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Evaluation of T-wave Morphology Parameters in Drug-Induced Repolarization Abnormalities

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Abstract—This study evaluates the predictive values of T-wave morphology parameters reflecting the repolarization changes by beat to beat calculation of parameters using different mathematical tools to identify additional markers sensitive to the variation induced by drug in the surface of the electrocardiogram. T-wave morphology indicators are extracted from nearly 6 hours recordings of two patients from a clinical d-Sotalol study. The results show that drug induced change in T-wave morphology as well as QT interval. In particular, parameters extracted from spherical coordinates of vectrocardiogram that were not tested before for drug effect evaluation show high sensitivity to small change induced by drugs.

Keywords—ECG; ventricular repolarization; T-wave morphology; d-Sotalol

I. INTRODUCTION

The pharmaceutical industry requires the measure of QT interval during the premarketing phase of drug evaluation. Drug induced prolongation of QT interval is the single common use of restriction of drug [1]. However, most arrhythmogenic drugs cause not only prolongation of QT corrected interval but also transmural dispersion of action potential duration and thus T-wave modifications [2]. Therefore, others parameters extracted from the T-wave morphology can be useful addition features to characterize repolarization abnormalities and may contribute to drug safety evaluation as well.

The aim of this study is to compare the predictive value of T-wave parameters reflecting the repolarization modifications as well as on the duration but also on the morphology and to identify additional markers sensitive to the variations induced by drug. As illustration, a beat to beat computation in the surface electrocardiogram (ECG) of different features using the d-Sotalol is proposed. The d-Sotalol is a commonly used antiarrhythmic drug that has beta blocking action (blocks adrenaline to the heart) and it is used to treat ventricular tachycardia as well as atrial fibrillation. Sotalol leads to increase the action potential duration, refractory period and the QT interval on the surface of ECG [3].

Classical and novel quantitative repolarization features are computed and compared. Each feature reflects the evolution of T-wave morphology before and after administrating the drug. Parameters are based upon different mathematical tools such as principal component analysis (PCA). PCA reduces the 12 leads ECG signal into a minimum dimensional space where

the redundancy and the intra-person variability is reduced. We also derive the vectrocardiogram leads from the same transformation to evaluate the interest of other parameters related to vectrocardiogram (VCG) which were not studied before in drug effect evaluation. After the presentation of the database in the next section, the ECG processing is detailed and the different parameters are described. In section III, the results are developed then discussed in section IV to end with a conclusion in section V.

II. METHODS

A. Study population

Standard 12-lead ECG was recorded from two healthy patients (female, Age: 30 and 34 years) during 8 hours for the first woman and 6 hours for the second. Administration of d-Sotalol was realized after 25 min from the beginning of recording.

B. ECG processing

The Electrocardiogram signals were processed using the validated software *Segmenta* [4], which provides a fully automatic segmentation of all beats based on wavelet transform decomposition and using an evolutionary algorithm to optimize the parameters and threshold of the decision process. *Segmenta* provides consistently a set of several classical ECG features (RR-interval, QT-interval, PR-segment, QRS duration...) [4].

To study drug influence, each 10 seconds recording was used to form a mean beat in the eight independent leads of the 12 lead ECG (I, II, V1-V6). An SVD was performed on the mean beats to reduce the ECG signal into a minimum space that captures 98% of the ECG energy. From singular value components, principal component analysis (PCA) was performed [5], the resulting component coefficients were used to project the ECG signal onto the orthogonal eigenvectors. The T-wave of the first principal component lead PC1 was used to analyze the T-wave morphology, the peak and the end point of T-wave. These features were detected using *Segmenta*, whereas the starting point was approximately calculated as mentioned in [6]. After that, the ST-T segment was filtered using a low pass Kaiser Window FIR filter with 20 Hz as cut off frequency.

On the other hand, the 8 independent leads were transformed to XYZ leads using the Inverse Dower

transformation to compute the spherical coordination parameters.

C. Parameters

Parameters were classified into four categories: (i) duration parameters; (ii) PCA based parameters; (iii) Morphological parameters and (iv) Parameters related to the spherical coordinates of the VCG.

• Duration parameters measured on PC1 lead

QTc interval: corrected QT interval was measured where the end of T-wave can usually be clearly distinguished from the beginning of the U-wave, using Fridericia formula:

$$QT_c = \frac{QT}{\sqrt[3]{RR}} \quad (1)$$

QRSd: QRS duration which is a time measuring of the QRS complex.

ToTe: Time interval from T-wave onset to T-wave end.

