Personalized Modeling Pipeline for Cardiac Electrophysiology Simulations of Cardiac Resynchronization Therapy in Infarct Patients

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Abstract

Cardiac Resynchronization Therapy (CRT) is associated with increased arrhythmogenic risk in infarct patients when pacing adjacent to a scar. We investigated the role of pacing location relative to scar on dispersion of repolarization, as a surrogate for arrhythmogenic risk. For this task, we developed a personalization and simulation pipeline that allows fast development of personalized computational models and simulation of cardiac electrophysiology. Twenty four models of left ventricular anatomy and scar morphology were built and repolarization sequences were simulated. Simulation results show that CRT increases dispersion of repolarization around a scar when pacing adjacent to it, thus, providing a mechanistic explanation of increased arrhythmogenic risk in infarct patients undergoing CRT.

1. Introduction

Cardiac Resynchronization Therapy (CRT) is an effective treatment for heart failure. However, there is evidence that CRT is arrhythmogenic in infarct patients. Particularly, pacing adjacent to a scar is associated with increased risk of ventricular tachycardia (VT) [1]. However, the underlying mechanisms of increased VT risk are not known.

CRT alters the heart's activation and repolarization sequences and it has been associated with increased dispersion of repolarization, a known risk factor for re-entry [2]. Thus, we hypothesize that CRT increases dispersion of repolarization in infarct patients when pacing adjacent to a scar, which explains their increased VT risk.

Investigating the role of pacing location during CRT on VT risk in the clinical setting is hampered by the anatomy of the coronary sinus, which limits where CRT pacing leads can be implanted. Computational models provide full flexibility, thus, allowing a detailed and systematic investigation of the role of pacing location. However, building clinically relevant models, that include realistic anatomy and scar morphology, and simulating cardiac electrophysiology (EP) at clinical time-scales remains a challenging task. Therefore, we developed a personalization pipeline, which allows fast development of infarct model cohorts and EP simulations.

The developed pipeline was used to build 24 personalized models of left ventricular anatomy and scar morphology, which were then used to investigate the role of pacing location on dispersion of repolarization, as a surrogate for VT risk. Our simulation results show that pacing adjacent to a scar increases dispersion of repolarization in its vicinity, which provides a mechanistic explanation for increased VT risk in CRT patients with infarct.

2. Methods

2.1. Patient cohort

Twenty four patients with ischemic heart failure undergoing CRT were included in our study. Details on patient characteristics can be found in [3].

Cardiac magnetic resonance imaging was performed using a 1.5-T scanner with a 32-channel coil (Philips Healthcare, Best, The Netherlands). A stack of short-axis slices was acquired $10 - 15$ minutes after contrast injection (gadobutrol 0.2 mmol/kg body weight) for late gadolinium enhancement magnetic resonance imaging (LGE-MRI). Further details on the imaging protocols can be found in [3]. In-plane resolution varied from 0.6×0.6 mm to 1.37×1.37 mm. Slice thickness varied from 8 to 20 mm.

2.2. Construction of personalized anatomical models

We developed a pipeline for fast construction of personalized anatomical models. The methods used are described

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in the following sub-sections. A schematic of the pipeline is shown in Figure 1.

2.2.1. Image segmentation and processing

Left ventricular (LV) endocardium and epicardium contours were manually drawn in each short-axis slice using the image segmentation software Eidolon [4]. The infarct scar and border zone (BZ) were segmented as the regions with signal intensity above 3 and 2 standard deviations from the mean signal intensity within healthy myocardium, respectively, as described previously [3]. The 2D scar and BZ segmentations were reconstructed in 3D using a statistical method for shape reconstruction based on the logarithm of odds function, as described previously [5].

2.2.2. Model generation

A finite element mesh of tetrahedral elements was generated by interpolating the LV endocardium and epicardium contours using Eidolon [4]. This mesh was then refined using the C-GAL library [6] to achieve a mean edge length of 0.8 mm. The 3D reconstructed scar and BZ segmentations were mapped onto the tetrahedral mesh and used to label mesh elements as scar, BZ, and healthy tissue. Fiber orientations were assigned to each anatomical model using a Laplace-Dirichlet rule-based algorithm [7].

