A Comparison of Three Methodologies for the Computation of $\mathcal{V}$-index

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Abstract

Spatial heterogeneity of ventricular repolarization (SHVR) can be assessed from surface ECGs using the $\mathcal{V}$-index. The purpose of this study was to compare three algorithms for its estimate (which, for conciseness, will be termed M0, M1 and M2 in here). In deriving the $\mathcal{V}$-index, the T-wave is modelled as a linear combination of a waveform (dominant T wave, DTW) and its derivatives, through scalar lead factors. M0, M1 and M2 differ in: i) number of DTW derivatives (2 for M0 and M1, 5 for M2); ii) numerical (M0 and M1) or analytical approximation (M2) of the DTW; and iii) a common DTW shared (M1) across beats.

Tests were performed on both synthetic and real data. 64-beats synthetic 12-lead ECGs for 40 pseudo-subjects were generated with a direct electrophysiological model for SHVR in the range 10-70 ms. Holter recordings collected on 68 healthy subjects before and after moxifloxacin administration were also considered.

M2 obtained the lowest bias on synthetic data for SHVR from 20 to 70 ms ($p < 0.05$). For SHVR $= 10$ ms, the three methods provided comparable results ($p > 0.05$). On Holter data, they were all able to detect the effects of moxifloxacin ($p < 0.05$) and the drug's peak times were comparable. While the three methodologies were all able to compute the $\mathcal{V}$-index on both synthetic and real data, M2 appeared to obtain more robust estimates.

1. Introduction

Spatial heterogeneity of ventricular repolarization (SHVR) is a key quantity for the development of ventricular arrhythmia and responsible for the genesis of the T-wave on the ECG. Being able to assess repolarization heterogeneity from the ECG signals could help clinicians to stratify subjects at risk of sudden cardiac death.

An index called $\mathcal{V}$-index was recently introduced [1] for such purpose. It is meant to directly estimate the standard deviation of ventricular myocytes' repolarization times (RTs) from the surface ECG. $\mathcal{V}$-index already proved to be sensitive to the administration of sotalol and moxifloxacin [2], and was tested and validated on synthetic dataset [1,3].

The $\mathcal{V}$-index was derived from a biophysical model of myocardial repolarization, where the T-wave is represented as a linear combination a single waveform, termed "dominant T-wave" (DTW), and its derivatives, through scalars ("lead factors"). The first algorithm (hereafter named M0), implemented to compute the $\mathcal{V}$-index [1], involved two lead factors and the numerical approximation of the DTW. The method was based on an iterative procedure in which a first estimate of the DTW was obtained by considering the first right eigenvector of the SVD of the multi-lead T-wave, and then refined at each iteration. Further details are available in [1].

However, such methodology had some limitations. In fact, the low number of DTW derivatives included in the model was a potential problem with large SHVR [4] and the efficiency of adding further derivatives was limited by the large noise corrupting numerical estimates of high order differentials [5]. To overcome such limitations, a new method based on the sinusoidal approximation of the DTW (hereafter termed M2) was recently proposed [6]. M2 models the DTW as a weighted sum of sinusoidal functions and provides more accurate estimates of the $\mathcal{V}$-index on synthetic data [6].

In this study, we aimed to: i) propose an extension of the original method M0 (called M1 in here), meant to estimate the $\mathcal{V}$-index when considering a DTW shared across all the beats; in fact, the noise in the estimates of the derivatives can be reduced when averaging more beats; ii) test and compare M0, M1 and M2, by means of computer simulations and Holter data.

1.1. Background: $\mathcal{V}$-index definition

The shape of the T-wave, as observed on the ECG Ψ, can be modeled by a linear equation that links the transmembrane potentials (TMP) to the surface potentials. The heart surface is divided into M contiguous regions (nodes):

$$\Psi = AD = A \begin{bmatrix} D(t-\rho_1) \\ \vdots \\ D(t-\rho_M) \end{bmatrix} \quad (1)$$

where Ψ is a vector of surface potentials, A $[L \times M]$ is a transfer matrix which is fixed for a given subject. $D(t)$

describes the average shape of the repolarization phase of the transmembrane potentials while ρ_m is the repolarization time.

