The Effect of Scar Tissue on Complexity of Activation Patterns in Simulated Human Ventricular Fibrillation

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Abstract

Ventricular Fibrillation (VF) is a severe cardiac arrhythmia. Early experiments provided evidence that the mechanism of VF is consistent with re-entry. In 3D the sources of re-entrant waves are lines of phase singularity called filaments. Filament interactions and filament numbers can be used to quantify the complexity of activation patterns in simulated VF. In this study we investigated how filament dynamics are affected by the presence of uniform and non-uniform simulated scars using computational models. A half ellipsoid representing an idealized human left ventricle with similar apex base dimension and wall thickness was used in the present study. The region of simulated scar was either uniform or contained a random mixture of excitable and inexcitable tissue. Increasing the radius of uniform scar increased the number of filaments compared to non-uniform scar. The size and the configuration of scar influenced the filament shape and numbers. Overall the uniform scar had more effect on filament dynamics compared to the non-uniform scar.

1. Introduction

When the normal electrical activation of the heart is blocked the activation wave can curl and rotate to continuously activate recovering tissue. These re-entrant waves are observed as spiral waves in 2D and scroll waves in 3D. Ventricular fibrillation (VF) is a severe form of arrhythmia in which electrical activation is sustained by re-entry [1]. In 3D, scroll waves rotate around a linear core called a filament. The number of re-entrant filaments quantifies the complexity of VF. Understanding filament dynamics gives an insight into the mechanisms that act to sustain VF.

Pre-existing scar tissue in VF patients can act to pin re-entrant filaments [2, 3], however the influence of scar regions on filament dynamics is not well understood. The scar region used in previous studies had smooth cylindrical edges, whilst in real tissue the region of scar has irregular edges as well as a border zone where the region of scar interlocks with regions of normal tissue. The aim of this study was therefore to use a computational model of human cardiac tissue electrophysiology to compare how simulated uniform and non-uniform scar influence the dynamics of re-entrant filaments.

2. Methods

2.1. Cell model

A simplified model of the human ventricular action potential [4] was used. This phenomenological model was chosen because it reproduces the action potential shape, action potential duration (APD) and rate dependence of APD. These are compatible with ionic models based on more detailed formulations and also with experimental studies. An important advantage of the phenomenological model is that it is much less time consuming to solve compared with detailed ionic models [5].

Two variants of the epicardial cell model were used, based on the parameters in the original paper [2]. The first variant (epiMod1) supported unstable re-entry, but had relatively flat action potential duration (APD) restitution. The second variant (epiMod2) had steeper APD restitution resulting in more unstable re-entry. For the variant epiMod1 the parameter τ_{v1} was changed from 60.0 to 10.0, and τ_{v2} was changed from 1150.0 to 20.0. In epiMod2, τ_{v1} and τ_{v2} were changed as for epiMod1, and in addition τ_{so1} was changed from 30.0181 to 28.0, and τ_{s2} from 16.0 to 40.0.

2.2. Tissue model and numerical method

We used a monodomain tissue model [5] with anisotropic diffusion. The diffusion coefficients were 0.001 cm^2ms^{-1} along fibres and 0.00025 cm^2ms^{-1} across fibres. The membrane capacitance was set to 1 μFcm^{-2}. The model was solved using an explicit finite difference method with no- flux boundary conditions imposed. The time step to solve the model was 0.005 ms and the space step 0.02 cm.

The left ventricle was represented by a half ellipsoid (base-apex 9.0 cm, wall thickness 1.1 cm) with uniform epicardial cells and incorporating the orientation of fibres, with 120° rotation between endocardial and epicardial surfaces. A simulated scar region was incorporated in geometry as described below.

