A Novel Mechanism of Anode-Break Stimulation Predicted by Bidomain Modeling

Ravi Ranjan, Gordon F. Tomaselli, Eduardo Marbán

Abstract—Anodal stimulation by external pacemakers has been explained on the basis of bidomain models of cardiac tissue. Bidomain models predict that anodal stimuli will hyperpolarize the underlying tissue while adjacent regions become depolarized (virtual cathodes), initiating excitation. We investigated the contribution of active cellular properties to anode-break stimulation. A bidomain model was implemented in which each cell contained realistic ionic currents, including those recruited by hyperpolarization. Simulations reveal that anode-break excitation can originate at the site of stimulation itself and not only from adjacent regions of induced depolarization. The threshold for initiating excitation at the site of stimulation is lower than that for stimulation initiating from adjacent depolarized regions. Thus, incorporation of active cellular properties into a bidomain model predicts a novel mechanism for anode-break stimulation of the heart. The results will improve our understanding of anodal pacing and its risks and benefits in patients. (Circ Res. 1999;84:153-156.)

Key Words: pacemaker ■ excitation ■ quantitative modeling ■ anisotropy

Experimentally, the mammalian heart can be activated by cathodal or anodal stimuli at both the make and break of the pulse.1-3 In fact, in early diastole, anodal-break stimulation has the lowest threshold,4 a phenomenon that may potentiate the risk of anodal pacing–induced ventricular fibrillation.4 In a bipolar pacing system, activation occurs from the lowest-threshold electrode, and at close coupling intervals, this may be the anode, increasing the risk of an arrhythmia, even during bipolar pacing. The mechanism of anodal stimulation remains controversial. The most plausible explanation emerges from bidomain models of cardiac tissue.5 6 Bidomain models, based on passive properties of the cardiac tissue, assume that the ratios of electrical conductivity along the fiber direction and perpendicular to it (anisotropy) differ in the intracellular and extracellular domains.5 The difference in anisotropy generates a complex distribution of transmembrane potential in response to anodal stimulation:6 the tissue directly underlying the stimulating electrode hyperpolarizes, while neighboring regions depolarize and function as “virtual cathodes.”7 6 The bidomain model predicts that excitation starts at the virtual cathodes and spreads to cover the remaining tissue.5 10

Recently, we identified an active mechanism for anode-break stimulation at the cellular level. Recruitment of ionic currents during anodally induced hyperpolarization enabled excitation on termination of the stimulus (“anode-break” response).11 12 Modification of an existing action potential model to include the ionic currents at hyperpolarized potentials reproduced the results. We thus incorporated the enhanced cellular model into a newly implemented bidomain model to explore the role of these currents in anode-break excitation.

Materials and Methods

A 2-dimensional network model was implemented. For a bidomain model, the intracellular ($V_i$) and extracellular ($V_o$) potential obey the following equations:

1. \[ \nabla \cdot \sigma \nabla V_i = I_m + I_n \]

2. \[ \nabla \cdot \sigma_n \nabla V_o = -I_m + I_n \]

where $I_m$ is the membrane current per unit volume, $I_n$ is the stimulus current applied in the intracellular domain, $I_n$ is the stimulus current applied in the extracellular domain, $\sigma$ and $\sigma_n$ are conductivity tensors in the intracellular and extracellular domains, accounting for tissue anisotropy.

For active membrane, the current per unit volume ($I_n$) is given by

3. \[ I_n = \beta \left( C_m \frac{\partial V_m}{\partial t} + J_{ion} \right) \]

where \( \beta \) is the ratio of membrane surface area to tissue volume, $C_m$ is the membrane capacitance per unit area, $V_m$ is the transmembrane potential, and $J_{ion}$ is the membrane ionic current density (per unit area). The transmembrane potential ($V_m$) is as follows:

4. \[ V_m = V_i - V_o \]

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**Model Parameters**

<table>
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<th>Parameter</th>
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</tr>
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<td>$\sigma_{xy}$</td>
<td>$1.2 \times 10^{-4}$ S/mm</td>
</tr>
</tbody>
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For the ionic current ($J_{ion}$), we used the Luo-Rudy phase I model as modified by Ranjan et al. Briefly, the model was changed to include the hyperpolarization-activated inward current $I_h$ and the inward rectifier current $I_{Kr}$ was modified to reflect the time-dependent block and unblock at hyperpolarized potentials. The Table lists the parameters that were used in the model. To solve for the transmembrane potential using the bidomain formulation, current flow was restricted to be either along or transverse to the fiber direction. This routine simplification fixes the crossterms of the conductivity tensor at zero.

