Towards a new generation of dynamic indices for the assessment of drug-induced proarrhythmic risk

Pablo Daniel Cruces[†‡1], Francisco Javier Alvarado Rodríguez[*§2], Romo-Vázquez[*3] and Pedro David Arini[†‡4]

[†]*Instituto Argentino de Matemática "Alberto P. Calderón", CONICET*
Saavedra 15 (C1083ACA), (+5411) 6786-0296, CABA, Argentina
[‡]*Instituto de Ingeniería Biomédica, Facultad de Ingeniería, UBA*
Paseo Colón 850 (C1063ACV), CABA, Argentina
[*]*Departamento de Ciencias Computacionales,CUCEI, Universidad de Guadalajara*
Blvd. Gral. Marcelino García Barragán 1421,Col. Olímpica, 44430 Guadalajara, Jalisco, México
[§]*Departamento de Electromecánica, Universidad Autónoma de Guadalajara, México*
[1]pcruces@fi.uba.ar
[2]francisco.alvarado@edu.uag.mx
[3]rebeca.romo@academicos.udg.mx
[4]pedro.arini@conicet.gov.ar

***Abstract*—The detection of proarrhythmic side effects in many marketed drugs has prompted the search for complementary non-invasive markers of cardiotoxicity risk. Novel indices based on the study of cardiac vector dynamics have now emerged. Herein, we use quaternion methods to study alterations in the angular velocity during ventricular repolarization. The assessment was conducted in patients with Torsade de Pointes episodes when undergoing a Sotalol treatment. The algorithm includes a Principal Component Analysis to homogenize the information from three databases and, at the same time, reduce the space to three dimensions. Significant differences were found ($p < 5E\text{-}4$) in the angular velocity of the second half of repolarization loop (T-wave). The ratio between the maximums of the angular velocity in both T-wave halves showed a trend to 1 in the proximity of an arrhythmic event and reached sensitivity/specificity pair of 97/100 (AUC 0.99) in the comparison of healthy population with at-risk patients. The high performance of the method exceeded the expectations of the standard measurement and it becomes a promising outcome for the development of safe drug therapies.**

***Index Terms*—Torsade de Pointes, quaternion, angular velocity**

I. Introduction

In the aftermath of the increase in the consumption of medications together with the majority portion of global deaths that occupy cardiovascular diseases [1], the study of proarrhythmic side effects has been placed at the forefront of scientific research and the pharmacological industry. In both antiarrhythmic drugs and other non-cardiac drugs, such as antidiuretics, antibiotics, antidepressants, among others, a significant incidence of Torsade de Pointes (TdP) episodes has been observed [2], [3]. TdP is a polymorphic ventricular arrhythmia that can potentially lead to death. Fig. 1 shows the spontaneous development of a TdP episode on the surface electrocardiogram (ECG). The ECG is a graphical representation of the instantaneous projection of the action potentials (APs) that develop in the heart and constitutes one of the most used non-invasive tools in the clinic.

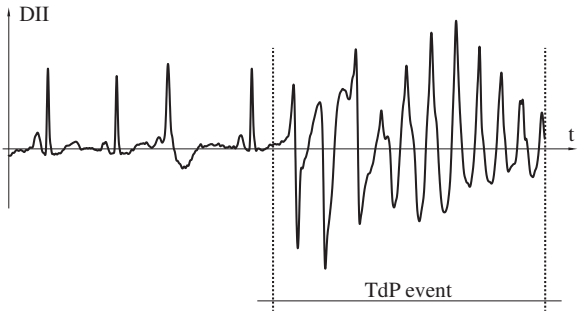

Fig. 1. Occurrence of a Torsade de Pointes event in a subject of the population under study. It is observed in DII lead of the ECG.

Currently, the proarrhythmic risk assessment of a drug is mainly determined through the measurement of the prolongation of the QT interval in the ECG [4], [5], which represents the total time of ventricular depolarization and repolarization (See Fig. 2). The QT interval is increased by the action of a drug on the ionic currents that underlying the APs. An excessive increase is a sign of cardiac risk [6]. However, proarrhythmic

effects have recently been observed in drugs that do not prolong the QT interval. In turn, there are drugs that prolong the QT interval but have not reported adverse effects on the heart [7], [8]. For these reasons, different international agencies encourage the search for independent complementary markers that allow the development of safe drugs[3].

