Dynamic Response of Electrocardiographic Indices During Abrupt Heart Rate Changes

Comparison between Young and Middle-aged Subjects

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Keywords: Ventricular Repolarization Dispersion, T-wave Morphology, Age.

Abstract: Abnormal modifications in ventricular repolarization dispersion (VRD) have been shown to constitute a substrate for malignant arrhythmias. In this work, we have induced abrupt heart rate (HR) changes to young and middle-aged healthy subjects through a Tilt-test and have analyzed the evolution of several VRD indices. Duration ones, based on electrocardiogram intervals; energy ones, developed through a Principal Components Analysis (PCA) in T-wave; and the morphology ones, extracted feature from an absolute T-wave. In both groups, results have shown significant decreases in early repolarization duration. These changes are responsible for the alterations in the total repolarization duration, because T-wave peak-to-end has not shown statistical significance. Moreover, we have found significant decreases in total, early and late repolarization energy, and in the T-wave amplitude. In another sense, we have observed that the repolarization energy obtained by PCA jointly with early T-wave slope and amplitude have been able to reflect VRD differences between young and middle-aged subjects. Finally, this work provides the range of values for VRD in normal conditions during abrupt HR changes. Outside this range, we could assume that it exists a cardiac risk.

1 INTRODUCTION

The electrical inhomogeneities in the cardiac repolarization process along the ventricular wall are usually called ventricular repolarization dispersion (VRD). Several works have shown that abnormal alterations of VRD are associated with a higher risk of developing ventricular arrhythmias (Surawicz, 1997).

Some authors have shown that alterations in VRD are correlated with changes in T-wave width (Fuller et al., 2000). It has also shown that T-wave widening can result from a differential shortening or lengthening of the action potential duration in both apex-base and transmural (Arini et al., 2008).

The T-wave peak-to-end interval has been suggested as a marker of transmural VRD (Zareba et al., 2000; Antzelevitch et al., 2007; Smetana et al., 2011), and so, the T-wave peak as an indicator of the full repolarization of epicardium. The translation of this concept to the standard electrocardiogram (ECG) is not straightforward, making it difficult to interpret of the relationship between T-wave peak-to end and transmural dispersion in a clinical population (Smetana et al., 2011). 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 (Mincholé et al., 2006).

Moreover, others have proposed repolarization indices such as the QT interval (Pueyo et al., 2004) or the T-wave peak-to-end interval (Mincholé et al., 2011) depend on heart rate (HR) and such dependence has also been related to arrhythmic risk. However, some researchers have objected the validity of these two indices as markers of VRD (Malik et al., 2000; Opthof et al., 2007) and have questioned their dependence of HR (Andersen et al., 2008). It has also been suggested that several morphological indices, such as the slopes and the area of the T-wave, are independent of HR (Merri et al., 1989).

On the other hand, several VRD descriptors based on Principal Component Analysis (PCA) have been used to differentiate normal and abnormal VRD patterns (Zabel et al., 2002) and have been used to quantify pathological characteristics of VRD at high HR (Smetana et al., 2004).

Finally, some authors have found that most repolarization indices are independent of age (Merri et al.,

Javier Teperino M., Bonomini M., Cruces P. and Arini P..
Dynamic Response of Electrocardiographic Indices During Abrupt Heart Rate Changes - Comparison between Young and Middle-aged Subjects.
DOI: 10.5220/0005253102640269
In *Proceedings of the International Conference on Bio-inspired Systems and Signal Processing* (BIOSIGNALS-2015), pages 264-269
ISBN: 978-989-758-069-7

1989). Nevertheless, others have shown that aging modulates the normal VRD (Huang et al., 2010).

In the present work, we have analyzed the response of several ECG indices to HR changes. So, we have determined the range of normal values outside which we could assume that it exists a cardiac risk. Finally, we have studied how aging might influence in the dynamic response of electrocardiographic indices during abrupt HR changes.

