Effect of Tissue Anisotropy on Extracellular Potential Fields in Canine Myocardium in Situ

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SUMMARY. The extracellular epicardial potential fields produced by simple depolarization waves in the in situ canine left ventricular myocardium were analyzed. A mathematical model that included tissue anisotropy was developed to explain the observed fields. Values of intracellular (i), extracellular (e), longitudinal (l), and transverse (t) resistivity which gave the best fit between the model and experimental data were (in ohm-cm, mean ± sd): r_ii = 852 ± 232, r_e = 1247 ± 210, r_l = 291 ± 38, r_t = 1677 ± 331. The potential fields around simple stimulated waves on the epicardium can best be explained if the extracellular wavefront voltage is (mean ± sd) 74 ± 7 mV for a wave propagating parallel to the local muscle fibers, and 43 ± 6 mV for a wave propagating perpendicular to these fibers. We conclude that the anisotropy of the electrical conductivity of cardiac muscle has important effects on the propagation of waves of depolarization and on the potential fields produced by depolarization in the intact heart. (Circ Res 50: 342-351, 1982)

THE conduction of the wave of cardiac depolarization depends on the flow of local circuit current in the extracellular and intracellular media of the myocardium (Fozzard, 1979). The current which produces ECG potentials also flows via these two media. Both the conduction of waves of depolarization and the generation by these waves of body surface electric fields can be qualitatively understood, using the assumption that the myocardium is electrically isotropic, that is, that the electrical properties do not depend on direction (Plonsey, 1969). However, experimental evidence shows that the assumption of isotropy is limited.

For example, conduction is several times faster longitudinally than transversely (Sano et al., 1959; Draper and Mya-Tu, 1959). This anisotropy can be explained by the anisotropic conductivity of cardiac muscle (Clerc, 1976; Roberts et al., 1979). It has been suggested recently (Spach et al., 1981) that anisotropy of conduction may be important in arrhythmias. It has not been shown that the anisotropy of cardiac muscle has a significant effect on the body surface ECG. However, anisotropy does affect measured extracellular potentials in cardiac muscle. For example, the extracellular voltage across a depolarization wave in in vitro ventricular trabeculae varies by a factor of three as the direction of propagation is changed (Clerc, 1976). In superfused myocardium in vitro, the form of the extracellular potential is strongly affected by electrical anisotropy (Spach et al., 1979). In situ canine ventricle, as well, potential fields around localized depolarization waves are qualitatively dissimilar to those expected on the basis of the assumption of electrical isotropy (Corbin and Scher, 1977; Roberts et al., 1979).

The purpose of our study was to provide a quantitative basis for understanding the extracellular potentials around local segments of depolarizing myocardiun in the in situ canine ventricle and to determine the intracellular and extracellular conductivity of myocardium of the intact heart and the effective strength of myocardial cells as potential sources. Although Spach et al. (1979) studied electrical anisotropy in a thin layer of muscle in vitro, they did not produce values of electrical conductivity or wavefront strength applicable to the intact heart. Neither did their study include the possibility that extracellular resistivity is anisotropic, although evidence (Clerc, 1976) indicates that both extracellular and intracellular forms of resistivity are anisotropic. For our study, we developed a simple mathematical model for computing extracellular potential fields in three-dimensional, anisotropic cardiac muscle. By fitting this model to data collected from an array of recording terminals on the in situ canine ventricle, we could determine the anisotropic electrical conductivities of intact canine ventricular muscle and show that including anisotropy in the analysis improves the agreement between model and experimental potential fields. The conductivities so obtained provide a quantitative basis for further exploration of the effect of myocardial anisotropy on conduction and on the generation of extracellular electric fields. In addition, we could determine the effective strength of the cardiac generator in longitudinal and transverse directions.

Methods

Experimental Procedure

Six dogs weighing 22-38 kg were anesthetized with morphine (1 mg/kg, im) followed by chloralose (75-100 mg/kg iv, supplemented as needed). The heart was exposed between the 4th and 5th ribs via a thoracotomy.

An 84-terminal, 9 X 16.5-mm array electrode was used for epicardial stimulation and recording. The array and the computer recording technique have been described previously (Roberts et al., 1979). The sampling rate was 1000/
The potential just prior to stimulation was taken as the baseline, and the time of stimulation was defined as zero sec. A stimulus synchronous with the computer sampling, 1.0 to 1.3 msec long, 1.5 to 3.0 times threshold, and with a rate slightly above the natural rate, was applied to one or more terminals.

The electrode array was placed on an area of the left ventricle relatively free of blood vessels, usually near the left anterior descending artery. To avoid injury to the heart, the electrode was not pinned or sutured in place but was hand-held against the heart. The reproducibility of the recorded maps indicated that any movement from beat to beat had a negligible effect on the results. The indiff erent electrode was on the animal’s torso remote from the heart.

No bathing solution covered the heart. The ventricles were open to the air. (However, the surface was not allowed to dry out.) The epicardial boundary will be discussed further, below. The electrode was oriented with its long axis approximately parallel to the epicardial fiber direction.

Three stimulating sequences were used. In the “central stimulus” sequence, the stimulus was applied to only the central terminal of the array. In the “longitudinal” sequence, the stimulus was applied to all seven terminals of one of the short (seven-terminal) edges of the array. For the “transverse” sequence, the stimulus was delivered to all 12 terminals along one of the long (12-terminal) edges of the array.

The central stimulus sequence utilized a constant current stimulus “sequence,” the stimulus was applied to only the central terminal of the array. In the “longitudinal” sequence, the stimulus was applied to all seven terminals of one of the short (seven-terminal) edges of the array. For the “transverse” sequence, the stimulus was delivered to all 12 terminals along one of the long (12-terminal) edges of the array.

