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Dynamic response of temporal and spatial ventricular repolarization dispersion indices during abrupt heart rate changes

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Abstract— **Ventricular repolarization dispersion (VRD) has been shown to constitute a substrate for arrhythmias. We analyzed the evolution of different electrocardiogram indices of VRD responding to changes in heart rate (HR) induced by a Tilt-test in healthy subjects. We studied temporal indices of VRD (T-VRD), based on ECG-intervals, and spatial indices of VRD (S-VRD), based on spatial correlation matrix eigenvalues of the electrocardiogram. In T-VRD analysis, the T-wave onset-to-peak I_{TOP} index showed significant decrease during abrupt RR decreases with respect to supine position. Regarding S-VRD, we observed a significant increase of the first eigenvalue of the ascending T-wave limb $I_{\lambda 1\text{A}}$ for abrupt RR decreases with respect to supine position. Conversely, we found non-significant changes in the T-wave peak-to-end I_{TPE} and in the first eigenvalue of the descending T-wave limb $I_{\lambda 1\text{D}}$. Results indicate that under HR increases the first portion of T-wave, I_{TOP} and $I_{\lambda 1\text{A}}$, has changed significantly with respect to supine position. Moreover, considering that VRD between two site either at epicardium and endocardium, or other apico-basal sites defines the peak of the T-wave, we can concluded that the global action potential duration distance responsible for I_{TOP} respond to abrupt increases of HR, whereas I_{TPE} and $I_{\lambda 1\text{D}}$, are not significantly altered.**

Keywords— **ECG signal processing, T-wave morphologies, Principal Component Analysis, ventricular repolarization**

1 INTRODUCTION

Several investigations have shown that an increase of ventricular repolarization dispersion (VRD) is associated with a higher risk of developing ventricular arrhythmias and/or sudden cardiac death [1]. In this work we have studied VRD measured from the so called Temporal Dispersion of Repolarization (T-VRD), based on the measurements of the T-wave intervals, and Spatial Dispersion of Repolarization (S-VRD) indices, based on the Principal Component Analysis (PCA) of the T-wave in the available independent leads, with the aim to evaluate which ones better reflect modifications of the VRD generated from heart rate (HR) changes, therefore constituting arrhythmia risk markers under abrupt decreases of RR interval (inverse of HR).

Experimental studies have shown that changes in T-wave width can be considered as markers of VRD. It was found in canine hearts that induced VRD determined from electrograms was strongly correlated with T-wave width at the ECG [2]. We have previously concluded that ECG T-wave widening can result from a combination of apex-base and transmural action potential duration (APD) heterogeneities caused by differential shortening or lengthening of the APD in some myocardial areas [3].

Some authors have considered the T-wave peak-to-end interval as a marker of transmural dispersion of repolarization [4]. Another study has shown that during Valsalva maneuver the T-wave width shortening seems to result from a width reduction from the onset to the T-wave peak rather than from the peak to the T-wave end [5]. However, the translation of this concept to the standard surface ECG is not straightforward making it difficult the interpretation of the relationship between T-wave peak-to-end and transmural dispersion in a clinical population [6]. Nevertheless, a number of investigations have found that T-wave peak-to-end interval was a marker of increased risk in conditions such as long QT syndrome [7] and post-myocardial infarction [8] among others. Also, ventricular repolarization indices such as the QT interval or the T-wave peak-to-end interval depend on heart rate (HR) [9] [10] and such a dependence has also been related to arrhythmic risk [11].

Repolarization descriptors based on PCA have been used in previous studies to distinguish normal and abnormal ventricular repolarization patterns [12] [13]. Other works have demonstrated that PCA descriptors derived from resting 12-lead ECGs allow independent assessment of post-myocardial infarction risk and an improved risk stratification when combined with other risk markers [14]. Besides, it has been shown that the T-wave

residuum calculated in 12-lead resting supine ECGs recordings differed in clinically well-defined groups such as healthy subjects, hypertrophic cardiomyopathy patients, dilated cardiomyopathy patients and survivors of acute myocardial infarction [15]. Also, several indices-based on PCA were calculated for quantification of the pathological characteristics of VRD at higher heart rates [16].

