A novel normalization of vectorcardiogram to enhance markers of differences between hERG and multichannel drugs

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***Abstract*— Torsade de Pointes is a polymorphic ventricular tachyarrhythmia potentially fatal that has been observed in a large number of common commercial drugs. Current markers used in pharmacological regulation do not have enough sensitivity/specificity. In this work, we present a novel technique for normalizing cardiac loops using principal component analysis. Then, using quaternionic techniques, the angular velocity of the cardiac electrical vector is obtained. This velocity is used to obtain highly efficient complementary parameters for determining the risk of certain drugs that differentially block repolarization ion channels. The results showed that the drugs that predominantly block *human ether-à-go-go-related gene* (hERG) channels show significant variations ($p < 0.001$) at the time of the highest plasma concentration. Also, a symmetry trend in angular velocity is observed. Moreover, the temporal parameters obtained showed greater efficiency as alternative measures to the standards. We hope that these insights will contribute significantly to the development of safe drug therapies.**

***Keywords*— Quaternion, Principal Component Analysis, Cardiac Risk.**

***Resumen*— La Torsada de Puntas es una taquiarritmia ventricular polifórmica potencialmente mortal que ha sido observada en gran cantidad de fármacos comerciales de uso común. Los marcadores actuales empleados en la regulación farmacológica no presentan suficiente sensibilidad/especificidad. En este trabajo, presentamos una novedosa técnica de normalización de los bucles cardíacos mediante un análisis de componentes principales. Luego, aplicando la teoría de cuaterniones se obtiene la velocidad angular del vector eléctrico cardíaco. Esta velocidad se emplea para la obtención de parámetros complementarios de gran eficacia para la determinación de riesgo de ciertos fármacos que bloquean diferencialmente canales iónicos durante la repolarización. Los resultados muestran que las drogas que mayormente bloquean los canales *human ether-à-go-go-related gene (hERG)* presentan variaciones significativas ($p < 0,001$) en el momento de mayor concentración en sangre. También se observa una tendencia de simetría en la velocidad angular. Asimismo, los parámetros temporales obtenidos muestran mayor eficiencia como medidas alternativas a los estándares. Confiamos en que estas ideas contribuyan significativamente al desarrollo de terapias farmacológicas seguras.**

***Palabras clave*— Cuaternión, Análisis de Componentes Principales, Riesgo Cardíaco.**

I. INTRODUCTION

IN a world where people feel continuously affected by stress, sleep disorders, poor nutrition or alcohol and/or narcotics use, pharmacological therapies become especially important to preserve health and life. A drug requires a careful evaluation process before being placed on the market, which involves a delicate balance: Very sensitive toxicity risk markers prevent the sale of potentially harmful drugs; but the high sensitivity, usually accompanied by low specificity, precludes the release of efficient products. Recently, a large number of marketed drugs with side effects associated with Torsade de Pointes (TdP) have been reported [1]. TdP is a potentially fatal polymorphic tachyarrhythmia. Currently, the regulatory framework for TdP requires a "thorough QT" study, a temporary electrocardiographic (ECG) measurement of ventricular electrical activity [2], [3]. However, its levels of sensitivity and specificity are still insufficient, among other reasons, due to uncertainties in the fiducial points of the ECG waves. Thus, a multiplicity of international organizations continuously promote research for non-invasive complementary markers [4].

We have previously shown a novel method for the determination of TdP risk markers caused by human ether-à-go-go-related gene (hERG) blockers, both in In Vitro models and human ECG recordings [5], [6]. hERG potassium channel blockers are associated with an increased TdP risk, however, sodium and calcium ion flux are also required for the proarrhythmic effect. Several drugs that combine blockers of different channels have shown lower torsadogenic risk. Therefore, it is expected that new risk markers are capable of differentiating the effect of pure hERG drugs from multichannel ones [7].

Herein, we show the normalization of the vectorcardiographic (VCG) signals that allows the computation of velocity markers of the cardiac electrical vector. These markers can not only differentiate multichannel effects but also give more accurate values of the extremes and peaks of ECG/VCG waves, which would also increase the specificity of the indices in the state of the art. We hope that these ideas will contribute to the development of safe pharmacological therapies.