2 METHODS

2.1 Database

A total of 17 subjects without previous cardiovascular diseases were retrospectively studied. Two groups were selected: Young Subjects (8 subjects, with a mean of 26.5±7.5 years old) and Middle-aged Subjects (9 subjects, with a mean of 65.8±11.2 years old). Subjects were recruited in the medical institution Clínica San Camilo of the Buenos Aires, Argentina and in all cases informed consent was signed. Each subject recorded has undergone a head-up tilt test trial according to the following protocol: 5 min in the supine position, 5 min tilted head-up to an angle of 70 degrees, and 18 sec during table movement. This method generates an abrupt acceleration of the heart rate. The ECG leads I, III, V1-V6 were recorded during the whole test using ECG View Eccosur equipment with a sampling rate of 1000 Hz.

2.2 Preprocessing

The ECG signals have been preprocessed as follows: 1) QRS complexes have been detected and normal beats have been selected according to the method in (Mendieta, 2012), 2) A Butterworth high-pass filter (0.5Hz, bidirectional) has been applied for baseline wander rejection and in order to reduce high frecuency noise, a Butterworth low-pass filter (100Hz, bidirectional) has been used, and 3) T-waves and QRS-complexes have been delineated using the wavelet-transform based method in (Mendieta, 2012).

2.3 Repolarization Indices

Several indices have been selected to describe the following characteristics of VRD on the surface ECG: 1) *Duration*, 2) *Energy* and 3) *Morphology*.

For all indices we have applied a multilead criterion to determine wave boundaries, where QRS_{END} and T_{END} are respectively the lastest reliable QRS-complex and T-wave ends at any lead (I, III, V1-V6). Also, the T-wave peak (T_{PEAK}) and R-wave peak (R_{PEAK}) as median values of all leads have been computed with an outlier protection rule.

For each ith beat, we have computed the aforementioned characteristics of VRD.

1) Indices of Duration: The total repolarization duration index ($\mathrm{T_{RD}}$), quantifying the total ventricular repolarization time, has been calculated as;

$$\mathrm{T_{RD}}_i = T_{\mathrm{END}_i} - QRS_{\mathrm{END}_i} \tag{1}$$

The early repolarization duration index ($\mathrm{E_{RD}}$) and the T-wave peak-to-end interval index ($\mathrm{T_{PE}}$), which several authors have linked to the full repolarization of epicardium and transmural repolarization respectively (Antzelevitch et al., 2007), have been computed as;

$$\mathrm{E_{RD}}_i = T_{\mathrm{PEAK}_i} - QRS_{\mathrm{END}_i} \tag{2}$$

and,

$$\mathrm{T_{PE}}_i = T_{\mathrm{END}_i} - T_{\mathrm{PEAK}_i} \tag{3}$$

2) Indices of Energy: We have obtained T-wave energy based on the PCA of the ECG leads. For the calculus of PCA indices in each ith beat, it has been considered three windows, one for total repolarization duration (time between QRS_{END} and T_{END}) and one for each portion (early and late) of the same T-wave (partitioned in T_{PEAK}). PCA has been applied in the set of the independent leads, from which 8 eigenvalues have been obtained. We have denoted them by $\lambda_{i,j}$ ($j = 1,\ldots,8$), where they are sorted so that $\lambda_{i,1} \geq \lambda_{i,2} \geq \ldots.. \geq \lambda_{i,8} \geq 0$. Then, we have computed the Total energy as the sum of the eight eigenvalues.

$$E_i = \sum_{l=1}^{8} \lambda_{i,l} \tag{4}$$

This way, we have obtained $\mathrm{E_T}$ for the full T-wave; $\mathrm{E_{ET}}$ for the first half of the T-wave (or Early T-wave) and $\mathrm{E_{LT}}$ for the Late T-wave (or T-wave peak-to-end).

