Propagation through Electrically Coupled Cells
Effects of Regional Changes in Membrane Properties

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SUMMARY. The normal process of excitation of the heart involves propagation of action potentials through cardiac regions of different anatomy and different intrinsic membrane properties. Although our understanding of these properties is still incomplete, it is well accepted that the parameters measured from a single cell penetration in an electrical syncytium (e.g., action potential duration, rate of rise, and velocity) reflect not only the properties of that cell but also the electrotonic interactions with other cells to which the recorded cell is electrically coupled. We have used simulation techniques to predict the spatial distribution of action potential parameters resulting from discretely localized alterations in the intrinsic membrane properties of some of the cells of an electrical syncytium. We have shown that the resulting spatial distribution is markedly different for alterations in plateau and pacemaker currents vs. rising phase currents, and that other factors, such as the site of stimulation and the underlying spatial pattern of cell-cell coupling resistance, also modify the spatial distribution of action potential properties resulting from a discrete regional change in intrinsic membrane properties. (Circ Res 53: 526-534, 1983)

THE sequence of excitation of the various regions of the heart involves the propagation of action potentials through electrically coupled cells that have differing anatomical patterns of connections and differing intrinsic membrane properties. In many cardiac regions (e.g., Purkinje vs. ventricle, endocardium vs. epicardium), there are easily measured differences in action potential properties (e.g., rate of rise, conduction velocity, action potential duration). Our knowledge of either the pattern of cell-cell coupling or of the regional variation in intrinsic membrane properties is far from complete. Nevertheless, it is possible with simulation techniques to explore the ways in which a particular spatial distribution of mathematically defined membrane properties produces a particular spatial distribution of action potential parameters. There are many examples of experiments in which electrotonic interactions have been shown to influence the action potentials recorded from a cell in an electrical syncytium [e.g., the AV node (Janse, 1969), Purkinje-ventricular junction (Mendez et al., 1969), isolated Purkinje strands with a sucrose gap-resistive barrier (Antzelevitch et al., 1980), electrically coupled cell aggregates (Clapham et al., 1980), and regional ventricular ischemia (Janse and van Capelle, 1982)].

In this paper, we investigate the relationship between the spatial distribution of intrinsic membrane properties (as described by \( I_m \), the membrane current, mA/cm\(^2\), as a function of voltage and time) and the resulting spatial distribution of action potential parameters. We find that a spatially discrete regional change in some membrane properties (e.g., plateau currents) produces a much larger and more gradually distributed spatial distribution in action potential duration (APD), whereas regional changes in currents associated with the action potential rising phase produce very discretely localized changes in the spatial distribution of conduction velocity and the rate of rise of the action potential. In addition, the spatial distribution of parameters determining the rate of spontaneous firing produces marked effects on the firing pattern of the cells, even when the entire system of cells is entrained at a common frequency.

Methods

A cardiac strand is composed of many individual cells, with irregular shapes, in contrast to an axon with a simple cylindrical membrane area (see Fig. 1). Very similar techniques can be derived for simulating action potential propagation in either an axon or a strand. We assume the cardiac cells have a constant surface-to-volume ratio, \( S_v \), and are electrically coupled so that the combination of cytoplasmic and intercellular resistance produces a net longitudinal resistivity \( R \) (ohm cm). For any cross-section of the strand, the number of cells intersected will be proportional to \( a^2 \), where \( a \) is the strand radius. For a short length \( \Delta x \) of the strand, we will assume that the cells are isopotential and have a total membrane area of \( \pi a^2 \Delta x S \), (volume \( \times \) surface/volume), or \( N S V_v \), where \( V_v \) is the average cell volume and \( N \) is the number of cells contained within the volume \( \pi a^2 \Delta x \). Thus, \( N = \pi a^2 \Delta x / V_v \). From the equivalent circuit shown in the figure, we can derive, for
FIGURE 1. Diagram of a cardiac strand and an equivalent cable circuit S and $R_s$ are the membrane area and longitudinal resistance for a length $\Delta x$.

