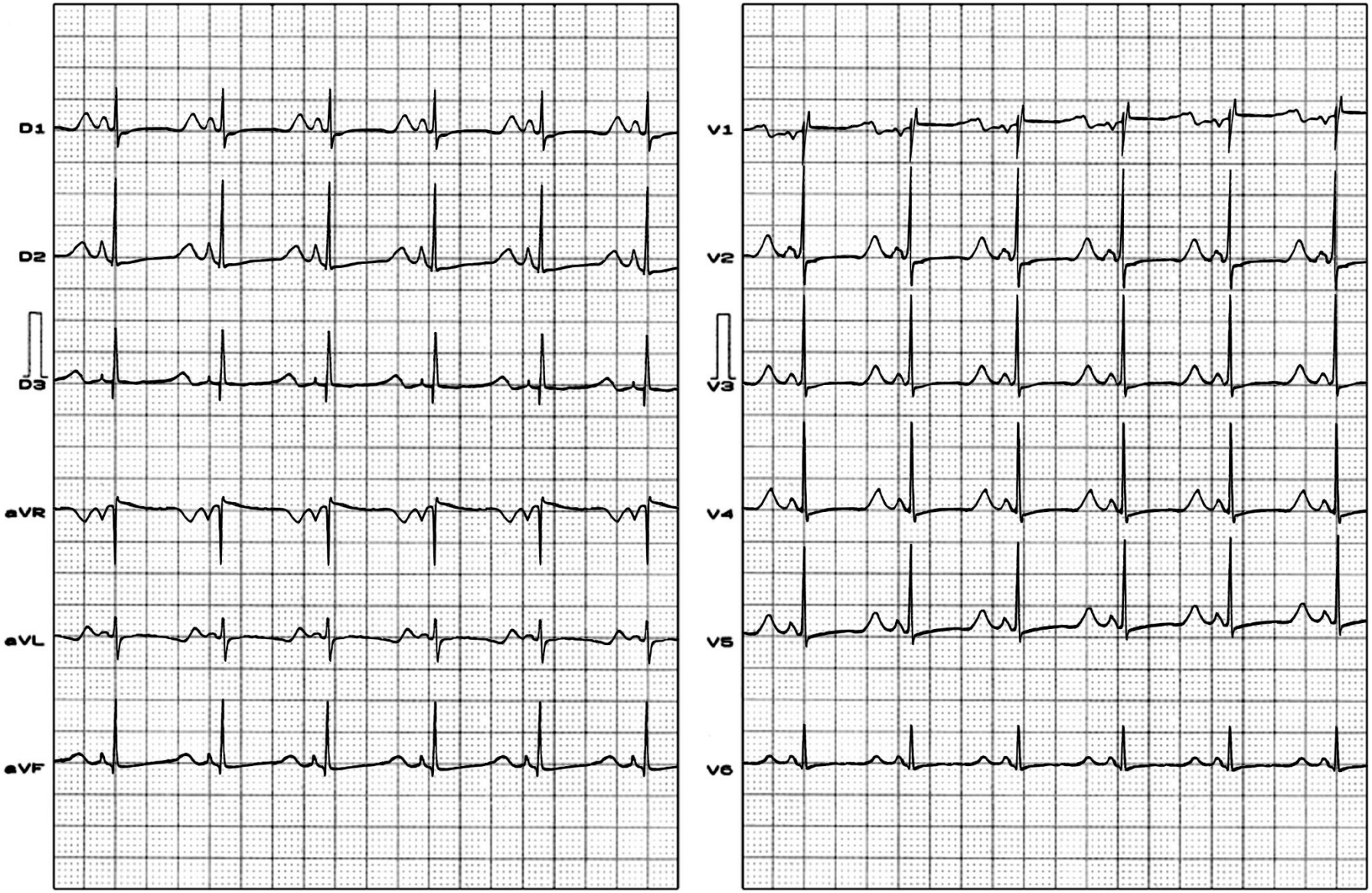


LQT3

It is considered the mirror image of BrS and both are considered allelic entities (**Cerrone 2001**). QT interval prolongation is due to a greater duration of the ST segment and late appearance of the T wave, consequently to the late inflow of Na^+ during phase 2 of the action potential that corresponds to ST segment in conventional ECG. The mutation is found in chromosome 3 and the affected gene is SCN5A. In this variant, the arrhythmic events in 60% of the cases occur during sleep or in night rest (**Zareba 1998**). The rate of events is lower than in the LQT1 and LQT2 variants; however, the lethality of each event is greater.
The male gender presents a greater risk.

