A Computational Model of Brugada Syndrome in 3D Heterogeneous Cardiac Tissue

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Abstract

Brugada syndrome is a genetic cardiac disorder associated with ventricular arrhythmias and sudden cardiac death. There are two classical interpretations of the ECG features and pathophysiological mechanism of the BrS: the repolarization disorder theory and the depolarization disorder theory. We employed our previously published phenomenological model of human myocytes to simulate the electrical activity of cardiac tissue in a 3D transmurally heterogeneous slab. Furthermore, we modified the model to reproduce the characteristics commonly associated to BrS action potentials. We assessed the insurgence of sustained reentry as a function of electrophysiological alterations and fibrosis distribution. Additionally, for each simulation, we computed simulated epicardial unipolar electrograms. Our results suggest that both electrophysiological and structural alterations are important factors in the induction of sustained reentry associated to BrS.

1. Introduction

Brugada syndrome (BrS) was initially described as a channelopathy affecting structurally normal hearts, but today it is recognized that subtle structural abnormalities contribute to the manifestation of the syndrome [1, 2]. BrS patients experience idiopathic ventricular arrhythmias and sudden cardiac death. Arrhythmic events in BrS originate from the epicardial layer of the Right Ventricular Outflow Tract (RVOT)[1], indeed previous studies showed that epicardial ablation of the pathological region suppresses the BrS electrocardiographic pattern and arrhythmic manifestations[2].

To date, the debate about the manifestation of the BrS ECG pattern and arrhythmic events is centered around the depolarization hypothesis and repolarization hypothesis [1, 2]. The repolarization hypothesis explains the ECG phenotype and the electrophysiological abnormalities (e.g., fractionation and low voltage observed in the electrograms) as the result of a shift toward repolarization in the membrane current balance, which can result in loss of action potential (AP) dome. Loss of AP dome would cause phase 2 reentry and ventricular arrhythmia[1].

The depolarization hypothesis states that the combination of conduction slowing and failure of excitation causes the BrS ECG pattern [2]. The presence of cardiac structural abnormalities and a reduced availability of sodium current in the RVOT would cause slow and discontinuous conduction and possibly excitation failure. Indeed, the RVOT of BrS patients harbors fibrosis and myocytes with reduced depolarization strength [1–3].

In this work, we developed a computational model of the right ventricle (RV) of a BrS patient as a 3D slab, modeling both electrophysiological alterations and fibrosis in a region resembling the RVOT. The model is used to determine the role of electrophysiological and structural abnormalities in the arrhythmogenesis of BrS. Furthermore, we compare simulated unipolar electrograms (UEGs) with UEGs recorded on BrS patients that are available in the literature. According to our model, the arrhythmic risk is modulated by three factors: I) the density of structural abnormalities; II) the intensity of the myocyte electrophysiological imbalance; III) the size of the pathological region.

2. Methods

Myocyte model

To perform the simulations, we employed our previously published phenomenological model of ventricular myocytes [4–6]. With different sets of parameters, the model reproduces the electrophysiological properties of both epicardium, endocardium and midmyocardium.

To replicate the phenotype of myocytes impaired by BrS, we modified the epicardial model to have slow upstroke velocity, prominent AP notch, and early repolarization (loss

of AP dome) depending on the actual membrane state [5]. Loss of AP dome happens when the transient outward current I_{TO} is strong enough to repolarize the membrane below its activation threshold. In our model the intensity of I_{TO} is increased when d_w^0 is decreased. The minimal d_w^0 used in our simulations ($d_w^0 = 0.3$) caused irreversible AP dome loss in the isolated myocyte model, whereas the maximal ($d_w^0 = 0.5$) caused a delayed dome AP morphology [5].

Numerical methods

The simulation of AP propagation was achieved by incorporating the myocyte model [6] in the monodomain formulation of cardiac tissue. The simulations were performed on a 3D slab of size $7 \times 7 \times 1\ cm$, representing the RV stretched out on a plane. The transmural distribution of myocytes across the slab was chosen as in [7]. We used a constant diffusivity $D = 1.171 \frac{cm^2}{s}$, obtained by Orovio et al.[8] from experimental measures of human myocardial tissue. In the transmural direction D was reduced by a factor 0.25 [9].