The central stimulus sequence utilized a constant current pulse. The current magnitude was measured so that the (anisotropic) gross tissue resistivity could be determined from the magnitude of the stimulus artifact at each terminal (Roberts et al., 1979).

The waveforms were edited for beat-to-beat stability. For each record, a typical beat was chosen for further analysis.

After the animals were killed, the tissue underlying the electrode was excised from three of the six hearts. The electrode was oriented with its long axis parallel to the epicardium at 100-µm intervals. The fiber angle of the exposed tissue was measured at every fourth section.

The central stimulus sequence used to obtain all tissue parameters (fiber orientation, conduction velocity, and anisotropic extracellular and intracellular conductivities). These parameters were used to compute activation times and potential fields for each of the three sequences. The RMS difference between the measured and computed (predicted) potentials was then calculated. The computed potentials for the longitudinal and transverse sequences were predicted entirely on the basis of tissue parameters determined from the central stimulus sequence. The computed potentials for the central stimulus sequence itself were not “predicted,” but rather were fit to our model.

In one case, we used potentials recorded from within the ventricular wall with a 16-terminal “plunge” electrode to verify that the potentials calculated along the electrode were in qualitative agreement with measured potentials (see Discussion).

### Data Analysis

To avoid complications in calculations of potential fields, we deliberately kept the system under study as simple as possible. The extent of the depolarization wave under study was comparable to or smaller than the distance to any non-epicardial electrical boundary (e.g., to the endocardium, approximately 1.0 to 1.5 cm), but large compared with the spatial extent of the rising phase of the action potential (approximately 1 mm). We used a small electrode array and usually considered only the time interval from 5 to 15 msec after stimulation in analyses. The period from 0 to 4 msec was not used because the depolarization potentials were very small in this interval, and to include them would have burdened the computer analysis. The 15-msec upper limit was chosen because part of the wave had passed beyond the boundary of the electrode array by this time.

To avoid the variation of fiber orientation with depth in the ventricular wall (Armour and Randall, 1970), we confined our attention to volumes of tissue small enough that this variation could be neglected. Detailed estimates of the effect of this variation on measured potentials indicated that we could safely ignore the rotation of fiber direction during the first 15 msec after stimulation.

Since we did not wish to study potential variations very near the depolarization wavefront, we did not use any potentials recorded within 1.0 mm of either the predicted or measured position of the wavefront in regressions or statistical analysis. Our results were not changed by rejection of potentials near the wavefront (see Results).

### Propagation of the Wave

For each waveform, the measured time of local depolarization was taken as the time the voltage was changing most rapidly. For the central stimulus sequence, an elliptically shaped wave propagated away from the central stimulation point (Fig. 1A). A nonlinear fitting program (MLAB, from the National Institutes of Health, Bethesda, Maryland) was used to find the parameters which minimized the RMS (root mean square) difference between model and measured times of local depolarization for the central stimulus sequence. Between the model and measured activation maps, the RMS error averaged 1.2 msec and the correlation coefficient between the model and measured activation maps ranged from 0.959 to 0.986, for the six central stimulus sequences.

The fitting procedure produced one set of values of \( v_1 \), \( v_2 \), and \( \theta_0 \) for each central stimulus sequence. Here, \( v_1 \) and \( v_2 \) are the longitudinal and transverse propagation velocities, respectively, and \( \theta_0 \) is the angle between the long axis of the electrode array and the long axis of the best-fit elliptically shaped wavefront. These values were used in all subsequent analysis to describe the propagation of the wave. The angles \( \theta_0 \) computed by fitting the observed activation times to the elliptically shaped propagating wave were near zero for all six experiments. The fiber direction in the tissue sections, determined by eye, agreed within ±10 degrees with the direction determined by the fitting procedure described above. The fiber direction determined from tissue sections was not used in quantitative data analysis.

Our calculations of potentials required that we know the entire three-dimensional shape of the depolarization wavefront. To obtain this, we made the assumption that the only angle on which the propagation velocity of a plane wave depends is the angle between the direction of propagation and the local fiber direction. We will refer to this as the assumption of axial symmetry: this property is a consequence of the local symmetry of myocardium about the axis of local myocardial fibers. We know of no evidence that contradicts this assumption. An observation that supports this assumption is that the velocity of conduction through the wall of the heart is approximately the same as the transverse velocity on the epicardium (see, for example, Fig. 7). With this assumption, the three-dimensional shape of a wave of depolarization from a single epicardial point of stimulation can be obtained by rotating the (elliptical) epicardial isochrone around an axis parallel to the long axis of the muscle fibers and passing through the point of stimu-
The surface so obtained is a prolate spheroid (Morse and Feshbach, 1953). This was the shape used in our simulations of the potentials generated by a wave of depolarization which originated at a single point of stimulation.

To simplify the calculation of potential fields due to the waves produced by the other two sequences, we approximated the line of discrete points of stimulation with an infinite, continuous line. This greatly simplified the wavefront surface used in the simulation. In this approximation, the wavefront is an infinite right cylinder. The cross-section of the cylinder is circular for the transverse sequence and elliptical for the longitudinal sequence. For example, for the longitudinal sequence, the lengths of the axes of the ellipse are exactly the same as for the central stimulus sequence: $v_l \times \text{time}$ and $v_t \times \text{time}$, where $v_l$ and $v_t$ are the longitudinal and transverse velocities, respectively. For the transverse sequence, the radius of the circle (which describes the cross-section of the wavefront used in the simulation for this sequence) is $v_t \times \text{time}$. The velocities $v_l$ and $v_t$ were obtained as described above from measurements of the activation times for the central stimulation sequence.