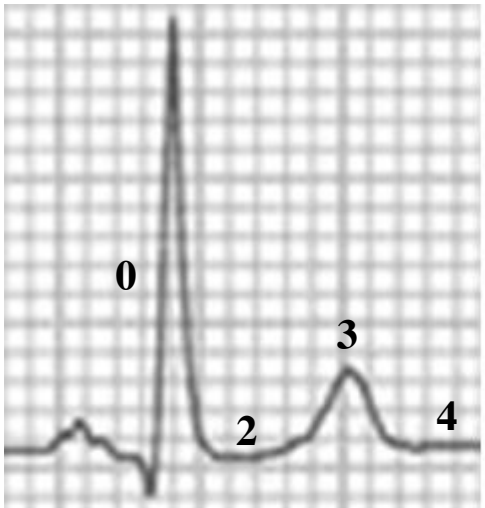
Main electrocardiographic characteristics of the LQT3 variant

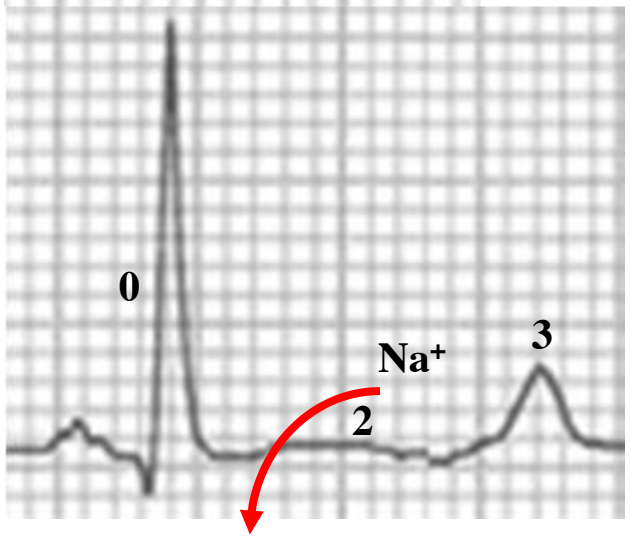
Heart rate: tendency to bradycardia in relation to age, and in some cases, HR decrease during strain. When HR increases, the QT interval shortens more than in the other variants. When it is verified that the arrhythmic episodes are pause-dependent or bradycardia-dependent, it is advised to implant a pacemaker with pacing at around 70-90 beats per minute. In this situation, a rate smoothing algorithm is programmed, enabling to temporarily increase HR after: PVCs, HR reduction 18% below the basal one, pauses related to T-U wave alterations, and recurrent pauses, thus preventing the occurrence of TdP (**Li 2003**).
ST segment: significant prolongation of this segment, with late appearance of T wave. The delta KPQ mutation causes the persistent entrance of sodium during phase 2 of the action potential with late reopening, which explains QTc increase.
QT interval: it is usually longer than in the LQT1 and LQT2 variants, and it presents a significant dependence on heart rate.
U wave: it could be more prominent subsequent to more prolonged repolarization of M cells. It increases in bradycardia and during pauses, and it may present alternating polarity.
QT interval dispersion: increased and considered a risk marker for malignant arrhythmias (**Day 1990**).
Association to structural heart disease: the QKP-1507-1509 mutation affecting the Na^+ channel (**Shi 2008**) may cause association to long QT interval by ST segment prolongation, biphasic T waves, multiple VT episodes, TdP and VF, conduction disorder as second degree AV block, LAFB, incomplete RBBB, intermittent third degree AV block, and presence of dilated cardiomyopathy.