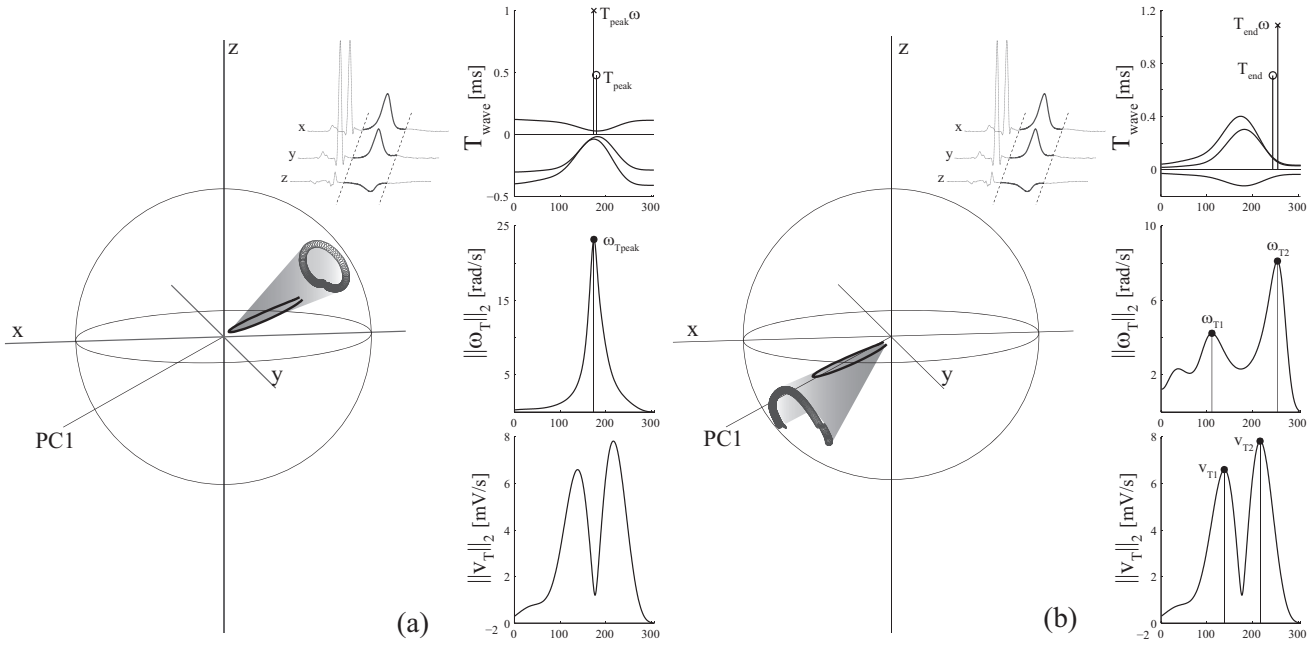

Fig. 1. T-wave loop normalization in the three-dimensional space. (a) Displacement towards negative values in principal component (PC1); (b) displacement towards positive values. The loop is projected onto the sphere of unitary radius. 2-norm angular (ω_T) and linear (v) velocity signals and their maximums are also shown. Dataset annotations points are marked with 'o'; fiducial points obtained from angular velocity are marked with 'x'.

