Incremental Pacing Induces Sustained Reentry in a Computational Model of Brugada Syndrome

Niccolò Biasi[1], Paolo Seghetti[2,3], Alessandro Tognetti[1,4], Edward J. Vigmond[5,6]

[1] Department of Information Engineering, University of Pisa, Pisa, Italy
[2] Health Science Interdisciplinary Center, Scuola Superiore Sant'Anna, Pisa, Italy
[3] Institute of Clinical Physiology, National Research Council, Pisa, Italy
[4] Research Centre "E. Piaggio", University of Pisa, Pisa, Italy
[5] IHU Liryc, Electrophysiology and Heart Modeling Institute, Pessac, France
[6] University of Bordeaux, Institut de Mathematiques de Bordeaux, Talence, France

Abstract

Brugada Syndrome is a form of idiopathic ventricular fibrillation. To date, there is no definitive theory about how ventricular fibrillation is initiated, or a consensus on its substrate. In this work, we report a computational study aimed at determining the role of the pacing protocol on the induction of sustained arrhythmias in Brugada Syndrome. We developed a computational model of Brugada Syndrome, including both structural and electrophysiological abnormalities in a slab of transmurally heterogeneous cardiac tissue. Starting from the clinical observation that cardiac episodes are more frequent at rest, we studied the effect of incremental pacing (i.e., with increasing pacing cycle length) on the generation of reentrant activity. Our results suggest that incremental pacing can unmask the arrhythmogenic substrate of Brugada Syndrome.

1. Introduction

Brugada Syndrome (BrS) is an inherited cardiac disorder associated with ventricular cardiac arrhythmias and sudden cardiac death, which most frequently occurs during sleep or at rest[1]. BrS is identified by specific electrocardiographic patterns. The diagnostic type-1 BrS ECG pattern is characterized by ST elevation and negative T wave in the precordial leads (V1-V2), whereas two other patterns (type 2 and 3) have more subtle alterations in the J wave but are not diagnostic unless converted into type 1 upon pharmacological challenge [2]. BrS was initially described as a channelopathy affecting structurally normal hearts, but today, it is accepted that subtle structural abnormalities contribute to its manifestation[3]. In BrS the electrophysiological and structural alterations are localized in the Right Ventricular Outflow Tract (RVOT), mainly at the epicardial level [4, 5]. However, the pathophysiological mechanism of BrS is still highly debated. Whereas experimental studies on canine right ventricular preparations (e.g., [6]) and in vivo monophasic action potentials recordings (e.g., [7]) suggest repolarization abnormalities are involved, other work relates BrS with cardiac fibrosis (e.g., [8, 9]). Currently, two major hypotheses are considered for the pathological mechanism of BrS, the repolarization hypothesis, and the depolarization hypothesis. The repolarization hypothesis proposes that an outward shift in the balance of membrane currents (sodium, calcium, or potassium) during phase 0-1 of the action potential (AP) leads to repolarization abnormalities in the tissue (i.e., loss of action potential dome), which in turn causes phase-2-reentry (P2R) and ectopic beats precipitating VF [10]. The depolarization hypothesis proposes that structural factors in the RVOT epicardium (e.g., localized diffuse fibrosis) slow down the ventricular conduction and cause fractionated EGMs typically observed in the BrS substrate. This phenomenon is exacerbated in presence of sodium or calcium channel blockers, or potassium agonists, leading to local excitation failure [3].

In this work, we developed a computational model of BrS including both structural and electrophysiological abnormalities in a simple anisotropic slab geometry. Inspired by the higher occurrence of arrhythmic events during sleep and at rest [1], we employed the model to study the effects of incremental pacing (i.e., with increasing pacing cycle length) on the induction of sustained arrhythmias. In particular, we employed a pacing protocol consisting of a fixed cycle length prepacing followed by an extrastimulus after a long interval. Our results show that sustained arrhythmia is induced with a larger range of extrastimulus intervals for larger basic cycle length (BCL). Thus, our model suggests that incremental pacing can unmask the arrhythmic substrate of BrS.
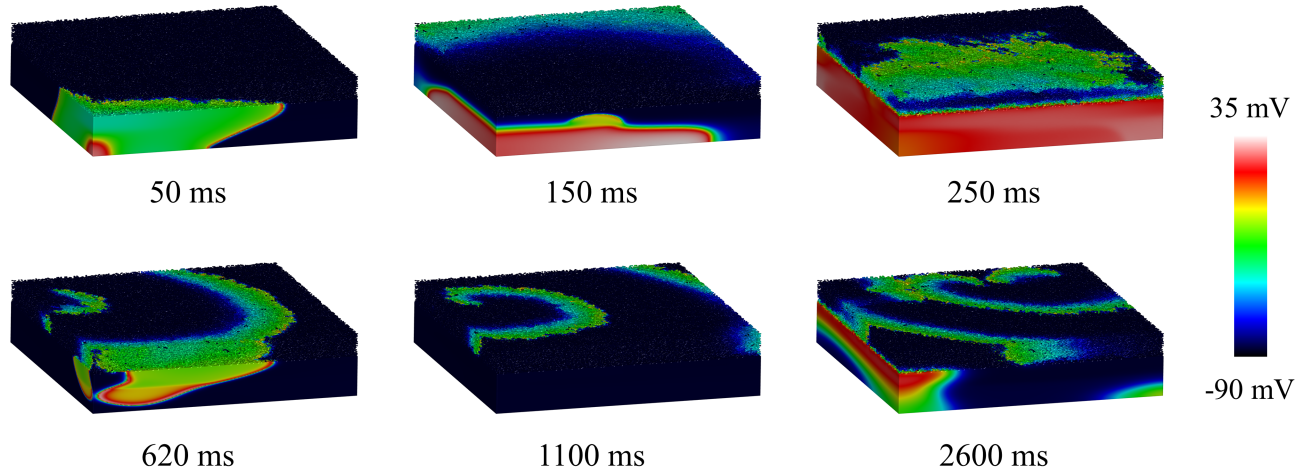
Figure 1. Sequence of snapshot showing induction of sustained reentry in the slab model. BCL was 800 ms and the extrastimulus interval 1200 ms. Time instants below the snapshots are relative to the delivery of the extrastimulus.

