In-silico Inducibility of Ventricular Tachycardia in Patient-Specific Post-Infarction Ventricular Models

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Abstract

After myocardial infarction, the evolution of the cardiac scar and the remodeling of the border zone play a critical role in the generation of life-threatening ventricular tachycardias. Three-dimensional and anatomically realistic biventricular models can help understand the mechanisms underlying reentrant arrhythmias in such circumstances.

In the present work, personalized models of infarcted hearts are built from late gadolinium enhancement cardiac magnetic resonance images. The electrical activity of these hearts is simulated under different remodeling scenarios of the scar border zone. After applying the same stimulation protocol applied by clinicians to the virtual heart of a patient presenting ventricular tachycardia (VT) and to a patient presenting no tachycardia, we could replicate the arrhythmogenic behavior of these hearts for specific conditions of structural remodeling of the border zone.

Our simulations reproduced realistic reentry patterns consistent with those obtained in the clinic, providing a better understanding of VT mechanisms.

1. Introduction

According to the World Health Organization (WHO), cardiovascular diseases are the leading cause of death worldwide, killing 17.9 million people in 2019 or 32% of all deaths recorded in the world. Of these deaths, 85% were due to heart attack and stroke [1]. The WHO highlights that early detection and treatment are essential for patients with these diseases or high cardiovascular risk (due to the presence of risk factors).

Among patients who have suffered a myocardial infarction, 10% of them have a high risk of death in the years following the infarction, with 50% of these deaths being caused by ventricular tachyarrhythmias [2].

This happens due to the arrhythmogenic nature of the remodeled tissue after the ischemic episode, once the healing process has finished and the myocardial infarction has reached its chronic stage [3]. This remodeled tissue, known as a myocardial scar, forms a substrate favoring the appearance of reentrant circuits.

Currently, late gadolinium enhancement cardiac magnetic resonance imaging (LGE-CMR) is the gold standard when it comes to characterizing ischemic lesions in vivo to plan possible interventions such as radiofrequency ablation, which aim to eliminate these possible reentrant circuits and reduce the risk of arrhythmias, fibrillation and, ultimately, death of the patient [3]. In the last decade, new methods based on computational simulations using personalized models offer a complementary vision of these mechanisms and their underlying causes, contributing to diagnosing and treating this type of pathology [3].

This paper addresses the analysis of the mechanisms responsible for the generation of ventricular arrhythmias after myocardial infarction. The electrophysiological changes in ventricular cells of an infarcted heart, especially in the border zone, can be summarized as a prolongation of the action potential duration and alterations in calcium dynamics [4]. These alterations in the cellular electrical activity are due to the functional remodeling of ion channels, electrogenic pumps, and ion exchangers. Regarding structural remodeling, one of the most important factors is the appearance of fibrosis, which is associated with an increased risk of arrhythmias. The presence of fibroblasts affects electrical impulse conduction as well as the electrical behavior of myocytes and their calcium dynamics [5, 6].

In the present work, we develop ventricular anatomically realistic models and try to induce reentrant activity to analyze the features of the scar and border zone responsible for these mechanisms. The pipeline described in this paper offers a powerful tool to help in diagnostic and therapeutic techniques.

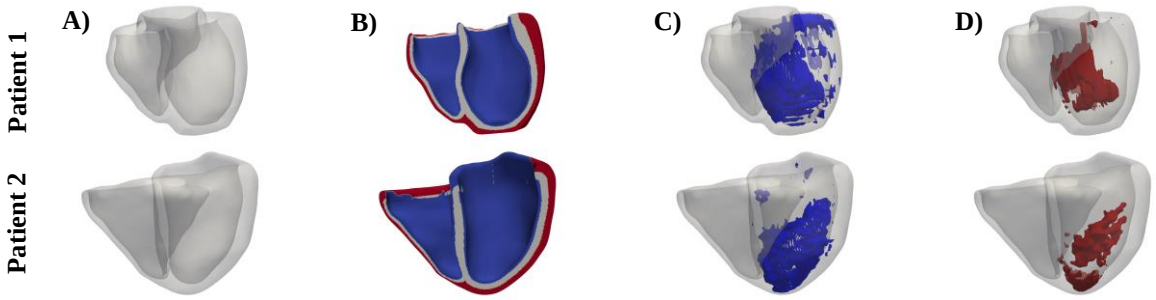

Figure 1. Personalized anatomical cardiac models of two patients. Top row: virtual patient presenting ventricular tachycardia (patient 1). Bottom row: virtual patient without clinical ventricular tachycardia (patient 2). (A) Anatomical volumetric mesh (B) Labeling of the endocardium, mid myocardium and epicardium regions in blue, gray, and red, respectively (C) Labeling of the border zone of the scar in blue (D) Labeling of the core of the scar in red.

