

T WAVE INDICES OF DRUG INDUCED CHANGES IN REPOLARISATION

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For the past decade prolongation of the QT interval has been used by the Regulatory Agencies as the principal biomarker to investigate the arrhythmogenic potential of new pharmaceutical compounds. It has been suggested that torsade de pointes (TdP) is unlikely to occur if a drug prolongs the mean QTc (in thorough QT studies) by less than 5ms and that the risk of TdP is substantially higher for prolongations of >20ms. With inherited long-QT syndromes there is a 5% exponential increase in the relative risk of a cardiac event for every 10 ms increase in QTc duration beyond 440ms. Although it is accepted that prolongation of QTc interval is associated with a significant increased risk of arrhythmia there is concern that when using QTc prolongation as a sole arbiter of pro-arrhythmic risk there is a possibility that safe, beneficial candidate drugs may not achieve regulatory approval because of benign QTc prolongation. Amiodarone may not have been approved if it had been subjected to a Thorough QT Trial and conversely some candidate compounds which induce a shortened QTc interval may be potentially arrhythmogenic (the short QT syndrome). Consequently much effort is being made to find combinations of clinical ECG biomarker indices which increase the sensitivity and specificity to predict the arrhythmogenic potential of new compounds.

The purpose of this article is to discuss the electrophysiological basis and potential shortcomings of some of the newer T wave biomarkers which have been shown empirically to be potentially useful in a limited number of studies, relate these newer indices to QTc prolongation and discuss how these newer clinical biomarkers are a clinical expression of some of the indices within the preclinical TRIaD biomarker of pro-arrhythmic risk. TRIaD stands for the combination of action potential (AP) indices: AP Triangulation,

Reverse use dependence, AP Instability and AP transmural Dispersion of repolarisation).

The seminal work by Antzelevitch demonstrated that the morphology of the T wave can be generated from the interplay of the lumped action potentials within the epicardial, M cell and endocardial layers of the myocardium. In the lumped model it has been shown that the peak T wave occurs when the epicardial AP returns to the isoelectric line and that the time of the end of T wave occurs when the M cell layer reaches isoelectric resting potential. In the wedge preparation the timing between the end of the epicardial AP and M cell AP gave an index of the dispersion of transmural repolarisation and the ECG clinical index of peak T wave to end T wave (pT-Te) has been shown to be an index of global dispersion of repolarisation and numerous studies have shown that a prolongation of this index is a strong predictor of TdP. When the measurement of pT-Te is made manually it is significantly longer than when measured by the automated ECG slope QT algorithms which tend to ignore the end of the T wave where the effects of drug induced inhibition of the rapid delayed potassium rectifier current (IKr) are most pronounced. Therefore manual methods or use of an automated QT algorithm which measures the true end of the T wave, as per the electrophysiological definition, may prove more accurate. In conditions of drug induced IKr inhibition there is a triangulation (triangular morphology) of all three myocardial layers, defined as a prolongation of phase 3 (AP)30 –AP(90). Because of the difference in the ratios of IKr to IKs (slow delayed potassium rectifier) channel densities between the M cell and the other two layers, the M cell layer is prolonged by a proportionately greater degree than the other cell layers. In the multicellular in silico models the prolongation of the simulated QT interval

can be shown to be directly related to the prolongation of the M cell AP and the global dispersion of repolarisation related to the difference between the lumped M cell AP and epicardial AP timings. In the lumped model during IKr inhibition the triangulation of the APs will result in a smaller instantaneous voltage differences between the endocardial and M cell APs generated at the time of cessation of the prolonged epicardial AP therefore resulting in flattening of the delayed T wave peak and a skewness or asymmetry of the T wave develops. It can be shown by simple geometric idealisation of a baseline ECG T wave as an isosceles triangle that if the post drug T wave peak were to be prolonged, the M cell AP would need to be prolonged by double that amount in order to maintain symmetry of the triangular T wave. The prolongation of the M cell AP is very rarely double the prolongation of the epicardial AP. M cell AP prolongation significantly beyond the endocardial AP duration will result in a notch on the T wave downslope as the M cell AP voltage is not attenuated by the endocardial AP for a significant proportion of the M cell AP downstroke. Therefore combined scores of flatness, asymmetry and notching as measured by the various methods is in effect simply a measure of the degree of IKr inhibition. The use of the morphology indices flatness, asymmetry and notching has been inspired by the Long QT syndrome (LQTS) 2 phenotype and would not be as successful applied to the ECG T waves of other LQTS phenotypes. Nevertheless, this method of T wave morphology scoring has been shown to be more sensitive in detecting IKr inhibition than prolongation of the QTc interval. Currently there is some clinical evidence in a small retrospective study that morphology indices combined with QTc prolongation may be used to predict TdP in a bradycardia model but we do not yet know the sensitivity nor specificity of T

