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The QT interval, its origin and importance of the knowledge of formulas for its measurement in different clinical circumstances

El intervalo QT, su origen e importancia del conocimiento de fórmulas para su medición en diferentes circunstancias clínicas

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ABSTRACT
The long QT syndrome is an arrhythmogenic channelopathy characterized by severe alterations in ventricular repolarization, electrocardiographically translated as a QT interval prolongation. The involvement of various ion channels in the genesis of cardiac action potential causes that alterations in their structure and function lead to the so-called syndrome and to the presence of malignant ventricular arrhythmias. In 1920, Bazett adapted the formula of the cardiac electrical systole duration to the QT interval of the electrocardiogram, and proposed normal values of QT for a given heart rate. After Bazett's description, several formulas were described in different clinical situations to calculate the corrected QT interval. The knowledge about how to measure the QT interval and about its correction as a tool for the diagnosis of arrhythmogenic conditions and prevention of primary or secondary malignant ventricular arrhythmias is of vital importance for its clinical use.

RESUMEN
El síndrome de QT largo es una canalopatía arritmogénica caracterizada por una grave alteración en la repolarización ventricular, traducida electrocardiográficamente por una prolongación del intervalo QT. La implicación de varios canales iónicos en la génesis del potencial de acción cardíaco hace que las alteraciones de estructura y función de ellos conlleven al llamado síndrome y a la presencia de arritmias ventriculares malignas. En 1920, Bazett adaptó la fórmula de la duración de la sístole eléctrica del corazón al intervalo QT del electrocardiograma, y propuso valores normales del QT para una determinada frecuencia cardíaca. Después de esta descripción, varias fueron las fórmulas descritas en diferentes situaciones clínicas para el cálculo del intervalo QT corregido. Es de vital importancia, para el uso clínico, el conocimiento sobre cómo medir el intervalo QT y de su corrección, como herramienta para el diagnóstico de afecciones arritmogénicas y la prevención de arritmias ventriculares malignas primarias o secundarias.

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INTRODUCTION

The long QT syndrome (LQTS) is an arrhythmogenic channelopathy characterized by severe alterations in

ventricular repolarization, and is electrocardiographically translated by aprolongation of the QT[1] interval, predisposing to sudden death from malignant ventricular arrhythmias, of the helicoidal tachycardia type (*torsades de pointe* in its original language).

11 years after identifying the main channels affected in this disease, hundreds of mutations distributed in 10 genes so far associated with the syndrome have been described. Genetic research conducted since then has shown that while the severe form of the disease is sporadic, there are common polymorphisms in genes related to this condition, which may confer susceptibility to the development of helicoidal tachycardia, particularly with the use of certain drugs, moreover, polymorphisms with regulatory properties that may also enhance or still the severity of a mutation have been identified. The understanding of the molecular processes of the disease has allowed optimizing treatment, improving survival of those affected, and generating a significant genotype-phenotype-treatment correlation.

Despite the progress, a quarter of the cases do not have mutations in the genes described so far, so LQTS continues to be object of research[1]. This paper aims to summarize the foundations of ventricular repolarization (QT interval) and the importance of its measurement in different clinical situations.

Márquez[2] states that in his opinion the term channelopathy can be strong. He would rather call it "disease of ion channels", considering that the basis of this disease is the presence of disturbances in ion channels responsible for the balance between the input and output of these during ventricular depolarization and repolarization. As to the latter concept, Márquez[2] himself suggests that from the electrocardiographic point of view, normal ventricular repolarization is represented by the ST segment and the T wave. However, the electrocardiographic parameter that is taken into account to assess the duration of repolarization is the QT interval. It is important to remember that this interval comprises not only repolarization, but also the ventricular depolarization, and that the QRS complex is included. This is fundamental to understanding why it can be prolonged in the presence of conduction disturbances, and not just for repolarization disturbances.

Some ionic basis of ventricular repolarization

Normal ventricular repolarization is caused by the balance between inward currents of sodium (Na +) and calcium (Ca +) and the outward currents of potassium (K +). The latter are various but can be grouped into two, those responsible for repolarization in the initial phase of the action potential, called transient outward (I_{TO}) and those in charge of the rest of repolarization known as "late rectifier"currents (Ikr, Iks, IKur). There are several mutations that may affect the ion channels and their effect can be grouped into three: disorder of the channel permeability, changeof its activation and dysfunction in its inactivation.

