EDITORIAL

An Update on QT Measurement and Interpretation Methodologies

Jean-Philippe Couderc, Ph.D. and Wojciech Zareba, M.D., Ph.D.

From the Heart Research Follow-up Program, Cardiology Division, University of Rochester Medical Center, Rochester, NY

The Food and Drug Administration (FDA) of the US Department of Health and Human Services is entrusted with the responsibility to regulate ECG medical devices and drugs in order to certify their safety and efficacy. Consequently, regulatory decisions are known to be significant driving forces for the research and development strategies of academic and private organizations. Currently, the Agency is facing a challenging issue in assessing the torsadogenic properties of new cardiac and noncardiac drugs because of the lack of appropriate surrogate markers. Indeed, the QT interval prolongation measured from standard 12-lead surface electrocardiograms (ECGs) has been shown to have very strong limitations for predicting the risk of drug-induced torsades de pointes. Consequently, the field of quantitative electrocardiography has become directly impacted by this regulatory concern creating significant scientific and commercial momentum around the development of better ECG technologies.

This regulatory concern was raised following the market approval of cisapride and terfenadine; these drugs became blockbusters in the US market after couple of years and were removed from the market following numerous reports about their torsadogenic properties. These drugs have been associated with a reduction of the rapidly activating inward rectifier repolarizing currents (Ikr) leading to a delay of the recovery phase of the heart ventricles (and a 5–10 ms QTc interval prolongation on the surface ECGs).[1,2] The torsadogenic role of these drugs is clear, yet the underlying arrhythmogenic mechanism remains to be elucidated.

Currently, the FDA requires from pharmaceutical companies that the QT-prolonging properties of any novel compound to be assessed using clinical trials specifically designed for this purpose (the thorough QT studies).[3] The level of precision required for QT measurements in these trials is much larger than the one expected in ECG equipment designed for clinical use.

Significant efforts to improve the QT technologies have been made during these past 5 years, and this supplement includes a set of articles from ECG equipment companies and academic groups providing an in-depth review of the QT issues and of selected QT technologies.

These articles describe methodological, technical, and electrophysiological aspects of the measurements of the ventricular repolarization duration including the effects of the autonomic regulation, the heart rate, and the heart rate adaptation of the QT interval. Dr. Extramania et al. review the role of cycle length on QT interval and present the RR bin technique as an alternative to reduce the effect of heart rate on this measurement. Dr. Mortara reports a study including a unique way of correcting his QT measurements, taking into account several previous RR intervals rather than the single previous one. The technical factors are important when measuring the QT interval, amongst these factors, the quality of the signal is driven by both the noise content and the amplitude of the ECG

Address for reprints: Jean-Philippe Couderc, Ph.D., MBA, Box 653, Heart Research Follow-up Program, Cardiology, University of Rochester Medical Center, Rochester, NY 14642, USA. Fax: 585-273-5283; E-mail: jean-philippe.couderc@heart.rochester.edu

signal. Dr. Badilini et al. present a method to reduce QT variability by optimal selection of the ECG strips from 12-lead Holter ECGs.

Most of the contributors of this supplement present their own algorithmic solution to improve automatic QT measurements. The article from Dr. Strachan et al. describes an algorithm imitating cardiologists' annotations based on a Hidden Markov Model. Dr. Zhou and coworkers presents several algorithmic alternatives according to the type of ECG signals with a strong focus on their clinical applications. Drs. Dota, Kors, and Xue describe validation studies of their software when compared to human-based metrics. These works suggest that the precision of QT measurements can be very similar to manually based QT measurements, in addition, several of these studies highlight the ability of computers to analyze a large set of cardiac beats in order to better control the effect of potential confounding factors, such as heart rate, heart adaptation, and signal quality, Unfortunately, all the reported studies are based on different sets of electrocardiographic recordings and comparing the precision of these technologies is a rather hazardous task. The field would benefit from a central repository of continuous ECGs from which data can be used for both development and validation of such technologies. It is why the Telemetric and Holter ECG Warehouse (THEW) initiative (www.THEW-project.org) is currently implemented at University of Rochester Medical Center and aims at providing such resources. An official agreement has been signed with the Food and Drug Administration in order to develop and grow this repository and to trigger research and development activities related to quantitative electrocardiography and cardiac safety.

To conclude, this supplement provides an overview of various technologies recently developed for improving the precision of the QT interval measurements from surface ECGs. The Supplement includes research works from major ECG equipment companies and demonstrate that by better controlling the various factors involved in the ventricular repolarization process and by refining computer algorithms, the QT precision can be significantly increased.

Conflicts of Interest: JPC and WZ are consultants for iCardiac Technologies Inc.

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