3) Indices of Morphology: Afterwards, we have computed an absolute T-wave (T^{ABS}), through the sum of the eight T-waves in each ith beat, let

$$T_i^{\mathrm{ABS}}(k) = \sum_{j=\mathrm{I,III,V1\text{-}V6}} |x_j(k)| \quad k = QRS_{\mathrm{END}_i}\ , \ \ldots\ , \ T_{\mathrm{END}_i} \tag{5}$$

where $x_j(k)$ is the ECG signal at lead j, then a polynomial fitting has been applied for each ith T^{ABS} obtaning $\tilde{T}_i^{\mathrm{ABS}}$. Then the following indices were calculated: T-wave Amplitude index ($\mathrm{T_A}$), calculated as the amplitude of the $\tilde{T}_i^{\mathrm{ABS}}$ wave peak; Slope of

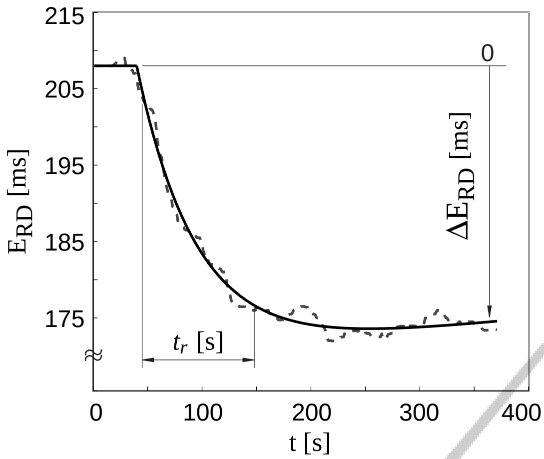

Figure 1: Example of characterization of E_{RD} index. The dotted line shows the index value and bold line represents the fitting curve.

Early T-wave index (S_{ET}), maximum slope obtained through a five point centered derivative in whole first half of $\tilde{T}_i^{ABS}$ wave and Slope of Late T-wave index (S_{LT}), absolute value of the maximum slope obtained through the five point centered derivative in whole second half of $\tilde{T}_i^{ABS}$ wave.

2.4 Series of Repolarization Indices

For each index, the values beat-to-beat have been concatenated and so obtained the series of values over time: RR, T_{RD}, E_{RD}, T_{PE}, E_T, E_{ET}, E_{LT}, T_A, S_{ET} and S_{LT}, during the Tilt-test Maneuver. A numerical interpolation has been applied using the R_{PEAK} values as time reference for all beats in order to resample to 1 Hz. It has also been applied a median filter with a windows size of 20 seconds. Series have been characterized through a numerical fitting with a linear combination of two exponentials, as shown in Eq. (6), where $a_0 ,\dots ,a_3$ are the fitting parameters.

$$\widetilde{f}_{(n)} = a_0 e^{a_1 . n} + a_2 e^{a_3 . n} \tag{6}$$

The optimization is based on the minimization of the sum squared error (SSE) of each series, as illustrated in Eq. (7) where $I_{(n)}$ represents the index under study.

$$\frac{\partial {e_r}^2}{\partial a_k} = \frac{\partial}{\partial a_k} \sum_{n=1}^{N} (I_{(n)} - \widetilde{f}_{(n)})^2 = 0 \tag{7}$$

We have obtained the optimum starting point of the Tilt-test Maneuver (so-called t_0), by minimizing the global error function for each adjustment an so, each series have been computed. An example of this fitting is shown in Fig. 1.

