Mulher de 36 anos com intervalo QT longo familiar sintomático

Female 36 Years Old Carrying a Symptomatic Familal Long QT Syndrome

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Case Report

36-year-old woman. She mentions that in year 2005, when she was 28 years old, she presented sudden cardiac death event related to physical strain.
ECG1:, post-event, reveals characteristic pattern of long QT interval.
Family history: her father died of sudden cardiac death at 46 years of age.
After the onset of therapy with beta blockers (propranolol 40 mg/day) she remained asymptomatic during 8 years.
Two months ago, she presented two pre-syncope events related to physical strain while taking beta blockers in a low dose (the patient does not tolerate higher doses of beta blockers due to hypotension and bradycardia).
The last ergometer test was made 3 years ago, and it did not show effort-induced arrhythmia; however, the basal QTc interval was prolonged (480 ms) and after strain it was 680 ms (up to 6 minutes of recovery) with maximal heart rate of 130 bpm.
What is the suspected variant by the electrocardiographic pattern?
What is the more appropriate approach in this case?
Warm regards,
Raimundo Barbosa-Barros M.D,

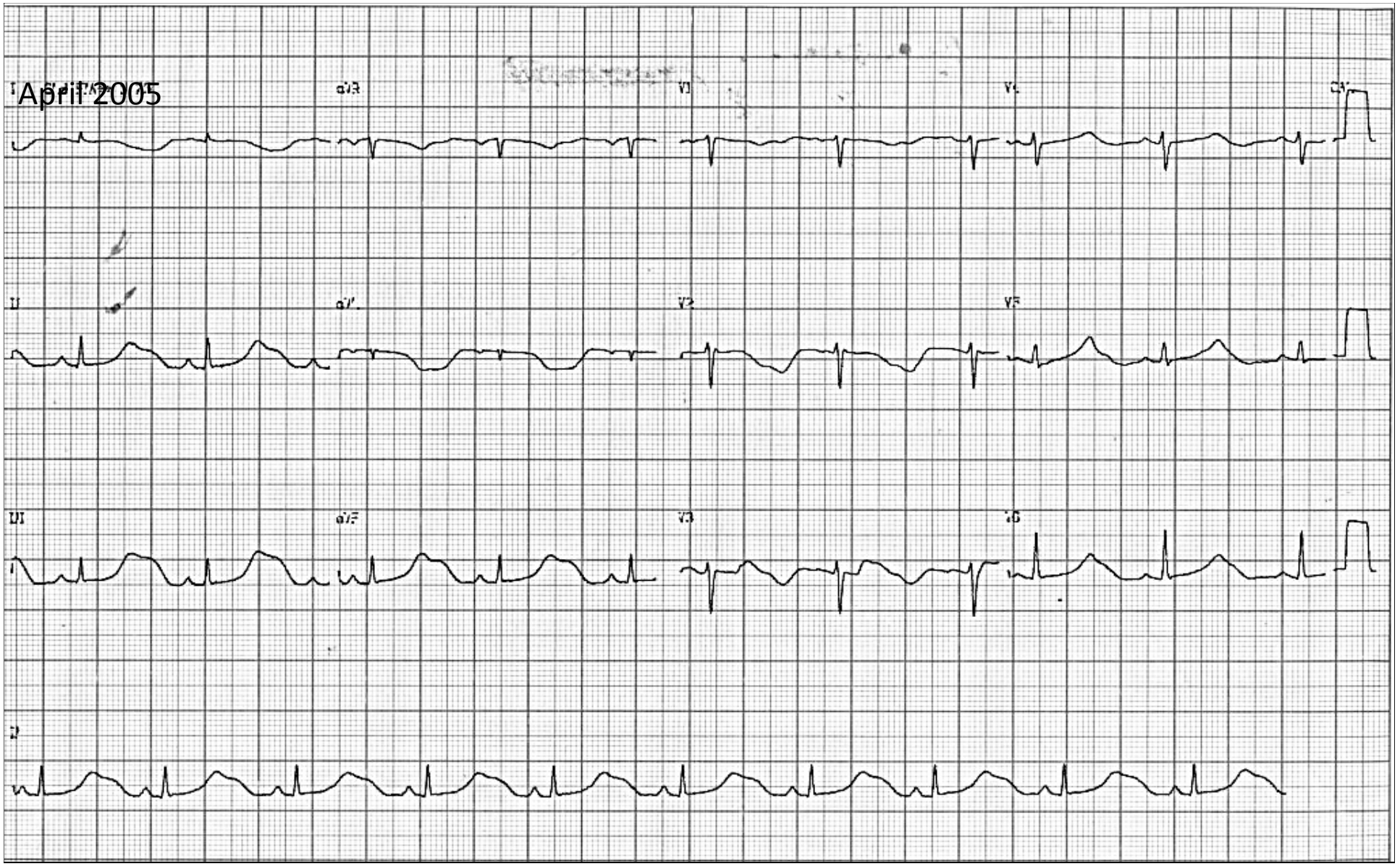
Portuguese

Mulher de 36 anos refere que no ano de 2005, quando tinha 28 anos de idade apresentara evento de morte súbita recuperada relacionada ao esforço físico.
ECG1 anexo pós evento revela característico padrão de intervalo QT longo.
Antecedentes familiares: Pai falecido de morte súbita aos 46 anos.
Após o início de terapia betabloqueante, (propranolol 40mg/dia) permaneceu assintomática durante 8 anos.
Há 2 meses apresentou dois episódios pré-sincopais relacionados com esforço físico na vigencia do fármaco beta-bloqueante a dose baixa. (A paciente não tolera doses mais elevadas de beta-bloqueante devido hipotensão e bradicardia.)
O último teste ergométrico realizado há 3 anos não mostrou arritmia esforço-induzida, porém o intervalo QTc basal estava prolongado (480ms) e no pós esforço de 620ms (até os 6 minutos da recuperação) com frequencia cardiaca máxima atingida de 130 bpm.

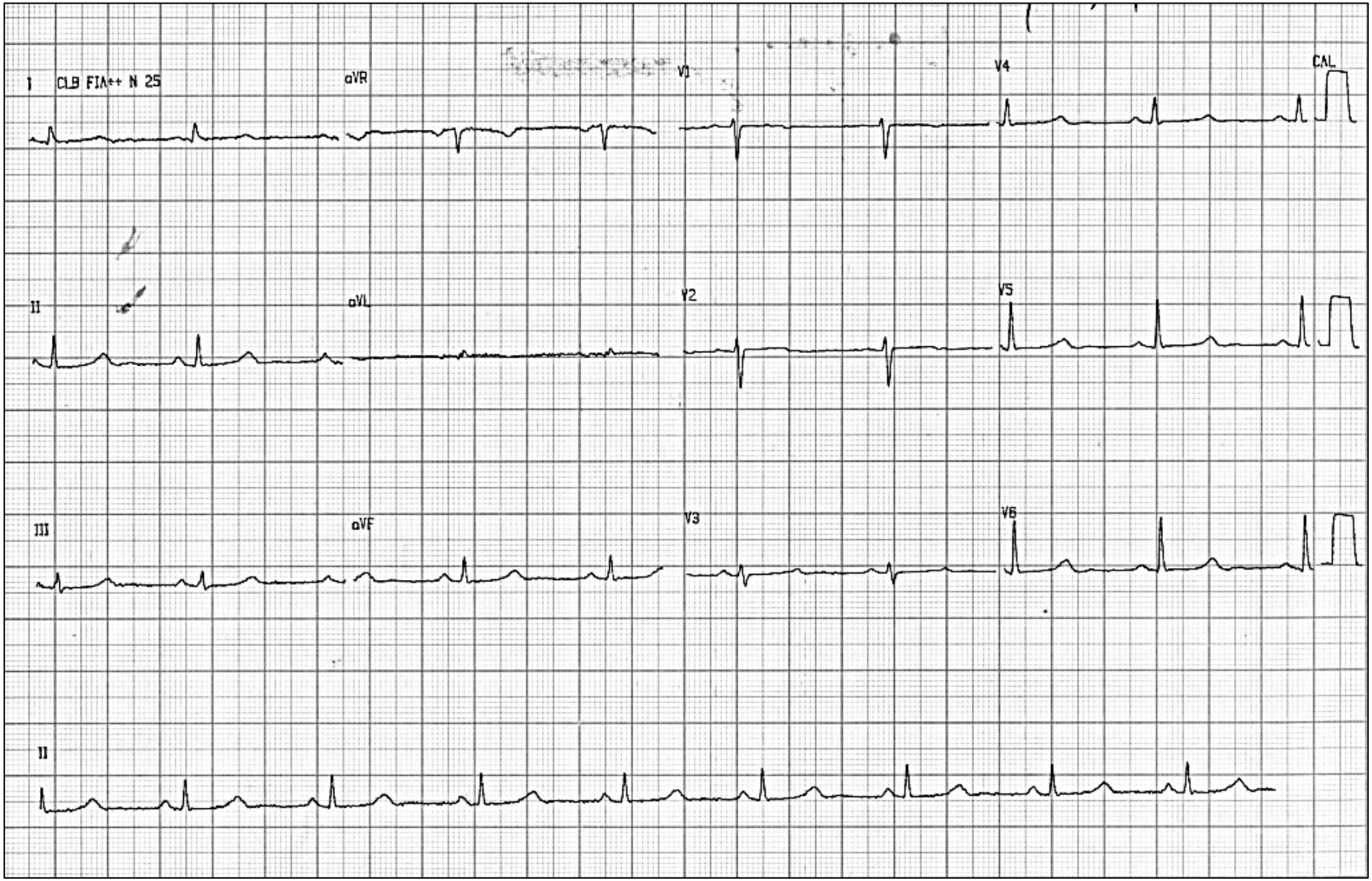
Qual a variante suspeita pelo padrão eletrocardiográfico?
Qual seria a abordagem mais adequada neste caso?

Um abraço a todos.

Raimundo **Barbosa-Barros M.D,**


April 2005

April 2009



Dear Andres,
The LQTS case Dr. Raimundo contributed is very entertaining.
1. The raw QT and the T wave morphology in both 2005 and 2009 are pretty much similar. The big difference is made by the giant U wave and T-U merge in 2005 ECG. The QUc was about 700 ms, reflecting a markedly prolonged repolarization. I wonder the 2005 ECG was taken post cardiac arrest. At that time, perhaps the patient's serum potassium level might be low.

2. The 2009 ECG showed QT prolongation with T wave patterns typical to type 1 LQTS (LQT1). A targeted gene mutation search on KCNQ1 is suggested.
Earlier this month, I predicted genotype for a LQTS family from Middle East. It only took three days from the time I read ECGs to the gene mutation identification and it was a novel homozygous mutation. The contributing doctor is working on family ECG screening...
In LQT1-3 arrhythmia comes in all-or-none fashion and the most typical one is TdP. I will leave therapeutic strategy to other LQTS experts.
Thank you very much!

Li
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Mao Tse-Tung
Li Zhang M.D.
Andrés Pérez-Riera M.D.
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长 城 留 念
Over The Great Wall of China
"Coca-Cola colonialism,"

What a difficult task Andrés!