Re-entry was initiated by imposing a single scroll wave on the tissue with the initial filament at the apex. Filaments were detected and recorded using phase analysis throughout simulations of 2000 ms. The membrane voltage was converted to phase using the time delay embedded method with a time delay of 2 ms. Voxels containing filaments were identified using convolution kernels and individual filaments were tagged using a grass fire algorithm. Individual filaments were counted and the number of voxels that made up the single filament were counted to estimate the length of each filament [6, 7].

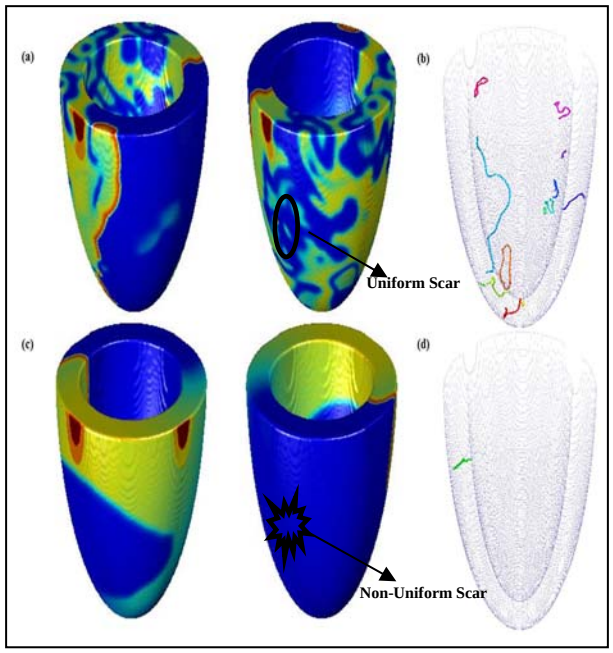

Figure 1. Snapshots of re-entry and corresponding filaments in (a) ellipsoid with epiMod2 dynamics 1996 ms after initiation with half depth increased radius uniform scar, views of front and back, (b) corresponding filaments, (c) ellipsoid with epiMod2 dynamics 1996 ms after initiation with increased radius non-uniform scar, views of front and back, (d) corresponding filaments.

2.3. Scar region

Scar was represented by a cylindrical region of inexcitable but diffusively coupled tissue with a radius of either 20 or 30 mm and extending either through the full width of the tissue or half way through. The region of scar was either uniform or non-uniform located in the middle of the wall as shown in Figure 1. To model the non-uniform cylindrical scar region, random numbers were used to get a mixture of 50 % excitable and 50 % inexcitable tissue.

3. Results

In each simulation the initial re-entrant wave broke up to form complex patterns of activity typical of VF. The number of filaments plotted against time for each simulation using epiMod1 and epiMod2 dynamics is shown in Figure 2(a) and (d). To obtain a clearer picture of the number of filaments, a moving average was calculated using rectangular window extending ±50ms from each time sample and plotted as shown in Figure 2(b) and (e). Overall, the presence of scar resulted in a small increase in the number of filaments (20 %). An increased radius of half depth uniform scar resulted in a higher number of filaments as shown in Figure 2(b) and (e).

When the filament touched both epicardium and endocardium it was considered as a transmural filament. If both ends of filament touched either epicardium or endocardium, it was considered as a U shaped filament. If the filament did not touch any surface it was considered as a ring filament [7]. The configuration of scar had an influence on the configuration of filaments. Increasing the radius in uniform full depth scar resulted in more transmural filaments whereas in half depth scar resulted in more U shaped filaments. Increasing the radius of non-uniform scar resulted in comparatively more ring filaments as shown in Figure 3(a) and (d).

We examined the lifetime of the initial filament in each simulation. During the course of time, the initial filament can divide in to multiple filaments or amalgamate with another filament to form one new filament or move towards the boundary and die. This was traced throughout each simulation by taking the overlap of filaments from two successive time steps [7]. Life time of a filament was calculated by the difference between the time of birth and time of death of a filament. When the initial filament amalgamated or divided into new filaments, the initial filament gene is passed into the new filament. This was traced throughout the simulation to find when the initial filament completely disappeared. The lifetime of initial filament was longest in increased radius half depth uniform scar. With epiMod2 dynamics, the initial filament was present until 2000 ms as shown in Figure 3(b) and (e). The filament with the longest lifetime of 2000 ms was seen in the increased radius half depth uniform scar as shown in Figure 3(c) and (f).