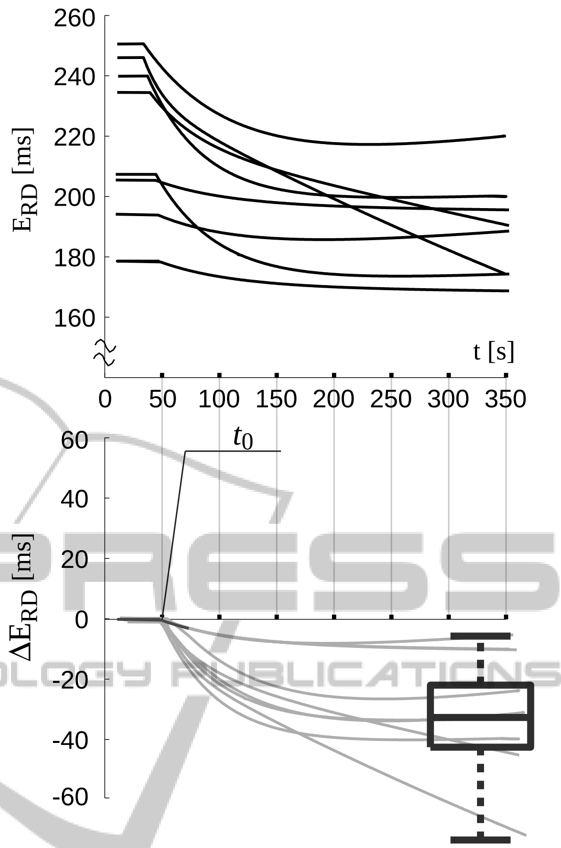

Figure 2: Evolution of E_{RD} for several subjects of the database. Example of normalization for statistical analysis (**SA#1**).

2.5 Characterization of Repolarization Series and Statistical Analysis

In order to analyze just the dynamics of each series following abrupt HR changes, we have performed a normalization procedure by subtracting, for all series samples, the value at t_0 of each series, see Eq. (8). For convenience, we have named I = I(t) where I represents the evaluated index.

$$\Delta \mathrm{I} = \mathrm{I} - \mathrm{I}(\mathrm{t}_0) \tag{8}$$

We have characterized each series of repolarization indices through two parameters, such as

1) Index variation (Δ), which characterize the index value difference between t_0 (0%) and 100% of change. Also, we have determined the indices with statistically significant changes respect to zero value (t_0) applying a two-sided Wilcoxon signed rank test. This procedure has been so-called **Statistical Analysis #1**, **SA#1** (see Fig. 2).

2) Response time (t_r), the time required to change from 10% to 90% of index value, as can be observed in Fig. 1.

Moreover, another statistical analysis has been performed for the comparison between two populations, Young and Middle-aged Subjects. A non-parametric two-sided Mann-Whitney U test has been used and when $p < 0.05$, differences have been considered statistically significant. This procedure has been so-called **Statistical Analysis #2** , **SA#2**.

3 RESULTS

The statistical results obtained for each series are shown in Fig. 3.a for young subjects and in Fig. 3.b for middle-aged subjects. Except ΔT_{PE} in both population and ΔS_{LT} in middle-aged subjects, all indices have shown significant differences in their values in response to physiological changes induced by abrupt HR changes. Moreover, not all indices reach the steady state at the same time. Table 1 shows t_r values in Mean±SEM for all proposed VRD indices in both population. Finally, in Table 2 we have pointed out the comparison between the two groups.

Table 1: Response time t_r expressed in seconds (Mean±SEM) for both groups Young and Middle-aged Subjects.

Indice	Young	Middle-aged
RR	171.3 ± 27.0	90.7 ± 27.3
T_{RD}	163.3 ± 21.9	100.0 ± 11.4
E_{RD}	150.6 ± 26.3	107.0 ± 11.3
T_{PE}	177.6 ± 30.2	104.2 ± 30.8
E_T	135.3 ± 26.9	149.3 ± 23.7
E_{ET}	133.1 ± 25.5	145.2 ± 23.0
E_{LT}	129.3 ± 24.5	147.8 ± 26.2
T_A	122.9 ± 26.7	134.1 ± 27.6
S_{ET}	114.8 ± 27.0	163.8 ± 29.8
S_{LT}	150.6 ± 33.8	158.6 ± 29.7

Table 2: Comparison (**SA#2**) between Young and Middle-aged Subjects (Mean±SEM).

	Young	Middle-aged	*p* value
ΔE_T	35.59±8.30	7.40±2.38	<0.05
ΔE_{ET}	23.68±5.92	5.46±1.95	<0.05
ΔE_{LT}	7.19±2.09	1.74±0.47	<0.05
ΔT_A	1.03±0.28	0.43±0.14	<0.05
ΔS_{ET}	0.018±0.005	0.006±0.004	<0.05

4 DISCUSSION

In this work we have proposed a multilead criterion to analyze VRD alterations caused by abrupt HR changes using duration, energy and morphology indices. To do so, we have studied each of them separately and then, we have hypothesized about their relationships and implications.