After expanding the function $D(t)$ around $\overline{\rho}$, with $\overline{\rho} = \frac{1}{M}\sum_{m=1}^{M}\rho_m$, eq. (1) can be expressed as:

$$\Psi \approx \sum_{k=1}^{N} w_k \frac{d^{k-1}}{dt^{k-1}} T_d(t) \tag{2}$$

where T_d is the DTW, w_k is a $[L \times 1]$ vector of lead factors and N is the number of terms included (T_d plus its derivatives) that contribute to model the potentials. The $\mathcal{V}$-index, for lead l, is then computed using [1]

$$\mathcal{V}\text{-index}_l = \frac{\text{std}\left[w_{2,l,b}\right]}{\text{std}\left[w_{1,l,b}\right]} = \left(\frac{1}{M}\sum_{m=1}^{M}\vartheta_m^2\right)^{\frac{1}{2}} \approx s_\vartheta \tag{3}$$

where b is the beat index and the standard deviation is computed along beats.

In conclusion, to estimate the $\mathcal{V}$-index, we need to compute two vectors of lead factors, *i.e.*, w_1 and w_2, and T_d by solving the inverse problem in eq. (2) for each beat.

2. Methods

2.1. $\mathcal{V}$-index computation

Method M0. The algorithm uses two lead factors and the numerical approximation of T_d. We refer the interested readers to [1] for more details.

Method M1. In M0, a specific DTW was estimated for each beat, independently. M1 assumes further that $D(t)$ does not change significantly between nearby beats and exploits this to reduce the impact of noise using a single DTW, shared across beats. The derivation follows the line of [1]. The function to minimize is now

$$\hat{e}^2 = \sum_{l=1}^{L}\sum_{b=1}^{B}\int_{\text{JT}} \left[\Psi_{l,b}(t) - w_{1,l,b}T_d(t) - w_{2,l,b}\dot{T}_d(t)\right]^2 \text{dt} \tag{4}$$

where b is the beat index and B the total number of beats.

In practice, the estimation process was the same employed in [1]. Briefly, after computing a first estimate of T_d, by considering the first right eigenvector provided by the SVD of the average beat $\frac{1}{B}\sum_{b=1}^{B}\Psi_b$, the lead factors can be estimated by solving a linear system for each beat separately. Then, an iterative algorithm that refined the estimate of T_d and lead factors was used. A new estimate of T_d was obtained by discretizing in time, for $\Psi_{b,l}(t)$ and $T_d(t)$, the solution of the Eulero-Lagrange equation obtained minimazing the functional (4). Lead factors were again computed by solving the linear system for each beat separately.

Differently than M0, since all the lead factors for any beat were available at each iteration, the iterative algorithm was stopped when the estimate of $\mathcal{V}$-index varied less than a certain threshold between successive iteration (here we used 0.01 ms).

Method M2. One of the main problem of numerical methods is that the observation Ψ can be rather noisy. Unfortunately, the impact of noise is emphasized when deriving in time T_d, and the higher the order of the differential the larger the noise. To overcome this problem, a new analytical model based on a trigonometric expansion of T_d was introduced in [6]. The set of trigonometric functions is closed under the operation of derivation and the inclusion of higher order derivatives is straightforward. Moreover, the nonlinear iterative optimization problem becomes now linear, at the cost of an iterative matrix factorization.

2.2. Synthetic ECG

Analysis were performed using synthetic 12-lead ECGs generated with a direct electrophysiological model (ECGSIM) [7] for several values of SHVR in the range 10-70 ms (step 10 ms). The forward model had 257 nodes and the repolarization time was provided for each node. The simulations were similar to those reported in [4].

For each value of SHVR, we generated 40 sets of 64 T-waves on which the three methodologies were applied and compared computing the $\mathcal{V}$-index. Each set was generated by randomly selecting a set of repolarization times, then reordered to follow a physiological rank ordering. Mean and standard deviation of $\mathcal{V}$-index were computed for each value of SHVR.

The performance was evaluated in two regards. First, the mean square error (MSE) between the synthetic ECGs and the fitted models was computed. Second, the bias between the true SHVR and the $\mathcal{V}$-index was calculated and the residues compared through the Wilcoxon signed rank test ($p < 0.05$). We performed the same tests after rescaling the $\mathcal{V}$-index to the true s_ϑ by means of a linear regression.