Anton Jervell and Fred Lange-Nielsen[3] in 1957 described for the first time a family with 6 children, 4 of whom had congenital deafness and syncopal episodes, 3 of them had sudden death. The electrocardiogram (ECG) of the cases showed an unusually long QT interval. Both parents were asymptomatic, had a normal ECG and had no hearing problems. In 1963, Romano[4] and Ward independently published a familiar cardiac syndrome characterized by recurrent syncope, family history of sudden death and QT prolongation without neuronal deafness. From these findings described above,the classification of homozygous and heterozygous LQTS arose, however, the molecular complexity of ion channels and genetic study have allowed a classification with emphasis on genetic disorders.

Ion channels are transmembrane proteins that transport ions across the cell membrane. Channels involved in LQTS are selective or specialized in the transport of a single ion and are voltage-dependent, that is, its activation occurs at a specific intracellular voltage that varies according to the channel subtype. The electrical and contractile phenomena occurring in cardiomyocytes are controlled by these structures. Ion channels develop macromolecular complexes, there is a main unit forming the channel pore and auxiliary proteins that regulate it. The disorder on thechannel function in LQTS can occur in two places: in the main protein or in regulatory proteins.

The disorder in the pore forming unit, known as alpha, generates the 3 most common subtypes of LQTS: LQTS1(involving the potassium channel IKs) LQTS2 (involvingthe potassium channel IKr) and LQTS3 (involvingthe channel sodium INa). Since they are the most common, they have been characterized better from both a clinical and genetic point of view. The so-called Jervell-Lange-Nielsen syndrome currently corresponds to the varieties of LQTS 1 and 5. Characteris-

tically, these patients present congenital deafness and have compound homozygous or heterozygous mutations affecting IKs current. Romano Ward syndrome ranges from LQTS 1 to 10 and is not manifested with deafness[1]. To clinically describe the 10 genotypes of LQTS is not the purpose of this article; the reader is referred to the work of Medeiros *et al*.[1], where each of them is detailed.

Origin of formulas for measuring the QT

It is important to ask ourselves: how is the QT interval measured and when is it normal?

The duration of mechanical systole was a topic of much interest among the pioneers of cardiovascular physiology of the nineteenth century. According to Cobos and García[5], A. D. Waller, now famous for his contribution to the birth of electrocardiography, proposed in 1891 the following expression for the normal duration of systole: Mechanical systole= K $xRR^{1/2}$, where K has a value of 0.343. In 1920, Bazett did nothing but to adapt this formula to the duration of the electrical systole of the heart, the QT interval, and suggested that the normal value for a given heart rate isKx RR ½, where K is 0.37 for males and 0.4 for females[5]. Thus, to determine whether a particular patient has a normal QT interval, their QT should be compared with the ideal QT derived from Bazett's formula. This ideal QT is one that can be read in the popular electrocardiograms rules. Subsequently, to the Bazett's expression, the forgotten L.M.Taran and N. Szilagyi, according Cobos García[5], proposed a formula from which the concept QT corrected arose, which is the QT interval that a particular patient would have, theoretically, at a frequency of 60 beats per minute. Therefore, the expression used today, which is erroneously attributed to Bazett, belongs to L.M. Taran and N. Szilagyi[5]. In classical texts of the sixties, the role of these authors is clearly recognized and the statement: "Taran and Szilagyi corrected QT interval or Bazett's formula modified by Taran and Szilagyi[5]" is heard.

With the formula considered as corrected QT (QTc) = QT measured / $RR^{1/2}$, it is interesting to know that only with it, the QTc for different clinical situations found in medical practice cannot be calculated. There are different mathematical models describing the relationship between QT interval and the heart rate. The relationship between the HR and QT interval is curvilinear. There are different mathematical forms that model the relationship between QT and HR. There are models of different types: parabolic, polynomial, linear, hyperbolic, exponential, tables and nomograms[6]:

a) Linear: QTc = QT + x (1 − RR)
b) Hyperbolic: QTc = QT + x (1/RR − 1)
c) Parabolic: QTc = QT/RRx
d) Logarithmic: QTc = QT − x Nl(RR)
e) Logarithmic modified: QTc = Nl(exp(QT) + x (1 − RR))
f) Exponential: QTc = QT + x (e–RR − 1/e)
g) Arc-tangent: QTc = QT + x (arctg(1.0) - arctg(RR))
h) Arc-hyperbolic cosine QTc = QT + x (ln(2+30,5) − arccosh(RR+1))

"Nl" is Napierian logarithm, "exp" is the exponential function based on the number e = 2,718.

To optimize each formula the "x" parameter must be found by solving the r ratio equation (RR, QTc(x)) = 0.

