A Method for Incorporating Changes in Extracellular Volume and Myocyte Size into the Cardiac Bidomain Equations

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Abstract

This study aims to develop a robust approach for integrating simultaneous changes in extracellular volume (ECV) and myocyte size into the cardiac bidomain equations. We developed a straightforward method for scaling conduction velocity (CV) in cardiac tissue as a function of ECV and myocyte radius (r). Simulations of apical pacing were performed in a computational model of human ventricular epicardium under control conditions (r=10.6 μm) and in myocyte hypertrophy (r=15.45 μm), and for three different ECV levels (21.5, 25 and 30%) that correspond to values reported in healthy and diseased hearts. Increasing ECV shortened total activation time (faster CV) under both control and hypertrophic conditions (control: 200, 189 and 178 ms; myocyte hypertrophy: 162, 154 and 145 ms; values for ECV of 21.5, 25 and 30, respectively). Increasing r to the myocyte hypertrophy state also shortened total activation time on average by 23%. These findings demonstrate that changes in both ECV and cell radius noticeably alter ventricular conduction. Future work will expand the method to include diffuse fibrosis and to match QRS durations in patient-specific hearts with normal and hypertrophic geometries.

1. Introduction

Extracellular volume (ECV) represents the percentage of extracellular space within a volume of myocardium. It is derived from magnetic resonance imaging (MRI) by combining pre- and post-contrast T1 mapping [1]. In clinical practice, ECV is used to describe changes occuring in the extracellular matrix that are caused by certain diseases and surgical treatments [2]. An increase in ECV from normal levels indicates either an expansion of the extracellular space from increased fibrotic content or edema, or from an increase in the ratio of extracellular to intracellular space within the myocardium resulting from a decrease in cell size [2]. Therefore, ECV and cell size should be studied simultaenously to better understand changes in ECV.

Changes in ECV from either an expansion of the extracellular space or from changes in cell size can alter cardiac electrophysiology. Specifically, they can modify the speed and shape of electrical waves propagating within the heart [3]. Integrating these effects into computer models of cardiac electrophysiology is therefore essential for replicating electrical conduction in patients with altered ECV. This study aims to formulate a robust approach for including changes in ECV measurements and cell size into the cardiac bidomain equations, and to determine their importance on the electrical activation of the human ventricles.

To achieve this goal, information on ECV and cell size were gathered from available literature on aortic stenosis (AS) patients. AS patients were used because they exhibit changes in both extracellular matrix and cell size [2]. We then scaled conduction velocity (CV) in the bidomain equation proportionally to simultaneous changes in ECV and cell size. Lastly, total activation time and CV were compared between computer simulations of left ventricular (LV) apical pacing in a finite element model of human ventricular epicardium with the ECV and cell size values obtained from healthy volunteers and AS patients.

2. Methods

2.1. Modifications to the Bidomain Equations

Within an arbitrary volume of ventricular myocardium (Figure 1A), we assume cardiac cells to be cylindrical and in parallel with a radius r and extracellular spacing s. For a fixed volume taken from the myocardium (Figure 1B)

containing the area of a single cylinder, it either expands or contracts with respect to changes in r and s. This in turn alters CV, which for the bidomain equations is proportional to

$$CV \propto \sqrt{\frac{\sigma_i \sigma_e}{(\sigma_i + \sigma_e)} \cdot \frac{1}{\beta}}, \quad (1)$$

where σ are the homogenized bidomain conductivities (S/m) of the intracellular (i) and extracellular (e) domains defined over the entire volume, and β (1/μm) is the ratio of membrane area to tissue volume. The equations for each can be rewritten in the following forms to take into account simultaneous changes in r and s. First, β becomes

$$\beta = f_i * \frac{2}{r}, \quad (2)$$

where the parameter f_i is the fraction of intracellular volume within the myocardium that can be written as

$$f_i = \frac{\pi r^2}{(2r+s)^2}. \quad (3)$$

Note, f_i is equal to $1 - f_e$ and f_e is $\propto$ECV measurements obtained from MRI.

When the radius (r) and/or spacing between cells (s) change within the myocardium, f_i and f_e also change, which in turn alters the intracellular (i) and extracellular (e) bidomain conductivities of the myocardium (σ_x), defined as

$$\sigma_x = f_x g_x, x \in \{i, e\}. \quad (4)$$

The g_x is a constant corresponding to the intrinsic conductivity of the corresponding domain in x. To account for changes in CV from an original state with r, s, and f_x to a new state with r', s', f'_x, the new homogenized bidomain intracellular and extracellular conductivities σ'_x are determined by scaling the original bidomain conductivities σ_x by S_x, defined as

$$S_x = \frac{\sigma'_x}{\sigma_x} = \frac{f'_x g_x}{f_x g_x} = \frac{f'_x}{f_x}. \quad (5)$$

Therefore, for an original set of predetermined bidomain conductivities (σ_x), the new conductivities are σ'_x=$\sigma_x S_x$. For this study, we used σ_x from a previous study that corresponded to healthy human ventricular tissue [4] with r=10.6 μm, β=0.14 μm^{-1}, and f_i=0.742.

