Quantification of Spatial Repolarization Heterogeneity: Testing the Robustness of a New Technique

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Abstract

The $\mathcal{V}$–index is a recently–proposed metric related to repolarization heterogeneity (RH) across the myocardium, a key quantity for the development of arrhythmias. The metric is derived from multi-leads ECG recordings and this paper investigates two of its properties: i) the dependency on the lead system (Frank's orthogonal vs. 12 standard leads); ii) the influence of errors in the location of the T-end position.

The first investigation was performed by simulations, using a forward ECG model (ECGSIM). In the lead system of interest, the $\mathcal{V}$–index was computed varying the standard deviation of RH (s_ϑ). The results showed that the average bias in the estimate of RH (at $\sigma_\varphi = 1$ ms) ranged from $-20.4 \pm 4.0\%$ ($s_\vartheta = 20.6$ ms) to $-26.3 \pm 4.0\%$ ($s_\vartheta = 70.9$ ms) for the standard system and from $-7.0 \pm 4.2\%$ to $-19.0 \pm 4.2\%$ for the Frank's one. While the bias diminished, the vulnerability to noise slightly increased.

Secondarily, 68 ECGs from the E-OTH-12-0068-010 THEW database were analyzed. To simulate mislocation, the T-end point was consistently moved (± 20 ms) around its correct position and the $\mathcal{V}$–index computed. The average differences in the $\mathcal{V}$–index estimates across the population were always smaller than 1%. This is a desirable property, given the discrepancies across methods in locating T-end positions.

1. Introduction

Spatial heterogeneity of ventricular repolarization is a key quantity for the development of arrhythmias. Despite many methods have been proposed and investigated in the past [1–3], a non–invasive quantification of Repolarization Heterogeneity (RH) is still an open issue [4].

We recently proposed an estimator of the standard deviation of RH, which was named "$\mathcal{V}$–index" [5]. The index was derived by introducing a simple stochastic model of ventricular repolarization, which takes into account both repolarization heterogeneity across the myocardium and random beat–to–beat variations in cells' activity. Combining this model with the Dominant T-wave formalism (DTW) [6], we were able to link the variability of *lead factors* [7] (i.e. the weights which modulate the DTW to generate the T–wave of each lead) with the standard deviation of the repolarization times. The resulting $\mathcal{V}$–index is a direct, model–based estimator of RH obtained from multi-leads ECG recordings.

Although the performances of the method have been deeply investigated in the original paper [5], some issues are still unexplored. Two of them will be investigated in this work: i) the dependency on the lead system used and ii) the influence of possible mislocation of the T–end position. Both of them are known to be common issues in actual investigations.

2. Method

2.1. An estimate of repolarization heterogeneity

Let us suppose to subdivide the myocardium in "nodes", each node m sharing a common transmembrane potential (TMP), $D(t)$, but having a specific repolarization time given by

$$\rho_m = \bar{\rho} + \Delta\rho_m. \quad (1)$$

At each node m, the repolarization delay $\Delta\rho_m$ is the deviation from the average repolarization time $\bar{\rho} = \frac{1}{M}\sum_{m=1}^{M}\rho_m$ in the given heartbeat.

We have recently [5] introduced a simple model to describe the distribution of these delays $\Delta\rho_m(k)$ among beats, being k the beat index. In particular we set:

$$\Delta\rho_m(k) = \vartheta_m + \varphi_m(k). \quad (2)$$

where ϑ_m models the *spatial variability* of the repolarization times for a given subject at a given HR, and $\varphi_m(k)$ describes difference in repolarization times which are observable among successive beats. The interested reader can refer to the original paper [5] for a more detailed description of this model. Here we briefly sketch the main

assumptions: i) each source in the heart has a constant–in–time repolarization delay ϑ_m (with respect to $\bar{\rho}$); ii) for each node, fluctuations of repolarization times across following beats are modeled as a normal random variable, i.e. $\varphi_m(k) \sim \mathcal{N}(0, \sigma_\varphi^2)$; iii) the random oscillations have the same intensity σ_φ in each source.

