Effects of the Discrete Pattern of Electrical Coupling on Propagation through an Electrical Syncytium

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SUMMARY We used numerical integration techniques to simulate action potential propagation along one-dimensional strands of cells coupled with electrical junctions. We considered the standard case to be a series of cardiac cells (20 μm in diameter, 50 μm long) with intercellular coupling such that the effective longitudinal resistance was 200 Ω cm. The membrane properties were represented by the model of Beeler and Reuter (1977) (Sharp and Joyner, 1980). By increasing R (and thus decreasing the space constant, L), we showed that effects due to the discrete cell length, ΔX, became apparent when ΔX/L was greater than about 0.2, producing an increased maximal dV/dt but a decrease in peak inward current. We also simulated the effects of a periodic spatial variation in R, representing a structure with groups of well-coupled cells but with minimal coupling between the groups. Even with a constant membrane model and cell size, variations in the spatial pattern of interconnection produced significant changes in action potential shape and velocity, with some patterns producing decremental conduction or propagation failure.


It is generally agreed that propagation of action potentials through a complex electrical syncytium such as the heart depends upon excitability properties associated with cell membranes and the pattern of interconnection of cells, including factors which are geometrical (e.g., fiber orientation) and electrical (e.g., effective conductance of the gap junctions between cells) (see recent reviews by Reuter, 1979; Vassalle, 1979; and Sperelakis, 1979). Evidence has accumulated that there are significant variations, throughout the heart, in both the excitability and the interconnection properties (DeFelice and Challice, 1969; Clerc, 1976; Pollick, 1976; Spach et al., 1979). Previous work on simulation or analytical studies of action potential propagation in the heart (Lieberman et al., 1973; Sharp and Joyner, 1980) have treated a strand of tissue as if it could be reduced to the core-conductor model appropriate for nerve axons. Previous work by Heppner and Plonsey (1970) showed that, for two coupled cells, the electrical transmission of the action potential was critically dependent upon the coupling resistance.

Ignoring, for the present work, other complications such as the limited extracellular space and the transverse tubular system, the assumption of a core-conductor model implies that the individual cells are much shorter than the length constant and that all the cells are homogeneously coupled together with low resistance junctions. Thus, the internal resistance per unit length is a composite of the cytoplasmic resistance and the intercellular resistance. These assumptions are not necessarily valid for regions of the heart where the cells are not lined up into strands or where the coupling between cells is neither of low resistance nor, possibly, homogeneous. In this paper we present simulations in which the cell size and excitable membrane properties are held constant, but the pattern of interconnection is varied. We do not mean to imply that the cell size and excitable membrane properties are constant throughout the heart, but we use this technique to isolate the effects of interconnection of cells on the propagation of action potentials.

Methods

The simulation method was as previously described (Sharp and Joyner, 1980) with each cell represented by a membrane model (Beeler and Reuter, 1977). We assume in all of our simulations that the individual cells are isopotential. With this assumption, the intercellular resistance includes the cytoplasmic resistance as well as the resistance at the junctional region between the cells. The cable equation was solved numerically by an extension of the implicit method of Crank and Nicholson (1947) (see Joynen et al., 1978). Parameters were as follows for normal conditions:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Definition</th>
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<tr>
<td>Δt</td>
<td>5 μsec</td>
<td>time interval for integration</td>
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<tr>
<td>ΔX</td>
<td>50 μm</td>
<td>spatial interval for integration</td>
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<td>a</td>
<td>10 μm</td>
<td>cell radius</td>
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<tr>
<td>R_i</td>
<td>200 Ω cm</td>
<td>longitudinal resistance</td>
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All of the simulations used $\Delta X = 50 \mu m$ except Figures 4-6, in which we specifically changed either $R_i$ or $\Delta X$ to show the equivalent effects on the action potential parameters. Computed parameters included the membrane current, $I$ (mA/cm$^2$), the transmembrane potential, $V$ (mV), and the extracellular field, $P$ ($\mu V$). The extracellular field was computed by the method of Spach et al. (1973, Eq. 2). This computation assumes a cylindrical strand in which the extracellular potential is much smaller than the transmembrane potential. For the potential field just outside the strand, the computation requires an integral, along the entire strand, of the total current (ionic plus capacitative) at each location along the strand. Thus, the extracellular field depends not only on the magnitude of the membrane current, but also on the spatial distribution of membrane current.