TpTe: Time interval from T-wave peak to T-wave end.

• Morphological T-wave parameters

All these parameters were computed from the T-wave of the PC1 lead [7][8].

Tamp: T-wave amplitude in T-wave peak.

Upslope: Ascending slope of the T-wave. Average value of the slopes at each point of the ascending part of the T-wave.

Downslope: Descending slope of the T-wave. Average value of the slopes at each point of the descending part of the T-wave.

Asym: As defined in [7], the asymmetry score of the T-wave computes the difference between the slope profile of the ascending and descending part after normalization of the first derivation of the T-wave and flipping the descending part to cover the ascending part.

$$Asym = \frac{\sum_{n=1}^N d(n)^2}{N} \quad (2)$$

Where $d(n)$ is the difference between the slope segments at point n .

Flatness: The flatness score is a modification of the kurtosis used in statistic. The T-wave area is normalized and the flatness is calculated as:

$$Flatness = 1 - \frac{M_4}{M_2^2} \quad (3)$$

With M_2 and M_4 are the second and the fourth central moments.

Notch: The notch score was obtained after computing the curvature signal from the first and second derivations of T-wave.

$$curvature = - \frac{\frac{d^2y}{dx^2}}{\left(1 + \left(\frac{dy}{dx}\right)^2\right)^{3/2}} \quad (4)$$

An up-down pair on the curvature signal reflects a real notch where the notch score is expressed as the value of the positive part.

• Principal component analysis based parameter

After performing PCA on the 8 independent leads, each eigenvalue obtained is a measure of the relevant of the corresponding component. Denoting by s_i the eigenvalue of the i^{th} eigenvector, the following parameters are obtained as:

$$PCA_1 = \frac{s_1}{\sqrt{\sum_{i=2}^8 s_i^2}} \times 100 \quad (5)$$

$$PCA_2 = \frac{s_2}{s_1} \times 100 \quad (6)$$

$$PCA_3 = \frac{s_3}{s_1} \times 100 \quad (7)$$

Several studies have demonstrated that the remaining components (from 4 to 8) reflect regional heterogeneity in repolarization [8]. These components are called the non-dipolar components and can be expressed as:

ATWR: Absolute T-wave residuum, the absolute value of the sum of last four eigenvalues.

RTWR: relative T-wave residuum, the ratio between the sum of the last four eigenvalues to the sum of all eigenvalues [8].

• Parameters related to the spherical coordinates of VCG

The three VCG leads (X,Y,Z) are derived from the 12 standard leads of ECG using the inverse Dower transformation, after that spherical coordinates were computed to obtain instantaneous vector magnitude V_n , azimuth angle $\alpha(n)$ and elevation angle $\beta(n)$ describing the following indicators [9]:

DEA: difference between elevation and azimuth angles

$$DEA = \frac{1}{N} \sum_{n=1}^N |\alpha(n) - \beta(n)| \quad (8)$$

RMMV: Ratio of maximum to mean vector magnitudes

$$RMMV = \frac{\max(V_n)}{\text{mean}(V_n)} \quad (9)$$

III. RESULTS

Fig 1 shows the time series of QTc interval, DEA , $RMMV$ and $PCAI$ for patient 1 in different recording time computed as described above. Each curve clearly indicates an evolution with time and then drug effect. This evolution appears qualitatively more clearly in the DEA time series. This figure also underlines the sensibility of the features in front the noise. We observe in the $RMMV$ and $PCAI$ time series an abrupt change which is much more reduced in the DEA time series.

PCA was applied for feature selection on a matrix containing the times series of parameters in vector lines. Only parameters contributing in the first three principal components that represent 70% of total information were retained. Fig 2 and Fig 3 show contribution coefficients of parameters in order of increasing relevance in the first three components for the 2 subjects.

Average and standard deviation values of the remaining parameters were listed in TABLE I for each 1 hour recording where the drug was taken at 8h:10. Due to space limitation, only some parameters for the first patient are mentioned. In order to evaluate the significance evolution of each parameter, Friedman test (FT) was applied which is a non parametric statistical test, performed on ranks [10]. FT was used to detect differences in treatments across multiple measures attempts. Unlike the other non parametric test, FT does not require the hypothesis that the samples are independent. In order to decide in which recording a parameter is significantly different from other based upon the mean rank differences of the parameter in each recording that Friedman test calculate, a multiple comparison test was applied after Friedman test once the p -value is significant ($p < 0.05$).