II. Materials and Methods

A. Clinical study dataset

The Electrocardiogram Ranolazine, Dofetilide, Verapamil, Quinidine (ECGRDVQ) database includes 12-lead ECG recordings of 22 healthy subjects (26.9 $\pm$ 5.5 y.o., 50% females) undergoing a randomized, double-blind, 5-period crossover clinical trial aimed at comparing the effects of four known QT prolonging drugs versus placebo: Single dose of 500 μg dofetilide, 400 mg quinidine sulfate, 1500 mg ranolazine, 120 mg verapamil hydrochloride [8]. Dofetilide and quinidine had similar pharmacokinetic profiles, peaking at 2.5h; the former is a pure hERG blocker and the last has slightly additional calcium and sodium channel block effects. Verapamil (peaked at 1h) and ranolazine (peaked at 4h) are potassium blockers with the addition of a strong calcium and sodium blocker respectively. There was a 7-day washout period between each 24-hour treatment period. Three 10-seconds ECG recordings in a supine position were obtained at each one of the following time-points: -0.5h (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 14, and 24 h (post-dose). ECG was recorded at 500Hz of sampling frequency (Fs) with an amplitude resolution of 2.5 μV with stable heart rates and maximum signal quality. The resulting 5232 ECGs were up-sampled to 1000 Hz. Semi-automatic annotations of fiducial points are provided in the files.

B. Preprocessing

The study of the cardiac electrical vector dynamics requires a spatial approach. Therefore, we obtained the orthogonal XYZ leads through the inverse Kors matrix. Ten T-waves of each record were segmented and averaged. A bi-directional 5^{th} order Butterworth filter was applied for noise reduction with a cut-off frequency of 10Hz.

C. Normalization of the T-wave loops

The XYZ signals of a T-wave constitute a three-dimensional loop (see Fig. 1). This loop has a velocity profile that is strongly affected by zero crossings due to the non-linearity of the baseline. To avoid these alterations, a principal component analysis (PCA) technique is applied in order to separate the loop from zero through its central axis. Then, the T-wave signals of 3 leads and N samples can be decomposed as [9]:

$$\text{T-wave} = [T_x, T_y, T_z] = USV^T \tag{1}$$

where $U = [u_1, u_2, u_3]$ is an 3x3 matrix, V is NxN and the singular values matrix S is 3xN. The movement of the loop avoiding the origin gives us two possibilities: to move the loop towards positive values in the first component or towards negative ones (See Figs. 1a and 1b). In this way, we add two possible offset values to the T-wave loop:

$$T_i' = T_i + k.u_1, \quad i = x, y, z \tag{2}$$

and T_i' are the new values on each axis after moving the T-wave loop k-times in the principal direction (PC1).

D. Velocity markers

Loops were then normalized to unitary sphere and quaternion method was applied for computing the angular velocity [6]. This method allows obtaining dynamic features, such as angular velocity, with very low computation uncertainty [10]. For each n^{th} sample a quaternion $q[\vec{n}]$ was obtained:

