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QT Interval and QT Variability

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1. Introduction

Sudden cardiac death (SCD) is among the most common types of mortality in developed countries. It for more deaths each year than the total number of deaths from AIDS, breast cancer, lung cancer and stroke together. SCD accounts for approximately 50% of all deaths from cardiovascular diseases and 20% of total mortality (1). In the general population, SCD mostly occurs in individuals who are unrecognized to be at risk (2,3).

Although the causes of SCD are multiple, the majority (80–85%) of sudden cardiac deaths is caused by acute ventricular arrhythmias (4). Traditionally, the risk of ventricular arrhythmias has been evaluated based on the duration of QT interval on a standard surface ECG.

2. QT interval

QT interval is measured in milliseconds (ms) from the Q-top, the beginning of the QRS complex, until the end of the T wave and reflects the time between the initial fast depolarization of the left ventricle and its subsequent repolarization (5). Duration of the QT interval is highly dependent on T wave morphology, which is determined by the differences in the time course of repolarization of 3 predominant ventricular myocardial cell types (endocardial, epicardial, and M cells) (6).

The start of the T wave is caused by the more rapid rate of decline of the plateau or phase 2 of the epicardial action potential, creating a voltage gradient and electrotonic current flow across the wall. The gradient gradually increases as the epicardial action potential continues to repolarize, reaching a maximum with full repolarization of epicardium; this juncture marks the peak of the T wave. Divergence of the plateau of the endocardial AP from that of the M cell occurs soon after that of epicardium, causing a voltage gradient between endocardium and the M region and thus a current opposite to that generated by the voltage gradient that develops between epicardium and the M region. Under normal conditions, current flow between the M region and epicardium is greater than that between the M region and endocardium, resulting in the inscription of the ascending limb of the upright T wave. Once epicardium is fully repolarized, continued repolarization of endocardium leads to a progressively larger voltage gradient between endocardium and the M region, giving rise to the initial descending limb of the upright T wave. The last cells to repolarize are the M cells, contributing to the final segment of the T wave. Full repolarization of the M region marks the end of the T wave (7,8).

In the presence of cardiac disease, ventricular repolarization heterogeneity is increased, leading to QT interval prolongation (9). However, QT interval duration is also affected by various noncardiac factors, such as age, gender, inflammation, changes in autonomic nervous tone, and electrolyte disturbances (10), thereby limiting its use in the analysis of the electrophysiological properties of ventricular myocardium. Furthermore, QT interval duration is highly dependent on heart rate. Despite a variety of methods that have been proposed to derive a rate-corrected (QTc interval), which would allow the comparison of QT values obtained at different heart rates, no consensus has been reached so far (11). Since there is growing evidence that QT interval prolongation by itself cannot accurately predict the pro-arrhythmic potential, other ECG parameters are considered more reliable and have been investigated in pre-clinical and clinical studies.

3. Long QT syndrome

The long QT syndrome (LQTS) is characterized by the appearance of long QT intervals in the electrocardiogram, an atypical polymorphic ventricular tachycardia displaying features of torsade de pointes, and a high risk for sudden cardiac death (12). Congenital LQTS can be further subdivided into six genotypes distinguished by mutations in at least five different ion channel genes located on chromosomes 3, 7, 11, and 21 (13,14). These mutations result in defects in the sodium channel (SCN5A, LQT3), the rapidly activating delayed rectifier channel (I Kr) (HERG, LQT2 or KCNE2, LQT6), and the slowly activating delayed rectifier channel (I Ks) (KvLQT1, LQT1 or KCNE1, LQT5), respectively. Acquired LQTS is a term long reserved for a syndrome similar to that encountered in the congenital forms but caused by exposure to drugs that prolong the duration of the ventricular action potential (15) or to QT prolongation secondary to bradycardia, electrolyte imbalance or remodeling of the ventricular myocardium that accompanies dilated and hypertrophic cardiomyopathies (16,17).

