Effect of Ischemia on the Spatial Heterogeneity of Ventricular Repolarization: a Simulation Study

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Abstract

Aim of this study is to assess, using numerical simulations, the effect of different degrees of ischemia on spatial heterogeneity of ventricular repolarization (SHVR), as evaluated by the V-index. Twelve-lead electrocardiograms were simulated using EGCSIM. Different degrees of ischemia were simulated in three regions, i.e., left anterior descending artery (LAD), right coronary artery (RCA) and left circumflex artery (LCX), by varying the size of the ischemic region (35 mm vs 50 mm), the amplitude of action potentials (APs; maximum reduction of 50%), and by shortening the AP durations (maximum reduction of 35%). The time progression of ischemia was simulated on a time window of 8 minutes in which 30 Monte Carlo simulations of 70 beats were generated each minute. V-index significantly increased at LCA and RCA of 11.2 $\pm$ 1.8 ms (+35.4%) and 12.6 $\pm$ 1.6 ms (+39.7%) with respect to baseline ($p<0.05$), for the ischemic region of 35 mm. The increment was larger for the 50 mm region, in which V-index approximately doubled. On the other hand, ischemia at LCX resulted in small changes of V-index of about 2 ms for both region sizes ($p<0.05$). The study showed that the V-index depended on the ischemic location, its size and electrophysiological changes of APs.

1. Introduction

Myocardial ischemia occurs when partial or complete blockage of a coronary artery prevents the myocytes from receiving enough oxygen. The effects of ischemia are often visible on the surface 12-lead electrocardiogram (ECG) and mostly result in changes of the ST segment and T-wave morphology.

At the cellular level, ischemia affects the action potential (AP) with the depolarization of the resting membrane, delayed initiation and decreased rate of rise in the AP upstroke, decrease of the AP amplitude, and shortening of AP duration (APD) [1]. Such electrophysiological changes determine a progressive modifications of the ST segment, T-wave amplitude and spatial heterogeneity of ventricular repolarization (SHVR).

The $\mathcal{V}$-index is a metric proposed to quantify the SHVR from the 12-lead ECG [2]. It is derived from a biophysical model of the T-wave [3] and estimates the standard deviation of repolarization times across the ventricles. In our previous studies, we quantified, in a human model of early-stage ischemia, that the $\mathcal{V}$-index was sensitive to the ischemic insult caused by prolonged balloon inflations during angioplasty, and progressively increased from the beginning of the stimulation [4]. Furthermore, the $\mathcal{V}$-index was found larger on subjects with acute myocardial infarction with respect to other causes of chest pain, when presenting at the emergency department [5], thus suggesting that a prolonged ischemia and subsequent tissue necrosis might lead to an increased SHVR. However, it is not clear whether the $\mathcal{V}$-index increase is associated with the location of ischemia and its size.

In this study, we investigated the effect of ischemia on the SHVR, as measured by $\mathcal{V}$-index from the surface 12-lead ECG, by means of computerized simulations. In particular, we assessed whether the ischemic location, its size and AP's electrophysiological changes affected the $\mathcal{V}$-index.

2. Methods

2.1. Background on $\mathcal{V}$-index

The $\mathcal{V}$-index is an estimate of the spatial dispersion of ventricular repolarization quantified from the surface ECG. Its mathematical formulation was based on the Equivalent Surface Source (ESS) model [3] and the repolarization time model [2]. According to the ESS model, the T-wave on the surface ECG was represented as a linear combination of the transmembrane APs, as follows

$$\boldsymbol{\psi}_k(t) = \mathbf{A} \begin{bmatrix} d(t-\rho_{k,1}) \\ \dots \\ d(t-\rho_{k,M}) \end{bmatrix}, \qquad (1)$$

where $\boldsymbol{\psi}_k(t) = \begin{bmatrix}\psi_{k,1}(t) & \cdots & \psi_{k,L}(t)\end{bmatrix}^T$ was a vector containing the multi-lead surface ECG with L leads at time t of the beat k, M was the total number of cells (or nodes), $d(t)$ was the AP (assumed to be similar between nodes during phase 3 of the AP), $\rho_{k,m}$ is the repolarization time of the m-th myocyte, and $\mathbf{A}$ was the subject-specific $L \times M$ constant transfer matrix.

