

An Electric Field Mechanism for Transmission of Excitation Between Myocardial Cells

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A long-standing dogma in basic electrophysiology of the heart has been that the atrial and ventricular myocardial cells are interconnected by low-resistance pathways mediated by gap-junction connexon channels.¹ This dogma became established based on the publications of a number of investigators, including Weidmann,² Woodbury and Crill,³ and DeMello.⁴ It was concluded that the input resistance of myocardial cells in a bundle was very low (eg, 30 K Ω), the length constant (λ) of the bundle was very long (eg, 1.5 mm), and that local-circuit action current spreads readily from cell to cell. The ultrastructure of mammalian myocardium showed presence of numerous gap junctions.⁵ This dogma has become ingrained in most textbooks and advanced reference books dealing with the heart.

This dogma still lives on despite the facts that it is now accepted that the input resistance is high (eg, 5 to 40 M Ω) and the length constant is very short (eg, 150 to 350 μ m) (see references in Sperelakis and McConnell^{6,7}). For example, an input resistance for myocardial cells, measured in isolated cell pairs, was \approx 27 to 37 M Ω ,⁸ and the λ value for myocardial bundles was reported to be 357 μ m.⁹ Propagation in cardiac muscle is now accepted as being discontinuous (or saltatory) in nature.¹⁰ In addition, gap junctions are scarce or absent in the hearts of nonmammalian vertebrates, such as birds, lizards, frogs, and fish (for references, see Reference 6). Despite this, the hearts in those lower vertebrates function normally.

The low-resistance dogma was first challenged in 1959 by Sperelakis and colleagues,¹¹ in experiments on frog heart. Subsequently, they published a series of studies on mammalian hearts based on biophysical measurements and demonstrated that, in many cases, there were not low-resistance connections between myocardial cells. Most of this evidence is summarized in two recent review articles.^{6,7} This evidence included data showing that parallel strands of myocardial cells within a bundle cause the bundle to act as a cable with a relatively long length constant (eg, 1.0 to 1.5 mm), and that the length constant of the bundle dominates and thus can explain the long λ obtained by Weidmann² and others.

In parallel with the biophysical experiments, we carried out a series of theoretical studies, beginning in 1969 and continuing up to the present time. One seminal study, published in 1977 by Sperelakis and Mann,¹² gave a physical circuit analysis and a mathematical computer analysis that demonstrated that an electrical transmission of excitation can occur between heart cells not interconnected by low-resistance pathways. The mechanism for this propagation over a chain of cells was by the electric field (EF) that develops in the narrow junctional clefts between cells (intercalated disks) when the prejunctional membrane fires an action potential (AP) giving rise to a negative cleft potential (V_{jc}). The mathematical model was subsequently refined and expanded in a series of studies.^{13,14} One of these studies showed that K⁺ accumulation at the cell junction would facilitate propagation by the EF mechanism.¹⁵ Another one of these studies¹⁶ showed that propagation had a staircase shape or discontinuous conduction, and that propagation velocity was close to the physiological value. All excitable units in the surface membrane of each cell fired simultaneously, and the delay at each junction was \approx 0.4 ms. Thus, almost all propagation time was consumed at the cell junctions, resulting in the staircase shape.

This staircase shape is similar to what was found in theoretical studies of propagation in cardiac muscle.^{17,18} Excitation jumped from cell junction to cell junction. The staircase propagation can account for the discontinuous conduction observed in cardiac muscle by Spach et al.¹⁹ Subsequent theoretical simulations conducted by Spach et al.²⁰ also showed discontinuous conduction. Pertsov and Medvinskii²¹ also concluded that propagation can occur between excitable cells without the necessity of gap-junction low-resistance connections.

Sperelakis and colleagues^{22,23} constructed electric circuits that mimicked excitable membranes of heart cells, and then placed a number of these excitable units in series to simulate a chain of myocardial cells not connected by low-resistance pathways. Stimulation of the first excitable unit/cell resulted in propagation of excitation over the entire chain, with junctional delays of \approx 0.5 ms. When the last cell of the chain was connected back to the first cell, reentry of excitation occurred repetitively. Transmission of excitation from cell to cell apparently occurred by a combination of the electric field mechanism and some local-circuit current. Capacitive coupling also was demonstrated to occur when the cells were connected by capacitors.