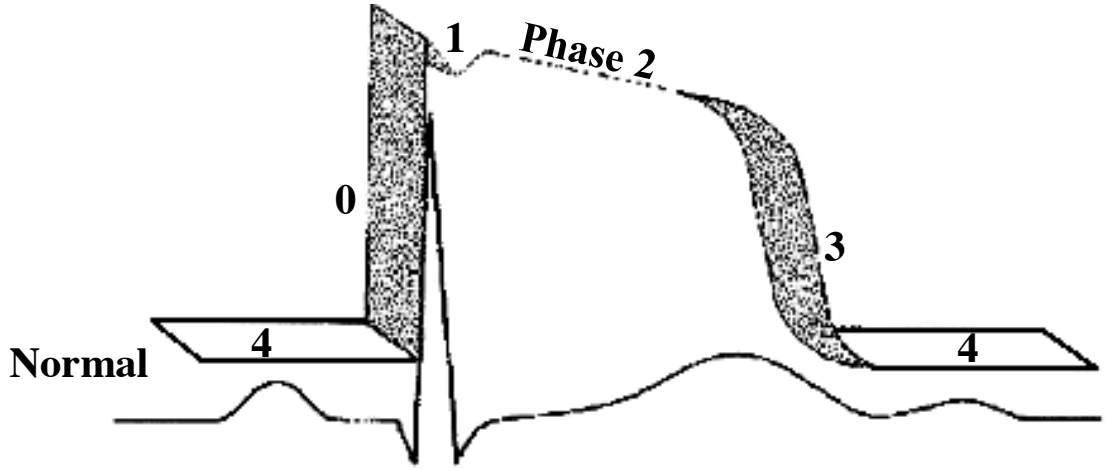
This ECG belong a new born with LQT3 variant. Clear ST segment prolongation and delayed appearance of T wave. affected gene: SCN5A, p21-24 mutation in chromosome 3, AP phase: plateau, dome or phase 2 by persistent sodium inflow.

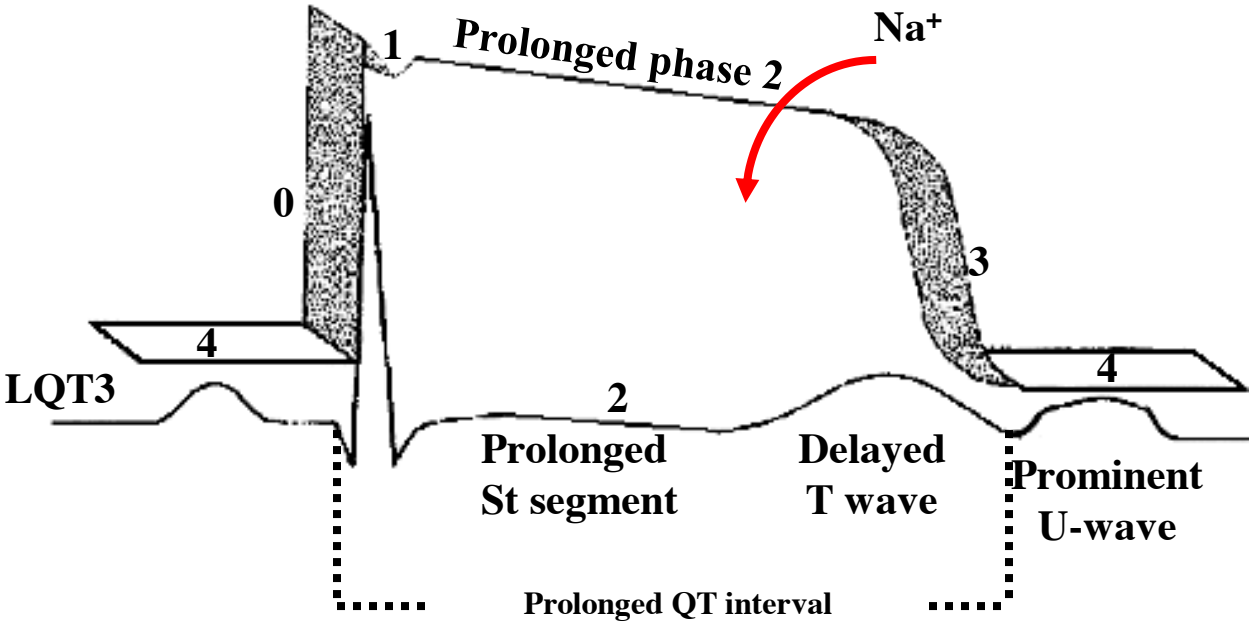
Normal ECG and action potential versus LQT3 ECG and action potential