QT is very prolonged on the first tracing with very abnormal T wave (except in VR lead, which is curious)

Qt is still long on the second tracing (> 44O msec)

Due to the clinical and familial history the diagnosis remains LQT syndrome even if the ECG is somewhat strange

No hypokalemia or hypocalcemia ? no other medication ? no Takotsubo ?

Otherwise I would say LQT2 but the true subtype need genetic analysis. I suppose you do not have.

Propanolol 40 mg daily is a very low dosing probably not enough for symptomatic LQTS

The safer would be to implant an ICD because of the possible previous cardiac arrest and because of syncope during exertion despite BB but if this was so simple ... the patient should have been already implanted 8 years ago the other possibility is to give larger dosing of BB (nadolol 80 mg daily)

I do not think that sinus node bradycadia or hypotension is a relevant problem at this step then an implantable loop recorder

Genetic analysis is very important, since LQT1 has an excellent prognosis once efficiently treated with BB

The tracing evokes rather LQT2 (notched T waves) but with a wide and ample T wave also suggestive of LQT1 in some aspects

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The ECG in 2005 is very abnormal with a markedly prolonged QT interval and T wave notching in the inferior leads. Would favor LQT2 or I_{kr} channelopathy. The markedly prolonged QT both in '05 as well as post exercise as well as recurrent sx on maximally tolerated beta blockers would favor defibrillator insertion. Some would suggest Left cardiac sympathectomy but I have given up on this mode of treatment as recurrences may be @50% over the long term and our data suggest that re enervation returns in time. See Scheinman Circulation)

Even with a defibrillator should be warned about exposure to QT prolonging drugs as well as prompt treatment to avoid excess body fluid losses (hypokalemia).

Final comments

By Andrés Ricardo Pérez-Riera **M.D.Ph.D.**

Given the increasing prevalence of LQTS and the associated risk of sudden cardiac death, primary care providers are likely to find themselves encountering challenging management decisions.

The mainstay of treatment for LQTS, unless there is an identifiable reversible cause, is lifestyle modification and beta-blocker therapy with the implantation of a cardioverter-defibrillator (ICD) in patients who have had a previous cardiac arrest and in those continuing to have symptoms despite beta-blockade.

Lifestyle modification comprises the following measures: (1)

Competitive sports or similar extreme exertion should be avoided. Possible exceptions could include golf, curling, cricket, billiards, or bowling. (2)

Even non-competitive swimming, especially for LQT1 patients, must be limited and, if performed, should be done under close supervision.

All patients must avoid other sympathomimetics and factors that may prolong the QT interval, such as medicines including quinidine, procainamide, sotalol, amiodarone, disopyramide, dofetilide, phenothiazines, tricyclic antidepressants, and methadone. (2;3)

Electrolyte losses due to vomiting, diarrhea, or excessive sweating should be replaced with electrolyte solutions in order to avoid hypokalaemia and hypomagnesaemia.

Patients with LQT2 should avoid startling acoustic stimulation such as alarm clocks 

Patients with confirmed congenital or acquired LQTS who have never had a cardiac arrest or experienced syncope, torsades de pointes, or ventricular tachyarrhythmias but who know of their condition through an incidental ECG finding or genotyping require pre-emptive management in order to reduce the risk of a potentially fatal cardiac event in the future.

In addition, all patients with congenital LQTS should be regularly monitored to assess the ongoing effectiveness of treatment and symptom control, as detailed under follow-up.

For the purposes of treatment, patients with congenital LQTS are classified as low- or high-risk. Low risk (probability of first cardiac event <49%) is defined as: men or women with LQT1 and QTc <500 ms; men with LQT2 and QTc <500 ms; women with LQT2 and QTc <500 ms; men with LQT3 and QTc <500 ms; women with LQT3 (irrespective of level of QTc prolongation). High risk (probability of first cardiac event 50% or higher) is defined as: men or women with LQT1 or LQT2 and QTc ≥500 ms; men with LQT3 and QTc ≥500 ms.(5)

Cardiac events may include syncope, ventricular tachyarrhythmias, torsades de pointes, or cardiac arrest.
As ventricular arrhythmias may arise during a state of high adrenergic tone, particularly increasing the occurrence of afterdepolarisations, beta-blockers are used to blunt adrenergic stimulation. Beta-blockers themselves do not shorten the QT interval, but their use is thought to prevent ventricular tachyarrhythmias.
High risk: corrected QT interval (QTc) >500 ms in men or women with LQT1 and LQT2 and in men with LQT3, and QTc >550 ms.
In LQT3 patients verified by genotyping, withholding beta-blockers is an option due to the high risk of bradycardia-induced ventricular arrhythmias in this group.
Low-dose beta-blockers are prescribed initially and titrated up as tolerated.
Dose adjustments may be required to avoid symptomatic bradycardia.
Options
Nadolol: adults: 40 mg orally once daily initially, increase according to response, maximum 320 mg/day
Or (we have not more nadolol in Brazil)

Propranolol: children: 1 mg/kg/day orally (immediate-release) given in 3 divided doses initially, increase according to response, maximum 8 mg/kg/day; adults: 30-160 mg/day orally (immediate-release) given in 3 divided doses; consult specialist for guidance on dose in neonates Or

Metoprolol: children: 1-2 mg/kg/day orally (immediate-release) given in 2 divided doses; adults: 50 mg orally (immediate-release) twice daily initially, increase according to response, maximum 300 mg/day;
Beta-blocker therapy should be continued unless contra-indicated or poorly tolerated.
As ventricular arrhythmias may arise during a state of high adrenergic tone, particularly increasing the occurrence of after depolarizations, beta-blockers are used to blunt adrenergic stimulation. Beta-blockers themselves do not shorten the QT interval, but their use is thought to prevent ventricular tachyarrhythmias.
Low-dose beta-blockers are prescribed initially and titrated up as tolerated.
Dose adjustments may be required to avoid symptomatic bradycardia.
In acquired LQTS where a reversible cause has been identified and treated, beta-blockers can be discontinued once the QT interval has normalized.

beta-blockers are widely reported to reduce the incidence of syncope and a SCD in patients with congenital LQTS.(6) Consistent with reports of a high sensitivity of patients with the LQT1 syndrome to adrenergic stimulation, greater than those with either LQT2 or LQT3 syndrome, (7) beta-blockers have been shown to reduce cardiac events very effectively in LQT1 patients.**(8)**

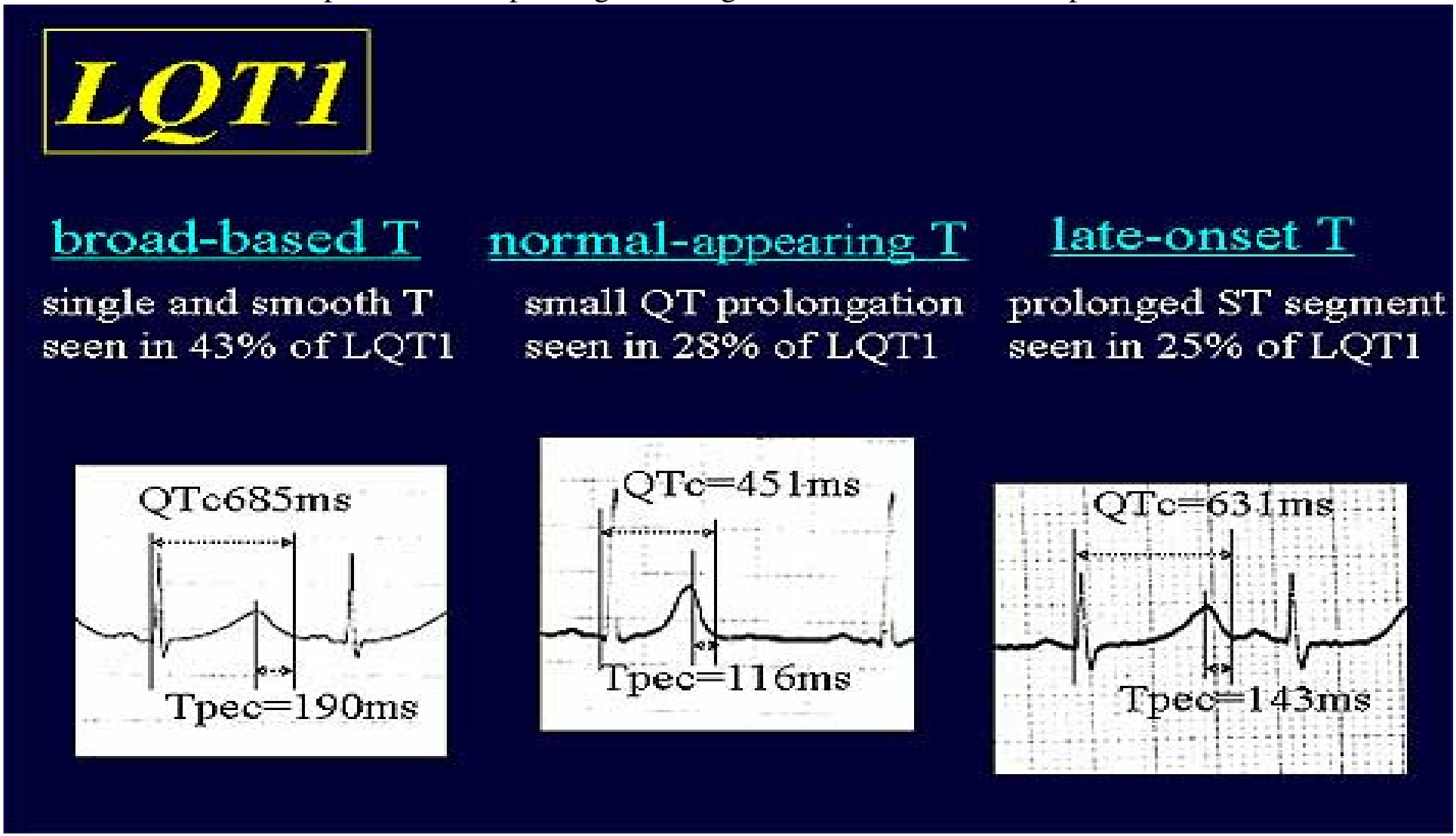
In patients with the Romano-Ward form of LQTS, cardiac events were reduced more in patients in whom beta-blockers caused a large decrease in corrected QT (QTc) dispersion.(9) In contrast, other clinical studies have shown that beta-blockers modified neither QTc interval nor QTc dispersion as measured with a 12-lead ECG(10) or an 87-lead body surface mapping system in the LQTS patients.(11)

Antzelevitch et al observed of little or no effect of therapeutic levels of propranolol (0.1 to 1 μmol/L) on the APD90 of the M cell in either the presence or absence of isoproterenol is in agreement with the latter observations. Nevertheless, the effects of isoproterenol to increase TDR and to produce spontaneous as well as PES-induced TdP were completely inhibited by propranolol in therapeutic concentrations. Their data point to a diminution of TDR during normal sympathetic tone or prevention of an augmentation in TDR in response to strong sympathetic stimulation as the basis for the antiarrhythmic effectiveness of propranolol. TDR under these conditions is measured by the difference in repolarization time of the epicardial and M regions; the interval between the peak and end of the T wave has been shown to provide an ECG index of this parameter. (12;13;14) This index may prove useful in discerning between the actions of propranolol to reduce TDR already augmented by normal sympathetic tone or its actions to prevent accentuation of TDR after a strong sympathetic discharge.

