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Cardiac Fiber Rotation Distorts Surface Measurements of Anisotropic Propagation

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Abstract— **Anisotropy is often determined experimentally from epicardial propagation measurements. We hypothesize that the direction of wave propagation on the epicardial surface is not aligned with the epicardial fiber orientation, due to intramural fiber rotation. In this paper, we modeled the effect of cardiac tissue fiber rotation on wave propagation. We used a three dimensional computer model of varying thickness with a 120 degree fiber rotation through the thickness. The angle difference between the direction of propagation and fiber orientation was most pronounced for thin tissue, and decreased with increasing tissue thickness. This angle also increased with the time elapsed since stimulation. Finally, we demonstrated that the fiber rotation from epicardium to endocardium results in inaccurate measurements of conduction velocities at the epicardium, particularly in thin tissues.**

I. Introduction

Cardiac muscle physiological characteristics such as conduction velocity, anisotropy, fiber rotation, and curvature are known to have significant effects on wave propagation patterns in the heart. Epicardial surface potential patterns are usually used to obtain information about these structural properties. There have been several published studies designed to determine anisotropy and conduction velocities [1-3] based on the epicardial potential measurements. There are also studies demonstrating the effect of fiber curvature [4] and intramural fiber rotation on epicardial surface wavefront propagation patterns and consequently, conduction velocity and anisotropy measurements [5, 6].

Looking through previous studies on ventricular myocardium, it is clear that wave propagation is anisotropic. Propagation is faster in the direction of myocardial fibers (longitudinal direction) than in the direction across the fibers within the sheet (transverse direction) than across sheets. Also, myocardial tissue fiber orientation is known to change from epicardium to endocardium. Therefore, anisotropy and fiber orientation have to be considered in designing measurement approaches for conduction velocity.

Taccardi and his colleagues [7] studied the transmural activation pattern of the canine left ventricle and demonstrated that the activation time isochrones resulting from an epicardial stimulus are different from the activation patterns when the wavefront is limited to propagate only on the epicardial surface.

Colli Franzone et al. [8] studied wave propagation patterns resulting from central point stimulation in a model of anisotropic ventricular muscle. They showed that the collision of the wavefront with the slab boundaries, as well as curvature of isochrones affect the local conduction velocity. They also mentioned that "the shape and separation of epicardial isochrones and spatial distribution of epicardial velocities varied as a function of site and depth of pacing [8]."

Punske et al. [9] used electrical mapping and studied the effect of fiber rotation on surface wave propagation in both wild type and genetically mutated mouse hearts. They discussed the importance of myocardial 3D structure on understanding the surface propagation patterns and how such understanding could be useful for electrical pathophysiology studies.

Knisely [10] used optical mapping and determined the changes in transmembrane voltage during stimulation and showed that these changes depend on fiber orientation. Pollard et al. [5] simulated three-dimensional propagation in the ventricular myocardium and studied the effect of intramural fiber rotation on the epicardial activity. They demonstrated that the rotation of fiber axes can accelerate the epicardial activation distance from stimulus.

The main purpose of this study is to investigate the effects of fiber rotation on the wave propagation patterns measured on the epicardium. We have also studied the influence of fiber rotation on estimates of conduction velocity and anisotropy ratio.

II. Methods

A. Tissue Simulations

A rat ventricular myocyte mathematical model from Pandit et al. [11] was used as the base single cell model. We created tissue slabs 2cm by 2cm with different thicknesses (1mm, 2mm, 4mm, and 1cm). Cells were considered to be aligned in different parallel layers, with all the cells within a layer oriented in the same direction. Fiber orientations were changed continuously and linearly 120 degrees from epicardium to endocardium in all slabs. A slab with no fiber rotation was also simulated as a reference for the purpose of comparison. Monodomain simulations were run with the Cardiac Arrhythmia Research Package (CARP) [12]. Longitudinal and transverse conductivity (g_L and g_t) values were 0.179 S/m and 0.019 S/m respectively. Time step was 1ms and the spatial discretization value 100μm.

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B. Stimulation

Central point stimulation was applied to the epicardial surface. Stimulation was modeled as current injection into a 0.5mm by 0.5mm by 0.25mm cube for 5ms with the amplitude of 50μA/cm^3. Simulations were done for all different thicknesses in CARP. Epicardial membrane potential and wave propagation was measured.