Lastly, since the f'_x, and r' are known from studies in AS patients (see next section), the s' can be solved for by rewriting equation 3 and using the quadratic formula

$$s'^2 + 4r's' + \left(4r'^2 - \frac{\pi r'^2}{f'_i}\right) = 0. \quad (6)$$

This is done in order to determine how changes in both r' and s' contribute to changes in ECV and CV. It is worth noting that for equation 3, the maximal f'_i occurs for s'=0 and is therefore equal to $\pi/4 \approx 0.785$. Thus, the minimum f'_e is then equal to $1 - f'_i = 0.215$, corresponding to an ECV of 21.5%.

2.2. Patient data

Data from previously published clinical studies were used as input for our computer simulations. The study by Krayenbuehl et al. reports the radius of cardiac myocytes to be 10.6 μm in healthy donor hearts and 15.45 μm in AS patients [5]. MRI studies report average ECV values ranging from 26.5% in healthy volunteers [1] to 29.9% in AS patients [2].

2.3. Bidomain simulations

Bidomain simulations were performed on a computational mesh of the epicardial surface of the human ventricles, which was developed for a previous study [6]. This mesh generates realistic activation times in the human heart as well as realistic electrocardiograms. All bidiomain simulations were performed on a desktop computer with the openCARP software (https://opencarp.org/) using a time step of 20 μs.

To investigate the impact of changes in ECV and cell size on activation time, simulations of apical pacing were performed in the model of human ventricular epicardium under control conditions (r'=10.6 μm) and in myocyte hypertrophy (r'=15.45 μm), and for three different ECV levels (21.5, 25 and 30%) that correspond to values reported in healthy and diseased hearts. An overview of the simulation parameters is provided in Table 1.

For each simulation, the LV apex was paced at twice stimulus capture threshold at a basic cycle length of 750 ms (80 bpm) for 10 beats. On the 10^{th} beat the activation time on each node of the mesh was computed at the maximum dV_m/dt of the action potential upstroke. Total activation time was obtained as the difference between the latest and earliest activation time. Conduction velocity was calculated using two nodes on the LV wall located 15 mm apart.

3. Results

Six simulations in the model of human ventricular epicardium were performed using the parameters in Table 1. Activation maps from all six simulations are shown in Figure 2. Overall, CV in the simulations with myocyte hypertrophy was 18% faster than in the control simulations, resulting in a 23% shorter total activation time. An increase of ECV resulted in faster CV and shorter total activation time in both the control and myocyte hypertrophy simulations. For both conditions, the ECV increase was modeled

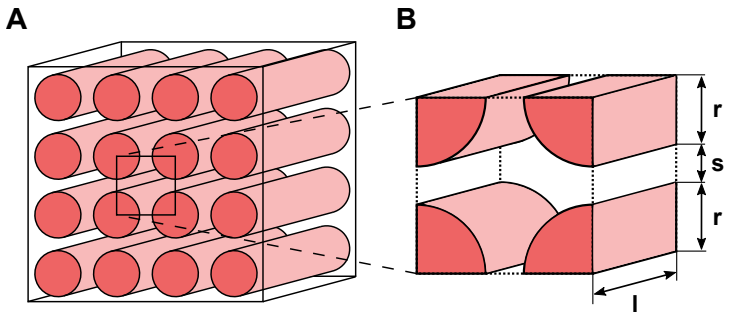

Figure 1. **A**. Cardiac cells are represented as cylinders within an arbitrary volume of myocardium. **B**. For a fixed volume taken from the myocardium in A, the dimensions of the front face are expressed in terms of the cell radius r and spacing between cells s.

Table 1. Simulation parameters. As illustrated in Figure 1, r stands for cell radius, s for intercellular spacing; β is the ratio of membrane area to tissue volume and S_e and S_i are scaling coefficients for extracellular and intracellular tissue conductivities, respectively.

		Extracellular volume (%)		
		21.5	25	30
Control	$r\ (\mu m)$	10.6	10.6	10.6
	$s\ (\mu m)$	0.0	0.484	1.217
	$\beta\ (1/\mu m)$	0.1481	0.1415	0.1321
	$S_e\ (-)$	0.833	0.969	1.163
	$S_i\ (-)$	1.058	1.011	0.943
Myocyte hypertrophy	$r'\ (\mu m)$	15.45	15.45	15.45
	$s'\ (\mu m)$	0.0	0.705	1.774
	$\beta'\ (1/\mu m)$	0.1016	0.0971	0.0906
	$S_e\ (-)$	0.833	0.969	1.163
	$S_i\ (-)$	1.058	1.011	0.943

by an increase of intercellular spacing s, as indicated in Table 1.