In this work we have analyzed how well T-VRD and S-VRD indices reflect changes of VRD under HR changes induced by tilt test maneuver, with the aim to identify potential markers of arrhythmic risk.

2 MATERIALS AND METHODS

2.1 Data Set

In the present work we used the ANS-UZ database which had been acquired at the University of Zaragoza for the study of the autonomic nervous system. This database comprised 17 healthy subjects with no previous cardiovascular diseases and with a mean age of 28.5 $\pm$ 2.8 years. Each subject recording had undergone a head-up tilt test trial according to the following protocol: 4 minutes in the supine position, 5 minutes in the standing position tilted head-up to an angle of 70 degrees, and 4 minutes back to the supine position. This procedure generates two step-like RR changes with stabilized RR intervals after each of them. The standard ECG leads I, III and the V1-V6 precordials were recorded during the whole test using equipment by Biopac ECG100C with a sampling rate of 1000 Hz. Four patients were excluded from further analysis because presented low SNR signal during ECG acquisition. Finally, a whole population of 13 patients were included, 8 males (mean 28.13 $\pm$ 2.30 years) and 5 females (mean 28.20 $\pm$ 3.35 years).

2.2 ECG Preprocessing

The ECG signals were preprocessed as follows: 1) QRS complexes were detected and normal beats selected according to the method in [17], 2) cubic spline interpolation was used for baseline wander rejection, and 3) T-waves were located and delineated using the wavelet-transform based method in [18]. Noisy beats were rejected when differences in mean isoelectric level with respect to adjacent beats were larger than 400 μV.

2.3 Temporal indices of Ventricular Repolarization Dispersion

As T-VRD indices, we computed the T-wave onset-to-peak interval, the T-wave peak-to-end interval, the T-wave width and the QT interval.

We applied a multilead criteria to determine wave boundaries, where T_{ON} is the earliest reliable T-wave onset at any lead and T_{END_i} is the latest reliable T-wave in the I, III, V1-V6 leads, applying the rules presented at [19]. Also, the T-wave peak as a median value of I, III, V1-V6 leads was computed with an outlier protection rule [19].

Then, for each ith beat, the following T-VRD indices were calculated:

* The T-wave width, quantifying the total repolarization phase, calculated as

$$I_{\text{TW}_i} = T_{\text{END}_i} - T_{\text{ON}_i} \tag{1}$$

* The T-wave onset-to-peak interval, quantifying the full repolarization of epicardium, calculated as

$$I_{\text{TOP}_i} = T_{\text{PEAK}_i} - T_{\text{ON}_i} \tag{2}$$

* The T-wave peak-to-end interval, that mainly represents dispersion of repolarization in the endocardium, calculated as

$$I_{\text{TPE}_i} = T_{\text{END}_i} - T_{\text{PEAK}_i} \tag{3}$$

* The QT interval, quantifying the full depolarization and repolarization of ventricles, calculated as

$$I_{\text{QT}_i} = T_{\text{END}_i} - Q_{\text{ON}_i} \tag{4}$$

2.4 Spatial indices of Ventricular Repolarization Dispersion

As S-VRD indices, we calculated T-wave morphology features based on the Principal Component Analysis of the 8 independent recorded ECG leads (I, III, V1-V6), computed by Singular Value Decomposition of the T-wave complex of the ECG. From there, S-VRD indices such as the ratio of non-dipolar components to the total energy, also called the T-wave residuum index and the three dipolar components, defined as each of the 3 eigenvalues expressed as percentage of the total energy.

For the computation of S-VRD indices in each ith beat, a window *W* corresponding to the T-wave was previously defined. The beginning and the end of Window were set at 155 ms and 255 ms before and after T-wave peak respectively.

Then, PCA was applied at each beat within the defined window *W* in the set of M=8 independent leads, from which M eigenvalues were obtained. We will denote them by λ_j ($j = 1, \ldots, M$), where they are sorted so that $\lambda_1 \geq \lambda_2 \geq \lambda_3 \geq ..... \geq \lambda_M \geq 0$. The first 3 eigenvalues quantify the energy of the so-called dipolar components while the last 5 eigenvalues represent the non-dipolar components of the T-wave.