The assumption that the individual cells are isopotential can be rigorously tested by comparing simulations in which the spatial interval for integration, $\Delta X$, is set equal to the cell length to simulations in which the $\Delta X$ chosen is much less than the cell length. We evaluated this by simulating a strand of cells (with cell length $50 \mu m$) with $\Delta X$ either $50 \mu m$ (case 1) or $10 \mu m$ (case 2). For case 2, an additional assumption must be made regarding the relative contribution of the cytoplasm and the cell junctions to the effective longitudinal resistance. If all of the resistance is in the cytoplasm, then the same value of $R_i$ would be used for all five segments which constitute each cell length, and, since the junctions would have negligible resistance, the strand would act as a simple core conductor similar to an axon. If the cytoplasmic resistance were much smaller than the junctional resistance, then the choice of the cell length as the $\Delta X$ would be justified, since no voltage deviations within a cell could exist. Since we are particularly interested in the effects of the discrete pattern of electrical coupling on action potential shape and conduction velocity, we evaluated these parameters for case 1 and case 2 as follows:

1. For a strand with effective longitudinal resistance of $\Omega$ ohm cm the maximal $dV/dt$ was 102.5 V/sec with $\Delta X = 50 \mu m$. For $\Delta X = 10 \mu m$ and with all of the resistance assumed to be in the cytoplasm, the maximal $dV/dt$ was 102.3 V/sec. For $\Delta X = 10 \mu m$ and the cytoplasmic resistance assumed to be $100 \Omega$ cm (and junctional resistance added to every fifth segment to produce an effective longitudinal resistance of $200 \Omega$ cm) the variation in maximal $dV/dt$ for the five segments which constituted a single cell was from 102.4 to 102.5 V/sec. The conduction velocity varied less than 1% for all three of these simulations.

2. We show in our results that an increase in the effective longitudinal resistance to $500 \Omega$ cm produces an increase in maximal $dV/dt$ to 115.0 V/sec of $\Delta X = 50 \mu m$. We tested the dependence of this effect on our assumption of $\Delta X = cell$ length by simulating a similar strand with $\Delta X = 10 \mu m$ and cytoplasmic resistance $10 \Omega$ cm (with junctional resistance adjusted to produce an effective longitudinal resistance of $5000 \Omega$ cm). For this case the range of maximal $dV/dt$ for the five segments constituting a single cell was 114.75 to 115.0 V/sec.

### Results

In the first case (Fig. 1), we simulate a strand in which there is a long region of normal $R_i$ ($200 \Omega$ cm) followed by a long region of higher $R_i$ ($1000 \Omega$ cm).

**Figure 1** Results of a simulation of a strand with a long initial region with $R_i = 200 \Omega$ cm followed by a long region with $R_i = 1000 \Omega$ cm. Points A and B are in the middle of the regions, respectively. Parameters plotted are: $V$ (membrane potential), $I$ (ionic membrane current density), and $P$ (extracellular potential at a location 2.5 $\mu m$ from the cell membrane). Vertical scale marks correspond to 10 mV ($V$), 0.025 mA/cm$^2$ ($I$), and 5 $\mu V$ ($P$). Horizontal scale marks are for 0.5 msec (part A) or 0.70 mm (part B). For part A, the parameters are plotted as functions of time with a horizontal shift for $V(B)$, $I(B)$, and $P(B)$ corresponding to the conduction time between the two points. For part B, the parameters are plotted as functions of distance with $V(A)$, $I(A)$, $P(A)$ plotted at the time when $V(A)$ exceeds 50 mV from the resting level; $V(B)$, $I(B)$, and $P(B)$ are plotted at the time when $V(B)$ exceeds 50 mV from the resting level. Cell diameter = 20 $\mu m$, cell length = 50 $\mu m$, $\Delta t = 10 \mu sec$, Beeler-Reuter membrane model.
The corresponding resting length constant are 1120 and 500 μm, so our cell length of 50 μm is still considerably less than either length constant. The three parameters of interest here are the membrane potential, the membrane ionic current density, and the extracellular field, all of which are functions of distance and time. Plots of these parameters as functions time for points A (in the first region) and B (in the second region) are shown in the upper part of the figure. Recordings from point B are shifted to the left by the conduction time between the two points to show that the change in R_i did not significantly affect the time course or amplitude of the membrane potential or the membrane ionic current density. The decrease in the extracellular field amplitude thus is due to the decrease in the spatial extent of the current density, as shown in the lower part of the figure. Here, the three parameters are plotted as functions of distance. The parameters for each point are plotted at times corresponding to the time at which the action potential has risen 50 mV from the resting potential at that point. Note that the spatial profile of all three parameters is much narrower for point B. As might be expected, the conduction velocity within the two regions is simply proportional to the \(-\frac{1}{2}\) power of R_i.