Management of patients with long QT syndrome is strongly dependent of the genetic basis of the disease. The trigger for most of the episodes of life-threatening arrhythmias of long QT syndrome is represented by a sudden severe increase in sympathetic activity, which is largely mediated through left cardiac sympathetic nerves. (12) Therefore B-adrenergic blockade represents the first line of treatment in symptomatic patients with long QT syndrome. It has been shown that in LQT1 patients B-blockers significantly reduce life-threatening events and these patients seldom need more than antiadrenergic therapy. Compared to LQT1 patients, LQT2 and LQT 3 patients have more life-threatening events despite treatment with B-blockers. (18) In these patients additional therapies are needed. In patients who remain symptomatic despite treatment with B-blockers (minority of LQT1 and the majority of LQT2 and LQT3 patients) left cardiac sympathetic denervation (LCSD) is to be considered. Although moderately invasive (it requires surgical removal of first four thoracic ganglia) it has proven effective since it was shown that with LCSD we can achieve about 90% reduction in cardiac events and with this a dramatic improvement in patients' quality of life. (19). Regarding ICD therapy it is uniformly agreed that in case of documented cardiac arrest ICD should be implanted immediately. However, there are significant differences in opinion regarding the use of ICDs in patients without cardiac arrest. It should not be forgotten that ICD do not prevent the occurrence of malignant arrhythmias and that most of arrhythmias in patients with long QT syndrome are self terminated. Furthermore pain associated with shocks can in turn perpetuate malignant rhythm disturbances through

massive catecholamine release. It is therefore of paramount importance to implant only to symptomatic patients since there to date no clear benefit of ICDs in asymptomatic patients with long QT syndrome has been demonstrated. (20)

4. Short QT syndrome

Short QT syndrome (SQTS) is an inheritable primary electrical disease of the heart, discovered in 1999. It is characterized by an abnormally short QT interval (<300 ms) and a propensity to atrial fibrillation and SCD (21). Like in the case of long QT syndrome there is more than one genetic mutation that can lead to a short QT interval in the ECG and so far gain-of-function mutations in *KCNH2*, *KCNQ1*, *KCNJ2*, encoding potassium channels and loss-of-function mutations in *CACNA1C* and *CACNB2b*, encoding L-type calcium channel subunits have been identified (22). Shortening of the effective refractory period combined with increased dispersion of repolarization is the likely substrate for re-entry and life threatening tachyarrhythmias (23). ICD is the therapy of choice in patients with a short QT syndrome. However, antiarrhythmic drug therapy may constitute a potential adjunct or even an alternative therapy in children and newborns, where ICD implantation is very challenging. To date several antiarrhythmic agents were tested in this patient population. Flecainide, sotalol and ibutilide (acting through blocking of the rapidly activating delayed rectifier potassium current) all failed to prolong the QT interval in patients with short QT syndrome.(24) In vitro electrophysiological studies showed that the mutation of the I_{Kr} channel led to a reduced ability of these antiarrhythmic agents to block the channel.(25) It was recently shown that quinidine, in contrast to flecainide, ibutilide and sotalol, can normalise the QT interval at resting heart rates. Additionally, quinidine also restored the heart rate dependence of QT interval towards an adaptation range of normal subjects.(26) Although studied extensively, the exact mechanism of its action for now remains incompletely understood. We have to keep in mind, however, that short QT interval can be a consequence of several gain- and loss-of-function mutations. Therefore for this patient population a uniform medical management currently cannot be recommended.

5. QT variability

Repolarization of the ventricular myocardium is a complex process that varies in duration from site to site and from beat to beat. The mechanisms that govern spatial heterogeneity in ventricular repolarization are well studied, and are largely related to variation in ion channel function and density from one myocardial region to another (27). Ventricular wall comprises of 3 cell types: epicardial, M and endocardial cells. Epicardial and M cell action potentials differ from endocardial cells with respect to the morphology of phase 1. These cells possess a prominent transient outward current mediated notch responsible for the 'spike and dome' morphology of the epicardial and M cell response. M cells are distinguished from the other cell types in that they display a smaller slowly activating delayed rectifier current, but a larger late sodium current and sodium-calcium exchange current. Because of these differences spatial heterogeneity in ventricular repolarization occurs.

