Transmural Differences in Rate Adaptation of Repolarization Duration Quantified from ECG Repolarization Interval Dynamics

A Mincholé[1,2], E Pueyo[2,1], P Laguna[2,1]

[1]CIBER - Bioingeniería, Biomateriales y Biomedicina, Spain
[2]Communications Technology Group, I3A, University of Zaragoza, Spain

Abstract

Rate adaptation of repolarization duration has been shown to provide relevant information for arrhythmic risk stratification. In this work we investigate rate adaptation of QT interval, T wave width (T_w), and distance from peak to end of the T wave (T_{pe}), in response to step like HR changes induced during tilt test. QT and T_w presented a pronounced memory effect completed in two phases: a fast initial one and a subsequent slow accommodation (mean time for QT to complete 90% of the change was 77.0 $\pm$ 20.6 s); while T_{pe}, considered a measure of transmural dispersion of repolarization, presents only a fast change, practically synchronous with HR change. Based on this finding, we propose a method to indirectly compute differences in APD restitution slopes of the midmiocardial cells (α_m) and epicardial cells (α_e) by making only use of the surface ECG: $\widehat{\Delta\alpha} = (\widehat{\alpha_m - \alpha_e}) = \Delta T_{pe}/\Delta RR$. In our study, the mean of $\Delta T_{pe}/\Delta RR$ across recordings is 0.0371 $\pm$ 0.0327 ms/ms, which are in agreement with theoretical studies in human ventricle (ten Tusscher 2006 model), where mean $\Delta\alpha$ is 0.0364 for the same RR range.

1. Introduction

Adaptation of repolarization duration to heart rate (HR) changes is thought to be critical in activation instability and therefore, provides relevant information for ventricular arrhythmic risk stratification.

Action potential duration (APD) has a strong dependence on heart rate (HR) [1]. The APD restitution (APDR) curve, measured using the so-called dynamic restitution protocol, represents a way to quantify the relationship between APD and RR (inverse of HR) under steady-state conditions [2]. APDR plays an important role in the development of ventricular arrhythmia. In particular, steeply sloped curves are hypothesised to induce alternans in APD leading to ventricular arrhythmias [3]. However, restitution properties are not uniform along the ventricular wall and, consequently, the APDR curve presents spatial variations. In some studies transmural dispersion of restitution has been proposed to act as a potent arrhythmogenic substrate [4], and increments in restitution dispersion have been associated with greater inducibility of ventricular tachycardia/fibrillation [5].

The main limitation on the usability of transmural dispersion of APDR curve is that its quantification requires invasive procedures. In this study we investigate methods to indirectly estimate dispersion of restitution by making only use of the surface electrocardiogram (ECG), particularly of the distance from T wave peak to T wave end (T_{pe}).

We start by considering the time interval from the peak to the end of the T wave, T_{pe}, which is generally accepted to reflect differences in the time for completion of repolarization by different cells spanning the ventricular wall. Some studies have measured and proposed T_{pe} as an index of transmural dispersion of repolarization and then helpful in forecasting risk for the development of life-threatening arrhythmias [6].

We characterize the T_{pe} dependence on RR by using models similar to those already proposed in the literature to analyze the QT/RR relationship [7], and we use cardiac computational modeling to shed light into the obtained results [8]. For APD in individual cells and also for QT interval, the adaptation process is characterized by two phases: a fast initial one and a subsequent slow accommodation [9].

Focusing our analysis on steady-state ECG segments, we measure differences in T_{pe} normalized by differences in RR, $\frac{\Delta T_{pe}}{\Delta RR}$, and we compare that ratio with the maximum transmural difference in dynamic APDR slopes evaluated for the same RR range.

ECG recordings analyzed in this study are collected from healthy subjects while performing a tilt-test protocol, and APDR curves are computed using the most electrophysiologically detailed human ventricular cell model available in the literature [10].

2. Methods

2.1. Population

Fifteen volunteers without any previous cardiovascular history underwent a head-up tilt test trial according to the following protocol: 4 minutes in the supine position, 5 minutes tilted head-up to an angle of 70 degrees and 4 minutes back to the supine position. 12-lead ECG was recorded during the whole test at a sampling frequency of 1000Hz. Mean age of the volunteers (11 male and 4 female) was 28.5 ± 2.8 years old.

When characterizing the T_w rate adaptation only 8 recordings were used due to problems in the T wave onset delineation.

2.2. ECG delineation

ECG delineation was performed using a wavelet-based delineator [11]. For the analysis of the different repolarization series, leads V2, V3 or V4 were used, choosing, for each subject, the one with more stable delineation marks. From those marks, QT, T_w and T_{pe} series were computed.

2.3. Data analysis

Rate adaptation of repolarization indices QT, T_w and T_{pe} is characterized in the present study using the method described in [7], which models the dynamic relationship between the RR intervals and each repolarization index. Figure 1 shows the model for the QT interval and, analogously, for T_w and T_{pe}.

