Uncovering Arrhythmic Substrate in a Heart Failure Patient Using Digital Twins

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Abstract

Heart failure patients with myocardial fibrosis are at increased risk of ventricular arrhythmias and sudden cardiac death (SCD). In clinical practice, arrhythmic risk stratification is typically performed using invasive procedures such as the electrophysiological study (EPS). In this study, we developed a personalized cardiac digital twin for a heart failure patient presenting with left ventricular hypertrophy, systolic dysfunction, and extensive non-ischemic myocardial fibrosis. We virtually replicated the EPS protocol to assess arrhythmic risk non-invasively. The simulations successfully reproduced the arrhythmias observed during the clinical EPS. Notably, only fibrotic configurations with thick heterogeneous border zones between dense fibrosis and healthy tissue were capable of reproducing the patient's arrhythmias, highlighting the critical role of microstructural variability in arrhythmia formation. These results illustrate the potential of digital twin technology for personalized arrhythmia risk assessment and for uncovering structural substrates not fully captured by standard imaging techniques.

1. Introduction

Systolic dysfunction, and extensive non-ischemic myocardial fibrosis are structural features often observed in heart failure patients at increased risk of ventricular arrhythmias and sudden cardiac death (SCD), a leading cause of mortality worldwide [1]. In Brazil, these patients are typically evaluated for implantable cardioverter-defibrillator (ICD) therapy through an invasive procedure known as electrophysiological study (EPS) or programmed ventricular stimulation (PVS). This protocol applies progressively shorter electrical stimuli via catheters placed in the heart to assess conduction properties and induce arrhythmias. In this context, digital twin technology has emerged as a promising alternative for non-invasive risk stratification. Recent studies [2] have shown that personalized cardiac models can reproduce patient-specific arrhythmic behavior and offer mechanistic insight into the underlying arrhythmogenic substrate.

This study investigates a heart failure patient with ventricular hypertrophy, reduced systolic function, and widespread non-ischemic fibrosis using a personalized cardiac digital twin. The model integrates patient-specific anatomy, fibrotic distribution, and estimated conduction velocities to virtually replicate the clinical EPS protocol. Simulations successfully reproduced the arrhythmic events observed during the invasive procedure. Notably, only fibrotic configurations with thick heterogeneous border zones between dense fibrosis and healthy tissue were capable of reproducing the patient's arrhythmias, highlighting the critical role of microstructural variability in arrhythmia formation. These results illustrate the potential of digital twin technology for personalized arrhythmia risk assessment and for uncovering structural substrates not fully captured by standard imaging techniques.

2. Methods

2.1. Patient Report

This study is based on data from a 71-year-old male patient under follow-up at the cardiology outpatient clinic of the University Hospital of the Federal University of Juiz de Fora. Cardiac magnetic resonance imaging (MRI) revealed a phenotype consistent with cardiomyopathy characterized by increased left ventricular wall thickness, particularly in the septal and anterior wall segments, associated with systolic dysfunction. Late gadolinium enhancement (LGE) sequences identified extensive areas of mid-myocardial fibrosis following a non-ischemic pattern, distributed across all basal and medial segments as well as the infero-apical

region. The enhancement pattern was suggestive of an infiltrative etiology, such as cardiac amyloidosis. Electrocardiographic analysis revealed a masquerading bundle branch block pattern without repolarization abnormalities.

An electrophysiological study was performed following the protocol described in [3]. The baseline rhythm (S1) was simulated by pacing a single site near the right ventricular outflow tract, repeated eight times with a basic cycle length of 600 ms. The first extrastimulus (S2) was applied at the same site, starting from an S1–S2 interval of 380 ms and progressively shortened in 10 ms steps until reaching either the absolute refractory period or a lower limit of 200 ms. After this point, the S2 interval was increased by 20 ms, and a third stimulus (S3) was introduced, following the same decremental steps. This procedure was repeated for a fourth extrastimulus (S4), completing the stimulation protocol. The clinical EPS induced sustained ventricular tachycardia, which progressed to ventricular flutter with hemodynamic instability (circulatory arrest), requiring immediate external electrical defibrillation.

2.2. Computational Model

Based on the MRI data, medical specialists manually segmented the regions of interest. Specifically, the epicardium, endocardium, and fibrotic tissue were delineated in short-axis planes, allowing simultaneous visualization of both ventricles. The segmentation was conducted using Segment [4]. After the manual segmentation, the 2D images were combined to form a 3D model. To this end, we followed the pipeline described in [5]. Seven short-axis images were segmented and used to construct the 3D geometrical model. This geometry was discretized with one million finite volumes, resulting in the mesh presented in Figure 1 (a).