**Boundary Conditions**

Our calculations of potentials assumed an infinite homogeneous medium. Three conditions which might have made this assumption inappropriate were the rotation of fiber direction in the heart wall, the boundary with the endocardium, and the epicardial boundary. The effects of the first two of these were minimized by working with waves of limited linear dimensions.

We feel that the epicardial boundary can be largely ignored. That is, the propagation of the wave of depolarization and the potentials it produces are essentially as if the experiment were carried out in an infinite medium. The argument depends on the following: (1) the epicardium is flat (since the area under consideration is small), (2) the muscle fibers parallel the epicardium, and (3) all points of stimulation are on the epicardium. Consider an infinite medium with parallel muscle fibers. Suppose a plane $P$ includes all points of stimulation and is parallel to the fiber direction. Then, since the medium is symmetrical about $P$, the potential fields produced by waves of depolarization originating on $P$ must be symmetrical about $P$. This means that there can be no currents normal to $P$. Therefore, one of the two half-spaces defined by $P$ can be replaced with an insulator without altering the propagation of waves or the potentials produced by waves in the remaining half-space. In our experiments, the plane $P$ is the epicardium, and the insulating half-space is air and the plastic body of our electrode.

The argument assumes that the epicardial sheath and the thin layer of fluid which moistens the epicardium have a negligible effect on wave propagation and potentials. That this is true is indicated qualitatively by the lack of noticeable differences between the shape of the potential fields produced by small wave surfaces and the shape produced by larger surfaces. If the thin epicardial tissue and fluid layer had a large effect on potentials, the effect should be most noticeable when the wavefront surface is small.

**Wavefront Voltages**

$V_{ol}$ and $V_{ot}$ denote the longitudinal and transverse extracellular wavefront voltages, i.e., the voltage change at an extracellular measuring point during the passage of a depolarization wavefront. One major problem prevents the unambiguous measurement of these voltages. The voltage change due to local depolarization is not clearly distinguishable from other voltage changes which occur during the process of depolarization. The large "intrinsic deflection" when a wave of depolarization passes the recording terminal is not sufficiently rapid to distinguish it clearly from the slower changes just before and just after local depolarization (Roberts et al., 1979).

The concept of "wavefront voltage" is useful despite the imperfect correspondence between the ideal and the real phenomena. The extracellular voltage at local depolarization in small strips of muscle in vitro has been used to determine intracellular and extracellular resistivity of cardiac muscle (Weidmann, 1970; Clerc, 1976; Weingart, 1977; Wojtczak, 1979; Hermansmyer, 1980). In the present study we did not determine wavefront voltage by simply measuring the voltage change during local depolarization. Rather, we chose $V_{ol}$ and $V_{ot}$ to be those values which produced the best fit (in the least-squares sense) between potential fields in the experimental and model central stimulus sequences.

For the case in which anisotropy in wavefront voltage is assumed, we used the following equation and calculated $V_{ol}$ and $V_{ot}$ by regression:

$$\phi_0(\vec{r}, t) = V_{ol}f_1(\vec{r}, t) + V_{ot}f_2(\vec{r}, t). \quad (1)$$

Here, $\phi_0(\vec{r}, t)$ is the independent variable (the measured extracellular potential at position $\vec{r}$ and time $t$), $V_{ol}$ and $V_{ot}$ are the regression coefficients (longitudinal and transverse wavefront voltages, respectively), and $f_1(\vec{r}, t)$ and $f_2(\vec{r}, t)$ are geometrical factors which depend on the position of the wave (via the time $t$) and on the field point $\vec{r}$. [See the Appendix for the form of the functions $f_1(\vec{r}, t)$ and $f_2(\vec{r}, t)$.

For the case in which $V_{ol}$ is assumed equal to $V_{ot}$ [uniform double layer theory (Frank, 1953)], the following regression equation was used:

$$\phi_0(\vec{r}, t) = V_0\left[f_1(\vec{r}, t) + f_2(\vec{r}, t)\right]. \quad (2)$$

Here, $V_0$ is the wavefront voltage (independent of the angle of propagation), and $f_1$ and $f_2$ are as before.

One aim in calculating wavefront voltages using Equations 1 and 2 was to compare the fit (judged by the RMS voltage error) when assuming the wavefront voltage is anisotropic (Eq. 1) with that obtainable while neglecting anisotropy (Eq. 2). Since the linear regression minimized RMS error, it is inevitable that the RMS error will be less in the first regression (Eq. 1) than in the second (Eq. 2). Equation 2 is a special case of Equation 1, with $V_{ot}$ constrained to equal $V_{ol}$.

To test further the usefulness of calculations which include wavefront voltage anisotropy, we applied the wavefront voltages obtained for the central stimulus sequence with regression Equations 1 and 2 to the prediction of potentials for the longitudinal and transverse stimulation sequences. In these calculations we also used the velocities, fiber angle, and gross electrical resistivities obtained from the central stimulus sequence. That is, every tissue property required for predicting the observed potentials for the longitudinal and transverse stimulation patterns was obtained from the central pattern. We could thus test the importance of including wavefront voltage anisotropy in cases in which it was unknown whether this would improve or worsen the prediction.

We also determined the rapidity of the effect on the accuracy of potential predictions of using, for both $V_{ol}$ and $V_{ot}$, the value of $V_{ol}$ obtained from Equation 1. This calculation showed the errors that occur if one obtains the wavefront voltage $V_{ol}$ from a transverse wave, assumes that the longitudinal voltage $V_{ol}$ is the same, and attempts to predict potentials in...
situations in which the difference between $V_{dl}$ and $V_{du}$ strongly affects the potential field.

We will refer to these three methods of calculating wavefront voltages from the central stimulus as Methods 1, 2, and 3:

**Method 1**—Using Equation 1, $V_{dl}$ and $V_{du}$ are calculated by regression.

**Method 2**—Using Equation 2, $V_u$ is calculated by regression, and both $V_{dl}$ and $V_{du}$ are set equal to the value of $V_u$ so obtained.