Duration variables. We have observed, in both young and middle-aged subjects, a statistical significant decrease of ΔT_{RD} and ΔE_{RD} in response to RR interval decrease, while ΔT_{PE} has not changed (see Fig. 3.a and Fig. 3.b). These results are consistent with a previous work (Cruces et al., 2014). In the latter, we have shown alterations in both T_W (T-wave width) and T_{OP} (T-wave onset-to-peak duration) during HR changes in another database (Autonomic Nervous System Database, University of Zaragoza). Our results are comparable to those in (Merri et al., 1989), where it has shown that QT interval and early duration (time interval between QRS-complex-end and T-wave-peak) are the only intervals with significant changes in VRD under HR changes . Conversely, Andersen et al. have calculated HR dependence for ECG duration markers showing independence in both T_W and T_{PE} (Andersen et al., 2008). In another sense, as it can be seen in Table 2, no significant changes in the duration indices have been observed in young with respect to middle-aged subjects according to the procedure **SA#2** described in Subsection 2.5.

Energy Variables. We have performed the energy of the T-wave by applying PCA method with the information of all ECG leads. In response to HR increases we have found statistically significant decreases of ΔE_T, ΔE_{ET} and ΔE_{LT} in both young and middle-aged subjects (applying **SA#1**), as we have shown in Fig. 3.a and Fig. 3.b.

Andersen et al. have computed and analyzed similar indices, such as early and late T-wave areas. They have shown dependence of HR in each one (Andersen et al., 2008), then we have consistent results with our energy indices obtained by PCA procedure.

Also, as we have observed in Table 2, the energy of total (ΔE_T), early (ΔE_{ET}) and late (ΔE_{LT}) repolarization have been able to reflects VRD differences between young subjects with respect middle-aged subjects (Subsection 2.5 **SA#2**).

Morphology Variables. Regarding morphologic analysis in young subjects, we have found statistically significant decreases in ΔT_A, ΔS_{ET} and ΔS_{LT} (see Fig. 3.a). Moreover, ΔT_A and ΔS_{ET} were significantly in middle-aged subjects and not significance of ΔS_{LT} index (see Fig. 3.b). Results obtained in young subjects were consistent with another work (Andersen et al., 2008), who have shown significant changes in both up and down slopes T-wave. Andersen et al. have concluded that those variations were just about T-wave amplitude decrease, because they have not