2. Materials and Methods

2.1. Patient data

The construction of personalized models requires a dataset of high-resolution images and complete information about the anatomy and infarcted regions of the heart. LGE-CMR images have been provided by the Teknon medical centre (Barcelona) and correspond to two real patients who have suffered a myocardial infarction, whose data have been previously anonymized.

Specifically, the two acquisitions correspond, one to a patient who presented clinical ventricular tachycardia and the other to a patient who did not present arrhythmic activity. The acquisitions were made after the myocardial infarction episode, the border zone and the scar were considered as a zone of structural remodeling (see Figure 1).

To develop the mathematical model of both hearts, we performed the segmentation of the images of the ventricle of the areas of the myocardial scar, the core of the scar, and the border area subject to remodeling, which characterizes the substrate for arrhythmias.

2.2. Patient-specific model reconstruction

For the reconstruction of the personalized models, from the acquired LGE-CMR images, we performed the segmentation of the structures of interest (ventricle anatomy, border zone and scar, shown in Figure 1), and then a 3D volume was generated using Seg3D software. In addition, an exhaustive smoothing of the volume was performed, and a three-dimensional mesh shaped by hexahedral elements with a spatial resolution of 0.4 mm was generated. Once the fully meshed volume was available, the different regions and structures of the heart were labelled: the right ventricle (RV), left ventricle (LV) and septum regions, the scar core labels and the border zone. The endocardium, mid-myocardium, and epicardium regions were labelled based on cardiac wall thickness at 17%, 41%, and 42%, respectively [3]. The labeled and meshed volumes were then used in the ELVIRA simulation software, which was solved by a modified version of O'Hara et al. (2011) model of human ventricle cells at the different nodes of the mesh [7, 8]. The scar region was considered non-conductive tissue. The border zone, affected by a remodeling process, was remodeled by reducing the longitudinal and transverse conductivity parameters to 50% of their value in healthy tissue, which implies a reduction in conduction velocity that varies depending on the direction of the fibre and the region of the myocardium.

Furthermore, to simulate the electrophysiological behavior of fibroblasts present in the border zone, we used the MacCannell et al. (2007) model [6] combined with the modified O'Hara myocyte model [7]. Different percentages of fibroblasts were introduced in the border zone (10%-80%) using a probabilistic function to randomly assign the nodes with the MacCannell et al. (2007) fibroblast electrical model. Coupling between myocyte and fibroblast was reduced by decreasing the diffusion coefficient by 50% [5]. Based on previous studies, electrophysiological remodeling was applied to the ventricular myocytes present in the border zone. We adapted ionic changes previously done in other ionic models, to modify O'Hara et al. (2011) model to achieve the experimental ranges in action potential changes [7]. These changes can be summarized as follows: I_{Na} was reduced to 38% of its normal value, I_{CaL} to 23%, and I_{Kr} and I_{Ks} to 80% and 70%, respectively [9]. These changes led to a 17% increase in action potential duration, a 44.9% decrease in depolarization velocity, and a 42.35% reduction in maximum potential, which is consistent with experimental observations of myocardial myocytes in the infarction border zone.

2.3. Conduction channels

Conduction channels are defined as continuous border zone corridors that are surrounded by scar tissue or an anatomical barrier and connect two areas of healthy tissue. The study of these channels has been shown to improve the accuracy of cardiac ablation procedures to prevent the appearance of arrhythmias since conduction channels represent an area favoring reentrant circuits. The characterization of the total mass of conduction channels can indicate the probability of ventricular tachycardia occurrence. Figure 2 shows the conduction channels obtained for patient 1, who suffered arrhythmias. Conduction channels were obtained automatically by the ADAS-VT software [10].

