Comments to the Editor

What Can We Learn from the Optically Recorded Epicardial Action Potential?

ABSTRACT Optical mapping using voltage-sensitive fluorescent dyes has become a major tool for studying excitation propagation in the heart. Computational and experimental studies have indicated that the optical upstroke morphology reflects the orientation of the subsurface excitation front. In a recent whole heart computational study performed by Bishop et al. (Bishop, M. J., B. Rodriguez, J. Eason, J. P. Whiteley, N. Trayanova, and D. J. Gavaghan. 2006. Synthesis of voltage-sensitive optical signals: application to panoramic optical mapping. *Biophys. J.* 90:2938-2945), an example was provided of two different directions of propagation having nevertheless very similar epicardial optical upstrokes. The goal of this comment is to clarify the interpretation of optical upstroke morphologies and reconcile the results obtained by Bishop et al. with previous computational and experimental studies.

Optical mapping utilizing voltage-sensitive fluorescent dyes has become a major tool for studying excitation propagation in the heart. While optical mapping is used primarily for surface recordings, it has been shown, both theoretically and experimentally, that subsurface layers contribute to the optical signals (1–7). These findings have generated a significant interest toward quantification of the subsurface contributions and their implications for the interpretation of optical mapping recordings and they led to the development of hybrid electrical-optical models (8,9). The main feature of hybrid models is that they combine the detailed ionic models of electrical propagation with the light transport models in myocardial tissue. Hybrid models have successfully explained the significant prolongation of the optical upstroke that has been observed experimentally in thick ventricular wall preparations (10,11) but also led to a quite unexpected prediction. According to such models, the shape of the optical action potential reflects the subsurface front orientation (9,11). Specifically, excitation fronts moving toward the recording surface produce optical upstrokes with their maximal slope near the peak of the optical action potential. In contrast, wave fronts moving away from the surface produce optical upstrokes whose maximal slope occurs at low signal values and thus the rate of rise slows down as the signal increases. Recent experimental studies designed to test this hypothesis are in excellent agreement with theoretical predictions (11). But how universal are these results?

In the April issue of the Biophysical Journal, Bishop et al. (12) report new findings that appear to contradict earlier reports. The authors present a computational example in which the upstroke shapes were similar despite significant differences in the direction of propagation of the excitation wave. Does this finding really mean that the shape of the optical upstroke does not always correctly predict the subsurface front orientation? Not necessarily. The key to resolving this controversy is the fact that the shape of the optical upstroke is determined not so much by the direction of the wave front propagation as by the orientation of the excitation front with respect to the surface.

Fig. 1, *A* and *B*, show schematically two propagation patterns with significantly different directions of propagation that nevertheless produce very similar optical upstrokes. In Fig. 1 *A*, the wave propagates transmurally from the endocardium toward epicardium, while in Fig. 1 *B*, propagation occurs parallel to the surface. In both cases there is a surface point at which the front has a similar orientation in the subsurface layers. The optical upstrokes recorded in Fig. 1, *A* and *B*, should therefore be very similar.

We believe that these two cases provide a plausible explanation of the phenomenon described by Bishop et al. Indeed, due to the complex geometry of their model, even a uniform stimulation of the entire endocardium can be expected to yield a significant variation in the surface wave front orientations. This scenario is similar to the one depicted in Fig. 1 *A*. In the case of apical stimulation, the rotating fiber orientation leads to a complicated intramural excitation pattern (13), in which the average subsurface angle θ of the wave front can deviate substantially from 90° (see Fig. 1 *B*) and in some locations be similar to those produced by endocardial stimulation.

Future studies of the above-mentioned paradox with detailed analyses of the wave front orientation will be highly beneficial and will lead to a better understanding of the factors affecting the shape of the optical action potential in thick ventricular tissue, as well as of the relationship between the optical upstroke and subsurface wave front orientation.

Submitted June 21, 2006, and accepted for publication August 9, 2006.