It was possible to show that the model in (1) could be approximated by

$$\boldsymbol{\psi}_k(t) \approx \boldsymbol{w}_{1,k}\, t_{d,k}(t) + \boldsymbol{w}_{2,k}\, \dot{t}_{d,k}(t), \tag{2}$$

where $t_{d,k}(t)$ was the so-called dominant T-wave [6], and

$$\begin{aligned} \boldsymbol{w}_{1,k} &= -\mathbf{A}\boldsymbol{\Delta}\boldsymbol{\rho}_{\mathbf{k}} \\ \boldsymbol{w}_{2,k} &= \frac{1}{2}\mathbf{A}(\boldsymbol{\Delta}\boldsymbol{\rho}_{\mathbf{k}} \circ \boldsymbol{\Delta}\boldsymbol{\rho}_{\mathbf{k}}) \end{aligned} \tag{3}$$

were called lead factors, with $\boldsymbol{\Delta}\boldsymbol{\rho}_k = [\Delta\rho_{k,1}, \cdots, \Delta\rho_{k,M}]^T$ a vector containing all $\Delta\rho_{k,m} = \rho_{k,m} - \bar{\rho}_k$, *i.e.*, temporal delay of the m-th myocyte from the average repolarization time, and with $\circ$ being the Hadamard (pointwise) product. This formulation hints that the T-wave mainly depends on a single waveform, *i.e.*, $t_{d,k}(t)$, and the repolarization time delays $\Delta\rho_{k,m}$ [6].

Sassi and Mainardi [2] proposed a statistical model of the repolarization time delay $\Delta\rho_{k,m}$ consisting of one term varying in space θ_m and another one in time $\phi_{k,m}$, as follows

$$\Delta\rho_{k,m} = \theta_m + \phi_{k,m}. \tag{4}$$

In particular, $\phi_{k,m}$ was modeled as a zero-mean i.i.d. Gaussian random variation for each beat k and node m.

Using the model in (3) and (4), it was possible to show that the spatial variance (*i.e.*, across m) of θ_m was approximately the ratio of the variances of the lead factors. The ratio was termed as "$\mathcal{V}$-index" [2] and its mathematical formulation was

$$v_l^2 = \frac{\mathrm{var}[w_{2,k,l}]}{\mathrm{var}[w_{1,k,l}]} \approx s_{\theta\theta}, \tag{5}$$

where l is the lead, $s_{\theta\theta} = \sum_{m=1}^{M} \theta_m^2/M$ is the spatial sample variance of θ_m. In practice, the $\mathcal{V}$-index is computed as average across leads of the ratios of standard deviations.

2.2. Geometrical and Electrical Models

A Matlab code transposition (R2020b, The MathWorks, Inc.) of the free software ECGSIM [7] was used to implement the ESS in (1).

The model had $M = 257$ nodes connected in a closed surface with a triangular mesh. The repolarization time ρ_m and the APD_m for each node m were provided by the software. APs were generated using a product of logistic functions as in [2].

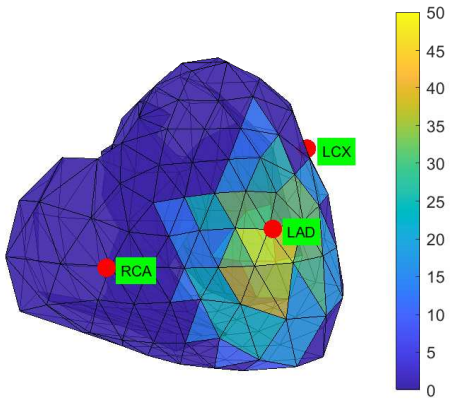

Figure 1: 3D model of the ventricles along with the position of the ischemic regions at LAD, RCA and LCX, marked with red dots. The colormap represents the amplitude reduction α_m (%) when an ischemic region of 50 mm radius centered at LAD is considered.

2.3. Model of Ischemia

Given the coordinates $\mathbf{p}_c = [x_c, y_c, z_c]^\intercal$ of the central node of the ischemic region, all nodes m whose position $\mathbf{p}_m$ was within the sphere centered in $\mathbf{p}_c$ of radius r were retained to be affected by ischemia.

The effects of ischemia on the APs in a given ischemic region have been modeled using a strategy similar to [8], where amplitude and duration of APs were reduced. APs were varied as follows

$$d_m(t) = \left(1 - \frac{\alpha_m}{100}\right) d\left(t - \rho_m - \frac{\beta_m}{100}\mathrm{APD_m}\right) \tag{6}$$

where $d_m(t)$ was the AP of the m-th node after applying the ischemic alterations, while α_m and β_m were percentage reduction of amplitude and APD, respectively.

Here, α_m and β_m were varied linearly from their maximum value at the central node of the region to 0 at the boundary, as in [8].

Figure 1 depicts the 3D model of the ventricles along with an example of spatial distribution of AP amplitude reduction α_m. Figure 2 reports the AP's electrophysiological changes (Fig. 2a-c), along with their associated surface ECG (Fig. 2d-f).