2.3. Holter Data

We compared the three methodologies by retrospectively analyzing the E-HOL-12-0140-008 dataset from the Telemetric and Holter ECG Warehouse (THEW) repository. It contained 24-h digital Holter recordings (12 standard leads, sampling frequency: 1 kHz, LSB: 3.75 μV) collected from 68 healthy subjects. For each participant, two registrations were performed when either a placebo or moxifloxacin (a 400 mg dose) was administrated. Drug's

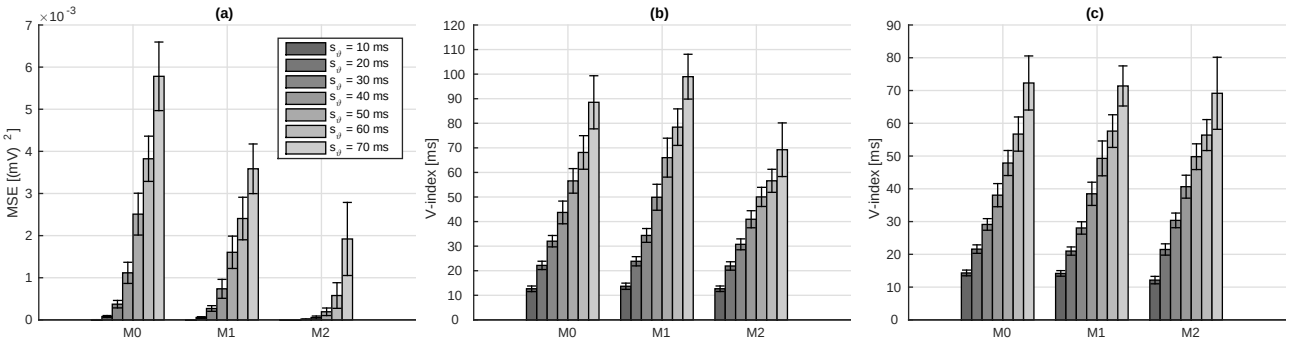

Figure 1. Mean and standard deviation of the MSE (a), $\mathcal{V}$-index (b) and rescaled $\mathcal{V}$-index (c) computed on the synthetic ECGs by means the three methodologies M0, M1 and M2. The rescaling equations were: i) 0.76 $\times\mathcal{V}$-index + 4.67 for M0; ii) 0.67 $\times\mathcal{V}$-index + 5.00 for M1; and iii) 1.00$\times\mathcal{V}$-index - 0.62 for M2.

serum concentration was assessed at 11 predefined instants ("time-points") during the entire day.

A standard preprocessing was performed to the ECG recordings (3^{rd} order Butterworth band pass filter 0.5-40 Hz, lead quality detection and isolectrical line set to 0 mV).

The protocol of the study was the same of [2]. For each time-point, we computed the $\mathcal{V}$-index on three consecutive 10-min windows. In each window, a set of "stable" beats was created by selecting those beats in which the two preceding RR values were within $\pm$ 25 ms, with respect to a constant $\widehat{\text{RR}}$ value, that maximized the number of selected beats.

The $\mathcal{V}$-index was computed only when 3 good quality leads and 64 stable beats were available in a window. Then, the average $\mathcal{V}$-index was computed for each time-point.

Three statistical analysis were run to compare the results obtained by the three methodologies. First, the $\mathcal{V}$-index values of the placebo arm were compared with those of the moxifloxacin one by means of the Wilcoxon signed rank test ($p < 0.05$ with Bonferroni correction), for each methodology separately.

Second, the average $\mathcal{V}$-index was computed for the moxifloxacin arm at each time-point for each methodology; then, we computed the linear correlation of such average arms across methodologies.

Finally, the time peaks of $\mathcal{V}$-index computed through the three methods were compared using the Wilcoxon signed rank test ($p < 0.05$).

3. Results

3.1. Syntethic ECG

Fig. 1 shows the results for the synthetic ECGs analysis. A lower MSE was obtained by M2 for all SHVR values ($p < 0.05$). The approximation error was worse for all methods when the value of s_ϑ was larger (fig. 1a), as expected.