Repolarization delays are one of the main ingredients for the genesis of T-wave $\mathbf{\Psi}(t)$ on the ECG. The link between $\Delta\rho$ and $\mathbf{\Psi}(t)$ can be derived through a biophysical model [6] and brings to the following approximate relation

$$\mathbf{\Psi}(t) \approx \underbrace{-\mathbf{A}\Delta\boldsymbol{\rho}}_{\mathbf{w}_1} T_d(t) + \underbrace{1/2\mathbf{A}\Delta\boldsymbol{\rho}^2}_{\mathbf{w}_2} \dot{T}_d(t), \qquad (3)$$

where the function $T_d(t)$ is the first derivative of $D(t)$ and $\Delta\boldsymbol{\rho} = [\Delta\rho_1, \Delta\rho_2, \ldots, \Delta\rho_M]^T$ is a vector of repolarization delays. $\mathbf{A}$ is a patient–dependent $[L \times M]$ transfer matrix accounting for the contribution of each node to the L-leads electrocardiographic recording in $\mathbf{\Psi}(t)$. The terms $\mathbf{w}_1$ and $\mathbf{w}_2$ are $[L \times 1]$ vector of lead factors, one for each lead.

We recently [5] proved that an estimate of the repolarization heterogeneity, quantified as the standard deviation of the repolarization times across the myocardium, can be derived from the the lead factors. In particular, we introduced the $\mathcal{V}$–index, defined as

$$\mathcal{V}_i = \frac{\mathrm{std}\left[\mathrm{w}_2(\mathrm{i})\right]}{\mathrm{std}\left[\mathrm{w}_1(\mathrm{i})\right]} \approx s_\vartheta = \left(\frac{1}{M}\sum_{m=1}^{M}\vartheta_m^2\right)^{1/2}, \qquad (4)$$

where the standard deviations (std) are computed on the lead factors of lead i across a certain number of consecutive beats (not across different leads).

In practical applications, the index in (4) requires the computation of $\mathbf{w}_1$ and $\mathbf{w}_2$. These can be obtained for multi–leads ECG recordings using the algorithms described in the appendix of [5].

2.2. Simulated data

To assess the influence of the lead system employed on the RH estimates, synthetic ECG recordings were built using a classic forward model, as implemented in ECGSIM (version 1.3, but we re-implemented it in MATLAB for simplicity) [8]. The construction of the signals was carried on along the lines of what described in our previous work [5, Section IV]. In here, once obtained a T-wave for a single synthetic beat in the 8 independent standard leads (V1–V6, aVR and aVL), the lead factors $\mathbf{w}_1$ and $\mathbf{w}_2$ were estimated. Then, the inverse Dower matrix [9] was employed to obtain an approximation of the ECG as collected by a Frank's leads system. Finally, $\mathbf{w}_1$ and $\mathbf{w}_2$ were recomputed on this second set of leads. As in [5], in here the sampling rate was 1000 Hz, but is was also reduced to 200 Hz to mimic what typically available in Holter recordings.

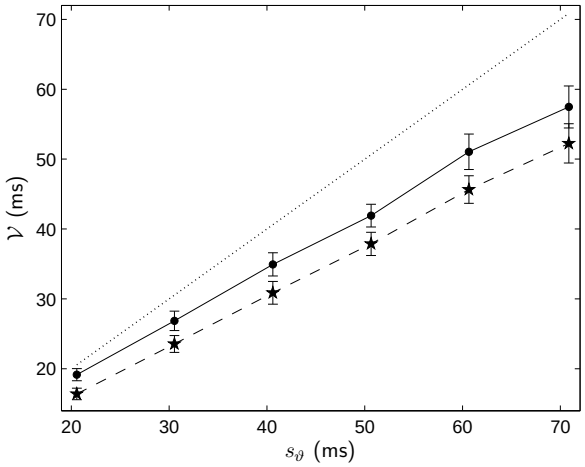

Figure 1. Mean estimates for the $\mathcal{V}$–index obtained on simulated ECGs (as described in section 2.2) for the 8 independent leads of the standard configuration (black stars) and the Frank's orthogonal system (black circle). The value of σ_φ is set to 1 ms. The vertical error bars span the mean $\pm$ the standard deviation of the estimates across the set of 40 runs.

The $\mathcal{V}$–index was computed for various repolarization heterogeneities by varying the standard deviation of ϑ from 20.6 ms to 30.5, 40.6, 50.6, 60.6 and finally to 70.9 ms. The power of the temporal heterogeneity σ_φ was instead varied in the range 0.1 to 50 ms. The $\mathcal{V}$–index was computed employing series of 128 beats. For each case, 40 independent runs were performed, to assess the variability of the estimates.