Sperelakis and colleagues^{24,25} (Sperelakis N, Ramasamy L, Murali KPV, unpublished data, 2002) then embarked on a study of propagation in cardiac muscle and smooth muscle with simulated APs using the PSpice program (Cadence Co)

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for electronic circuit analysis and design. One advantage of this computer program is that the actual complex circuit can be drawn, and the values for the circuit components readily changed. The parameter values (for standard conditions) were selected to give a resting potential (RP) of -80 mV for myocardial cells and -55 mV for smooth muscle cells, AP overshoot to $+30$ mV and $+10$ mV, and maximal rate of rise of the AP ($+dV/dt$ max) of ≈ 150 V/sec and 10 V/sec, respectively. The parameter values were selected to reflect an input resistance of 20 M Ω for myocardial cells and 30 M Ω for smooth muscle cells and an input capacitance of 100 pF and 50 pF, respectively. Cell length was assumed to be 150 μ m and 200 μ m, respectively. Each simulated cell had 3 or 5 excitable units to represent the surface membrane (SM) and one excitable unit to represent each junctional membrane (JM) (intercalated disk). There were no low-resistance connections between cells. Most experiments were done on a linear chain of 6 cells (cardiac muscle) or 10 cells (smooth muscle). Electrical stimulation (rectangular current pulse of 0.5 nA and 0.5 ms) was applied to the inside of the first cell (cell No. 1) of each chain.

Stimulation of cell No. 1 caused excitation of that cell, followed by sequential activation of the other cells in the chain.²⁴ There was a junctional delay of ≈ 0.4 ms (cardiac muscle) or 4 ms (smooth muscle). The surface membrane units in each cell fired simultaneously, thus causing propagation to have a staircase shape (discontinuous conduction). Therefore, almost all of the propagation time is consumed at the cell junctions. A relatively large EF potential (negative) developed in each junctional cleft (V_{jc}) when the prejunctional membrane (pre-JM) fired an AP. This negative cleft potential depolarizes the postjunctional membrane (post-JM) by an equal amount due to a patch-clamp action. Thus, the post-JM is brought to its threshold for firing, which then brings the surface membrane to its threshold. The post-JM and pre-JM fire slightly before the surface membrane. V_{jc} causes a pronounced step on the rising phase of the AP in the post-JM. The magnitude of V_{jc} is a function of several factors, including the value of R_{jc} , the radial resistance (shunting) of the junctional cleft (which reflects the closeness of apposition of the two junctional membranes). The higher the R_{jc} , the greater the V_{jc} , and hence the faster the propagation velocity.

The extracellular longitudinal resistance had a dual effect on propagation velocity (θ).²⁵ The cell chain was assumed to be bathed in a large volume of Ringer solution connected to ground and having longitudinal (R_{ol}) and radial (R_{or}) components. Increase of R_{ol} and R_{or} above the standard values of 1.0 K Ω each, first produced some slowing of θ (eg, at 10 K Ω and 100 K Ω), followed by marked speeding of θ (eg, at 1.0 M Ω and 10 M Ω). The latter result indicates that local-circuit current flow between cells cannot be the mechanism for transmission of excitation across the junctions. This conclusion is also consistent with the observation that large increases in R_{jc} , the longitudinal resistance of the junctional cleft, higher than the standard value of 7Ω (eg, to values as high as 7.0 M Ω) had no effect whatsoever on θ .