$\mathcal{V}$-index values were compared to the SHVR selected in the model. M2 obtained the lowest bias for several SHVR (from 20 ms to 70 ms) while M0 and M2 performed better and were comparable ($p > 0.05$) when s_ϑ was 10 ms. After linearly rescaling the $\mathcal{V}$-index values, M2 was still the method which provided the lowest average bias (10 ms, 30 ms and 40 ms; $p < 0.05$), then M1 was better just in one case (20 ms; $p < 0.05$). In all the other SHVR considered, there were no differences between the average bias across methods (fig. 1b). The rescaling equations were: i) 0.76 $\times\mathcal{V}$-index + 4.67 for M0; ii) 0.67 $\times\mathcal{V}$-index + 5.00 for M1; and iii) 1.00$\times\mathcal{V}$-index - 0.62 for M2.

3.2. Moxifloxacin ECG

All methods were able to detect the effects of moxifloxacin. Figure 2 shows the $\mathcal{V}$-index values computed on the moxifloxacin and placebo arms for all the three methodologies.

$\mathcal{V}$-index values were statistically different between placebo and moxifloxacin arms at several time-points; in particular, when the effect of moxifloxacin was more relevant.

Second, a statistically significant linear correlation between the average $\mathcal{V}$-index values (in the moxifloxacin arm) was found only when comparing M0 and M2 ($R^2 = 0.83$, $p < 0.05$); M1 vs M2 and M0 vs M1 did not provide a statistical significant linear correlation ($p > 0.05$).

Finally, the time peak distributions of $\mathcal{V}$-index were: i) $4.50(3.00, 6.00)$ h for M0; ii) $4.00(2.00, 6.00)$ h for M1; and iii) $5.00(3.00, 8.00)$ h for M2. No statistically significant differences were found when comparing such distributions between each other ($p > 0.05$).

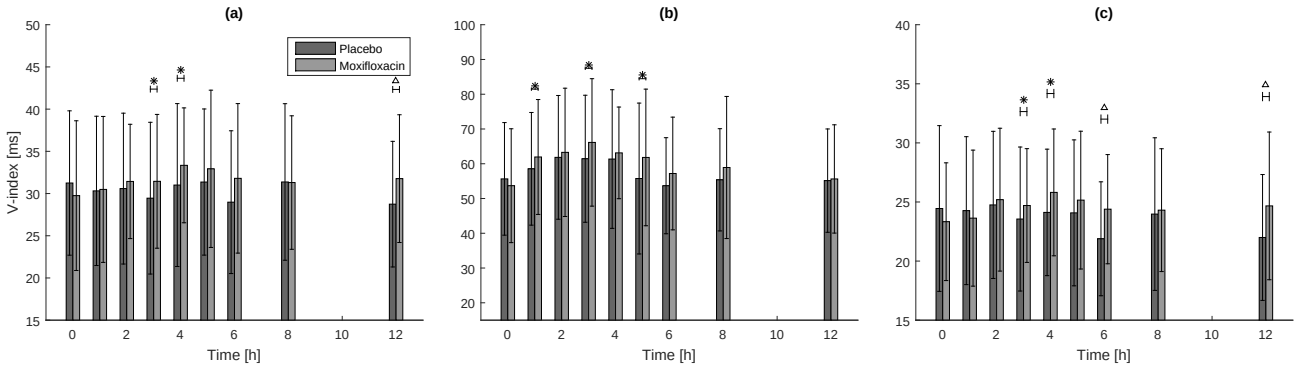

Figure 2. $\mathcal{V}$-index values for the placebo and moxifloxacin arms computed by M0 (a), M1 (b) and M2 (c). $*$ refers to $p < 0.05$ and Δ to Bonferroni correction.

4. Conclusion

Noninvasive assessment of the SHVR is gaining acceptance as a tool for characterizing the heterogeneity of the ventricular repolarization [8–10].

In such context, a new metric known as $\mathcal{V}$-index was introduced to estimate the standard deviation of ventricular myocytes' repolarization times. The index can be computed by using different algorithms. In this study, we compared three methodologies meant to computed the $\mathcal{V}$-index, which were based on different assumptions.

We obtained that a higher number of lead factors (when considering M2) resulted in a more robust estimate of high values of SHVR, confirming the results reported in [4, 6]. Moreover, the analytical form, having more reliable estimate of DTW derivatives, obtained the lowest values of MSE between data and model. On real data, all methods were able to detect the effects of moxifloxacin.

Overall, results showed that all the three methods were able to estimate the $\mathcal{V}$-index in both synthetic and real data. However, the analytical scheme, allowing us to consider more lead factors, seemed to provide a more reliable estimate of SHVR, *i.e.*, lower bias, on synthetic data.

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