At the junctional region between the two regions, the three parameters plotted in Figure 1 show interesting changes over a considerable length, even though the transition in R_i is made abruptly. In Figure 2, we show these changes for a strand with a spatial distribution of R_i as shown in part A. For parts B, C, and D, we have plotted membrane potential, ionic membrane current density, and extracellular potential as functions of time for the locations indicated by the cell numbers. As the action potential approaches the region of high R_i (compare cell 70 to cell 40), there is an increased magnitude and rate of rise of the membrane potential and a decrease in the time integral of the ionic membrane current density, but no appreciable change in amplitude. The extracellular potential shows the most striking changes, with the early positive phase being accentuated and the later negative phase diminished. As was shown in Figure 1, these parameters for a cell in the center of the high resistance region (cell 100) are the same as at a location far away from the high resistance region (cell 40) except for a decreased magnitude of both phases of the extracellular potential. As the action potential approaches the second region of low resistance there are other changes which occur (compare cell 120 to cell 40). The rate of rise of membrane potential is now decreased and the peak is rounded with an early partial repolarization. The membrane ionic current density has a slightly increased amplitude and a marked prolongation. The extracellular potential now has a diminished positive phase but a negative phase of increased magnitude and duration. At cell 130, just after a decrease in R_i, the membrane potential has a slow rate of rise with a delayed rapid phase of depolarization that is also seen as an electrotonic interaction at cell 120. The membrane ionic current density has a low amplitude but prolonged time course. The extracellular field has a very small positive phase and a large, prolonged negative phase.

It should be noted here that the results of Figures 1 and 2 would be expected also for an axon of infinite length, for which the division into segments of length ΔX is a purely theoretical division for the sake of computation (Joyner et al., 1980). If we now consider that the ΔX for a strand of electrically coupled cells actually represents a physical parameter (cell length), then we can examine the consequences of changes in cell length and/or intercellular coupling on the shape and velocity of a propagating action potential. Several features of the Beeler-Reuter model were not directly derived from experimental data (in particular, the activation kinetics of the sodium current). Therefore, a quantitative application of these results to ventricular muscle must be considered cautiously. If we repeat the simulation of Figure 1, but now use R_i = 8000 Ω cm for the second half of the strand (instead of R_i = 1000 Ω cm), there are now noticeable differences in the rising phases of the action potentials in the two regions (Fig. 3). The two voltage waveforms are superimposed to show that the response in the normal region (marked by an “*” at three points) has, compared to the response where R_i = 8000 Ω cm, a smaller maximal dV/dt, and a higher peak amplitude. The segment with higher R_i has a decreased peak inward current (even though the maximal dV/dt is greater) and a reduced extracellular field.

Figure 4 illustrates that these changes are due to the discrete nature of the cells. The abscissa is in units of either ΔX/50 or (R_i/200)^0.5 and the ordinate is the maximal dV/dt obtained from the propagating action potential. Identical results were obtained by having ΔX = 50 μm and varying R_i or by having R_i = 200 Ω cm and they varying ΔX. The critical parameter determining the rising phase of the action potential was shown to be ΔX/L, where L = (0.5 a R_i/R_m)^0.5 and is this a measure of the cell size in units of the resting electrotonic length constant. Similarly, as shown in Figure 5, the velocity of propagation also depends on this parameter. In this figure the abscissa is the same as for Figure 4. For the ordinate, we plotted the ratio of the measured conduction velocity to that predicted from the homogeneous axon results where, if ΔX is vanishingly small, velocity does not depend on ΔX; and the velocity should vary inversely as R_i. Again, the presence of discrete cell length produces an effect (decreased velocity) that varies as ΔX/L.