2.3. Simulation setup

We performed simulations of cardiac EP using our models of personalized anatomy and the Cardiac Arrhythmia Research Package (CARP) [8, 9] to investigate the role of LV epicardial pacing location relative to scar in dispersion of repolarization. The mathematical model and parameters used, pacing locations, and computed metrics are described in the following sections.

2.3.1. Electrophysiology models

Propagation of cardiac action potentials was simulated using a Reaction-Eikonal model [10], which allows the use of coarser spatial resolutions than the cardiac monodomain model, thus, reducing computational cost. This model was coupled with the Ten Tusscher model for the action potential of human ventricular cells [11]. No difference in ionic currents between endocardium and epicardium cells was considered in this study.

2.3.2. Model parameters

Transversely isotropic conduction velocities of 0.67 and 0.3 m/s in the longitudinal and transverse directions, respectively, were assigned to healthy tissue. The BZ was assigned isotropic conduction velocity of 0.15 m/s, corresponding to 50% of the transverse velocity in healthy tissue, according to experimentally measured values [12, 13]. The scar core was modeled as unexcitable non-conducting tissue, assuming it consists of predominantly collagenous non-conducting material [14].

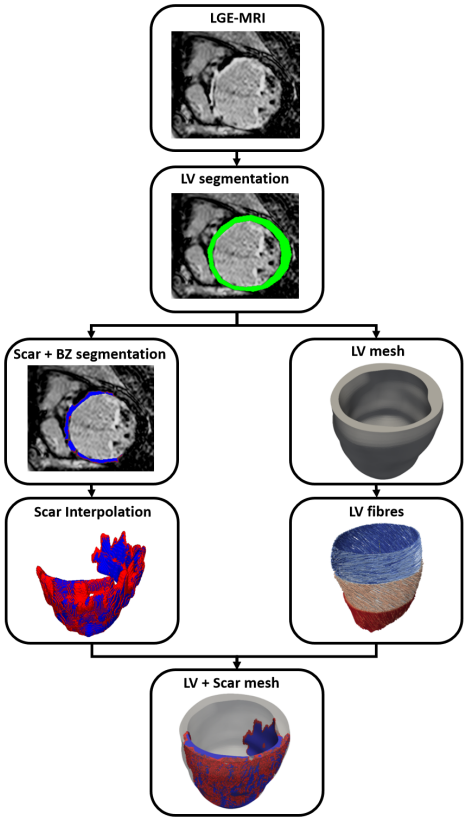

Figure 1. Pipeline for construction of models of personalized anatomy. From left to right: the left ventricular (LV) wall is manually segmented; the scar and border zone (BZ) thresholded; an LV tetrahedral mesh is generated and rule-based fibers are assigned; the 2D scar and BZ segmentations are interpolated to 3D and merged with the tetrahedral mesh to label mesh elements as healthy, scar, and BZ.

2.3.3. Pacing locations

Pacing locations at 0.5 and 4.5 cm from the scar surface were chosen for each model. Distances from scar were computed using eikonal-based activation maps [10], where activation was initiated at all vertices on the scar surface and the core of scar was set as non-conducting. The conduction velocity was set to 1 m/s, thus giving activation time equal distance.

2.3.4. Repolarization sequences and metrics

One paced beat was simulated for 1 second. Repolarization times were computed as the instant where the transmembrane voltage reached a threshold of -70 ms following activation. Local dispersion of repolarization was computed as the magnitude of the repolarization gradient at each mesh point.

Experimental [15] and simulation [16] studies have demonstrated that a repolarization gradient of 3 ms/mm can lead to uni-directional block, a pre-requisite for re-entry inducibility. Assuming that the larger the volume of tissue with high gradients, the higher the probabity of uni-directional block, we computed the volume of high repolarization gradients (HRG), which are above 3 ms/mm, as a metric of dispersion of repolarization and a surrogate for VT risk.

3. Results

3.1. Personalized anatomical models

Two examples of the resulting 24 LV models are shown in Figure 2. Healthy tissue is shown in gray, whereas scar core and BZ are shown in blue and red, respectively. Each model was generated on a desktop workstation with 6 cores and 64GB of RAM in less than 2 hours.

