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QT-INTERVAL OF THE RESTING ECG: ITS ROLE AND MEASUREMENT METHODS

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The review summarizes the most update knowledge on the resting ECG QT-interval physiology, current measurement standards and interpretation.

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Marked prolongation of the QT interval (iQT) is recognized as a factor associated with an unfavorable prognosis and increased mortality risk, not only related to cardiovascular diseases but also across other causes [1, 2]. This determines the need to assess iQT when analyzing the electrocardiogram (ECG). However, a number of factors make its evaluation in clinical practice very difficult. For example, S.Viskin et al. (2005) showed that less than 25% of 877 physicians, including 771 cardiologists, were able to correctly estimate iQT on 4 proposed ECGs (analysis of these recordings by 25 internationally recognized experts was used as a standard) [3]. The main reasons for the errors were: incorrect determination of the end point of the T wave, estimation of the corrected iQT (QTc), as well as the choice of threshold values. In addition to the problems already mentioned, difficulties may also arise with the adequate selection of the measurement leads and their adjustment for factors that may affect ventricular repolarization (heart rate, rhythm and conduction disturbances, WPW phenomenon, electrocardiostimulation, etc.). In preparation for this review, we conducted a survey among 144 functional diagnosticians and cardiologists and found that the greatest difficulty among specialists is the evaluation of iQT in atrial fibrillation and wide QRS (54% and 61% of respondents, respectively).

The purpose of this paper is to summarize the basic information about the physiology of iQT, modern standards of its measurement and interpretation of values obtained during the registration and analysis of resting ECG in 12 conventional leads. It should be noted that aspects related to QT interval changes during functional testing represent an independent topic of study and are not discussed in this review.

Definition and causes of changes in iQT

The iQT on the ECG is measured from the beginning of the Q wave to the end of the T wave and includes the QRS complex and ST segment, corresponding to the processes of ventricular depolarization and repolarization. Thus, iQT characterizes the total duration of ventricular excitation and recovery (Fig. 1). The processes of ventricular de- and repolarization are realized through electrolyte currents in cardiomyocytes. The process of ventricular depolarization is carried out by the entry of sodium ions into the cardiomyocyte through fast sodium channels (I_{Na}), the operation of which is encoded by the SCN5A gene. Ventricular repolarization results from oppositely directed ionic currents: a fast sodium current and a slow calcium current ($I_{Ca\ L}$) directed inward to the cardiomyocyte, and potassium ions leaving the cardiomyocyte through potassium channels (I_{to}, I_{Kr}, I_{Ks}, I_{K1}). CACNA1c, KCND3, KCNH2, KCNQ1, and KCNJ2 genes are responsible for the functioning of channels involved in ventricular repolarization [4-6]. Mutations in these genes can be manifested by changes in the duration of iQT on surface ECG and lead to dangerous arrhythmias - ventricular tachycardia of the «pirouette» type due to the resulting inhomogeneity of repolarization in different areas of the myocardium.

In addition to genetic factors, weakening or strengthening of the function of ion channels that determine ventricular repolarization can be caused by the influence of a number of factors: drugs (the current list is available at www.crediblemeds.org), electrolyte disorders, hypo- and hyperthermia, hypoxia, intoxication, infections, etc. [7, 8]. However, it has been shown that 5-10% of people who de-

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velop ventricular tachycardia of the «pirouette» type under the influence of iQT prolonging drugs also have mutations in genes associated with the syndrome of prolonged iQT [9,10].

Selection of leads for iQT analysis

Normally, the duration of iQT in different ECG leads may differ by more than 50 ms. The method of assessing the risk of ventricular arrhythmias in patients with cardiovascular pathology is based on the study of differences in the duration of the ventricular repolarization phase in different parts of the myocardium (iQT dispersion) [11].