Since the pathological substrate of BrS is located in the epicardial layer of the RVOT [1, 2], we enclosed a pathological semicylindric region (BrS region) in the epicardial layer of the healthy 3D slab. The BrS region is made by BrS myocytes and has a homogeneous percentage of diffuse fibrosis.

Before starting the simulations, the tissue was initialized in the resting state (i.e., $V_M = -85\ mV, u = 0, w = 0$), then the 3D slab was stimulated from the endocardial layer with a square wave moving at $200 \frac{cm}{s}$ [10] to mimic the activation from the Purkinje Network. In healthy conditions, the total activation time of the 3D slab was $\simeq 50ms$, which is reasonable for the human RV [10]. To stimulate the cardiac tissue, we used strength twice the diastolic threshold for $2\ ms$. We performed temporal integration using an explicit Euler scheme (time step of $\Delta t = 0.02\ ms$) and we approximated spatial derivatives with standard second-order finite differences (spatial resolution of $\Delta x = 0.015\ cm$). No-flux boundary conditions were used at the edges of the 3D slab.

We carried out multiple simulations adopting different values of fibrosis percentage, d_w^0, and radius of the BrS region in order to determine the contribution of electrophysiological and structural abnormalities to the onset of arrhythmias. Diffuse fibrosis was modeled as a random distribution of inexcitable obstacles of size $0.3mm \times 0.3mm \times 0.3mm$ ($2\Delta x$) with no flux boundary conditions [11]. We varied the percentage of fibrotic tissue (F_p) between 0.2 and 0.8 with a step of 0.06 in order to include fibrosis percentages observed in BrS patients[3]. We varied d_w^0 between 0.3 and 0.5 with a step of 0.05. We did not perform simulations for d_w^0 lower than 0.3 because for such values the myocyte model never recovers the AP dome, even after several successive excitations. We varied the radius of the BrS region (R_B) between $1.5\ cm$ and $3.5\ cm$ with a step of $0.5\ cm$.

For each combination of d_w^0 , R_B , F_p, we ran 10 simulations, since the distribution of fibrosis in the BrS region was random, and estimated the probability of cardiac arrhythmia as the number of simulations that had sustained reentry over the total number of simulations (i.e., 10). For each simulation, we set a duration of 4 seconds and recorded the incidence of sustained reentry if there still was depolarized tissue at the end of the simulation. For each simulation we generated UEGs 1 mm above the epicardial layer, both in the healthy and pathological tissue. UEGs were obtained by assuming an infinite and homogeneous volume conductor and calculating the cardiac dipole source density [12].

3. Results

Sustained reentry in the 3D model of BrS

If fibrosis was not present, depolarization of the tissue was homogeneous, in the same direction as the depolarization wave in the healthy tissue. The presence of fibrosis in the BrS region caused slowing of conduction and fragmentation of the propagating wavefront, for any value of d_w^0. Increasing the fibrosis percentage accentuated the depolarization abnormalities, until conduction block occurred. If electrophysiological abnormalities were present in the BrS region, we observed orthodromic reentry [13] when $d_w^0 < 0.5$, regardless of the fibrosis percentage. If $d_w^0 = 0.5$ there was no reentry since the myocytes never lose the AP dome. When $d_w^0 \geq 0.4$, the second AP in the BrS region showed a fully restored dome. On the contrary, when $d_w^0 \leq 0.35$, consecutive APs did not have a restored dome.

No reentrant activity occurred in the healthy tissue if either fibrosis or electrophysiological abnormalities were not present in the BrS region. When both fibrosis and electrophysiological abnormalities were introduced in the BrS region, their interplay generated reentrant circuits. Indeed, inexcitable obstacles may induce breakup of lost dome waves in the BrS region and consequently generate small spirals. If these spirals sustain for a time longer than the refractory period of the healthy tissue, the healthy tissue can activate again.