From these models different formulas were derived: Bazett 1920, Fridericia 1920, Mayeda 1934, Adams 1936, Larsen and Skulason 1941, Ashman 1942 Schlamowitz 1946, Ljung 1949, Simonson 1962, Boudolas 1981, Rickards 1981, Hodges 1983, Kawataki 1984, Sarma 1984 Kovacs 1985, Van de Water 1989, Lecocq 1989, Rautaharju 1990, Todt 1992, Sagie (Framingham) 1992, Arrowood 1993, Yoshinaga 1993, Wohlfart 1994, Klingield 1995, Hodges 1997 and Matsunaga 1997[6].

The presentation of the mathematical models and formulas of QTc is not intended to cram the reader with the knowledge of their origins, or the formulas themselves, but it is intended to present the complexity of the issue. QT measurement is very often overlooked or poorly performed; however, LQTS is known by clinicians and cardiologists, who may evade the measure and correction of this interval because sometimes it is not simple. Viskin*et al*.[7] reported that less than 40% of physicians that are not cardiologists, less than 50% of cardiologists and over 80% of electrophysiologists, knew how to measure it correctly.

Some formulas for calculating QTc[6] are shown in the **table**.

Table. Formulas for calculating QTc.

Denomination	Formula
Bazett modified by Taran and Szilagyi[5]	$QTc = QT / (RR)^{½}$
Fridericia	$QTc = QT / (RR)^{(0,33)}$
Framingham	QTc = QT + 0,154 (1−RR)
Hodges	QTc = QT + 1,75 (FC − 60)
Sarma	QTc = QT - B1 Exp (-k1 . RR) QTc = QT [1-Exp (-k2 . RR)] $QTc = QT (RR)^{½} + B3$ $QTc = QT (RR)^{½}$ *
Strength equation	QTc = 453,65 × RR1/3.02 (R2 = 0,41)
Van de Water	QTc = QT – 0,087 (RR – 1000)
Matsunaga	QTc = log (600) QT / (log RR)
Kawataki	$QTc = QT/RR^{(0,25)}$
Mayeda	QTc = QT/RR x 0,604
Larsen and Skulason	QTc = QT + 0,125 (1 – RR)
Schlamowitz	QTc = QT + 0,205 (1 – RR)
Wohlfart	QTc = QT + 1,23 (FC – 60)
Boudolas	QTc = QT + 2,0 (FC – 60)
Sagie	QTc = QT + 0.154 (1 – RR)
Malik	QTc = QT/RR x 0,371
Lecocq	$QTc = QT/RR^{(0.314)}$

B and k: are regression parameters.
Exp: exponential function with base e = 2,718.
FC: heart rate.
RR: RR distance.
* It is stated that this formula is better than Bazett's

The usefulness of many formulas is given by their use in different clinical circumstances. The sympathetic and parasympathetic nerve block can be performed with propranolol and atropine. The standing + atropine combination is purely an activity of the sympathetic nervous system, the supine position + propranolol combination is purely an activity of the parasympathetic nervous system[8]. For these postural changes, Hodges correction showed QTc increases and decreases for the supply of atropine and propranolol, respectively. Individual correction would better adapt to the dynamic changes of the RR, which inevitably affect when correcting the QT interval in the right form[9]. Regarding the autonomic nervous system it is important to remember the usefulness of adrenaline to unmask the presence of LQTS, primarily for types 1 and 2. It is particularly effective to detect asymptomatic forms of LQTS1 (sensitivity, specificity, positive and negative predictive value of 92.5, 86, 76 and 96%, respectively). It may also be useful in diagnosing LQTS2 with lower sensitivity and specificity. It is not useful for LQTS3 or other forms of LQTS. Under normal conditions, sympathetic stimulation induces phosphorylation of the IKs potassium channel, and optimizes its function resulting in a shortening of the action potential. In LQTS patients, especially type 1, a paradoxical response to administration of low-dose epinephrine (0.025-0,2µg/kg/min) is observed which lengthen the QT interval more than 30 ms[10-13].

Fridericia and Framingham formulas have proven to be more useful for determining the QTc at one minute after peak exercise, with which it has been possible to prove that they are superior in establishing LQTS when compared with Bazett and Hodges formulas[14].

During sleep, in young patients, since they have a high heart rate, Hodges and Bazett formulas overcorrect the QTc, and Framingham and Fridericia formulas underestimate it. However, Hodges has the best approximation during sleep[15].