4. Discussion and conclusions

In this study, we have used a computational model of human cells and idealized left ventricle tissue to examine how re-entrant activity during simulated VF is modified by the presence of uniform and non-uniform scar. The results show that increasing the size of uniform scar has more effect on filament dynamics than non-uniform scar region.

This study has several limitations resulting from our simplified model of structure and function. We used a simplified model of idealized left ventricle.

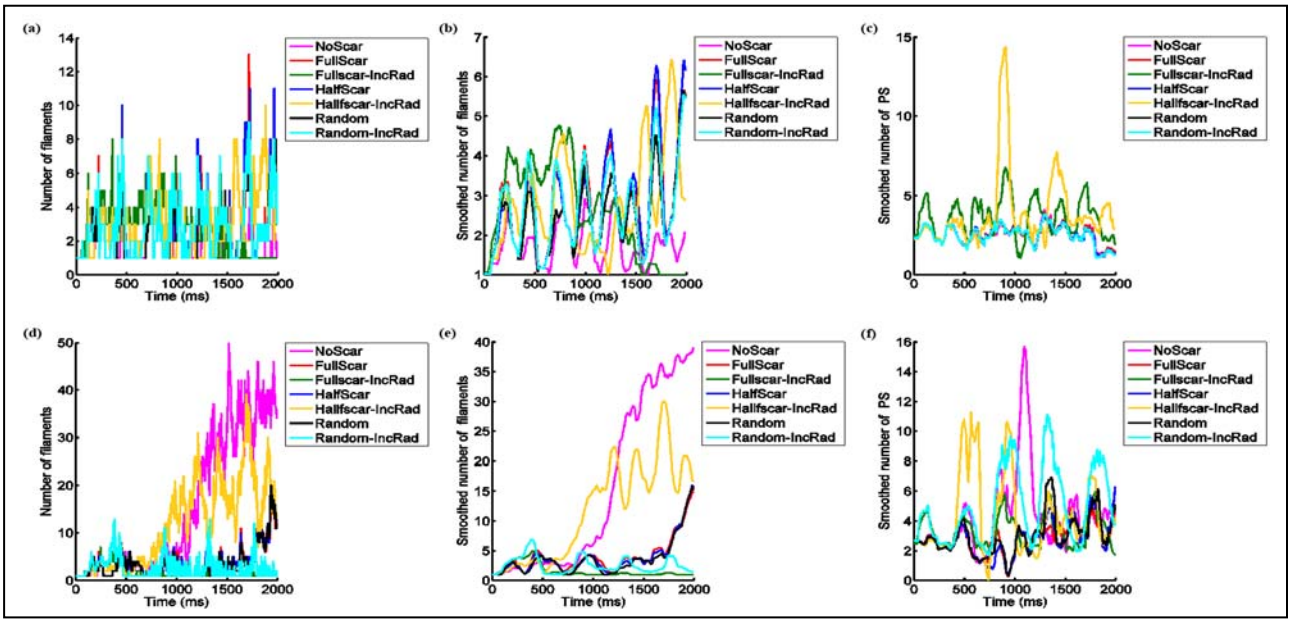

Figure 2. (a) and (d) Change in number of filaments over time,(b) and (e) smoothed number of filaments, (c) and (f) change in epicardial PS over time (ms). Results for epiMod1 (top row) and epiMod2 dynamics (bottom row).

