Normal Ventricular Repolarization Dispersion Range with Abrupt Heart Rate Changes

Pablo D. Cruces[1,2], María P. Bonomini[2], Marcos J. Teperino[2], Ana Mincholé[3], Pablo Laguna[4], Pedro D. Arini[1,2]

[1] Argentine Institute of Mathematics, Alberto P. Calderón, CONICET, Buenos Aires, Argentina
[2] Biomedical Engineering Institute, School of Engineering, University of Buenos Aires, Argentina
[3] Department of Computer Science, University of Oxford, UK
[4] BSICoS, Aragón Institute of Engineering Research (I3A), University of Zaragoza, Spain

Abstract

Abnormal alterations in ventricular repolarization dispersion (VRD) have been shown to constitute a substrate for arrhythmias. In this work, we have induced abrupt heart rate (HR) changes to 17 healthy subjects through a Tilt-test Maneuver and have analyzed the evolution of several VRD indices. Duration ones, based on ECG intervals; complexity ones, developed through a Principal Components Analysis in T-wave; and the amplitude one, extracted feature from an absolute T-wave. Results have shown statistically significant decreases in T-wave onset-to-peak, finding that these changes are responsible for the alterations in the T-wave width and in the QT interval. Also, simultaneously it has been observed that T-wave peak-to-end has not shown statistical significance. Moreover, we have found statistically significant decreases and increases of the ratio of the 2nd to the 1st eigenvalue in early and late T-wave respectively. On the other hand, from measurement response times, we have observed that the shape of the T-wave undergoes to a fast initial reduction in amplitude and a posterior slow shifting towards the QRS-complex. Finally, several VRD indices have reached the steady state before the RR interval. This work provides the range of values for VRD in normal conditions during abrupt HR changes. Outside this range, we could suppose that it exists a cardiac risk.

1. Introduction

Several works have demostrated that abnormal changes of ventricular repolarization dispersion (VRD) are associated with a higher risk of developing ventricular arrhythmias [1].

Experimental studies have shown that induced VRD was strongly correlated with T-wave duration modifications [2] and 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 VRD [4]. The translation of this concept to the standard 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 [5]. Moreover, others have proposed repolarization indices such as the QT interval [7] or the T-wave peak-to-end interval [6] depend on heart rate (HR) and such a dependence has also been related to arrhythmic risk. Likewise, VRD descriptors based on Principal Component Analysis (PCA) have been used in previous studies to distinguish normal and abnormal VRD patterns [8] and were used to quantifify pathological characteristics of VRD at high HR [9]. In addition, morphological indices have been exposed by others to improve the description of VRD, such as T-wave symmetry and T-wave area [10]. In this study, we have analyzed how well ECG indices reflect changes in VRD under abrupt HR changes, with the aim of determining the range of normal values outside which we could suppose that exists a cardiac risk.

2. Methods

2.1. Data set

The Autonomic Nervous System Database (ANS-UZ) has been acquired by the University of Zaragoza. It includes 17 healthy subjects with no previous cardiovascular diseases (28.5 ± 2.8 years). 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 dur-

ing the whole test using equipment by Biopac ECG100C with a sampling rate of 1000 Hz.

2.2. ECG 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 [11], 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 [11].

2.3. Repolarization indices

Variables have been selected to describe the following morphological characteristics of VRD on the surface ECG: 1) *Duration*, 2) *Complexity* and 3) *Amplitude*.

For all variables we have applied a multilead criteria to determine wave boundaries, where T_{ON} and QRS_{ON} are respectively the earliest reliable T-wave and QRS-complex onset at any lead and T_{END} is the latest reliable T-wave end in the I, III, V1-V6 leads. 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 morphological characteristics.

1) Duration: The QRS-onset to T-wave-end interval (QT), quantifying the full depolarization and repolarization of ventricles, was computed as;

$$\text{QT}_i = T_{\text{END}_i} - QRS_{\text{ON}_i} \tag{1}$$

The T-wave width (T_W), quantifying the total repolarization time, was calculated as;

$$\text{T}_{\text{W}_i} = T_{\text{END}_i} - T_{\text{ON}_i} \tag{2}$$

The T-wave onset-to-peak interval (T_OP) and the T-wave peak-to-end interval (T_PE), which several authors have linked to the full repolarization of epicardium and transmural repolarization respectively [12], have been computed as;