What is the suspected variant by the electrocardiographic pattern? Answer LQT1

Japanese researches (Minoru Horie) descried three patterns of T wave in LQT1 variant:

1. The broad-based T pattern defined as a single and smooth T was seen in 43% of patients,
2. The normal appearing T pattern of a small QT prolongation was seen in 28% of patients
3. The late-onset T pattern with a prolonged ST segment was seen in 25% of patients.



LQTS is caused by distinct mutations in different genes, so the phenotype differs depending on the genotype. In the experimental model, it has been shown that the interval between the peak and the end of the T wave (Tpe) on transmural ECG reflects transmural dispersion of repolarization (TDR), which is amplified by beta-adrenergic stimulation in the LQT1 model. Cardiac events are more frequently associated with enhanced adrenergic factors in LQT1. Minoru Horie et al. sought to identify the genotype-specific changes in body surface 12-lead ECGs, to determine whether Tpe in 12-leads ECG reflect TDR and whether exercise stress testing can help to differentially diagnose LQT1 and LQT2. They studied 51 patients with LQT1 variant, 31 patients with LQT2 and 35 healthy control group. The parameters of repolarization studied were **T wave morphology, QT, QTc, Tpe, and Tpec**. The clinical characteristics of the study population are shown in Figure 1 next slide.

In LQT1, syncope was induced by exercise, and 30 of the patients were symptomatic.

In LQT2, 17 of the patients were symptomatic and syncope was induced by sleep, auditory stimulation, and bradycardia. Baseline ECG data showed that QTc and Tpec were longer in the LQT1 and LQT2 groups compared to control (510 ms, 520 ms, 402 ms, respectively; and 142 ms, 195 ms, 99ms, respectively).

On exercise, in LQT1 the QTc is lengthened to 590 ms from 452 ms at baseline, and the Tpec is lengthened to 258 ms from 108 ms at baseline. The end of the T wave is not clearly distinguishable because of this lengthening.

In LTQ2, the bifid pattern is clearly seen on exercise. Figure 2 illustrates the change of T wave pattern in LQT2 group..

In LQT1, the QTc is longer on exercise compared to baseline (599 ms vs 511 ms, respectively), whereas there is no change in LQT2. Tpec is longer in LQT1 on exercise compared to baseline (215 ms vs 142 ms), whereas it is decreased on exercise in LQT2 (163 ms vs 197 ms).

Figure 1

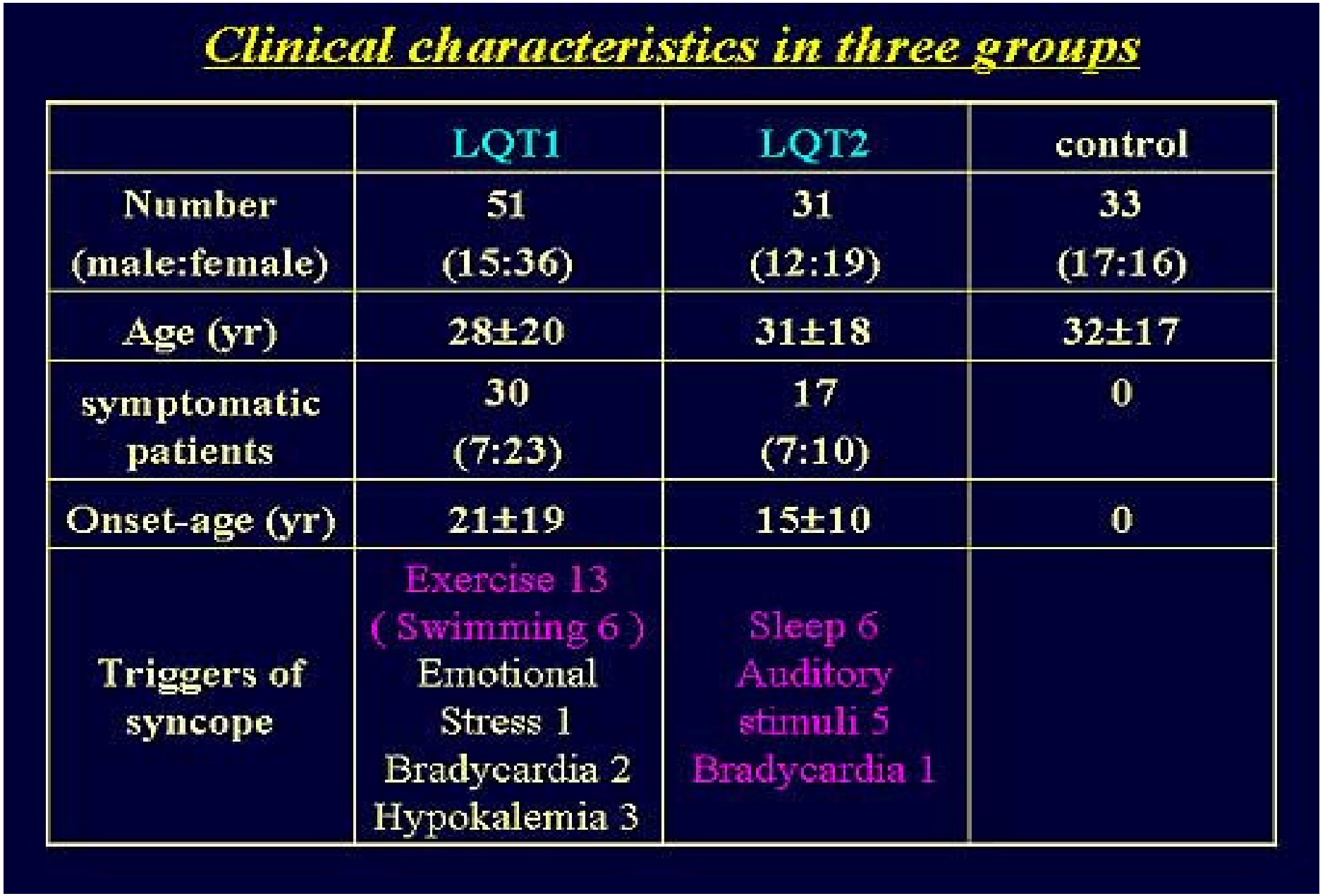

Clinical characteristics in three groups
LQT1
LQT2
control
Number (male:female)
51 (15:36)
31 (12:19)
33 (17:16)
Age (yr)
28±20
31±18
32±17
symptomatic patients
30 (7:23)
17 (7:10)
0
Onset-age (yr)
21±19
15±10
0
Triggers of syncope
Exercise 13
(Swimming 6)
Emotional Stress 1
Bradycardia 2
Hypokalemia 3
Sleep 6
Auditory stimuli 5
Bradycardia 1

Figure 2

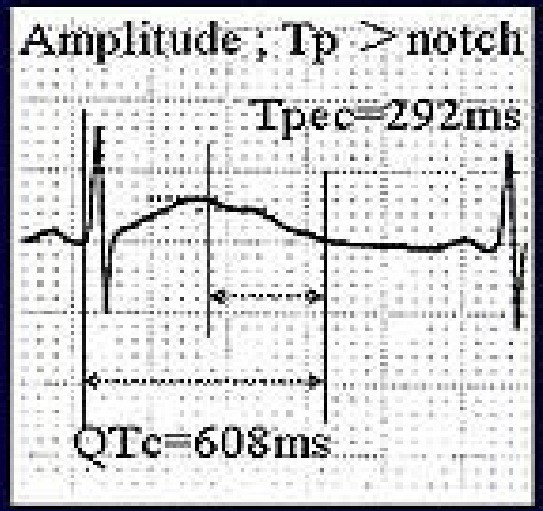
LQT2

Broad-based T

thought to be typical in LQT1, was also seen in 34% of LQT2 at rest

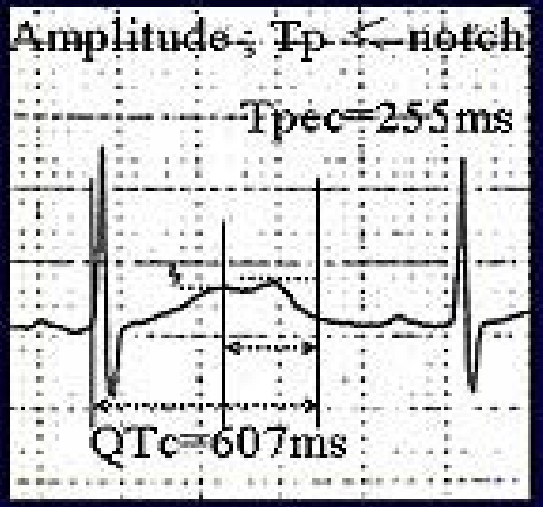
Bifid T with notchS

bifid T with a small notch seen in 33% of LQT2



Bifid T with notchL

bifid T with a larege notch seen in 25% of LQT2



At baseline, LQT1 and LQT2 have three types of T wave patterns. Broad-based T pattern is seen in 40-50% of LQT1 and 30% of LQT2 patients, so differentiation is not possible. However, exercise stress does differentiate the two genotypes. LQT1 has morphologic changes of the T wave into a broad-based T and there is significant QTc prolongation mainly due to Tpec prolongation with negative Tpe/RR slope.
In LQT2, exercise produced a prominent notch on T wave with no significant change in QTc and Tpec.
The change of T wave pattern during exercise in the LQT1 and LQT2 groups we can see in figure 3.
Horie and colleagues conclude that exercise testing is useful to facilitate genotyping of most common variants of the LQTS. Exercise induces genotype-specific changes in the T wave pattern. Exaggerated prolongation of the QT interval in LQT1 was primarily due to an increase in Tpe, presumably reflecting TDR Tpe interval increases during exercise in LQT1 but not in LQT2, which may partially account for the finding that fatal cardiac events in LQT1 are more often associated with exercise.(15). Patients with LQTS become symptomatic in adolescence, but some become at age of ≥20 years such as the present case. Since it remains unknown whether clinical features of symptomatic LQTS patients differ depending on the age of onset, Sakaguchi et al (16) aimed to examine whether triggers for cardiac events are different depending on the age in genotyped and symptomatic LQTS patients. The authors identified 145 symptomatic LQTS patients, divided them into three groups according to the age of first onset of symptoms (young <20, intermediate 20-39, and older ≥40 years), and analyzed triggers of cardiac events (VT, syncope, or cardiac arrest). The triggers were divided into three categories:

1. Adrenergically mediated triggers: exercise, emotional stress, loud noise, and arousal;
2. Vagally mediated triggers: rest/sleep; and
3. Secondary triggers: drugs, hypokalemia, and AV block.

In the young group, 78% of the cardiac events were initiated by adrenergic triggers and 22% were vagally mediated, but none by secondary triggers. The adrenergic triggers were significantly lower in the intermediate group. The secondary triggers was significantly larger in the older group than in the other two groups (0% in young vs 23% in intermediate vs 72% in older.). Concerning the subdivision of secondary triggers on the basis of genotype, hypokalemia was only observed in LQT1, drugs mainly in LQT2, and AV block only in LQT2. Arrhythmic triggers in LQTS differ depending on the age of the patients, stressing the importance of age-related therapy for genotyped LQTS patients.

