Transition From a Continuous to Discontinuous Understanding of Cardiac Conduction

Madison S. Spach

This personal reflection that celebrates the 50th anniversary of Circulation Research focuses on an area of integrative electrophysiology—the extension of continuous medium theory to the discontinuous nature of cardiac propagation produced by the cellular interconnections (gap junctions). It is appropriate to note that as a clinician who shifted to the laboratory, my collaboration with Drs Roger Barr, J. Francis Heidlage, and Paul Dolber has provided me long-term training and checks on ideas that involve conduction theory, computer modeling, and cardiac architecture. That process has been particularly influenced by advances in this field that involve the measurement and mathematical modeling of ionic channel currents, as well as the immunohistological targeting of cardiac gap junction connexins. Although journal references are not used here, I have felt compelled to mention a few scientists who advanced selected ideas about the spread of currents in cardiac muscle.

Continuous Cardiac Conduction Theory

It is noteworthy that the widespread use of optical mapping to measure spiral waves that represent the behavior of cardiac wavefronts at a macroscopic size scale illustrates the contemporary importance of continuous medium theory. Interestingly, van Cappele first described complex spiral wave activity for cardiac muscle in 1980 by generating a computer model of a continuous isotropic sheet. Nine years passed before this phenomenon was experimentally confirmed in cardiac muscle. With spiral waves, the nonuniformities necessary to initiate the conduction disturbances that lead to reentry are induced experimentally as repolarization inhomogeneities (primarily by introducing stimuli at two different sites). Spiral waves are mentioned at the outset because the concept of spiral waves at a macroscopic level and the concept of discontinuous conduction at a microscopic level have both gained acceptance during the past two decades as paradigms for mechanisms of cardiac arrhythmias. Thus, it may be of interest to the reader to consider how experiments done in the 1950s, as well as answers to questions that arose through the mid-1970s, indicated that cardiac muscle behaves electrically as a continuous medium.

The application of continuous cable theory to cardiac muscle began with Wiedmann’s experiment on a Purkinje fiber in 1952. The current he injected into a single cell altered the potential in cells that were multiple cells distant from the cell into which current was injected. He found a satisfactory fit of the falloff of the transmembrane potential with the solutions provided by continuous cable theory. After the electron microscope came into use about 1954, however, it became clear that cytoplasmic continuity between cardiac cells did not exist, because there was the high-resistance membrane around cells. This feature presented quite a paradox for a continuous medium. Woodbury and Crill then performed an experiment in which they injected current into a cell of a two-dimensional bundle. They found that the length constant of decay of the transmembrane potential in the longitudinal and transverse directions extended considerably beyond a cell’s length and width, respectively. They concluded that there must be low-resistance connections between cells to get the current from one to another, and these connections were subsequently demonstrated by Lloyd Barr to be the gap junctions (nexuses). Thus, by the late 1960s, the paradox seemed resolved. In intracellular space, there are connections between cells of sufficiently high conductance (or low resistance) to cause cardiac tissue to behave electrically like a continuous syncytium. This theory was then used in experiments at a macroscopic scale to explain differences in propagation from region to region on the basis of a difference in the sarcolemmal membrane characteristics of the ionic currents.

Ionic currents by themselves, however, do not determine propagation because the membrane characteristics must be combined with a theory that accounts for the structural properties of the conduction path. In the 1960s, it became apparent that the conduction velocity in cardiac bundles is greater in the direction of the long axis of the fibers than in the transverse direction, and in 1976 Clerc postulated that these directional differences in conduction velocity were due to a directional difference in axial resistivity. Using the assumption of a continuous but anisotropic medium for calf myocardium, he derived directional differences in resistance. The values of resistance he derived accounted for the directional velocity differences according to the classic inverse square relationship that Hodgkin had noted for a continuous cable. That is, in a continuous medium (even if anisotropic) the velocity varies inversely with the square root of the axial resistance while the temporal shape of the action potential remains constant.