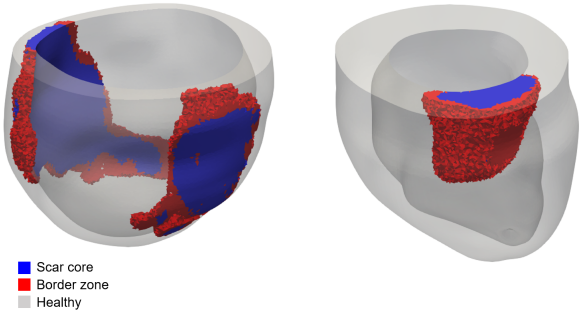

Figure 2. Personalized models of left ventricular anatomy and scar morphology. Healthy tissue is displayed in gray, scar core in blue, and border zone in red.

3.2. Effect of pacing location on repolarization

Repolarization sequences where simulated for each model in $\approx$ 14 minutes using 32 cores of a large shared memory system consisting of 640 cores and 5TB of RAM.

An example of the spatial distribution of repolarization gradients within the LV is shown in Figure 3-A). High repolarization gradients (HRG) appear in the border zone and around the LV lead. The volume of HRG around the scar is larger when pacing near instead of away from it. A boxplot of the volumes of HRG (1 cm) around the scar when pacing 0.5 and 4.5 cm from the scar for all models are shown in Figure 3-B). The volumes are significantly (P $<$ 0.000001) larger when pacing near the scar than away from it.

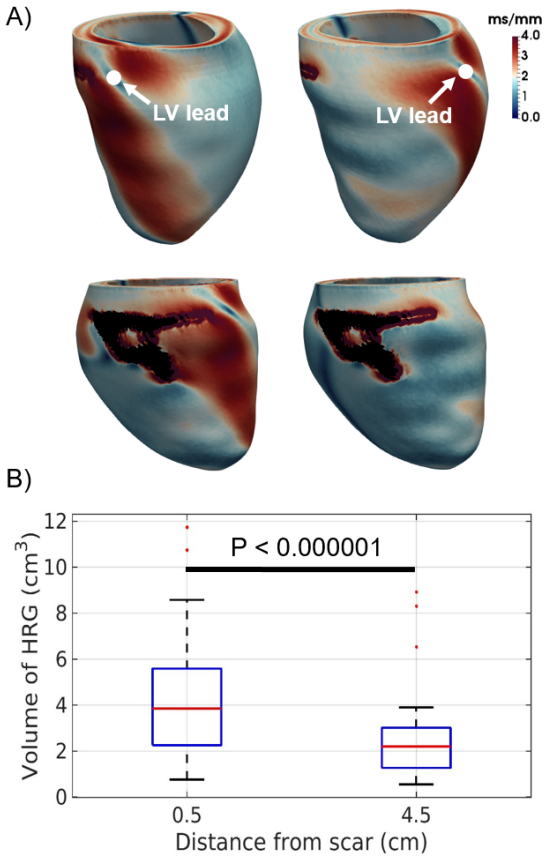

Figure 3. A) Spatial distribution of repolarization gradients when pacing 0.5 cm (left panes) and 4.5 cm from scar (right panes). B) Comparison between the volume of high repolarization gradients (HRG) around the scar when pacing 0.5 and 4.5 cm from the scar.

4. Discussion

The personalization pipeline developed in this study allows fast development of model cohorts while employing the Reaction-Eikonal model allows running EP simulations at a time-scale compatible with the clinical setting, thus, facilitating clinical translation of computational modeling.

Re-entrant arrhythmias in patients with infarct typically originate at the scar, particularly at the BZ, where ectopic foci are more likely to occur [17]. The high repolarization gradients observed around the scar when pacing adjacent

to it, as shown by our simulations, may be sufficient to cause uni-directional conduction block of a nearby ectopic focus and lead to re-entry [2, 18]. Thus, increased volume of high repolarization gradients around a scar when pacing adjacent to it provides a plausible mechanistic explanation for increased VT risk in infarct patients undergoing CRT and suggests that pacing away from a scar may mitigate VT risk in these patients.

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