Origin of Epicardial ST-T Wave Potentials in the Intact Dog

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SUMMARY Ventricular repolarization was analyzed by measuring epicardial potential distributions in intact dogs with single or multiple ectopic foci. During the S-T segment there was a maximum at each ectopic focus and a minimum at the terminal site(s) of excitation. During the latter half of the T wave the distributions became more complex, and two maxima evolved from the initial one at each ectopic site. The measured epicardial potentials were simulated by means of a model of ST-T wave events that is suitable for study of single and multiple ectopic beats with fusion, a model we call the "SI model." Intracellular potentials around the ventricles during repolarization were calculated from measured excitation sequences and known action potential shapes. The extracellular potentials around the ventricles were computed from the intracellular ones by a simplified ventricular geometry. The satisfactory agreement between the theoretical and measured extracellular potential distributions shows that the complex changes which occur throughout the ST-T wave are predicted well on the basis of changes in the intracellular potential distributions. In contrast to the well known liability of the T wave from beat to beat, the results show that for any single beat the events of repolarization proceed in an entirely repeatable and deterministic fashion. The results present a way to directly represent cardiac extracellular events during the ST-T wave, a method analogous to the use of isochrones during QRS, and they imply that in the future it will be possible to achieve a more precise quantitative understanding of the events of the ST-T wave than thus far has been possible for QRS.

DIRECT MEASUREMENTS of repolarization from the epicardial surface of the dog heart by means of numerous, chronically implanted electrodes have recently shown that the electrical events of cardiac repolarization are sometimes simple and sometimes complicated, but are always highly organized from place to place around the heart and completely reproducible from beat to beat.1 This report is concerned with the question of how these structured sequences of electrical events during repolarization come about; in particular, how are sequences of extracellular potential distributions that are experimentally recorded from the epicardium following ectopic beats in normal hearts related to underlying changes in intracellular potentials as determined by the preceding sequence of depolarization?

The selection of ectopic beats in normal muscle for specific consideration is based on a number of advantageous factors associated with this experimental situation for the study of repolarization. First, understanding repolarization in normal muscle is a prerequisite for understanding how it is changed by abnormalities such as ischemia. Second, ectopic beats produce depolarization sequences which are much simpler than those of normal excitation.3 Third, the ectopic beats that are considered allow cardiac geometry to be represented in a simplified fashion, since at a given time the differences in the phase of depolarization or repolarization of different parts of the ventricles occur primarily around the heart, approximately in a ring parallel to the atrioventricular ring, but not primarily in an apex to base direction. Finally, it previously has been established for normal hearts that the potential distributions during repolarization are influenced primarily by (1) the time difference between the earliest and latest areas of ventricular activation, and (2) the characteristic tendency of the epicardium to depolarize before the endocardium, with unidirectional change in repolarization progress across the wall.2 For ectopic sequences in normal muscle, the effects from the differences in activation times are quite large relative to the effects from changes in repolarization progress across the wall for most times during repolarization. Consequently, these sequences make possible a more precise examination of how depolarization times affect repolarization, since the transmural variations are inconsequential.

Previous experimental or theoretical work is of severely limited value insofar as describing any detailed characteristics of repolarization of the total heart is concerned. A major obstacle has been that no generally accepted way has existed for measuring and then representing a detailed sequence of events for the total heart in repolarization in a fashion analogous to the method of isochrones as used for depolarization. As a consequence, most information about repolarization is either in the form of action potentials from individual fibers,4 which have an unknown relation to total heart repolarization, or else is stated in the form of average properties from which specific details of particular sequences cannot be deduced. For example, the "ventricular gradient" of Wilson5 shows that some of the action potentials of the heart have a different duration than others, but does not show which ones or how many. Refractory period measurements,6,7 which are more detailed, have been used to determine that repolarization occurs at different intervals after depolarization in different layers of muscle from the epicardium to the endocardium, but again these results are average characteristics over large regions. Theoretical models of repolarization have had similar limitations. For example, the T wave model of Harumi et al.8 and Burgess et al.9 has been useful for determining moment by

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moment ventricular effects as seen in body surface T wave vectors for a restricted class of depolarization and repolarization sequences, but has not been used to provide detailed body surface distributions or any information about the heart itself. For very small structures, highly detailed calculations of repolarization events have been performed for individual nerve fibers but these results have had an unknown applicability to the total heart.

To provide a detailed explanation of how the events of repolarization come about, the following combined experimental-theoretical procedure was adopted. First, for a particular ectopic pacing site, the timing of depolarization was measured, with special emphasis on points along an imaginary ring around the heart. Second, these depolarization times were used to calculate the intracellular potential distributions around the ring, making use of an experimentally measured action potential shape and assuming that all the action potentials around the ring had the same shape, although different timing, and that there was no change in the shape whatever the excitation sequence. Third, the extracellular potential distribution around the epicardial ring was computed using the approach that the ring of ventricular muscle produces the same electrical effects as a single large strand. Fourth, the sequence of computed extracellular potential distributions was compared with the corresponding sequence of measured potential distributions.