4. Discussion

Our study demonstrates that an expansion of ECV increases CV and results in a shortening of total activation time under both control conditions and in myocyte hypertrophy. The increase in cell radius accelerated ventricular conduction on average by 18% and shortened total activation time by 23%. These findings indicate that ventricular conduction is noticeably altered not only by changes in cell radius, but also in ECV in the absence of myocyte hypertrophy.

The observed acceleration of CV in the simulations with increased r corresponds to experimental findings reported in rabbits with heart failure [7]. Their hearts exhibited myocyte hypertrophy, represented in our approach by increased r, and also showed faster conduction velocity when compared to controls.

In the absence of fibrosis, our study demonstrates that an increase in ECV solely due to an expansion of extracellular space (s) increases CV and shortens ventricular activation time. However, this situation is rarely the case in clinical practice. Often, in patients with diffuse myocardial fibrosis, the extracellular space is filled with an excessive amount of collagen that reduces specific conductivity of the extracellular space. As a consequence, CV decreases [3], especially in the transverse fiber/myocyte direction, leading to discontinuous conduction that favors arrhythmia [8].

4.1. Limitations and future work

In this work we studied CV and total activation time in a single heart model with a fixed geometry. Since the heart size changes in hypertrophy, in future studies we plan to perform simulations in hearts with patient-specific geometries that correspond to normal and hypertrophic states.

Secondly, our model shows that increased ECV leads to faster conduction, which is not always the case in clinical practice, especially not in patients with diffuse myocardial fibrosis. Future work will focus on the implementation of diffuse fibrosis into this method by altering the homogenized extracellular bidomain conductivities. This work will be combined with the patient-specific modeling mentioned above to investigate the effects of increased ECV from diffuse fibrosis in combination with changes in cell size on QRS duration and arrhythmogenesis. If discrepancies still exist between the model and patient ECGs after the addition of fibrosis, we will explore the possibilities of reducing the intracellular conductivity and altering ion channel properties to better match the diseased state, as reported in literature [9].

Lastly, our study lacks experimental and histological validation. Future studies in cardiac diseases that cause myocardial hypertrophy are necessary to link ECV values

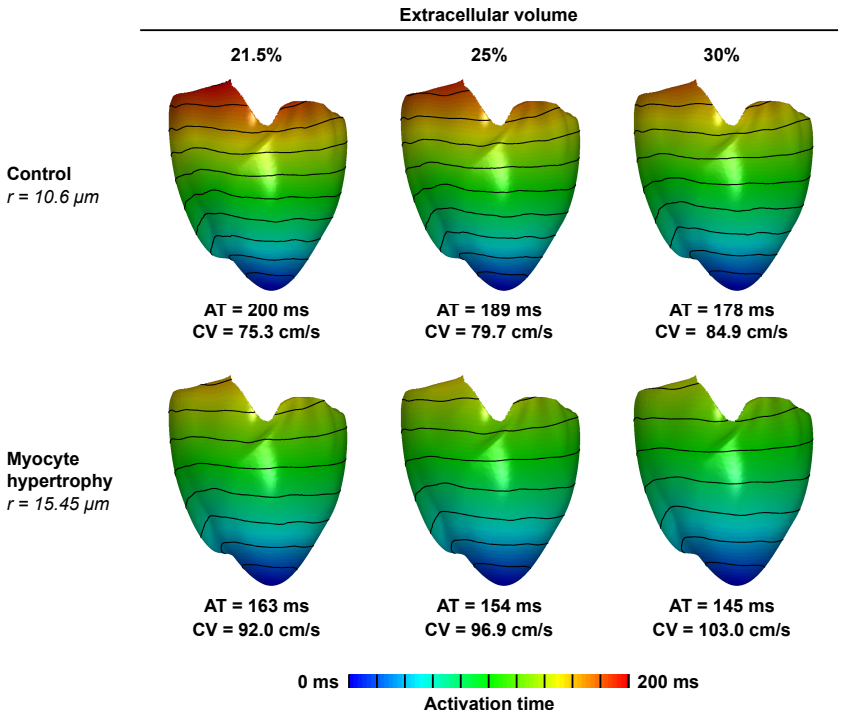

Figure 2. Activation maps are shown for the computer simulations of apical pacing along with their respective total activation times (AT) and conduction velocities (CV). The positions of the activation maps correspond with the simulation parameters in Table 1. Isochrone lines have a spacing of 20 ms.

with the levels of myocyte hypertrophy and diffuse myocardial fibrosis from tissue histology and with measurements of CV and total activation time.

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