a homogeneous strand (Joyner et al., 1982):

$$\frac{1}{R_S} \frac{V_{j+1} - 2V_j + V_{j-1}}{\Delta x^2} = C_m \frac{\partial V_j}{\partial t} + I_m$$  

(1)

We introduce a superscript to indicate time, with $V_j^{\text{t+1}}$ being the membrane potential of segment $j$ at time $t$. We approximate $\partial V_j/\partial t$ as a forward difference, $(V_j^{\text{t+1}} - V_j^{\text{t}})/\Delta t$. We replace the second central difference (Crank and Nicholson, 1947) with the average of the second central difference at time $t$ and at time $t+\Delta t$. We can then rearrange to:

$$-KV_j^{\text{t+1}} + (2K + 1)V_j^{\text{t+1}} - KV_{j+1}^{\text{t+1}} = K(V_{j+1}^{\text{t}} + V_{j-1}^{\text{t}}) - 2(K - 1)V_j^{\text{t}} + \Delta t I_m/C_m$$  

(2)

where

$$K = \Delta t/(2 R_s C_m S_0 \Delta x^2)$$

for each segment $j$.

This has the general form of

$$b_j V_j^{\text{t+1}} + d_j V_j^{\text{t+1}} + a_j V_j^{\text{t+1}} = c_i.$$  

(3)

As described previously (Lieberman et al., 1973; Joyner et al., 1978), this set of equations can be easily solved at each time step for $V_j^{\text{t+1}}$ for $j = 1, 2, \ldots, M$ by matrix techniques.

If we now allow the strand to be spatially inhomogeneous, we must describe the parameters $S$ (the surface area of each segment) and $R_s$ (the resistance in ohms between the centers of two adjacent segments) as functions of distance along the strand. We define $a(x)$, $I_m(x)$, and $S(x)$; then derive $S(x)$ and $R_s(x)$. Note that $R_s(x)$ will be derived as the resistance for a length $\Delta x$ to the right along the strand from location $x$. In discrete terms, if $x$ is defined as zero at the left end of the strand, then each of these parameters will be assumed to be constant over each discrete segment length so the actual form used in the simulation is, for each parameter, a set of values (e.g., $S(1), S(2), \ldots, S(M)$) corresponding to the $M$ segments used for the simulation. With these conventions:

$$S(j) = \pi a^2(j) \Delta x S_i(j)$$  

(4a)

The basic equation derived from the conservation of current at segment $j$ is now:

$$\frac{V_{j+1} - V_j}{R_s(j - 1)} - \frac{V_j - V_{j-1}}{R_s(j)} = \frac{S(j) C_m \partial V_j/\partial t + I_m(j)}{R_s}.$$  

(5)

As in the Crank-Nicholson method, we substitute the average of $V$ values at time $t$ and time $t+\Delta t$ for the terms on the left and rearrange as:

$$-K'(j)V_{j-1}^{\text{t+1}} + (K(j) \pm K'(j) + 1)V_j^{\text{t+1}} - KV_{j+1}^{\text{t+1}} = K'(j)V_j^{\text{t+1}} + K(j)V_{j+1}^{\text{t+1}} - (K'(j) + K(j) - 1)V_j^{\text{t}} - \Delta t I_m/C_m$$  

(6)

where

$$K'(j) = \Delta t/ S_0(j) C_m R_s(j)$$

and

$$K'(j) = \Delta t/ S_0(j) C_m R_s(j) - 1.$$  

This equation has the same general form as Equation 3, except now:

$$b_j = -K'(j)$$

and

$$a_j = -K(j)$$

$$d_j = K(j) + K'(j) + 1$$

$c_i$ = the right side of Equation 6

and the solution method is identical.

One important aspect of this general numerical technique is that the definition of $S(j)$ becomes the only difference in the method for axons or strands. Specifically, for an axon, $S(j) = 2a(j)$, whereas for a strand of electrically coupled cells, $a(j)$ and $S(j)$ are separately defined as the strand radius and the cell surface-to-volume ratio, respectively.