Combining Equations 2 and 3 gives a parabolic equation:

$$\frac{\partial V_m}{\partial t} = \frac{-(\nabla \cdot \hat{\sigma} \nabla V_m) + I_{in}}{\beta} - J_{ion}$$

Equation 5 was solved for $V_m$ in the next time step using Euler’s method with the current $V_o$. Combining Equations 1, 2, and 4 gives an elliptical equation:

$$(\hat{\sigma}_x + \hat{\sigma}_y) \nabla^2 V_m = -\hat{\sigma}_z \nabla^2 V_m + (I_{in} + I_{in}^*)$$

Equation 6 was solved for $V_m$ in the next time step with the new $V_m$ using the alternating direction implicit method. A time step of 5 $\mu$s and a space step of 30 $\mu$m were used. A 2-dimensional sheet measuring 5 mm by 2.5 mm was used. At the tissue boundary, no flux boundary condition was used. The stimulating electrode was 0.5 mm by 0.25 mm in size and injects current in the extracellular domain. Only one quadrant was modeled to reduce computational time. The simulations were done on an INDIGO R10000 Silicon Graphics Workstation.

**Results**

A resistive bidomain model was implemented first to test the validity of the computation method used in the present study. The results of the passive model generated in the present study (not shown; see Reference 11) mimic those obtained with numerical methods. The model with unequal anisotropy produced a dog-bone distribution of the transmembrane potential typical of bidomain models. The dog-bone distribution disappeared when the anisotropy ratio was made equal in the 2 domains.

Having validated the computational method, we next implemented the active model. Figure 1 shows the transmembrane potential distribution as a function of $x$ and $y$, calculated using the modified Luo-Rudy model at 8 time points during and after delivery of a 0.3-mA, 10-ms anodal stimulation. The lower left-hand corner of the sheet is stimulated. Anodal stimulation results in the establishment of virtual cathodes in the convexity of the hyperpolarized region. The depolarization induced in the virtual cathodes suffices to initiate excitation, which then propagates to cover the entire tissue.

Next, we explored the predictions of the model at lower stimulation strengths. By analogy to our previous cellular work, we reasoned that recruitment of active membrane properties might suffice to produce an anode-break response.

At stimulation thresholds lower than those resulting from the virtual cathode. Figure 2 shows the response to a 0.15-mA, 10-ms anodal stimulus. Once again, virtual cathodes are induced, but now the extent of depolarization is not enough to initiate excitation. On termination of the stimulus, the depolarization decays toward resting levels (10- and 15-ms time frames). Nevertheless, the tissue underneath the stimulating electrode had been hyperpolarized sufficiently to elicit an anode-break response. The excitation in this case initiates directly underneath the stimulating electrode and then propagates throughout the tissue. No such excitation was observed in bidomain simulations using the original Luo-Rudy action potential model. Reassuringly, the response to cathodal stimulation was identical for both the modified and unmodified action potential models (not shown).

Given that the extent of depolarization induced in the virtual cathode depends on the relative anisotropy ratios in the intracellular and extracellular domains, the relative contribution of the 2 mechanisms for anodal excitation would also be expected to depend on these values. For Figures 1 and 2, we used an extracellular anisotropy ratio of 2.5 and an...
intracellular ratio of 7.5. These values are representative of ratios reported for cardiac tissue and used in previous bidomain models (ranging from 1.5 to 4 in the extracellular domain and from 5.8 to 11.7 intracellularly). To examine the role played by the disparity in intracellular and extracellular anisotropy ratios on stimulation threshold, we varied the ratios in the 2 domains. Figure 3A shows the anodal stimulation threshold determined using a bidomain model with a fixed intracellular anisotropy ratio of 8 and a varying extracellular ratio. For extracellular anisotropy ratios of 1 to 2, anodal excitation originates at the virtual cathodes and is an anode-make stimulation. For extracellular anisotropy ratios of 2, the new mechanism of anode-break stimulation appears: excitation starts directly underneath the stimulating electrode, as an anode-break response. When it is present, the excitation threshold for the novel anode-break mechanism is lower than that for the conventional mechanism of stimulation from the induced virtual cathodes. Figure 3B shows the anodal stimulation threshold determined using a bidomain model with a fixed extracellular anisotropy ratio of 2.5 and a varying intracellular anisotropy ratio. Once again, for a range of intracellular anisotropy ratios (<10), excitation occurs at the site of stimulation itself at lower thresholds before the virtual cathode becomes the site of excitation at higher stimulus strengths.