$$q[\vec{n}] = (0, T[\vec{n}])/\left\|T[\vec{n}]\right\| \tag{3}$$

Using the temporal differentiation of $q[\vec{n}]$,

$$\dot{\vec{q}}[n] = (q[\vec{n+1}] - q[\vec{n}]) \cdot Fs \tag{4}$$

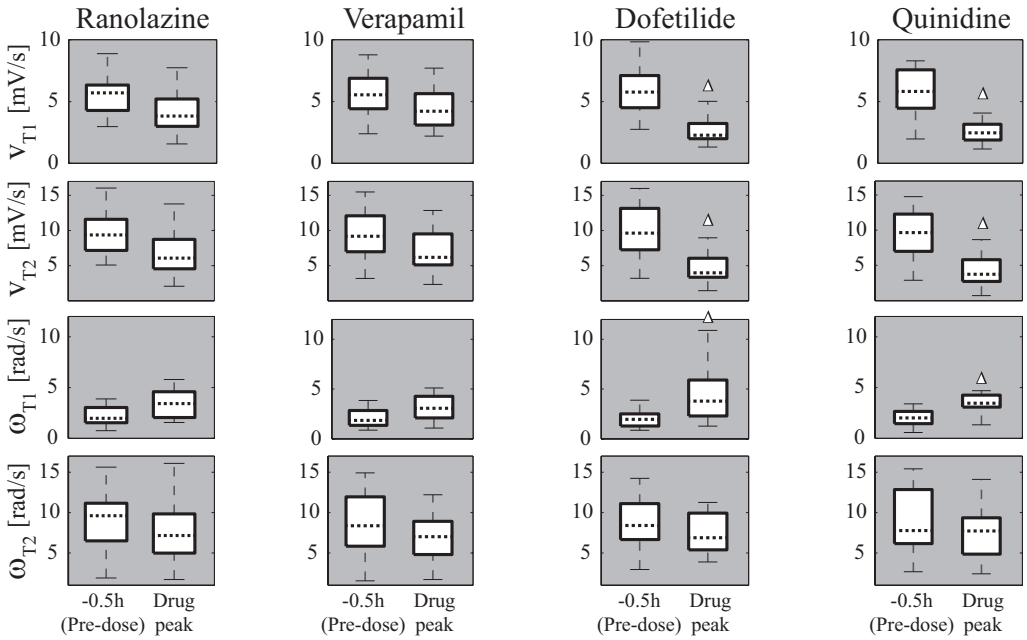

Fig. 2. Box and whisker diagrams comparing velocity values during pre-dosing and maximum plasma concentration. A mark 'Δ' indicates statistically significant differences ($p < 0.001$).

we obtained the angular velocity and its maximums (ω_{T1} and ω_{T2}) from the imaginary part of the Poisson formula [11]:

$$\omega[\vec{n}] = \vec{q}[n] \times \vec{\dot{q}}[n] \tag{5}$$

On the other hand, the linear velocity $v[n]$ and its maximums (v_{T1} and v_{T2}) could be obtained by differentiation:

$$v[\vec{n}] = (T[\vec{n+1}] - T[\vec{n}]) \cdot Fs \tag{6}$$

Finally, since we have obtained two possible displacement values, we obtain the 2-norm maximum velocity for each one. As can be seen in Fig. 1, the angular velocity maximums also indicate the peak (Fig. 1a) and the extremes (Fig. 1b) of the T-wave. These maximums strongly approximate the dataset annotations. Consequently, we obtain not only useful morphology descriptors for the study of ionic conduction changes, but also temporal markers of fiducial points. These markers allow us to define higher specificity variants of the standard indices:

$$QT_\omega = (\omega_{T2} - \omega_{QRSend})/\sqrt{RR} \tag{7}$$

where ω_{QRSend} is the last maximum of angular velocity using the same methodology with the QRS complex. QT_ω represents an alternative measure of QTc, the index used in regulatory studies. Here, QTc is the QT corrected by the Bazzet formula, ie. QT divided by the square root of RR interval (inverse of heart rate). Also,

$$JT_{p\omega} = (\omega_{Tpeak} - \omega_{QRSend})/\sqrt{RR} \tag{8}$$

could be an alternative of JTpc (also corrected by the Bazzet formula), a measure of early ventricular repolarization duration which has been shown to be a useful marker for distinguish QT prolonging hERG blockers from those affecting multiple ion channel currents [7].

E. Statistical analysis

Linear and angular velocity maximums are evaluated throughout each time-point and for each drug (see Sec. II-A). A population evaluation was also carried out to observe that the indices were not affected during the administration of placebo. A Kolmogorov-Smirnov normality test was applied, followed by a Wilcoxon test to assess significant changes ($p < 0.001$). An additional analysis of the temporal evolution of the dynamic indices was applied with the mean estimation using bootstrapping techniques.

Finally, the novel temporal markers $JT_{p\omega}$ and QT_ω are evaluated via correlation with standards QTc and JTpc.

III. Results

In the Fig. 2, we have shown the comparison between maximum values of each velocity (See Fig. 1) during pre-dose recordings and maximum of drug plasma concentration. Dofetilide shown the greatest differences in both linear and angular velocities. The reduction in linear velocities are accompanied by an increase of angular velocity during early repolarization, possibly associated with the influx of calcium and sodium ions. Quinidine also shown similar effects with lower p-values. Strong calcium or sodium blocks would seem to reduce the effect on velocities caused by the block of hERG potassium channels, since Ranolazine and Verapamil showed more moderate trends with non-significant differences.

The largest changes in velocities occur at the point of highest drug concentration in the blood. In the Fig. 3 we show Dofetilide-induced changes (mean ± 95% confidence interval) from control (pre-dose) to 24h post-dose.