**Method 3**—Both $V_{dl}$ and $V_{du}$ are set equal to the value of $V_{du}$ obtained by Method 1.

Of these three methods of determining wavefront voltage by regression, Methods 2 and 3 are consistent with the uniform double layer theory (Frank, 1953), since the wavefront voltage is assumed to be the same for any direction of propagation. Method 1 allows the two wavefront voltages to be different, and is therefore inconsistent with the uniform double layer theory.

Intracellular and Extracellular Resistivity

As noted earlier (see Methods), our statistical computations of the resistivity $\rho_t$ and $\rho_l$ so obtained, and with the extracellular wavefront voltages determined from linear regressions, it was possible to obtain values of the intracellular ($i$), extracellular ($o$), longitudinal ($l$), and transverse ($t$), resistivities, as follows (Roberts et al., 1979):

\[
\rho_i = \rho_l \Delta / V_{oi},
\]

\[
\rho_t = \rho_l \Delta / V_{ot},
\]

\[
\rho_{dl} = \rho_{lt}(\rho_l - \rho_i),
\]

\[
\rho_{dt} = \rho_{lt}(\rho_l - \rho_t).
\]

Here, $\Delta$ is the magnitude of the transmembrane action potential, which we assumed to be 100 mV; and $V_{oi}$ and $V_{ot}$ are the longitudinal and transverse extracellular wavefront voltages, respectively.

Data acquisition and processing were done on a laboratory minicomputer, the LM2 (Kehl et al., 1975). Isochrone plots (e.g., Fig. 1) and isopotential plots (e.g., Fig. 2) were drawn by a computer program, which interpolated linearly between values at the recording sites.

**Results**

Results of a typical experiment are shown in Figures 1–6.

**Activation Sequence**

The propagation of the wave for the central stimulus sequence is illustrated in Figure 1A. From the measured times of local depolarization, values of longitudinal and transverse velocity and fiber angle were determined, and a predicted activation sequence was computed from these values.

The velocities thus determined were then used to predict the activation sequence for the longitudinal sequence (Fig. 1B) and the transverse sequence (Fig. 1C). In Figure 1B, one terminal failed to stimulate, but the wave nonetheless largely moved longitudinally. As noted earlier (see Methods), our statistical comparisons of measured and predicted potentials excluded points measured within 1.0 mm of either the predicted or measured position of the depolarization wave, so that small errors between predicted and measured activation times had little effect on the statistical comparisons of predicted and measured potential maps.

The velocities determined from the central stimulus sequences for the six cases studied were: longitudinal, $v_l = 57 \pm 6$ (SD) cm/sec; transverse, $v_t = 24 \pm 3$. These agree with previous results (Roberts et al., 1979).

**Measured and Model Potentials**

Figure 2A shows a recorded isopotential map 6 msec after stimulation, and Figure 2B shows the corresponding predicted map.

In Figures 2–4 below, the model potentials were computed only at the positions and times at which the potentials were measured. For example, in Figure 2, D, E, and F, the potentials between recording terminals were interpolated linearly between the terminals. Thus, although the model predicts a discontinuous change in potential at the wavefront, the plots show the potential changing continuously from one terminal to the next, even when the wavefront is between the two terminals. Similarly, in Figure 3, the plots of predicted potentials (dashed curves) show the potential changing continuously from 1 msec to the next, even though the wave has passed the recording point in that 1-msec interval. Again, this is because the potential was computed at each millisecond and straight lines were drawn between potentials at adjacent time points.

Recorded isopotential maps at 15 msec are shown in Figure 2, Band C, for the longitudinal and transverse sequences. Figure 2B illustrates the distortion of the potential field that results from the loss of one stimulating terminal (see Fig. 1B). The additional distortion due to the coarseness of the terminal spacing results in the apparently greater spatial potential gradient on the left side of the wavefront in Figure 2B. The gradient was about the same all along the wavefront; the voltage changed by 40 to 55 mV over a 1-mm region where the gradient was steepest.
FIGURE 2. Isopotential maps. The dashed lines represent the location of the wave (obtained from the corresponding activation map) at the time for which the isopotential maps are drawn. The fiber direction is nearly vertical, as shown in Figure 1. Isopotential maps at 5 mV intervals. A, B, C: The experimentally measured maps for the central, longitudinal, and transverse sequences, respectively. The central stimulus sequence is shown at 6 msec after stimulation; the other two sequences are shown at 15 msec. D, E, F: The corresponding predicted maps. The central stimulus sequence is shown at 6 msec after stimulation; the other two sequences are shown at 15 msec. Note the positive potentials outside the expanding wavefront in A and B. These potentials are reproduced in the predicted maps in D and E. The uniform double layer theory is incapable of accounting for these positive potentials (see text). The map in B is somewhat distorted by the appearance of one stimulating terminal. The conduction velocities and wavefront voltages used in producing D, E, and F were obtained from the central stimulus sequence (see text).

Comparing Figure 2, B and C, it is evident that the voltage drop across the wave is greater for the longitudinal wave than for the transverse wave. This difference is reproduced in the predicted maps, Figure 2, E and F. The data in Figure 2, B and C, do not fulfill the requirement of the uniform double layer theory that the wavefront voltage be the same for all angles of propagation.