The presence of structural abnormalities did not induce sustained reentry if the myocytes maintained or recovered the AP dome. Indeed, Fig. 1 shows that no reentry occurs if $d_w^0 \geq 0.4$, since the myocytes recover the dome in the second AP. The results from our model suggest that both depolarization and repolarization abnormalities are needed for the occurrence of arrhythmic events in BrS, coherently

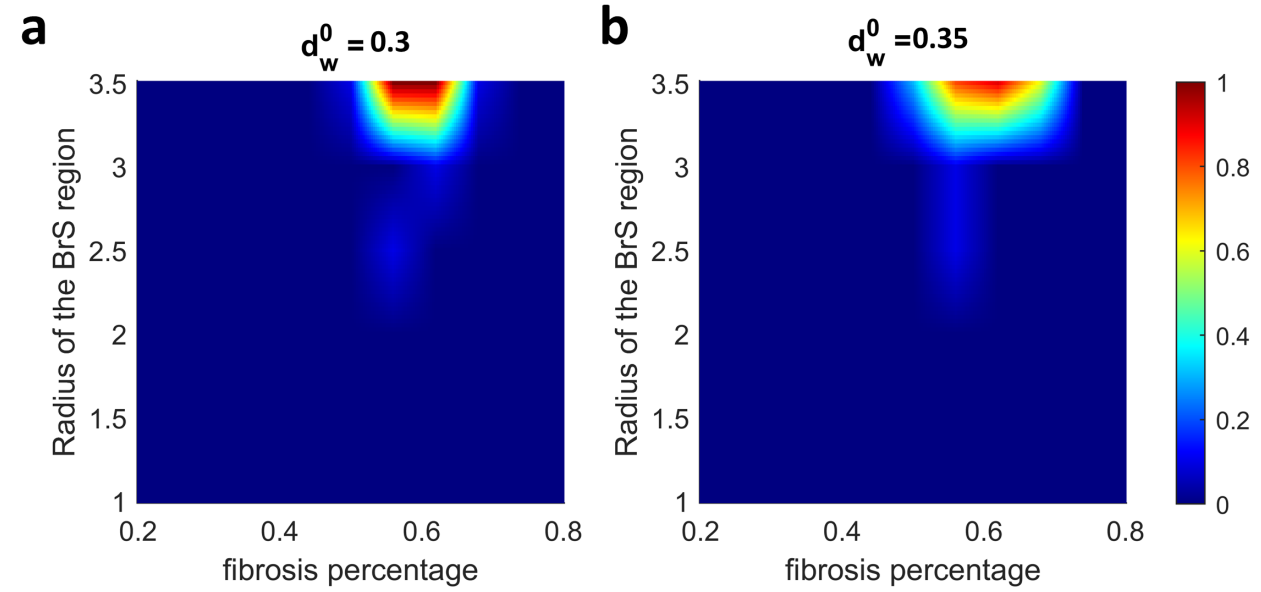

Figure 1. Probability over 10 trials of sustained reentry in the healthy tissue, at the end of 4 seconds of simulation. Setups with no reentrant activity ($d_w^0 = 0.4$, $d_w^0 = 0.45$) are not shown. a) when $d_w^0 = 0.3$, reentrant circuits are likely to arise in the BrS region, however since the I_{TO} is stronger, the APs are unlikely to excite the healthy tissue. b) when $d_w^0 = 0.35$, the reentrant circuits are more likely to excite the healthy tissue since the electrophysiological imbalance is lower.