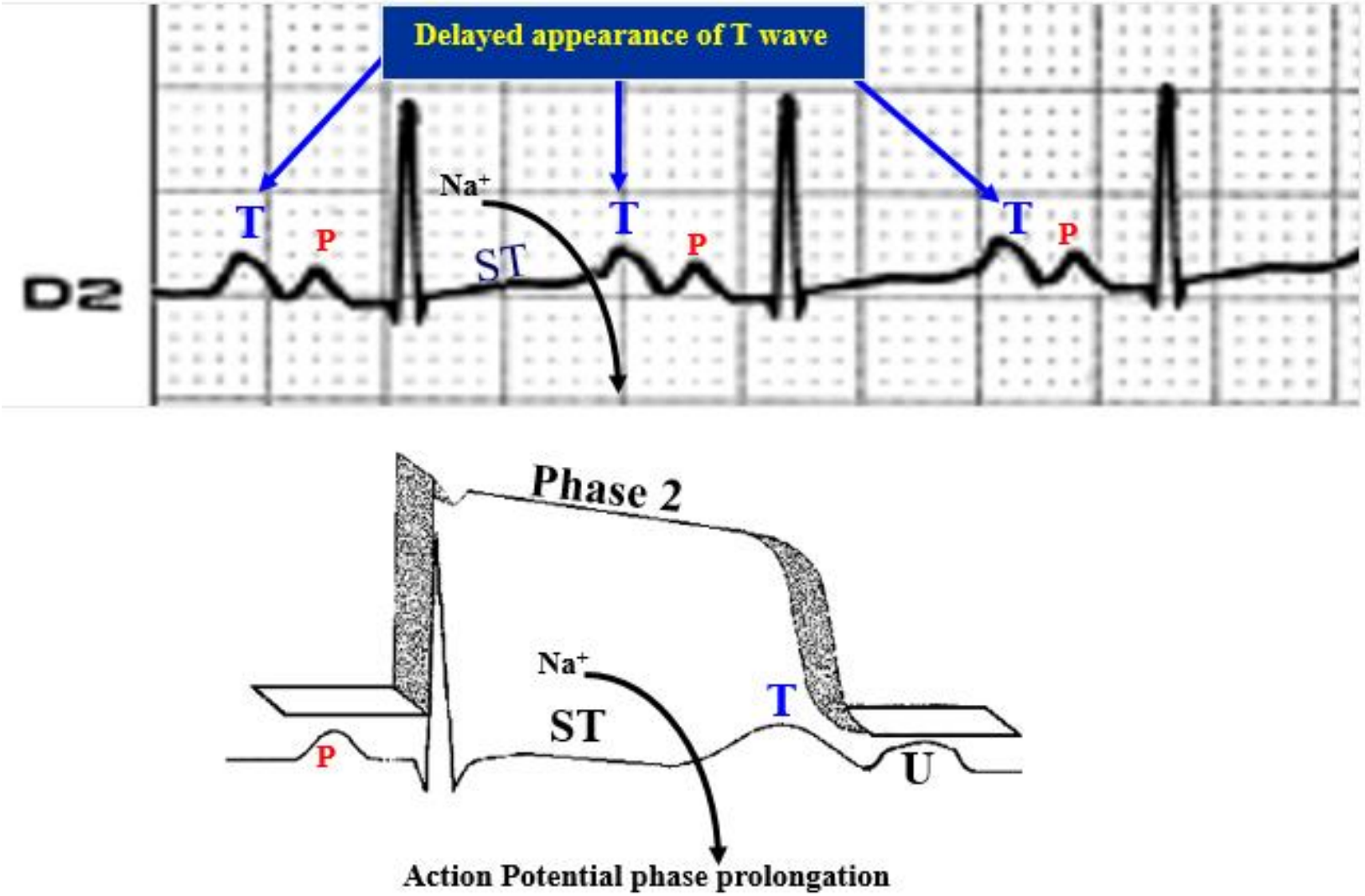


Delayed appearance of T wave





Characteristics of LQT3 variant, SCN5A mutation



In the upper part of the figure shows II with clear prolongation of the ST segment and late T wave appearance. In the lower part of the it shows a time correlation between the monophasic action potential of the rapid fiber and the ECG of a patient carrier of LQT3 variant. Check the phase 2 prolongation and concomitant greater ST segment duration.