In this work, we aim to evaluate the efficacy in risk prediction of a new generation of indices based on the dynamics of the cardiac electrical vector. This approach, developed from quaternion algebra, was highly effective in recent works on drug effects in both isolated rabbit heart model [9] and human at-risk patients with history of arrhythmia [10]. Herein, we will assess the modification of the angular velocity of the cardiac vector prior to TdP triggering in patients undergoing a Sotalol treatment, a well-known drug with proarrhythmic potential. We focus on ventricular repolarization since increased dispersion and premature ventricular contractions have been associated with the risk of arrhythmias [11], [12]. We are confident that our results can contribute to the development of safe drug therapies.

II. Materials and Methods

A. Dataset

The study was composed of three study populations.

1) Recorded Torsades de Pointes Event: This database is the aim population of the study and was obtained through a project with Telemetric and Holter ECG Warehouse (THEW) [13]. It includes Holter records (long-term ECG) from six patients (48 $\pm$ 25 y.o., 3 male and 3 female) who experienced one or multiple episodes of TdP during recording. They were subsequently enrolled for a diagnostic test based on dl-sotalol IV (at 2mg/kg body weight). The TdP events are marked. Four patients had a history of drug-induced TdP while the other ones had a history of a congenital TdP tendency. Each recording consists of 8-lead ECG signals at Fs 180Hz and 16 bits of resolution.

2) Sotalol IV and History of TdPs: This population consists of 16 patients (58 $\pm$ 12 y.o., females: 70%) with documented TdP in the context of a drug with QT-prolonging potential: sotalol, sumatriptan, amiodarone, bisacodyl, cipramil, furosemide, clarithromycin, erythromycin, roxithromycin [14]. Each individual record includes 12-lead ECG at 1kHz of Fs and $5\mu V$ resolution following the same protocol as in first database. None of these subjects experienced episodes of TdP during the challenge.

3) Physikalisch - Technische Bundesanstalt: From this dataset, we have selected all recordings from 52 volunteers (43 $\pm$ 15 y.o., females: 25%) with no previous cardiovascular diseases [15], [16]. The database has been acquired at the Department of Cardiology of University Clinic Benjamin Franklin in Berlin, Germany, and has been provided to the users of PhysioNet. Each record includes 15 simultaneously measured signals: the 12 standard ECG leads together with the 3 orthogonal Frank leads. Each signal was digitized at 1000 samples per second with 16 bits of amplitude resolution.

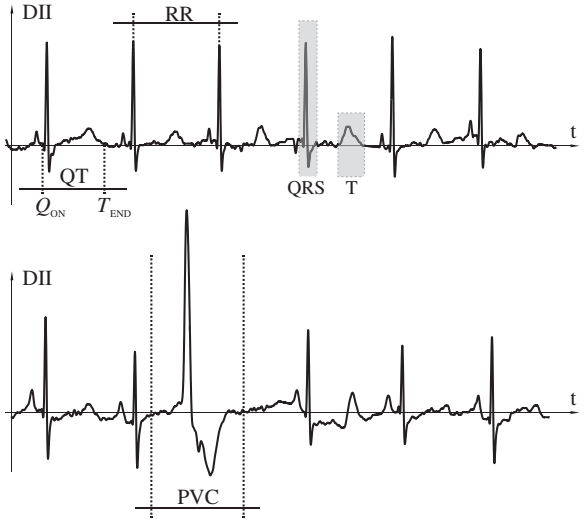

Fig. 2. Upper panel: Normal ECG signal observed in DII lead; With the Q_{ON} and T_{END} marks the standard QT index is constructed; RR represents the reciprocal of the heart rate. Lower panel: Premature ventricular contraction during T-wave.

B. Preprocessing

Since TdP events occur at different times of the day in each record of the population under study (Sec. II-A1), we selected a segment of 1 hour before the crisis. The signals of this dataset have been resampled to 1 kHz for a frequency unification. It does not affect the velocity computation since quaternion methods ensure velocity parameters with strong correlation (>98%) between 180Hz and 1000Hz [17].In each ECG lead an 80Hz Butterworth low-pass filter was applied to remove high frequency noise. Also, a 0.5Hz Butterworth high-pass filter was applied for baseline wander correction. Both were 5th order and bidirectional to reduce phase distortion. All QRS complexes were automatically delineated using a Wavelet-transform based method [18]. If a ventricular premature contraction (PVC) do appear in some record, the QRS mark was eliminated. These PVCs are easily detectable because they manifest as large amplitude deflections during ventricular repolarization (See Fig. 2). Its appearance is usually linked to increased ventricular dispersion and its consequent risk of, as in this case, an arrhythmic event [11], [12].