Traditionally, iQT is assessed in the II standard leads, because initially ECG was recorded only in the standard leads (ECG recording in the thoracic leads was proposed later). In addition, in the II standard leads, as a rule, waves and intervals are best seen, because the vector axis of the heart has a posterolateral direction, and the value of iQT in the II standard leads has average values in comparison with the duration of iQT in other leads [12]. In cases where it is difficult to determine the end of the T wave in the II standard leads, the use of V5, V6, or I is recommended as an alternative. According to the recommendations of the American College of Cardiology on ECG Standardization and Interpretation 2009 (AHA/ACC/HRS), the lead in which it is maximally expressed should be used to measure iQT, which may be in leads II (traditionally priority), I, V1-V5 [13]. To improve the accuracy of iQT estimation and reproducibility of its measurements, it is necessary to perform estimation not in one but in several (3-5) consecutive cardiac cycles, which may be especially useful in the presence of sinus arrhythmia in patients.

IQT measurement methodology

According to the AHA/ACC/HRS guidelines, the tangent method described in 1952 is considered to be the most reliable method for determining the end point of the T wave. According to the tangent method, the end of the T wave corresponds to the intersection of the tangent drawn from the top of the T wave along the descending part of the T wave and the isoline, for which the continuation of the PQ interval is taken (Fig. 2). If there is a biphasic T wave, the phase of the T wave with the highest amplitude is selected for the tangent. When using the threshold method, the point of intersection of the final part of the T wave with the isoline is taken as the end of the T wave, which is defined as the line connecting the end of the T wave and the next P wave (Fig. 2). Occasionally, T wave on the ECG may be double-humped or biphasic, and the end of the T wave should be measured after the second peak. At times it can be difficult to distinguish between the double-humped T and U waves (QT+U), to this end, viewing all ECG leads may be helpful to facilitate the distinction. As a rule, an isoline area is defined between the T and U waves. If a U wave is observed after T, the nadir of the cleavage, the lowest point between T and U, is considered as the final part of T. The most common variants of the relationship between T and U are presented in Fig. 3.

In general, both methods produce comparable results. Thus, according to A.S.Vink et al. (2018), who compared the diagnostic accuracy of the tangent and threshold methods on a population of patients with verified congenital long QT syndrome (n=1484), iQT measured by the tangent method was on average 10.4 ms shorter than by the threshold method [15]. According to the authors, the use of both methods allows the identification of patients with prolonged QT interval syndrome (LQTS) with high accuracy.

Measurement of iQT in automatic ECG analysis, effect of signal processing on iQT

Since modern computerized ECG systems have the ability to perform automated ECG analysis, which in many cases subsequently forms the basis of the physician's opinion, it is useful to summarize the basic principles and factors of ECG processing that can affect the results of iQT measurement.

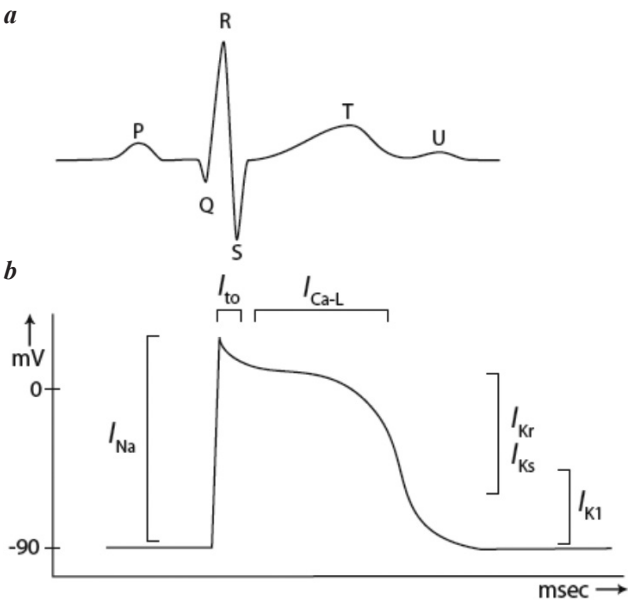

Fig. 1. Schematic representation of the ion currents that determine the action potential. ECG intervals (a) correlated with action potential phases (b). Adapted from Postema PG, Wilde AA-M, 2014 [4]. Explanation in the text.