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Experiments That Led Us to Conclude That Cardiac Propagation Is Discontinuous

In the late 1970s, we encountered serious difficulties in applying the above ideas to the analysis of the propagation of depolarization at a microscopic level. The difficulties are most clearly illustrated by recapitulating the paradoxical events as they occurred at that time. We were attempting to account for the variations in the shape and amplitude of extracellular potential waveforms that we recorded in normal mature canine ventricular muscle.

Initially, our interpretations and computer simulations were based on the assumption that the tissue behaved electrically as a continuous but anisotropic medium, eg, that the time course of the upstroke of the action potential remains constant when propagation occurs in different directions. The computed and measured results demonstrated gratifying agreement. We therefore considered the results to be important because the analysis showed that, while the shape of the transmembrane potential remained constant with different directions of conduction, associated variations in the shape of the extracellular potential waveforms provide a sensitive index of changes in velocity. Because our computer simulations were based on a constant shape of the transmembrane potential, we recorded action potential upstrokes while the direction of conduction was varied. When we compared the photographs of the action potentials, the multiple upstrokes appeared to have the same shape as Clerc had shown in calf myocardium. So, our initial conclusions were that continuous medium theory also applied to our results in mature canine ventricular muscle.

However, soon thereafter we encountered extracellular waveforms in which multiple notches and slurs occurred when the direction of conduction was changed from the longitudinal to transverse direction related to the fiber axis. These complex extracellular waveforms could not occur if the myocardium behaved as a continuous medium, even if it was anisotropic. Thus, we were faced with the following dilemma: Had we made an inadequate analysis of the ventricular transmembrane potentials?

We therefore performed new experiments to test the basic assumption that cardiac muscle behaves electrically as a continuous medium. We used digital recording rates of 30 000 Hz to measure the intracellular potential at single sites while the direction of conduction was varied with respect to the orientation of the fibers. For each record, the transmembrane potential was calculated by subtracting the extracellular potential (measured at the impalement site) from the intracellular potential. The results showed that indeed the shape of the transmembrane potential upstroke changed when the velocity was altered under conditions in which the membrane properties could not have changed. Fast upstrokes were associated with low transverse propagation velocities and slower upstrokes were associated with high longitudinal velocities. These changes were just the opposite of those produced by intrinsic changes in the excitatory ionic currents.

We therefore considered that the directional changes in the shape of depolarization were due to variations of electrical load produced by recurrent discontinuities in intracellular resistance which, in turn, are created by the cellular connections (gap junctions). Thus, at a cellular level cardiac propagation is a discontinuous process.

At that time, it was well appreciated that changes in the safety factor of conduction are monotonically related to the maximum rate of rise of the transmembrane potential ($V_{\text{max}}$), ie, the safety factor increases with increases of $V_{\text{max}}$ and it decreases with decreases of $V_{\text{max}}$. By assuming that cardiac muscle is best represented electrically as a discontinuous structure, one could predict an unexpected kind of propagation that would not be possible in a continuous structure. We reasoned that the geometric arrangement of the cellular connections that produce the discontinuities of resistance reverses the usual association of high velocity and high safety factor when there are disturbances in the membrane properties, such as a decrease in the available sodium conductance that is associated with early premature action potentials. This inverted relationship suggested that propagation within a single bundle could undergo one-way directional block, ie, propagation could continue in the transverse direction when block occurs in the longitudinal direction, with resultant reentrant propagation. Such a prediction was confirmed experimentally by delivering a train of regular stimuli followed by a single premature stimulus to a single site in atrial muscle bundles.

Conclusion

The arrhythmogenic and therapeutic implications of discontinuous cardiac conduction have been demonstrated by numerous investigators during the past two decades. A major feature illustrated by this personal reflection is different though, and is the following—it is important to check the basic assumptions one is using to interpret experimental and computer simulation results, because the initial ones used were wrong and it was a second look that led to the right directions.

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