We compared and contrasted the potential predictions using the three methods for determining the wavefront voltages $V_{ol}$ and $V_{ot}$. The comparison is illustrated in Figures 3-5. The dashed curves show the results of using each of the three methods. Figure 3 shows some typical potentials as a function of time after the stimulus. As noted earlier, only the central stimulus sequence was used to determine the wavefront voltages, which were then applied to the prediction of potentials for all three sequences. The short dashes show the predictions based on regression when the wavefront voltages were not constrained (Method 1). The medium dashes show predictions for which the wavefront voltages $V_{ol}$ and $V_{ot}$ were constrained to be equal (Method 2). If both $V_{ol}$ and $V_{ot}$ are set equal to the value of $V_{ot}$ determined by Equation 1 (Method 3), the result is the predicted potentials indicated by the long dashes in Figures 3-5. This latter method of determining $V_{ol}$ and $V_{ot}$ is intended to illustrate the consequences of using the transverse wavefront voltage for both wavefront voltages.

For the longitudinal sequence (Fig. 2E), the predicted potential at a terminal does not depend on which column of the array the terminal is in. Similarly, for the transverse sequence (Fig. 2F), the potential does not depend on which row the terminal is in. Therefore, it is possible to get a composite picture by averaging the measured potentials over columns or rows for longitudinal or transverse stimulation, and comparing the resulting average potentials with the predicted potentials. This is done in Figure 4, for the 9- and 15-msec maps. The two predictions utilizing the uniform double layer theory are shown, as is the
Figure 4. Predicted and measured potentials as a function of distance from the stimulus point, for the multiple stimulation sequences. Vertical line is predicted position of the wave of depolarization. A: Longitudinal wave at 9 msec after stimulation. B: Transverse wave at 9 msec. C: Longitudinal wave at 15 msec. D: Transverse wave at 15 msec. The experimental potentials have been averaged across rows (longitudinal wave) or columns (transverse wave). The solid and dashed lines have the same meaning as in Figure 3.

Figure 5. RMS voltages of maps and RMS error as a function of time. The solid line is the RMS voltage of the entire experimental map at each time. The dashed lines represent the RMS error between the measured map and predicted maps. The methods of prediction associated with each dashed line are the same as for Figures 3 and 4. A: Central stimulus sequence. B: Longitudinal sequence. C: Transverse sequence.

Prediction of the theory which includes anisotropic wavefront voltage. The uniform double layer theory fails to predict major features of the measured potential maps, particularly the large positive potentials which precede a longitudinal wave.

Figure 5 shows the RMS error between predicted and measured maps for the central, longitudinal, and transverse sequences, as a function of time after the stimulus.

The wavefront voltages used in predictions for all three sequences shown in Figures 2–5 were determined, as described earlier, from the maps for the central stimulus sequence. For this sequence, it is therefore hardly surprising that the RMS error for the prediction utilizing the uniform double layer theory is larger than the error when \( V_{oi} \) is allowed to differ from \( V_{ol} \). The fact that the error is reduced, as pointed out in Methods, is a necessary consequence of the method (linear regression) used to obtain the wavefront voltages \( V_{oi}, V_{ot}, \) and \( V_{u} \).

The reduction in error for the other two sequences is not merely a necessary consequence of the mathematical method. This reduction shows that parameters can be obtained for one stimulation pattern, and then these parameters can be applied to new situations to achieve a good fit between measured and predicted results.

We calculated the average errors between predicted and measured potentials for all six experiments over

* For a purely longitudinal epicardial wave, as in Figure 2, there is transverse current flow in the depth of the myocardium. This is necessary for the genesis of the positive potentials ahead of a longitudinal wave.
the interval from 5 to 15 msec for each of the three regression methods of prediction described above and in Methods. The results for the central stimulus sequence were (in mV; mean ± SD, n = 6): RMS potential of the experimental map, 21.2 ± 4.8; RMS error when \( V_a \) is forced to have the value of \( V_a \) determined by regression, 4.60 ± 0.68; RMS error when \( V_a \) is forced to be equal to \( V_a \) and minimizing the error, 3.17 ± 0.26; RMS error allowing \( V_a \) to be different from \( V_a \) and minimizing RMS error, 2.45 ± 0.40. The corresponding voltages for the longitudinal and transverse sequences taken together were 20.9 ± 3.5, 5.34 ± 0.99, 4.01 ± 0.54, and 2.61 ± 0.39 mV. The errors are about twice as large for the worst of the three prediction methods as for the best method.

**Wavefront Voltages**

The average wavefront voltages for the six experiments, determined by linear regression, were: \( V_a = 74 ± 7 \) mV, \( V_e = 43 ± 6 \) mV. The range of \( V_a \) was 65 to 82 mV, and the range of \( V_e \) was 33 to 51 mV, for the six hearts studied. The difference between \( V_a \) and \( V_e \) was remarkably constant, ranging only from 29 to 32 mV for the six hearts. The ratio of \( V_a \) to \( V_e \) was 1.75 ± 0.12, with a range from 1.66 to 1.97.

There are several possible sources of variability when the wavefront voltages are determined by regression. The first, and probably the largest, is the variability from dog to dog. Another possible source of error is the data selection. As described in Methods, in the regression we used only maps in the interval from 5 to 15 msec after the stimulus, and we excluded potentials recorded within 1.0 mm of the wave. The voltages determined by regression were insensitive to the distance from the wave within which data were excluded. For example, choosing for this distance 0.0, 0.5, 1.0, or 2.0 mm resulted in the following values of \( V_a \): 68, 67, 65, and 69 mV, respectively, for one typical experiment. (The variation in \( V_a \) was even smaller).

This lack of sensitivity to the selection criterion might suggest that any selection on the basis of proximity to the wavefront is unnecessary. However, including points very close to the wave would have produced large disagreements between predicted and measured potentials close to the wavefront. These would have dominated the RMS error between the predicted and measured potentials and reduced the usefulness of statistical comparisons between predicted and measured maps.