LQT3 variant management

Pacemakers are particularly useful in babies or small children with 2:1 AV block or patients with documented TdP induced by bradycardic pauses in patients with LQT3. However, data indicate that cardiac events still occur in patients in high risk with implanted pacemaker. Because the most recent models of ICD include a pacemaker function (without defibrillators), they are not likely to be used in patients with LQTS. Pacemakers on their own could be used in patients in low risk with LQT3. DDD-ICDs should be considered in severe cases. Mexiletine, a sodium channel blocker may improve protection in this subset of patients. Mexiletine significantly shortens QT interval in patients with LQT3, but not LQT2. Patients with LQT3 shorten their QT intervals in response to an increase in HR much more than LQT2 patients and healthy controls. The LQT3 patients are more prone to benefit from Na^+ channel blockers and cardiac pacing, because they are in a greater arrhythmic risk (**Blaufox 2012**). Some specialists advise using a β-blocker combined with mexiletine in patients with LQT3. Mexiletine significantly shortens QT/QTc intervals in the LQT3 variant. Patients with ICD, with frequent appropriate shocks, show immediate clinical improvement, with the removal of proper shocks after adding mexiletine. Severe symptoms are common in children with LQT3 and are associated to longer QTc intervals. ICD implantation is associated with significant morbidity. Mexiletine shortens QT.

Flecainide (**Windle 2001**): Low oral dose of flecainide – a strong sodium channel blocker in an open state – shortens QT interval and normalizes T wave pattern in the LQT3 variant. Flecainide provides a rational basis at cellular and molecular level, which indicates that sodium channel blocker in open state could be useful for the pharmacological treatment of LQT3 (**Nagamoto 2000**).

Next table, shows the score created by Schwartz to estimate the probability of the presence of congenital LQTS. The score system considers the definitive diagnosis when it is greater than 3 (≥4). Nowadays, often the diagnosis could be made with certainty by DNA tests. The predictive power of the Schwartz and Keating criteria, using DNA tests as reference, allows determining a better diagnostic strategy. The existing clinical criteria has a good specificity in the identification of mutation carriers. However, its sensibility is too low for clinical use. The analysis of QT duration in isolation is more useful (QTc ≥430 ms), because its sensibility is much superior, although its specificity is barely acceptable. Genetic testing should be the test of choice (**Hofman 2007**).

Schwartz criteria for the diagnosis of Congenital Long QT syndrome

ECG findings (QTc)	Score
≥ 480 ms	3
460 to 470 ms	2
450 to 460 ms (in men)	1
Other ECG manifestations	Score
Torsade de pointes	2
T wave alternans	1
Notches in 3 T leads	1
Low HR for the age	0.5
From history	Score
Syncope before stress	2
Syncope without stress	1
Congenital deafness	0.5
Family history	Score
Relative with definitive LQTS	1
Unexplained SCD in first-degree relative <30 years old	0.5
Probability of LQTS by score	Score
Low	1

QT interval or electrical systole

Concept: time interval existing between the first recognizable part of QRS until the end, recognizable of T wave (the latter could be hard to determine). End of T wave is defined as the return of the wave to the baseline in the TP segment. Thus, we have to correct the QT interval duration (QTc), using the formula proposed by Bazett in 1920 (**Bazett 1920**), where the corrected QT is estimated by:

$$QTc = \frac{QT \text{ measured}}{\sqrt{RR}}$$

Bazett's formula has been criticized because it tends to provide an incorrect result in the cases of short QT intervals, and high heart rates tend to provide longer results than real. This lack of precision of Bazett's formula has encouraged the creation of new QT interval measurement methods, such as that of Fridericia, who used the cube root of RR (**Fridericia 1920**). QTcF = QT/3√RR and Framingham's method: QTc = QT + 0.154 (1-RR) and Hodges's formula: QTc = QT + 105 (1 + RR-1). None of the four formulas have proven to be clearly better than the rest. Bazett's formula is used for automatic analysis and in large clinical trials.

QT interval duration is inversely proportional to heart rate.

The normal range of the QT interval in adults varies between 350 ms and 440 ms. Shorter or longer values in the QT interval cause a tendency to potentially fatal ventricular arrhythmias.

