Review

Non-Invasive Electrophysiological Markers Associated With Long QT Syndrome

Andrey V. Ardashev¹, Viktor A. Snezhitskiy², Lyudmila V. Kalatsei²

¹ Medical Research and Educational Center of Lomonosov Moscow State University, Moscow, Russia; ² Educational Institution «Grodno State Medical University», Grodno, Belarus

Long QT syndrome (LQTS) is a life-threatening channelopathy, characterized by permanent or transient QT interval prolongation on the 12-lead electrocardiogram and syncope associated with malignant ventricular rhythm disturbances, particularly polymorphic ventricular tachycardia also known as torsade de pointes. Corrected QT (QTc) interval measurement remains the initial source of LQTS diagnosis in any patient, but the «borderline» QTc interval prolongation should induce further investigation. Genetic testing has the greatest value to provide definitive diagnosis in such situations, but it can’t be applied to each patient routinely, putting aside that it can often be incomprehensive, costly or unavailable. The present review discusses the most promising non-invasive electrophysiological markers associated with Long QT syndrome, particularly in absence of visible QT interval prolongation and clinical manifestations.

Keywords: long QT syndrome, corrected QT interval, QT interval dispersion, T wave alternans; QT-RR hysteresis, QT interval variability; T-peak – T-end interval.

To cite this article:
Неинвазивные электрофизиологические маркеры, ассоциированные с синдромом удлиненного интервала QT

А.В. Ардашев, В.А. Снежицкий, Л.В. Колоцей

Синдром удлиненного интервала QT (СУИ QT) — это потенциально жизнеугрожающая каналопатия, сопровождающаяся удлинением интервала QT на 12-канальной ЭКГ, синкопальными состояниями и высоким риском внезапной сердечной смерти вследствие развития полиморфной желудочковой тахикардии типа «пируэт». Удлинение интервала QT свыше 500 мс является общепринятым фактором риска и самостоятельным предиктором развития жизнеугрожающих желудочковых аритмий, однако не менее опасны и «немое», латентное течение СУИ QT, без очевидных клинических проявлений с нормальными или «пограничными» значениями продолжительности интервала QT. Генетическое тестирование имеет наибольшую ценность для постановки окончательного диагноза в таких ситуациях, но его нельзя применять у каждого пациента рутинно, не говоря уже о том, что оно часто может быть неполным, дорогостоящим или недоступным. В настоящем обзоре обсуждаются наиболее перспективные неинвазивные электрофизиологические маркеры, ассоциированные с СУИ QT, особенно при отсутствии видимого удлинения интервала QT и характерных клинических проявлений.

Ключевые слова: синдром удлиненного интервала QT; корригированный интервал QT; дисперсия интервала QT; альтернация зубца T; гистерезис QT-RR; вариабельность интервала QT, интервал T-peak – T-end.

INTRODUCTION

Long QT syndrome (LQTS) is a life-threatening channelopathy, characterized by permanent or transient QT interval prolongation on the 12-lead electrocardiogram and syncope associated with malignant ventricular rhythm disturbances, particularly polymorphic ventricular tachycardia (PVT) also known as torsade de pointes (TdP) [1, 2]. Excessive QT interval prolongation is predisposed to arrhythmogenesis due to asynchronous repolarization of different areas of the ventricular myocardium and consequently the increase in the general length of repolarization, which induces early afterdepolarizations and spatial dispersion of refractoriness.

LQTS may be either congenital or acquired. To date more than 600 mutations of 17 different genes responsible for a hereditary form of LQTS have been identified (LQT1-17) [3], mostly being associated with the mutations in the genes coding for cardiac ion channels (sodium, potassium and calcium) and their channel interacting proteins. Acquired LQTS is associated with exposure to QT prolonging drugs, electrolyte imbalance (hypokalemia, hypocalcemia, hypomagnesemia), structural cardiac diseases (myocardial infarction, myocarditis, hypertrophic cardiomyopathy), metabolic and endocrine abnormalities or after recent conversion to sinus rhythm in patients with atrial fibrillation [4].

In its most characteristic cases, with obvious QT interval prolongation, stress-induced syncope and family history of sudden cardiac death, the diagnosis of LQTS is quite uncomplicated for cardiologists to suspect. However, in cases of borderline or intermittent QT interval prolongation and in absence of clinical manifestations, a correct diagnosis may be more difficult.