We tested the hypothesis that the voltages determined by regression might depend on the time after the stimulus by performing regressions using potentials from individual maps. Figure 6 shows the wavefront voltages for one central stimulus sequence for every map with at least one acceptable potential ahead of the wave (in resting tissue) and one behind the wave (in depolarized tissue). (It is necessary to have potentials both ahead and behind the wave to determine both \( V_a \) and \( V_e \).) By “acceptable,” we indicate that the potential was recorded at least 1.0 mm from the wavefront. Except for the anomalous values from the 18-msec map, the voltages all are concentrated near the values \( V_a = 65, V_e = 33 \) mV which were determined from the entire series of maps from 5 to 15 msec.

**Calculation of Resistivities**

For each central stimulation sequence, we computed intracellular, extracellular, longitudinal, and transverse resistivities (see Methods). The results of these measurements for the six hearts studied were (mean ± SD): \( r_i = 852 ± 232, r_o = 1247 ± 210, r_l = 291 ± 38, r_t = 1677 ± 331 \). The gross tissue resistivities were \( r_i = 213 ± 25, r_e = 705 ± 80 \) ohm-cm. The latter two resistivities agree with previous results, but the other four resistivities differ substantially from previously reported values (Roberts et al., 1979).

This disagreement is due to the improved method of determining wavefront voltages \( V_a \) and \( V_e \) in the present study. These voltages affect the calculated values of \( r_l, r_{ol}, r_{il}, \) and \( r_i \) (Eqs. 3–6).

**Discussion**

Myocardial cells are typically 70 µm long and 15 µm wide (Truex and Copenhaver, 1947; Laks et al., 1967). The anatomical anisotropy produces an electrical anisotropy (Rush, 1963; Clerc, 1976). Since myocardial cells are depolarized by local circuit currents which are affected by the tissue resistivity (Fozzard, 1979), the velocity of depolarization is anisotropic (Clerc, 1976; Roberts et al., 1979).

In view of the anisotropy of tissue resistivity (Rush, 1963) and of conduction velocity, it is not surprising that the extracellular voltage drop across a propagating depolarization wave depends on the direction of propagation. We have found that the extracellular voltage across a longitudinal wave is 1.75 ± 0.12 times as great as the voltage across a transverse wave.

Previous measurements of wavefront voltage present a fairly wide range of values. The wavefront voltage for a wave crossing the left ventricular wall during a normal sinus beat has been reported as “in the order of 40 mV” (van Oosterom and van Dam,
This is in agreement with our measurements ($V_{oi} = 43 \pm 6$), since transverse propagation occurs in much of the free wall of the ventricles in normal ventricular depolarization (Scher and Young, 1956; Durrer et al., 1970).

We used plunge electrodes in one of the experiments to verify that predictions based on epicardial measurements were supported, at least qualitatively, by intramural potentials. To do this, we inserted a 16-terminal plunge electrode into the wall of the ventricle where the three stimulating sequences with the epicardial array had been recorded. We stimulated at the epicardial terminal and measured the depolarization potentials at the other 15 terminals. The predictions based on the central stimulus sequence with the epicardial array were confirmed by the intramural recordings (Fig. 7).

Vander Ark and Reynolds (1970) reported a voltage of 74.1 ± 8.3 mV across depolarization waves on the ventricular epicardium. This presumably corresponds to our longitudinal wavefront voltage, $V_{oi} = 74 \pm 7$ mV. These authors also reported that the voltage across transverse waves was 29.5% smaller than the longitudinal voltage. Our ratio of $V_{oi}/V_{ot}$ implies that $V_{oi}$ was 43% less than $V_{ot}$. Vander Ark and Reynolds interpreted their results as supporting the uniform double layer concept, but their finding that the voltage across a transverse wave was less than that across a longitudinal wave supports the present study.

Other measurements have produced smaller values for wavefront voltages than in the present study. Solomon and Selvester (1971) found a mean voltage of 26 mV across normally propagated waves in the outer 4 mm of the canine left ventricle, and smaller voltages near the endocardium. In vitro endocardial muscle fibers exhibit longitudinal wavefront voltages around 23 mV (Weidmann, 1970; Clerc, 1976). Clerc's results imply that the (extracellular) transverse wavefront voltage is only one-third as large as the longitudinal voltage in his preparation. We do not know why the wavefront voltages in these studies were lower than in our study. In another in vitro study (Spach et al., 1979), there were effects of tissue anisotropy, but the extracellular voltages were very small.

**Comparison with Uniform Double Layer Theory**

The uniform double layer theory was introduced by Frank (1953). In this model, the wave is represented by a uniform double layer current source.

It is unclear how this model should be extended to accommodate the known (Rush, 1963) electrical anisotropy of myocardium. Such an extension was required to compare with the results of our model. In our statistical comparisons above, we have assumed that the wavefront voltage is independent of the direction of propagation of the wave.

Another approach would be to assume that the current dipole moment per unit area of the wave is the same, regardless of the direction of propagation. This would give results far removed from experimental observation. This is because, if the equivalent source current density is constant, the voltage across the wave should vary directly with the gross tissue resistivity, i.e., $V_{oi}/V_{ot} = n/r_t$. Our measurements of resistivity above would then require that $V_{oi}/V_{ot} = 0.30$. This is much different from the experimental ratio of wavefront voltages given above, $V_{oi}/V_{ot} = 1.75 \pm 0.12$. Thus, the equivalent current density is far from the same for different angles of propagation.

A question which is raised by our work is whether tissue anisotropy should be considered in the "forward problem" of electrocardiology. This is a difficult question for which the present study does not provide an answer. An approach to determining the importance of cardiac anisotropy in the "forward problem" would be to develop a model in which the four resistivities $\rho_{io}$, $\rho_{oi}$, $\rho_{ot}$, and $\rho_{to}$ would be inserted as parameters, and to examine the effect on computed body surface potentials of using the values of resistivities determined in the present study, as compared with assuming isotropy. The mathematical problem of how to use these resistivities in a complete model of the heart in the torso remains largely unsolved at this time.