2.4. Experiments

A set of computerized experiments was performed to assess the link between $\mathcal{V}$-index and ischemia for the main two coronary arteries. In particular, regions near the two branches of the left coronary artery, *i.e.*, left anterior descending artery (LAD) and left circumflex artery (LCX),

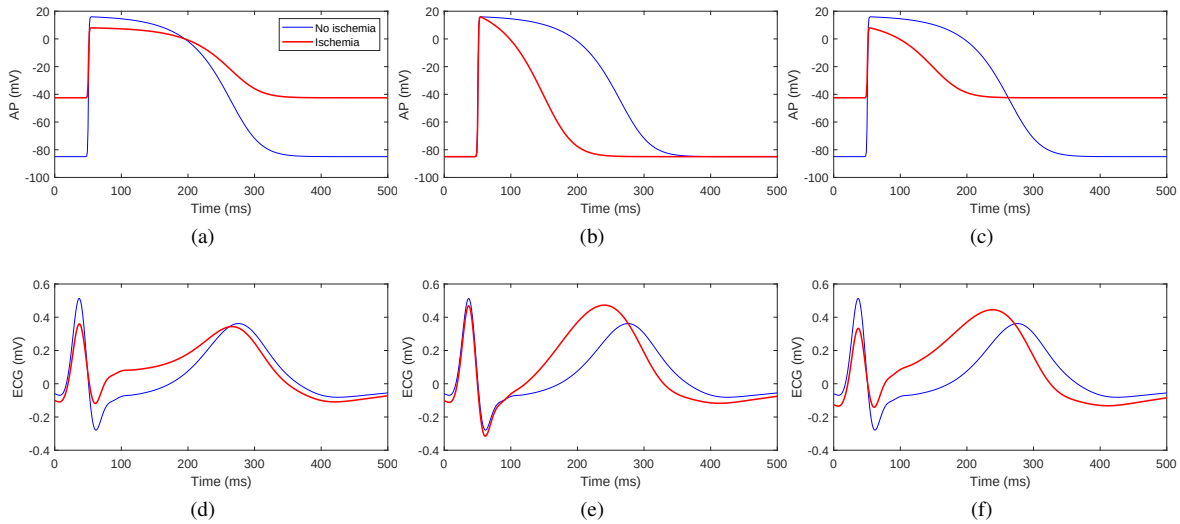

Figure 2: Example of electrophysiological changes of APs during ischemia for a randomly selected node when (a) 50% AP amplitude reduction, (b) 50% APD reduction, and (c) both effects combined, were applied. Their corresponding surface lead-I ECG (d-f) is reported below casewise. Modified signals are reported in thick red lines, whereas the ones without modifications are depicted with thin blue lines. The ischemic region is the one in Fig. 1.

and the right coronary artery (RCA) were considered as target for ischemia. Two region sizes were simulated by setting $r = 50$ mm (as in [8]), and $r = 35$ mm.

Eletrophysiological changes of APs were simulated by extrapolating the results from the works of Kébler *et al.* [1] and Shattock *et al.* [9]. Both research groups investigated about the time progression of ischemia on animal models. The studies reported an AP amplitude reduction of about 50% and an APD reduction of 35% after 7/8 minutes from the beginning of the ischemic insult. In addition, Shattock *et al.* [9] investigated on ischemic preconditioning by repetitive cycles of complete occlusion of the LAD. The occlusions applied lasted 8 minutes each and changes in ST elevation and APD were measured for each minute. Due to preconditioning, ST elevation and APD changed differently depending on the cycle. Here, in order to consider different eletrophysiological changes, we simulated the first two consecutive stimulation cycles of occlusions reported in [9]. To do so, for the first cycle, the maximum values of α and β were linearly changed from 30% to 50% and from 0% to 25% from minute 1 to 8, respectively. Similarly for the second cycle, α and β were linearly changed from 10% to 50% and 0% to 35%.

For each minute, 30 Monte Carlo simulations of 70 beats each were generated with $\phi_{k,m}$ values extracted from a zero-mean Normal distribution with $\sigma_\phi = 1$ ms, as in [2]. Surface T-waves were filtered using standard ECG preprocessing (Butterworth filter, 3rd order, 0.5-40 Hz, zero-phase).

Lead factors $\boldsymbol{w}_{k,1}$ and $\boldsymbol{w}_{k,2}$ were estimated using an iterative procedure for each beat k [2], and the $\mathcal{V}$-index was then calculated. The $\mathcal{V}$-index calculated with no AP modifications was used as reference $\mathcal{V}_{\text{ref}}$ to build $\Delta\mathcal{V} = \mathcal{V} - \mathcal{V}_{\text{ref}}$. A t-test with a significance level of 0.05 was performed to test $\Delta\mathcal{V}$ against a null increment.

3. Results

The reference $\mathcal{V}$-index was $\mathcal{V}_{\text{ref}} = 31.8 \pm 1.8$ ms (standard deviation computed across the 30 simulations).