wave morphology indices to predict TdP in other clinical settings. Invoking the Amiodarone contradiction, this safe antiarrhythmic may produce morphological T wave changes indicating IKr inhibition but the incidence of TdP is very rare when in clinical use.

The preclinical TRIaD indices have been shown to be predictive of drug induced arrhythmogenicity in over 700 animal drug trials. The pathophysiological model interrelating these indices has shown that AP instability, AP triangulation and Reverse use Dependence are in order of decreasing relative importance. The index of spatial and temporal dispersion of repolarisation is a product of these three phenomena.

The problems of translating interspecies physiological differences remain insurmountable (eg the rabbit AP has inherent triangular morphology before drug induction of triangulation) and mandate that rigorous phase I human cardiac safety studies be performed. Fortunately, it is possible to translate the various preclinical indices within TRIaD to surrogate human ECG biomarkers some of which have already been mentioned. In the presence of IKr inhibition the phenomenon of AP triangulation is inevitably associated with prolongation of the QTc interval, pT-Te is a surrogate marker of global dispersion of repolarisation, reverse use dependence is associated with a steep QT/R-R interval gradient and indices of increased short term QT variability measured by Poincare plots have been shown to be predictive of TdP. It is therefore possible to dynamically combine the human surrogate indices for TRIaD with the morphological indices of the T wave to create a human TRIaD equivalent. With accumulating evidence based clinical studies using these new clinical biomarkers at our disposal, which in a species specific way may duplicate some of the important preclinical tests, there is a

seductive cost and time saving argument which may lead us to proceed directly to clinical cardiac safety studies.

Accurate measurement of the true end of the QT interval, enables accurate measurement of the changes in QT intervals during thorough QT trials thereby reducing standard error and measurement variability. This results in higher statistical power with less subject recruitment. Accurate measurement of QT interval enables accurate measurement of T wave asymmetry, pT-Te, QT variability and therefore accurate measurements of the clinical equivalents of TRIaD.

Slope based automatic QT algorithms are ubiquitous and do not measure the true end of the T wave as is illustrated in **Figure 1**. In this figure, the blue and red traces represent the magnified curvilinear tail ends of T waves from the same subject before and after sotalolol, after alignment of the respective Q wave onsets. The yellow vertical markers represent the manually measured end of the T waves. The blue oblique lines are projections of the maximum T wave tangents and where these

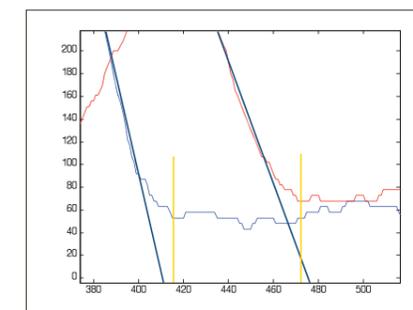


Figure 1

cross some arbitrary threshold is deemed to be the end of the T wave as measured by the slope method. Because of the divergence of these two tangents it can be seen that there is the potential for a great deal of variability between the difference in end of T wave times (therefore difference in QT intervals)

as measured by the slope method compared to the 'gold standard' manual method, particularly as the ECG isoelectric baseline varies.

There are methods to measure the true end of the T wave as per the electrophysiological definition. **Figure 2** represents such a method. This method is based upon the upright T wave and its inverted image being virtually merged until there is best least squares fit between their common isoelectric baselines. The first time point of intersection of the respective baselines being the end of the T wave.

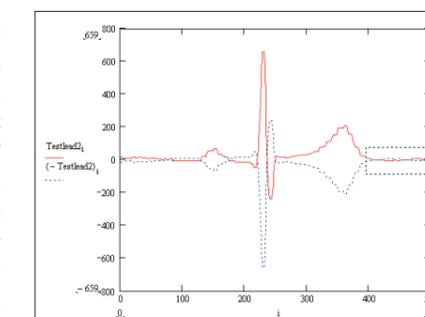


Figure 2

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