**Appendix**

**Potential Field Calculations in Three-Dimensional Anisotropic Cardiac Muscle**

Our basic tissue model (Roberts et al., 1979) extends to anisotropic myocardium a model that has been used previously for isotropic tissue (Miller and Geselowitz, 1978). Our model consists of two parallel, continuous, anisotropic, conducting media, the intracellular (i) and extracellular (o) media, connected at each point in space by the cell membrane.

The flow of current in the two media is described by:

$$\mathbf{j}_i = -\sigma_i \mathbf{\nabla} \phi_i,$$

$$\mathbf{j}_o = -\sigma_o \mathbf{\nabla} \phi_o.$$  \hspace{1cm} (8)

Here, $\mathbf{j}_i$ and $\mathbf{j}_o$ are the intracellular and extracellular current densities, $\phi_i$ and $\phi_o$ are the electric potentials, and $\sigma_i$, $\sigma_o$ are the electrical conductivities, which are second-rank tensors (see below) for anisotropic myocardium. This is in agreement with our measurements ($V_{oi} = 43 \pm 6$), since transverse propagation occurs in much of the free wall of the ventricles in normal ventricular depolarization (Scher and Young, 1956; Durrer et al., 1970).

The meaning of the four types of line is the same as in Figure 3. The theory which accounts for wavefront voltage anisotropy (short dashes) agrees qualitatively with the measured waveform.
sotropic tissue. The source of electric fields is the membrane potential $\phi_m$:

$$\Phi_m = \Phi_e - \Phi_a. \quad (10)$$

Another important relation is the conservation of electric charge:

$$\nabla \cdot (\vec{j} + \frac{\partial}{\partial t} \rho) = 0. \quad (11)$$

Although we will not always explicitly write in the dependence of $\vec{j}, \rho, \Phi_e$, and $\Phi_a$ on position $\vec{r}$ and time $t$, all of these variables are functions of $\vec{r}$ and $t$. We assume that $\sigma$ and $\alpha$ are constants.

We wish to calculate the extracellular potential fields for a given membrane potential field. Algebraic manipulations of Equations 8-11 yield:

$$\nabla \cdot (\sigma \frac{\partial}{\partial t} \vec{V}_o(\vec{r}, t) = -\nabla \cdot \sigma \nabla \Phi_a(\vec{r}, t) \quad (12)$$

This is a differential equation from which the extracellular potential $\Phi_e$ can be calculated (within a constant gradient) from a given $\Phi_a$. From Equation 12 it is apparent that if the gradient of $\Phi_a$ is zero then there will be no extracellular electric fields (provided there are no other sources).

The solution of Equation 12 can be facilitated by the following coordinate transformation (Nicholson, 1967):

$$x' = x/\sqrt{\alpha}, \quad y' = y/\sqrt{\alpha}, \quad z' = z, \quad (13)$$

where

$$\alpha = \frac{\alpha_e}{\alpha_a}, \quad \alpha = \alpha_e + \alpha_a, \quad \alpha_0 = \left(\begin{array}{c} \alpha_e \alpha_e \\ \alpha_a \alpha_a \end{array}\right), \quad \alpha_a = \left(\begin{array}{c} \alpha_e \\ \alpha_a \end{array}\right), \quad \alpha = \left(\begin{array}{c} \alpha_0 \\ \alpha_a \end{array}\right). \quad (14)$$

In Equation 16, the conductivity tensors are given for a coordinate system $x, y, z$ in which the longitudinal (l) axis is aligned with the $z$-axis. In this particular coordinate system, the conductivity tensors are diagonal. With this transformation, Equation 12 can be partially solved for the case of an infinite homogeneous medium. The result is:

$$\Phi_a(x', y', t) = -\frac{e_0}{4 \pi} \int \left\{ \frac{\partial}{\partial x} \frac{\partial}{\partial x'} + \frac{\partial}{\partial y} \frac{\partial}{\partial y'} \right\} \frac{1}{(1 - z'^2)} dS', \quad (17)$$

where $\sigma_0$ operates on the dummy integration variable $z' = (x' + iy' + kz')$, and $i, j$, and $k$ are unit vectors in the $x, y, z$ directions, respectively.

Equation 17 is a general expression for the extracellular potential $\Phi_e$ in terms of spatial derivatives of the transmembrane potential. Again, it is clear that there can be no extracellular electric fields unless the spatial gradient of the transmembrane potential is nonzero; this is also true for isotropic tissue (Miller and Geselowitz, 1978).

We now introduce approximations appropriate to normal depolarization of the myocardium. We assume that $\Phi_a(\vec{r}, t) = \Phi_e$ if $\vec{r}$ is in tissue not yet depolarized, and $\Phi_a(\vec{r}, t) = \Phi_a$ if $\vec{r}$ is in a depolarized region. Here $\Phi_e$ and $\Phi_a$ are constants. This approximation assumes the transmembrane potential is a step function, and neglects (1) the finite time required for the rising phase of the action potential, and (2) any deviation from constancy of the plateau phase. We assume, further, that depolarized regions are separated from resting regions by smooth surfaces. We define $\Delta = \Phi_e - \Phi_a$, the magnitude of action potential (approximately 100 mV).