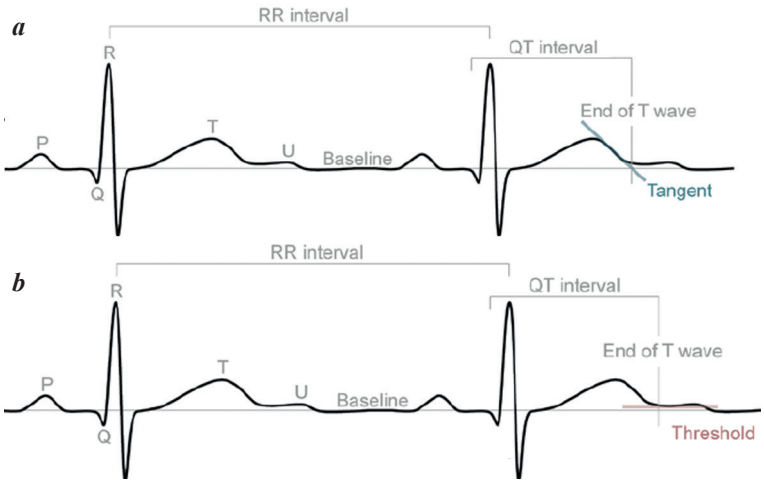

Fig. 2. The most commonly used ways to estimate the end of the T wave: a - tangent method, b - threshold method.

The international standard and the equivalent Russian all-Union State Standard for analyzing electrocardiographs (i.e., with automatic ECG analysis) establish the recommendation to determine the beginning of the T wave by the earliest possible onset in all synchronously recorded leads, and the end - by the latest possible end (Fig. 4) [16-18]. This approach, when QT dispersion is high, may well be responsible for a significant increase in QT and QTc relative physician measurement in II or other leads. Most manufacturers of stand-alone analyzing electrocardiographs and ECG analysis computer programs are known to follow this recommendation. It seems likely that the same approach will continue in the prospective common standard currently under development [18].

In automatic ECG analysis, interval measurements can be made either on a representative QRS-T complex, selected automatically among the complexes of the dominant form, or on superimposed median beat (SMB) complexes within each lead separately or in a global median beat (automated global median beat methods - GMB). In Russian, the designation «average complex» is often used instead of the more correct «median». The implementation of a particular complex selection method can have an impact on the iQT measurement results [19-22].

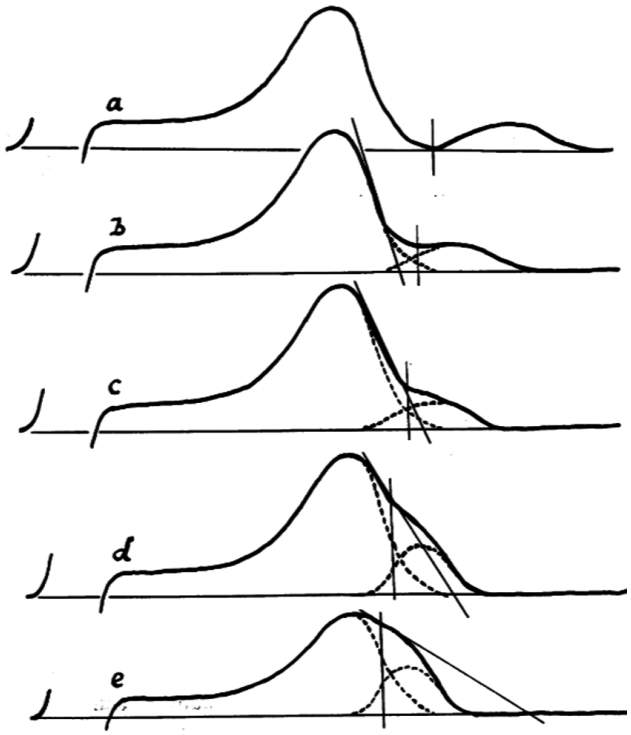

Fig. 3. Determination of the end iQT by the tangent method (adapted from E. Lepeschkin, B. Surawicz, 1952), where the dashed lines indicate the true contours of the T and U waves, the solid lines correspond to the termination of the iQT by the tangent and threshold methods: a - the intersection of the descending part of T with the isoline best determines the end of QT; b - the point of intersection of the tangent with the isoline is located earlier than the true end of the T wave, which in this situation can be determined through the nadir (lowest point) of the cleavage, i.e. c - the intersection of the tangent with the isoline is located between the cleavage and the true end of T and characterizes the end of T wave more accurately than the nadir; d - the tangent method overestimates the true duration of T wave, but nevertheless describes it more accurately than the threshold method; e - the tangent method significantly overestimates iQT, the optimal result can be obtained by averaging the calculations of both methods.