Then, for each ith beat, the following S-VRD indices were calculated:

* Relative T-wave residuum, quantifying the relative contribution of non-dipolar components with respect to the total energy, calculated as

$$I_{\text{TWR}_i} = \frac{\sum_{l=4}^{8} \lambda_{i,l}}{\sum_{l=1}^{8} \lambda_{i,l}} * 100 \tag{5}$$

* The energy of the first 3 components expressed as % of the total energy was calculated with the indices

$$I_{\lambda 1 T_i} = \frac{\lambda_{i,1}}{\sum_{l=1}^{8} \lambda_{i,l}} * 100 \tag{6}$$

$$I_{\lambda 2 T_i} = \frac{\lambda_{i,2}}{\sum_{l=1}^{8} \lambda_{i,l}} * 100 \tag{7}$$

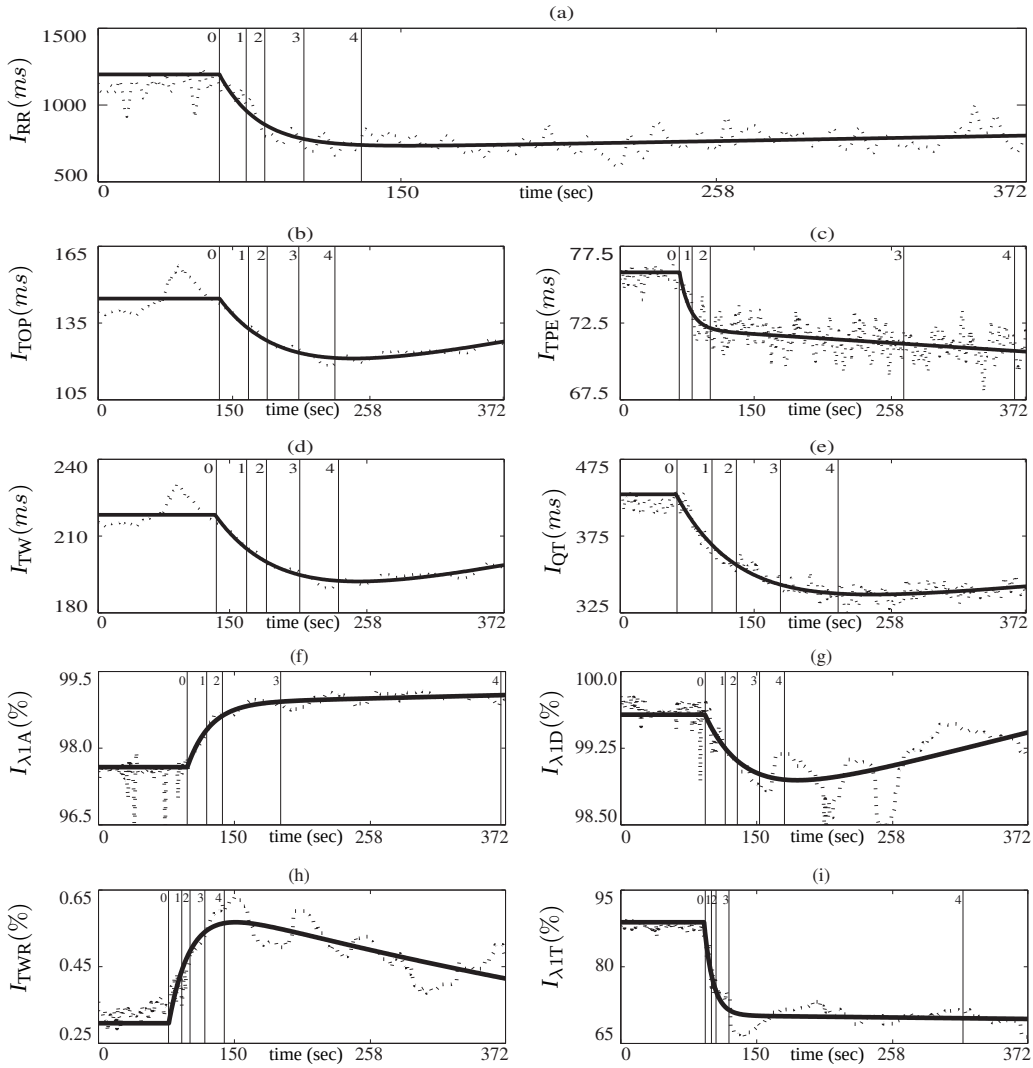

Figure 1: Temporal and spatial indices response for one patient of database. (a) RR interval, (b) T-wave onset-to-peak interval,(c) T-wave peak-to-end interval, (d) T-wave width, (e) QT interval, (f) First dipolar component of ascending T-wave, (g) First dipolar component of descending T-wave, (h) T-wave residuum, (i) First dipolar component of full T-wave. Vertical lines 0, 1, 2, 3, and 4, indicate t_0, t_{50}, t_{70}, t_{90} and t_{100} respectively, which represent the $\%$ of change related to the index status in supine position.

$$I_{\lambda 3T_i} = \frac{\lambda_{i,3}}{\sum_{l=1}^{8} \lambda_{i,l}} * 100 \tag{8}$$

