EDITORIAL

New Era for Digital ECG: FDA Requires Digital ECG Submission for Tested Drugs

Wojciech Zareba, M.D., Ph.D.

From the Cardiology Unit, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York

Recent developments in understanding of genetic etiology and channelopathies underlying inherited forms of the long QT syndrome (LQTS) contributed to major progress in basic and clinical electrophysiology of cardiac arrhythmias and to increasing awareness of the important role of repolarization abnormalities in arrhythmogenesis.¹⁻⁴ Abnormal kinetics of three potassium currents (IKr, IKs, Kir2.1) and one sodium current (INa), due to mutations in six ion channel genes, were identified to cause QT prolongation and a propensity to polymorphic ventricular tachycardia (torsades de pointes) leading to syncope or sudden death. Function of ion channels could be affected by various pharmacological agents, which frequently are not developed to target specific channels but do influence their function.⁵ Secondary QT prolongation, caused by the unwanted action of drugs affecting ion channels, is of major concern because it may lead to torsades de pointes and sudden death in a large number of individuals exposed to such medications.⁵ Drugs (including quinidine, sotalol, terfenadine, cisapride, erythromycin) affecting the function of potassium channels have already been shown to cause torsades de pointes ventricular tachycardia. Some of them (affecting function of IKr channel) have been withdrawn from the market (terfenadine) or their recommended use restricted (cisapride).

Many approved and newly developed drugs may affect ion (especially potassium) channels, and they

require careful preclinical and clinical evaluation. Preclinical evaluation of a drug consists of quantitative analysis of ion channel function using cellular models, and subsequently, repolarization analysis in myocardial tissue or animal models. However, clinical studies with comprehensive analysis of repolarization duration and morphology provide critical information about the effect of a tested drug and its safety. Information about deleterious effects of a drug on repolarization and its proarrhythmic properties have usually been acquired in phase III and phase IV clinical studies, that is, after a number of cases with torsades de pointes (and death) have been identified. Regulatory agencies (e.g., the FDA), medical community, and professional societies (e.g., ISHNE) are eager to identify drugs that potentially will cause QT prolongation and serious life-threatening arrhythmias before they become widely used. For this reason, all currently tested drugs have to undergo careful evaluation regarding the effect on repolarization (QT interval duration in particular).

In the October 2001 issue of the *Annals of Non-invasive Electrocardiology*, the ISHNE Task Force under the leadership of Dr. Arthur J. Moss, proposed guidelines for evaluating the effect of drugs on repolarization.⁶ These guidelines rely on a combination manual/visual evaluation of QT duration and increasingly on digital ECG signal processing. There are several benefits of digital ECG data acquisition that use standard resting ECG recordings

Address for reprints: Wojciech Zareba, M.D., Ph.D., Heart Research, Cardiology Unit, University of Rochester, Box 653, 601 Elmwood Ave., Rochester, NY 14642. Fax: 716-273-5283; E-mail: heartwz@heart.rochester.edu

and 24-hour (or even longer) Holter ECG recordings. Continuous access to monitored digital ECG data allows the analysis of:

- Dose-dependent effects of a tested drug (and possible arrhythmias)
- Assessment of adaptation of QT to a wide spectrum of changing heart rate, including night hours (not available when using resting ECGs)
- Analysis of dynamic features of repolarization including the QT-RR relationship (regression analysis, slope), QT or repolarization morphology variability, or T-wave alternans
- Application of novel algorithms for repolarization analyses including an automatic area based approach or T-wave loop morphology

Such a comprehensive digital-ECG based approach is likely to improve early identification of drugs that might have proarrhythmic properties.

Digital ECG data acquisition also provides the opportunity to improve quality control of ECG analysis and allows more comprehensive auditing (review) of ECG interpretation. In particular, the FDA is interested in reviewing ECG recordings acquired during drug testing with additional access to the interpreter's annotation. This process will not only better document QT measurements, but will allow the inspection of repolarization morphology (TU wave) in single and multiple (superimposed) leads. Access to digital ECG recordings will provide the opportunity to achieve better comparisons of repolarization duration and morphology when recorded off and on a tested drug. The majority of currently used ECG machines record ECG signals in digital format, however, the format of data acquisition and storage is proprietary and varies among manufacturers. Similarly, digital acquisition of long-term Holter recordings is replacing analog recordings, but again, the format of digital ECG data files is diverse among manufacturers of Holter systems. For these reasons, there is a need to develop a uniform standard for ECG/Holter output files that allows universal access to acquired data.