$$\text{T}_{\text{OP}_i} = T_{\text{PEAK}_i} - T_{\text{ON}_i} \tag{3}$$

and,

$$\text{T}_{\text{PE}_i} = T_{\text{END}_i} - T_{\text{PEAK}_i} \tag{4}$$

2) Complexity: We have obtained T-wave complexity based on the PCA of the ECG leads. For the calculus of PCA indices in each ith beat, it has been considered two windows, 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 $\lambda_{i,1} \geq \lambda_{i,2} \geq ..... \geq \lambda_{i,8} \geq 0$. Then, we have computed the roundness of T-wave loop as,

$$\lambda 21_i = \frac{\lambda_{i,2}}{\lambda_{i,1}} * 100. \tag{5}$$

being $\lambda 21_{\text{ET}}$ and $\lambda 21_{\text{LT}}$ the ratio of the 2nd to the 1st eigenvalue in early and late T-wave respectively.

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

$$T_i^{\text{ABS}}(k) = \sum_{j=\text{I,III,V1-V6}} |x_j(k)| \quad k = T_{\text{ON}_i}\ ,\ \ldots\ ,\ T_{\text{OFF}_i} \tag{6}$$

where $x_j(k)$ is the ECG signal at lead *j*, then a polynomial fitting has been applied for each ith T^{ABS} obtaning $\tilde{T}_i^{\text{ABS}}$. Then the T-wave Amplitude ($\text{T}_{\text{A}i}$), has been calculated as the amplitude of the $\tilde{T}_i^{\text{ABS}}$ wave peak.

2.4. Series of repolarization indices

The temporal evolutions of RR, QT, T_W, T_OP, T_PE, T_A, $\lambda 21_{\text{ET}}$ and $\lambda 21_{\text{LT}}$ have been calculated during 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 each *"temporal evolution"* or *"series"* of repolarization indices. 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. (7), where $a_0\ , \ldots\ , a_3$ are the fitting parameters, as

$$\widetilde{f}_{(n)} = a_0 e^{a_1 . n} + a_2 e^{a_3 . n} \tag{7}$$

The optimization is based on the minimization of the sum squared error (SSE) of each series, as illustrated in Eq. (8) where $I_{(n)}$ represents the index under study.

$$\frac{\partial {e_r}^2}{\partial a_k} = \frac{\partial}{\partial a_k} \sum_{n=1}^{N} (I_{(n)} - \widetilde{f}_{(n)})^2 = 0 \tag{8}$$

In order to find the optimum starting point of the Tilt-test Maneuver (so-called t_0), we have computed the adjustment of the indices associated to the 10 seconds window centered around the point of position change (supine-standing) previously defined on the protocol, thus obtaining global error function for each adjustment.

2.5. Analysis of series

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. (9). For convenience, we have named I = I(t) where I represents the evaluated index.

$$\Delta \mathrm{I} = \mathrm{I} - \mathrm{I}(\mathrm{t}_0) \tag{9}$$

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

1) Response time (t_r), the time required to change from 0% to 100% of index value (see Fig. 1).

2) Initial delay (Θ_D), computed as the difference between starting points of the evaluated index and the Tilt-test Maneuver. The latter has been obtained from RR initial value (see Fig. 1).

3) Index variation (Δ), which characterize the index value difference between t_0 (0%) and 100% of change. We have determined the indices with statistically significant changes respect to zero value (t_0) applying a two-sided Wilcoxon signed rank test (See Fig. 2).

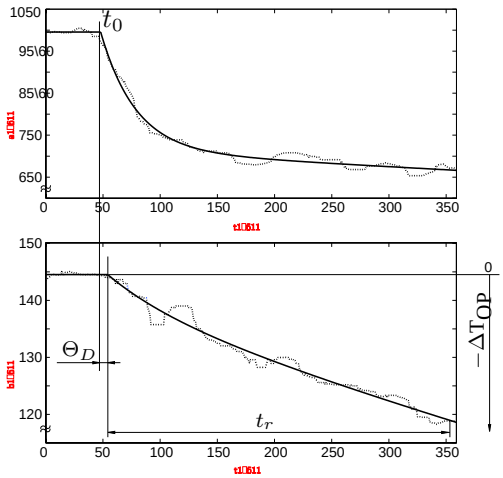

Figure 1. Example of fitting and characterization for a particular patient. The dotted line shows the index value and bold line represents the fitting curve.

