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Investigation of Parameters Highlighting Drug Induced Small Changes of the T-Wave's Morphology for Drug Safety Studies

Tobias Baas, Ksenija Gräfe, Antoun Khawaja and Olaf Dössel

Abstract— **In guideline E14, the American Food and Drug Administration (FDA) requests for clinical studies to investigate the prolongation of the heart rate corrected QT-interval (QTc) of the ECG. As drug induced QT-prolongation can be caused by changes in the repolarisation of the ventricles, it is so far a thorough ECG biomarker of risk for ventricular tachyarrhythmias and Torsade de Pointes (TdP). Ventricular repolarisation changes not only change QT but also influence the morphology of the T-wave. In a (400 mg single dose) Moxifloxacin positive control study both, QTc and several descriptors describing the T-wave morphology have been measured. Moxifloxacin is changing two shape dependent descriptors significantly ($P \leqslant 0.05$) about 3 to 4 hours after a 400 mg oral single dose of Moxifloxacin.**

I. INTRODUCTION

QT-prolongation can cause the development of life threatening ventricular tachyarrhytmias such as Torsade de Pointes (TdP) and ventricular fibrillation often leading to cardiac death. QT-prolongation and TdP has been identified as a side effect of many commonly used medications [1]. Thus QT-analysis plays a major role for pharmaceutical industry on their way to developing new drugs.

ICH E14 is a set of guidelines for clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonarrhythmic drugs [2]. In this guideline the QT-interval is in focus and thorough QT studies are reclaimed.

The prolongation of the QT-interval is usually caused by a drug induced change of the repolarisation of the ventricles. As the T-wave in the ECG represents the repolarisation of the ventricles, proarrhythmic effects on the humans heart should be detectable by analysing the morphology of the T-wave in the ECG. J.P. Couderc gives an overview of methods developed to analyse static and dynamic aspects of the ventricular repolarisation (VR) process when recorded from a non invasive ECG. The analysis is extended from the VR duration to its morphology [3].

Graff et al. investigated T-wave morphology changes of a I_{Kr}- blocking antipsychotic compound (Lu 35-138) measured by a descriptor based on asymmetry, flatness and notching. T-wave morphology was a more reliable indicator of I_{Kr} inhibition than QT_c [4].

T.Baas K. Gräfe and O. Dössel are with Karlsruhe Institute of Technology, Institute of Biomedical Engineering, 76131 Karlsruhe, Germany Tobias.baas@kit.edu

A. Khawaja is with Biosigna, Medical Diagnostics, 80337 Munich, Germany

II. MATERIALS

In this work 84 Holter ECGs from 42 participants, 30 men and 12 woman from the thorough QT Study 2 of the Telemetric and Holter ECG Warehouse (THEW) were considered [5]. The resolution of the recording was 16 bit with a sample frequency of 1000 Hz. Every participant was measured twice, once with a single oral dose of 400 mg Moxifloxacin administered about 1.5 hours after starting the measurement, and once for control purpose with a placebo administered. Time of dose, lunch and dinner were equal for all participants and for both recording days. Also the blood plasma concentration of Moxifloxacin was measured by using the same measurement schedule for all participants.

III. METHODS

A. Fiducial Point Detection

The ECG data was automatically delineated. For QRS-delineation a wavelet based algorithm was used. The algorithm detects the R-peak by analysing detail coefficients of a wavelet decomposition of the original ECG signal. In a second step, after the R-Peaks are detected the Q and S-peaks are localized. Having the QRS complex delineated, the T-wave has to be found and the end of the T-waves is determined. This is done by a method that computes a patient specific template out of hundreds of T-waves of the participant. To get a clean and realistic T-wave template, T-waves are sorted carefully by Principal Component Analysis (PCA) and a Hotelling's T^2 threshold. After template generation, the end of the template T-wave, $T_{end,T}$ is detected very precisely using a wavelet based algorithm. The patient specific template is then stretched by $s(n) = 0.88$ to 1.13 to get a set of templates, $T_s(n)$ all having a different width according to T-wave changes during the ECG recording. The set of templates is then shifted along the time window of every RR-interval $Y(i)$, where a T-wave is expected. The correlation coefficients between the templates, $T_s(n)$ and the signal parts, $Y(i)$ are calculated. The combination of shift factors, $k(t)$ and template, $T_s(n)$ corresponding to $s(n)$ is used for calculating the position of the particular T-end, $T_{end}(i)$. [6]

$$T_{end}(i) = T_{end,T} \cdot s_{best} + k_{best} \tag{1}$$

B. T-wave Alignment

The delineated ECG is used for analysing the morphology of the T-wave. All T-waves of a participant have to be aligned according to their T-peak. As the T-peak is not detected by the correlation algorithm this needs to be done first. The ECG-signal of every heart beat i between 360 ms before