The severity of LQTS in adulthood can be risk stratified with information regarding genotype, gender, QTc duration, and history of cardiac events. Beta-blockers effectively reduce but do not eliminate the risk of both syncopal and life-threatening cardiac events in adult patients with mutation-confirmed LQTS.(17)
The phenotypic expression of LQTS is time dependent and age specific, warranting continuous risk assessment in affected patients. Furthermore, the biophysical function, type, and location of the ion-channel mutation are currently emerging as important determinants of outcome in genotyped patients. These new data may be used to improve risk stratification and for the development of gene-specific therapies that may reduce the risk of life-threatening cardiac events in patients with this inherited cardiac disorder.(18)
Our dearest " cleaver sister" and friend Dr Li Zhang observed fourth ECG types of repolarization in LQT1 variant (19):

1. **Infantile ST-T wave:** observed in children aged 2 months to 2 years. eventually fast HR and RV dominance. A short and ill-defined ST segment merged immediately with the T-wave upslope, giving the appearance of a diagonal line to the T-wave upslope. Bifid T waves are frequent, with the second component producing the peak of the T wave in all leads. The T-wave downslope is steep. Frequently, the T wave has broad-based, is peaked, and asymmetrical. The QTc interval is from 450 to 490ms.

2. **Broad-based T wave:** is a single, smooth, broad-based T wave that is present in most leads, mainly evident in the precordial leads. The absence of a distinct T-wave onset enhanced the broad-based appearance. The QTc is from 450 to 530ms.

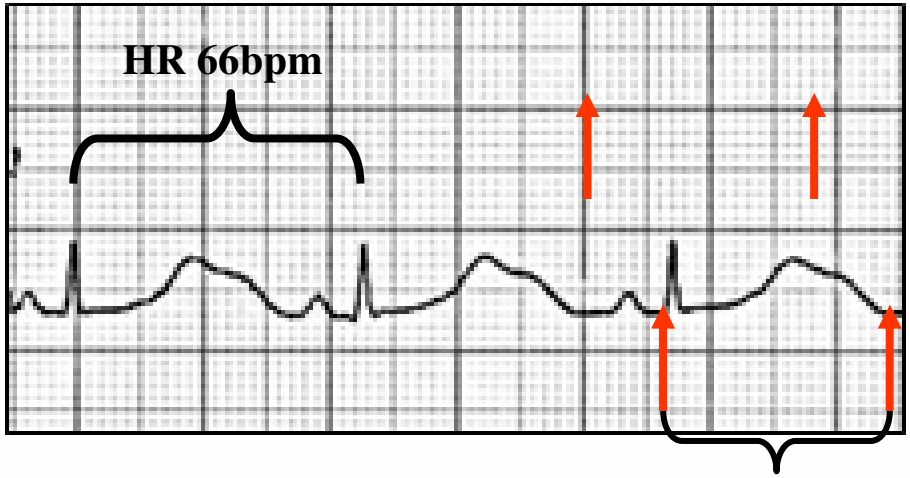
3. **Normal-appearing T wave:** Normal T-wave shape, QT form 420ms to 490ms.

4. **Late-onset normal-appearing T wave:** "like LQT3 variant" prolonged ST segment with late onset T wave and normal shape. QTc is from 450 to 530ms.

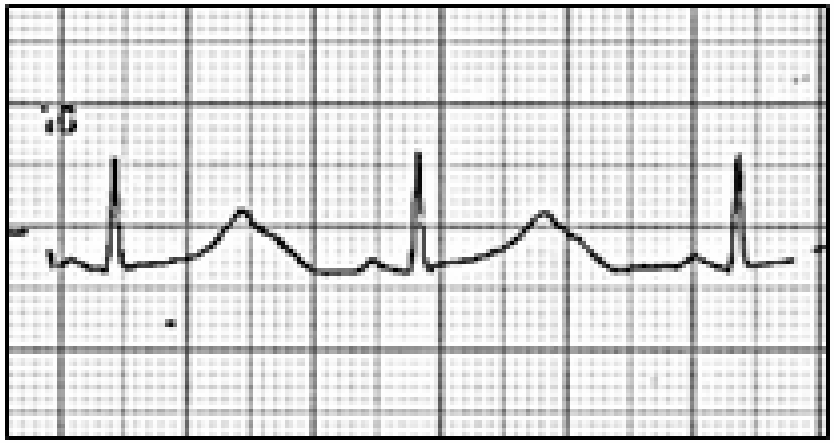
April 2005

The present case.

DII



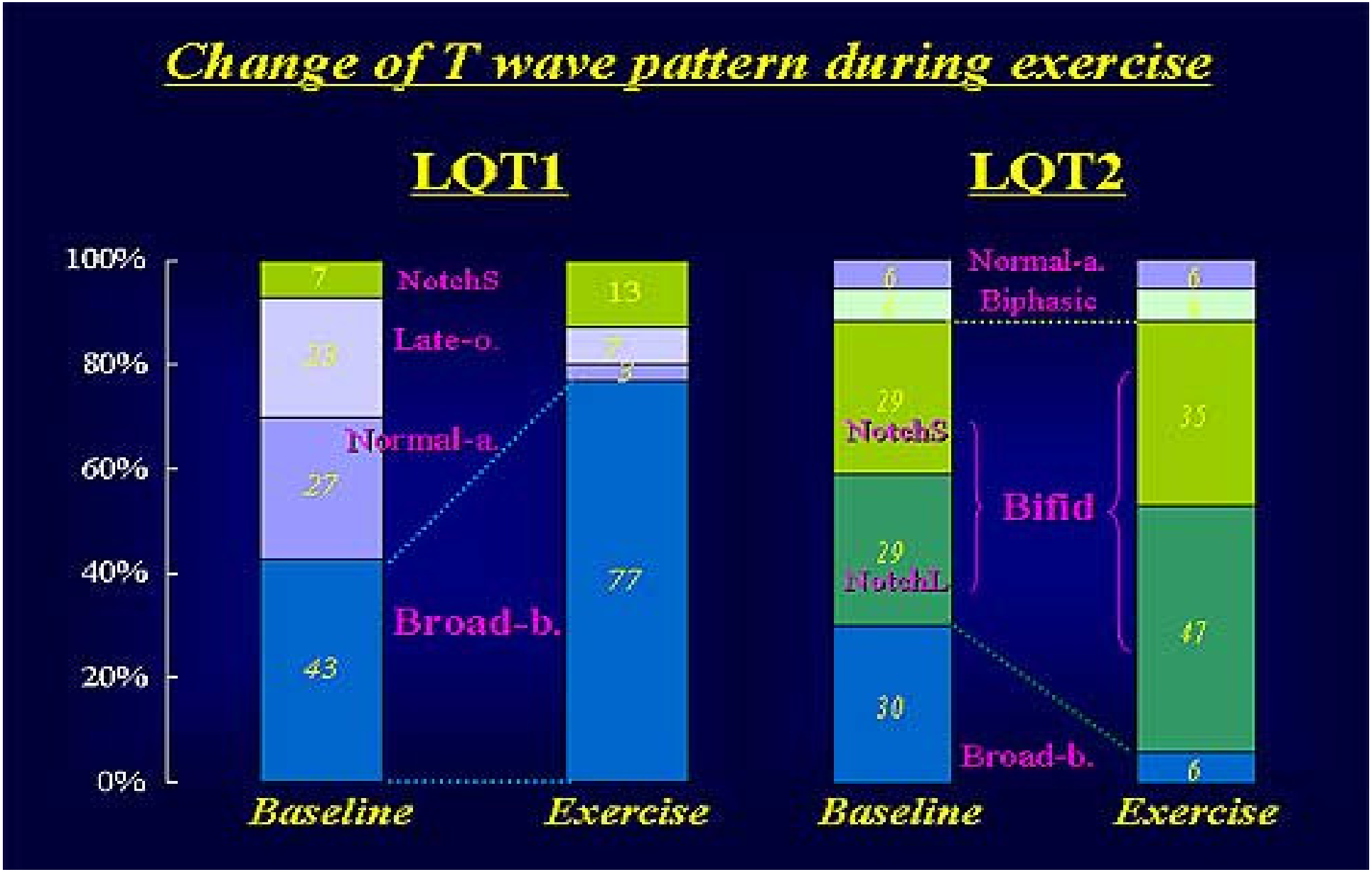
V6



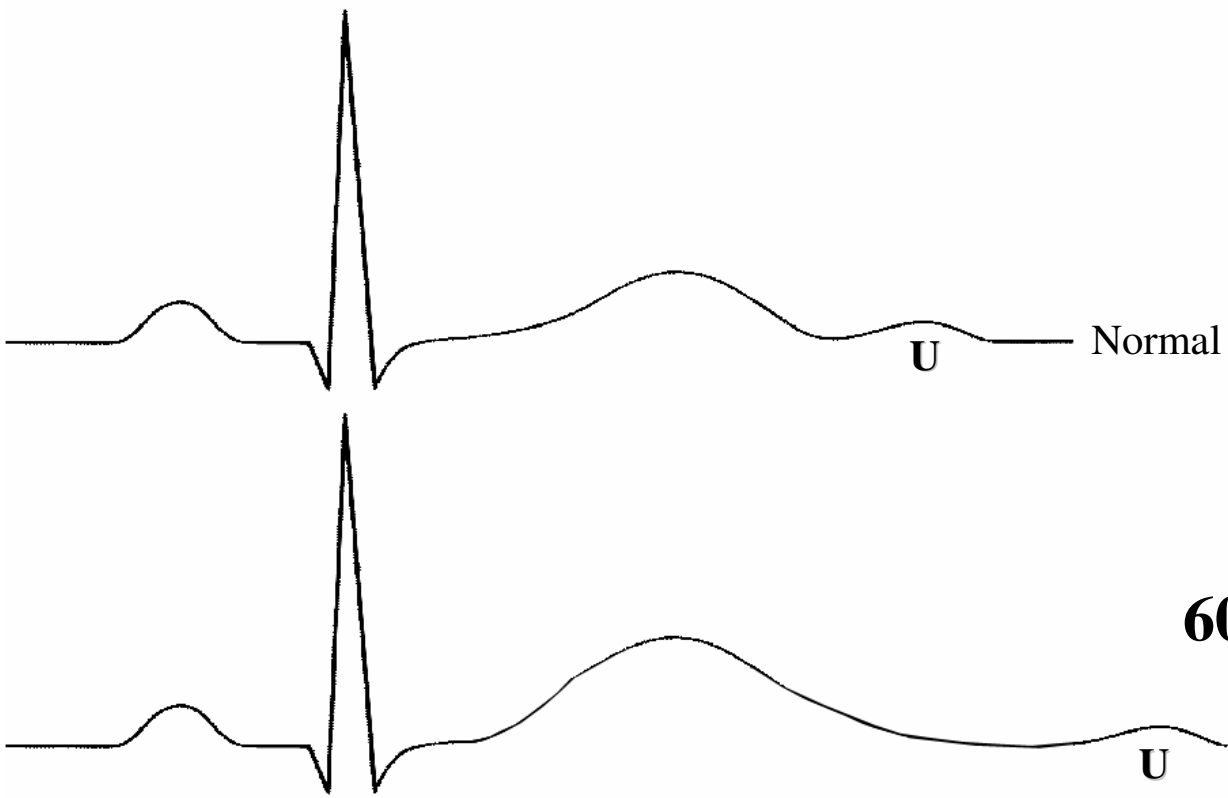
Broad-based prolonged T waves. QT = 700ms