3. Results

Figure 2 shows statistical results obtained from each index value. Except ΔT_{PE}, all indices have shown significant differences in their values in response to physiological changes induced by abrupt HR changes. We have been able to observe a significant decrease in ΔQT, ΔT_W, ΔT_A and ΔT_{OP}. We have found the highest statistical significance in ΔT_{OP}. Moreover, not all indices reach the steady state at the same time. Table 1 shows t_r and Θ_D values in Mean$\pm$SD for all proposed VRD indices. As it can be seen, T_{OP} is the first to begin its change but it has the highest response time. Also, it should be noted that several indices reach their steady state while RR is still changing.

Table 1. Mean $\pm$ SEM of response time (t_r) and initial delay (Θ_D).

Indice	t_r (s)	Θ_D (s)
RR	172 ± 22	$-$
QT	183 ± 25	19 ± 5
T_{OP}	223 ± 12	10 ± 3
T_{PE}	176 ± 20	13 ± 5
T_W	220 ± 19	14 ± 3
T_A	120 ± 26	13 ± 4
$\lambda 21_{ET}$	81 ± 12	18 ± 3
$\lambda 21_{LT}$	90 ± 14	18 ± 8

4. Discussion

In the present study, we have described the dynamics of VRD through several repolarization indices. We have observed a statistically significant decrease of QT in response to RR decreases (see Fig. 2). This behavior has been detected previously [7,10,13]. We have observed in this work that alterations in both QT and T_W are caused by changes in T_{OP} (VRD index with highest statistical significance). The HR dependence of the latter has been found in some works [10], but it has not in others [13]. The study of the characteristic times (Θ_D and t_r) allows us to suppose that the reason of the previous controversy has to do with different durations of the protocols of both works [10] [13] (i.e. since T_{OP} changes slowly, a sufficient time to detect its change is required).

Regarding amplitude index, we have found statistically significant decreases in T_A. This result is consistent with other works [13]. Furthermore, some indices reach the steady state faster than RR, which enables us to suppose that the reduction of their values has a physiological limit.

On the other hand, in response to high HR, we have found respectively statistically significant decreases and increases of $\lambda 21_{ET}$ and $\lambda 21_{LT}$. We can hypothesize that alterations in VRD, induced by high HR, produce the flattening of the first portion of the loop and the second portion becomes rounded.

5. Conclusion

Since T_{OP} has shown statistical significance and T_{PE} has not, we have concluded that HR increments induce a shift in the peak position towards the QRS-complex. In the

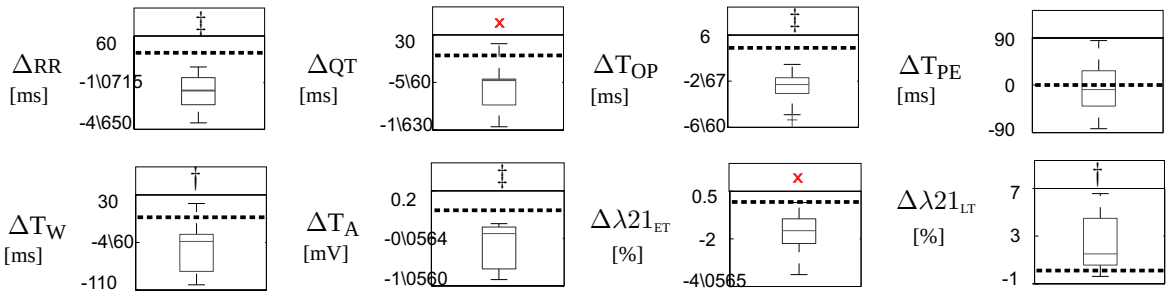

Figure 2. Box and Whisker diagram for all repolarization indices. Statistical significance has been signed as 'x' for $p<0.05$, '†' for $p<0.005$ and '‡' for $p<0.0005$. A '+' mark indicates an outlier.

same way, T_A has shown significant decreases, thus HR increases induces a T-wave decrement in amplitude. These effects have a physiological limit because several indices reach the steady state before RR, i.e. some ECG indices have less capability of changing than others. This study constitutes a basis for setting normal conditions of the repolarization process. Further investigations are needed to determine the VRD alterations in patients with cardiac disease and make a comparison with normal range of values. Finally, 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.

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Address for correspondence:

Pablo D. Cruces
Argentine Institute of Mathematics, 'Alberto P. Calderón', Saavedra 15, C1083ACA C.A.B.A, Argentina
pcruces@fi.uba.ar