# Geometrical and Temporal ECG Features for Quantification of Increased Ventricular Repolarization Dispersion in an Experimental Heart Rabbit Model

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## Abstract

*Abnormal increase of ventricular repolarization dispersion (VRD) is an important risk factor for severe arrhythmia development. An increased VRD implies a modification of the spatio/temporal T wave morphology. Our objective is to study the ECG derived VRD feature markers that better represent the electrical modifications generated by increased VRD in an In Vitro rabbit heart experiment which has global VRD induced, at all myocardium areas, by supplying d-Sotalol ($dS$) and by premature ventricular stimulation (PVS). Temporal (T-wave duration, $T_W$) and geometrical (mean repolarization axis, $\Theta_{XT}$, measured respect to a fix reference X axis) features were shown as the better markers of increased VRD, with the higher discrinant power in the T wave duration. Results are: $T_W$: (95$\pm$7 ms) vs (118$\pm$15 ms) for Control vs PVS; $T_W$: (78$\pm$10 ms) vs (133 $\pm$29 ms) for Control vs dS; $\Theta_{XT}$: (35$\pm$51$^o$ ) vs (117$\pm$49$^o$ ) for Control vs dS.*

## 1. Introduction

The QT interval is used to quantify ventricular repolarization ($VR$). Moreover $QT$ dispersion ($QT_d$) has also been proposed as an index to assess ventricular repolarization dispersion ($VRD$). However, there are controversial studies that examine the relation between $QT_d$ and $VRD$. Our hypothesis is that $VRD$ implies widening of the T wave and the T wave width will be a better $VRD$ indicator. The ECG were analyzed in two ways: Temporal Analysis from all-lead absolute value summation signal and Geometrical Analysis from Singular Value Decomposition ($SVD$) of all ECG lead. We analyzed the ECG signal in control and an increased $VRD$ ($IVRD$) which was induced artificially in a In Vitro rabbit heart experiment [1]. The Temporal Analysis was done by computing the T-wave amplitude, T-wave area and T-wave width values. While, in Geometrical Analysis, $\Theta_{RT}$, angle obtained from the total cosine R to T angle between mean depolarization and repolarization axis was estimated [2] for comparison purpose. Moreover to avoid the uncertainty in the R wave reference axis estimation we propose the $\Theta_{XT}$ angle. This angle was obtained from the mean repolarization axis respect to a reference *X* axis linked to the tank. The present work aims to find sensitive $IVRD$ indexes on the surface ECG that quantify directly this phenomena.

## 2. Methods

### 2.1. Experimental model

The model consisted of an In-Vitro system which records the electrical activity of isolated rabbit (New Zealand white male, 2.8-3.8 Kg) hearts beat-by-beat. The heart was perfused through the aorta and immersed in a tank filled with Tyrode's solution. The temperature of both solutions, the perfusion and the tank, was maintained at $38 \pm 0.5^oC$ and bubbled with $O_2$, with a flow of 700-900 ml/h and a pressure of 70 mmHg. Care was taken to fix the hearts in the same position relative to the electrode matrix on the tank. The sinus node was destroyed and $IVRD$ was induced by two different protocols: supplying d-Sotalol ($dS$) [3] and by premature ventricular stimulation ($PVS$) [4]. In both experimental protocols an artificial pacemaker was used. The stimulating electrodes were positioned in the right auricle for the $dS$ protocol and at the middle of the base of each ventricle for $PVS$ protocol (Fig.1). An equilibrium period of 30 minutes was monitored to be sure the heart is arrhythmias free, stable in amplitude and with no manifested ischemia. We used two different models. In the first one the heart was placed in a tank of 10 cm diameter by 10 cm high which includes 30 Ag-AgCl electrodes of 2 mm diameter homogeneously distributed mounted in the wall of the tank in an array of 5 rows (inter-electrode distance 15 mm) and 6 columns (angular distance 60$^o$). This was used in the $dS$ protocol. The second model con-