As pointed out by Lieberman et al. (1973), there is a critical high value of R_i for which propagation for homogeneous strands of discrete elements will fail, and this critical value is decreased at higher
values of $\Delta X$. Some interesting consequences of this effect are shown in Figure 6. Here, we simulated a strand, as in Figure 1, with an initial region of $R_i = 200 \, \Omega \text{cm}$ followed by a region of $R_i = R_i^*$. We found the critically high value of $R_i^*$ for successful propagation as a function of the segment length used for the simulation (part A, with the ordinate expressed as the resulting length constant). We used the resulting length constant as the ordinate in order to illustrate the linear relationship, implying a constant critical value of $\Delta X/L$. In parts B, C, and D we plot membrane potential vs. time for a series of points spaced 800 $\mu$m apart for three simulations. In each case, $R_i$ for the first 3 mm was 200

Figure 2 Part A: Spatial distribution of $R_i$ along a strand, cell length = 50 $\mu$m. Parts B, C, D: Plots vs. time of membrane potential (part B), ionic membrane current density (part C), and extracellular potential (part D) for six points along the strand diagrammed in part A. Curves for different points are offset vertically for clarity with a zero line for each point labeled with the cell number. The vertical offset for each zero line corresponds to 100 mV (part B), 0.2 mA/cm$^2$ (part C), or 20 $\mu$V (part D).

Figure 3 Simulated results for membrane potential ($V$), membrane ionic current ($I$), and extracellular field ($P$), for two segments of a strand in which there is a long region of normal $R_i$ (200 $\Omega$ cm) followed by a long region of high $R_i$ (8000 $\Omega$ cm). Results are plotted for segments in the centers of the two regions, respectively. The curves are superimposed by a time shift corresponding to the conduction time between the two points. Results for the low resistance region are marked at several points with an "*". Scale factors are as for Figure 1.

Figure 4 Effects on maximal $dV/dt$ produced by either increasing $\Delta X$ (cell length) or increasing $R_i$. On the abscissa, the scale represents the relative effects of either parameter change on the ratio of $\Delta X$ to the resting length constant.
The assumed cell length was 400 (B), 200 (C), or 100 (D) μm, and the results show propagation failure (B), decremental conduction (C), or successful propagation (D, but notice change in action potential waveform for the rising phase).

We now consider a particular case in which, as opposed to long regions of a constant value of Rₐ between cells, we distribute the intercellular resistance inhomogeneously so that some groups of cells are connected with low resistance junctions but the connections between the groups is varied. This corresponds roughly to an anatomical pattern of "islands" of cells which are well coupled but with a small amount of surface contact between adjacent "islands." We assume that all cells within a group are connected with an Rₐ of 200 Ω cm in a linear array. Each group has only one cell-to-cell contact with each adjacent group, and all the groups are in a linear array. The overall anatomy is then completely specified by two parameters: N, the number of groups, and L, the total length of the system.

The membrane potential vs. time for a strand with Rₐ = 200 Ω cm over a length of 6 mm, followed by a length of 8 mm with Rₐ = 11,500 Ω cm. For each part, the points for which the membrane potential is plotted are 800 μm apart, but the ΔX used for the simulation was 400 (B), 200 (C), or 100 (D) μm. The individual curves are offset vertically for clarity.
of cells in a group, and $R_i^r$, the intercellular resistance between groups. The effective value of $R_i$ between adjacent cells is shown graphically in Figure 7 for $N = 5$. The effective longitudinal resistance measured over a length much greater than N cells would then be $(200(N - 1) + R_i^r)/N$, the weighted average of the individual $R_i$ values. For $N = 1$, this reduces to the homogeneous strand already discussed if $R_i^r = 200 \, \Omega \cdot \text{cm}$. For a given value of effective longitudinal resistance, there exists, for each value of N, a unique value of $R_i^r$. Thus, we can select a value for effective longitudinal resistance and see how propagation is affected by the parameter N as a measure of the "packaging parameter" of this tissue representation.