Finally, to increase the persuasiveness of the final comparisons, the above procedure was conducted in each heart for a number of ectopic sites and combinations of two sites. Since the results included numerous distributions, simple and complex, the possibility of computation artifact or accidentally favorable comparison of computed and measured results is greatly decreased, with a corresponding increase in the confidence with which the consistent results can be attributed to inherent repolarization properties of the heart.

The advantage of this procedure is that, on the one hand, it allows for the detailed computation of extracellular potential distributions millisecond by millisecond on the basis of experimentally well established results and, on the other hand, it produces a result which can itself be verified in detail. At the same time, it is theoretically straightforward to a degree that it is possible to execute the computational procedure without becoming ensnarled in complex considerations of cardiac anatomy. Consequently, it provides a good test of whether the detailed events of repolarization in normal muscle, both simple and complicated and including their progression in time, can be explained from considering only activation times and a single action potential shape; i.e., can the complicated sequence of changes be given a basically simple explanation?

Methods

We used the same type of intact dog preparation and study procedure that was reported previously for measuring ventricular intramural and epicardial potential distributions throughout the heart. The difference in these dogs was that only epicardial electrodes were implanted; 75 electrodes similar to those previously reported provided extensive coverage of the ventricles and the atria. Bipolar pacing wires were sutured to the sinus node area to control atrial rate, and similar pacing electrodes were sutured at seven sites around the ventricles near the atrioventricular ring to result in equidistant separations for producing ectopic foci. The wires were looped within the chest and distal ends implanted superficially beneath the skin of the abdomen. The eight dogs prepared as above did well postoperatively and underwent study 14–25 days postoperatively. Prior to study, the body surface isopotential maps returned to the preoperative state as judged by visual comparison. Furthermore, the recording procedure first measured the epicardial repolarization distributions for the normal excitation sequence, and the repolarization distributions were similar to those previously reported. Thereby each heart was considered to be normal. Detailed checks ensured the absence of local injury effects in the waveforms recorded at each site.

EXPERIMENTAL MEASUREMENTS

Each dog was studied under sodium pentobarbital anesthesia (30 mg/kg, iv). Wires from the heart were exteriorized and connected for rapid sequential recording of the waveforms in groups of 15 epicardial points simultaneously. All potentials were recorded in reference to the left leg. Eight reference epicardial leads and lead II were recorded simultaneously with 15 data points to ensure that there were no beat-to-beat changes in the excitation sequence during each run.

All sequences for each dog were recorded at the same fixed pacing rate, which fell within the range of 90–140 beats/min. The pacing stimulus was 1-msec impulses at 1.5 times the threshold value. The stimuli were synchronized to pace the atrium, followed in 40 msec by the stimulus to the ventricle. This ensured that there were no beat-to-beat changes in the excitation sequence due to fusion via activation through the His bundle and that there was no change in the heart rate due to interpolated beats. The epicardial sequences were recorded while either one or two ventricular sites were stimulated. To test the effects of alternating time intervals between two ectopic foci, two sites at opposite sides of the heart were paced simultaneously and, while holding one constant, the other was delayed incrementally in a stepwise fashion for each new sequence.

The pacing sequence was controlled by a PDP-11/20 computer which synchronized the pacing stimuli with the data recording. The recording system consisted of 24 AC amplifiers with the output of each being sampled at a rate of 1,000 samples/sec. The waveforms were displayed immediately on a Tektronix 4002 display unit and after each beat was determined to be free of artifact, the waveforms were recorded on digital tape. At the end of each experiment the heart was removed, the electrode sites were documented, and measurements were made of the distance between electrodes and of the size of the ventricles.

The digital recorded waveforms were redisplayed and photographed for detailed inspection of each waveform to ensure no baseline shifts (maximum shift ± 50 μV in final maps). A second computer program was used to convert the waveforms from time sequences to potential distributions, and epicardial potential maps were printed for every 4 msec
throughout the ST-T waves. The unipolar waveforms were also utilized to construct isochrone epicardial activation sequences. Previous atrial and ventricular activation studies showed that the same isochrones were produced by analysis of either unipolar or bipolar waveforms. To compare the measured epicardial potentials with the computed extracellular potentials, the final epicardial potential maps were used to construct a plot of the potential around the circumference of the ventricle at a series of points around the imaginary ring shown in Figure 1A.