To make the simulations even more realistic, the 3D model is refined by considering heterogeneous cell electrophysiology along the transmural axis and tissue anisotropy. Transmurality is obtained by solving a Laplace field equation along the 3D domain subject with Dirichlet bordary conditions. The resulting field ranges from 0 to 1 and it is used to assign endocardial, mid-myocardial, and epicardial cells. Anisotropy arises from the organization of cardiac cells into fibers and sheets, creating preferential directions for electrical signal propagation. Since these directions are challenging to obtain from medical exams, an estimation is made using a Laplace-Dirichlet Rule-Based Algorithm [6].

2.3. Fibrosis

It is well documented that fibrosis in cardiac tissue significantly increases the risk of arrhythmias. Furthermore, at the transition between fibrotic and healthy tissue, a region known as the border zone (BZ) is formed, containing a mix of overloaded and healthy cells. The BZ is highly anisotropic, with impaired conduction, making it a highly arrhythmogenic substrate [7]. Unfortunately, due to the limited resolution of imaging techniques, capturing the microanatomical details of these structures remains unfeasible. Therefore, in this study, the healthy tissue and the fibrotic core were modeled as compact structures composed exclusively of conductive and non-conductive cells, respectively. The border zone, in turn, was modeled in layers, as illustrated in Figure 1 (b). The proportion of active cells varies linearly from 0% to 100% as a function of the number of layers, with the inner layers having a lower proportion of active cells than the outer layers.

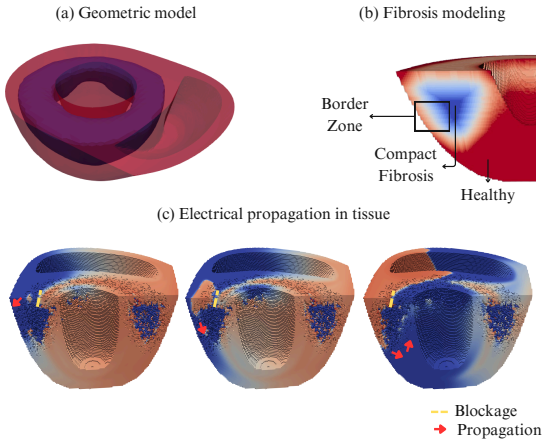


Figure 1. (a) Geometric model of the patient heart. The healthy region is shown in red, and the fibrotic region in blue. (b) Modeling of fibrosis with a compact inactive core and a border zone with a linear variation in the number of active cells. (c) Transmembrane potential (-86 mV to 40 mV) showing reentry formation around a fibrotic region due to the occurrence of unidirectional block.

Different models were generated with varying BZ thicknesses: 2, 4, 6, 8, 10, and 12 mm. Each millimeter corresponds to a layer thickness of 500 µm. To evaluate the system's behavior under different microstructural configurations, distinct microscopic patterns of fibrosis were also randomly generated. The distribution of active cells in each layer of the BZ was determined using a random selector controlled by a seed, ensuring both variability and reproducibility. Ten different seeds were considered for each thickness value, resulting in 60 electrophysiological variants of a single cardiac digital twin.

2.4. Mathematical Model

For the simulations, the Ten Tusscher cellular model [8] was employed to describe the excitation dynamics of cardiac cells. This cellular model was coupled with the Mon-

odomain model. The homogeneous Neumann condition is applied at the boundary to ensure that the domain is electrically isolated. Moreover, as outlined in [8], specific parameters of the cellular model are adjusted according to the cell type. This allows the model to account for the heterogeneity of cardiac tissue by incorporating distinct action potentials for each cellular phenotype along the transmural axis. The cardiac tissue conductivity tensor σ was modeled as anisotropic, incorporating the fiber orientation and a prescribed anisotropy ratio. The simulations were conducted using the MonoAlg3D open-source software [9]. Temporal discretization was set at $\Delta t = 0.02\ ms$, while spatial discretization was $h = 500\ \mu m$. To detect arrhythmias during the EPS simulations, a custom script was developed to monitor the number of activations in each volume compared to the number of applied stimuli. An arrhythmia was defined as occurring when more than 90% of the volumes exhibited activations exceeding the total number of stimuli delivered during the EPS protocol.