Genetic testing has the greatest value to provide definitive diagnosis in such situations, but it can’t be applied to each patient routinely, putting aside that it can often be incomprehensive, costly or simply unavailable. That’s why physicians have to perform more accessible additional testing, which provides in turn a great variety of electrophysiological markers, sometimes over- or on the contrary underrated.

The aim of this review was to analyze the features and limitations of the non-invasive electrophysiological markers associated with long QT syndrome and torsades de pointes.

MATERIALS AND METHODS

This review was conducted according to the PRISMA guidelines [5]. Comprehensive research was conducted on PubMed, EMBASE, Google scholar and eLIBRARY databases by using the terms «long QT syndrome», «QT interval dispersion», «T wave alternans», «QT–RR hysteresis», «QT interval variability», «T-peak – T-end interval», «torsades de pointes» and their Russian equivalents for studies published until September 1, 2021. Two authors independently screened titles and abstracts to identify relevant studies in English and Russian. Duplicates were removed. Full texts of the chosen articles were independently assessed by two authors. The search was supplemented by a screening of studies included in recent systematic reviews and meta-analyses.

Inclusion criteria were: original studies, reviews and meta-analyses analyzing electrophysiological markers of long QT syndrome and/or torsades de pointes

Exclusion criteria were: case reports, studies with less than 10 subjects, studies on pediatric patients, articles in language other than English and Russian (Fig. 1).

RESULTS

1. QT interval

QT interval is defined as the time from the start of the Q wave to the end of the T wave of the 12-lead ECG, which represents depolarization and subsequent repolarization of the ventricular myocardium. On the standard ECG the onset of the QRS complex is usually easily identifiable, in contrast to the end of the T wave, which is affected by its morphology, amplitude and presence of the U wave, which represents Purkinje fibers repolarization [6]. The end of the T wave can be measured manually or automatically with the help of threshold method (fig. 2, a), slope method (fig. 2, b) and their variations or novel-method proposed by A. Hunt [7]. The latter is based on the axiomatic principle that the T wave end point is the first point of intersection of the T wave with a superimposed inverted image of itself, so the T wave becomes a template which measures itself (Fig. 2, c).

It is a common knowledge that QT interval varies in the different leads of the same ECG. Different clinical studies have suggested measuring QT interval only in the limb leads, in all 12 leads, in the lead with the highest T wave, in the aVL lead, where the U wave is usually isoelectric, and in «quasi-orthogonal» I, aVF and V2 leads [1, 2, 4]. Differences...
in approaches lead to differences in the assessment of the normal QT interval.

According to the AHA/ACCF/HRS Guidelines for the Standardization and Interpretation of Electrocardiogram [8], the QT interval should be measured in all 12 ECG leads, and in further calculations, the lead with the longest QT interval should be used (usually it is V2 or V3 lead). If the duration of the QT interval in this lead exceeds its duration in other leads by more than 40 milliseconds, it should be considered erroneous, and it is proposed to use the QT interval duration measured in one of the standard leads.

QT interval is known to be influenced by age and gender. In young and middle-aged women it is longer than in men. During puberty QT interval in boys shortens due to the effect of testosterone which accelerates potassium flow through the fast potassium channels, while in girls its duration remains unchanged. This difference varies from 12–15 ms in young people, decreases to 6–10 ms in the older age groups and practically levels out in old age [9]. Also QT interval in men has been reported to be longer in winter than in summer, being the longest in October [10].

According to the results of the NHANES study, QT interval values increase in proportion to the age of the patients, reaching maximum values in people over 70 [11]. Since QT interval gender difference decreases in older age groups, it means that increase in QT duration with age is not parallel and seems more expressed in men. Increase in the QT interval with age can be explained by a combination of factors. Aging processes change the myocardium itself with the development of myocardial fibrosis, and also change the ratio of the influence of the sympathetic and parasympathetic nervous system, which can slow down myocardial repolarization. In addition, patients in the older age group take more drugs that can cause QT interval prolongation.

2. Corrected QT interval (QTc)

The most significantly QT interval depends on the heart rate. The first attempt to standardize the QT/RR adaptation was made in 1920 by English physiologist H. Bazett. The formula he proposed a hundred years ago (QTc = QT/√RR) is still used by medical professionals all over the world due to its simplicity and reliability. It works more precisely in the range from 60 to 100 beats per minute, but it can give erroneous results both at slower (excessive correction) and higher (insufficient correction) heart rates. A few dozens of other formulae were designed to replace Bazett’s formula (among them Fridericia, Mayeda, Kawataki, Youshinaga (for children), Boudoulas, Ashman, Karialexinen, Adams, Ljung (for patients with hypokalemia), Schlamowitz, Framingham, Simonson, Akhras & Rickards, Hodges, Kovach, Arrowood, Sarma, Lecocq, Rautahaju, Dmitrienko, e.c.), but none of them proved to be universally reliable [6].