$T_{end}(i)$ and $T_{end}(i)+50$ ms, $X(i)$ is cut out. To prevent the algorithm of detecting a wrong T-peak cause of noise in the signal, a mean filter with a window size of 30 ms is used to filter the extracted signals $X(i)$. The highest value of every filtered wave $M_{X_f}(i)$ is detected. All unfiltered waves $X(i)$ are aligned according to this point. The signals are cut out to ± 120 ms measured from T-peak. The left border values of the waves are set to zero to eliminate potential baseline wander from the ECG signal.

The used ECG-leads have been chosen to include only positive T-waves. After aligning all T-waves of the recording according to their T-peak, outliers need to be detected. This is done by applying a PCA on all T-waves. The Hotelling's T^2 value is a measure of the variance of a single wave compared to the whole dataset of waves.

$$T^2 = \sum_{i=1}^{N} \frac{b_i^2}{\alpha_i} \tag{2}$$

In this equation N is the number of waves in the dataset, b_i is the i-th score of the wave belonging to the i-th eigenvalue, α_i. For further investigations all waves having a T^2 value smaller than the mean plus the standard deviation σ are considered.

C. T-wave Means

To ingestive drug induced morphology changes of the T-wave, it is necessary to eliminate morphological influence caused by other parameters like e.g. heart rate. This is done by generating T-wave templates T_{m1} out of 10 successive T-waves. Four thresholds λ_1 to λ_4 have been defined to decide whether a T-wave from the ECG recording can be considered for T_{m1}.

$$\lambda_1: \quad \Delta RR \quad < \pm 80ms \tag{3}$$

$$\lambda_2: \quad \Delta QT \quad < \pm 30ms \tag{4}$$

$$\lambda_3: \quad A_{T_{m1}} \quad > \frac{1}{N^2} \sum_{i=1}^{N} \left| A_T(i) - A_{T_{m1}} \right| \tag{5}$$

$$\lambda_4: \quad M_{T_{m1}} \quad > \frac{20}{N-1} \sum_{i=1}^{N-1} \left| T_e(i) - T_e(i+1) \right| \tag{6}$$

If one threshold failed the window is shifted right to the next wave. The first threshold λ_1 considers the heart rate variability ΔRR of all 10 waves. According to λ_1, λ_2 considers the QT-interval variability ΔQT. Further more, the variance between the 10 successive T-waves has to be small (λ_3). The variance is measured using the sum of the difference of the area under each wave, $A_T(i)$. This value is divided by the square of the number of considered waves N and needs to be smaller than the area under the mean wave T_{m1} (λ_3). The fourth threshold considers the end of the T-waves. As the onset of all T-waves are set to zero, a baseline wander in the ECG signal, a noisy or wrong detected T-wave interval causes a high variance of the amplitude at the end of the T-waves $T_e(i)$. The sum of all absolute values of the differences is divided by the number of differences, $N-1$. This value has to be smaller than 5% of the maxima of the mean T-wave $M_{T_{m1}}$ (λ_4). The algorithm tries to find as many mean waves T_{m1} in the 24h ECG as possible. To prevent the template from noise and baseline wander, a second mean wave template T_{m2} is generated by tilting the first one to bring T_e to zero. Both mean waves are used for further morphology investigation in parallel.

D. Evaluating Intervals

To evaluate the change of the morphology of the T-wave, intervals of 15 minutes duration are defined. The first interval is set to the last 15 minutes of the pre-dose recording. Post-dose the signal is divided into 60 intervals again with a length of 15 minutes each. Thus a total of 915 minutes of every ECG recording is considered. In all intervals j, the mean waves $T_{m1}(i)$ and $T_{m2}(i)$ are combined to the master mean waves T_{MA1} and T_{MA2}. Figure 1 shows T_{MA1} of one participant during the two recording days.