Values of $\Delta\mathcal{V}$-index were dependent on the ischemic region, its size and stimulation cycle. In particular, LAD and RCA regions were found to largely increase the $\mathcal{V}$-index at the end of both cycles (Fig. 3a, 3c, 3d and 3f; $p < 0.05$). The region size also significantly altered the value of $\mathcal{V}$-index (Fig. 3a vs 3d and Fig. 3c vs 3f; $p < 0.05$). Different cycles resulted in different $\Delta\mathcal{V}$-index for both regions. On the other hand, LCX showed small changes in $\Delta\mathcal{V}$-index (< 2 ms; $p < 0.05$ only for the first cycle) across the 8 minutes (Fig. 3c and f). Average and standard deviation of $\Delta\mathcal{V}$-index at the 8th minute are reported in Table 1.

Table 1: Average and standard deviation of $\Delta\mathcal{V}$-index values at the 8th minute. $*$ refers to t-test with $p < 0.05$.

Size (mm)	Cycle	LAD (ms)	LCX (ms)	RCA (ms)
35	1st	$11.2 \pm 1.8^*$	$-0.5 \pm 0.6^*$	$12.6 \pm 1.6^*$
	2nd	$13.1 \pm 2.1^*$	-0.3 ± 0.7	$14.3 \pm 1.7^*$
50	1st	$39.1 \pm 4.4^*$	$-0.7 \pm 1.0^*$	$24.5 \pm 3.3^*$
	2nd	$41.7 \pm 4.6^*$	0.2 ± 1.1	$26.9 \pm 3.5^*$

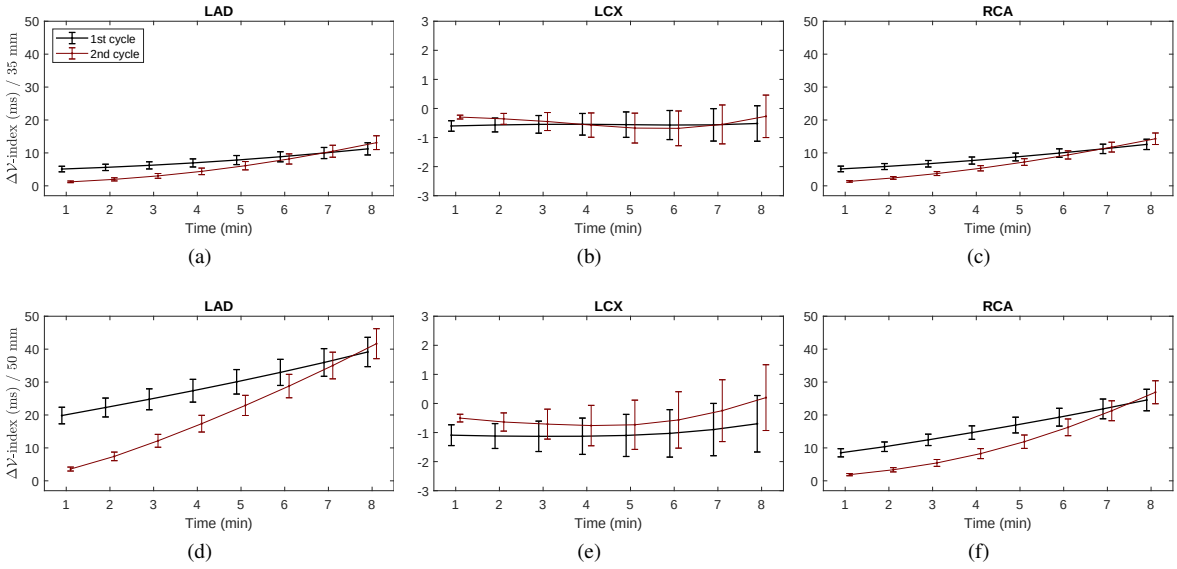

Figure 3: Mean and standard deviation (across the 30 simulations) of $\Delta\mathcal{V}$-index for each simulated scenarios: ischemic region, region size $r = 35$ mm (a-c) and $r = 50$ mm (d-f), and both first and second cycle of simulated occlusion.

4. Discussions

In this study, we investigated on the effects of ischemia on the SHVR, as measured by $\mathcal{V}$-index, by means of computerized simulations. As expected, electrophysiological changes of APs affected the value of $\mathcal{V}$-index. The results were in line with what observed in our previous study [4], in which a $\mathcal{V}$-index increase was observed with respect to baseline during occlusion of the coronary arteries.

Although the $\mathcal{V}$-index was found to increase with ischemia, the interpretation of this result cannot be solely associated to an augmented variance of repolarization times ($\Delta\mathcal{V}$ increased in the first minute in Fig. 3 where no APD change was applied). Indeed, during ischemia, one of the assumptions of the model, *i.e.*, similarity of APs during phase 3 of the cardiac cycle, might break depending on the amount of ischemic tissue involved. In this case, the $\mathcal{V}$-index becomes also sensitive to the voltage gradient generated by the amplitude reduction of the APs.

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