In the initial phase of the program, the strand parameters are set up, with computation of $S(j), R_s(j), K(j), K'(j), b_j, a_j$, and $d_j$. At each time step, the function $I_m(j)$ is evaluated for each segment and then used to compute the array $c_i$. The matrix equation formed by Equation 6 is solved for $V_i^{\text{t+1}}$ for $j = 1, 2, \ldots, M$. The specific $I_m$ functions are: (1) the Purkinje (P) model of McAllister et al. (1975), and (2) the ventricular (V) model of Beeler and Reuter (1977).

Simulations of action potential generation in two coupled cell aggregates were done by simply integrating the equations presented by Irisawa and Noma (1982) for the sinoatrial (SA) node. At each time step, the equations were integrated for each cell aggregate, with the coupling current between the aggregates included in the integration step for each aggregate. The solutions for the SA node model were initiated from a potential of $-60$ mV. Stable solutions were obtained after about five action potentials had been produced.

Simulations were programmed in FORTRAN on a VAX 11/780 digital computer (Digital Equipment Corp.). Our standard parameters used for the strand simulations included a time step of 5 usec, a segment length of 100 $\mu$m (less than 10% of the resting length constant, see Joyner, 1982), longitudinal resistivity 200 ohm cm and $S_0 = 0.5$ $\mu$m$^{-2}$ (Sommer et al., 1979). We assumed that the ends of the strands were sealed, using boundary conditions as previously described (Joyner et al., 1978).
Results

Passive Cable Properties: Strand vs. Axon

If the I_m function is simply resistive (i.e., \(I_m = V_i/R_m\)) where \(R_m\) is the specific membrane resistivity (ohm cm²), then Equation 1 can be written, for a homogeneous strand, as:

\[
\frac{1}{R_m S_v} \frac{\partial^2 V}{\partial x^2} = C_m \frac{\partial V}{\partial t} + V/R_m
\]

for the strand, as compared with the well-known equation:

\[
\frac{a}{2R_a} \frac{\partial^2 V}{\partial x^2} = C_m \frac{\partial V}{\partial t} + V/R_m
\]

for an axon.

Using the general form (Jack et al., 1975):

\[
L^2 \frac{\partial^2 V}{\partial x^2} = T \frac{\partial V}{\partial t} + V
\]

where \(L\) is the length constant and \(T\) is the time constant, the \(L^2 = \alpha R_m/2R_a\) for the axon and \(L^2 = R_m/R_a S_v\) for the strand, independent of the strand radius. The time constant, \(T\), is \(R_m C_m\) for both. The input resistance for current injected into the center of an axon or strand of infinite length is \((r_m r_a)^{1/2}\), where \(r_m\) is the membrane resistance per unit length (ohm/cm) and \(r_a\) is the longitudinal resistance per unit length (ohm/cm). For the axon, \(r_m = R_m/2\pi a\) and \(r_a = R_a/\pi a^2\). For the strand, \(r_m = R_m/\pi a^2 S_v\) and \(r_a = R_a/\pi a^2\). The input resistance for the axon is \((r_m r_a)^{1/2}\) and for the strand is \((r_m R_a/\pi a^4 S_v)^{1/2}\). Notice that the dependence of the input resistance on the radius is different for the axon vs. the strand. For the strand, the parameter \(\alpha\) is the strand radius and the input resistance varies with \(a^{2}\). For the axon, the parameter \(\alpha\) is the cell radius and the input resistance varies with \(a^{1.5}\).

Regional Changes in Plateau Currents

There are large differences in the durations of action potentials in different regions of the heart. In the ventricular wall, there is a gradient of action potential duration (APD) and functional refractory period (FRP), with the endocardial values being about 20 msec longer than the epicardial values [see review by Burgess (1982)]. One possible mechanism for this phenomenon is a spatial gradient in the intrinsic membrane properties (the \(I_m\) function) from endocardium to epicardium. We can evaluate the ability to predict the distribution of intrinsic properties by the distribution of APD and/or FRP by simulating a strand with a known spatial distribution of intrinsic properties in order to compute the resulting distribution of APD and FRP. In the V model, the intrinsic APD can be shortened or lengthened by changing several parameters. For this example, we use a 20% reduction in the slow inward current, \(I_{Ca}\), to produce a final APD gradient of approximately normal magnitude.