**DERIVATION OF INTRACELLULAR POTENTIAL DISTRIBUTIONS**

To calculate the intracellular potential at each point along the epicardial ring being considered, the ring was divided into 60 equal segments, as shown in Figure 1A, and each point was identified with a specific anatomical location (Fig. 1A-2 and 1A-3). We assigned one action potential shape to all epicardial sites and another action potential shape to all endocardial sites. These shapes (Fig. 1B-1) were the same as those published by Moore et al. We made similar measurements in vitro and our results also showed shorter duration of the epicardial action potentials as compared to those from the endocardial fibers. The duration of the action potentials was determined by the duration of the Q-T interval for the normal excitation sequence recorded initially in each experiment at the same rate as all of the other sequences. The action potentials then were divided into 90-100 equal time divisions (3-4 msec each). Activation times were assigned to each of the 60 points of the band on the basis of the measured isochrone activation maps. The value of the intracellular potential at each position was computed for any instant throughout the ST-T wave by knowing the time of activation of each site and the time of the instant being considered. An example of this procedure and the result for a single instant is shown in Figure 1B. The activation sequence shown for the band (Fig. 1B-2) was that measured for a single ectopic focus located laterally on the left ventricle (position 30). The time instant indicated in lead II (Fig. 1B-1) was 260 msec from onset of QRS. The values computed at each position for this instant produced the epicardial and endocardial intracellular distributions shown in Figure 1B-3. Although only the epicardial intracellular potentials were used for computing extracellular potentials, the associated endocardial intracellular distribution was derived for each instant in order to compare the computed transventricular gradient with the computed transmural gradient at the same time. Note for the instant shown, the transmural gradient was small at all positions as compared to the transventricular gradient.

**Figure 1** Epicardial bond (A) and method (B) of deriving the intracellular potential distribution along the band. The stippled area in A shows the imaginary epicardial band for which extracellular potentials were computed on the basis of intracellular potentials. The procedure for deriving the epicardial, as well as the underlying endocardial, potential for each of the 60 positions for any instant during repolarization is shown in B. The endocardial (Endo) and epicardial (Epi) ventricular action potentials shown in B (I) were those assigned to each of the 60 positions.
THEORETICAL MODEL

Since ectopic beats produce potential distributions primarily influenced by the transventricular gradient and since alterations in the excitation sequence do not change the shape of intracellular potentials, the intracellular distribution for any instant during repolarization can be derived from known shapes of intracellular action potentials if the excitation sequence is known. Thus, in principle, one could compute the extracellular distributions of the ventricle from the derived distributions in intracellular space. Such simulations have been limited primarily to simple structures with shapes similar to long cylindrical cells, such as isolated nerve fibers and Purkinje strands. These geometrical approximations are important not only because they greatly simplify the computations involved but because they make it reasonable to assume that the internal (intracellular) voltage gradients vary only in the longitudinal direction of the cylinder and, thereby, the net membrane current-density distribution is directly proportional to the second spatial derivative of the intracellular potential.

The geometry of the ventricle was represented as a single epicardial band of muscle having toroidal shape which extended from the lateral borders of the right and left ventricles at the atrioventricular ring to the midseptal region anteriorly and posteriorly, as shown in Figure 1A. This band of muscle was considered to have a width of approximately \( \frac{1}{3} \) the distance from the apex to the base of each heart and to have a depth of 3 mm. To further simplify the calculations, the geometry of a cross-sectional slice through the band around the ventricles was represented as a circle with radius \( a \), as shown in Figure 2A. The radius was chosen such that the perimeter of the circle was the same as the perimeter of the actual muscle band. Distance along the axis of the toroid formed by the epicardial band around the heart is designated \( z \). If it is assumed, for the moment, that the ring formed by the axis of the toroid around the epicardium has a small enough curvature of the axis \( z \) that the curvature can be ignored, then the toroid can be replaced by a cylinder and the derivation of the extracellular potential distribution from the intracellular one is the same as for Purkinje strands.

More specifically, the conductivity within the cylinder is \( \sigma_i \) and the conductivity in extracellular space is \( \sigma_e \). Assume that during repolarization the intracellular potential, \( \phi_i \), varies only as a function of \( z \), and that the effect of the boundary in extracellular space (i.e., the body surface) can be neglected. Therefore, the second spatial derivative of the intracellular potential, \( \phi_{ii} \), can be computed and the potential at a recording point on the surface of the cylinder becomes

\[
\phi_s(z,t_s) = \frac{a \sigma_i}{4 \sigma_e} \int_0^\infty \frac{\partial^2 \phi_i}{\partial z'^2} \frac{1}{a \left( \frac{z'-z}{a} \right)^2} dz'
\]

(1)

The variable \( z' \) denotes the position of a current element contributing to the extracellular potential, \( \phi_s \), at \( z \) for time instant \( t_s \). For each value of \( z, z' \) is varied to sum the contributions of all current elements along the entire axis of the cylinder. Note that the membrane current at all points of the cylinder contributes to the extracellular potential at point \( z \).

Equation 1 can be corrected to take into account the fact that the curvature of the axis of the toroid around the epicardium is nonzero. The correction is achieved by modifying the denominator of the integrand so that the distance along the axis, \( z' - z \), is replaced by the distance in a
straight line between positions \( z' \) and \( z \). This distance, \( d \), is given by the equation

\[
d = \frac{c \sin \left[ \pi \frac{z-z'}{c} \right]}{\pi}
\]

(2)

where \( c \) is the circumference of the ring axis around the epicardium.