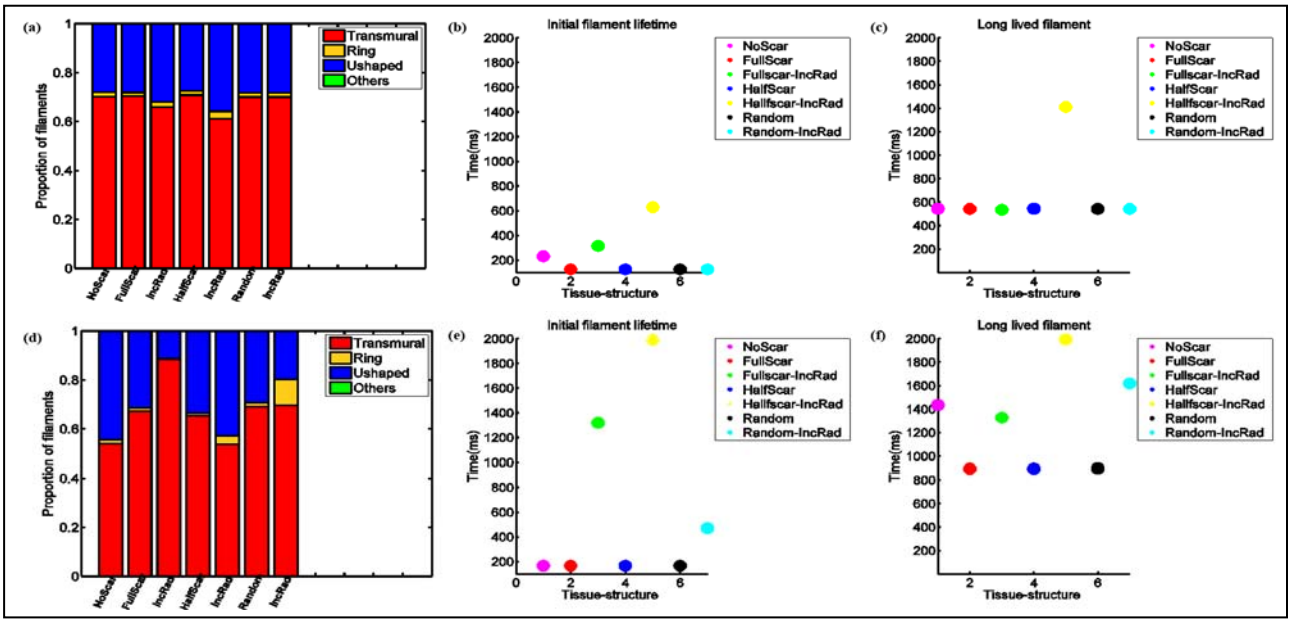

Figure 3. (a) and (d) configuration of filaments, (b) and (e) lifetime of initial filament before death or division, (c) and (f) long lived filaments. Results for epiMod1 (top row) and epiMod2 dynamics (bottom row).

Further studies will examine the effect of uniform and non-uniform scar region in idealized geometry incorporating left and right ventricles.

It is difficult to observe 3D arrhythmia mechanisms experimentally and only phase singularities (PS) can easily be observed as the intersection of the filament with the surface of the tissue.

The surface area of the idealized left ventricular geometry used in this study was roughly around 18000 mm^2. If the human heart is considered as an ellipsoid with a diameter at base of 80 mm and a base to apex distance of 100 mm, the surface area is roughly around 21000 mm^2 which is around 1.2 times the surface area of idealized left ventricle used in this study. Experimental studies [8, 9] have reported to observe median number of 8 epicardial phase singularities. This can be linearly scaled to around 6.7 epicardial PS. But in the epiMod1 dynamics with no scar (Figure 2e), the PS observed was around 4.9. This can be justified by using simplified idealized left ventricle.

Fibre orientation in and around the region of scar was not varied in the simulations whereas in the actual cardiac tissue, the fibre orientation might restructure during the formation of myocardial scar region [10].

Despite these limitations, we have managed to compare the influence of simulated region of scar with regular and irregular edges on re-entrant filaments during VF which is hard to observe experimentally.

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