For a long time, it was believed that the dependence of QT interval on the heart rate is linear and obeys the model $QT = \beta + \alpha \times RR$. However, further studies have shown that this relationship is highly individual and can be linear, power, parabolic, logarithmic, exponential or may represent any other subject-specific curvature.

Recently developed by S. Rabkin et al. age and gender-adjusted spline-formula is based on the NHANES (U.S. National Health and Nutrition Examination Survey) population study and was shown to be relatively independent of heart rate and was superior to other formulae, including some other more recently proposed. It was developed on the basis of the flexible regression spline approach which permitted modeling of almost any shape of the QT-RR relationship [6, 12].

It is also important to note that this formula can only be used in patients with sinus rhythm in the absence of left ventricular hypertrophy, intraventricular conduction disorders, ST-segment elevation myocardial infarction, and significant ST-T changes [12, 13].

However, the question remains: which duration of QTc interval can be called excessive. In the original 1985 LQTS diagnostic (Schwartz) criteria any QTc (there and further on QT interval values are calculated with the help of Bazett formula) $\geq 440$ ms was considered prolonged. In the later editions of the same criteria QTc values were ranged from 3 points for QTc $\geq 480$ ms, 2 points for QTc $= 460–479$ ms (both suggest intermediate probability of LOTS even without any other risk factors) to 1 points for QTc $= 450–459$ ms in males (low probability) [14].

According to the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death LQTS is diagnosed in corrected QT $\geq 480$ ms in repeated 12-lead ECGs or $\geq 460$ ms in the presence of unexplained syncope [15].

2009 AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram states that a QTc $\geq 450$ ms in males and $\geq 460$ ms in females is considered prolonged [8]. Several reviews have labeled QTc values within 20 ms of these limits as borderline [16, 17] (see Table 1). But borderline QTc value is not sufficient enough for a diagnosis of LQTS or even possible LQTS.
In the study by DJ Tester et al., 27% of patients with a known LQTS genetic defect had a QTc interval less than 440 ms [18]. On the other hand, the data derived from 79,743 ambulatory subjects has shown that the 99th percentile of QTc distribution is 470 ms for males and 480 ms for females, which means that approximately 10% to 15% of all people have QTc values ≥ 440 ms and don’t have LQTS [19]. That’s why if physicians rely only on QTc value, without any additional markers, it may result in premature and incorrect diagnosis.

3. QT interval dispersion

QT interval dispersion (QTd) is measured as the difference between the maximal and minimal QT intervals within a 12-lead ECG. Its measurement is based on the assumption that each ECG lead measures regional repolarization, and consequently dispersion serves as a marker of spatial dispersion of ventricular recovery time. C.P. Day et al. put forward the hypothesis that the risk of life-threatening arrhythmias is directly proportional to the increase in the QTd and not to the prolongation of QT interval itself [6, 20].

Later, it was shown that QT dispersion does not directly reflect the dispersion of recovery time and that it results mainly from variations in the T wave morphology and the errors of QT interval measurement [6]. Moreover, surface ECG is able to estimate only the end of the repolarization, while its onset remains undetected (it is known to be situated near the T wave peak), which makes these data insufficient for correct estimation of the repolarization phase.

Reported normal values of QT interval dispersion vary from 10 to 71 ms, with only significantly high values (more than 100 ms) [21], potentially having practical predictive value in genesis of ventricular arrhythmias. Increase in QT dispersion has been associated with risk of sudden cardiac death in patients with ischemic heart disease [22], diabetes mellitus [23] and peripheral vascular disease [24]. However, the prognostic value of QTd remains controversial in patients after myocardial infarction [25] and in patients with congestive heart failure [26]. In patients with LQTS, increased QTd is reported to be associated with high susceptibility to ventricular arrhythmias, and also predicts efficacy of antiadrenergic therapy [27].

4. QT-RR hysteresis

In recent years it has been found that the QT interval duration does not depend solely on the duration of the preceding RR interval or on a small number of preceding RR intervals, but is influenced by a long history of preceding heart rate. This phenomenon has been called QT-RR hysteresis and its increase considered a potential biomarker of arrhythmic risk. It is characterized by longer QT intervals at a given RR interval while heart rates are increasing during exercise and shorter QT intervals at the same RR interval while heart rates are decreasing during recovery. It is calculated as the QT interval difference between exercise and 1 to 2 minutes into recovery at heart rates of approximately 100 b.p.m.