Combining Equations 1 and 2 results in

\[
\phi_e(z,t_e) = \frac{\alpha \sigma_1}{4 \sigma_0} \int_{z^*}^{z_e} \frac{\partial^2 \phi_i}{\partial z'^2} dz'
\]

(3)

This equation gives the extracellular potential, \( \phi_e \), at one point; finding the value of \( \phi_e \) for this one point involves the intracellular potential values at all of the 60 epicardial locations. To compute the potential distribution the integral of Equation 3 was repeatedly evaluated for the different values of \( z \). This integral was approximated numerically by using the values of the intracellular potential at each position. The distance, \( dz' \), of each of the segments was determined from the measured circumference of the ventricle of the heart under study. For the sequences to be shown the heart had a circumference of 18 cm and, thereby, \( dz' \) was assigned a value of 3 mm. The value for the radius \( a \) was assigned to result in the cross-sectional circumference of the cylinder equivalent to that of the hypothetical epicardial band, e.g., in the cases to be shown a was 12 mm. We used a ratio of intracellular to extracellular conductivity of 1 to 3.18

Equation 3 was the basis of our calculation of the extracellular potentials from the intracellular potential distribution. To estimate the effect of the membrane current of an isolated single segment on the extracellular potential at all sites, the second spatial derivative of the intracellular potential of one segment was assigned a value of 2.0 mV/mm² with a value of zero assigned to the remainder of the 60 segments. The resultant computed extracellular potential distribution, shown in Figure 2B, illustrates that nearby points are greatly affected and there is a rapid decline in the effect with distance, while a small but definite effect is present at the most distant point. For the purpose of the calculations a comparison was made of the results shown in Figure 2B, which were computed on the basis of Equation 3 (angular method) with those produced by Equation 1 (linear method which ignores the curvature around the ventricles). The results were very similar except that the effect at the most distant point was greater with the use of Equation 3; i.e., at the most distant point the extracellular potential decreased to 15% of its peak value with Equation 3 and to 8% when computed with Equation 1. A similar comparison was made for the sequences studied, and this also showed essentially identical results.

For purposes of clarity in presenting the combined experimental and theoretical results we use the following terminology:

**Ectopic focus or site:** A location where ventricular activation is initiated by stimuli delivered at 1.5 threshold value by an artificial pacemaker via bipolar electrodes.

**Epicardial band:** The area of epicardial muscle indicated by the imaginary epicardial band shown in Figure 1A.

**Extracellular curve:** The measured or computed extracellular potential distribution as it varies along the length of the epicardial band.

**Maximum:** The highest extracellular potential for any area being considered in the epicardial potential distribution or in the curve showing the extracellular potential values along the epicardial band.

**Minimum:** The antonym of *Maximum*.

**Second derivative:** The second spatial derivative of the intracellular potential in the epicardial band. Since the net membrane current is directly proportional to the second spatial derivative of the intracellular potential for the model being considered here, we use the two terms synonymously.

**Transmural gradient:** The intracellular potential difference that exists across the ventricular free wall at any site; i.e., the intracellular gradient between the epicardium and the underlying endocardium.

**Transventricular gradient:** The intracellular potential difference that exists between two or more sites which are located on an axis similar to that described by the epicardial band; i.e., the intracellular gradient existing between the lateral left ventricle and the lateral right ventricle (RV).

**Results**

The excitation sequences and repolarization distributions were remarkably constant from dog to dog, even for complex sequences. The sequences to be presented were selected because the distributions show the varying complexities that can occur during ventricular repolarization beginning with a single excitation focus and going on to two widely spaced foci which excite with a varying time relationship between the two, and because only after viewing a number of instants in a variety of sequences is it apparent that the theory satisfactorily predicts not only the major extracellular events of the location of the maxima and minima and the location of the steepest gradients, but it also predicts in the proper sequential order many of the fine details of the increasing and decreasing values of the maxima and minima and their relationship to one another. The results are presented for a single dog to allow comparison of similar times for different sequences. Figure 3 shows the location of the 75 electrodes used to measure the epicardial potential distributions.

**Single ectopic focus**

For the left ventricular ectopic focus shown in Figure 4 the epicardial activation sequence (I and II) showed that the isochrones moved in a unidirectional manner from the lateral left ventricle to terminate on the lateral right ventricle. The epicardial potential distribution that initiated the ST segment (III) is presented to illustrate the initial potential distribution in relation to the epicardial activation sequence to emphasize the relationship between the initial positions of the maxima and minima to the earliest and latest sites of excitation.
Anterior Posterior

Figure 3. Epicardial electrode positions for recording potential distributions. The arrangement of the 75 electrodes provided extensive coverage of the epicardial surface of the left and right ventricles (LV and RV) and the area as shown.