Finally, we observed a high correlation (> 0.9) between the temporal parameters ($JT_{p\omega}$ and QT_ω) and their standard ECG measurements. However, QTc showed correlation reductions at the time-points close to the drug peak. We show in Table I the Dofetilide-induced changes which were the more significant.

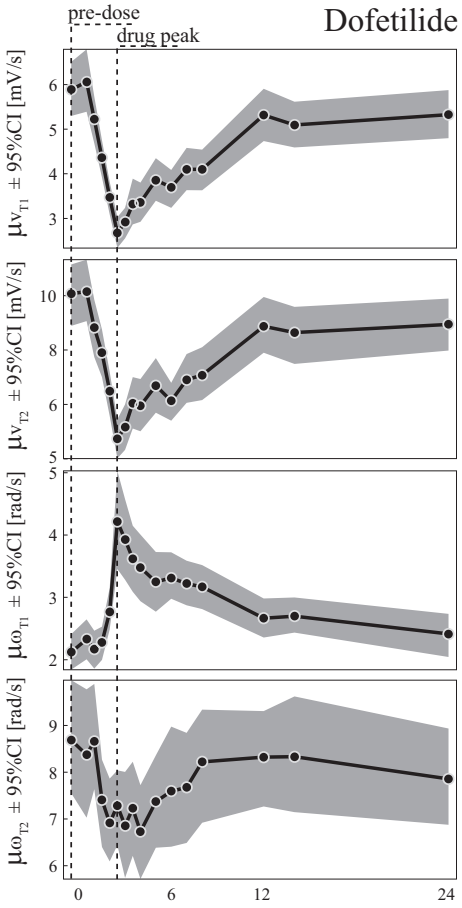

Fig. 3. Drug-induced velocity changes throughout the 24h duration of the trial. The mean of the linear and angular velocity maximum in each half of the T-wave is shown.

TABLE I
DOFETILIDE-INDUCED CHANGES IN STANDARD VALUES AND THEIR ALTERNATIVE MEASUREMENTS (MEAN ± SD).

Marker	Pre-dose	Drug-peak
QTc [msec]	391.8±18.7	474.4±33.4
QT_ω [msec]	390.7±13.7	435.3±18.7
JTp [msec]	226.7±19.8	256.1±41.8
$JT_{p\omega}$ [msec]	235.8±23.1	272.5±43.0

IV. DISCUSSION

In this work, a novel PCA normalization method of vectorcardiogram loops is presented. The results indicate that velocity markers could be useful markers for distinguish QT prolonging hERG drugs from those that affect multiple cardiac repolarization ion channel currents. The trends observed in the four drugs under study were similar, however, only those that predominantly affect delayed potassium channels showed statistically significant changes (See Fig. 2). This would indicate that late sodium current or calcium current blocks oppose effects of hERG block. This fact agree with the results observed in temporal parameters JTp and Tpe (T-wave peak to end) [8]. Since Dofetilide is a pure hERG blocker, its velocity changes were the most significant (See Fig. 3) compared to those observed in Quinidine.

It is also interesting to note that in previous studies we have shown that Sotalol (high cardiac risk pure hERG blocker) tends to a symmetry in the velocities in response to the risk of TdP [12]. In Fig. 2, we have a consistent result since oppose alterations are observed between and ω_{T2}. The greater significance observed in ω_{T1} could be associated with the entry of sodium and calcium early repolarization.

On the other hand, we have previously evaluated the QT_ω in animal model as an alternative measure of QTc [5]. Although this measurement was not carried out with the normalization presented here, we can infer that the measure of the QTc from the maximum angular velocity obtained with quaternions could increase the efficiency of the standard measurement. This approach avoids the determination of the fiducial points from the ECG signals, which is the fact that has led to strongly question the current temporal indices [13].

V. CONCLUSION

The new dynamic measures obtained through quaternions after normalization of the vectorcardiogram loops have shown robustness when evaluated in different drugs. Moreover, a novel alternative for measuring the parameters used in drug regulation was presented. These markers could complement current standards and strongly contribute to the development of safe pharmacological therapies.

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