In addition, all the T-waves were partitioned into two portions. Then, the first 3 dipolar components of the ascending T-wave limb, expressed as % of the total energy of the first T-wave portion, were calculated with the indices $I_{\lambda 1A_i}$, $I_{\lambda 2A_i}$ and $I_{\lambda 3A_i}$. Besides, the first 3 dipolar components of the descending T-wave limb, expressed as % of the total energy of the second T-wave portion, were calculated with the indices $I_{\lambda 1D_i}$, $I_{\lambda 2D_i}$ and $I_{\lambda 3D_i}$.

2.5 Series of T-VRD and S-VRD indices

Beat-to-beat the T-VRD and S-VRD indices were computed during supine position and during the standing position tilted head-up to an angle of 70 degrees. Also for the sake of robustness, it was applied a median filter with a windows size of 20 beats on all series of indices. Once the T-VRD and S-VRD series were obtained, an adjustment from a linear combination of two exponentials was applied as shown in equation (9). The aim of this adjustment was to characterize the abrupt change and the subsequent stabilization of the indices during the Tilt-test maneuver.

$$\widetilde{f}^{i}_{(x)} = a_0 e^{a_1 x^i} + a_2 e^{a_3 x^i} \tag{9}$$

The optimization is based on the minimization of the sum of squared error of each series in each ith beat, calculated as

$$\frac{\partial e^2}{\partial a_k} = \frac{\partial}{\partial a_k} \sum_{i=1}^{n} (f^i_{(x)} - (a_0 e^{a_1 x^i} + a_2 e^{a_3 x^i}))^2 \tag{10}$$