2.3. THEW database

To test the robustness of the $\mathcal{V}$–index against mislocation of T–end positions, we used the E-OTH-12-0068-010 database, provided by the Telemetric and Holter ECG Warehouse of the University of Rochester (THEW). The data were collected and previously analyzed by Kääb *et al.* [10] and consisted of 68 ambulatory ECG recorded in supine position (12 standard leads, sampling rate: 1000 Hz, durations of about 1.5 to 4 minutes).

The database included fiducial points, which we used. To reduce the occurrence of misclassifications, we marked as abnormal those beats which had a correlation factor with an average template smaller than 0.9. Band pass filtering (3^{rd} order Butterworth filter, $[0.05, 40]$ Hz) was used to reduce baseline wandering and high-frequency disturbances. A zero DC component in each lead, as set by the band-pass filtering, is not expected in the model of equation (3). Thus a common baseline level was subsequently restored.

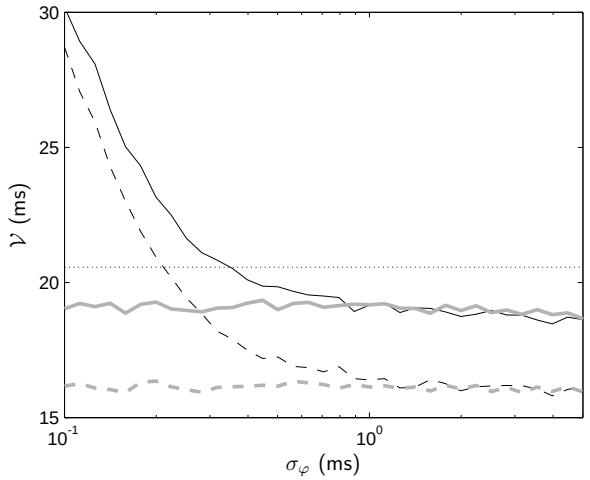

Figure 2. Mean estimates for the $\mathcal{V}$–index obtained on simulated ECGs for the 8 independent leads of the standard configuration (sketched lines) and the Frank's orthogonal system (continuous line). The figure refers to the case $s_\vartheta = 20.6$ ms (horizontal dotted line) and two simulations are comprised in the graph: broadband 30 μV peak-to-peak noise added to the synthetic ECGs (black), and no noise added (gray thick lines).

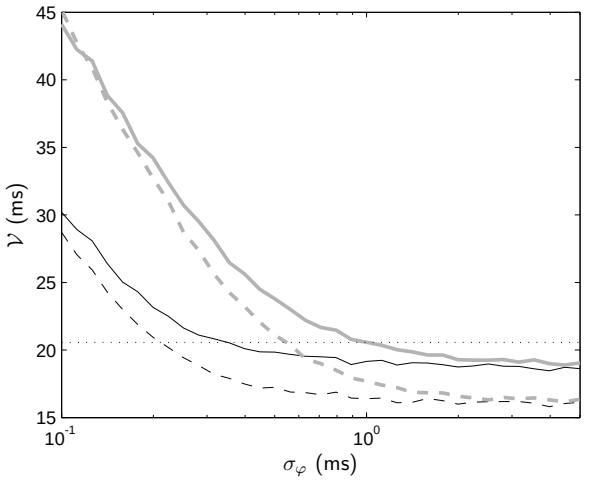

Figure 3. Black lines: as in figure (2). The second simulation included here (thick gray lines) was obtained sampling the synthetic ECG signals at 200 Hz instead of 1000 Hz (broadband 30 μV peak-to-peak noise was still added).

An automatical detection of the J and T–end points on the vector magnitude (VM) signal was performed: i) the J point as the first minimum after the R peak; ii) the end of the T wave according to Surawiczs method [11]. Then, the JT interval was extracted from each beat and the $\mathcal{V}$–index computed. Only those JT intervals for which the function $T_d(t)$ showed a cross-correlation larger than 0.9 with a common template were included in the computation.

Finally, to simulate an error in the location of the T–end, the T–end point was consistently shifted (± 20 ms) around its initial position and the $\mathcal{V}$–index recomputed.

3. Results

Figure 1 shows the bias in the estimates of the $\mathcal{V}$–index for the standard lead system (stars) and for the Frank's one (circles). The bias in the estimate of RH is function of s_ϑ, as theoretically shown in [5]. It is, on average, lower when employing the orthogonal lead system. In details, its value (at $\sigma_\varphi = 1$ ms) ranged from $-20.4 \pm 4.0\%$ ($s_\vartheta = 20.6$ ms) to $-26.3 \pm 4.0\%$ ($s_\vartheta = 70.9$ ms) for the standard system and from $-7.0 \pm 4.2\%$ to $-19.0 \pm 4.2\%$ for the Frank's one.