Rows A and B of Figures 4 and 5 illustrate the major events during the ST-T wave. (1) During early repolarization (192 msec) the maximum was in the area of the ectopic focus and the minimum was located near the site of terminal ventricular excitation on the opposite ventricle. (2) The maximum increased in magnitude and the steepest gradients were maintained in that area while it remained stationary in position with a greater magnitude than that of the minimum on the lateral right ventricle, as well as that of the nearby minimum on the right atrium (192 and 260 msec). (3) Thereafter, the magnitude of the maximum began to diminish and there was a shift of the area of steepest gradients away from the ectopic focus (292 msec). Once the magnitude of the initial maximum began to decrease there were rapid changes in that area; two positive peaks developed from the initial maximum and these peaks shifted anteriorly and posteriorly toward the minimum on the opposite ventricle (Fig. 5, 316 and 332 msec). It should be noted that in comparing the measured extracellular curve in Figure 5, row B at 316 msec to the associated total epicardial potential distribution in Figure 5, row A, there are two positive peaks in the extracellular curve, whereas there is only one maximum on the LV in the epicardial map. This difference is due to the relation of the position of the imaginary band shown in Figure 1A as related to the location of the potential maximum on the LV; i.e., moving around the ventricle to each of the 60 positions along the band results in the potential contours being crossed sequentially to produce the two peaks, one anteriorly and the other posteriorly on the LV. The minimum remained stationary while it increased in magnitude to achieve its greatest value after the maximum had decreased from its peak value. (4) While the minimum remained stationary, the two positive peaks continued to shift away from the initial ectopic focus toward the minimum. This was associated with a shift of the

Figure 4. ST-T wave sequential events for a single ectopic focus on the lateral left ventricle. The format used for this figure, in combination with Figure 5, is that for each of the four sequences to be presented: The epicardial isochrone activation sequence (I) is shown first along with the excitation times assigned to each of the 60 segments comprising the epicardial band (II). The epicardial potential distribution during the early ST segment is shown in III. The pacing symbol indicates the ectopic site. The epicardial outlines represent an anterior view of the heart (left) and a view of the posterior (diaphragmatic) surface as seen from below. Positive potentials are indicated by the darkened areas and negative potentials by the light hashed areas. The time of the arrow pointing to the lead II waveform represents the time from the onset of ventricular activation. Each section shows (A) the measured epicardial potential distributions, (B) the measured potentials surrounding the ventricle in the area of the imaginary epicardial band, and (C) a graph for the area of the band of the epicardial and endocardial intracellular potential distributions (Endo and Epi $\phi_i$), the second spatial derivative of the epicardial intracellular potential (dashed line) and the computed extracellular epicardial distribution along the band (thickened solid line). The measured potential values at each of the 60 positions shown in B for the epicardial band were taken from the epicardial distributions shown in A at positions indicated in C. The ectopic site was at position 30.
steepest gradients toward the minimum (332 msec). During the latter part of the T wave the anterior and posterior maxima decreased in magnitude with continued movement toward the stationary minimum until they were located on the right ventricle (352 msec). Terminally, most of the epicardial surface of the ventricle had positive potentials with the anterior and posterior maxima persisting while the minimum shifted to the most negative area nearby on the right atrium (368 msec).

The accompanying theoretical results shown in row C of Figures 4 and 5 can be compared with the measured curves in row B. Note that the transmural gradient at all sites is much less than the transventricular one, a condition which persisted until the terminal 40 msec of the T wave. The initial stationary position of the maximum at the ectopic focus (192 and 260 msec) was associated with the nadir of the intracellular potential distribution in the ventricles, and this resulted in a positive peak of the second spatial derivative at that site (position 30). The concomitant increase in the magnitude of the maximum was reproduced faithfully in the computed extracellular potentials and this was related to the increase in the intracellular gradients in that area.

The time of the peak value of the maximum and the subsequent decrease in magnitude of the computed extracellular potentials compared favorably with the recorded distributions. This decrease was related to the intracellular potentials in that area nearing the resting potential level, and the shape of the spatial intracellular potential distribution at 292 msec indicates the influence of the well known terminal slow component of ventricular action potentials. At this time there was a change in the relationship of the shape of the extracellular potential curve and the shape of the second derivative; at 192 and 260 msec both curves had a single positive peak but by 292 msec the second derivative consisted of two positive peaks while the extracellular potential curve continued with a single maximum that broadened and decreased in magnitude. This lack of proportionality between the extracellular potential curve and that of the second spatial derivative of the intracellular potential (net membrane current) occurred repeatedly in all of the sequences; i.e., while the second derivative varied from being quite similar to quite different in shape as compared to the measured extracellular potential curve, the computed and measured extracellular curves showed good agreement.

The subsequent development of two maxima in the epicardial potential distributions was predicted in the computed curves (316 and 332 msec). These evolved as the two positive peaks of the second derivative shifted farther apart. This shift was determined intracellularly by the gradually increasing area of muscle that had reached resting potential, beginning at the ectopic focus, with the result that the areas of epicardial muscle undergoing active repolarization shifted anteriorly and posteriorly toward the right ventricular site of highest intracellular potential, a site which did not change in position throughout the ST-T wave (i.e., the site of the extracellular minimum). The peak negative value of both the computed and measured extracellular curves occurred between 316 and 332 msec while both curves showed the continued shift of the two maxima toward the minimum (332 and 352 msec). Intracellularly this was related to the increasing area of muscle in the left ventricle that had reached the resting potential level with the resultant decreasing area of muscle undergoing active repolarization in the opposite ventricle.