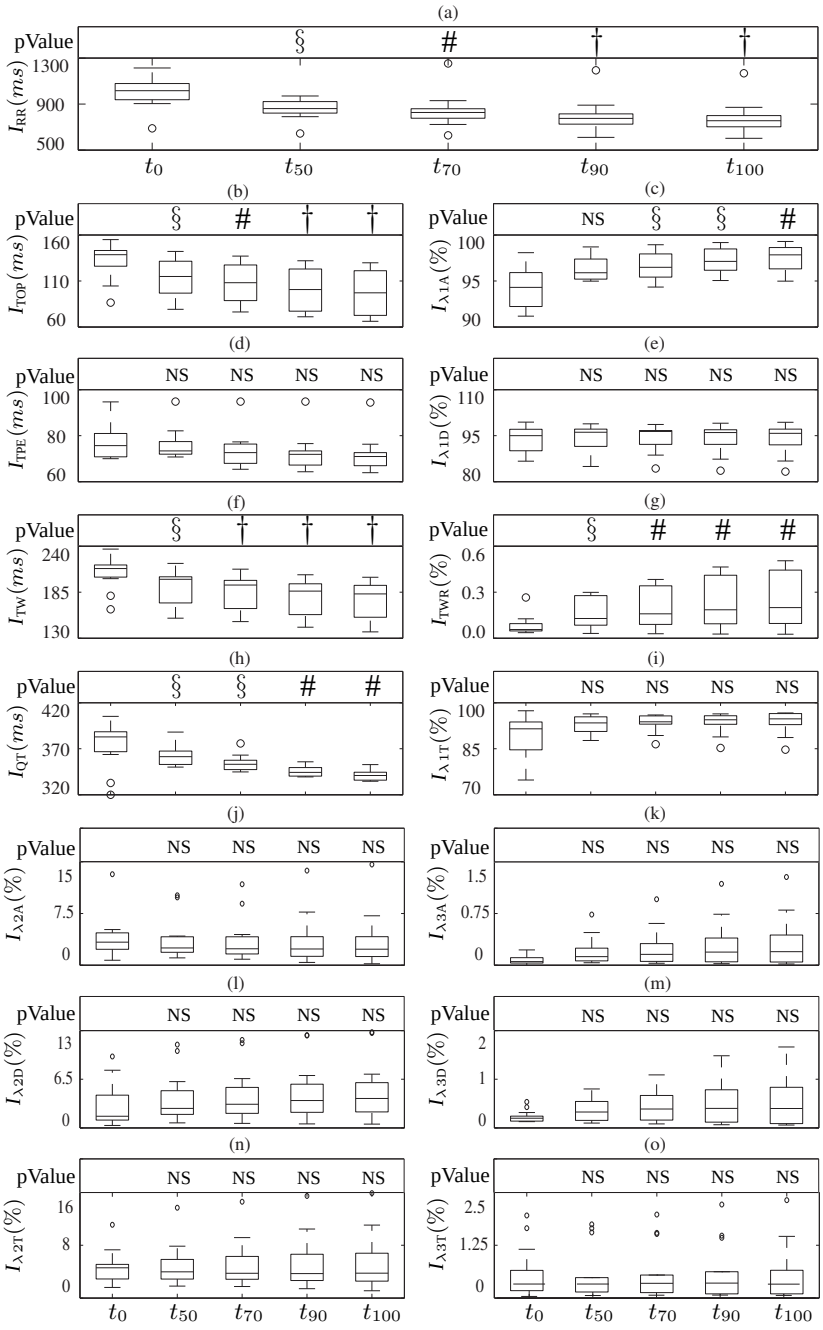

Figure 2: Box and whisker diagrams for studied indices. (a) RR interval, (b) T-wave onset-to-peak interval, (c) First dipolar component of ascending T-wave, (d) T-wave peak-to-end interval, (e) First dipolar component of descending T-wave, (f) T-wave width, (g) T-wave residuum, (h) QT interval, (i) First dipolar component of entire T-wave, (j) Second dipolar component of ascending T-wave, (k) Third dipolar component of ascending T-wave, (l) Second dipolar component of descending T-wave, (m) Third dipolar component of descending T-wave, (n) Second dipolar component of full T-wave, (o) Third dipolar component of full T-wave. Significant differences against supine position are marked as '§'($p<0.05$), '#'($p<0.01$), '†'($p<0.005$), and 'NS'(non-significant). Outliers are marked with 'o'. Each box is related to the $\%$ of change with respect to the index status in supine position: t_0, t_{50}, t_{70}, t_{90} and t_{100}.

In order to find the optimum starting point of the Tilt-test Maneuver (t_0), we have computed the adjustment of T-VRD and S-VRD indices from supine to standing position, associated to the 20 beats window centered around the point of position change (supine-standing) previously defined on protocol Tilt-test Maneuver, thus obtaining global error function for each adjustment. Also, we characterized T-VRD and S-VRD indices values during 4 additional time instants t_{50}, t_{70}, t_{90} and t_{100} which express the percentage of change of each index with respect to t_0.

2.6 Statistical Analyses

In order to determine the statistical significance of T-VRD and S-VRD between supine position and abrupt RR decreases, a non-parametric two-sided Mann-Whitney U test was used. When p value was < 0.05, differences were considered statistically significant.

3 RESULTS

Some indices presented significant alterations in response of physiological changes produced for abrupt variations in HR. Figure 1 shows an illustrative example of the evolution of T-VRD and S-VRD indices in a particular patient during Tilt-test Maneuver. The evolution of each index is represented by dotted-line and the bold-line refers to the indices computed from the adjustment function, as we have explained in the equations (9) and (10). Also, the vertical lines indicate a percentage of change related to the index status before the tilt is started (see Fig.1).