Figure 2 shows the results of strand simulations, with the strand divided into 200 segments, each 100 \(\mu\)m long. Part A shows a comparison of the normal V membrane model and the same model with 80% of the normal \(I_n\). These two action potentials are nonpropagating solutions [membrane action potentials (MAPs)] of the normal or modified Beeler-Reuter (1977) equations. Part B shows the propagating action potentials (PAPs) computed for segment 100 of strands with three different spatial distributions of membrane properties. Action potential 1 is the result obtained when all segments have the normal V model. Action potential 3 is the result obtained when all segments have the modified V model with a shorter duration. Action potential 2 is the result obtained when all of the segments have the normal V model, except for the central 30 segments, which have the 80% \(I_n\) model. Action potentials 1 and 3 have the same durations as the normal and 80% \(I_n\) solutions for isolated cells, as shown in part A, but, in both cases, the action potential peak amplitude is decreased, as shown before (Sharp and Joyner, 1980). Action potential 2 has an intermediate duration, indicating that the duration in the central region is not determined solely by the intrinsic properties of that region, but is also affected by the adjoining normal regions. Part C illustrates the spatial distribution of APD for the same three strand simulations. For a homogeneously normal strand, the duration is nearly constant at 274 msec. For the strand in which all of the segments have the 80% \(I_n\) model, the duration is nearly constant at 223 msec. The middle curve is the result when only the central 30 segments have the 80% \(I_n\) model. Note that the minimal APD occurs at the center of the altered region, but the APD shortening is much less than that predicted by the intrinsic membrane model. The very large spatial extent of the APD effects is much more than might be expected from a purely passive spread of potential determined by the resting length constant. For the V model and the values of \(R_e\) and \(S_v\), we use \(200 \text{ ohm cm} \times 0.5 \text{ }\mu\text{m}^{-1}\), the resting length constant is 1.2 mm. Part D of the figure shows the determination of FRP for the central segment of the three strands as described above. We modeled the stimulation of the strand by a 1.5 times threshold current injected into the left end (segment 1) and then, after a variable delay, we injected a 0.5-msec current pulse into the central segment (segment 100). The abscissa is the stimulus delay (with the conduction time from segment 1 to segment 100 subtracted), and the ordinate is the minimal stimulus for that delay which was able to initiate a second propagated action potential. Note that part D is on an expanded time scale compared with part B. The shift in refractory periods shown in part D parallels the shift in APDs of part B, indicating that the refractory period of a region within an electrically coupled syncytium is determined by the APD of that region, even though (as in case 2) the APD of the region is quite different.
from the region's intrinsic APD, as determined by the membrane properties of that region. Two other phenomena are illustrated by the upper and lower curves of part C. For homogeneous strands, there is an increased APD (and increased FRP, not shown) at the site of stimulation [as shown experimentally by Toyoshima and Burgess (1978)] and a decreased APD when the action potential runs into the sealed end [cf. Kootsey and Johnson (1980)].

**Interactions between a Purkinje Region and a Ventricular Region**

There are large differences in the action potential shape and conduction velocity between Purkinje and ventricular regions. Experimental work (Mendez et al., 1969; Myerburg et al., 1972) has shown "electrotonic" interactions at the Purkinje-ventricular junction (PVJ) such that the Purkinje action potential decreases in duration but maintains a high \( V_{\text{max}} \) as it approaches the junctional region. Although there are obvious geometrical differences between the thin Purkinje strand and the relatively large papillary muscle (or endocardial wall) [cf. the "funnel" hypothesis of Mendez et al. (1969)] and suggestions of localized changes in cell-cell coupling resistance (Martinez-Palomo et al., 1970), we will emphasize the changes in membrane properties by modeling a one-dimensional strand of constant radius, \( S_v \), and \( R_n \) in which the left half of the strand has the P membrane model and the right half of the strand (segments 101–200) has the V membrane model.