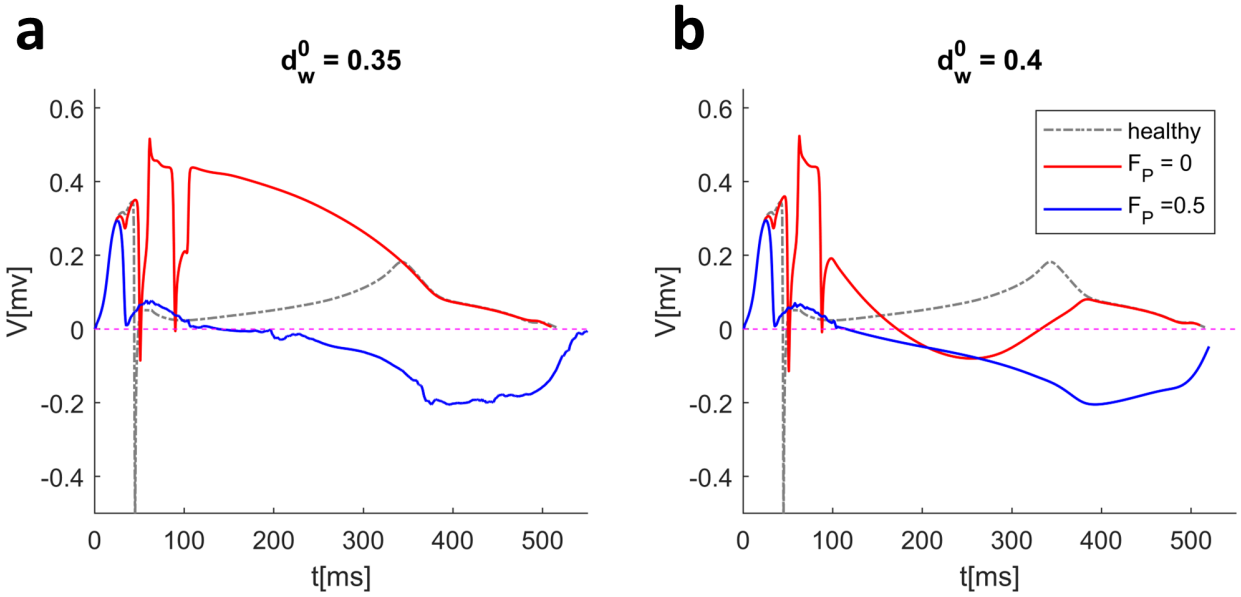

Figure 2. Representative UEGs generated above the center of the BrS region. Increasing the fibrosis percentage reduces both J and ST elevation. a) when $d_w^0 = 0.35$, the permanent loss of AP dome causes ST elevation. Two deflections are caused by the two orthodromic APs in the BrS region. b) when $d_w^0 = 0.4$, deflections are caused by 2 orthodromic APs (the first lost dome, the second delayed dome). ST elevation is not present due to the recovery of AP dome.

with the more recent idea that both abnormalities may be present in the BrS substrate[1, 14].

Simulated UEGs

In this section, we comment the morphology of UEGs taken above the center of the BrS region, from simulations

where no sustained reentry occurred. All UEGs had delayed activation (considered as the time of minimum of the R peak) and a variable degree of J/ST elevation (refer to Fig.2). In our model the J wave is generated by the voltage gradient between epicardium and midmyocardium when the BrS myocytes lose the AP dome, thus elevation of the J wave was always present. If the myocytes recover the AP dome during their second orthodromic AP ($d_w^0 \geq 0.4$), no further elevation is present in the UEG. On the contrary, if the myocytes never recover the AP dome (typically $d_w^0 = 0.3$ or $d_w^0 = 0.35$), the epicardium-midmyocardium gradient prolongs in time and causes ST segment elevation. In our model, the midmyocardium is the last tissue to repolarize, thus during repolarization two opposite voltage gradients contribute to the genesis of T wave in a UEG: the epi-midmyocardial gradient, which generates a positive signal, and the endo-midmyocardial gradient, which generates a negative signal. In healthy conditions, since the epi-mid gradient is the closest to the recording electrode, the polarity of the T wave is positive. On the contrary, in each trial where structural abnormalities were present in the BrS region, the polarity of the T wave was negative (Fig. 2). As already discussed in [11], the signal intensity in the simulated UEGs is inversely proportional to the fibrosis percentage of the tissue that generates the signal. Since fibrosis is only present in the epicardial layer of the BrS region, the endo-mid gradient has a relatively greater contribution in the genesis of the T wave, thus the polarity shifts toward negative values when fibrosis is present in the epicardial layer.

The presence of the fibrosis distribution caused also fractionation of UEGs. Indeed, the fractionation observed in UEGs recorded in BrS patients is believed to be caused by fibrosis [2]. Note that the fractionation caused by fibrosis (Fig. 2, in blue) is different from the wide deflections that are caused by the reentrant APs (Fig. 2, in red). Notably, by increasing the fibrosis percentage in the BrS region, J/ST elevation reduces (Fig.2). Indeed, the replacement of pathological tissue with fibrosis can be compared to an ablation procedure, which is known to remove the pathological features of UEGs in BrS patients.

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