2.5. Calibration from ECG

Estimating cardiac tissue conductivity values remains a challenging task [10]. In this study, the conductivity tensor was calibrated based on ECG acquired during the EPS, following endocardial surface stimulation at the RV outflow tract. The use of ECG obtained after catheter stimulation is justified by the negligible influence of the Purkinje system in this particular scenario. By adopting this approach, we circumvent the complexities of modeling the Purkinje system at this initial stage [11], thereby streamlining the calibration process for the digital twin. Assuming a conductivity ratio of 10 [12], a binary search algorithm was employed to fine-tune the conductivity along the fiber direction, σ_l. This calibration process involved comparing the time required for electrical excitation to propagate across the entire biventricular mesh with the QRS duration measured from the patient's stimulated ECG. The real QRS measured for the patient was $176.49\ ms$, while the QRS obtained through the adjustment was $173.12\ ms$, with $\sigma_l = 4.8209375 \times 10^{-4}\ mS\ \mu m^{-1}$.

3. Results

Based on the model described in the previous section, the induction of ventricular arrhythmias in the patient was evaluated by implementing the electrophysiological study protocol. The average number of reentries cases obtained for each border zone thickness at different stimulation intervals, as well as the number of arrhythmias recorded during the patient's electrophysiological study (left, first column), are presented in Figure 2. Arrhythmias could not be induced for border zone thicknesses of $2\ mm$ and $4\ mm$. The number of arrhythmias observed in the simulations increased with the thickness of the BZ. This is expected, as large BZ volumes increase the regions of slow propagation and source-sink mismatch. Comparing the simulations with the patient's exam, our results suggest that the patient's BZ thickness is between 10 and 12 mm.

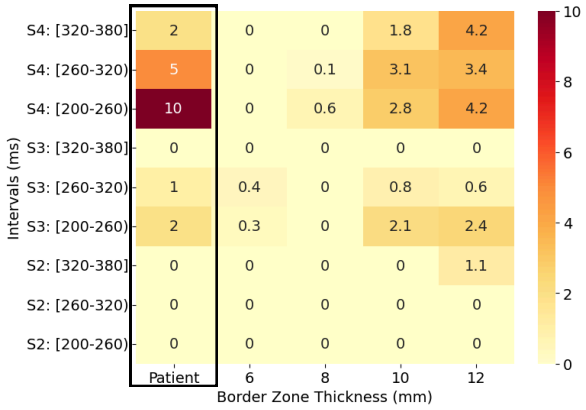


Figure 2. Average number of reentry cases predicted by the model vs. real patient cases, by border zone thickness.

Finally, Figure 1 (c) shows the formation of a reentrant circuit around the fibrotic region due to a unidirectional block.

4. Conclusion

In this work, a digital twin was developed for a patient with heart failure. The model was personalized using the patient's magnetic resonance imaging data and stimulated electrocardiograms acquired during the electrophysiological study. The resulting digital twin was then used to computationally reproduce the electrophysiological study protocol, a procedure traditionally performed invasively to stratify the risk of cardiac arrhythmias.

The patient in question presents extensive regions of myocardial fibrosis. However, the exact spatial pattern of this fibrosis cannot be fully resolved by current non-invasive imaging techniques. Nevertheless, as highlighted in our previous studies [13], these patterns can play a critical role in determining arrhythmic risk. To investigate this, we created 60 electrophysiological variants of a single cardiac digital twin by varying the thickness of the fibrotic border zone (BZ)—the transitional region between dense fibrotic tissue and healthy myocardium. For each selected thickness, ten distinct fibrotic patterns were randomly generated to explore microstructural variability within the BZ. Only the simulations incorporating thicker border zones were able to accurately reproduce the patient's arrhythmic events observed during the electrophysiological study.

The structural features observed in this patient challenge straightforward classification. Despite the presence

of systolic dysfunction, the ventricular walls are markedly thickened, and cardiac MRI revealed diffuse and extensive mid-myocardial fibrosis with a non-ischemic pattern. The simulated fibrosis configurations required to reproduce the patient's arrhythmic events mirrored this diffuse distribution and were consistent with patterns typically seen in infiltrative cardiomyopathies such as cardiac amyloidosis. These findings raise the possibility of an underlying infiltrative process, even in the absence of a definitive diagnosis. These insights highlight the potential of digital twin technology to uncover structural arrhythmic substrates not apparent through standard imaging techniques.

In the future, we plan to expand our cohort of patients with digital twins to further evaluate the potential of this technology in assessing the risk of cardiac arrhythmias.

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