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0006-3495/06/11/3959/02 $2.00

doi: 10.1529/biophysj.106.091835

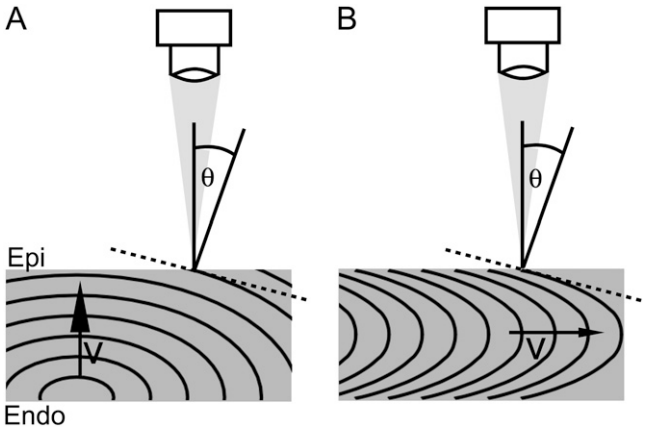

FIGURE 1 Two different modes of propagation resulting in similar optical upstroke morphologies. Shaded rectangles represent cross sections through slabs of myocardium; solid black lines are activation isochrones. Arrows indicate the directions of propagation, v the propagation velocity. Dashed lines mark tangents to the wave fronts at a chosen surface point; their orientations are quantified by the angle θ between the normals to the wave front and to the surface, respectively. (*A*) Endocardial point stimulation. (*B*) Wave front propagation after epicardial point stimulation (far from the stimulation site).

REFERENCES

1. Baxter, W. T., S. F. Mironov, A. V. Zaitsev, J. Jalife, and A. M. Pertsov. 2001. Visualizing excitation waves inside cardiac muscle using transillumination. *Biophys. J.* 80:516–530.
2. Bray, M. A., and J. P. Wikswo. 2003. Examination of optical depth effects on fluorescence imaging of cardiac propagation. *Biophys. J.* 85: 4134–4145.
3. Ding, L., R. Splinter, and S. B. Knisley. 2001. Quantifying spatial localization of optical mapping using Monte Carlo simulations. *IEEE Trans. Biomed. Eng.* 48:1098–1107.
4. Efimov, I. R., V. Sidorov, Y. Cheng, and B. Wollenzier. 1999. Evidence of three-dimensional scroll waves with ribbon-shaped filament as a mechanism of ventricular tachycardia in the isolated rabbit heart. *J. Cardiovasc. Electrophysiol.* 10:1452–1462.
5. Girouard, S. D., K. R. Laurita, and D. S. Rosenbaum. 1996. Unique properties of cardiac action potentials recorded with voltage-sensitive dyes. *J. Cardiovasc. Electrophysiol.* 7:1024–1038.
6. Knisley, S. B. 1995. Transmembrane voltage changes during unipolar stimulation of rabbit ventricle. *Circ. Res.* 77:1229–1239.
7. Janks, D. L., and B. J. Roth. 2002. Averaging over depth during optical mapping of unipolar stimulation. *IEEE Trans. Biomed. Eng.* 49: 1051–1054.
8. Bernus, O., M. Wellner, S. F. Mironov, and A. M. Pertsov. 2005. Simulation of voltage-sensitive optical signals in three-dimensional slabs of cardiac tissue: application to transillumination and coaxial imaging methods. *Phys. Med. Biol.* 50:215–229.
9. Hyatt, C. J., S. F. Mironov, M. Wellner, O. Berenfeld, A. K. Popp, D. A. Weitz, J. Jalife, and A. M. Pertsov. 2003. Synthesis of voltage-sensitive fluorescence signals from three-dimensional myocardial activation patterns. *Biophys. J.* 85:2673–2683.
10. Gray, R. A. 1999. What exactly are optically recorded ''action potentials''? *J. Cardiovasc. Electrophysiol.* 10:1463–1466.
11. Hyatt, C. J., S. F. Mironov, F. J. Vetter, C. W. Zemlin, and A. M. Pertsov. 2005. Optical action potential upstroke morphology reveals near-surface transmural propagation direction. *Circ. Res.* 97:277–284.
12. Bishop, M. J., B. Rodriguez, J. Eason, J. P. Whiteley, N. Trayanova, and D. J. Gavaghan. 2006. Synthesis of voltage-sensitive optical signals: application to panoramic optical mapping. *Biophys. J.* 90:2938–2945.
13. Bernus, O., M. Wellner, and A. M. Pertsov. 2004. Intramural wave propagation in cardiac tissue: asymptotic solutions and cusp waves. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 70:061913.

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