The mechanism of QT-RR hysteresis has been attributed to a lagging QT response to different directional changes in RR interval during exercise and recovery, however later in the studies by D.J. Pelchovitz et al. it has been found that changes in the QT interval duration exercise and recovery are predominantly mediated by autonomic nervous system [28]. The study by A.D. Krahn has shown that increased QT-RR hysteresis is highly specific for LQTS (46 +/-19 ms in not genotyped LQTS patients vs 19 +/- 11 ms in healthy controls 1 minute into recovery) [29]. These observations were confirmed and expanded by J.A. Wong et al., who performed provocative testing of patients with suspected LQTS that consisted of a modified Bruce protocol treadmill exercise test. According to this study, increased QT-RR hysteresis was identified in LQT2 patients only, and not in LQT1 or LQT-negative patients (average 15ms in LQT1 phenotype vs 40 ms in LQT2) [30]. Beta-blockers were reported to reduce QT-RR hysteresis in both subtypes [30-32].

5. Short-term QT interval variability (ST-QTV)

QT interval variability is a measure of the spontaneous fluctuations in the duration of the QT interval during the 24/48 h ambulatory ECG monitoring. In resting conditions QTV results mainly from heart rate variability (HRV) and is dependent on individual-specific QT-RR curvatures. Variation in QT duration at a constant RR interval is caused by beat-to-beat variability of the overall ventricular repolarization, which has been acknowledged as arrhythmic risk marker. Increased short-term QTV has been associated with sudden death in animal experiments and multiple clinical situations, including coronary artery disease, myocardial infarction, ischemic and non-ischemic cardiomyopathy [35]. The QT Variability Index (QTVI) is ratio of normalized QT variability to normalized heart rate variability, and therefore includes an assessment of autonomic nervous system tone. QTVI is defined as log10 [(QTV/QTM²)/(RRV/RRm²)], where QTV represents the QT interval variance, QTM is the mean QT interval, RRV is the RR interval variance, and RRm is the mean RR interval [6].
Increased ST-QTV has been reported in LQTS patients with different genetic mutations. Groups that included LQTS2 and LQTS3 mutation carriers showed also increased QTVI [33]. In LQTS1 patients ST-QTV changes seem less pronounced and there is no increase in QTVI was found. Moreover, increases in QT in LQT1 may be seen only after sympathetic stimulation [34]. In patients with drug-induced LQTS, documented TdP was associated with increased QT in the absence of QT prolongation [35, 36]. ST-QTV was already elevated before drug-administration in these patients, identifying the diminished repolarization reserve, even in absence of visible QT interval prolongation, which proves its ability to unmask latent QT prolongation.

6. T wave morphology

Presence of an abnormal T wave morphology is one of the important ECG features of LQTS. Later investigations of T wave changes were mainly focused on its duration, amplitude and symmetry. Each subtype of congenital LQTS is known to have its own characteristic features. LQT1 patients usually have tall early-onset and broad-based T waves. LQT2 genotype is linked with low amplitude, often bifid, asymmetric or notched T-waves. LQT3 patients tend to have long ST-segment and late narrow and peaked T waves [37]. But these T wave features are often subtle and can be overlooked by a non-expert in the field of channelopathies (Fig. 3).

Novel software-based means of the T wave analysis allow quantitative evaluation of such morphological features as flatness, asymmetry, and notching with the help of principal component analysis. Morphology combination score (MCS) proposed by A. Porta-Sanchez et al. can be calculated automatically from these measures using the equation:

\[ MCS = 1.6 \times \text{flatness} + \text{asymmetry} + \text{notch score} \]

The study has shown that MCS was significantly higher in LQTS patients compared with control subjects and in LQTS2 patients compared with LQT1 patients. Moreover, it also was increased in patients with LQTS and normal QT duration compared with controls, which makes T-wave analysis quite valuable in borderline phenotypes.

7. T-wave alternans

Both congenital and acquired LQTS are associated with T-wave alternans (TWA) — beat-to-beat variations in the amplitude, morphology and polarity of the T waves with each subsequent contraction that reflect the spatiotemporal heterogeneity of ventricular repolarization. In experiments TWA usually occurs at very fast heart rates (200–300 bpm) due to steep slope of action potential duration restitution at short diastolic intervals [39]. But if the repolarization reserve is initially reduced (as it happens in LQTS) TWA manifests at normal heart rates and is often potentiated by bradycardia in presence of early afterdepolarizations.

