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Effects of boundaries and geometry on the spatial distribution of action potential duration in cardiac tissue

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ABSTRACT

Increased dispersion of action potential duration across cardiac tissue has long been considered an important substrate for the development of most electrical arrhythmias. Although this dispersion has been studied previously by characterizing the static intrinsic gradients in cellular electrophysiology and dynamical gradients generated by fast pacing, few studies have concentrated on dispersions generated solely by structural effects. Here we show how boundaries and geometry can produce spatially dependent changes in action potential duration (APD) in homogeneous and isotropic tissue, where all the cells have the same APD in the absence of diffusion. Electrotonic currents due to coupling within the tissue and at the tissue boundaries can generate dispersion, and the profile of this dispersion can change dramatically depending on tissue size and shape, action potential morphology, tissue dimensionality, and stimulus frequency and location. The dispersion generated by pure geometrical effects can be on the order of tens of milliseconds, enough under certain conditions to produce conduction blocks and initiate reentrant waves.

1. Introduction

It is well known that electrical activity in cardiac tissue generally is spatially heterogeneous, with variations in action potential shapes and durations across the tissue (Gussak et al., 2003). This heterogeneity can arise either from static or dynamical processes. Static heterogeneity generally is associated with intrinsic gradients in cellular electrophysiology (Gussak et al., 2003; Clark et al., 1993; Patel and Campbell, 2005; Sun and Wang, 2005; Antzelevitch and Fish, 2001; Szentadrassy et al., 2005) or cell-to-cell coupling (Cherry et al., 2007; Engelman et al., 2010) occurring throughout the tissue. Even without static heterogeneity, the underlying nonlinear dynamics of cardiac tissue (Nolasco and Dahlen, 1968; Guevara et al., 1984) can produce bifurcations and heterogeneity in repolarization at fast pacing rates (Watanabe et al., 2001; Qu et al., 2000). These dynamically induced heterogeneities also can give rise to spatial gradients, such as those associated with spatially concordant and discordant alternans (Watanabe et al., 2001; Qu et al., 2000; Pastore et al., 1999; Fenton et al., 2002).

Although standard static and dynamical heterogeneities have been studied widely, very little is known about the role boundaries and geometrical properties play in determining the spatial distribution of action potential properties in tissue. Even when the depolarizing wave propagates at a constant velocity, differences in repolarization can occur from loading effects at the boundaries or site of stimulation. As a result, the action potential duration (APD), which for a given propagating wave is defined at every point as the difference between the repolarization and depolarization times, can vary spatially. The effects of wavefront curvature (Comtois and Vinet, 1999; van Oosterom and Jacquemet, 2009), obstacles (Sampson and Henriquez, 2002; Krogh-Madsen and Christini, 2007), tissue bath (Bishop and Plank, 2011), boundaries (van Oosterom and Jacquemet, 2009; Siso-Nadal et al., 2008; Cain and Schaeffer, 2008), and interactions with intrinsic heterogeneities (Sampson and Henriquez, 2005) have been investigated previously, but other properties like tissue size, shape, and dimensionality as well as stimulus frequency and location, all of which can influence spatial heterogeneity, have not been studied quantitatively. These effects arise even in otherwise homogeneous tissue and are mediated by electrotonic (diffusive) currents between neighboring cells. As a result, the shape of the action potential (AP) (Cherry and Fenton, 2004) also impacts the way in which APD is distributed in tissue.

This manuscript focuses on the importance of tissue structure in determining the spatial distribution of APD in otherwise

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homogeneous tissue. In particular, we will discuss how properties including tissue geometry, size and dimensionality; stimulus frequency and location; and AP shape all can contribute significantly to the overall spatial distribution of APD in the absence of intrinsic electrophysiological gradients.

2. Methods

2.1. Models of cardiac action potentials

Two different models of cardiac action potentials were used. In many cases, we used the Fox–McHarg–Gilmour (FMG) model (Fox et al., 2002), which is a robust description of canine ventricular cells. To demonstrate how action potential shape can influence boundary effects, the three-variable phenomenological model of Cherry and Fenton (Cherry and Fenton, 2004) was used with two different parameter sets that achieve the same action potential duration but with different action potential shapes. For consistency with Ref. Cherry and Fenton (2004), we refer to the two parameter sets as Model 1 and Model 2. All initial values and parameter values are as given in the original references, with the exception of four parameters in Model 1, which were adjusted to ensure the conduction velocities of Model 1 and Model 2 were equal and to fine-tune the APDs of the two parameter sets to produce identical values at the stimulus site in a 4 cm × 4 cm square geometry. The modified parameter values for Model 1 are as follows: $\tau_{v1}^{-}=100$, $\tau_{v2}^{-}=20$, $\tau_{w}^{+}=568.4$, and $\tau_{d}=0.18$.