C. Segmentation

In order to construct the time series of the first dataset, a single T-wave from an averaged beat was obtained for each minute throughout the hour before the

crisis of each patient. For this purpose, ten consecutive beats were taken throughout each minute requiring a correlation greater than 0.9 among the QRS complexes ($Q\widehat{R}S \pm 60ms$). The T-waves were obtained as all the samples from $Q\widehat{R}S_i + 60ms$ (T_{ON}) to $Q\widehat{R}S_{i+1} - 150ms$ (T_{END}) for each i^{th} beat of the ten. Every averaged T-wave were then obtained and the noise were reduced by applying a 10Hz Butterworth low-pass filter to each one.

D. Principal Component Analysis

The study of the angular velocity of the cardiac electrical vector requires a three-dimensional space that can usually be obtained directly from the vectorcardiogram [19] or indirectly from an inverse transformation of the ECG such as the Kors matrix [17]. Since the present work analyzes a series of records from three databases with different adquisition methods, Principal Component Analysis (PCA) is a reasonable way to homogenize the information and at the same time, reduce it to three orthogonal axes.

From each matrix $A_{\text{T-WAVE}}$ with the eight independent ECG leads (I, II, V1-V6) and N samples, a Singular Value Decomposition were computed for each averaged T-wave,

$$A_{\text{T-WAVE}} = USV^T \tag{1}$$

where U is an 8x8 matrix, V is NxN and the eight singular values are in the primary diagonal of the 8xN matrix S. The first three quantify the energy of the so-called dipolar components of the signal $\vec{T_{\text{3-D}}}$. The five other singular values represent the non-dipolar components of the T-wave and are not considered in the present analysis. Finally, the decomposed signal DS results:

$$DS_{(8\times N)} = S_{(8\times 8)} V^T_{(N\times 8)} \rightarrow \vec{T_{\text{3-D}}} = DS_{(3\times N)} \tag{2}$$

In Fig. 3, a three-dimensional T-wave resulting from the decomposition is shown.

E. Angular velocity

The angular velocity ω is a three-dimensional vector orthogonal to the rotation of the cardiac electric vector and $||\omega||_2$ represents the speed in each sample. With the quaternion algebra, the difficulties involved in obtaining it from traditional methods, such as Euler Matrices, is avoided. The main advantages are related to the speed of computation and the propagation of uncertainties [20].

For the n^{th} sample of $\vec{T_{\text{3-D}}}$ in the three dimensional space ($\vec{T_n}(x, y, z)$) obtained from PCA, a quaternion $\vec{q_n}$ was built.

$$\vec{q_n} = \frac{(0, \vec{T_n})}{\left\|\vec{T_n}\right\|} \tag{3}$$

TABLE I
STANDARD DIAGNOSTIC WITH QT_c INTERVAL INDEX.

Diagnosis	**Young (≤15yo)**	**Adults**	
		Male	Female
Normal	$QT_c < 440$	$QT_c < 430$	$QT_c < 450$
Borderline	$440 - 460$	$430 - 450$	$450 - 470$
Prolonged	$QT_c > 460$	$QT_c > 450$	$QT_c > 470$

Then, using the temporal differentiation of $\vec{q_n}$ with the sampling frequency Fs, we had

$$\dot{\vec{q}}_n = (\vec{q_{n+1}} - \vec{q_n}) \cdot Fs \tag{4}$$

and the angular velocity was obtained from the imaginary part of the Poisson formula [21]:

$$\vec{\omega_n} = \dot{\vec{q}}_n \times \vec{\bar{q}}_n \tag{5}$$

In Eqs. 4 and 5, $\vec{\bar{q}}_n$ indicates the quaternion conjugate and the '$\times$' symbol refers to the Hamilton multiplication rule which follows the fundamental formula of quaternions, ie: $i^2 = j^2 = k^2 = ijk = -1$.

Finally, it is interesting to analyze ω in both halves of the T wave since each one meets different repolarization processes: The first half is linked to apex-to-base repolarization, while the second half is linked to transmural repolarization from epicardium to endocardium. Thus, the maximum angular velocity in each half was obtained as:

$$\begin{cases} \omega_{T1} = max(\|\vec{\omega}(T_{\text{ON}} : T_{\text{PEAK}})\|_2) \\ \omega_{T2} = max(\|\vec{\omega}(T_{\text{PEAK}} : T_{\text{END}})\|_2) \end{cases} \tag{6}$$

where T_{PEAK} is obtained from $max(\left\|\vec{T_{\text{3-D}}}\right\|_2)$ (see Fig. 3).