2. Methods

All the finite element monodomain simulations were performed in an anisotropic slab of size 3x3x0.7 cm, roughly corresponding to RVOT dimensions [4], and discretized with hexahedral elements of size 150x150x75 μm. The models were solved on a desktop computer with the finite element software openCARP (https://opencarp.org/) [11] using a time step of 20 μs. Transmural heterogeneity was included in the model by dividing the slab into three regions corresponding to endocardium (36% of the thickness), midmyocardium (28% of the thickness), and epicardium (36% of the thickness). Additionally, we introduced diffuse fibrosis in the epicardial layer by randomly removing the 75% of the hexahedral elements [12]. Note that, due to the element size, the fibrotic pattern tends to arrange in a planar fashion. The ionic current was described with the ten Tusscher et al[13] model with a modified I_{to} formulation[14]:

$$I_{to} = I_{to}^f + I_{to}^s \qquad (1)$$

$$I_{to}^f = G_{to} F_f a_f i_f \left(V_m - E_k\right) \qquad (2)$$

$$I_{to}^s = G_{to} \left(1 - F_f\right) a_s i_s \left(V_m - E_k\right) \qquad (3)$$

The I_{to} current considered two contributions: a fast recovery (I_{to}^f) and a slow recovery (I_{to}^s) current. Both the two types of I_{to} are defined according to an activation (a_f, a_s) and an inactivation gate (i_f, i_s). F_f indicates the fraction of fast recovery transient outward current, whereas G_{to} is the maximum transient outward conductance. A recent experimental study showed that F_f is transmurally heterogeneous along the myocardium [14]. In the endocardial layer, transient outward current has been found to be mostly slow recovery, whereas in the epicardial layer, transient outward current recovers faster. In the midmyocardium both I_{to}^f and I_{to}^s are expressed. Thus, we set $F_f = 0$ in the endocardium, $F_f = 0.5$ in the midmyocardium, and $F_f = 1$ in the epicardium. To simulate electrophysiological alterations of BrS, we introduced linear endo-epi gradient in I_{to} density. We set $G_{to} = 4.6\ nS/pF$ in the endocardium, $G_{to} = 5.3\ nS/pF$ in the midmyocardium, and $G_{to} = 6\ nS/pF$ in the epicardium. The healthy value for G_{to} is 1 nS/pF. Furthermore, we reduced the maximum sodium conductance to 33% of its normal value in the epicardium. For each simulation, the cardiac slab was stimulated in a corner with a fixed BCL for ten beats. BCL was varied between 700 and 1100 ms with steps of 100 ms. After the prepacing phase, the slab was stimulated again after a long pause (i.e., the extrastimulus interval). For each BCL, we varied the extrastimulus interval from 1150 ms to 1250 ms in steps of 5 ms, and identified the extrastimulus intervals for which sustained reentry was induced.