For this special distribution of $\Phi_a(\vec{r}, t)$, the right side of Equation 17 can be converted to the surface integral:

$$\Phi_a(x', y', t) = \frac{1}{4\pi} \int_S \left\{ V_a n_k + V_a (n_u i + n_v j) \right\} \cdot \nabla \frac{1}{|\vec{r}' - \vec{r}|} dS'. \quad (19)$$

Circulation Research/ Vol. 50, No. 3, March 1982

Here, $\Phi_a$ is the surface or surfaces separating depolarized tissue from resting tissue; $n_u, n_v$, and $n_k$ are the $x', y'$, and $z'$ components of the local unit normal vector to $S'$ (pointing from active to resting tissue), and $V_a$ and $V_a$ are constant voltages given by:

$$V_a = \Delta (n_u/\alpha), \quad (20)$$

$$V_a = \Delta (n_k/\alpha). \quad (21)$$

Equation 19 can be shown to reduce to the standard solid-angle formulation (Frank, 1953) for isotropic tissue.

The most direct and general method of performing the surface integral in Equation 19 is by means of numerical integration. In cases where the surface $S'$ has some symmetry, it may be possible to calculate the integral completely or partially by analytic means. We consider three of these special cases below. The first case, that of a plane wave, is useful in order to identify the meaning of the constant voltages $V_a$ and $V_a$ in Equation 19, and because any smooth surface looks like a plane if the observation point is close enough to the surface. The other two cases which will be discussed were used to approximate the shape of the wavefront surfaces encountered in the present study.

**Special Case—Plane Wave**

It is possible to analytically integrate Equation 19 if $S'$ is a plane. The result is that the extracellular potential is constant in each half-space defined by the plane, and the potential changes discontinuously by a voltage $V_a(x')$ across the plane where

$$V_a(x') = \frac{Vo}{cos y' + V_o sin y'}. \quad (22)$$

Here, $y'$ is the angle between the propagation direction of the wave (i.e., the normal to the plane) and the fiber direction in the transformed (primed) coordinate system. This agrees with a previous result (Roberts et al., 1979, Eq. 1) when the coordinate transformation (Eq. 13) is accounted for. Equation 22 shows that a voltage drop $V_a$ occurs with the passage of a wave moving longitudinally, and a drop $V_a$ occurs when a wave passes transversely. This justifies the designation of $V_a$ and $V_a$ as the longitudinal and transverse wavefront voltages, respectively.

**Special Case—Spheroidal Wave**

When a depolarization wave moves away from a point of stimulation, the surface defining the wavefront can be approximated by a prolate spheroid, which is the surface swept out by rotating an ellipse about its long axis (the fiber axis) (see Methods). The extracellular potential field in this case can be expressed as a surface integral over the prolate spheroid (Eq. 19). We performed a second coordinate transformation, into a prolate spheroidal coordinate system (Morse and Feshbach, 1953), in order to express the potential field due to such a surface. For the sake of brevity, we omit the lengthy calculations involved in integrating Equation 19, and give only the result, which is exact:

$$(V_a - V_m) (\xi^2 - 1)\xi - \frac{\pi}{k} \sum (4k + 1)Q_{2k}(\xi)\xi P_{2k}(\eta) \xi > \xi_o, \xi \leq \xi_o, \xi < \xi_o. \quad (23)$$

Here, $P_m$ and $Q_m$ are Legendre functions of the first and second kinds, respectively, $\xi$ and $\eta$ are prolate spheroidal coordinates. This coordinate system is illustrated in Figure 8. In these coordinates, the wavefront surface $S'$ is defined by $\xi = \xi_o$. The infinite series in Equation 23 was found to converge rapidly; only three terms were needed to obtain 0.1 mV accuracy where the convergence was worst, which was just outside the spheroid in the longitudinal direction.

Inside the spheroid $(\xi < \xi_o)$, the potential is independent of position according to Equation 23. Outside $(\xi > \xi_o)$, the potential is proportional to $(V_a - V_m)$. The constancy of the potential inside the wave is not a general property in this model, but occurs only with certain surface shapes.

We checked Equation 23 by direct numerical integration of Equation 19 for the on-axis case. We also checked that the potential...
sequence and the potentials predicted with Equation 23. Comparing the difference between the measured potentials of the central stimulus drop across the wave given by Equation 22 is the same as that given by Equation 23 for all angles α.

Special Case—Right Elliptical Cylinder

When a wave is initiated by an infinite line of stimulation in the infinite homogeneous medium described above, an infinite right cylindrical wave of elliptical cross-section results (see Methods). We used seven or 12 stimulus points in a line as an approximation to a wavefront with the shape of an infinite right elliptical cylinder. We did not find a suitable series expansion for the potential due to a wavefront with the shape of an infinite right elliptical cylinder. Therefore we calculated these potentials by numerical integration of Equation 19. We did find an analytic expression for the integral over a thin flat infinite ribbon. Therefore we needed only to divide the infinite right elliptical cylinder into ribbons parallel to the axis of the cylinder, calculate the integral over each ribbon analytically, and sum over the ribbons. The width of the ribbons was reduced until no further changes occurred in the computed potentials. This occurred with 25–100 ribbons.

Determination of Wavefront Voltages by Linear Regression

Provided the wavefront voltages \( V_a \) and \( V_d \) are known, Equation 23 could be used to calculate the potential at each field point. The wavefront voltages were determined, as described under Methods, by choosing those values of \( V_a \) and \( V_d \) that minimized the RMS difference between the measured potentials of the central stimulus sequence and the potentials predicted with Equation 23. Comparing Equations 1 and 23, the functions \( f_i(r, t) \) and \( f_i(r, t) \) are defined for use in the regression.

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FIGURE 8. Prolate spheroidal coordinate system. The radial coordinate \( s \) is defined by \( \xi = (r_1' + s r_1')/a \). The angular coordinate \( \eta \) is defined by \( \eta = (r_2' - s r_2')/a \). The third coordinate is the azimuthal angle \( \phi \), which need not be considered in the problems discussed in this study because the potential has azimuthal symmetry. See text.
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