Figure 2 illustrates statistical results of both T-VRD and S-VRD indices. Each index is expressed for five time instants during the Tilt-test Maneuver in reference to the percentage of change of index value respect to the status in supine position. Regarding T-VRD and S-VRD indices, we observed a significant decrease in I_{TOP}, I_{TW} and I_{QT} indices (Fig.2(b,f,h)) accompanied by a significant increase in the $I_{\lambda 1 A}$ and I_{TWR} indices (Fig.2(c,g)) respectively. Conversely, in Fig.2(d,e,i), we can observe non-significant changes in I_{TPE}, $I_{\lambda 1 D}$ and $I_{\lambda 1 T}$. Moreover, in Fig.2(j,k,l,m,n,o) we can observe non-significant changes in the second and third dipolar components. These results complement the information and allows to hypothesize about energy dispersion and its vinculation with ECG time intervals.

4 DISCUSSION

VRD is a measure of inhomogeneous recovery of excitability during repolarization process. This ventricular heterogeneity is mainly attributable to differences in activation times and APD in different heart areas. The APDs differs not only between myocytes of different ventricular layers [20] but also between posterior and anterior endocardial layers, apex and base [21], and left and right ventricles [22]. Thus, increments in VRD values that are higher than normal are associated with an increased risk of developing reentrant arrhythmias [1].

We have observed a statistically significant decrease of the QT interval which occurs in response to statistically significant RR interval decreases (Fig.2(a,h)). These results could be a complement of the QT/RR dynamic studies reported by others [9] [11] .

Figure 2f shows a statistically significant shortening in T-wave width during Tilt-test Manuever. We hypothesize that this phenomenon might evidence the viability of the T-wave width to mark very early signs of VRD and its potential use to detect arrhythmia risk. The T-wave width shortening appears to result from a width reduction from the onset to the T-wave peak rather than from the peak to the T-wave wave end. These results are consistent with those observed in [5] and this may be related to the spatio-temporal distribution of APD modifications [3].

The ECG dipolar model is based on the concept that the cardiac electrical activity is equivalent to dipole placed within the thorax changing its module and phase throughout the cardiac cycle. According to this model the total myocardial electrical activity could be represented in the 3D space and the dipolar components should reflect the global morphologic pattern of the analyzed T-wave.

Moreover, regarding the first dipolar components, we have observed a significant increase for the first half of T-wave accompanied by a non-significant change in the second half of the T-wave. Simultaneously, we have observed a non-significant change in both the second and third dipolar components. Based on this results we could conclude that global VRD only changed in the PCA principal direction and also, only to the first portion of the T-wave, as we can see in Fig.2(b,c).

While the dipolar components explain an important fraction of the T-wave morphology in the ECG, the local heterogeneities are not well accounted in this model. Therefore, we analyzed the non-dipolar components, quantified by the T-wave residuum, as a measurement of the local VRD. Moreover, when quantifying the non-dipolar components, the T-wave residuum index presented a significant increase to abrupt RR decreases, as we notice in Fig.2(g).

5 STUDY LIMITATIONS

Because in this study we only use healthy patients, other clinical trials will be helpful to define whether the T-VRD and S-VRD indices are useful to quantify cardiac risk in patients with arrhythmic events, and to better assess the accuracy of these indices in identifying patients with different degrees of cardiac risk.

6 CONCLUSIONS

We have concluded that under abrupt HR increases both indices of the first half of T-wave, I_{TOP} and $I_{\lambda 1 A}$, have changed significantly with respect to supine position. Moreover, due to the fact that repolarization dispersion between two sites either at epicardium and endocardium, or other apico-basal sites defines the peak of the T-wave, we concluded that the global APD distance responsible for I_{TOP} repolarization respond to abrupt increases of HR, whereas dispersion of repolarization, I_{TPE} and $I_{\lambda 1 D}$, are not significantly altered during the Tilt-test Maneuver, at least fort this levels of HR change.

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