The nomogram method for correcting the QT interval is more accurate than the other three methods: Bazett, Fridericia and Framingham. With heart rates between 60 and 100 beats/min, the linear regression equation is:

$$QT = 237 + 0.158 \times RR \ (P < 0,001)$$[16]

When a 24-hour Holter is used in healthy subjects no significant difference inQTc values among the different formulas are found[17].

Considerations for the measurement of QT interval[6]

1. Record the ECG at baseline and at rest, and avoid postprandial period.
2. Keep a few minutes of rest before performing the ECG, to allow the QT interval to adapt to the heart rate (it takes 1-3 minutes).
3. The QT interval should be measured:
   a) Manually, preferably using the limb leads which show betterthe end of the T wave.

b) From the beginning of the QRS complex to the end of the T wave, measuring in 3-5 beats. The U wave probably corresponds to the late repolarization of medium myocardial cells and should be included in the measurement, if it is wide enough to be attached to the T wave. When measuring, it is often found that the end of the T wave is not clear, in such cases the end of this wave should be determined by extrapolation using the tangent method[18].

4. The measurement of the QT interval should be adjusted to the heart rate, which is called QTc interval. This correction is useful to make it independent of the heart rate of each individual and transform it into a comparable measure of the electrical activity between healthy and ill patients.
5. The best way to determine the QTc has not yet been achieved because studies are not prospective. Some authors argue that the Framingham formula is the most suitable mode from the epidemiological point of view, based on empirical data obtained from large population samples.
6. Avoid measuring the QT interval in cardiac cycles with large variation in the sinus interval or in those preceded by arrhythmias.
7. A stress test can be performed to rule out a marked QT prolongation during the recovery phase.
8. QT measurement is particularly changeable if the patient is in atrial fibrillation, because the QT interval varies from beat to beat depending on different RR intervals.
9. The QTc lengthens with age, it is longer in adult women than in men of the same age, and the longest QTc is found shortly after awakening.

When can the QTc interval be considered normal?

It has been suggested that the QT interval should be measured preferably in the D_{II} and V_5 leads, where it has been registered to have greater predictive power. It reflects the duration of ventricular repolarization and is measured from the start of the Q wave to the end of the T wave. Conventionally, Bazett's formula is used to correct the length of the interval according to the heart rate ($QTc = QT / RR^{1/2}$, expressed in seconds). It is advisable that the physician performs a manual measurement and should not rely on automated measurements that, while useful for other intervals, are usually imprecise in the calculation of the QT interval; this is a dynamic range and normal limits depend on several factors. While a QTc interval ≥ 440 ms in men and ≥ 460 ms in women has been considered abnormal, in this range we can find both carriers of mutationsand healthy subjects. In families with LQTS1, no case with positive genotype has a QTc < 410 ms, and none with a negative genotype has a QTc > 470 ms. A QTc > 440 ms is effective for detecting patients with mutations associated with LQTS, a QTc > 470 ms is useful for detecting patients at risk of developing symptoms and a QTc > 500 ms has been found in symptomatic patients with treatment[6].

As mentioned, the QT measurement includes QRS duration, thus in the presence of branch blocks, wherein the values of QRS duration are increased with respect to its normal value, an increase in QT occurs. Sometimes the measurement of QT is left out if QRS duration ≥ 120 ms. In these circumstances the JT interval (measured from the point J to the end of the T wave) is more appropriate than QT as a measure of ventricular repolarization[19]. The JT interval is independent of QRS duration and represents a better index of ventricular repolarization[20].

Finally, it should be mentioned that observing variations of T wave (macro and microalternans) is as important as measuring the QT. These variations are related to alterations in repolarization, which vary from beat to beat, and cause its successive changes. In LQTS patients, there has been increased presence of T macroalternans prior to episodes of helicoidal tachycardia[21-23], although other studies have not shown this relation[24]. In LQTS patients, during the day, it is easier to observe the T wave macroalternans, perhaps related to the regional variations in the circadian rhythm. Despite having described the presence of this macroalternans prior to helicoidal tachycardia episodes, which may be a warning sign, no significant differences in T macroalternans in patients with symptomatic and asymptomatic LQTS, nor among patients under treatment with beta-blockers or without them have been reported. The beat-to-beat variations of T-wave are related to changes in the action potential in its ionic currents[25,26].

CONCLUSIONS

The measurement and calculation of the QTc interval can be challenging for daily clinical practice. The knowledge about how to measure the QT interval and

its correctionis vital for clinical use, as a tool for the diagnosis of arrhythmogenic conditions and prevention of primary or secondary malignant ventricular arrhythmias.

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