For a given value of effective longitudinal resistance, both the action potential shape and conduction velocity vary with the N value chosen. Figure 8 shows, for an effective longitudinal resistance of 1000 $\Omega \cdot \text{cm}$, the changes in the upstroke of the action potential (plotting V and dV/dt) as the parameter N is varied (parts A–C correspond to $N = 1, 5, \text{and} 13$). For $N = 1$, the action potential shows a symmetrical rising phase as shown by the simple monophasic shape of dV/dt. For all values of N, we plotted V and dV/dt for two segments, each centrally located within a group of well-coupled cells, with a distance between the segments being about 1 mm. The first segment plotted in each case is about 5 mm from the point of stimulation. Comparison of the responses at the two segments plotted for each value of N indicates successful propagation. Decremental propagation occurred for $N > 14$. As the parameter N is increased, several phases of the upstroke become apparent with a general prolongation of the rising phase but an increase in the maximum value of dV/dt (part B). Following the peak of the action potential, there is an early partial repolarization phase (negative dV/dt) which is accentuated more at larger values of N. For larger values of N (part C) the maximal value of dV/dt is decreased and the rising phase shows several components. The graph of part D shows how the maximum value of dV/dt varied with N, for this particular value of effective longitudinal resistance (1000 $\Omega \cdot \text{cm}$).

In the previous results, the effective longitudinal resistance was held constant by varying the parameter $R_i^r$ as N was varied. Thus, the corresponding values of $R_i^r$ for $N = 1, 5, 13, \text{and} 15$ were 1000, 4200, 10600, and 12200 $\Omega \cdot \text{cm}$. One might expect to find some relationship between this peak value of $R_i^r$ and the success or failure of propagation, since $R_i^r$ is the limiting factor for current flow from one group of cells to an adjacent group of cells. From Figure 8, it was clear that the conduction velocity decreased as N increased. More complete data is shown in Figure 9. For this plot, each point represents the results of a simulation in which a strand was represented by 200–500 segments where the $R_i$ between adjacent segments was 200 $\Omega$ cm except as needed to create
a desired effective longitudinal resistance with a
desired value of $N$. The solid line indicates the
results for $N = 1$ and has, as expected on this log-
log plot, a slope of $-0.5$, but the points have a small
negative deviation at higher values of $R_i$ (see Fig.
5). Several connected sets of points correspond to
the listed value of $R_i$; and the number with each
point is the value of $N$. Several features are appar-
etent in these results. First, for all values of effective
longitudinal resistance, an increase in the value of
$N$ produces a decrease in the conduction velocity.
Second, as $N$ increases, the occurrence of decre-
mental conduction and conduction failure depends
on the value of $R_i$. For $R_i$ equal to or less than 6500
$\Omega$ cm, propagation is always successful. For $R_i$
greater than or equal to 8000 $\Omega$ cm, conduction
failure will occur for $N$ greater than some critical
value, with the critical $N$ value being lower for
higher $R_i$ values. In this case, conduction failure
occurs from $R_i = 8000$ ($N > 26$) or for $R_i = 10000$
($N > 16$), but these specific values depend upon the
membrane model used and the cell length.