Figure 3 shows a diagram of the strand (top) and the spatial distributions of \( V_{\text{max}} \) (part A) and APD (part B). \( V_{\text{max}} \) is nearly constant in the P region at 310 V/sec and in the V region at 105 V/sec. The transitional region is very short, with an asymmetry such that the \( V_{\text{max}} \) of the P segments is very well maintained, while the \( V_{\text{max}} \) of the proximal V region is slightly increased over 5–10 segments. The open circles for the top curve are from a strand simulation in which the P model was used for all 200 segments. The open circles for the bottom curve are from a strand simulation in which the V model was used for all 200 segments. In contrast, the APD distribution (part B) shows a much longer distance and is clearly asymmetrical, with APD shortening occurring throughout the region with the P membrane model (over about eight resting length constants) and APD lengthening occurring to much less extent into the region of the V model. We also examined the spatial distribution of conduction velocity along this strand. We defined the activation time for each segment as the time at which the peak inward current occurred at that segment. We then calculated the conduction velocity through each segment as the segment length divided by the difference in the activation times of that segment and the next segment to the right. With this definition, the conduction velocity had essentially the same spatial distribution as the \( V_{\text{max}} \).
The asymmetry of the APD distribution for this strand is related to the particular differences of the plateau phases of the two models. As shown in Figure 4, if we model a strand in which the left and right halves both have a ventricular model (but with the right half having the 80% \( I_n \) modification as described above), the resulting APD distribution (filled circles) is symmetrical, although effects are clearly seen over many resting length constants. We now add to this strand a resistive barrier, produced by raising \( R_o \) between segments 100 and 101 to a value of 4000 ohm cm, keeping \( R_a \) at 200 ohm cm for all other segments. The resulting APD distribution (open circles), compared with the distribution without a resistive barrier (filled circles), now shows less shortening of the APD in the region with an intrinsically longer APD and less lengthening of the APD in the region with an intrinsically shorter APD, with an abrupt drop in APD across the barrier. The value of 4000 ohm cm was chosen, since this is the maximal value of resistivity over a 100-\( \mu \)m length which will allow propagation with the Beeler-Reuter model with normal coupling resistance throughout the rest of the strand, yet the plateau interactions are still prominent.

Interactions between Two Spontaneously Firing Regions

Interesting interactions between regions of different intrinsic membrane properties can also be seen when the differences in membrane properties alter the intrinsic automatic rate of firing of the two regions. Recent voltage clamp studies on regions cut from the rabbit sinoatrial node (Noma and Irisawa,
1976; Irisawa and Noma, 1982; Brown et al., 1982) have been summarized into a mathematical model for the membrane properties, as illustrated in Figure 5 [see Appendix to Irisawa and Noma (1982) for specific equations used]. The solutions obtained are membrane action potentials (nonpropagated), produced by evaluating the currents at a holding potential of —60 mV and then allowing the membrane potential to change with time. The upper and lower panels of the figure show solutions of the normal model and the model with the slow inward current increased by a factor of 2. The altered model has a faster pacing frequency (smaller cycle length), as well as an increased \( V_{\text{max}} \) and peak amplitude.

Figure 6 summarizes the results obtained when these two models are simultaneously solved, each for a cell aggregate with one square millimeter of surface area, with a variable coupling resistance between the two aggregates \( (R_c) \). Part A is a diagram of the simulation system. We find that the two aggregates are entrained to a common cycle length at coupling resistances up to 25 \( \Omega \). However, this common cycle length is never equal to the intrinsic cycle length of either aggregate. Part B shows the common cycle length of the two aggregates as a function of the coupling resistance. The solid line indicates the intrinsic cycle length of the normal model, the dashed line indicates the intrinsic cycle length of the altered model, and the dotted line indicates the intrinsic cycle length of a model with 1.5 times the normal value of \( L_{m} \). At low coupling resistances, the common cycle length approaches the value for the model with 1.5 times the normal value of \( L_{m} \). As the coupling resistance is increased, the common cycle length decreases. Although the two aggregates are entrained at a common cycle length, they do not fire simultaneously. Part C shows that the latency between the action potentials generated by the two aggregates increases with the coupling resistance, with a nearly linear relationship between latency and coupling resistance. In addition, the two aggregates have different action potential shapes, as indicated in part D of the figure, where the \( V_{\text{max}} \) of both aggregates is plotted as a function of the coupling resistance. The open circles are for the aggregate with the intrinsically higher \( V_{\text{max}} \) (the altered model), while the filled circles are for the aggregate with the normal model. At very low coupling resistances, the \( V_{\text{max}} \) of each aggregate is equal to the value obtained by a model with 1.5 times the normal \( L_{m} \), but as the coupling resistance is increased, the two aggregates begin to have \( V_{\text{max}} \) values closer to that predicted by the intrinsic membrane models (dashed line and solid line). One apparent anomaly is that the \( V_{\text{max}} \) of the aggregate with the normal intrinsic model actually decreases below the normal intrinsic \( V_{\text{max}} \) (solid line). This decrease is produced by the cycle length of the
aggregate at this coupling resistance (see part B), which is decreased, compared with the normal cycle length.

