Electrocardiographic Method for Identifying Moxifloxacin-induced Ventricular Repolarization Abnormalities

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Abstract

We developed a new technique for the measurements of repolarization abnormalities from surface ECGs; this method improves sensitivity and specificity of the current technique used to identify the presence of a drug called moxifloxacin. This drug is used as a positive control compound in clinical studies investigating the level of drug cardiotoxicity related to the ventricular repolarization process. We describe a new technology and the preliminary results revealing the superiority of our technique in comparison to QT interval prolongation. This technology may play an important role in the future of drug-safety assessment.

1. Introduction

Currently, the US Food and Drug Agency (FDA) recommends pharmaceutical companies to test the safety of all new compounds for their potential QT prolonging effect but the Agency does not provide standard around the technique used for measuring the QT interval from the surface ECG (1). Instead, the FDA requires that the technique used during new drug application is validated on a positive control group which consist of a group of healthy individuals on and off an antibiotic drug called moxifloxacin that is known to prolong the QT interval of 5-10 msec (2).

A prolongation of the QT interval (QTc≥500 msec) from the surface electrocardiogram (ECG) is associated with a strong risk of "torsade de pointes" (TdP), a rare and dangerous type of polymorphic ventricular tachycardia (3). Unfortunately, this relationship weakens for smaller QT prolongation. The consequence is that a small drug-induced QT prolongation is not accepted as a perfect surrogate marker of an increased risk for TdP: there is a dissociation between QT prolongation and the risk of TdP. Some drugs will prolong significantly the QT interval and do not have history of cardiac events, others will be associated with very small prolongation but have clear torsadogenic properties. Consequently, the FDA faces a challenging issue and it recognizes the need for other electrocardiographic markers than QT prolongation for identifying dangerous drug-induced repolarization abnormalities from the surface ECGs.

In this study, we present a set of new ECG parameters designed to specifically quantify delay within the ventricular repolarization process of the heart from surface ECGs. We used a technique based on the singular value decomposition of the repolarization signals and measure specific intervals within the resulting two first eigenvectors. Then, we validated these new parameters and compared their ability to identify the presence of moxifloxacin in ECGs and in comparison to QT/QTc prolongation.

2. Methods

The Heart Research Follow-up program at University of Rochester was granted the access to a small subset of recordings from the ECG Warehouse from a randomized placebo-controlled parallel study including 40 healthy individuals (18 females). Age was not different between placebo and moxifloxacin arm (27.5±7.9 vs. 26.5±7.9 yrs, p=0.38). One hundred and sixty ECGs from the baseline, placebo and moxifloxacin arms were analyzed. Individuals were de-identified.

The technical specifications of the signal were 180 Hz sampling frequency and an amplitude resolution of 6.25 μV/bit coded on 16 bits.

The measurements of the RR intervals and repolarization intervals were based on the technology developed a University of Rochester (COMPAS software). The identification of the end of the T-wave on lead II is computed based on a technique identifying the crossing- point between the baseline and the descending slope of the T-wave (least-square technique). The end of the T-wave is visually checked by technicians and manually adjusted using an on-screen caliper if the automatic algorithm failed to correctly identify the end of the T-wave. We measured three QT intervals in Lead II and the average QT value is reported.

The apex of the T-wave relied on method using a parabola fitting the T-wave, the maximum of the parabola identified the time location of the apex. QT apex and TpTe intervals were such as QT=QTapex+TpTe. The

amplitude of the ECG signal at the apex of the T-wave was defined as the T-wave magnitude.

The vectorcardiographic measurements were based on the Principal Components Analysis of the repolarization segment defined between the J point and the point located 220 ms before the next R peak. The method relies on the computation of the Singular Value Decomposition (SVD) [8], in which any matrix **A** *(MxN)* can be written as:

$$A = USV^T$$

where **U** is a *(M x N)* column-orthogonal matrix, **S** a diagonal matrix with elements superior or equal to zero (the eigenvalues: $\lambda_1 ... \lambda_N$), and **V** an *(N x N)* orthogonal matrix containing the singular vectors.