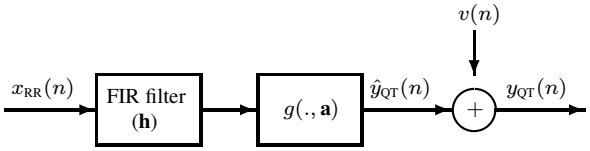

Figure 1. Block diagram describing the QT/RR relationship consisting of a time invariant FIR filter (**h**) and a nonlinear function described by vector **a**.

Impulse response **h** includes information about the memory of the system, that is, a characterization of the influence of a history of previous RR intervals on each QT measurement. The function denoted as $g(.,\mathbf{a})$ follows in this study a linear relation and accounts for scaling and translation. The optimum values of the FIR filter response **h**=[h(0),..., h(N-1)]^T and of vector **a**=[a(0) a(1)]^T are searched to minimize the relation between the output $\hat{y}_{QT}(n)$ and the actual QT interval series $y_{QT}(n)$. N is set to 180 s based on previous studies [7]. In this work, $\hat{\mathbf{h}}$ vector and $\hat{\mathbf{a}}$ are computed by using a "Quasi-Newton" optimization technique described in [12].

The time required for QT, T_w and T_{pe} to complete 90% of their rate adaptation is denoted by t_{90} and is computed by setting a threshold of 0.1 to the cumulative sum of $\hat{\mathbf{h}}$: c(n)= $\sum_{i=n}^{N} h(i)$. The same procedure is repeated to calculate t_{70}, t_{50} and t_{25} by replacing the threshold with 0.3, 0.5 and 0.75, respectively.

T_{pe} has been proposed as a measure of transmural dispersion of repolarization. Based on the fast dynamics of the T_{pe} series to a sudden HR change, we propose a method to indirectly compute differences in APD dynamic restitution slopes along the ventricular wall by making only use of the surface ECG.

Tilt test induces two step-like RR changes being able to obtain three steady stages in which RR and T_{pe} are computed. These RR and T_{pe} values are the mean of each of the three 50 s steady intervals: 150-200 s in the supine, 500-550 s in the tilted and 700-750 s back in the supine position. Using the three intervals, two RR changes are obtained in each recording: 'HR accel.' where the RR get shorter and 'HR decel.' where the RR get longer.

α_e and α_m, denoting the slopes of the restitution curve for endo/epicardial and midmyocardial cells respectively, are computed for an specific RR range: $\alpha_e = \Delta APD_{epi}/\Delta RR$ and $\alpha_m = \Delta APD_{mid}/\Delta RR$. Noting that $\Delta T_{pe} = \Delta APD_{mid} - \Delta APD_{epi}$, the difference $\Delta\alpha = (\alpha_m - \alpha_e)$ can be estimated as:

$$\widehat{\Delta\alpha} = \frac{\Delta T_{pe}}{\Delta RR} \tag{1}$$

where ΔT_{pe} and ΔRR represent variations for the analyzed RR range in T_{pe} and RR respectively.

Dynamic restitution curves of midmyocardial and epicardial cells have been derived following the method described in [10].

3. Results and discussion

3.1. Rate adaptation of repolarization indices

Tilt test induces a step like heart rate change when the person is tilted, that will help us to investigate the rate adaptation of QT, T width (T_w), and T peak to T end (T_{pe}) intervals. In fig. 2, the evolution of HR, QT, T_w and T_{pe} indices are shown during the tilt test trial.

Figure 3 shows an example of QT, T_w and T_{pe} rate adaptation profiles obtained for a subject of the study.

From the cumulative sum c(n) shown in fig. 3, it can be observed how QT and T_w adaptation are completed in two phases, a fast one and a slow one, in concordance with previous studies [9]. T_{pe}, considered as a measure of transmural dispersion, shows a much shorter memory.

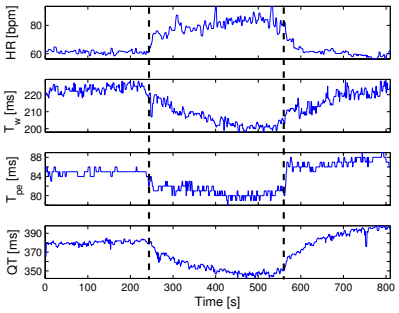

Figure 2. Example of the dynamics of HR, QT, T_w and T_{pe} during the tilt test. Dashed lines show the time instant when the bed is tilted up to 70 degrees and when the bed is back to the supine position