Terminally (368 msec) both the computed and measured extracellular curves showed an anterior and posterior maximum on the right ventricle. However, while the computed curves predicted the minimum to remain stationary, the measured epicardial distributions showed the minimum to
shift nearby on to the right atrium. This singular discrepancy of the location of the minimum occurred in most sequences during the last 40 msec of the T wave. The difference can be explained from the graphs of the epicardial and endocardial intracellular potentials. Only during the terminal T wave (368 msec) did the transmural gradient approximate or exceed the transventricular gradient, a condition that resulted extracellularly in positive ventricular epicardial potentials and negative atrial potentials, the atrium reflecting the negative ventricular endocardial potentials.1

TWO EPICARDIAL FOCI WITH SYNCHRONOUS ONSET

To determine the effect of two ectopic foci on repolarization, the same site noted above and a site on the opposite side of the heart were paced simultaneously, a situation that is an experimental counterpart of fusion beats that can occur naturally.20, 21 The epicardial activation sequence (Fig. 6-I and 6-II) consisted of the isochrones moving with a unidirectional orientation from each of the lateral ectopic sites toward the septum with the terminal excitation sites located anteriorly and posteriorly next to the septum on the left ventricle. The duration of ventricular activation was 98 msec as compared to 147 msec for the single ectopic focus. The initial S-T segment distribution consisted of two maxima and two minima (Fig. 6-III); the maxima were at the ectopic sites on opposite sides of the heart and the minima were located anteriorly and posteriorly next to the septum in the areas where excitation had terminated (126 msec).

The changes throughout the ST-T wave were the same for each of the two ectopic foci, changes that reproduced those of a single ectopic focus. At 132 msec (Fig. 6, rows A and B) the two maxima were of greater magnitude than the two minima and the steepest gradients occurred around the maxima. While both maxima and both minima remained stationary, the magnitude of the two maxima increased more than the minima (196 and 272 msec). When the values of the two maxima had reached their peak and began to decrease at approximately the same time, the steepest gradients shifted away from the maxima toward the minima (Fig. 7, 288 and 300 msec). Thereafter, the positive potentials at the two ectopic sites continued to decrease with two positive peaks emerging from the maximum at each ectopic focus. This resulted in a more complex epicardial distribution with four positive peaks shifting toward the two stationary minima adjacent to the septum (324 msec). This complex distribution continued with the two minima remaining stationary while four maxima continued to shift away from the original lateral ectopic foci into the regions adjacent to the minima (324 and 344 msec).

The theoretical results satisfactorily predicted the initial two maxima and two minima, their locations, and the subsequent proper sequential changes with the development of even more complex distributions during the latter part of the T wave (rows B and C of Figs. 6 and 7). The origin of these epicardial distributions which became more complex during the T wave can be seen to be related to the same type of spatial intracellular potential changes that occurred with a single ectopic focus. However, in contrast to the single ectopic sequence, the locations of the maxima and minima were much closer together and the shifts in the multiple maxima and the steepest gradients occurred over shorter distances. The direction of these shifts were reproduced in the computed potentials and the development of two separate maxima from an initial one at each of the two pacing sites was accounted for by the spatial intracellular distributions which can be seen from 288 to 324 msec (Fig. 7). Note that the continued shift of the four maxima toward the two

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**Figure 6** Two ectopic foci with synchronous onset. Note from the activation sequence of the epicardium (I) and that of the epicardial band area (II) that the early S-T segment distribution (III) consists of a maximum at each of the two ectopic foci and a minimum in each of the two areas of terminal excitation. The two vertical arrows in II indicate the terminal excitation sites.
stationary minima was reproduced in the computed extracellular curves and that intracellularly this was related to the increasing area of muscle that had reached the resting potential value, beginning at each ectopic focus. The two minima continued at the two unchanging sites where the intracellular potential remained highest throughout. Again, during terminal repolarization (344 msec) a prominent atrial minimum developed in the measured distributions; the predominant gradient evident in the spatial intracellular distributions at this time had changed from the previous transventricular one to a transmural one in the regions undergoing terminal repolarization.

TWO ASYNCHRONOUS ECTOPIC FOCI WITH MODERATE DELAY OF ONE FOCUS

Since the previous sequence produced complex repolarization distributions with similar events occurring synchronously in each ventricle, a further test of the theory would be to delay the onset of one of the two ectopic foci to produce asynchronous repolarization events. Figure 8 (I and II) shows the activation sequence when the onset of the right ventricular ectopic focus was delayed 50 msec after that of the left ventricular focus. The isochrones were oriented similarly to those of the previous sequence but there was delayed progression of those on the right ventricle. The end result, as compared to the previous sequence, was a rightward shift in the anterior and posterior areas of terminal excitation to the right ventricle next to the septum.

The duration of ventricular activation was 122 msec. The early S-T segment epicardial distribution at 152 msec (Fig. 8-III) consisted of a maximum at each of the two ectopic foci and two minima located in the right ventricular paraseptal areas.