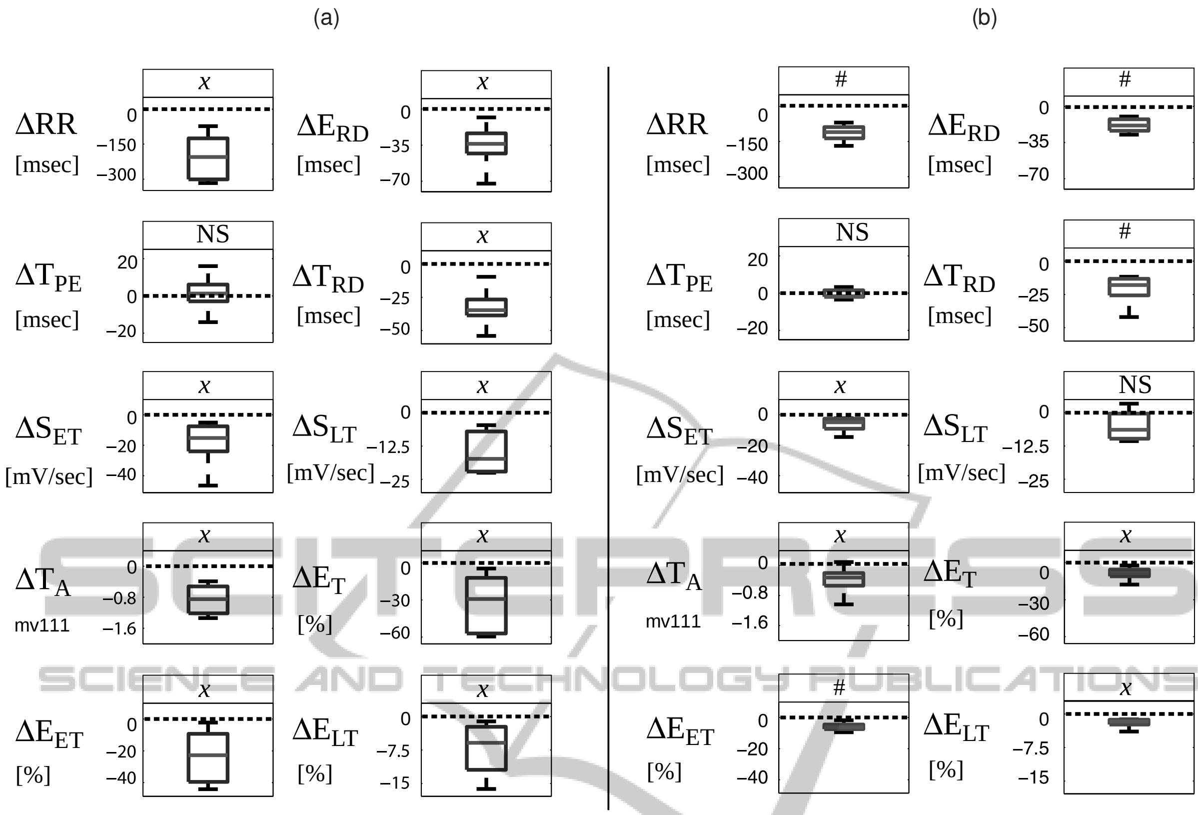

Figure 3: Box and Whisker diagram for all VRD indices. (a) Young subjects; (b) Middle-aged subjects. Statistical significance (**SA#1**) has been represented as 'x' for p<0.05 and '#' for p<0.005. Non significant changes have been indicated as NS.

found modifications in T-wave onset-to-peak. However, our results suggest that both T-wave amplitude and early repolarization duration were responsible for those variations. Also, we have found significant differences between young subjects and middle-aged subjects in T_A and S_{ET} indices (as we have explained in **SA#2**). Conversely, no significant changes in S_{LT} has been observed with **SA#2**.

Response Time. Table 1 shows that RR index reach the steady state after duration, energy and morphology VRD indices for young subjects. Conversely, for middle-aged subjects the time required to change from 10 % to 90 % (t_r) in the VRD indices are greater than the t_r measured in the RR index. These results allows us to hypothesize that there are different times of adaptation under abrupt HR changes, possibly related to aging effects. Also, as it can be seen, duration indices have shown faster adaptation to high HR in middle-aged subjects than in young subjects. However, energy and morphology indices are faster in the latter population.

5 CONCLUSION

Given that E_{RD} and T_{RD} indices have shown statistical significance and T_{PE} has not, we have also concluded that HR increases induce a shift in the T-wave peak position towards the QRS-complex. We have concluded that under abrupt changes in HR, the main alterations of VRD correspond to the variations in the the duration of action potentials which do not affect differentially epicardium from endocardium tissues.

Moreover, T_A, S_{ET}, E_T, E_{ET} and E_{LT} have shown statistically significant differences under HR increases. We can hypothesize that these effects have a physiological limit because several repolarization indices reach the steady state before RR interval (Young Subjects) and others indices have presented aging effects due to they reach the steady state after RR interval (Middle-aged Subjects).

Some authors have shown that several repolarization indices are independent of age (Merri et al., 1989), nevertheless others have shown that aging modulates the normal VRD (Huang et al., 2010). In our study we have concluded that the energy of total (E_T), early (E_{ET}) and late (E_{LT}) repolarization have been able to reflects VRD differences between young and middle-aged healthy subjects.

Finally, this study constitutes a basis for setting normal conditions of the ventricular repolarization process in young and middle-aged subjects.

ACKNOWLEDGEMENTS

This work was supported by Consejo Nacional de Investigaciones Científicas y Técnicas CONICET, under project PIP #538 and PICT 2008 #2108 Agencia Nacional de Promoción Científica y Tecnológica, Argentina.

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