It is important to emphasize that the method of determining the onset and termination of waves recommended by the standards discussed herein may itself result in increased duration of iQT. Different measurement methods in different ECG machines can lead to difficulties in clinical evaluation of iQT results monitoring [23]. Also, the authors are not aware of any automatic ECG analysis system that implements tangent method detection of the end of the T wave.

Semi-automatic tools of ECG measurement and analysis are becoming widespread: after automatic marking of P-QRS-T complexes, various electronic «rulers and circulators» are at the doctor's disposal to correct the position directly on the cardiograph display or computer of the automatically set marking of waves. For iQTs, such semi-automated analysis improves the accuracy and reproducibility of the results [18, 19]. According to S.Viskin, inter-operator differences in experts' measurements during manual measurement ranged from 34 to 80 ms. In semi-automated analysis of ECGs from the PTB Diagnostic ECG Database open ECG database, the inter-expert variation of single ECG measurements in determining the onset of the Q and the end of the T waves was 2.43±0.96 ms and 7.43±3.44 ms, respectively [24], which is significantly smaller than the previously cited inter-expert variation.

It is known that the result of ECG interval measurements may depend on the noise level. Interference with myogram and electromechanical motion noise can lead to errors in the determination of iQT due to partial overlap of the frequency spectrum with the ECG. For example, in a visual analysis of relatively stationary 10-second fragments of the Holter monitoring of 523 healthy individuals, it was shown that even moderate noise levels contributed more to QT changes than HR fluctuations [25]. The use of ECG filters can also lead to changes in the magnitude of iQT. According to N.B.McLaughlin et al. who included ECGs of 25 healthy individuals recorded under different filtering modes, automatic measurement of iQT by 5 different algorithms gave a mean value discrepancy of 62 ms with SD of 54 ms [26].

The above factors do not seem to significantly affect the estimation of the corrected QTc (comparison of measured QTc with threshold values) in most cases [27]. However, in expert cases, as well as in any doubts about the results of automatic measurement iQT, manual measurement should be performed taking into account the recommendations below, if possible disabling ECG filtering. Possible discrepancies between measurements and estimates of duration iQT should be taken into account when assessing its dynamics (monitoring) in ECG series.

IQT measurement correction

IQT duration is known to be dependent on HR. In normality, QT is inversely proportional to HR, so correction of QT measurements for HR is necessary for their

adequate comparison. The search for an optimal formula for estimating corrected iQT (QTc) has been ongoing for a century. However, so far it has not been found. The most commonly used formulas for correction iQT are presented in Table 1. A study by I.Androsova (2021) compared 4 main formulas for estimating corrected iQT (QTc): Bazett, Friderici, Framingham and Hodges [28]. It turned out that the Bazett formula is the most unstable formula and is the worst at eliminating the relationship between HR and QTc interval. However, the Bazett formula continues to be used in clinical practice to identify patients with lengthening and shortening of iQT. A 2015 study of iQT assessment in 702 children aged 0-6 years with sinus tachycardia showed that the Bazett formula identifies patients with prolongation of iQT better than others and is more suitable for use in clinical practice compared to the Friderici, Framingham, and Hodges formulas [29]. The more accurate the correction formula, the less the calculated values depend on HR. In this respect, the Friderici formula is superior to the Bazett formula, but both do not fully solve the problem at hand [36-38].

Given the nonlinear nature of QT and HR relationships, the efficiency of QT normalization by HR of different formulas at different ranges of HR values is not the same. In 2005, Zareba and Moss conducted a comparative study to identify the most optimal formula for verifying patients with LQTS. The study analyzed six commonly used QT correction formulas in a cohort comprising 569 patients with LQTS and 772 healthy relatives. Their findings indicated that the Rautaharju formula was the most informative for distinguishing between patients and healthy individuals across the HR range of 61-100 beats per minute (bpm). Additionally, the Hodges formula was identified as the most effective within the same HR range, while the Bazett formula demonstrated superior performance at HRs exceeding 100 bpm. At the same time, F.Schnell, referring to his own results of analyzing iQT in 5000 elite athletes shows that the Bazett formula works correctly in the range of HR from 60 to 90 beats/min. [39].