The present case is a mix of type 1 and type 2 of Zhang LQT1 classification(19) because we observe a bifid pattern (infantile ST-T wave) and Broad-based T wave

Figure 3


Change of T wave pattern during exercise
LQT1
LQT2
100%
80%
60%
40%
20%
0%
7
NotchS
13
23
Late-o.
7
3
Normal-a.
27
77
Broad-b.
43
Baseline
Exercise
6
Normal-a.
6
Biphasic
29
NotchS
35
Bifid
29
NotchL
47
30
Broad-b.
6
Baseline
Exercise

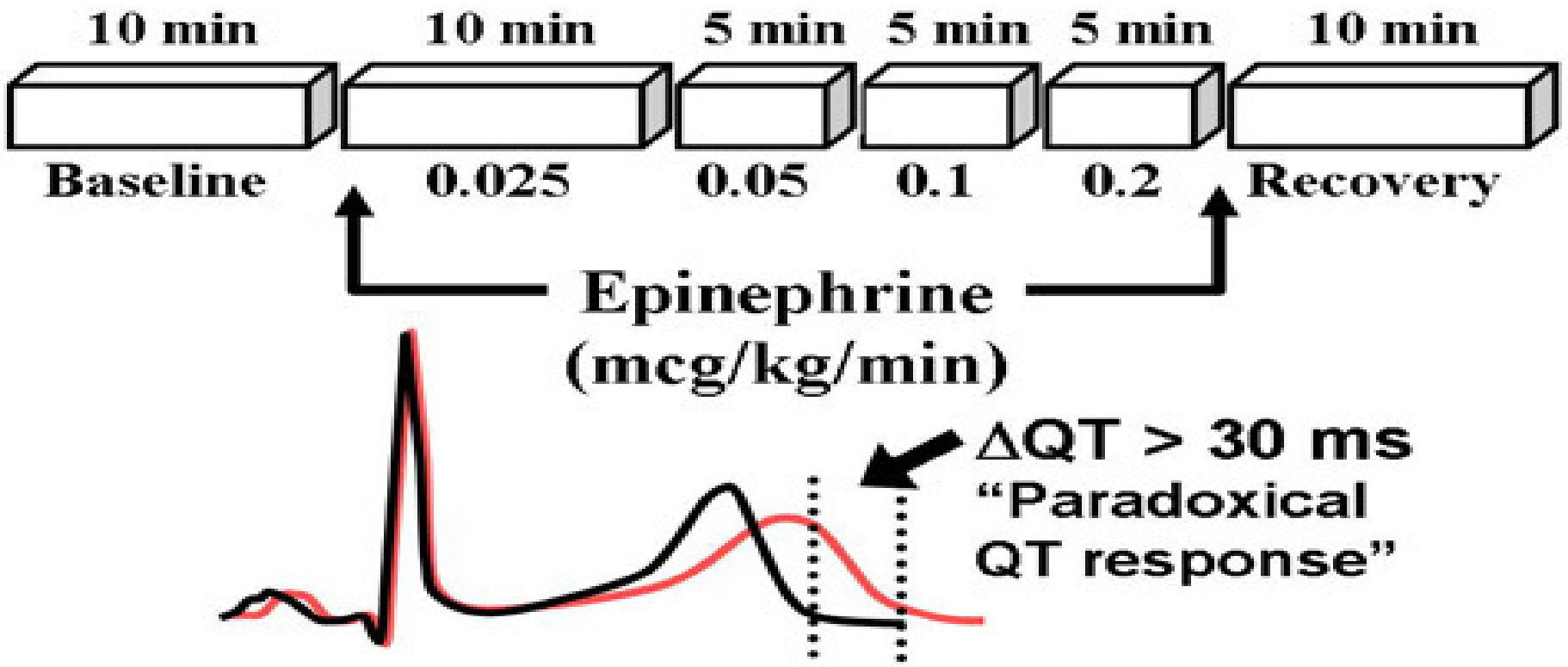
Characteristics of LQT1 variant or kvLQT1 defect



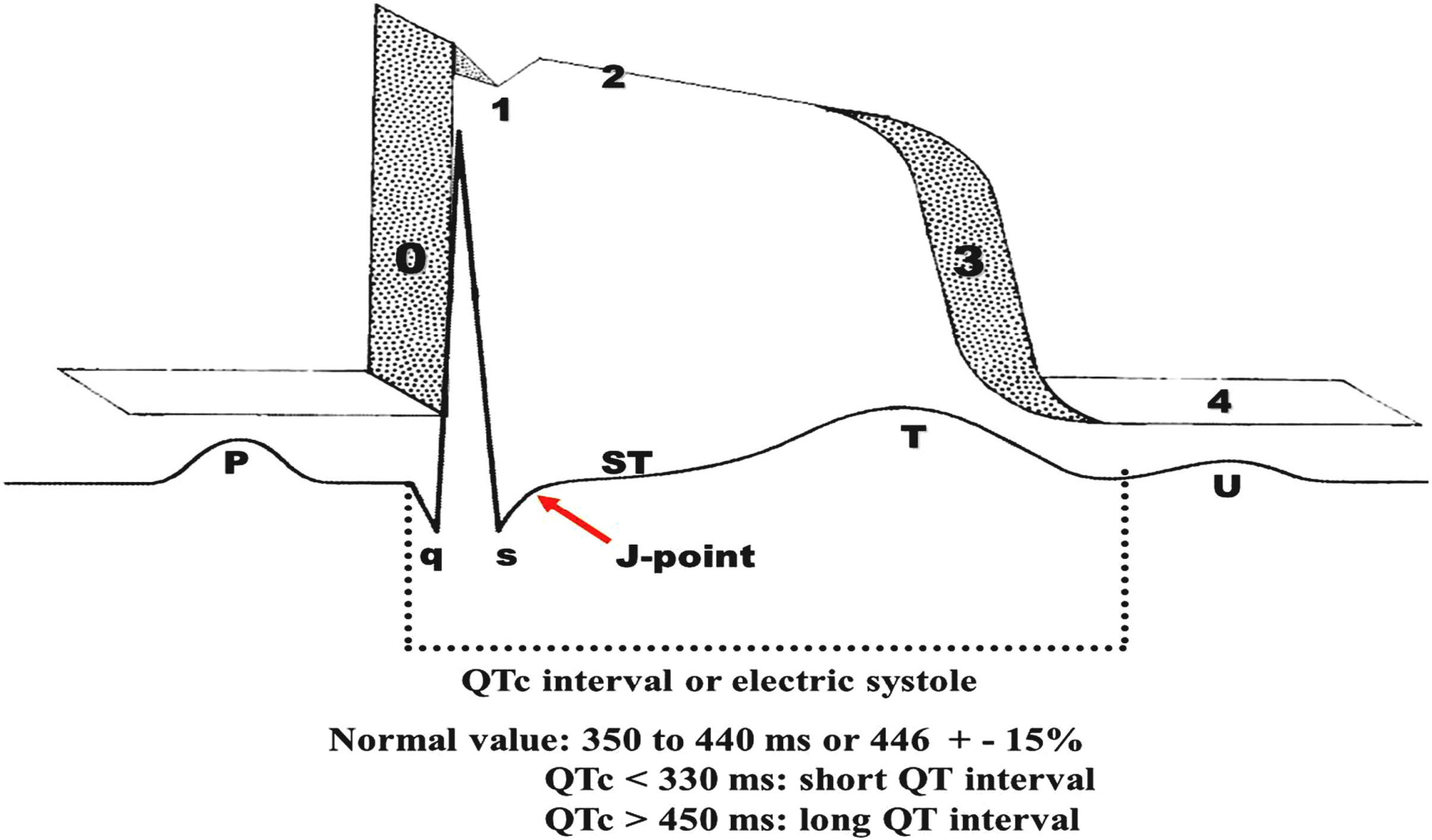
Events triggers: *Exercise, especially swimming*

60% of total

1. **Broad-based prolonged T waves.**
2. **Moderate HR dependence of QT interval.**
3. **Mutation on Short arm of chromosome 11.**
4. **Mutation: 11p15.5.**
5. **Affected channel in the action potentialAP: I_{ks} delayed rectifier potassium current.**
6. **Single variant with high % of events during exercise or swimming.**



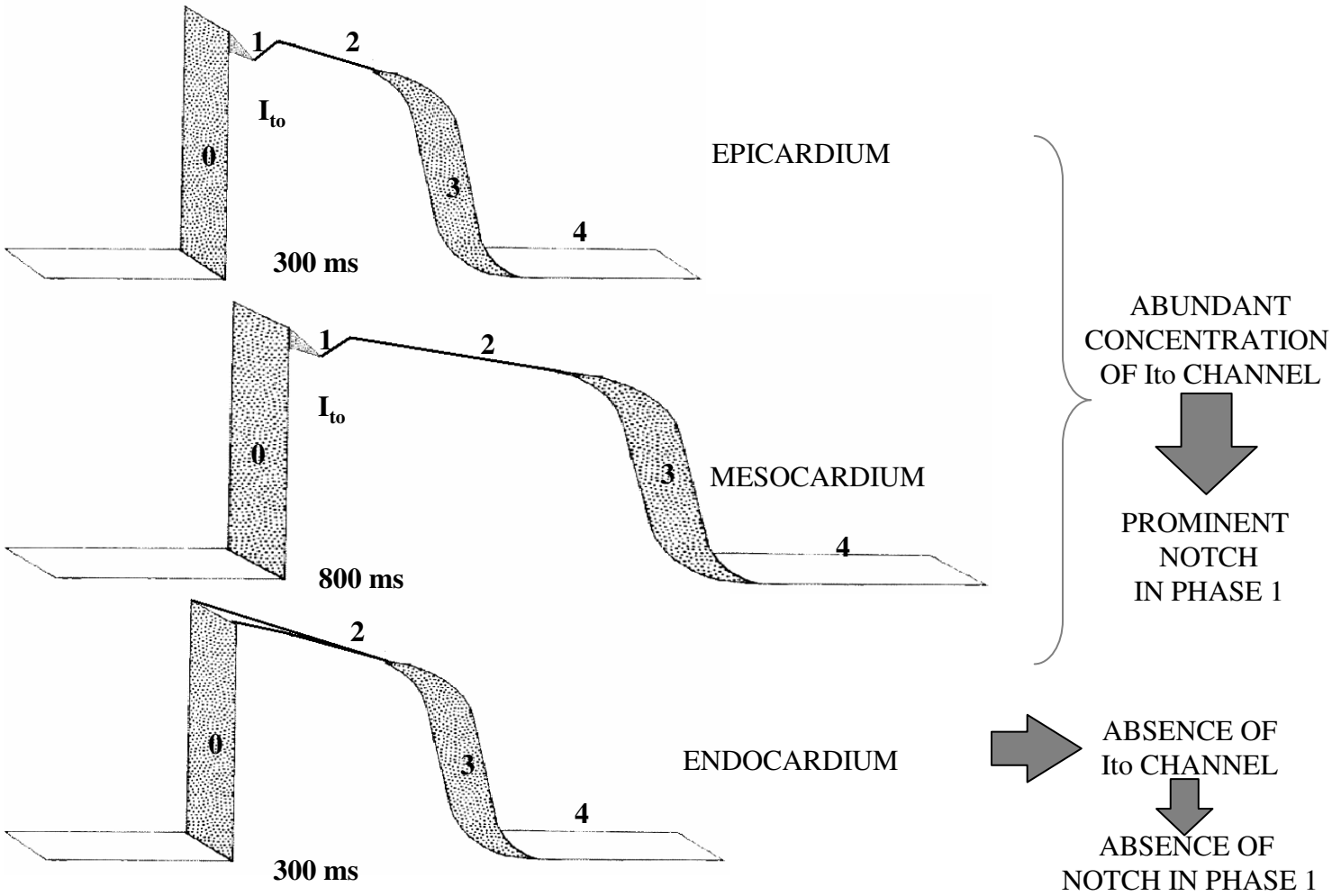
The Mayo Epinephrine QT Stress Test (Mayo Clinic Proceedings 2002) and demonstrated that paradoxical lengthening of the absolute QT interval during low-dose epinephrine infusion has 75% positive predictive value and 96% negative predictive value with respect to LQT1 This clinical diagnostic test is now used in heart rhythm centers throughout the world in an effort to unmask patients with concealed LQT1.