All remaining parameters show clear evolution after d-Sotalol administration. In patient 1, QTc increases significantly from the recording 7h:55 where the mean rank $m_1=1.77$ to $m_2=6.96$ at 12h:55 than it decreases to $m_3=5.03$ at 14h:55, PCA_2 increases significantly from $m_1=1.52$ at 7h:55 to 7.99 at 13h:55 then no significant evolution has detected from 13h:55 to 14h:55, $RTWR$ increases from $m_1=1.77$ at 7h:55 to $m_2=7.69$ at 12h:55 then it decreases at 13h:55 to $m_3=6.67$, $Flatness$ and $downslope$ increase from 7h:55 to 13h:55 then no significant evolutions were found, $Upslope$ decreases from 7h:55 to 13h:55 then it increases from 13h:55 to 14h:55, DEA decreases significantly from 7h:55 where $m_1=7.99$ to 13h:55 where $m_2=1.5$ and increases from 13h:55 to 14h:55, $RMMV$

decreases also to $m_2=1$ at 13h:55 then it increases significantly $m_3=1.9$ at 14h:55, $Tamp$ decreases significantly from $m_1=7.68$ at 7h:55 to $m_2=1$ at 13h:55 after that no significant evolution was found, $TPTe$ increases from 7h:55 ($m_1=3.57$) to 13h:55 ($m_2=6.15$) then it decreases to $m_3=4.72$ at 14h:55. Patient 2 has mainly the same evolution for all parameters.