The early repolarization events were similar to those of the previous sequence with the maxima increasing in magnitude with the steepest gradients nearby while the two minima remained stationary (Fig. 8, rows A and B); however, the magnitude of the right ventricular maximum remained less than that of the one on the left ventricle (212 and 272 msec). The maximum at the left ventricular ectopic site began to diminish from its peak value (272 and 284 msec) at approximately the same time as it did in the two preceding sequences. While it decreased in magnitude with the emergence of two positive peaks (Fig. 9, 304 msec), the maximum at the delayed right ventricular ectopic site continued to increase in magnitude with steep gradients surrounding it. The maximum subsequently diminished in magnitude but, in contrast to the changes that occurred at the left ventricular ectopic site, two positive peaks did not emerge nor did the maximum change in position (320 msec). This resulted in the simultaneous presence of three maxima and two minima during the latter part of repolarization (336 and 364 msec) in contrast to four maxima during this interval when the two ectopic foci had a simultaneous onset. Terminally (364 msec) the maximum at the right ventricular focus finally shifted away from the delayed ectopic site and moved toward the posterior minimum. This occurred at a time when there was continued shift of the two left ventricular maxima toward the right ventricle (364 msec).

The computed and measured extracellular curves were similar for each of the instants noted above. However, these curves changed in a complex way as related to changes in the shape of the second derivative. At the two ectopic sites at 212 msec (Fig. 8) the second derivative showed positive peaks of similar magnitude but at 272 msec the second derivative positive peak at the delayed right ventricular focus was greater than the one on the left; yet the extracellular curve at both instants showed that the maximum at the right ventricular focus was of lower magnitude.
than the maximum at the left ventricular focus. This difference in the shape of the extracellular potential curve and that of the second derivative can be seen to be related to the extracellular effects produced by the two negative peaks of the second derivative in close proximity to the single positive peak at the RV ectopic focus whereas these two negative peaks had relatively little effect at the more distant LV ectopic site (272 msec).

The time of the peak value of the left ventricular maximum and its subsequent decrease with the shift of the steepest gradients toward the minimum were reproduced in the computed extracellular curves at 272 and 284 msec, along with the continued increase in magnitude of the right ventricular maximum at 304 msec (Fig. 9). The subsequent decrease in magnitude (320 msec) of the RV maximum while it remained at the same site without the emergence of two maxima, was predicted and the continued presence thereafter of three maxima and two minima was associated with...
the asymmetry of the spatial intracellular potential distribution of the two ventricles as shown in 336 and 364 msec (Fig. 9).

TWO ASYNCHRONOUS ECTOPIC FOCI WITH MARKED DELAY OF ONE FOCUS

A final test of the two ectopic sites would be to markedly delay one of them to determine if the events at that site would detectably influence the epicardial distributions; i.e., these should be influenced primarily by the marked predominance of the quite early focus which would tend to produce distributions like those of the single ectopic focus. The activation sequence that resulted when the onset of the right ventricular focus was delayed 75 msec after the one on the left is shown in Figure 10-1. The major effect of the incremental delay on ventricular activation was to shift the terminal excitation sites to the lateral right ventricle as compared to their positions in the right ventricular paraseptal areas when the two ectopic sites had a moderately asynchronous onset.

The epicardial distributions had the same number of maxima and minima throughout the ST-T wave as had occurred with the previous sequence. However, the two minima were located more laterally than before and their positions coincided with the terminal excitation sites (Fig. 10, 188 to 272 msec). The major difference from the previous sequence was that the maximum at the delayed RV site remained smaller in magnitude throughout and terminally it showed no shift away from the ectopic site. Also, it reached its peak positive value 25 msec later than in the previous sequence.

Again, the computed and measured extracellular potential distributions showed good agreement. This sequence has two interesting features. First, although the epicardial distributions were similar to those of the single ectopic focus, the effect of the very late focus was quite detectable throughout the ST-T wave as evidenced by the maximum at the late ectopic site. This maximum, in turn, was produced by the associated positive peak in the second derivative which occurred within the broad region of high intracellular potentials extending throughout the late repolarizing right ventricle amidst which there was a small area of muscle with lower potentials due to slightly earlier repolarization at the RV ectopic site (Fig. 10, row C). Second, the magnitude of the maximum at the late RV ectopic site remained at a lower level than occurred in the previous sequences with two ectopic foci, yet the associated positive peak of the second derivative reached the highest values encountered in any of the sequences (Fig. 11, 328 and 340 msec). This drastic lack of proportionality between the shape of the second derivative curve and the extracellular potential curve can be seen to be related to the two negative peaks in the second derivative; they were located closer to the RV ectopic site and farther away from the LV ectopic site than had occurred in the previous sequences when the onset of ventricular activation at the two ectopic sites had been more synchronous.