Discussion

Limitations of the Technique

Our use of simulation techniques to study the properties of propagating action potentials requires assumptions about the membrane properties of the cells and the anatomy of the preparation. We used three published membrane models for Purkinje cells, ventricular cells, and sinoatrial node cells (McAllister et al., 1975; Beeler and Reuter, 1977; Irisawa and Noma, 1982). All of these models were formulated from voltage studies which are difficult to perform and interpret. In particular, the magnitude of the current responsible for the rising phase in each of these models was adjusted to match the experimentally observed rate of rise of the action potential. In the P and V models, the descriptions of the fast sodium current are basically modifications of the Hodgkin and Huxley (1952) equations for the squid axon, since quantitative measurement of the cardiac sodium current was not available at the time the models were formulated and is available now in only a few preparations (Brown et al., 1980; Ebihara et al., 1980). In the SA node model, the parameters for excitation come more directly from the voltage clamp results, but the parameters chosen are from a wide range of experimentally observed current magnitudes (Brown et al., 1982). The pacemaker current of the P model has recently been reinterpreted as an inward current instead of the outward 'K2' current (DiFrancesca, 1982), but this has no effect on our results, since we directly stimulated the region of the P model. In addition, the effects of the pacemaker current on the plateau (in the P model) because it was assumed to have very marked inward rectification.

We have used one-dimensional strand simulations for all of our propagation studies. We showed, in Methods, that, for a strand of electrically coupled cells, propagation parameters are not affected by the strand radius. Thus, propagation along a thin Purkinje strand and propagation along parallel pathways through the ventricular wall can both be considered one-dimensional processes. For the interactions between P cells and V cells, we chose to use a geometrically homogeneous strand with regional changes in membrane properties in order to stress the interactions due to the different membrane properties. The obvious anatomical 'funnel' present at the PVJ would accentuate the effects of the V cells on the P cells. One assumption that we make is that all of the cell surface membrane is equivalent in terms of being exposed to an extracellular space which is isopotential and has no ionic accumulation or depletion. Since we are studying only a single action potential in the strand simulation (not a train of high frequency stimulations), the ionic accumulation or depletion effects should be very small. The problem of access resistance along narrow intercellular clefts (Levin and Fozzard, 1981) must be considered in a more quantitative model; however, the major effect is to reduce the effective capacitance being filled and thus increase the conduction velocity. Presently, uncertainties in the kinetics and magnitude of the inward currents of P and V cells, as well as the appropriate morphometric parameters, make this extension an interesting but very difficult project. The results on coupled pacing regions are done with only two regions coupled by a resistor. This situation is closely related to experimental work by DeHaan et al. (see 1982 review) on coupled cell aggregates and, also, to experimental work on cardiac strands with regions separated by a sucrose gap (Antzelevitch et al., 1980), but may also be extrapolated to the normal, more distributed spatial inhomogeneity of the sinoatrial node area (Lu et al., 1965; Sano et al., 1978; MacKaan et al., 1980).