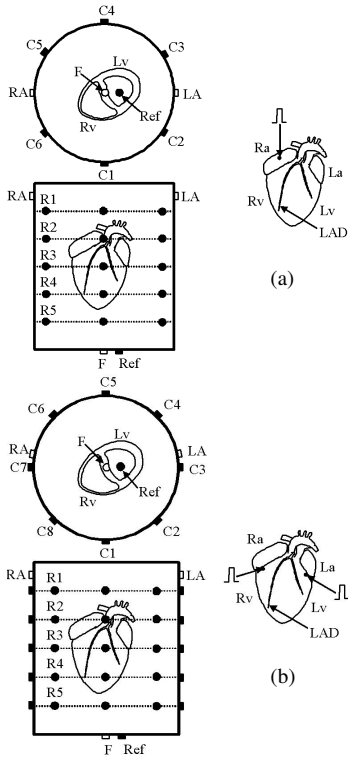


Figure 1. a) Superior and frontal views showing the $5 \times 6$ matrix electrodes. b) Superior and frontal views showing the $5 \times 8$ matrix electrodes. Panel a and show the standard leads F, LA, RA and REF. Also show left atrium ($L_a$), right atrium ($R_a$) and left descending artery (LAD). At the right the stimulation site for $R_a$, right ventricle ($R_v$) and left ventricle ($L_v$).

sist in a tank of 7 cm diameter by 7 cm high including 40 recording electrodes homogeneously distributed in a 5 rows $\times$ 8 columns array. The distance between electrodes is 10 mm and the angular distance is $45^o$. Also Ag-AgCl electrodes 2 mm in diameter were mounted in the wall of the tank. This model was used in the $PVS$ protocol. In both tanks, the electrodes having the Wilson Central Terminal points as reference since extra electrodes are positioned for that (Fig.1). For $dS$ protocol Tyrode's solution was perfused for 30 minutes (control period ($C_{dS}$)) after that $dS$ solution was added and perfused (60 mM) to generate increased dispersion situation ($D_{dS}$). Both during $C_{dS}$ and $D_{dS}$ the ECG was recorded and the different derived variables measured. For $PVS$ the heart was stimulated in some cases from right ventricle ($R_v$) and in others from left ventricle ($L_v$) at basal cycle length ($BCL$) during a train of 49 beats. After that train, at $50^{th}$ beat , a premature beat was generated at a coupling interval corresponding to the Effective Refractory Period ($E_{rp}$) plus 5 ms. $E_{rp}$ was estimated on each case prior to the $PVS$ operation, The ECG measurement obtained from the $48^{th}$ and $49^{th}$ beats were averaged and used as control measures prior to ventricular stimulation ($C_{PVS}$) at the $50^{th}$ beat. The premature beat was elicited in order to generate dispersion paced either at $R_v$ or $L_v$ ($D_{PVS}$). In the $dS$ protocol (n=10) the hearts were paced at a $BCL$ of 500 ms. In the $PVS$ protocol (n=10) the heart artificial excitation was achieve from the $R_v$ (n=5) or from the $L_v$ (n=5) at a $BCL$ of 400 ms. The premature beats were elicited at 167$\pm$7.2 ms for $R_v$ stimulation and 168$\pm$11.5 ms for $L_v$ stimulation.

## 2.2. Data acquisition and signal processing

The ECG was acquired with instrumentation amplifiers with a gain factor of 1000, and a bandwidth of 0.05-300 Hz. They were digitalized at a sampling rate $f_s = 1000$ Hz, and 12-bit resolution. A band-stop filter to remove 50-Hz was used and the baseline movement was compensated with a cubic spline algorithm. Once the heart electrical activity became stable the beats corresponding to the first row leads were recorded simultaneously, after that the same procedure was applied in a sequential manner to the remaining rows. A beat, the $i^{th}$, is selected from the ECG recordings of each $r^{th}$ row, $r = 1, ..., 5$, obtaining the $i_r^{th}$ beat. After selecting and segmenting the $i_r^{th}$ beat from each row, a signal, $x_{c,r}(n)$ is obtained for each derivation. Being $c$ the column in the electrode matrix ($c = 1, ...L$) and $r$ the row with $L$ = 6 for $dS$ protocol and $L$ = 8 for $PVS$ protocol. In vector form, $\mathbf{x}_{c,r}$, was obtained as:

$$\mathbf{x}_{c,r} = [x_{c,r}(0), ..., x_{c,r}(N-1)]^T \quad (1)$$

The five $i_r^{th}$ selected beats are aligned, assuming that they represent simultaneous electrical activity, since electrical stability through all the registers has been met. The alignment was made with the QRS complex maximum upstroke slope. Selecting a beat implies taking a window, 400 ms in width, including the VR phase. For each experimental condition ($C_{dS}$, $D_{dS}$, $C_{PVS}$, $D_{PVS}$) 30 or 40 ECG lead recordings were obtained for $dS$ and $PVS$, respectively. Expressing the selected segmented signals as:

$$\mathbf{X} = [\mathbf{x}_{1,1}, \ldots, \mathbf{x}_{L,1}, \ldots, \mathbf{x}_{1,5}, \ldots, \mathbf{x}_{L,5}]^T \quad (2)$$

From the matrix $\mathbf{X}$ ($5L \times N$) the ECG parameters were measured. $\mathbf{X}$ characterize each experimental condition.

### 2.2.1. Temporal analysis

In order to quantify the $VR$, the signal obtained from summation of the absolute ECG value was calculate as:

$$x_M(n) = \sum_{c=1}^{L} \sum_{r=1}^{5} |x_{c,r}(n)| \quad (3)$$

Then we measured T-wave onset ($n = n_o^M$), T-wave end ($n = n_e^M$ and T-wave peak position ($n = n_p^M$). From the fiducial points the derived indexes are: T-wave maximum amplitude, $T_M = x_M(n_p^M)$, T-wave width $T_W = \frac{(n_e^M - n_o^M)}{f_s}$ and T-wave area, $T_A = \sum_{n=n_o^M}^{n_e^M} x_M(n)$. All these time instant estimates, $n_o^M$, $n_e^M$ and $n_p^M$, are refered relative to the QRS fiducial point. The fiducial points were detected by using a threshold-based algorithm on the differentiated signal [5]. Once the maximum and minimum of the differentiated signal were detected (maximum slope points) a threshold $K$ was established to detect the $n_o^M$ at the time location where the differentiated signal fall down by a factor $K$=0.8 previous to the maximum slope instant, and by a different factor, $K$=0.2, posterior to the minimum slope instant to detect the $n_e^M$. The $n_p^M$ position was determined by the zero-crossing on the differentiated signals.

### 2.2.2. Geometrical analysis

To study the spatial $VR$, the ECG matrix $\mathbf{X}$ is subjected to $SVD$ [2]. $SVD$ is defined as: being $\mathbf{X}$ a $M \times N$ matrix, with $M = 5 \times L$ electrodes and $N$ being the number of selected samples, then there are two orthogonal matrices: $\mathbf{U} = [\mathbf{u}_1, \ldots, \mathbf{u}_M] \in \mathbb{R}^{M \times M}$ and $\mathbf{V} = [\mathbf{v}_1, \ldots, \mathbf{v}_N] \in \mathbb{R}^{N \times N}$ such that: $\mathbf{\Sigma} = \mathbf{U}^T \mathbf{X} \mathbf{V} = [diag(\sigma_1, \ldots, \sigma_M)\ \mathbf{0}]$ where $\mathbf{\Sigma} \in \mathbb{R}^{M \times N}$. The singular values $\sigma_j$ are ordered such that $\sigma_1 \geq \sigma_2 \geq \ldots \geq \sigma_M \geq 0$. Besides this, if $\sigma_1 \geq \ldots \geq \sigma_p > \sigma_{p+1} = \ldots = \sigma_M = 0$ then, rank$(\mathbf{X}) = \mathbf{p}$ and range$(\mathbf{X}) = span\{\mathbf{u}_1, \ldots, \mathbf{u}_p\}$. If rather we truncate the expansion for those eigenvalues more significant we can obtain range$(\mathbf{X})$ as the minimum dimensional space which contained around 98% of the total energy [2]. The parameters which represents the ventricular gradient ($VG$), computed as the angle between depolarization and repolarization, were obtained from the minimum decomposition subspace. Then

$$\mathbf{X} = \mathbf{U}\mathbf{\Sigma}\mathbf{V}^T = [\mathbf{U}_1 \mathbf{U}_2] \begin{bmatrix} \mathbf{\Sigma}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{\Sigma}_2 \end{bmatrix} \begin{bmatrix} \mathbf{V}_1^T \\ \mathbf{V}_2^T \end{bmatrix} \quad (4)$$