Next table , correlates QT interval corrected according to the heart rate, using three formulas: Bazett, Fridericia, and Framingham.

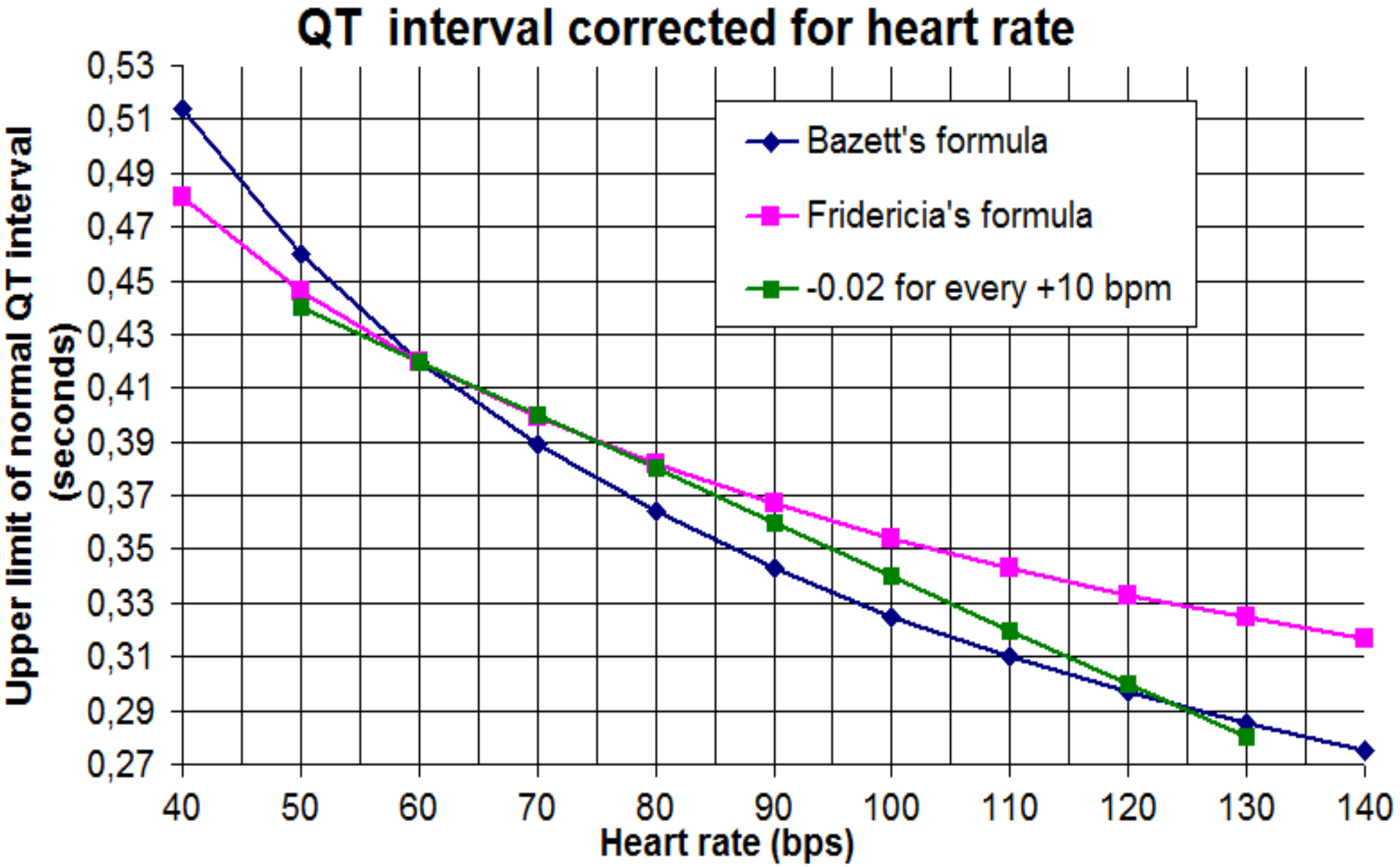


Figure: Upper limit of the normal QT interval, corrected according to the heart rate by the formulas of Bazett, Fridericia and 0.02 s subtracted from QT per every 10 bpm increase in heart rate. Until 0.42 s (≤420 ms) is considered a normal QTc in this diagram.

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