The matrix **A** is constructed from the 12-lead standard ECG signals. **A** has the following size: (M x N) where N is the number of leads available in the recordings and M is the number of samples defining the duration of the repolarization signal for a given cardiac beat. The product of **A·V** provides the projection of the original data onto the principal components. The repolarization signal within the space defined by the three first components (ev_1, ev_2, ev_3) is called the T-loop. The ev_n signals are the eigenleads. The plane ($ev_1 \llcorner ev_2$) defines the preferential plane of the T-loop (Fig. 1).

The T-loop morphology is assessed by computing the ratio of the two first eigenvalues (λ_2/λ_1). This ratio is proportional to the roundness of the T-loop. The planarity of this loop is quantified by λ_3. These values were normalized.

We define new repolarization measurements independent from the localization of the end of the T-wave. We arbitrary choose the point where the heart vector reaches its maximum value (MV). MV is detected at time, $t = T_{MV}$, where equation 1 is fulfilled.

Eq.1) $$MV = \max\left\langle VECG(t) - VECG(T_Q) \right\rangle,$$

Where:

$$VECG(t) = ev_1(t)\,\vec{i} + ev_2(t)\,\vec{j},$$

and T_Q is the time coinciding with the beginning of the QRS complex. So, in conclusion Eq.1, can be re-written as:

$$MV = \max\left\langle \sqrt{\{ev_1(t) - ev_1(T_Q)\}^2 + \{ev_2(t) - ev_2(T_Q)\}^2} \right\rangle$$

As it is shown in Fig. 1, we defined novel intervals we called 30% of Early, Late and Total Repolarization Durations ($ERD_{30\%}$, $LRD_{30\%}$ and $TRD_{30\%}$). These intervals are centered on the time of MV. Precisely,

$$ERD = T_{MV} - T_E$$

where T_E is the value for t, where Eq.2 is fulfilled:

Eq.2)

$$\left\| VECG(t) - VECG(T_{MV}) \right\| = MV \cdot 30\%,$$

with $t < T_{MV}$;

$$ERD = T_L - T_{MV},$$

where T_L is the value for t, where Eq. 3 is fulfilled.

Eq.3)

$$\left\| VECG(t) - VECG(T_{MV}) \right\| = MV \cdot 30\%,$$

with $t > T_{MV}$.

Finaly, $TRD = ERD + LRD$

The choice for 30% of the MV value was an a-priori choice. We used binary logistic regression to identify the ECGs of individuals recorded after moxifloxacin dosing. A best subset regression model was selected based on the AIC criterion.(4) The comparison between models was done using receiver operating characteristics curves (ROC). Area under the ROC curves was used to compare the discriminant power of the designed models.

Table 1: Analysis of central tendencies. The values in bold are highlighting the parameters (corrected for heart rate) that show a moxifloxacin effect ($|\Delta|>0$).

	Mean difference vs. placebo	95% CI		P value
T mag. (mV)	**-0.026**	**-0.054**	**0.002**	**0.034**
QT offset	**12.1**	**-1.1**	**25.1**	**0.037**
αL (μV/ms)	**-0.36**	**-0.66**	**-0.06**	**0.009**
αR (μV/ms)	**0.58**	**0.08**	**1.08**	**0.012**
TpTe (ms)	-0.5	-5.9	4.9	0.43
$\lambda 2/\lambda 1$	0.01	-0.07	0.11	0.37
Planarity ($\lambda 3$)	-0.01	-0.03	0.01	0.26
$LRD_{30\%}$ (ms)	0.07	-5.10	5.24	0.48
$ERD_{30\%}$ (ms)	**10.3**	**2.9**	**17.7**	**0.003**