The mechanisms responsible for temporal fluctuations in repolarization, however, are poorly understood. Several clinical studies over the past decade have examined beat-to-beat

variability in QT interval of the surface electrocardiogram (ECG) as a means for quantifying temporal repolarization lability (28).

Recently, a PC-based electrocardiogram software program has been developed that in real time, acquires, analyzes, and displays QT variability in each of the 8 independent channels that constitute the 12-lead conventional electrocardiogram (29). The system also analyzes and displays the QT variability from QT-interval signals that are derived from multiple channels and from singular value decomposition such that the effect of noise and other artifacts on the QTV results are substantially reduced compared with existing single-channel methods.

When analysis begins, templates for the overall ECG signal in each channel are first formed. To construct the initial templates, the first 20 beats are collected into a single averaging bin. Then, the mode of the probability function of the R-R interval is created for those beats and its maximum determined. Finally, those 10 beats that are closest to the determined maximum are selected, and a template ECG wave for the same beats is then obtained by averaging the superimposed ECG signals based on the fiducial point of the QRS wave.

After the initial global templates have been constructed, breaking points called PQbreak (between the P wave and the QRS complex), QTbreak (between the QRS complex and the T wave), Tend (the final point of the T wave), and Pini (the initial point of the P wave) are used to construct individual templates for the 3 principal waveforms QRS, T, and P.

The principal steps of the algorithm used in analyzing QT variability are described in detail, as follows:

1. The template beat $\phi(n)$, where n is the sample number, is constructed from the selected beats using a signal averaging technique. Only those beats with shape similar to the template are selected for averaging. Because the program automatically determines the borders of each wave component (P, QRS, and T templates, as described previously) and therefore the time window for matching of waves, its remaining task is to shift the particular incoming wave component with respect to the template until obtaining an acceptable match. The matching algorithm is based on the least square deviation of the incoming wave vs the template.
2. The matching of waves is performed in 2 substeps. First, a broader time interval containing the complete wave component is used to reach the best fit. Second, each wave of any incoming beat is shifted to or from the trigger point to achieve the best alignment with the template in the appropriate time window. For this purpose, an error function of time shifting is defined as the sum of the squared differences between the template wave (P, QRS, or T) and the appropriate shifted version of the incoming beat.
3. The program uses the QT variability algorithm to generate, in real time, the time series of the QT interval along with that of the R-R interval. Time series are analyzed according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Clinical Electrophysiology (30) using specific indices such as the SD of normal-to-normal (NN) R-R and QT intervals (SDNN R-R and SDNN QT, respectively), the root mean square (RMS) of the successive interval difference (RMSSD R-R and RMSSD QT), and so on.

6. Clinical application

Although QT interval prolongation has been proposed as a risk factor for death in an apparently healthy population in patients after myocardial infarction in diabetic patients,

and patients with advanced heart failure, its direct relation to pro-arrhythmic risk remains questionable (1,17).

While measuring subtle variation in QT interval duration is technically challenging, new methodology (28,29) has enabled investigators to study the effect of disease states on ventricular repolarization variability, and the prognostic value of the QT interval variability measurement. QT variability has been shown to be elevated in congestive heart failure (CHF) (28), ischemia (31), and some types of hypertrophic cardiomyopathy (26). Increased QT variability was also found to predict appropriate implantable cardioverter-defibrillator shocks in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial-II) study (33), as well as total mortality and sudden death in post-myocardial infarction patients without implantable cardioverter-defibrillators (34).

Based on the current clinical evidence it appears that although currently considered 'the golden standard' QT interval measurement will in the future be replaced by novel, more reproducible automated methods that will allow for better prediction of arrhythmic events in various clinical settings.