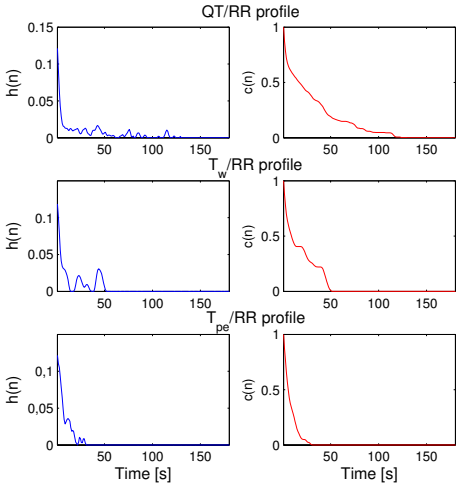

Figure 3. Example of the rate adaptation profiles for the different repolarization features: QT, T_w and T_{pe}. The impulse response h(n) and the cumulative sum c(n) of h(n) are shown.

In order to quantify the adaptation time for QT, T_w and T_{pe} intervals, the mean across subjects of t_{90}, t_{70}, t_{50} and t_{25} have been evaluated (see table 3.1).

QT and T_w present a pronounced memory effect (about 80-90 s required to complete 90% of the adaptation), T_{pe} presents a faster adaptation (about 46 s). Besides, QT and T_w need about 20 s to complete 50% of the whole adaptation while T_{pe} needs only 6 s, which indicates that in the case of T_{pe} the fast phase of adaptation has a larger contribution to the whole adaptation process than in the case of QT and T_w.

This behaviour is also observed in fig. 4, which represents the percentage of completed adaptation for QT and T_{pe} as a function of time. It can be observed that T_{pe} presents a fast change, practically synchronous with HR change, while QT is much slower in the adaptation.

	QT	T_w	T_{pe}
$t_{90}(s)$	77.0 ± 20.6	93.4 ± 47.8	46.0 ± 50.3
$t_{70}(s)$	38.1 ± 12.3	46.7 ± 19.7	13.3 ± 16.9
$t_{50}(s)$	18.5 ± 8.5	20.2 ± 15.7	5.7 ± 8.4
$t_{25}(s)$	3.8 ± 3.0	8.1 ± 10.7	1.7 ± 2.1

Table 1. Mean $\pm$ std across subjects of the 90 % (t_{90}), 70% (t_{70}), 50% (t_{50}) and 25% (t_{25}) of the complete rate adaptation.

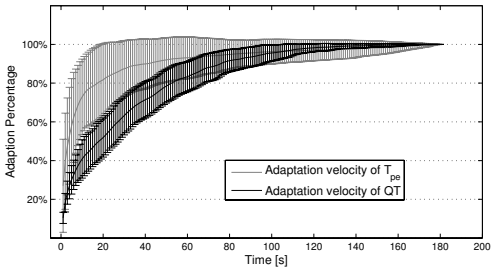

Figure 4. Adaptation velocity of T_{pe} and QT intervals.

The fast adaptation of T_{pe} indicates that transmural dispersion of repolarization is memoryless, as opposed to repolarization duration measurements. This phenomenon is consistent with previous theoretical studies which have shown that APD at different transmural ventricular layers have the same characteristic slow HR accommodation but different initial fast HR adaptation, being midmyocardial cells faster than epicardial ones [8].

In this work we have not taken into account differences in heart rate accelerations and decelerations. Although both process are always carried out in two phases, it is known that rate adaptation of QT is longer in heart rate decelerations than in heart rate accelerations [9].

3.2. Differences in APD restitution slopes from the surface ECG

The method proposed in the present study, estimates the maximum difference in the APD dynamic restitution slopes $\Delta\alpha$ along the ventricular wall using the surface ECG.

Dynamic restitution curves of midmyocardial and epicardial cells have been derived from ten Tusscher 2006 model [10] and are shown in figure 5.

We have compared the mean of $\Delta T_{pe}/\Delta RR$ across recordings and RR ranges with the mean of the theoretical $\Delta\alpha$ computed for the same RR ranges. The mean of the theoretical $\Delta\alpha$ is 0.0364 $\pm$ 0.0217 ms/ms, which is consistent with the mean of $\Delta T_{pe}/\Delta RR$, which is 0.0371 $\pm$ 0.0327 ms/ms. To illustrate this, fig. 6 presents the difference between the theoretical value of $\Delta\alpha$ and $\Delta T_{pe}/\Delta RR$ for each tilt test recording and RR jump (HR accelera-

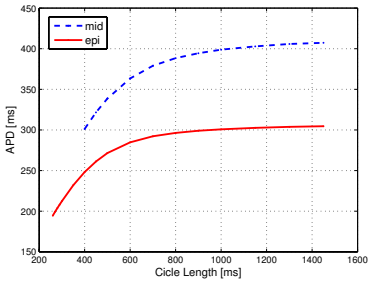

Figure 5. Dynamic restitution curves of the midmyocardial and epicardial individual cells, using the ten Tusscher 2006 model.

tion/deceleration). The mean $\pm$ std value of the individual differences is -7.3E-4 $\pm$ 0.0256 ms/ms. Standard deviation quantifies the intra subject variability.