Almost every year 1-2 new formulas appear in the list of formulas for estimating iQTc. However, in clinical practice, the Bazett formula is used for the diagnosis of LQTS and risk stratification in patients with cardiac pathology. Several population-based studies have previously reported an association between QTc and all-cause mortality. In the well-known Fremingham study (n=6895; mean follow-up=27.5 years), where the Bazett formula was used, a strong association was observed between an increase in iQTc for every 20 ms and all-cause mortality (hazard ratio [HR], 1.14; 95% CI, 1.10-1.18; P<0.0001), coronary heart disease-related mortality (HR, 1.15; 95% CI, 1.05-1.26; P=0.003), and sudden cardiac death (HR, 1.19; 95% CI, 1.03-1.37; P=0.02). [40]. Similar analyses using other formulas have not been reported.

In a study of healthy subjects conducted by E.G. Schouten et al. where QTc was also determined by the Bazett formula, an increase in QTc above 440 ms was associated with a significant relative risk of all-cause mortality [41]. Thus, at present, the European Society of Cardiology recommends using the Bazett formula (irrespective of HR) for estimation of iQT in clinical practice, and the FDA recommends using the Friderici formula for conducting clinical trials of drugs (Table 1) [42].

It is important to understand that changes in the QT interval in response to changes in HR do not occur immediately, it takes some time, in this regard, a term such as QT/RR hysteresis was proposed, which characterizes the duration of delay in the change of QT value in response to changes in RR [43]. Since the traditionally used formulas for QTc calculation include only one RR interval of the preceding complex, when starting to analyze the QTc value, it is necessary to make sure that the adaptation of iQT to the HR level on the ECG under study has already been achieved, otherwise the calculated QTc will not reflect the true state of repolarization of the ventricular myocardium in a given patient. Failure to comply with inpatient requirements can cause serious diagnostic error.

Some special cases of QT correction by HR have their own peculiarities. In sinus arrhythmias, especially in young individuals, different RR interval durations may lead to an error in determining the prolongation iQTc and misinterpreting it. A similar situation can occur in atrial fibrillation, as both short and very long RR intervals can occur in this rhythm disorder. Therefore, in patients with sinus arrhythmias, iQTc should preferably be determined during stable sinus rhythm, and QTc values obtained on ECG with arrhythmias should be interpreted with caution. In cases where the RR interval shows significant variability, the iQT should be measured in several consecutive cycles (at least 3) and the QTc value averaged to avoid overestimating or underestimating the iQT [44]. In case of premature supraventricular or ventricular contractions,

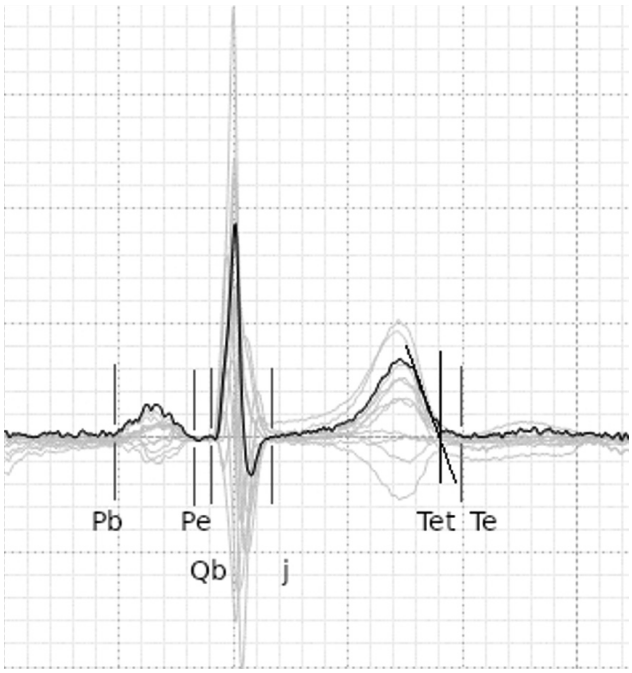

Fig. 4. Pattern of measurement of iQT on a global median ECG complex. Gray shows the signals in 12 common leads, black shows the signal in lead V2. Vertical lines labeled Pb, Pe, Qb, j, Te are the result of automatic detection of waves boundaries. Tet - the result of determining the right border of the wave T by the tangent method.

measurements in the complexes immediately following the pause should be avoided because ventricular repolarization is altered in this complex.

