

Drug-Induced T-Wave Morphology Changes

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e-ISBN: 9788793102583
Available From: December 2013
Price: € 0.00

Description:

The risk of life-threatening ventricular tachyarrhythmia such as Torsades de Pointes (TdP) is assessed in drug trials by measurement of QT prolongation on the ECG. However, the QT interval is not a strong biomarker for TdP risk. Especially, the sensitivity and specificity of the measurement is limited. Investigation of alternative biomarkers to assess the risk of drug-induced arrhythmia is therefore an active area of research. Much of the current research is based on the drug-induced changes in the morphology of the T-wave.

Drug-induced inhibition of the delayed rectifier potassium current (IKr) can cause delayed cardiac repolarization and lead to development of TdP. Inhibition of the potassium current appears as QT interval prolongation and changes in the morphology of the T-wave on the ECG. IKr inhibiting drugs and their effect on ECG markers of abnormal repolarization therefore play a central role in this thesis.

In our first study, we used common classification methods to separate congenital and drug-induced IKr inhibition from healthy controls who were not taking any medication during the trial period. We investigated separation of data by two electrocardiographic repolarization parameters: The heart rate-corrected QT interval (QTc) and the MCS, a composite score of T-wave morphology which measures flatness, asymmetry and the presence of notches on the ECG. Changes in the T-wave morphology were better at separating normal from abnormal repolarization compared to QTc. Also, nonlinear boundaries can provide better classifiers than linear boundaries. In our second study we investigated the electrocardiographic T-wave peak-to-end interval (Tpe), a commonly used measurement, thought to represent transmural repolarization heterogeneity. Repolarization heterogeneities induced by torsadogenic drugs are thought to be responsible for inscription of electrocardiographic T-wave and the QT interval. However, there is no widely accepted approach which can be used to assess repolarization heterogeneity. The Tpe interval was proposed to quantify transmural dispersion of repolarization (Tdr) in previous vitro experiments. However, there have been an increasing number of reports of inconsistencies about whether the Tpe interval can be used to predict arrhythmia. It also remains controversial what the Tpe measurements actually represents. However, it is important to quantify how the Tpe interval is correlated with the whole heart repolarization time, represented by the QT interval. We therefore investigated whether the Tpe interval is correlated with QT prolongation induced by two torsadogenic drugs. Despite significant QT prolongation with both IKr-inhibiting drugs, the Tpe interval remained almost unchanged. Thus, at least, this study raises a doubt about usefulness of Tpe as a biomarker for repolarization changes and torsadogenic potential in drug safety studies. In our third study we propose a new method for assessing abnormal repolarization characteristics on the ECG. The T-wave is down-sampled to a minimal number of samples in such a way that reconstruction of the original T-wave is possible. Using a combination of 8 samples extracted from the down-sampled T-wave as features it was possible to separate normal from abnormal repolarization significantly better compared to QTc. In addition, this approach has the advantage, unlike the QT interval, of being robust to the T-wave end determination. In the down-sampled ECG representation of the T-wave, it is further indicated that Tpe interval may shorten following IKr inhibition and that the most prominent drug-induced repolarization changes occur on the ascending segment of the minimal T-wave representation. Collectively, this work may lead to improved prediction and interpretation of ECG-related abnormal repolarization.

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