F. Statistical analysis

All the exposed methodology was developed to characterize dynamics one hour before the crisis of patients in Recorded Torsades de Pointes Event database (Sec. II-A1). Then, it was sought to distinguish this risk population (+TdP) from healthy volunteers (Hs, Sec. II-A3) or other patients who received the same treatment but did not suffer TdP events (-TdP, Sec. II-A2). The values of ω_{T1} and ω_{T2} were obtained for both complementary populations in the first ten consecutive beats of each record which reach a correlation greater than 0.9 among the QRS complexes. A two-sided Wilcoxon signed rank test was performed to obtain a significance value (p) on the group means.

G. Standard measurement

Finally, in order to make a comparison with the current standard measure, the QT interval was obtained with the correction of the heart rate using the Bazett formula [6], as:

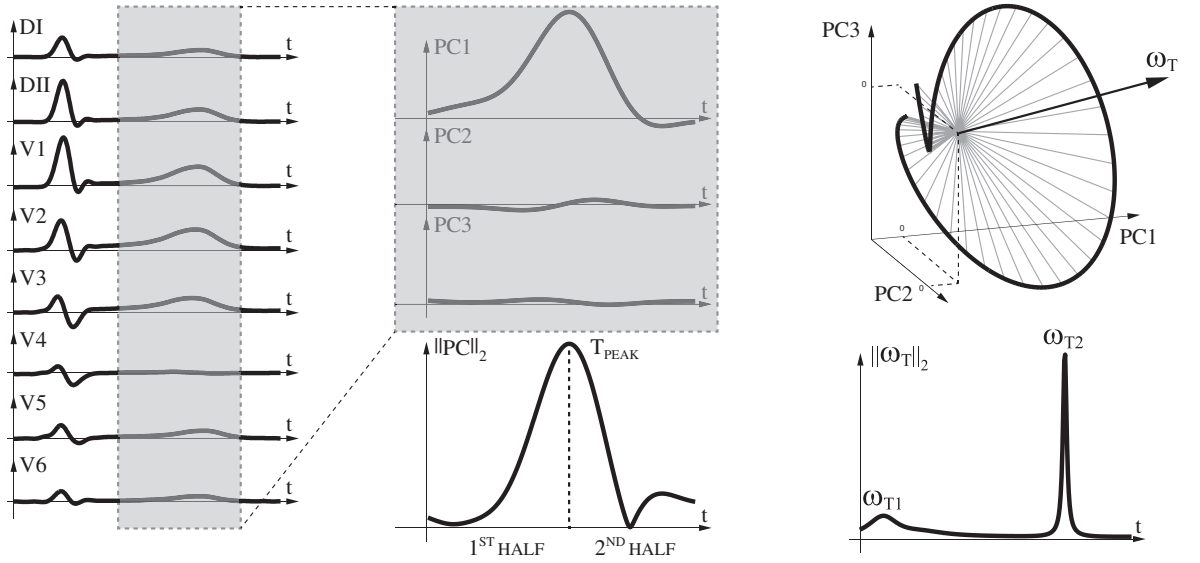

Fig. 3. Decomposition into three principal components (PC) of a T-wave from eight independent leads. The maximum of the 2-norm of the components is computed to separate the halves of the T-wave. From the three-dimensional signal, the angular velocity vector (ω_T) and its maximum in each half are computed.

TABLE II
MEAN (μ) AND STANDARD DEVIATION (σ) OF MAXIMUM ANGULAR VELOCITY IN EACH HALF OF THE T-WAVE. THEY ARE REPORTED FOR THE THREE POPULATIONS. A '*' SYMBOL INDICATES SIGNIFICANT DIFFERENCES AGAINST +TDP.

Index	**+TdP**	**-TdP**	**HS**
	$\mu \pm \sigma$	$\mu \pm \sigma$	$\mu \pm \sigma$
ω_{T1} [rad/s]	51.4 ± 41.2	94.0 ± 163.4	38.1 ± 46.9
ω_{T2} [rad/s]	76.3 ± 37.5	191.3 ± 249.1	338.6 ± 219.0*

$$QT_c = \frac{T_{\text{END}} - Q_{\text{ON}}}{\sqrt{RR}} \tag{7}$$

where T_{END} is the end point of ventricular repolarization (T-wave), Q_{ON} the point of the depolarization onset (QRS complex). Both marks are obtained using a wavelet delineation method [18]. RR is the reciprocal of heart rate (See Fig. 2). The standard diagnosis is made according to Table I.