2.2. Computational methods

The model equations were integrated using the explicit Euler method. For the FMG model, the spatial resolution was 0.0125 cm and the time step size was 0.02 ms. For Model 1 and Model 2, the spatial and temporal resolutions were 0.01 and 0.02 ms, respectively. The diffusion coefficient was set to 0.001 cm^2/ms, and no-flux boundary conditions were used throughout. As discussed by Clayton et al. (2011) and Niederer et al. (in press), the values of the time and space steps used are small enough to provide a sufficiently resolved solution. For non-rectangular geometries, the phase-field method (Fenton et al., 2005; Bueno-Orovio et al., 2006) was used to implement the no-flux boundary conditions. Central stimulus sites were chosen to be the smallest possible square regions able to produce a propagating wave, which in most cases was 7 × 7 computational nodes for both models. Line stimuli were chosen to be the same width (7 computational nodes) to facilitate comparison. For the three-dimensional cases, spherical regions of diameter 11 nodes were used, and the comparisons in one and two dimensions used linear and circular stimulus regions with the same diameter. The three-dimensional simulations were run in parallel using MPI on 40 processors of the Cray XT3 system at the Pittsburgh Supercomputing Center.

2.3. Measurement of depolarization and repolarization times and APD

Depolarization time was measured as the time when the voltage reached 10% of its full depolarization. Similarly, repolarization time was measured as the time when the voltage repolarized to the same voltage value, corresponding to 90% of repolarization to the resting membrane potential. In both cases, linear interpolation was used to obtain more resolved timing data. APD was measured as the difference between the repolarization and depolarization times, as indicated in Fig. 1A. Dispersions in any of these values were measured as the difference between the maximum and minimum values obtained over the entire domain.

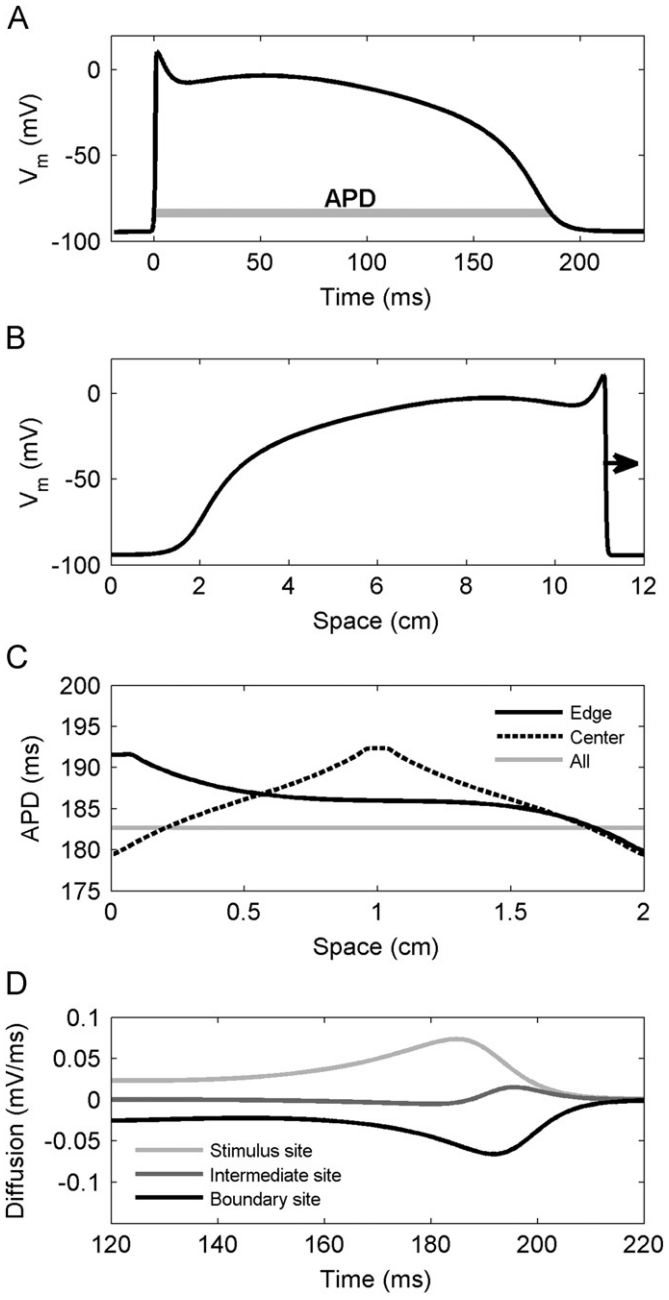

Fig. 1. Action potential properties of the Fox–McHarg–Gilmour (FMG) model (Fox et al., 2002) in a one-dimensional cable. (A) Action potential from the center of a cable 2 cm long stimulated at one end. Action potential duration (APD) is indicated. (B) Profile of a wave propagating from left to right 220 ms after initiation at the left edge. A long cable (12 cm) was used to fit an entire wavelength. (C) Spatial distribution of APD along the cable for a stimulus at the left edge (solid), at the center (dashed), or everywhere (gray) to eliminate the effects of coupling. (D). Diffusion current during repolarization for the center stimulus case of panel C at locations within the stimulated region (light gray), at the boundary (black), and halfway between (dark gray). Within the stimulated region, the current is large and positive, which lengthens APD. At the boundary, the current is large and negative, which shortens APD.