3. Results

The QT interval is dependent on the heart rate from prior beats. Thus, QT must be corrected in order to ensure a fair comparison of this duration between ECGs recorded at different heart rate. The correction formulae readily available (Bazett and Fridericia) are imperfect because the QT-RR relationship is different between individuals. An alternative strategy to the pre-defined formulae is to use a pooled-formula. It is defined from baseline recordings (off-drug and off-placebo). Each QT interval measurement is associated with the RR intervals from the immediately preceding beat. Then, QT-RR

relationship is defined using a linear regression modeling technique from ECGs of the overall study population. The correction is done by normalizing the QT measurements to a heart rate of 60 bpm (or RR=1000msec). One may define this correction method as follow: the linear regression model provides the coefficients describing the relationship between RR and a parameter called P:

Eq. 4) $$P = \beta \times RR + \alpha$$

by simple mathematical transformation, we can expressed the heart rate corrected value of the parameter P (Pc) such as:

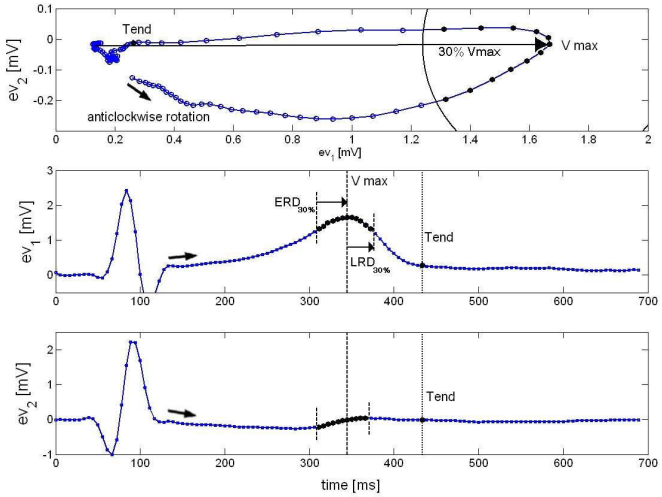

Figure 1. Definition of the $ERD_{30\%}$, $LRD_{30\%}$ and $TRD_{30\%}$ parameters based on a geometric threshold in the preferential plane of the T-loop (circle perimeter). The two intervals identified in the T-loop are represented within the signals of the two first eigenvectors (ev1 and ev2).

Eq. 5) $$Pc = P + \beta \times (1 - RR)$$

Where RR is expressed in seconds and β has no unit. All results presented in the following paragraphs have been corrected for heart rate using this technique.

Table 1 provides the changes in values of repolarization parameters controlled for the effect of placebo. The table reveals significant QT prolongation as well as significant changes in T-wave morphology due to the drug moxifloxacin.

The binary logistic regression was used to design statistical models combining repolarization parameters in order to identify the ECG tracings of individuals who received a dose of moxifloxacin. First, we defined a model relying exclusively on "classic" parameters namely QTc, RR, gender and age. Again, QTc was corrected using pooled formula. This model called clinical model performed poorly and QT and RR were the only parameters significantly contributing to the model. Fig. 2 describes the ROC curve of the clinical model, optimal threshold provided a sensitivity and specificity of 58% and 82%, respectively.

When adding the vectorial and scalar measurements to the list of parameters entered in the binary logistic model $ERD_{30\%}$, $TRD_{30\%}$ and αR were the three first selected parameters. QTc did not enter the model. The selection of the new model was based on the AIC criteria penalizing the model for each incremental parameter added to the model. This new model provided a better identification of ECGs from individual on moxifloxacin. The sensitivity was 73.7%, and the specificity was 89.5%. The area under the ROC curve was increased from 0.71 to 0.85.

The third model was based on two additional parameters (QTapex and TpTe). This new model is associated with an area under the ROC curve increased by 0.20 and an optimal discrimination between placebo and moxifloxacin ECGs with 95% sensitivity and 79%specificity (see Fig. 2).

