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

PD Arini¹, ER Valverde², GC Bertrán³, P Laguna⁴

¹Argentine Institute of Mathematics, CONICET, Buenos Aires, Argentine
²School of Engineering, University of Buenos Aires, Buenos Aires, Argentine
³Institute of Medical Research Dr A Lanari, University of Buenos Aires, Buenos Aires, Argentine
⁴Aragón Institute of Engineering Research, University of Zaragoza, Spain

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, TW) and geometrical (mean repolarization axis, ΘXT, measured respect to a fix reference X axis) features were shown as the better markers of increased VRD, with the higher discriminant power in the T wave duration. Results are: TW: (95±7 ms) vs (118±15 ms) for Control vs PVS; TW: (78±10 ms) vs (133±29 ms) for Control vs dS; ΘXT: (35±51°) vs (117±49°) for Control vs dS.

1. Introduction

The QT interval is used to quantify ventricular repolarization (VR). Moreover QT dispersion (QTd) has also been proposed as an index to assess ventricular repolarization dispersion (VRD). However, there are controversial studies that examine the relation between QTd 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, ΘRT, 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 ΘXT 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 ± 0.5°C and bubbled with O2, 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°). This was used in the dS protocol. The second model con-
Figure 1. a) Superior and frontal views showing the 5 × 6 matrix electrodes. b) Superior and frontal views showing the 5 × 8 matrix electrodes. Panel a and show the standard leads F, LA, RA and REF. Also show left atrium (La), right atrium (Ra) and left descending artery (LAD). At the right the stimulation site for Ra, right ventricle (Rv) and left ventricle (Lv).

Effective Refractory Period (ERP) plus 5 ms. ERP was estimated on each case prior to the PVSS operation. The ECG measurement obtained from the 48th and 49th beats were averaged and used as control measures prior to ventricular stimulation (CPVS) at the 50th beat. The premature beat was elicited in order to generate dispersion paced either at Rv or Lv (DPVS). In the dS protocol (n=10) the hearts were paced at a BCL of 500 ms. In the PVSS protocol (n=10) the heart artificial excitation was achieve from the Rv (n=5) or from the Lv (n=5) at a BCL of 400 ms. The premature beats were elicited at 167±7.2 ms for Rv stimulation and 168±11.5 ms for Lv 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 = 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 ith, is selected from the ECG recordings of each rth row, r = 1, ..., 5, obtaining the ith beat. After selecting and segmenting the ith 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 PVSS protocol. In vector form, x_{c,r} was obtained as:

\[ x_{c,r} = [x_{c,r}(0), ..., x_{c,r}(N-1)]^T \] (1)

The five ith 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}, CPVS, DPVS) 30 or 40 ECG lead recordings were obtained for dS and PVSS, respectively. Expressing the selected segmented signals as:

\[ X = [x_{1,1}, ..., x_{L,1}, ..., x_{1,5}, ..., x_{L,5}]^T \] (2)

From the matrix X (5L × N) the ECG parameters were measured. 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:

\[ x_u(n) = \sum_{c=1}^{L} \sum_{r=1}^{5} |x_{c,r}(n)| \] (3)
Then we measured T-wave onset \((n = n_p^o)\), T-wave end \((n = n_p^e)\) and T-wave peak position \((n = n_p^m)\). From the fiducial points the derived indexes are: T-wave maximum amplitude, \(T_M = x_u(n_p^m)\), T-wave width \(T_W = \frac{(n_p^m - n_p^o)}{f_w}\)

and T-wave area, \(T_A = \sum_{n=n_p^o}^{n_p^m} x_u(n)\). All these time instant estimates, \(n_p^o\), \(n_p^m\) and \(n_p^e\), are referred 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 \(n_p^M\) 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 \(n_p^M\). 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 \(X\) is subjected to \(SVD\) [2]. \(SVD\) is defined as: being \(X\) 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:

\[
\mathbf{U} = [\mathbf{u}_1, \ldots, \mathbf{u}_M] \in \mathbb{R}^{M \times M} \quad \text{and} \quad \mathbf{V} = [\mathbf{v}_1, \ldots, \mathbf{v}_N] \in \mathbb{R}^{N \times N}
\]

such that: \(\mathbf{X} = \mathbf{U} \Sigma \mathbf{V}^T = [\mathbf{diag}(\sigma_1, \ldots, \sigma_M) \mathbf{0}]\) where \(\Sigma \in \mathbb{R}^{M \times N}\). 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(\(X\)) = \(p\) and range(\(X\)) = \(\text{span}\{\mathbf{u}_1, \ldots, \mathbf{u}_p\}\). If rather we truncate the expansion for those eigenvalues more significant we can obtain range(\(X\)) as the minimum dimensional space which contained around 98% of the total energy [2]. The parameters which represents the ventricular gradient (\(V_G\)), computed as the angle between depolarization and repolarization, were obtained from the minimum decomposition subspace. Then

\[
\mathbf{X} = \mathbf{U} \Sigma \mathbf{V}^T = [\mathbf{U}_1 \mathbf{U}_2] \left[ \begin{array}{cc} \Sigma_1 & 0 \\ 0 & \Sigma_2 \end{array} \right] \left[ \begin{array}{c} \mathbf{V}_1^T \\ \mathbf{V}_2^T \end{array} \right] \tag{4}
\]