Representation of minimal and maximal normal values of QTc interval and its correlation with monophasic action potential.

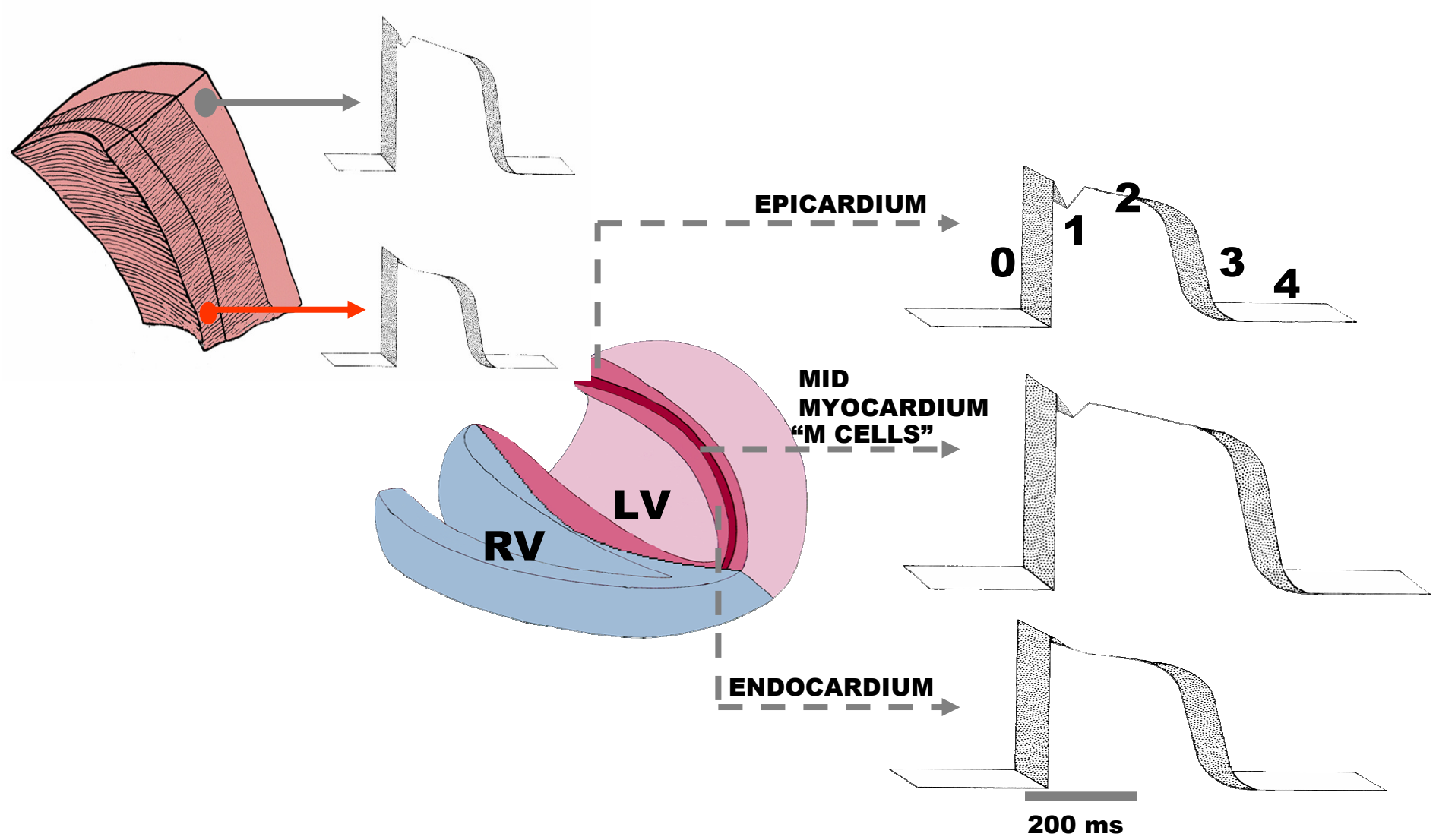
QTc values < 330 ms are considered short QT interval. Values of QTc > 450 ms are considered long QT intervals. Normal values of QTc are between 350 to 440 ms or 446 + - 15%.

Epicardium, mesocardium and endocardium: heterogeneity in ventricular wall thickness

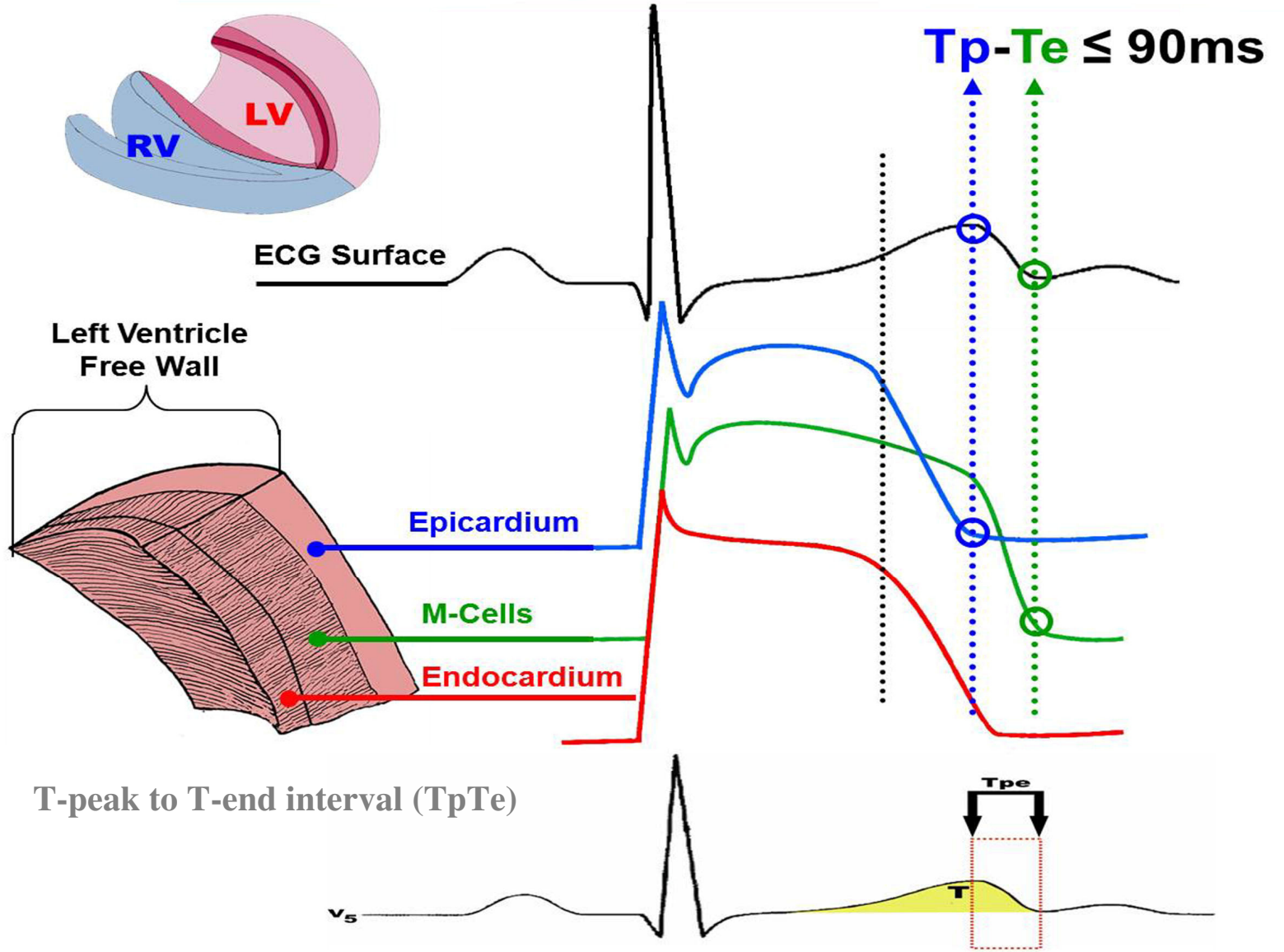


Outline of action potential in ventricular wall thickness. Differences in epi, meso and endocardium action potential profile and duration. The heterogeneous character of action potential is clearly observed in the 3 areas.