Results for Inhomogeneous Strands

The results of these simulations illustrate the important principle that the electrical activity of cells within an inhomogeneous electrical syncytium cannot be simply predicted from the intrinsic membrane properties of the cells. In addition, the spatial distribution of action potential properties resulting from an abrupt spatial distribution of membrane properties cannot be predicted by cable theory in terms of the resting length constant. The distribution of action potential properties closely related to the action potential upstroke (e.g., \( V_{\text{max}} \), conduction velocity) very closely parallels the spatial distribution of membrane properties (Fig. 3A). The distribution of properties associated with the plateau phase (e.g., APD, FRP) is extremely broad and is clearly not due to passive electrotonus. This finding is compatible with earlier experimental work on both ventricular strands (Cranefield and Hoffman, 1958) and Purkinje strands (Vassalle, 1966) in which the repolarization process was shown to be regenerative. From our simulation results (Fig. 3B), the Purkinje model is more sensitive to electrotonic influences during the plateau than is the ventricular model, but we are not aware of any directly comparable experimental studies. Mendez et al. (1969) found, at the junctional region between Purkinje strands and a papillary muscle, shortening of the Purkinje APD with very little lengthening of the ventricular APD, but in this preparation the large difference in size between the Purkinje strand and the papillary muscle could explain the asymmetrical effects.

The differences in APD and FRP in different ventricular regions have been examined both in intact ventricles (Martins and Zipes, 1980) and in pieces cut from endocardial or epicardial regions (Moore et al., 1965; Cohen et al., 1976; Gilmour and Zipes, 1980). The preservation of APD differences in the isolated preparations suggests that there are differences in the intrinsic membrane properties.
Although it may be that the endocardial ventricular region has some prolongation of APD due to the presence of an endocardial layer of Purkinje cells, our simulation results (Fig. 3B) indicate that, with the membrane models we used, this effect would be very small. In addition, we simulated a one-dimensional strand of 200 segments (total length 2 cm) of which only the first five segments had the P membrane model (500 μm length, corresponding roughly to the thickness of the endocardial Purkinje layer), whereas the rest of the strand had the V membrane model. In this case, the prolongation of the action potential in the proximal V segments was less than 1 msec.

Results for Coupled Pacemakers

Pacemaker entrainment has been studied in many preparations [see recent reviews by DeHaan et al. (1982) and Ypey et al. (1982)]. The results shown in Figures 5 and 6 are produced by solutions of the SA node model (Irisawa and Noma, 1982) with no modified parameters except the scaling factor for I, and the value of R, the coupling resistance. The surface area chosen is somewhat arbitrary, but would represent a group of cells with a group diameter of about 150 μm if the cells had an S, of 0.5 μm. Identical results are obtained for larger areas if R, is scaled down by the same factor by which the area is scaled up. Several interesting results are present:

1. The membrane resistivity of the SA node model is about 15 kΩ cm² during diastole, giving an input resistance of about 1.5 MΩ for each of the aggregates; yet, they show entrainment when coupled to each other by a resistance of up to 25 MΩ. Similar values of input resistance (1–2 MΩ) and minimal coupling resistance for entrainment (40–80 MΩ) were obtained by Clapham et al. (1980) for embryonic cell aggregates that were 100–200 μm in diameter.

2. The cycle length of the entrained aggregate pair varies with the coupling resistance. At low coupling resistance, the aggregate pair acts as a single group, with minimal latency and with values of cycle length and Vₘ₉₉₉ appropriate for an aggregate with 1.5 times the normal Iₚ. At higher coupling resistance, the entrained aggregate pair has a cycle length closer to but not the same as the intrinsic cycle of the faster aggregate, even though the latency is now long (up to 50 msec) and the values of the individual aggregates are similar to those predicted by their individual membrane properties. The increase in latency with increased coupling resistance is also very comparable to that observed experimentally for cell aggregates (Clapham et al., 1980), as well as for Purkinje strands pulled through a sucrose gap (Antzelevitch et al., 1980). Simulations of two coupled pacing cells with different intrinsic rates, using a more general pacing model (van Capelle and Durrer, 1980), also show (cf. their Fig. 3, p. 458) entrainment at a cycle length different from either of the intrinsic cycle lengths.
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