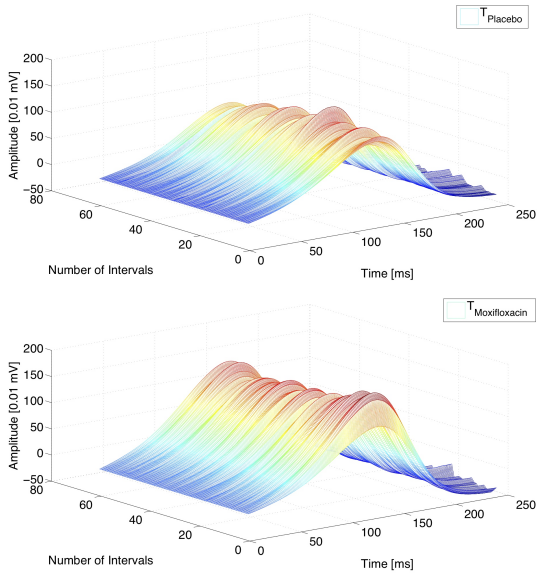

Fig. 1. 3D plot of all master waves T_{MA1} for placebo control day (top) and day of Moxifloxacin administration (bottom).

E. Descriptors

To describe the morphology of the T-wave, four descriptors ψ_1 to ψ_4 have been defined. While ψ_1 to ψ_3 are calculated for T_{MA1} and T_{MA2}, ψ_4 is only calculated for T_{MA1}.

$$\psi_1 = max(T_{MA}) \tag{7}$$

$$\psi_2 = \frac{\frac{1}{n}\sum_{k=1}^{n}\left(T_m(k)-\overline{T_m}\right)^3}{\left[\sqrt{\frac{1}{n}\sum_{k=1}^{n}\left(T_m(k)-\overline{T_m}\right)^2}\right]^3} \tag{8}$$

$$\psi_3 = \frac{\frac{1}{n}\sum_{k=1}^{n}\left(T_m(k)-\overline{T_m}\right)^4}{\left[\frac{1}{n}\sum_{k=1}^{n}\left(T_m(k)-\overline{T_m}\right)^2\right]^2} \tag{9}$$

$$\psi_4 = \sum_{k=l}^{m} T_{MA}(k) \;\; k := \{i | T_{MA}(k) \geq 0.6 \cdot \psi_1\} \tag{10}$$

ψ_1 represents the maximum of T_{MA1} and T_{MA2} respectively. The skewness of the master waves are considered in ψ_2, while the kurtosis is considered in ψ_3. The skewness is a

measure coming out of the the statistical mathematics and describes the asymmetry of a probability distribution. The skewness indicates whether a distribution spreads out more to the left (lower values) or to the right (higher values). The Gaussian distribution has a skewness of zero. Similar to the skewness, the kurtosis is the peakedness factor of the probability distribution. The fourth descriptor represents the size of the area under the curve of the maximum 30% of the curves amplitudes.

IV. Results

For all descriptors the values for the day on which Moxifloxacin was administered and the placebo control day are computed and the difference between the days for every single 15 minutes interval $\Delta\psi_1$ to $\Delta\psi_4$ is calculated.

A. Time Course of Descriptors

These results are compared to the Moxifloxacin blood plasma concentration for all participants. As a reference also the differences of the corrected QT-intervals are computed. Figure 2 shows the distribution of ΔQT_c as boxplots for all patients and separated for all intervals. It can be seen, that the values significantly increase during the first three hours post-dose. This is correlated to the blood plasma concentration represented by the green diamond symbols in Figure 2.

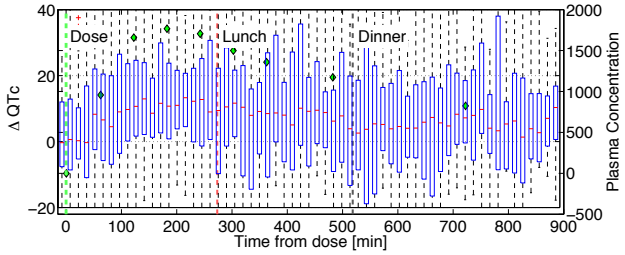

Fig. 2. ΔQTc-boxplot for all T-waves during 15 minutes pre-dose to 15 hour post-dose from all participants. Blood plasma concentration is represented by green diamonds in the diagram. Time of dose (green dashed line), lunch (red dashed line) and dinner (gray dashed line) are marked.