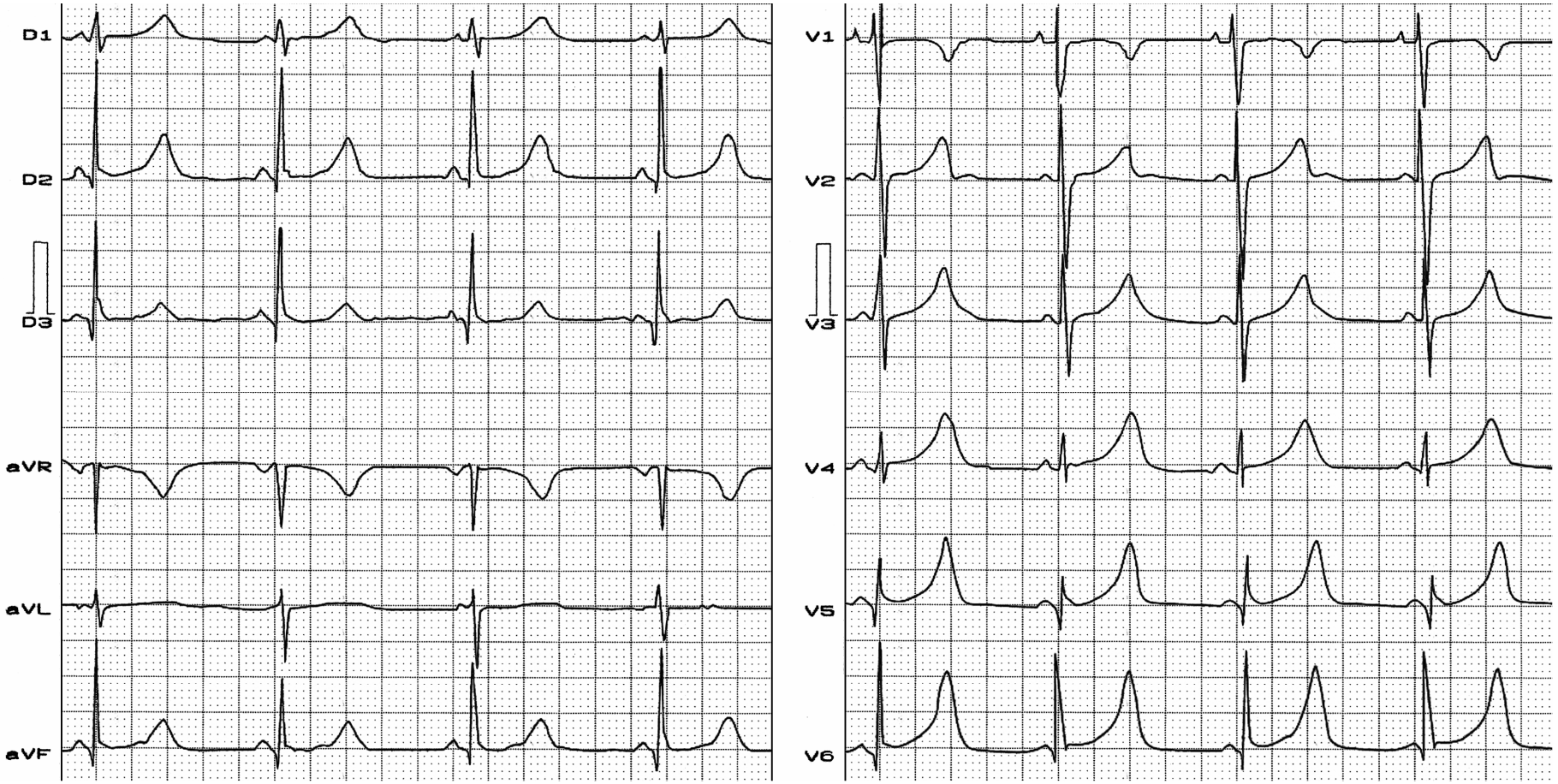
Action potential of ventricular contractile cells in wall thickness: epicardium, mesocardium and endocardium: heterogeneity.



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



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 the Tpeak/Tend interval (Tpe) is 94 ms in men and 92 in women when measured in the V5 lead. Tpe prolongation to values ≥120 ms is associated to a greater number of events.



ECG from a patient with a LQT1. Typical wide-based T-waves with a large amplitude are observed.

ECG for LQT1

Resting ECG for LQT1. Should be undertaken in all suspected cases.(20)

QT interval and corrected QT interval (QTc) should be assessed.

T-wave morphology (monophasic or multiphasic) should be assessed.

QT interval is measured from onset of the initial wave of the QRS complex to where the T wave returns to the isoelectric baseline.

QTc calculated using Bazett's formula: QT divided by the square root of the RR interval, where the RR interval is the interval between each QRS complex (ideally that immediately preceding the QT interval and averaged for 3 to 5 complexes). All measurements in seconds.

prolonged QT intervals associated with a broad-based T wave.

ECG for LQT2

low-amplitude and notched T waves

ECG for LQT3

long ST segments with a late-appearing T wave resulting in a long QT interval

ECG for hypokalaemia and hypomagnesaemia ST depression, flattened T waves, prominent U waves, and prolonged QT interval in hypokalaemia; ECG changes of co-existing hypokalaemia in hypomagnesaemia

ECG for hypocalcaemia isolated prolongation of the QT interval

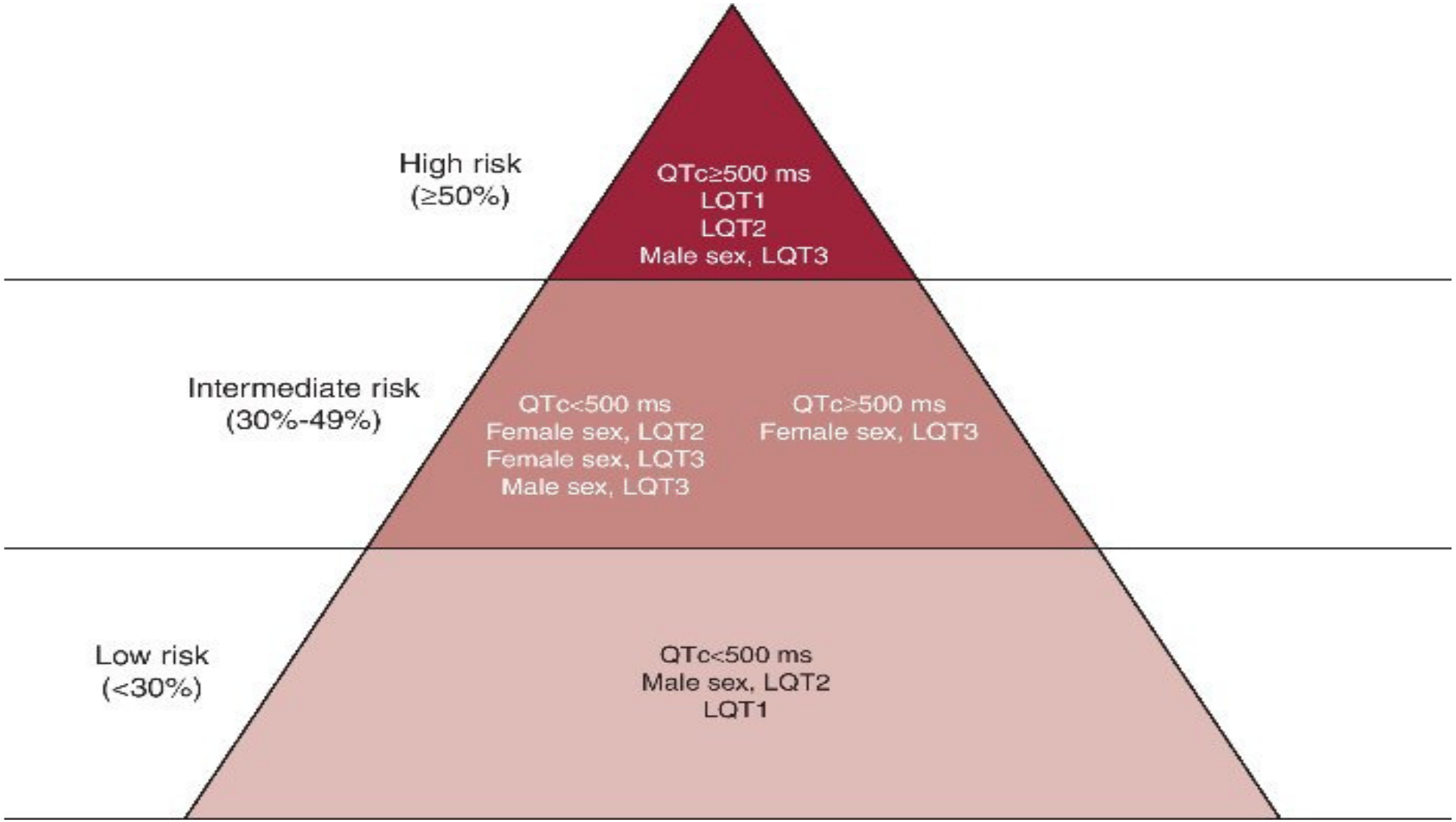
ECG for complete AV block sinus rhythm with normal atrial rate (represented by P-wave rate), no relationship between P waves and QRS complexes, widening of QRS complex, ventricular rate (represented by QRS complex rate) <50 bpm

serum potassium hypokalaemia

serum magnesium hypomagnesaemia

serum calcium hypocalcaemia

Testes stable-for Long QT syndrome
Holter monitor intermittent QT and corrected QT interval prolongation associated with ventricular arrhythmias
exercise tolerance test QT and corrected QT interval prolongation
echocardiography assessment of regional wall motion and valve function
genetic testing mutations in the KCNQ1 gene in LQT1, mutations in the KCNH2 gene in LQT2, mutations in the SCN5A gene in LQT3
adrenaline (epinephrine) test QT and corrected QT interval prolongation



Risk stratification in Long QT Syndrome, according to the QTc interval duration, genotype, and gender. QTc, corrected QT. Reproduced with permission from Priori et al.(5)

Value of QT interval:

Defined as the interval that extends from the onset of QRS until the end of the T wave. It is measured in leads II, V5 and V6, considering a proper value as the one that is greatest. By using simultaneous multichannel leads, the QT interval can be measured since the earliest onset of the QRS complex in any lead, until the end of the T wave, where the slope of the descending limb joins the baseline in any lead, being careful not to include the U wave by mistake. In non-simultaneous ECGs, it is advised to measure in the V3 lead, because this one is perpendicular to the axis of U in the FP (21).

In the cases where the RR intervals are irregular, we should measure in three successive cycles and estimate the average.

More recently introduced formulas for an adjustment of the QT interval as a linear function or RR power or heart rate for adults and for children are efficient to remove the HR dependence of adjusted QT, and they are clearly preferable to both Bazett and Fridericia's formulas. QT adjustment made by Bazett's formula underestimates QTc values when the heart rate increases(22)

Many formulas have been proposed to adjust the QT interval for HR. The one most used is Bazett's formula (23) proposed in 1920 from a plot of QT intervals measured in 39 young individuals, where the value of QTc is obtained from dividing the QT interval measured in seconds per square root of RR in seconds.

Bazett's formula.

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

For the female gender and in the age range between 50 and 79 years of age, Bazett's formula is inappropriate to test new drugs or other applications (24).

The formula introduced by Fridericia (25) also in 1920, uses the cube root of RR.

In both genders, and in people older than 40 years, Bazett's formula leaves a strong residual positive correlation (r=0.32) and the Fridericia formula leaves a negative correlation (r = -0.26 to -0.32) with HR and adjusted QT values may be substantially wrong, particularly when HR is high. (26). During sleep, by the predominance of vagal tone, the QT interval prolongs 18 ms at a HR of 60 bpm and 21 ms at a HR of 50 bpm, in comparison to a state of being awake (27).

Sagie et al (28) developed a method, studying more than five thousand adults between 28 and 62 years of age from a cohort from the Framingham study. The authors prepared a table for both genders, where they estimate the average values of QT expected for several lengths of the RR cycle expressed in seconds and heart rates. The method consists of subtracting 0.02 sec (2 ms) from QT in seconds for every increase of 10 bpm in heart rate. If the HR is not too high or low, the upper limits of the QT interval may be grossly estimated taking QT = QTc in a heart rate of 60 bpm, and subtracting 0.02 sec from QT for every increase of 10 bpm of HR. For example, taking a normal QTc≤0.42 sec, QT would be expected to be 0.42 sec or less, a HR of 60 bpm. For a HR of 70 bpm, the expected QT would be approximately ≤0.40 sec; for 80 bpm, the expected QT would be ≈≤0.38 sec. Thus, the average value, the normal upper and lower limits are determined both for the male and the female genders.