Discussion

The results show that the potential distributions surrounding the heart during the ST-T wave can vary from quite simple to quite complex and that these distributions can be satisfactorily predicted from the spatial intracellular potential distributions throughout the ventricles. We call this model the "SI model" because it involves the spatial analysis of intracellular potentials, an analysis based on well known principles. The satisfactory agreement between the theoretically predicted and the measured epicardial potential distributions supports the interpretation that ven-

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**Figure 10** Two asynchronous ectopic foci with marked delay of one focus. Note that the epicardial distributions closely resemble those of the single ectopic focus; however, even though the lateral right ventricular site had a very late onset, its effect during repolarization is clearly evident with a maximum persisting at that site.
Late repolarization events for two asynchronous ectopic foci with marked delay of one focus. The maximum at the markedly delayed ectopic focus remained small in magnitude and constant in position while two maxima emerged from the early ectopic site on the left ventricle.

Ventricular repolarization potential distributions are determined by the spatial distribution of the intracellular potentials and relatively simple geometric relationships. There were markedly different and complex spatial intracellular potential distributions from sequence to sequence although the shape of the ventricular action potential remained identical for all positions during all sequences. This emphasizes that the major factor required to understand and predict the extracellular ST-T wave is the change produced in intracellular space around the entire ventricle; i.e., this allows one to determine the net membrane current in the form of the second spatial derivative of the intracellular potential, and through the geometric relationships embodied in Equation 3 the complex effects of currents in extracellular space determine the potential at any site.

Extracellular potential distributions provide a method previously lacking to describe in detail the events of repolarization of the total heart in a way that is analogous to the use of the isochrone method used to describe in detail the events of depolarization of the total heart. The SI model presented here extends the quantitative analysis of ventricular repolarization potentials produced on the body surface, as represented by the well known theoretic model of the T wave of Harumi et al. to the direct study of extracellular potentials on the heart. When considering repolarization models of these two types, it is important to emphasize that there are different requirements for the quantitative explanation of the origin of potentials on the body surface vs. those on the heart. For determining the potential at a site distant from the heart, the characterization of the cardiac sources can be simplified by using a single dipole to represent the equivalent cardiac generator, or by using multiple dipoles with each of the dipoles representing a separate ventricular segment. However, for predicting the potential at a site on the heart, where the repolarization potentials in intracellular space change over a distance greater than that to the recording point, the cardiac sources have to be resolved in more detail, such as in the form of membrane current and potential distributions.

Van Dam and Durrer showed that when the total heart was depolarized simultaneously the body surface T waves appeared similar to those recorded with normal excitation sequences. Their results appear superficially to be contradictory to those presented here. This is because if all ventricular intracellular action potentials were of identical shape and all were depolarized simultaneously, during repolarization there would be no intracellular potential difference either transmurally or transventricularly, and the second spatial derivative of the intracellular potential (net membrane current) would be zero with the effect that there would be no potential change in extracellular space. This seeming contradiction is resolved, however, by noting that the shapes of the ventricular action potentials are different transmurally because of the inherent characteristic of the normal ventricle to repolarize unidirectionally from epicardium to endocardium. Thereby, with simultaneous depolarization of the heart, although there would be no transventricular gradient, the transmural gradients throughout the ventricular walls would produce positive T waves on the epicardium and negative T waves at the endocardium, a situation that occurs normally. This situation would appear to be similar to normal repolarization, since in normal repolarization the transmural gradient is significantly large in relation to the transventricular gradient.

The marked discrepancies found between the shape of the spatial intracellular potential distributions and the shape of ventricular action potentials illustrate the lack of correlation between spatial and temporal events. Van Dam and Durrer showed...
noted that even though refractory periods were measured in several ventricular areas the results still did not provide sufficient information to explain the form of the epicardial T waves they recorded. Pipberger et al. used unipolar records from the cardiac surface, intramurally, and in the cavity to study repolarization and found a complete lack of uniformity in the T-polarity distribution from one animal to another. They also found no correlation of the surface and subendocardial T waves with the polarity of these waves. More recently, Autenrieth et al. studied repolarization using suction electrodes to record monophasic action potentials, and related action potentials from different areas of the surface of the heart to each other and to body surface T waves using statistical measures. Additionally, it is widely known that the T wave is quite labile; i.e., there are beat-to-beat changes easily produced in T waves due to changes in cardiac rate, temperature, blood supply, etc. It might be inferred from the above that repolarization involves cardiac phenomena that have, to some degree, a basically random nature. The results of this report show that just the opposite is the case, i.e., the events of repolarization proceed in an entirely repeatable and deterministic fashion.

The fundamental change in the approach to repolarization that is incorporated into this manuscript, as compared to previous reports, is the explicit incorporation of spatial relationships into the analysis by means of intracellular and extracellular potential distributions. The use of such distributions has the additional advantage that they are easily associated, as an intermediary form, with well known features of intracellular action potentials and with extracellular epicardial waveforms, and even can be related to body surface events in a detailed way. Considering the above, the more extensive spatial distribution and longer time course allow a more explicit experimental measurement of the characteristics of ventricular repolarization, as compared to depolarization, especially since these characteristics are spatially determined by sources over the entire ventricle during repolarization vs. a narrow area during depolarization. That is to say, the results of this report imply that in the future it will be possible to achieve a more precise quantitative understanding of the events of the ST-T wave than has thus far been possible for QRS.

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