The time course of descriptor $\Delta\psi_1$ and $\Delta\psi_4$ did not show any significant correlation to the plasma concentration. Figure 3 shows the boxplot of $\Delta\psi_1$ for T_{MA1}. The boxplots for T_{MA2} of $\Delta\psi_1$ and $\Delta\psi_4$ showed similar courses.

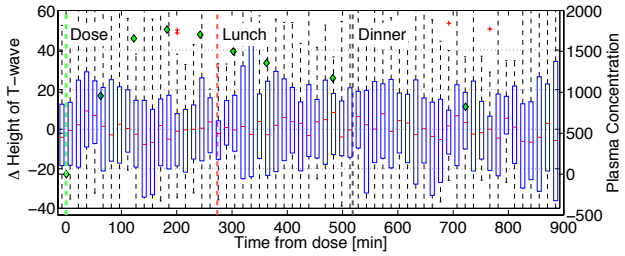

Fig. 3. $\Delta\psi_1$-boxplot of T_{MA2} of all T-waves during 15 minutes pre-dose to 15 hour post-dose from all participants.

The time course of $\Delta\psi_2$ showed a high correlation to the plasma concentration. In Figure 4 the values of $\Delta\psi_2$ for T_{MA2} decrease significantly during the first four hours post-dose. A very similar time course can be observed for T_{MA1}.

The change of $\Delta\psi_3$ of T_{MA2} is also significant during the first four hours as Figure 5 shows. However, the time course of $\Delta\psi_3$ of T_{MA1} does not show any significant change.

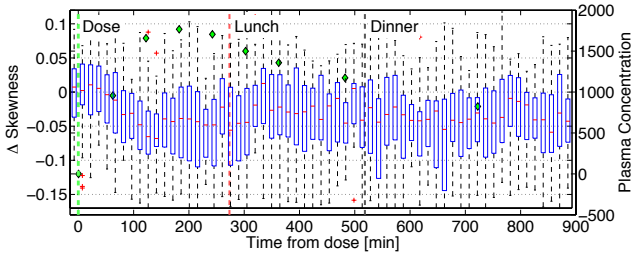

Fig. 4. $\Delta\psi_2$-boxplot of T_{MA2} for all T-waves during 15 minutes pre-dose to 15 hour post-dose from all participants.

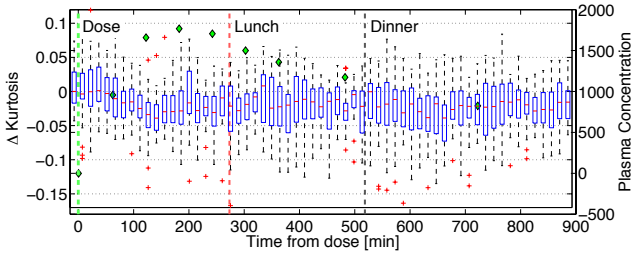

Fig. 5. $\Delta\psi_3$-boxplot of T_{MA2} for all T-waves during 15 minutes pre-dose to 15 hour post-dose from all participants.

B. t-Test

To control the statistical significance of the descriptors a t-test of the null hypothesis was performed. The t-test proofs whether a descriptor for the day with Moxifloxacin administration and for a placebo control day is independent of random samples from normal distributions with equal mean against the alternative of different means. A significance level of $P \leq 0.05$ stands for a high probability of real independent means.

The t-test was performed on all descriptors and separately for every interval. Table I shows the values for the descriptors in the interval pre-dose and the maximal median values post-dose for T_{MA1} and T_{MA2}. Furthermore the corresponding values of the t-test are shown.