It is known that in atrial fibrillation QTc values calculated by the Bazett formula are somewhat overestimated (comparisons were made with QTc measured against the background of restored sinus rhythm). For more adequate QTc determination in AF, it is recommended that 5-10 complexes be included in the analysis. More accurate results, in comparison with the Bazett formula, according to different authors, are given by the formulas Friderici, Sagie [45-48]. This may be important, for example, when deciding the choice of therapy in cancer patients [49].

To exclude the contribution of the dilated ventricular complex to QT increase in the presence of intraventricular conduction disturbances, the calculation of modified iQT is proposed: QTm = QT - 50% QRS (with subsequent calculation of QTc using the Bazett formula) [50]. Initially, this method of correction was used in patients with ECS, but later it was shown to be possible to use it in patients with left and right bundle branch block. Another method of QT correction by HR for slowing intraventricular conduction has been tested in patients treated for COVID-19. The essence of the correction is to subtract from QTc, calculated according to the Bazett formula, the value by which the initial ventricular complex dilated: QTc - (QRS - 100 ms) [51].

Methods of QT correction by HR on the background of LBBB, significantly superior to the previously described approaches in terms of accuracy, were proposed by Yu.E.Teregulov et al. (2022): 1) linear regression method with modification of Bazett (QTc = 120.5692 + 0.6315 x QTcB), Friderici (QTc = 130.4425 + 0.6024 x QTcF) and Sagie (QTc= 125.4726 + 0.6182 x QTcS) formulas; 2) the method of QT compensation for QRS widening due to LBBB, in which not QTc according to Bazett, but directly the measurement result iQT are taken as subtracted: QT - (QRS - 100 ms) [52]. However, these formulas are very difficult to use on a regular basis in daily clinical practice.

Normal and pathologic QTc values

According to current clinical guidelines, QTc values >480 ms on ECG series indicate a high risk of congenital LQTS, < 320 ms a high risk of congenital short QT syndrome, even in the absence of other features; QTc > 500 ms has a high risk of fatal ventricular arrhythmias, regardless of the cause of prolongation of this interval. QT prolongation is also associated with an increased risk of fatal arrhythmias in many diseases, such as ischemic heart disease, acute cerebral circulatory disorders, acute myocardial infarction, atrial fibrillation, chronic heart failure, and others. [31, 53-59].

Normal values of QTc, calculated using the Bazett formula, according to large population studies, lie between 350-450 ms in men and 360-460 ms in women. In studies conducted on patients and their relatives with LQTS, it was shown that in individuals with and without identified mutations, the ranges of QTc values overlap between

Table 1.

Some formulas for QT correction by heart rate

Title	QTc formula, s	Source	n	Normative values, ms	
				men	women
Bazett	QTc = QT/ √RR	Bazett	39	350-450	360-460
		AHA/ACC/HRS guidelines [10]		346-472	346-482
		S.Viskin [30]	>60 000	350-450	360-460
Friderici	QTc = QT/3√RR	Friderici	50	<450	<470
		AHA/ACC/HRS guidelines [13]		349-468	348-468
		Mason et al [31]	79 743	355-438	365-450
Dmitrienki	QTc = QT/RR0.413	Dmitrienki [32]	13 039	<465	< 516
Framingham	QTc = QT + 0.154 × (1-RR)	Sagie	5 000	332-420	344-432
		AHA/ACC/HRS guidelines [13]		350-449	351-467
		Luo S [33]	10 303	368-457	368-457
Hodges	QTc=QT+0,00175×(HR-60)	Hodges*			
		Luo S [33]	10 303	372-457	372-457
Rautaharju	QTc = QT + 0.24251 - 0.434 × e-0.0097 × HR	Rautaharju PM [34]	14 379	<40 years: 430 40-69 years: 440 ≥70 years: 455	<40 years: 440 40-69 years: 450 ≥70 years: 460
Rabkin	QTc = [QTˆ (60,0,50.3) + 1000 × QT - QTˆ (HR, sex, age)]/1000**	Rabkin S [35]		<450	<470