C. Activation Time

As longitudinal intracellular conductivity (g_L) is greater than transverse conductivity (g_T), wave propagation speed (conduction velocity, CV) is greater in the fiber direction. We defined activation time as the instant when membrane potential crossed zero in the positive direction. Activation time was calculated for each cell on the epicardium. Activation time isochrones were then constructed.

D. Anisotropy ratio

After finding the isochrones corresponding to each activation time, we used a simple least square error algorithm in Matlab to fit an ellipse to them. For each ellipse, we found the rotation angle and its major and minor axes. The Anisotropy ratio (AR) was defined as the ratio of the major to the minor axis of the ellipse.

E. Conduction Velocity

Using activation times on the epicardial surface, the velocity of wave propagation was calculated using the following equation:

$$|v(x,y)| = \frac{1}{|\vec{\nabla} T(x,y)|}, \qquad (1)$$

where v(x, y) and T(x, y) are the velocity and activation time for each point on the epicardial surface respectively. The velocities measured at the points on the ellipse in the direction of its major and minor axes were used as the longitudinal and transverse CV, respectively. CV was measured for all different slab thicknesses.

III. Results

Fig. 1 shows the contour plot of activation time (isochrones) for different thicknesses on the surface. Wave propagation direction and speed can be seen from the activation time isochrones. Fibers are aligned in the horizontal direction. Fig. 1 clearly shows that the major axis of the ellipse is not aligned with the epicardial surface fiber orientation. This discrepancy is most pronounced in thinner tissues. It can also be noted that for a specific thickness, isochrones corresponding to different latencies after the stimulus are not oriented in the same direction.

The angle of propagation for different thicknesses is plotted in Fig. 2. It can be seen that the angle of propagation is significantly different from the fiber orientation for 1mm and 2mm slabs (respectively 29^o and 20^o at 25ms). It can also be noted that the angle of wave propagation is increasing with the time elapsed from the stimulus. As indicated by the purple line in fig. 2, if there is no fiber rotation in the tissue slab, the wave will propagate with no distortion and the angle of propagation will be very close to zero.

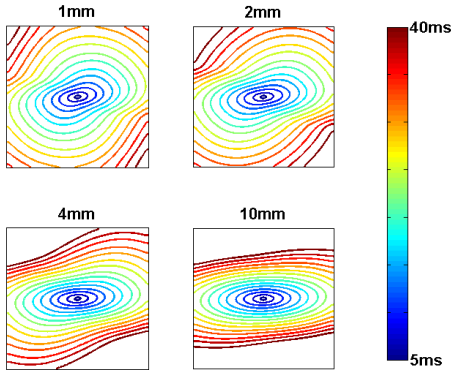

Figure 1. Activation time isochrones of the epicardial surface. Fibers are oriented in the horizontal direction. Isochrones are less aligned with the fiber orientation in thinner tissues.

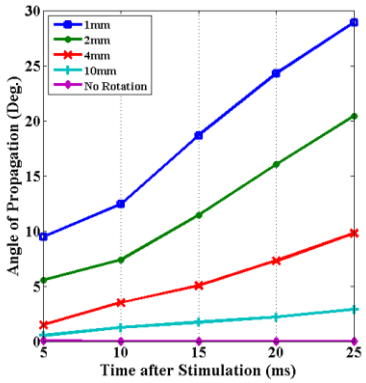

Figure 2. Angle of wave propagaion for different thicknesses. Wavefront is less aligned with the fiber direction in thinner tissues. This discrepancy increases with the time elapsed since the stimulus.

Anisotropy ratio is a dimensionless parameter representing the ratio of longitudinal to transverse conduction velocity. Higher ARs thus imply a larger difference between the longitudinal and transverse CV. As shown in Fig. 3, maximum AR is obtained in tissue with no fiber rotation. In slabs with fiber rotation, the AR observed in epicardial measurements is reduced. As slabs with fiber rotation get thicker the AR increases and approaches the "true" AR value of tissue with no fiber rotation.