V. Conclusions and Future Works

A. Conclusions

A new way of analysing the T-wave in the ECG for highlighting drug induced small morphological changes of the T-wave is presented. Two of the four introduced descriptors showed a significant change while the Moxifloxacin blood plasma concentration was high. Also the time course had a high correlation to the blood

TABLE I

EXTREME MEDIAN VALUES OF DESCRIPTORS AND SIGNIFICANCE LEVEL

Descriptor	$Median_{t=0}$	$P_{t=0}$	$Median_{best}$	P_{best}	$Time\ [min]$
Δ QTc	-0.33	0.68	13.3	0.05	225
$\Delta\psi_1$ (T_{MA1})	-2.27	0.74	-8.10	0.31	165
$\Delta\psi_1$ (T_{MA2})	-4.12	0.78	9.19	0.93	45
$\Delta\psi_2$ (T_{MA1})	0.0131	0.46	-0.0914	0.31	225
$\Delta\psi_2$ (T_{MA2})	0.0073	0.79	-0.068	0.02	150
$\Delta\psi_3$ (T_{MA1})	0.0035	0.07	0.0266	0.22	105
$\Delta\psi_3$ (T_{MA2})	0.00	0.82	-0.039	0.01	150
$\Delta\psi_4$ (T_{MA2})	-356	0.78	738	0.65	495

plasma concentration.

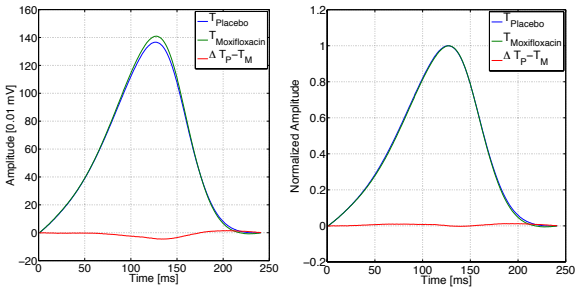

Fig. 6. T_{MA2} in the last 15 minutes pre-dose, participant *1213*. Left: Amplitude original, right: Amplitude normalized

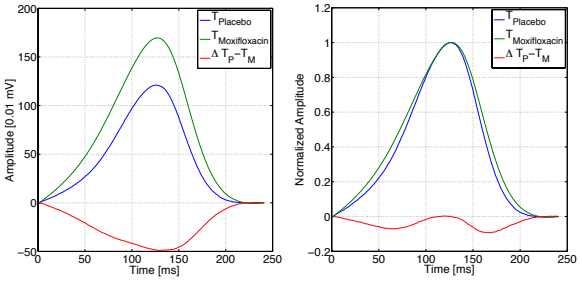

Fig. 7. T_{MA2} in the first 15 minutes, 3.5 hours post-dose, participant *1213*. Left: Amplitude original, right: Amplitude normalized

Descriptor ψ_2 which is a measure of the asymmetry of the T-wave showed decreased values during drug influence. This means an elongated trail at the right and corresponds with the fact of QTc prolongation caused by Moxifloxacin. ψ_3, as a measure of the peakedness of the T-wave, showed also decreased values under Moxifloxacin influence. This means that the wave becomes broaden. This was observed when comparing the T-wave of a participant under Moxifloxacin influence and pre-dose. Figure 6 on the left side shows the T-wave of participant *1213* during the last 15 minutes pre-dose. Figure 6 on the right side shows the same waves, but with normalized amplitude. It can be seen that the waves are nearly congruent for both days. There is only a small difference in the amplitude of the wave. In Figure 7 on the left the waves of the same participant as in figure 6 are shown, but 3.5 hours post-dose. In Figure 7 on the left, the different shape cannot be identified because of the high differences in the amplitudes. Figure 7 on the right shows the normalized waves. It can be seen, that the wave is clearly broaden under the influence of Moxifloxacin. The large difference in amplitude, which can be observed, is also discernible. The analysis of the height of the T-wave was done using the descriptor ψ_1. The difference for both recording days showed a high, more or less constant variance over the whole measurement (Figure 3). In Figure 1 T_{MA1} is plotted for all intervals. It can be seen that the amplitude changes from one day to the other. It seems as if the wave on the Moxifloxacin day was increased, but it can also be observed that the waves in the middle of the control day increases suddenly and significantly. We conclude that Moxifloxacin increases the amplitude of the T-wave, but there are other unknown parameter increasing the amplitude of the T-wave as well.

B. Future Works

In future, efforts will be done in order to improve the T-wave descriptors to reach smaller variances during the day. The number of participants should be increased. Also the number of T-waves which can be included for the analysis should be increased. The outlier detection must be improved to reach that goal.

To enhance the quality of clinical drug safety studies, a complex analysis of all parameters extracted from every single heart beat and in particular from the T-wave will be performed. Methods known from the time series analysis can be used to extract new information. The descriptors of the investigation will be considered in this analysis.

VI. ACKNOWLEDGMENTS

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