3. Results

Figure 1 and 2 show an example of sustained reentry induced by a long extrastimulus interval. A prominent notch is observed in the endocardium, and a lost dome action potential is observed in the midmyocardium ($t = 50\ ms$). Such dispersion of repolarization induces P2R in the midmyocardium ($t = 150\ ms$). The newly generated AP shows delayed dome morphology, due to the presence of both slow and fast recovery I_{to} (2). Indeed, in the epicardium, where I_{to} recovers quickly, both action poten-
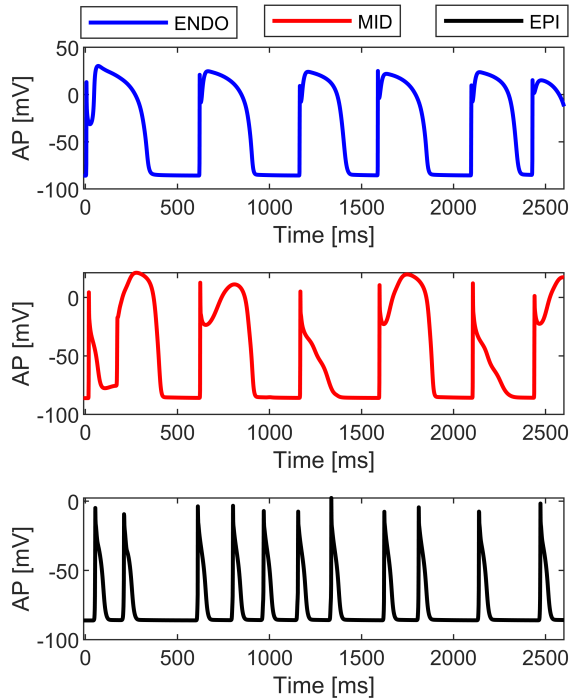
Figure 2. Membrane potential in three layers (EPI: epicardium, MID: midmyocardium, and ENDO: endocardium) during induction of sustained reentry. BCL was 800 ms and the extrastimulus interval 1200 ms. Time is relative to the delivery of the extrastimulus.

tials are devoid of dome. Consequently, the presence of fibrosis coupled with the very short action potential induced sustained reentry by percolation in the epicardium [12, 15]. The reentrant activity in the epicardium can depolarize the midmyocardium if it is able to sustain for long enough while the underlying tissue recovers ($t = 620\,ms$). Thus, sustained tachycardia was induced in the model and was governed by reentry near the percolation threshold in the epicardium. Interestingly, alternans of lost dome and delayed dome action potentials can be observed in the midmyocardium (Fig. 2).

Figure 3 shows the values of extrastimulus interval inducing sustained arrhythmia for different BCLs. We observed that for each BCL, a vulnerable window exists wherein an extrastimulus induced sustained arrhythmia. For lower BCLs, the width of the vulnerable window was larger and sustained arrhythmia occurred for lower extrastimulus intervals. Indeed, sustained arrhythmia occurred when I_{to}^s was near to complete recovery. For BCLs higher than 1000 ms we did not observe sustained arrhythmia for any value of the extrastimulus interval, suggesting that incremental pacing played an important role in the ar-
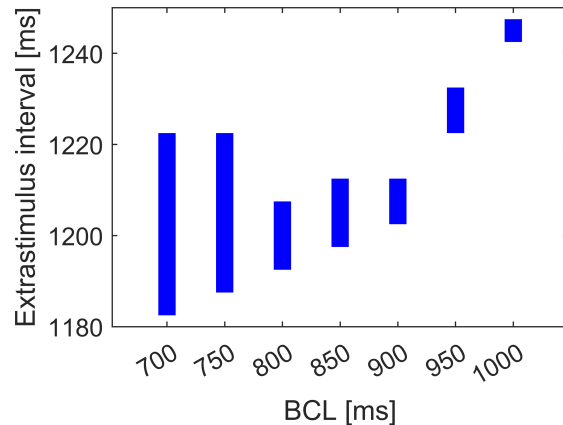

Figure 3. Extrastimulus intervals inducing sustained arrhythmia for different basic cycle length.

rhythmic behavior of BrS.

4. Conclusion

In this work, we carried out a computational study to assess the contribution of incremental pacing to the development of arrhythmic events in BrS. First, we confirmed reentry near the percolation threshold as a putative mechanism of BrS-related arrhythmias that combines electrophysiological and structural abnormalities. We proposed such a mechanism in a previous computational study employing a phenomenological model [16]. Additionally, our results highlighted a rate-dependent behavior that is explained by the dynamics of I_{to}^s, suggesting a potential novel role of slow recovery transient outward current in the arrhythmogenesis of BrS. Indeed, we observed that incremental pacing induced sustained reentry in our computational model. Whereas the results are promising, the computational study presented in this work has some limitations. First, we employed a simple slab geometry, thus confirmation of the results in anatomically detailed geometry is needed. Second, we only employed a single fibrotic pattern neglecting its random nature. For more robust results, future work should be carried out on multiple geometries with different fibrotic patterns. Moreover, we wish to explore different options for fibrosis representation, such as the edge splitting method, and the additional effect of myocyte-fibroblast coupling [17]. Finally, our future works will aim to assess the role of sodium and transient outward conductances, and to determine their relationship with incremental pacing.

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Address for correspondence:

Niccolò Biasi
Largo Lucio Lazzarino 2, Pisa, Italy
niccolo.biasi@phd.unipi.it