The ECG total energy was represented in a 3D subspace, then $\mathbf{U}_1 \in \mathbb{R}^{M \times 3}$ and $\mathbf{\Sigma}_1 \in \mathbb{R}^{3 \times 3}$. Let $\mathbf{S} = \mathbf{U}_1^T \mathbf{X}$ be the projection of $\mathbf{X}$ onto $\mathbf{U}_1$. Each column of $\mathbf{S}$ associated to time instant $n$ is $\mathbf{s}(n) = [s_1(n), s_2(n), s_3(n)]^T$ which is the projection of the $M$ dimensional columns of $\mathbf{X}$, denoting the spatial dependence of the ECG, into the three main components spanded by $[\mathbf{u}_1, \mathbf{u}_2, \mathbf{u}_3]$, meaning $\mathbf{S} \in$ span$[\mathbf{u}_1, \mathbf{u}_2, \mathbf{u}_3]$. The rows $s_i(n)$ $i = 1, 2, 3$, are the transformed signals in the dipolar representation. The algorithm for detecting $n_o^D$; $n_e^D$; $n_p^D$ was applied onto the composed signal $x_D(n)$ which represent the module of the cardiac electrical vector, as in (5)

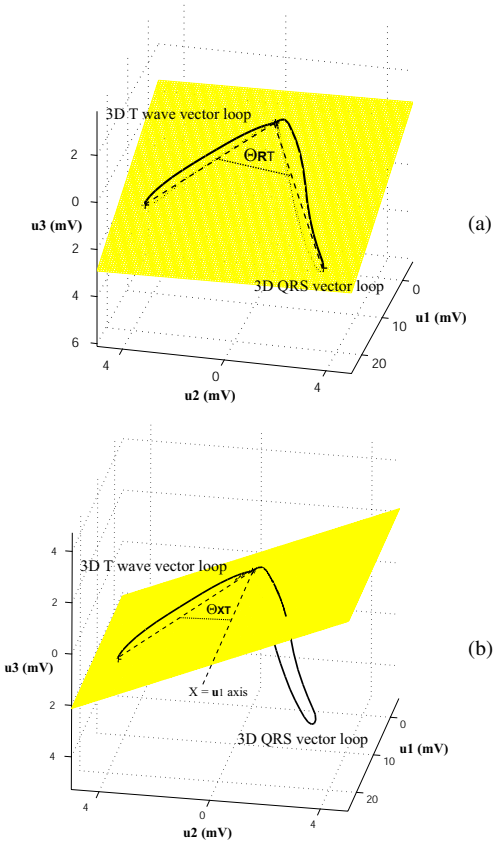


Figure 2. Schematic view of the QRS and T wave vector loops. a) $\theta_{RT}$ and b) $\theta_{XT}$

$$x_D(n) = \sqrt{\sum_{i=1}^{3} s_i^2(n)} \quad (5)$$

With these fiducial point the T wave matrix can be segmented as: $\mathbf{S}_T = [\mathbf{s}(n_o^D), \ldots, \mathbf{s}(n_e^D)]$. To estimate the depolarization dominant direction we search for the maximum value of $x_D(n)$ in the first 80 ms which is associated to the R wave peak, $n_{R,p}$. From this location, a depolarization QRS wave matrix, $\mathbf{S}_{QRS}$ , can be segmented by taking 30 ms interval centered at $n_{R,p}$. This interval time was marked by their onset, $n_{R,o}$ and by their end $n_{R,e}$ as: $\mathbf{S}_{QRS} = [\mathbf{s}(n_{R,o}), \ldots, \mathbf{s}(n_{R,e})]$. Then the angle between $VR$ and depolarization was calculated to express $VG$ [6]. This descriptor named total cosine R-to-T ($T_{CRT}$)[2] was calculated as:

$$T_{CRT} = \frac{1}{(n_{R,e} - n_{R,o} + 1)} \sum_{n=n_{R,o}}^{n_{R,e}} \cos \angle(\mathbf{s}(n), \mathbf{s}(n_p^D)) \quad (6)$$