**Discussion**

Routine bidomain models explain anodal stimulation of cardiac tissue on the basis of the different anisotropy ratios in the intracellular and extracellular domains of cardiac tissue. To examine the role played by the disparity in intracellular and extracellular anisotropy ratios on stimulation threshold, we varied the ratios in the 2 domains. Figure 3A shows the anodal stimulation threshold determined using a bidomain model with a fixed intracellular anisotropy ratio of 8 and a varying extracellular anisotropy ratio. For extracellular anisotropy ratios of 1 to 2, anodal excitation originates at the virtual cathodes and is an anode-make stimulation. For extracellular anisotropy ratios of >2, the new mechanism of anodal stimulation appears: excitation starts directly underneath the stimulating electrode, as an anode-break response. When it is present, the excitation threshold for the novel anode-break mechanism is lower than that for the conventional mechanism of stimulation from the induced virtual cathodes. Figure 3B shows the anodal stimulation threshold determined using a bidomain model with a fixed extracellular anisotropy ratio of 2.5 and a varying intracellular anisotropy ratio. Once again, for a range of intracellular anisotropy ratios (<10), excitation occurs at the site of stimulation itself at lower thresholds before the virtual cathode becomes the site of excitation at higher stimulus strengths.
Mechanism of Anode-Break Stimulation

ization induced in the virtual cathodes suffices to induce excitation. This mechanism predominates at higher stimulus strengths, because it occurs during the stimulus itself (Figure 1).

This mechanism of anode-break stimulation at lower stimulus strengths is different from the mechanisms proposed earlier, even though it can be argued that in both cases the site of stimulation is the hyperpolarized region of tissue underlying the electrode. Based on the mechanism proposed by Roth,9 the depolarization induced in the virtual cathode diffuses to the adjoining hyperpolarized region and excites it, resulting in anode-break excitation. In the new mechanism proposed in the present study, the diffusion of charges from the depolarized virtual cathodes is not enough to cause excitation in the hyperpolarized regions. As shown in Figure 2 (15-ms time frame), the entire tissue returns to resting membrane potential levels after the end of the stimulus. But the hyperpolarization induced in the region underlying the electrode is enough to recruit the hyperpolarization-activated current, I_h, and cause excitation in these areas independent of diffusion of charges from adjoining areas. This excitation then proceeds to cover the remaining tissue. At higher stimulus strengths, the previously proposed mechanism of anode-break stimulation seems more plausible: that is, diffusion of charge from the virtual cathode occurs at a faster rate and induces excitation in the hyperpolarized regions before anode-break stimulation under the electrode.

The range of stimulus strengths that elicits anode-break excitation at the site of stimulation depends on the anisotropy ratios assumed in the model (Figure 3). The degree of hyperpolarization underneath the excitation electrode does not primarily depend on the anisotropy ratios, but the depolarization induced in the virtual cathodes does depend on the disparity of anisotropy ratios in the 2 domains. The higher the disparity in the ratios, the greater the depolarization in the virtual cathodes. As a result, when the disparity in ratios is greater (at extracellular anisotropies of 1 to 2 in Figure 3A and intracellular anisotropy ratio of >10 in Figure 3B), the depolarization induced at the virtual cathode is high enough for anodal excitation at stimulus strengths below those needed for anode-break stimulation. This window of stimulation with lower thresholds assumes significance after considering the fact that the threshold for anodal-break excitation, as reported by existing bidomain models, is about 3 to 5 times higher than that determined experimentally.10 At the most realistic anisotropy ratios (corresponding to ≈3 in Figure 3A), the anode-break mechanism is quite prominent. Nevertheless, experiments in cardiac tissue6 will be important in establishing the relative importance of these 2 mechanisms.

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References

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