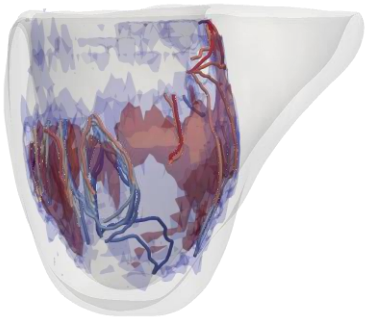

Figure 2. Patient 1 - specific model with scar labels and segmentation of conduction channels

2.4. Stimulation protocol

One of the necessary conditions to trigger an arrhythmia is the application or appearance of premature stimulation. The anatomically realistic models of the ventricles with the scar and the border zone are the ideal substrate to nest a reentry if premature stimulation is applied within the vulnerable time window.

The following protocol was applied to simulate the appearance of early stimuli, mimicking the protocol applied by clinicians to induce ventricular tachycardia in vivo, applying several stimuli always at the same site, the apex of the right ventricle. A 6 stimuli train (S1-S6) with a basic cycle length of 430 ms was initially applied. After this, up to three early stimuli (E1-E3) were applied. Each new extra stimulus was applied 300 ms after the previous stimulus (basal or extra) and this 300 ms interval was reduced in steps of 10 ms until reaching the refractory period of the stimulated zone for which the stimulus did not propagate. If the stimulus was applied earlier until reaching the refractory period (the stimulation did not propagate), the extra stimulus was fixed at 20 ms after the last time instant before the refractory period, and the process was repeated with a new extra stimulus until a reentry occurred.

3. Results

The stimulation protocol described above was repeated in both anatomical models corresponding to patient 1 and patient 2 for different model versions of the border zone. In the first scenario, the border zone was simply modeled by a reduction in conductivity (50%). In the following scenarios, we added a specific percentage of fibroblasts from 10% to 80%. Finally, in the tenth scenario, the border zone had ionic remodeling, reduced conductivity in the tissue and no fibrosis.

Simulation performance	Patient 1	Patient 2
0% fibroblasts	Non-VT	Non-VT
10% fibroblasts	Non-VT	Non-VT
20% fibroblasts	Non-VT	Non-VT
30% fibroblasts	Non-VT	Non-VT
40% fibroblasts	Non-VT	Non-VT
50% fibroblasts	Non-VT	Non-VT
60% fibroblasts	Non-VT	Non-VT
70% fibroblasts	VT	Non-VT
80% fibroblasts	VT	Non-VT
Ionic remodeling	Non-VT	Non-VT

Table 1. The outcome of the simulations for different settings of fibroblast density. VT means persistent ventricular tachycardia was observed; non-VT means that the stimulation protocol finished without tachycardia.

As can be seen in Table 1, in the case of patient 1, who presented ventricular tachycardia in the clinic, the induced arrhythmia only appeared when 70% of fibrolasts or more were considered in the border zone. In the model considering ionic remodeling alone, no reentry was generated without the addition of fibroblasts. Moreover, the site through which the reentry travelled matches one of the conduction channels identified, as can be seen in Figure 3. On the other hand, the patient who did not present ventricular tachycardia in the clinic did not present either VT in any of the performed simulations, regardless of the amount of fibrosis.

Figure 3 shows the temporal evolution of action potential propagation after an early stimulus from the stimulation protocol. It can be seen how the stimulus propagates normally and extinguishes, but 600 ms after the stimulation, the area corresponding to the conduction channel is still activated. The delay in the conduction channel ends up causing the exit of excitation from the septum wall towards the right ventricle.

The impulse propagates through the entire ventricle again and, when it reaches the conduction channel, the propagation is delayed again and causes a reentry, which results in persistent tachycardia.

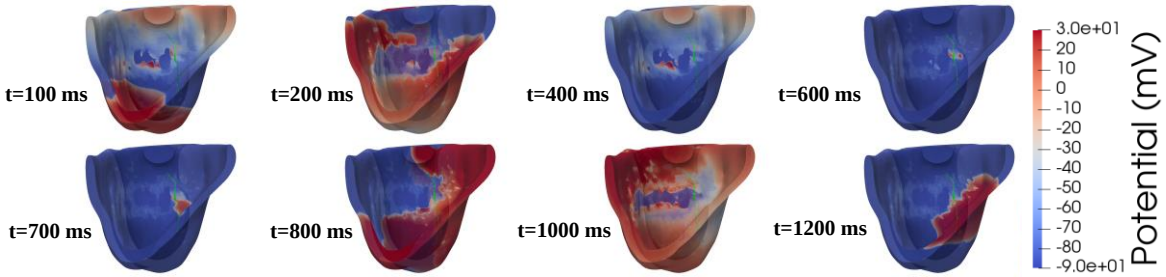

Figure 3. Time evolution of the cardiac action potential. The time instants correspond to the time elapsed since the application of the early impulse.