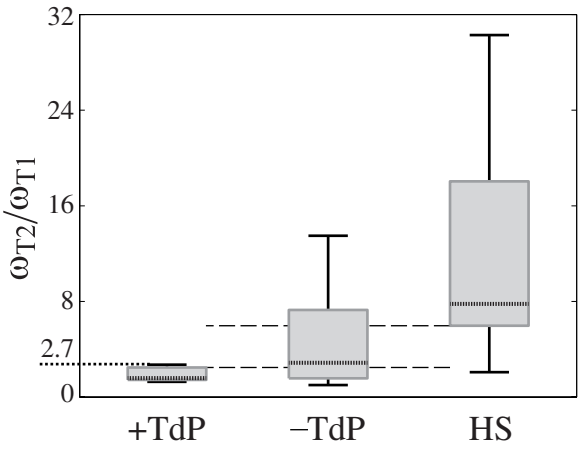

Fig. 4. Box and whiskers diagram for the three populations. For +TdP, it was obtained the mean of the last ten minutes before de event of each patient. Dotted lines indicate median values and dashed lines show the difference between the lower quartile of HS and the upper one of +TdP.

III. RESULTS

In Table II, mean and standard deviation values of both ω_{T1} and ω_{T2} are listed. The latter showed statistically significant differences between healthy subjects (HS) and the risk population (+TdP) one hour before the TdP episode with p<5E-4.

The trend observed in the risk population indicates that the maximum angular velocity of the first half of the T-wave increases while that of the second half decreases. Therefore, the ratio between the two parameters (ω_{T2}/ω_{T1}) was analyzed and compared with the values in the other populations. In Fig. 4, we show a box and whiskers diagram comparing this ratio in the three populations. The differences between the healthy population and the risk population are enhaced, reaching a p-value of less than 5E-5. In addition, the differences between +TdP and the subjects who, while under the same treatment, do not suffer arrhythmia (-TdP) are increased.

Using as threshold the upper limit of the +TdP diagram in Fig. 4 ($\omega_{T2}/\omega_{T1} = 2.7$), a sensitivity / specificity pair of 50 / 100 (Area under the curve, AUC = 0.68) was reached between + TdP and -TdP, and of 97 / 100 between + TdP and Hs (AUC = 0.99). On the other hand, the standard QT_c index was not able to differentiate the +TdP and -TdP populations and it reached a pair of 67 / 85 between + TdP and Hs.

IV. Discussion

The indices that characterize the dynamics of the cardiac electrical vector have recently shown great potential as risk markers, both in acute coronary syndrome [17] and drug-induced arrhythmias [9]. On the other hand, obtaining the angular velocity from quaternions overcomes the difficulty encountered in the traditional methods regarding the generation of ill conditioned matrices and the propagation of numerical uncertainties. In this work, the maximum angular velocities in ventricular repolarization were studied for the first time in records that capture episodes of TdP of patients undergoing Sotalol treatment.

Currently, international regulatory agencies require a QTc index analysis for drug approval [4], [5], [22]. However, it has insufficient specificity and depends strongly on an accurate definiton of the T_{END} point, which is often not possible [23]. In fact, the risk patients studied here have suffered TdP events and only 67% had QTc values in the risk range (see Sec. III and Table I).

The ω_{T2}/ω_{T1} ratio showed a trend to 1, equalizing the maximum angular velocities of both T-wave halves as the TdP event approaches. This could suggest a greater epicardial activity, explaining the spontaneous appearance of premature beats in risk situations, and a moderation of transmural activity. The relationship between the transmural repolarization dispersion and cardiovascular risk is still under debate in the scientific community.

Finally, the high performance of the method in differentiating between + TdP and Hs populations, exceeded the expectations of the standard measurement. At the same time, it allowed us to observe a significant difference with the subjects who, despite receiving the same drug, did not experience TdP. The latter is an interesting contribution to the challenge of discovering parameters that allow pharmaceutical industries the development of safe drugs.

V. Conclusion

The findings of this work constitutes a further sign of a paradigm shift towards studies on cardiac vector dynamics for risk assessment. The relationship between maximum angular velocities in both T-wave halves represents a valuable contribution to future research involving the development of drugs that affect different ion channels during ventricular repolarization. We are hopeful that a deepening of these ideas will be able to offer a tool to overcome current measures that will undoubtedly complement the development of safe pharmacological therapies.

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