The ECG total energy was represented in a 3D subspace, then \(\mathbf{U}_1 \in \mathbb{R}^{M \times 3}\) and \(\Sigma_1 \in \mathbb{R}^{3 \times 3}\). 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 \(\mathbf{S} \in \text{span}\{\mathbf{u}_1, \mathbf{u}_2, \mathbf{u}_3\}\). The rows \(s_i(n)\) \(i = 1, 2, 3\), are the transformed signals in the dipolar representation. The algorithm for detecting \(n_p^o\), \(n_p^m\), \(n_p^e\) was applied onto the composed signal \(x_u(n)\) which represent the module of the cardiac electrical vector, as in (5)

\[
x_o(n) = \sqrt{\sum_{i=1}^{3} s_i^2(n)} \tag{5}
\]

With these fiducial point the T wave matrix can be segmented as: \(S_T = \{s(n_p^o), \ldots, s(n_p^e)\}\). To estimate the depolarization dominant direction we search for the maximum value of \(x_o(n)\) in the first 80 ms which is associated to the R wave peak, \(n_{R,P}\). From this location, a depolarization QRS wave matrix, \(S_{QRS}\), 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: \(S_{QRS} = \{s(n_{R,O}), \ldots, s(n_{R,E})\}\). Then the angle between \(VR\) and depolarization was calculated to express \(V_G\) [6]. This descriptor named total cosine R-to-T (\(T_{CRT}\))[2] was calculated as:

\[
T_{CRT} = \frac{1}{(n_{R,E} - n_{R,O} + 1)} \sum_{n=n_{R,O}}^{n_{R,E}} \cos \angle(s(n), s(n_p^e))
\tag{6}
\]

\(T_{CRT}\) as in (6), representing the same concept already present by Wilson [6]. Negatives values shows very large
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 IV RD, we better propose to estimate the angle between a fix reference and the T wave as VRD index, so avoiding uncertainties generated by QRS loop estimation. We propose the \( \theta_{XT} \) angle as:

\[
\theta_{XT} = \angle(x, s(n^m_1)) \quad (7)
\]

obtained from the total cosine \( x \) axis to T angle. We take as the X axis the principal component \( u_1 \) from the control beat and keeping it for reference both for control and IV RD situation. This measures the mean VR axis difference respect to a X-reference axis linked to the tank (see Fig.2). \( u_1 \) 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 \( \pm \) 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 IV RD 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 amplitude giving value to these markers as IV RD indicators. Also, \( \Theta_{RT} \) and \( \Theta_{XT} \) did not show to be IV RD markers when the IV RD was generated by PVS stimulation. On the other hand dS generated IV RD, 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 IV RD. 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 bet-

derestimated the VR axis variation with IV RD. 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 IV RD 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 IV RD.

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References


Address for correspondence:
Pedro David Arini
Instituto Argentino de Matemática, Saavedra 15 piso 3 (1083)
Buenos Aires, Argentina
pedroarini@yahoo.com.ar

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

<table>
<thead>
<tr>
<th></th>
<th>( C_{dS} )</th>
<th>( D_{dS} )</th>
<th>( p )</th>
<th>( C_{PVS} )</th>
<th>( D_{PVS} )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_M )</td>
<td>( mV )</td>
<td>2.2( \pm )0.8</td>
<td>2.4( \pm )0.9</td>
<td>0.05</td>
<td>1.7( \pm )0.4</td>
<td>2.4( \pm )0.8</td>
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<td>( T_A )</td>
<td>( A_{dS} )</td>
<td>(5.7( \pm )2.5)( 10^4 )</td>
<td>(11.3( \pm )6.0)( 10^4 )</td>
<td>0.047</td>
<td>(3.8( \pm )1.2)( 10^4 )</td>
<td>(5.9( \pm )2.3)( 10^4 )</td>
</tr>
<tr>
<td>( T_W )</td>
<td>( ms )</td>
<td>78.0( \pm )10.3</td>
<td>133.6( \pm )29.6</td>
<td>0.006</td>
<td>95.2( \pm )7.9</td>
<td>118.5( \pm )15.7</td>
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<tr>
<td>( \Theta_{RT} )</td>
<td>degree ((^o))</td>
<td>41( \pm )17</td>
<td>73( \pm )42</td>
<td>0.05</td>
<td>149( \pm )7</td>
<td>133( \pm )22</td>
</tr>
<tr>
<td>( \Theta_{XT} )</td>
<td>degree ((^o))</td>
<td>35( \pm )51</td>
<td>117( \pm )49</td>
<td>0.009</td>
<td>137( \pm )65</td>
<td>129( \pm )64</td>
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