$T_{CRT}$ as in (6), representing the same concept already present by Wilson [6]. Negatives values shows very large

Table 1. Results for Temporal and Geometrical Analysis, p value denotes significative difference

| | $units$ | $C_{dS}$ | $D_{dS}$ | $p$ | $C_{PVS}$ | $D_{PVS}$ | $p$ |
|---|---|---|---|---|---|---|---|
| $T_M$ | $mV$ | 2.2±0.8 | 2.4±0.9 | 0.05 | 1.7±0.4 | 2.4±0.8 | 0.028 |
| $T_A$ | $mV.ms$ | (5.7±2.5)$10^4$ | (11.3±6.0)$10^4$ | 0.047 | (3.8±1.2)$10^4$ | (5.9±2.3) $10^4$ | 0.007 |
| $T_W$ | $ms$ | 78.0±10.3 | 133.6±29.6 | 0.006 | 95.2±7.9 | 118.5±15.7 | 0.007 |
| $\Theta_{RT}$ | $degree\ (^o)$ | 41±17 | 73±42 | 0.05 | 149±7 | 133±22 | $NS$ |
| $\Theta_{XT}$ | $degree\ (^o)$ | 35±51 | 117±49 | 0.009 | 137±65 | 129±61 | $NS$ |

differences in the orientation of the QRS complex and T wave loops. We use as performance index the angle, $\theta_{RT} = \arccos(T_{CRT})$, (Fig.2), rather than the cosine. This index has to estimate both, the QRS vector and the T wave vector, with the associated uncertainties in both estimations. Since the hypothesis is that only T wave vector varies with $IVRD$, we better propose to estimate the angle between a fix reference and the T wave as $VRD$ index, so avoiding uncertanties generated by QRS loop estimation. We propose the $\theta_{XT}$ angle as:

$$\theta_{XT} = \angle(\mathbf{x}, \mathbf{s}(n_p^v)) \tag{7}$$

obtained from the total cosine $\mathbf{x}$ axis to T angle. We take as the *X* axis the principal component $\mathbf{u}_1$ from the control beat and keeping it for reference both for control and $IVRD$ situation . This measures the mean $VR$ axis difference respect to a *X*-reference axis linked to the tank (see Fig.2), $\mathbf{u}_1$ in this case . We recall here that all hearts are geometrically aligned in the tank with respect to the main left artery, so making plausible to compare $\theta_{XT}$ angles between different cases.

## 3. Results

Table 1 presents the mean ± SD obtained by measuring $T_M$, $T_A$ , $T_W$, and by computing $\theta_{RT}$, $\theta_{XT}$ during $PVS$ and $dS$ supply protocols respectively and compare with respectively controls by the Wilcoxon test. Non-parametrical test was chosen since the distribution of variables to be compared was unknown.

## 4. Discussion and conclusions

Generation of $IVRD$ by $PVS$ stimulation results in increases of the $T_M$, $T_A$, $T_W$, suggesting that action potential (AP) duration modified differently at different myocardial areas thus increasing both T-wave duration, area and and amplitude giving value to these markers as $IVRD$ indicators. Also, $\Theta_{RT}$ and $\Theta_{XT}$ did not show to be $IVRD$ markers when the $IVRD$ was generated by $PVS$ stimulation. On the other hand $dS$ generated $IVRD$, did not significantly modify neither $T_A$ or $T_M$, nevertheless $T_W$ duration was enlarge significantly suggesting again different modifications of AP duration at different areas by the $dS$ induced $IVRD$. The $\Theta_{RT}$ and $\Theta_{XT}$ showed to be markers; with higher significance for the $\Theta_{XT}$ corroborating the hypothesis that the fixed reference to the tank better estimated the $VR$ axis variation with $IVRD$. The lack of differences in $\Theta_{XT}$ together with the much reduced $T_W$ enlargement (23 ms vs 55 ms) of the $PVS$ again $dS$ shows a much reduced induction of $IVRD$ with $PVS$ than with $dS$. Also this results seems to indicate a superior power of $T$ width, $T_W$, than ventricular gradient based indexes to quantify $IVRD$.

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