For a fixed high value of $R_i$ we find that, for $N$
> 1, the action potential is encountering a succes-
sion of "barriers" to current flow. Thus, a periodic
pattern of intercellular resistance should lead to
periodic variations in action potential shape. The
data of Figure 10 were generated by simulating
strands with an $R_i$ distribution as shown in Figure
7, but with $R_i$ fixed at 4200 $\Omega$ cm, while $N$ is varied
from 1 to 51. The two horizontal lines correspond
to the cases where $N = 1$ and $R_i = 4200$ or 200 $\Omega$
cm, with corresponding values of maximum $dV/dt$
of 113 and 102 $V/sec$. The maximum $dV/dt$ is
plotted for each case as a function of distance.
Segment 250 on the abscissa always corresponds to
the center of one of the periodic series of $R_i$ changes.
The results for each value of $N$ were obtained from
the central region of a long (500 segments) strand,
and these changes in maximum $dV/dt$ were indeed
periodic with distance. For large values of $N$, the
action potential shape should approach the normal
waveform in the central region between $R_i$ peaks,
as shown for the case $N = 51$. Since propagation is
occurring in a left-to-right direction, the rise in $dV/$
dt to the right of the center point is easily under-
stood, since the action potential is approaching a
high resistance barrier. The decline in $dV/dt$ to the
left of the center point is due to the electrical load
imposed by the region of low $R_i$, on the action
potential that has just gone through a region of
high $R_i$. For intermediate values of $N$, the results
are somewhat surprising. For $N = 5$, the maximum
$dV/dt$ is greater than for $N = 1$, even though the
effective longitudinal resistance is lower (effective
$R_i = 4200$ for $N = 1$, 1000 for $N = 5$). Recall that,
for the homogeneous strand, the effects on action
potential shape depended on $\Delta X/L$. Thus, for $N$
= 5, the effective $L$ has decreased by approximately
$\left(\frac{4200}{1000}\right)^{0.5} = 2.05$; but, since the five segments
between each peak of $R_i$ is nearly isopotential, the
effective $\Delta X$ is about five times longer than the true
segment length of 50 $\mu$m. Thus, the rising phase of
the action potential shape, for a given effective
longitudinal resistance, is very sensitive to the way
in which the resistance is distributed, but the changes
can be explained on the basis of changes in the
effective $\Delta X$ (for intermediate values of $N$) or
on the basis of variable load encountered by the
propagating action potential (for large values of $N$).

Discussion

In this study we have presented results of simu-
lated propagation along a unidimensional electrical
syncytium of cells with constant cell dimensions
and cell membrane excitability properties (the Bee-
ler-Reuter model for ventricular muscle cells). For previous simulations of nerve axons, we have utilized the core-conductor representation in which the $\Delta X$ used was some arbitrary small length over which the membrane was "nearly" isopotential. In the present work, the $\Delta X$ corresponds to a single cell, but the same general form of solution method was used with the added condition that the parameter $R$, which generally represents cytoplasmic resistivity [$\Omega$-cm] is now equated to a value that includes the cytoplasmic resistivity and the cell-to-cell resistance into an equivalent term, and is also variable over distance. With this modification we have modeled two types of intercellular geometry: the case where all the cell-to-cell couplings have some value $R_s$, and the case in which the cells are arranged into groups so that, within each group, cell-to-cell resistance is low, but the group-to-group resistance ($R_g$) can be much higher. Our investigations are necessarily qualitative to the extent that both the specified geometry and the specified membrane model are oversimplifications, but we feel that the general features of the geometrical effects should be independent of the specific modeling assumptions we have made. One particular qualification we should add is that the relationship between the changes in the action potential shape and the parameter $\Delta X/L$ is affected by the choice of membrane model for the simulations. This might be expected since the effective 'space constant' in the region of the rising phase of the action potential depends on the rapidly changing membrane conductance.

It is generally appreciated that the temporal shape of a propagating action potential will change if the membrane properties of the tissue are changed (e.g., following changes in the extracellular potassium concentrations (Dominguez and Fozzard, 1970) or in response to a premature stimulus (Singer et al., 1967). For a homogeneous axon, it has been shown (Hodgkin, 1954) that changes in longitudinal resistivity do not affect the shape of the propagating action potential. Regional changes in longitudinal resistance of axons have been shown to produce changes in action potential shape at the transitional zone (Joyner et al., 1980). Several authors have shown changes in conduction velocity in cardiac tissue depending on directional differences in cell-to-cell coupling (Sano et al., 1959; Clerc, 1976; Spach, 1979). Changes in action potential shape due to changes in the direction of propagation were observed in the AV node (Janse, 1969) and, more recently, in the atrial and ventricular endocardium (Spach et al., 1981). Propagation in the direction of high $R$, produced changes in action potential shape (as compared to the shape for propagation in the direction of low $R$), including increases in the maximal $dV/dt$ and notches in the rising phase (cf. our Figs. 3 and 4).