In 1998, ISHNE with the participation of several Holter manufacturers developed the "ISHNE Holter Standard Output File Format" aiming to permit the interchange of data between systems (recorders) from different Holter manufacturers.^{7,8} The description of the format can be found at the

ISHNE web site (www.ishne.org) in the technical section. Few manufacturers implemented or are in the process of implementation of the ISHNE format in their Holter systems.

On November 19, 2001, the FDA organized public meeting focused on "Electronic Interchange Standard for Digital ECG and Similar Data" during which the FDA described concrete plans to request ECG data in a standard digital format whenever ECG information is submitted to the FDA by pharmaceutical companies seeking the approval of a drug.⁹ This requirement calls for the development of a standard digital format, which will have to be used instead of the manufacturers' proprietary digital formats. The FDA, with Dr. Norman Stockbridge leading efforts of standardization, proposed an XML file format, which is receiving wide approval for short-term (standard) ECG recordings. Its suitability for long-term recordings has to be discussed because a binary format (like ISHNE Standard Output File Format) might provide a vehicle that would provide easier handling of large data sets than the XML format. The FDA's plan is to finalize the standard for digital ECG data by April 1, 2002 and then, within a few months, to implement the requirement of submitting the data from ECG studies in such a standard format to the agency.

These implementation of a standardize system for submitting ECG data to FDA will have several implications. Most importantly, digital electrocardiology will enter a new era with benefits not only for the regulatory system, but also for clinical and research activities. A uniform standard of digital ECG will allow the interchange of the data acquired by a variety of recording systems therefore allowing invigorated research based on multicenter collaboration. Broad access to digital data will also trigger further research focused on ECG signal processing with the development of new algorithms and tools for clinical use. The year 2002 is the year of Willem Einthoven, the father of electrocardiography. It has been 100 years since the publication of Einthoven's description of ECG recordings, but the field of electrocardiology has remained stagnant for the last few decades. Regulatory requirements of a standard digital ECG format will open a new era in electrocardiology prompting users to take advantage of the digital signal and leverage electrocardiology to a higher clinical and research application level.

REFERENCES

1. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome: Prospective longitudinal study of 328 families. *Circulation* 1991;84:1136-44.
2. Zareba W, Moss AJ, Schwartz PJ, et al. Influence of the genotype on the clinical course of the long QT syndrome. *N Engl J Med* 1998;339:960-965.
3. Splawski I, Shen J, Timothy KW, et al. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. *Circulation* 2000;102:1178-1185.
4. Zareba W, Rosero S. Long QT syndrome. E-Medicine World Medical Library 2001. <http://www.emedicine.com/med/topic1983.htm>
5. Haverkamp W, Breithardt G, Camm AJ, et al. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs. Clinical and regulatory implications. *Cardiovasc Res* 2000;47:219-233.
6. Moss AJ, Zareba W, Benhorin J, et al. ISHNE Guidelines for Electrocardiographic Evaluation of Drug-related QT Prolongation and Other Alterations in Ventricular Repolarization: Task Force Summary. *Ann Noninvas Electrocardiol* 2001;6:333-341.
7. Zareba W, Locati EH, Maison Blanche P. The ISHNE Holter Standard Output File Format: A step toward compatibility of Holter systems. *Ann Noninvas Electrocardiol* 1998;3:261-262.
8. Badilini F. The ISHNE Holter Standard Output File Format. *Ann Noninvas Electrocardiol* 1998;3:263-266.
9. FDA website containing information about November 19 meeting and "Proposed Standard for Exchange of Electrocardiographic and Other Time-Series Data": <http://www.fda.gov/cder/regulatory/ersr/default.htm#ECG>