4. Discussion and conclusions

The QT prolongation is recognized as an imperfect surrogate marker of drug cardiotoxicity. There are drugs associated with QT prolongation without inducing TdPs. (5) Most drugs removed form the marker because of their torsadogenic properties commonly carry I_{Kr}-inhibition property. If the tested drug interacts with more than one ion current then it is likely that this interaction may mitigate or exacerbate the effect on the ventricular repolarization process. This observation defines the fundamental problematic around the assessment of drug-safety when measuring repolarization abnormalities from the surface ECG signal. Can we identify ECG abnormalities evidencing ion-specific inhibition? And can we assess the presence of ion interactions and their resulting impact on the predisposition for arrhythmic events?

In this study, we report two preliminary findings: 1) the QT interval was not the best repolarization interval for the quantification of presence of moxifloxacin which is a drug specifically associated with I_{Kr}-inhibition, and 2) using other parameters than QT interval measurements allows for better identifying moxifloxacin-induced repolarization abnormalities.

In a study involving erythromycin, another antibiotic drug with dose-dependent I_{Kr}-inhibition properties, Antzelevitch et al. demonstrated the presence of "a prominent dispersion of repolarization across the ventricular wall, setting the stage for induction of TdP-like tachyarrhythmias displaying characteristics typical of

reentry" in a canine model and at higher dose than those measured in human plasma (10- 100 µg/ml) (6). This group demonstrated that QT prolongation is often associated with an increased heterogeneity of cardiac repolarization across the cardiac ventricle wall due to a prolongation of the action potential of the middle cells of the myocardium (so-called M cells) but not in the epicardial and endocardial cells and such heterogeneously delaying process may be the mechanism triggering the TdPs.

In a more recent work from Chen et al., moxifloxacin was studied and at hyperdose (~18 fold above the typical unbound Cmax exposure in clinical exposure) was associated with an increased risk of inducing TdPs (7). This group also reported a concentration-dependent prolongation of the QT interval and of the TpTe interval (potential surrogate marker of transmural repolarization dispersion). The lack of TdP reports for moxifloxacin is attributable to "its predicable PK profile and other dose-limiting effects".

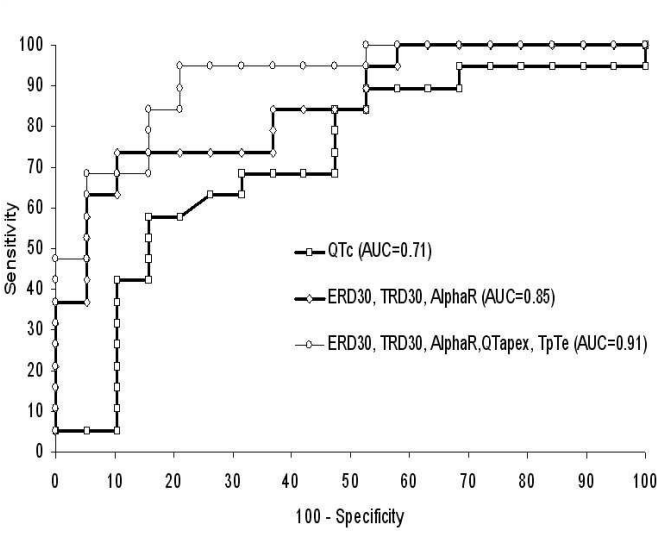

Figure 2. The figure describes the three ROC curves for the logistic models implemented in this study. AUC: Area under the ROC curve. AlphaR is αR.

To conclude, we evidenced the presence of other electrocardiographic markers of moxifloxacin-related abnormalities in surface ECGs than a prolongation of the QT interval. Our new parameters provide increased sensitivity and specificity for the detection of moxifloxacin-induced repolarization delay. Once these results are validated on an independent dataset, these new parameters may play a role in the future of drug safety evaluation.

Acknowledgment

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