Experiments were done to ascertain the effect of adding gap-junction (g-j) channels in parallel with the EF mechanism (Sperelakis N, Murali KP, unpublished data, 2002). To do

this, a variable resistance was placed across each junction in the chain, from the inside of one cell to the inside of the contiguous cell. It was found that adding only one g-j channel increased θ slightly, and adding 10 or 100 channels produced further increase in θ . However, adding 1000 or 10 000 channels caused θ to greatly increase way above the physiological value and the excited length to encompass all cells in the chain. Therefore, in those tissues in which gap junctions are present, only a small fraction of the channels must be open at any instant of time. Vaidya et al²⁶ reported that, in connexin43 (Cx43)-deficient knockout mice, propagation velocity is slowed in late embryonic ventricular muscle. In Cx40 knockout adult mice, conduction velocity in the His-Purkinje system was slowed to $\approx 59\%$ of the wild-type control.²⁷ It is very important to note that propagation did occur in the absence of connexons. The slowing of propagation observed is consistent with the present results.

Experiments were also performed to examine transverse propagation between parallel chains of myocardial cells, with no low-resistance connections between cells in each chain or between chains (Sperelakis N, unpublished data, 2002). The longitudinal resistance of the interstitial fluid (ISF) space between chains (R_{ol2}) and the radial (or transverse) resistance of the interstitial space (R_{or2}) was increased above their standard values of 100 K Ω and 100 Ω , respectively. The closer the packing of the parallel chains within a muscle bundle, the higher the R_{ol2} and the lower the R_{or2} . With the standard values, stimulation of cell No. 1 of the top chain (A-chain) produced propagation down the A-chain, followed by transverse propagation into the B-chain, then followed by propagation into the C-chain. The velocity of activation of cells in the B-chain and C-chain was faster than that in the stimulated A-chain, probably indicating multiple crossover points. Stimulation of cell No. 1 of the B-chain produced propagation down the B-chain, followed by transverse propagation simultaneously into the A-chain and C-chain. Raising R_{ol2} to 1.0 M Ω and 10 M Ω (to reflect tighter packing of the chains) caused faster transverse propagation. Raising or lowering R_{or2} had only little effect on transverse propagation, thus indicating that local-circuit current flow into the neighboring chains was not involved. Therefore, it is likely that the EF potential, developed in the interstitial space when the surface membrane units fire an AP, is the mechanism for the transverse spread of excitation. That is, R_{ol2} is equivalent to R_{jc} for longitudinal propagation. Barr and Plonsey²⁸ reported a similar electrical interaction through the interstitial space between parallel fibers of excitable cells. It was shown that when two isolated bundles of cardiac muscle are closely appositioned over a short distance, when one bundle was stimulated, the impulse jumped to the second bundle after a short delay.²⁹

In summary, the PSpice simulation shows that transmission of excitation across cell junctions in cardiac muscle and smooth muscle can occur by an electrical mechanism that does not involve low-resistance gap-junction connections and local-circuit current flow. The mechanism that is involved is the EF negative potential (V_{jc}) that develops in the narrow junctional clefts during excitation of the prejunctional membrane, which causes depolarization of the postjunctional

membrane to its threshold. The magnitude of V_{jc} depends on the magnitude of R_{jc} , the radial (shunt) resistance of the junctional cleft. R_{jc} reflects the closeness of apposition of the pre-JM and post-JM. Propagation along a chain of cells not only can occur when the external longitudinal resistance (R_{ol}) is very high but also is actually speeded. This fact, along with the fact that raising the longitudinal resistance of the junctional cleft (R_{jcl}) to very high values had no effect on propagation velocity θ , argues that local-circuit current flow is not involved in transmission from cell to cell. Transverse propagation also occurs between parallel chains of cells not interconnected by low-resistance pathways. Given that the external radial (transverse) resistance of the interstitial space (R_{or2}) had little or no effect on transverse propagation, this indicates that local-circuit flow is not the mechanism for the transverse spread of excitation. It is likely that the EF that develops in the narrow interstitial space during firing of the surface membrane of a cell acts to excite the cell in the neighboring chain. Consistent with this view, the longitudinal resistance of the interstitial space (R_{ol2}) had a pronounced effect on transverse propagation. Therefore, propagation can occur both longitudinally and transversely by an electrical means that does not involve gap-junction connections and local-circuit current. When gap-junction channels are added, they work in parallel with the EF mechanism to speed velocity. But, when 1000 or 10 000 channels are added, propagation velocity becomes very fast and nonphysiological.

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