Conduction velocities were calculated, using velocity measurements based on the gradient of activation times (1) as described in Methods. The velocities in the directions of the major and minor axes were used as estimates of longitudinal and transverse CV, θ_L and θ_t respectively. These results are summarized in Fig. 4. θ_L increases as the tissue thickness increases. Propagation velocities along the major axis are slower than expected for "pure longitudinal propagation" (based on θ_L for the tissue with no rotation, measured as 51cm/s).

On the other hand, propagation velocities along the minor axis are faster than pure transverse propagation. θ_t is also higher for thinner tissues. In tissue with no fiber rotation, the θ_t is 17cm/s.

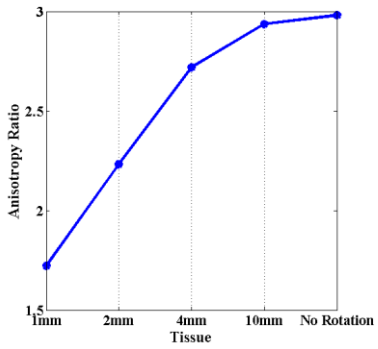

Figure 3. Anisotropy ratio for different slab thicknesses. Anisotropy ratios are measured 20 ms after stimulation. Measurements are more accurate for thicker tissues.

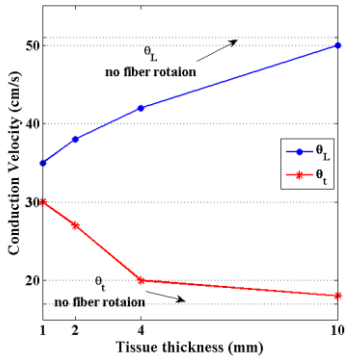

Figure 4. Longitudinal and transverse conduction velocities. Measurements from thicker tissues are closer to the true values.

IV. Discussion

It is apparent that the cardiac tissue fiber rotation has a significant effect on the wave propagation patterns. Consequently, measurements of conduction velocity are affected by this rotation. Electrical coupling between different layers of the tissue which are not aligned in the same direction causes the wave propagation on the surface not to be in the same direction as the fiber orientation.

Fiber rotation is known to be varying 120 degrees linearly from epicardium to endocardium. Thinner tissues have fewer layers, so there is a larger angle difference between the fiber orientations of each layer. This angle difference between electrically coupled layers, results in distortion of wave propagation. This distortion is more significant in thinner tissues.

As the thickness of the tissue increases, layers have less angle difference. Also, layers that have more angle difference from the epicardial surface are located deeper in the tissue in comparison with thinner tissues. Since deep layers are less electrically coupled to the epicardium, they have less effect on the wave propagation on the surface.

Fig. 2 shows that the angle of propagation not only depends on the thickness of the tissue but also varies with time. It takes some time for the stimulus applied to the epicardium to propagate through the tissue to stimulate deeper layers and the endocardium. As different layers are stimulated, the electrotonic loading effect of other layers is changing. This causes the wave propagation to change direction with the time. The angle of propagation approaches its steady state value as the wavefront propagates through the whole tissue.

Distortion of wave propagation causes errors in measurements of CVs and ARs. AR is a structural parameter and depends on the speed of wave propagation in different directions. Using the conventional method for measuring the CVs based on epicardial measurements leads to inaccurate results. The actual AR value of the tissue is the value in Fig. 3 related to the tissue with no fiber rotation. Fitting ellipses to the activation time isochrones and considering the direction of propagation equal to the direction of those ellipses, not only yields an inaccurate estimate of the fiber orientation (Fig. 2) but also results in an error in measurement of the AR (Fig. 3). As previously explained, the thicker the tissue is, the less the epicardium is affected by the electrical activity of other layers due to electrical coupling.

V. Conclusion

Electrotonic loading by underlying layers of cardiac tissue distorts propagation along the tissue surface. This angle difference not only depends on the thickness of the tissue, but also increases with time elapsed from the stimulus. These errors can thus be reduced, but not eliminated completely, by obtaining measurements as soon as practical after the stimulus is delivered. Care must be taken when interpreting anisotropic propagation velocities measured experimentally, in particular in thin tissues, such as the ventricular walls of rat and mouse hearts.

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