Our results illustrate some of the hazards involved in applying the core-conductor model to propagation through an electrical syncytium of cells. For an axon, a simulation of a large number of short segments will approach the continuous "real world" by making the segments vanishingly short. However, for the syncytium, when the cell length exceeds the $\Delta X$ used for the simulation, the segments are no longer equivalent. Especially for regions of the heart where conduction velocity is low and intercellular resistance may be high (e.g., nodal tissue), it is likely that cell-to-cell resistance is much higher than the cytoplasmic resistance across a single cell. It is also clear that these regions have complex anatomical arrangements with a large amount of connective tissue surrounding groups of cells and the cells are generally quite small. Another area in which the simple core-conductor model might not be applicable is the area of a "mottled" infarction in which there may well be "islands" of normal tissue interspersed with regions of injured and perhaps electrically uncoupled cells. Variations in fiber orientation may also produce effects not predicted from the uniform core conductor model since, while propagation along a bundle of cells may be continuous and rapid, propagation in a transverse direction between bundles may occur through infrequently spaced areas of contact, and thus the action potential shape would vary with the direction of propagation, as has recently been demonstrated experimentally by Spach et al. (1981).

The geometrical effects we are studying are in some ways similar to other work on models of inhomogeneous axons (Goldstein and Rall, 1974; Khodorov and Timin, 1975; Joyner et al., 1980). In these models, the effects of an alteration in axon radius encountered by a propagating action potential are similar to the results we show in Figure 2, where the alteration in electrical load is produced by a regional change in intercellular resistance. The results for a homogeneous strand with high intercellular resistance, or the periodic distribution of high intercellular resistance, are fundamentally different, since the effects are produced by the discrete size of the coupled cells. There is an interesting analogy between these results and the saltatory conduction produced in myelinated axons (Fitzhugh, 1962; Moore et al., 1978). In these axons, there are small active patches of membrane separated longitudinally by much longer regions of myelination. Therefore, the nodes might be considered as discrete elements coupled to each other by the longitudinal resistance of the internodal regions. However, this analogy is not really productive in understanding the effects of discrete cell size on cardiac propagation. For the myelinated fiber, the nodal length is very much shorter than the space constant. Also, considering the internodal region as a simple resistor is not appropriate, since we showed earlier (Moore et al., 1978) that the conduction velocity is strongly affected by the myelin capacitance, minimally affected by the nodal length, and not affected at all by the length of the internodal
region. An intuitive explanation of the changes we have shown in the rising phase of the action potential as the discrete cell length becomes an appreciable part of the length constant (or when a nearby isopotential group of cells is poorly coupled to another group of cells) is that the early part of the action potential is prolonged due to the difficulty in passing current from cell to cell, whereas the rate of rise is increased because, once excitation is established, there is less current flow on to the next region to be excited. An exact description of these effects will demand more quantitative information on the kinetics of the sodium current.

For homogeneously distributed longitudinal resistances and cell lengths much less than the resting length constant, there is no effect of $R_i$ on the temporal shape of the action potential or the ionic membrane current. The spatial extent of these parameters during the upstroke of the action potential is decreased with increasing $R_i$, and, thus, the extracellular field potential is decreased with increasing $R_i$. When there are regional differences in $R_i$, there are changes at the transitional region, in the temporal shape of the action potential, the ionic membrane currents, and the extracellular field, all of which can be explained by the variation in electrical load encountered by the propagating response.

From our present simulations we may summarize the following points about the effects of the distribution of intercellular resistance on propagation:

1. When the cell length becomes an appreciable fraction of the resting length constant, there are several deviations from the simple core-conductor theory. The action potential shape shows increased maximal $dV/dt$ but a prolonged rising phase. The maximal inward current is decreased in magnitude and the conduction velocity is decreased.

2. For a periodic arrangement of cells in well-coupled groups with poor coupling between groups, there are two important parameters: $N$ (the number of cells in a group) and $R_i$ (the effective coupling resistance between groups). (a) For a given level of effective longitudinal resistance, increases in $N$ (with corresponding increases in $R_i$) produce lowered conduction velocity but increased maximal $dV/dt$, unless $N$ exceeds a critical value at which conduction fails, this critical value being lower for higher values of effective longitudinal resistance. (b) For a given level of $R_i$, increases in $N$ produce a decrease in effective longitudinal resistance and thus (for a moderate range of $R_i$) an increase in conduction velocity. For larger $R_i$ values, increases in $N$ lead to conduction failure due to the increasing electrical load imposed by the increasing number of well-coupled cells adjacent to each region of increased resistance and also to the limitation to current flow produced by the high localized resistance.
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