LETTER

REPLY TO ENTCHEVA:

The impact of T-tubules on action potential propagation in cardiac tissue

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Since our observation that T-tubules can fail to propagate action potentials in diseased hearts (1), our studies have focused on understanding the consequences of these electrical defects for local Ca^{2+} release (2) and force production (3). More recently, we have started to explore the causes of electrical defects (4), focusing on the presence of electrical conduction failures, seemingly associated with a local drop in membrane excitability (5). The methodology developed through our work has allowed us to quantitatively assess T-tubular conductivity, thus permitting evaluation of the efficiency of passive spread of voltage changes across the cardiac cell. Although these passive electrical properties have been discussed in our article in some detail (4), the implications of the findings at the tissue level have been not been adequately explored.

In her letter, Entcheva (6) suggests a very inspiring scenario, carrying our finding to another level of complexity. Particularly interesting are the suggested implications of how voltage heterogeneities found in cells can affect the surrounding tissue: (*i*) electrical failure could be proarrhythmogenic, as supported by our previous works, and/or (*ii*) electrically heterogeneous myocytes could respond nonuniformly to external electric fields, such as applied via pacing leads and for defibrillation. The potential impact of T-tubules on intercellular propagation of action potentials is intriguing. So far, T-tubules have only been considered as a determinant of cell capacitance in propagation of passive depolarization (7). In fact, common and oversimplified schematizations generally neglect the extracellular electrical resistance. However, as demonstrated in our work, the complexity of the T-tubular system could yield regional extracellular resistances that exceed intracellular ones.

It is important in this context to underline that T-tubular conductivity strongly depends on the geometry of the T-tubular system itself. T-tubular diameter (8), T-tubular density (9), and ultrastructural organization giving rise to diffusion barriers (10) may well vary across species, perhaps explaining some of the differences in parameter ranges cited by Entcheva (6). In addition to differing phosphorylation levels of associated proteins (11), these changes can regionally modify T-tubular conductivity, making it hard to generalize the dynamic impact of T-tubules on propagation of passive depolarizations. Cardiac myocytes also deform with every cardiac cycle, and this is associated with alterations in subcellular membrane systems, such as T-tubules, which may further affect local ion gradients and diffusion.

We thank Emilia Entcheva for her insightful comments on how this complex network of membrane invaginations may affect action potential propagation at tissue levels, beyond conventional considerations related to the rapid spread of electrical activation throughout cells (6). Targeted FRAP experiments in intact beating tissue preparations may help to unravel the broader implications of extracellular electrical resistance across the transversal and axial tubular network for action potential propagation in physiological and pathological conditions.

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The authors declare no conflict of interest.

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