7. Pharmaceutical application

Pro-arrhythmic drug effects have been one of the most common reasons for withdrawal of drugs from the market in many therapeutic areas. Currently, the potential pro-arrhythmic effects of drugs are addressed in accordance with The 'International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use' (ICH) E14 clinical guidance issued in May 2005. The centre-piece of the guidance is the 'thorough QT/QTc study' (TQT), which is a dedicated study with the primary objective to quantify the effect of a new molecular entity on the QT interval (35).

Although considered the 'golden standard', use of QT interval duration as a surrogate marker for the prediction of drug-induced arrhythmias has several pitfalls (36,37):

- Many drugs affect both QT interval duration and heart rate. Since all current heart rate correction methods are imperfect, it is difficult to distinguish the drug-related changes in QT interval from those caused by heart rate alterations.
- Since QT interval duration is dependent on several non-cardiac factors (e.g. inflammation, autonomic nervous system), the therapeutic effect of drugs on the underlying disease may mask the potential adverse drug effects on cardiac repolarization and QT interval.
- QT interval is used as a surrogate marker of arrhythmias; however, its relationship to the arrhythmic events has been seriously questioned in the recent clinical studies.
- It is assumed, but has not been proved, that even a small drug-induced increase in QT interval indicates some risk of arrhythmias.

Given these limitations it is clear that in order to adequately address pro-arrhythmic risk of drugs it is necessary to look beyond the drug-induced changes of QT interval. Other drug-induced ECG changes, associated pro-arrhythmic risks, and threshold of magnitude of changes should be considered as a cause for concern. Therefore, novel advanced ECG technologies should be developed to better define drug-induced arrhythmogenesis.

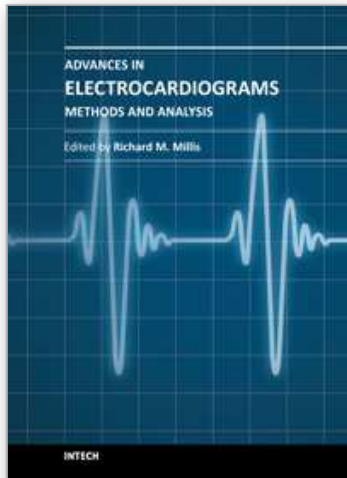
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Advances in Electrocardiograms - Methods and Analysis

Edited by PhD. Richard Millis

ISBN 978-953-307-923-3

Hard cover, 390 pages

Publisher InTech

Published online 25, January, 2012

Published in print edition January, 2012

Electrocardiograms are one of the most widely used methods for evaluating the structure-function relationships of the heart in health and disease. This book is the first of two volumes which reviews recent advancements in electrocardiography. This volume lays the groundwork for understanding the technical aspects of these advancements. The five sections of this volume, Cardiac Anatomy, ECG Technique, ECG Features, Heart Rate Variability and ECG Data Management, provide comprehensive reviews of advancements in the technical and analytical methods for interpreting and evaluating electrocardiograms. This volume is complemented with anatomical diagrams, electrocardiogram recordings, flow diagrams and algorithms which demonstrate the most modern principles of electrocardiography. The chapters which form this volume describe how the technical impediments inherent to instrument-patient interfacing, recording and interpreting variations in electrocardiogram time intervals and morphologies, as well as electrocardiogram data sharing have been effectively overcome. The advent of novel detection, filtering and testing devices are described. Foremost, among these devices are innovative algorithms for automating the evaluation of electrocardiograms.

How to reference

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Bojan Vrtovec and Gregor Poglajen (2012). QT Interval and QT Variability, Advances in Electrocardiograms - Methods and Analysis, PhD. Richard Millis (Ed.), ISBN: 978-953-307-923-3, InTech, Available from: <http://www.intechopen.com/books/advances-in-electrocardiograms-methods-and-analysis/qt-interval-and-qt-variability>

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