Note: n, sample size; *, original study could not be lifted; **, QTˆ denotes HR-dependent spline function accounting for sex (given by a numeric variable) and age. The point of the formula proposed by Rabkin is to normalize QT not to the standard HR = 60 beats/min, but to the distribution of HR of healthy men aged about 50 years at HR = 60 beats/min.

420-490 ms [60]. Identification of mutation carriers in the «gray» zone is of great importance, because in such patients, despite the absence of prolongation of QT on ECG, it is recommended to prescribe beta-blockers (class IIa) for prophylactic purposes [61]. For this purpose, additional tests with QT interval estimation, such as Holter monitoring [62], ECG in the early period of outgrowth [63], can be used in such patients. However, these tests are not currently included in the classical criteria for the diagnosis of LQTS, as the change in iQT in these tests remains highly controversial. The lower boundary values of QTc lie between 340-360 ms. Schematically, normal, borderline and pathologic QTc values calculated by the Bazett formula are presented in Fig. 5.

A very important point is that it is incorrect to transfer normal, borderline, and pathologic values developed using the Bazett formula to other formulas. As stated above, the correction iQT are different when using different formulas. For iQTc using the Friderici formula, the normal range of values lies in the region of 355-438 ms in men and 365-450 ms in women [31]. The normative values of other frequently used formulas are presented in Table 1. However, a detailed division into normal, borderline and pathological values for them has not been developed, which significantly limits their use in clinical practice.

CONCLUSION

Evaluation of iQT on standard ECG can identify patients at high risk for life-threatening arrhythmias and sudden death, but proper measurement and interpretation of iQT is challenging. Summarizing the above data it should be noted that QT and QTc intervals should be measured manually, for which it is advisable to use leads (in order of preference) II, V5, V6, V2 on ECG. In case of poor visualization of the T wave, it is recommended to use any lead where this wave is maximally pronounced. QT interval prolongation or shortening should be judged by the value of the corrected QT interval (QTc), which in clinical practice is calculated using the Bazett formula.

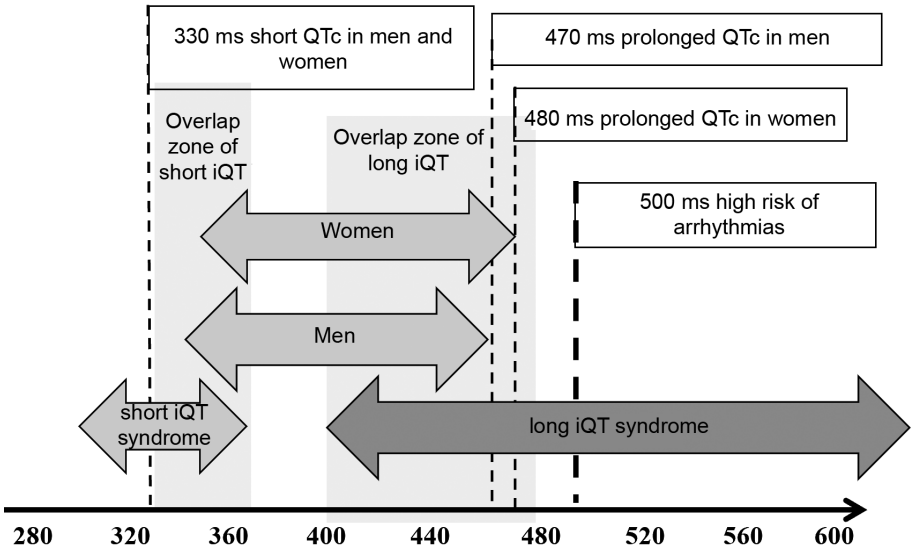

Fig. 5. Normal, borderline and pathologic QTc values according to the Bazett formula (adapted from R.M.Lester et al., 2019) [44].

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