4. Discussion and conclusion

The features of cardiac scar after a heart attack are crucial factors determining the development or not of ventricular tachycardia. In this work we have developed different ventricular models for two different patients who have suffered a myocardial infarction, to analyze the characteristics of the scar leading to ventricular tachycardia.

The novelty of this research lies in the use of personalized tools with a high level of detail in the model building and characterization of the remodeling of the border zone. These models accurately predict the occurrence of reentry, for which the coincidence of the induced reentry in patient 1 with the segmented conduction channel has been verified. According to the simulation outcomes for both patients, the density of fibroblasts in the model plays a crucial role in the appearance of reentry.

Further investigations are needed to increase the number of cases and scenarios, which will allow us to characterize and understand the role of structural and electrophysiological remodeling in the generation of VT after myocardial infarction.

Acknowledgments

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References

[1] Who.int. 2022. Cardiovascular diseases (CVDs). [online] Available at: <https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)> [Accessed 18 March 2022].

[2] Bhar-Amato, J., Davies, W. and Agarwal, S., Ventricular Arrhythmia after Acute Myocardial Infarction: ‘The Perfect Storm’. Arrhythmia & Electrophysiology Review, 6(3), p.134. Aug 2017

[3] Lopez-Perez, A., Sebastian, R., Izquierdo, M., Ruiz, R., Bishop, M. and Ferrero, J., Personalized Cardiac Computational Models: From Clinical Data to Simulation of Infarct-Related Ventricular Tachycardia. Frontiers in Physiology, 10. May 2019.

[4] Decker, K. and Rudy, Y. Ionic Mechanisms of Electrophysiological Heterogeneity and Conduction Block in the Infarct Border Zone. American Journal of Physiology-Heart and Circulatory Physiology, 299(5), pp.H1588-H1597. Nov 2010.

[5] Gomez, J., Cardona, K., Romero, L., Ferrero, J. and Trenor, B. Electrophysiological and Structural Remodeling in Heart Failure Modulate Arrhythmogenesis. 1D Simulation Study. PLoS ONE, 9(9), p.e106602. Sep 2014.

[6] MacCannell, K., Bazzazi, H., Chilton, L., Shibukawa, Y., Clark, R. and Giles, W. A Mathematical Model of Electrotonic Interactions between Ventricular Myocytes and Fibroblasts. Biophysical Journal, 92(11), pp.4121-4132. Feb 2007.

[7] O'Hara, T., Virág, L., Varró, A. and Rudy, Y. Simulation of the Undiseased Human Cardiac Ventricular Action Potential: Model Formulation and Experimental Validation. PLoS Computational Biology, 7(5), p.e1002061. May 2011.

[8] Dutta S, Mincholé A, Quinn TA, Rodriguez B. Electrophysiological Properties of Computational Human Ventricular Cell Action Potential Models under Acute Ischemic Conditions. Prog Biophys Mol Biol. Feb 2017.

[9] Mendonca Costa C, Plank G, Rinaldi CA, Niederer SA, Bishop MJ. Modeling the Electrophysiological Properties of the Infarct Border Zone. Front Physiol. 9;9:356. Apr 2018.

[10] Soto-Iglesias, D., Penela, D., Jáuregui, B., Acosta, J., Fernández-Armenta, J., Linhart, M., Zucchelli, G., Syrovnev, V., Zaraket, F., Terés, C., Perea, R., Prat-González, S., Doltra, A., Ortiz-Pérez, J., Bosch, X., Camara, O. and Berruezo, A. Cardiac Magnetic Resonance-Guided Ventricular Tachycardia Substrate Ablation. JACC: Clinical Electrophysiology, 6(4), pp.436-447. Apr 2020.

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