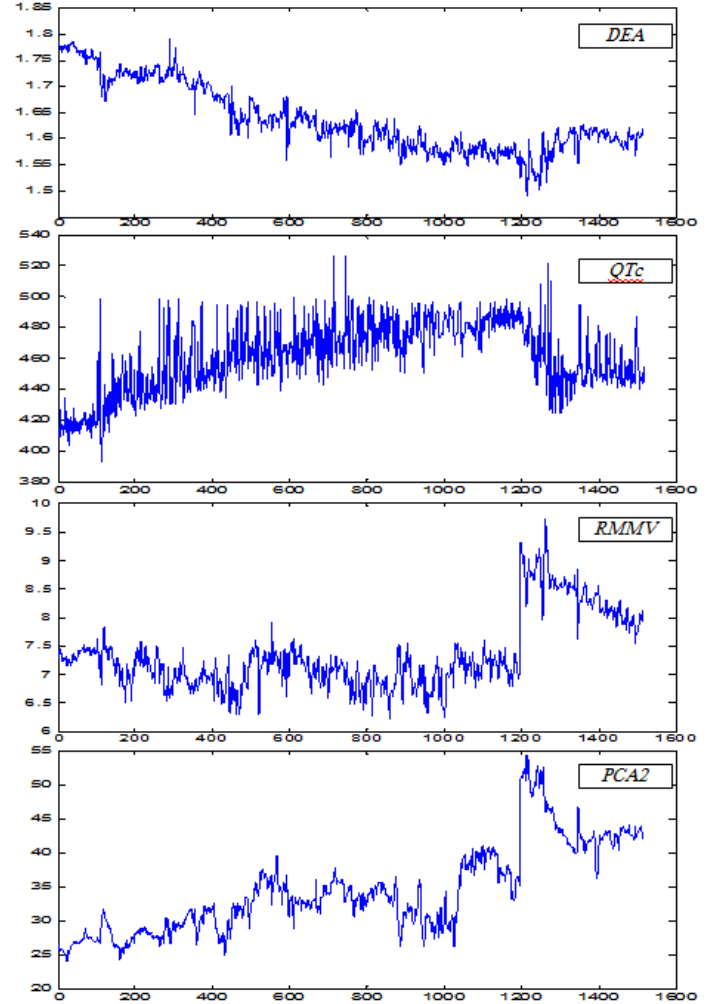


Fig. 1. Time series of DEA , QTc , $RMMV$ and $PCAI$ respectively for patient 1

TABLE I. PARAMETER CHANGES IN TIME FOR THE FIRST PATIENT, THE SYMBOL ‘*’ INDICATES HOURS AFTER D-SOTALOL ADMINISTRATION

	DEA	RMMV	PCA2	RTWR	Asym	Tamp	Downslope	QTc
07:55	1.765 ± 0.01	7.343 ± 0.1	26.642 ± 0.94	0.0096 ± 0.0003	0.153 ± 0.006	318.077 ± 11.28	3.179 ± 0.16	419.385 ± 11.06
*08:55	1.719 ± 0.01	7.144 ± 0.2	27.796 ± 1.49	0.0097 ± 0.0007	0.186 ± 0.03	300.106 ± 13.63	2.971 ± 0.16	438.411 ± 14.51
*09:55	1.701 ± 0.02	6.88 ± 0.19	29.531 ± 1.76	0.0106 ± 0.0011	0.217 ± 0.04	277.514 ± 11.01	2.755 ± 0.15	455.095 ± 16.32
*10:55	1.640 ± 0.01	7.083 ± 0.33	34.047 ± 2.25	0.0126 ± 0.0012	0.215 ± 0.04	237.076 ± 14.43	2.347 ± 0.17	466.457 ± 13.35
*11:55	1.611 ± 0.02	6.966 ± 0.26	33.13 ± 2.07	0.0156 ± 0.0015	0.228 ± 0.04	230.876 ± 10.48	2.226 ± 0.14	473.975 ± 13.19
*12:55	1.574 ± 0.01	7.073 ± 0.29	35.04 ± 4.29	0.0182 ± 0.0017	0.205 ± 0.05	205.818 ± 14.66	1.929 ± 0.18	483.385 ± 7.95
*13:55	1.590 ± 0.078	8.746 ± 0.29	47.079 ± 4.33	0.0158 ± 0.0013	0.156 ± 0.04	152.15 ± 17.08	1.370 ± 0.22	455.92 ± 18.47
*14:55	1.603 ± 0.01	8.118 ± 0.23	42.251 ± 1.86	0.0153 ± 0.0009	0.195 ± 0.02	170.662 ± 7.88	1.664 ± 0.11	454.565 ± 11.68

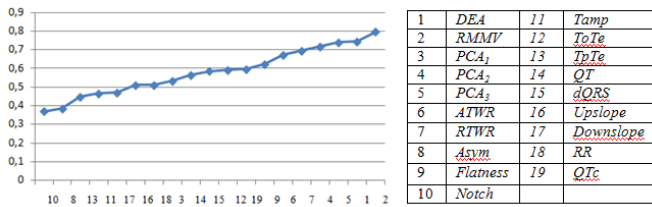


Fig. 2. Parameter contributions in the first 3 components for patient 1.

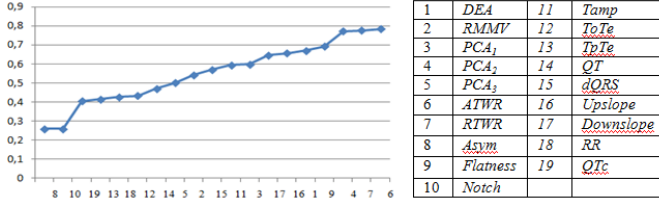


Fig. 3. Parameter contributions in the first 3 components for patient 2.

IV. DISCUSSION

After d-Sotalol administration, all parameters derived from the T-wave show clear evolution as the corrected QT interval during time recording. The amplitude of the T-wave was decreased leading to increase the flatness. The decreasing in *Upslope* and increasing in *Downslope* can be explained by the increasing of *TpTe* leading to increase descending segment of the T-wave.

At the end of the recording, the evolution of parameters has changed suggesting that the concentration of d-Sotalol in plasma was reduced. However, not all parameters have the same sensibility with respect to drug concentration. Only some parameters *DEA* and *RMMV* have shown significant evolution in patient 1 and maximum evolution in patient 2 passing from the first to the second hour of recording where the effect of d-Sotalol was still reduced. In parallel some parameters (*QTc*, *Flatness*, *Tamp*, *Downslope* and *PCA2*) have showed maximum evolution in early hours then no significant changes was noticed, whereas other parameters still change for the last hours even with reduced concentration of Sotalol (*DEA*, *RMMV*, *RTWR*, *TpTe*).

V. CONCLUSION AND PERSPECTIVES

During the past decade, a number of drugs have had their authorization revised because they induced a prolongation of the QT interval. QT prolongation is now the subject of increased regulatory review and is considered a significant risk factor for drug evaluation.

In this study, we proposed to identify here a set of T-wave parameters which can be useful to evaluate drug effect on repolarization. In particular, parameters related to the spherical coordinates (*DEA*, *RMVV*,...) of VCG have demonstrated a high sensitivity to small concentration of d-Sotalol. These results have to be assumed as preliminary due to the limited number of patients. Our current objective is now evaluating the T-wave morphological features in a larger database during longer period. This strategy would be carry out using QT parameters evolution with a placebo

and another type of drugs such as moxyfloxacin in order to take into account circadian rhythm.

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