In the pediatric group, the normal upper limits for the QTc interval duration have been estimated between 440 ms and 450 ms, except for newborn babies in the female gender, where this value may reach up to 562 ms and between 1 and 2 months of age, 454 ms.

The normal lower limit of QT has been estimated in 370 ms, and in teenagers from 12 to 16 years of age, it is 362 ms (29). In babies younger than 1 year, it is essential to determine these extreme values, because the Sudden Infant Death Syndrome (SIDS) could be caused both by congenital long or short QT syndrome. Sudden Infant Death Syndrome refers to any sudden death that has occurred during sleep in a baby less than 6-to12 months of age, that remains unexplained after a thorough investigation, including autopsy, careful examination of the scene where the death occurred, and review of the clinical history (30).

The tables of linear regression are recommended, instead of the Bazett's formula to estimate QTc. Besides, the estimation of the QTc interval should not be attempted when RR interval variability is significant, just as it often happens with atrial fibrillation, or when the identification of the end of T wave is not reliable.

The following table shows the respective predictive values of QT (mean, lower and upper normal values) expressed in seconds in both genders, taking into account the length of the RR cycles. (see tables next 2 slides)

Table Mean Predicted QT Values at Various RR Cycle Lengths QT for Men (Seconds)

RR (seconds)	HR (Beats/min)	Mean Value	Lower Limit	Upper Limit
0.50	**120**	**0.299**	**0.255**	**0.343**
0.55	**109**	**0.307**	**0.263**	**0.351**
0.60	**100**	**0.314**	**0.270**	**0.358**
0.63	**92**	**0.322**	**0.278**	**0.366**
0.70	**86**	**0.330**	**0.286**	**0.347**
0.75	**80**	**0.337**	**0.293**	**0.381**
0.80	**75**	**0.345**	**0.301**	**0.389**
0.85	**71**	**0.353**	**0.309**	**0.397**
0.90	**67**	**0.361**	**0.317**	**0.404**
0.95	**63**	**0.368**	**0.324**	**0.412**
1.00	**60**	**0.376**	**0.332**	**0.420**
1.05	**57**	**0.384**	**0.340**	**0.428**
1.10	**55**	**0.391**	**0.347**	**0.435**
1.15	**52**	**0.390**	**0.355**	**0.443**
1.20	**50**	**0.407**	**0.363**	**0.451**
1.25	**48**	**0.414**	**0.370**	**0.458**
1.30	**46**	**0.422**	**0.378**	**0.466**
1.35	**44**	**0.430**	**0.386**	**0.474**
1.40	**43**	**0.438**	**0.394**	**0.482**
1.45	**41**	**0.445**	**0.401**	**0.489**
1.50	**40**	**0.453**	**0.409**	**0.497**

QT for Women (Seconds)

RR (seconds)	HR (Beats/min)	Mean Value	Lower Limit	Upper Limit
0.50	**120**	**0.311**	**0.267**	**0.354**
0.55	**109**	**0.318**	**0.274**	**0.362**
0.60	**100**	**0.326**	**0.282**	**0.370**
0.63	**92**	**0.334**	**0.290**	**0.378**
0.70	**86**	**0.341**	**0.297**	**0.385**
0.75	**80**	**0.349**	**0.305**	**0.393**
0.80	**75**	**0.357**	**0.313**	**0.401**
0.85	**71**	**0.364**	**0.321**	**0.408**
0.90	**67**	**0.372**	**0.328**	**0.416**
0.95	**63**	**0.380**	**0.336**	**0.424**
1.00	**60**	**0.388**	**0.344**	**0.432**
1.05	**57**	**0.395**	**0.351**	**0.439**
1.10	**55**	**0.403**	**0.359**	**0.447**
1.15	**52**	**0.411**	**0.367**	**0.455**
1.20	**50**	**0.418**	**0.374**	**0.462**
1.25	**48**	**0.426**	**0.382**	**0.470**
1.30	**46**	**0.434**	**0.390**	**0.478**
1.35	**44**	**0.441**	**0.397**	**0.486**
1.40	**43**	**0.449**	**0.405**	**0.493**
1.45	**41**	**0.457**	**0.413**	**0.501**
1.50	**40**	**0.465**	**0.421**	**0.509**

For the risk of sudden cardiac death, borderline QTc in the male gender is 431-450 ms, and in the female one 451-470 ms. An “abnormal” QTc in men is a QTc greater than 450 ms, and in women, above 470 ms (31). The values of QTc vary with gender (adult women have a longer QTc than men) and are accepted as normal up to a maximal of 0.45 sec (450 ms) for men and 0.47 sec (470 ms) for women.

Differences in QTc duration related to gender are not observed in infants and between the 10 and 13 years of age. This difference in QTc duration is already observed between 14 and 18 years.

For children, the upper limit of a normal QTc interval is 0.46 sec (460 ms).

In newborn babies, QTc is greater, and could be normal up to 490 ms (0.49 sec). Some authors propose that the upper limit is a value a little lower for QTc: 450 ms in newborn babies, and 440 ms after that age. Approximately 5% of normal newborn babies have a QTc interval >440 ms. Newborn babies with QTc >440 ms in the fourth day of life have an increase in the risk of sudden cardiac death, with some of them corresponding to the so-called Sudden Infant Death Syndrome (SIDS). In the congenital short QT interval syndrome, SIDS is attributed one point in the Gollob score. A HR of 60 bpm, a QTc interval >350 ms is extremely rare in healthy people. A QTc interval using the Bazett’s formula <370 ms, <350 ms and <330 ms are attributed 1, 2 and 3 points in the mentioned score (32) The normal lower limit of QT beneath which arrhythmias may occur, is 330 to 350 ms.

The mean QTc interval in the fourth day of life is 400 ms (+/-20 ms) and, unlike adults, it does not present gender differences. In healthy children, there is a physiological QTc prolongation by the second month (mean of 410 ms) followed by a progressive decline, and in the sixth month, the QTc interval returns to the values recorded in the first week.

A QTc close to 500 ms is a clear element to take into account as a potential generator of torsades de pointes.

In cases of very high HR and in carriers of long QT interval, the end of the T wave could be overlapping with the P wave of the following cycle; in such cases, a tangent should be made in the descending limb of the T wave, considering as the end of the T wave, the point of intersection with the baseline. When the HR is too low or too high, the use of the Bazett’s formula may not be so refined; however, it remains as the predominant methodology in clinical practice.

Infusion of epinephrine in a low dose, administered gradually “in crescendo” (0.05, 0.1, 0.2, and 0.3 microg x k(-1) x min(-1)) in patients carriers of the LQT1 variant of congenital long QT syndrome with normal basal QT interval, causes paradoxical prolongation of QT interval, which does not occur in normal people (33). The infusion of epinephrine is a powerful test to forecast the genotype of LQT1, 2 and 3 variants of long QT syndrome, and to improve the clinical diagnosis of patients with a positive genotype, especially those carriers of variant LQT1 (34). The QT interval constitutes the classical measurement of ventricular repolarization, while this parameter includes ventricular depolarization. Thus, in the existence of branch block or ventricular pre-excitation, the measurement of ventricular repolarization using the QTc interval could be incorrect. In such cases, the measurement of JT/JTc interval is more precise than the QT/QTc interval, since it excludes depolarization. The measurement of JTc could be useful to identify LQTS cases with borderline values, where the QT interval could be normal in the rest of the ECG. We find an example in patients carriers of post-surgery tetralogy of Fallot, who develop pattern of CRBBB as a result from ventriculotomy in the RV free wall. In these cases, the measurement of the JTc interval is more accurate to detect prolonged repolarization than QT interval measurement. Baseline: In newborn babies and infants, there are rarely ST segment elevations that go beyond 1 mm above the baseline. Unlike adults, this line should be considered the TP segment of the previous complex and not the PR segment. Figure.

Value of VCG with automatic reading of QTc

As the measurement of the QTc interval is less reliable in children than in adults, the search for new and better tools for measuring is justified. Swedish authors(35) investigated if the VCG by Frank’s method is better than 12-lead ECG to measure QTc in congenital long QT syndrome (LQTS) in children. The authors studied 35 children known to be carriers of LQTS by genetic confirmation (29 with the KCNQ1 mutation and 6 with the KCNH1 mutation) and compared them to a control group of 35 normal children matched by gender and age. From the 35 children with LQTS genetically confirmed, 30 (86%), received a correct diagnosis using the measurement of QTc by VCG/Frank’s automatic method, 29 (82%). This percentage turned out to be much greater than when using QTc measurement by ECG, whether manual or automatically. The automatic measurement of QTc by VCG seems to be a better predictor of LQTS than the measurement made with 12-lead ECG, whether manual or automatic.

Normal values for QTc

The association between long QT interval and SIDS has been clearly established. Several studies have been made to determine the evolution of the QT interval in full-term newborn babies. Meanwhile, the data on the QT interval in newborn pre-term babies are rare. With the goal of knowing the QT interval in premature newborn babies, Séguela et al (36) made a single-center prospective study in a neonatal intensive care unit, in premature newborn babies, without heart disease, family history of congenital long QT syndrome, unstable hemodynamic state, or administration of drugs with the capacity of inducing QT interval prolongation. An ECG was made in similar conditions weekly until the discharge for each baby. The QTc was estimated with the Bazett's formula. In total, 309 ECGs were made in 87 children, with gestational ages ranging 14-36 weeks. In the first ECG, the QTc interval increased after birth in premature babies with <30 weeks of gestation – and next, started decreasing. In premature babies >30 weeks, QTc was not observed to increase initially. When plotted against post-menstrual age, the first QTc increased, next it decreased after 32 weeks. These data suggest that the QTc interval varies with post-menstrual age in very premature babies, reaching a peak in 32 weeks. These variations in QTc duration in development may lead to a specific vulnerability for QT prolongation with the use of medications in premature children. This study highlights the need for specific pharmacological studies in this population.

Effect of the position to sleep: sleeping face down increases the QTc and JTc intervals and decreases HR variability, potentially increasing the vulnerability for SIDS. Consequently, back to sleep is the position of choice, not just for full-term newborn babies, but also for premature babies after hospital discharge (37) Among young adults with extremely low weight at birth, a significant difference was verified in relation to the PR, QTc intervals durations and QT dispersion when compared to young adults born in term and with normal weight. Regardless of the pathophysiological mechanisms, the potential risk of this population to develop ventricular arrhythmias when using drugs capable of extending the QT interval stands out (38) During the first 24 hours, the QTc is 370 and 530 ms with a mean value of 420 ms.

Since the second day of life until the 2 years of age, the normal value of QTc is 370 to 420 ms with an average of 400 ms. Between 2 years and 4 years of life, normal QTc is 380 to 420 ms with an average of 400 ms. Between 8 and 10 years, the normal QTc value is between 400 ms and 430 ms with an average of 410 ms.

Between 11 and 14 years, the normal value of QTc is between 400 ms and 420 ms with an average of 410 ms.

For adults, the normal value of QTc is between 350 and 440 ms with an average of 380 ms.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