The $\mathcal{V}$–index is independent of σ_φ in the range explored (Figure 2), when no noise is added. However, things change when a 30 μV peak–to–peak broadband noise is superimposed to the ECGs. Then, the estimated values grow for $\sigma_\varphi <\approx 1$ ms, suggesting that the variance of the elements in $\mathbf{w}_2$ is overestimated due to the noise. However, in practical situations, in what we consider a physiological range ($\sigma_\varphi \in [0.5 - 4]$ ms), the estimated $\mathcal{V}$–index is rather independent from both the extent of the underlying beat–to–beat variability and the level of superimposed noise (at least up to a peak–to–peak noise amplitude of 30μV which is a mandatory limit for commercial ECG devices [12]).

We also explored further how the picture changes when the sampling frequency is reduced (see Figure 3). While the general behavior does not change with respect to Figure 2, the smaller number of points available decreases the efficacy of the SVD noise reduction capability, and a larger bias in the values of the $\mathcal{V}$–index starts to appear for growing values of σ_φ.

Secondarily, the influence of the misplacement of the T–endpoint in the estimate of the $\mathcal{V}$–index are reported in Figure 4. The average percent relative error across the population in the E-OTH-12-0068-010 THEW database is always smaller than 1% for displacements in the range of ± 20 ms. The variability of the error increases with the width of the displacement, as shown by the 5% and 95% percentiles in the figure, and an erroneous anticipation of the T-end is slightly more critical. However, the larger relative error was always smaller than about 10%.

4. Conclusions

In this paper we investigated the robustness of a newly introduced index of RH, the $\mathcal{V}$–index. The index proved to be largely independent from errors in the location of the T-end position. This is an interesting property for practical

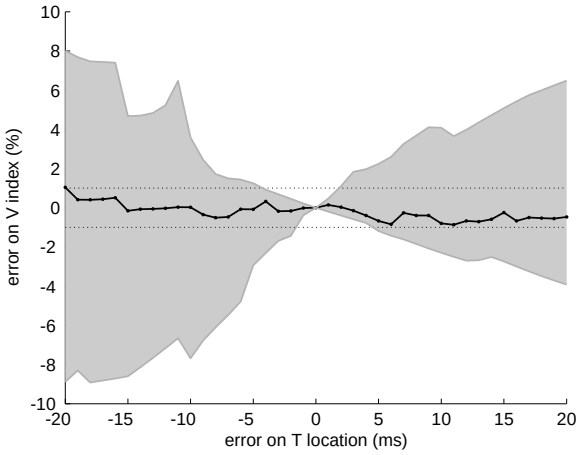

Figure 4. Percent relative error on the estimates of the $\mathcal{V}$–index. It was evaluated displacing artificially the end of the T wave of a maximal quantity (abscissas). The continuous line reports the mean value obtained on the E-OTH-12-0068-010 THEW database. The gray area includes 90% of the error population (it was drawn between the 5% and the 95% percentiles). The two dotted horizontal lines marks the $\pm 1\%$ values.

applications.

Then, we also verified that the bias in the estimate of the RH through the $\mathcal{V}$–index is smaller when using the Frank's orthogonal lead system. This result might look surprising at first sight, given the smaller number of concurrent recordings at disposal. However, the reason simply lies in the fact that the different estimates for the $\mathcal{V}$–index in each lead (see equation (4)) are averaged for the final estimate. The bias in the X, Y and Z lead cancel out much more that what happens for the standard system. However, a larger number of leads is still an advantage as Figure 3 shows: with 8 independent leads the convergence to the actual value of the estimator begins for smaller values of σ_φ. Thus, when the number of leads employed is decreased, the vulnerability to noise slightly increased, as expected. Surely, other ways of pooling the values $\mathcal{V}_i$ (instead of simply averaging them) should be explored to reduce the bias's impact on the index.

Finally, the work also showed that a reduction in the sampling frequency of the ECGs employed, from 1000 to 200 Hz, is acceptable as long as a high quality recording, with a low noise level, is used. This is also interesting for practical studies, where only Holter recordings at lower sampling rate are often available.

Future analysis should focus on the dependence of the $\mathcal{V}$–index on the number of beats employed. In here we used 128 beats but ECG recordings, collected in stationary conditions, of such duration might not be available.

Acknowledgements

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