Electrocardiography and Repolarization Abnormalities: Benefits and Limitations of Fully Automated Methods for QT Measurement

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During early phase trials of new drug safety in humans, prolongation of the rate-corrected QT interval has become a surrogate marker for heterogeneity of ventricular repolarization that can cause potentially fatal arrhythmic events. Thorough QT studies have been designed to test for clinically significant QT prolongation by the new drug in comparison with placebo, using a positive control such as moxifloxacin in addition to demonstrate adequate test sensitivity of the method used for QT determination. Measurement of QT may be done manually, automatically, or by adjudication of selected automated samples. Although full automation of QT measurement might lead to cost-effective benefits, several important problems limit the fully automated evaluation of QT. Variability and ambiguity of T wave morphology when repolarization becomes abnormal limits precision of QT measurement by all methods. Automated measurement of QT is improving, but in the absence of a universally accepted ECG definition of the end of the T wave, QT measurements have become proprietary engineering solutions that differ among ECG core labs and among algorithm developers. Significant differences of QT measurements occur between different single ECG leads, between single leads and global intervals of duration (from the earliest onset in any lead to the latest offset in any lead), and between and within different generations of automated algorithms in digital electrocardiographs from different manufacturers. Looking toward the future, it should be appreciated that prolongation of the unidimensional QT duration is not necessarily equivalent to complex heterogeneity of repolarization, and we are likely to move beyond evaluation of the QT interval alone as a marker of arrhythmogenicity. Alternative measures of repolarization such as T wave symmetry, T wave notching, and PCA of the T wave loop might further increase the benefit of fully automated ECG algorithms in drug safety testing.