When the fluctuations in the amplitude of the T-wave are large enough that they can be recorded on a surface electrocardiogram, it is called macrovolt T-wave alternans the important but uncommon marker of arrhythmic susceptibility and precursor of sudden cardiac death. Microvolt TWA are more common, but not visible to the naked eye [37]. They can be detected only on subtle levels with the computerized techniques of Spectral and Modified Moving Average methods.

Microvolt TWA has been described in patients with congestive heart failure [38], hypertrophic cardiomyopathy [41] and LQTS [42]. In a study by Takasugi et al. it was found that microvolt TWA has high sensitivity but comparatively low specificity for LQTS and is strongly associated with TdP history [42].

8. T-peak – T-end interval

Tpeak–Tend (Tp-e) interval seems to be another promising marker of arrhythmic risk, which has been reported as an index of transmural dispersion of repolarization. It is defined as the time difference between the peak and the end of the T-wave, and in case of negative or biphasic ones it could be measured on the interval from the nadir to the end of the T-wave. The increased duration of the Tp-e interval may reflect the period when the epicardium is completely repolarized, but the subendocardial layer (M-cells) is still recovering. It forms an electrical substrate for subsequent depolarization, leading to ventricular arrhythmias. The Tp-e to QT interval ratio (Tpe/QT ratio) is less heart rate dependent than Tp-e itself, because it remains constant despite dynamic changes in heart rate.

According to recent studies, an increase in the Tpeak–Tend duration also increases the risk of life-threatening arrhythmias and, consequently, sudden cardiac death, in patients with Brugada syndrome [43, 44], hypertrophic cardiomyopathy [45] and slow coronary flow [46].

There has been reported an association of prolonged Tp-e interval with a high risk for developing TdP in patients with both acquired and congenital long QT syndromes [47].
Tp-e interval can also be prolonged in patients with a history of drug-related TdP and serve as a marker of drug-induced abnormal repolarization [48].

But a number of studies showed that the duration of the QT interval and Tp-e are closely related, and prolongation of Tp-e seems a fraction of total QT-interval prolongation [47, 49]. So, Tp-e interval cannot be used to distinguish symptomatic patients with LQTS from asymptomatic and can be used only as additional repolarization marker.

**CONCLUSIONS**

QTc interval measurement remains the initial source of LQTS diagnosis, but the «borderline» QTc interval duration should be the key to further electrophysiological investigation. Moreover, the formula used to calculate the corrected QT interval should take into account the individual nature of the relationship between the size of the QT interval and heart rate and should be adapted to the gender and age of the patients. At present, the spline QTc formula seems the most suitable for these criteria, but Bazett formula is traditionally used in all international guidelines and scores.

QT interval dispersion doesn’t seem an accurate indicator of spatial heterogeneity of ventricular repolarization and cannot be used to quantify its degree, but can be applied to determine the QT interval variability index. Tpeak–Tend interval cannot be applied to distinguish symptomatic patients with LQTS from asymptomatic and can be used only as additional repolarization marker. Nowadays, QT-RR hysteresis and short-term QT interval variability are the most promising electrophysiological markers even in absence of visible QT interval prolongation, which proves their ability to unmask latent QT interval prolongation.

**ADDITIONAL INFORMATION**

**Competing interests.** The authors declare that they have no competing interests.

**Funding source.** This study was not supported by any external sources of funding.

**REFERENCES**


(In Russ.). DOI: 10.25299/2221-7885-2018-16-5-533-541
СПИСОК ЛИТЕРАТУРЫ


ИНФОРМАЦИЯ ОБ АВТОРАХ

*Людмила Владимировна Колоцей, ассистент; e-mail: lkolotsey@mail.ru; ORCID: 0000-0001-5211-709X; eLibrary SPIN: 8435-3422
Andrey V. Ardashev, MD, PhD, Professor; e-mail: ardashev@yahoo.com; ORCID: 0000-0003-1908-9802; eLibrary SPIN: 9336-4712
Viktor A. Snezhitskiy, MD, PhD, Professor; e-mail: vsnezh@mail.ru; ORCID: 0000-0002-1706-1243; eLibrary SPIN: 1697-0116

* Corresponding author / Автор, ответственный за переписку

DOI: https://doi.org/10.17816/cardar100224