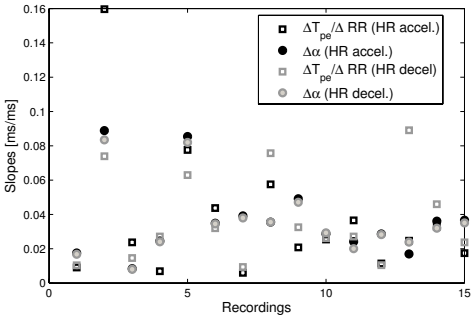

Figure 6. Experimental $\Delta T_{pe}/\Delta RR$ computed from the 15 recordings in the two RR ranges and each theoretical $\Delta\alpha$ derived from the ten Tusscher 2006 model.

This method could be used and applied on drugs safety studies since some drugs alter restitution curves developing ventricular repolarization dispersion and eventually inducing arrhythmia.

4. Conclusions

In this study, we have characterized the adaptation of QT, T_w and T_{pe} to changes in heart rate induced by tilt test. QT and T_w present two phases, fast and slow, in their rate adaptation, while T_{pe} adaptation is much faster, practically synchronous with HR. Our results indicate that transmural dispersion of repolarization is memoryless as opposed to repolarization duration measurements.

Dispersion of restitution has been proposed as a marker od arrhythmogenic substrate. The method proposed in this study allows to estimate the dispersion in the slopes of the dynamic APD restitution curves along the ventricular wall by making only use of the surface ECG.

Acknowledgements

This work was supported by TEC2007-68076-C02-02 from CICYT/ FEDER Spain and by CIBER-BBN, Spain.

References

[1] Franz MR, Swerdlow CD, Liem LB, Schaefer J. Cycle Length Dependence of Human Action Potential Duration In Vivo. J Clin Invest 1988;82:972–979.

[2] Koller ML, Riccio ML, Gilmour Jr RF. Dynamic restitution of action potential duration during electrical alternans and ventricular fibrillation. Am J Physiol Heart Circ Physiol 1998;275:1635–1642.

[3] Riccio ML, Koller ML, Gilmour Jr RF. Electrical Restitution and Spatiotemporal Organization During Ventricular Fibrillation. Circ Res 1999;84:955–963.

[4] Nash M, Bradley C, Sutton P, Clayton R, Kallis P, Hayward M, Paterson D, Taggart P. Whole heart action potential duration restitution properties in cardiac patients: a combined clinical and modelling study. Experimental physiology 912339 54 2006;91(2):339–54.

[5] Pak H, Hong S, Hwang G, Lee H, Park S, Ahn J, Moo Ro Y, , Kim Y. Spatial dispersion of action potential duration restitution kinetics is associated with induction of ventricular tachycardia/fibrillation in humans. Journal of cardiovascular electrophysiology 2004;15(12):1357–63.

[6] Antzelevitch C, Shimizu W, Yan G, Sicouri S, Weissenburger J, Nesterenko V, Burashnikov A, Di Diego J, Saffitz J, Thomas G. The m cell: its contribution to the ecg and to normal and abnormal electrical function of the heart. J Cardiovasc Electrophysiol 1999;10:1124–1152.

[7] Pueyo E, Smetana P, Caminal P, Bayes, Malik M, Laguna P. Characterization of qt interval adaptation to rr interval changes and its use as a risk-stratifier of arrhythmic mortality in amiodarone-treated survivors of acute myocardial infarction. IEEE Trans. Biomed. Eng. 2004;51(9):1511–20.

[8] Pueyo E, Laguna P, Rodrguez B. Mechanisms of ventricular rate adaptation as a predictor of arrhythmic risk. In Heart Rhythm, volume 29th Annual Scientific Sessions. 2008; .

[9] Lau CP, Freedman AR, Fleming S, Malik M, Camm AJ, Ward DE. Hysteresis of the ventricular paced QT interval in response to abrupt changes in pacing rate. Cardiovasc Res 1988;22:67-72.

[10] Ten Tusscher K, Panfilov A. Alternans and spiral breakup in a human ventricular tissue model. Am J Physiol Heart Circ Physiol 2006;291(3):H1088–H1100.

[11] Martínez JP, Almeida R, Olmos S, Rocha AP, Laguna P. A Wavelet-Based ECG Delineator: Evaluation on Standard Databases. IEEE Trans. on Biomedical Eng. 2004;51(4).

[12] Nocedal J, Wright S. Numerical Optimization. Springer; 135–143.

Address for correspondence:

Ana Mincholé
Departamento de Ingeniería Electrónica y Comunicaciones
Maria de Luna 1, 50018, Zaragoza, Spain
E-mail address: minchole@unizar.es