Determination of Transmural Location of Onset of Activation From Cardiac Surface Electrograms

Mary Jo Burgess, MD, Robert L. Lux, PhD,
Philip R. Ershler, PhD, and Ronald Menlove, PhD

Methods of estimating depth of origin of ventricular activation from cardiac surface electrograms were evaluated in experiments on eight dogs. The ventricles were paced via multielectrode needle arrays placed transmurally in from four to six locations in the wall of the left ventricle. A multiplexed data-recording system was used to simultaneously record from 64 unipolar cardiac surface electrodes during pacing at each multielectrode needle site. The four indexes evaluated were the maximum and average gradients of activation isochrones around the site of earliest epicardial activation, the QRS area at the site of earliest epicardial activation, the interval between the QRS onset computed from all 64 epicardial surface electrograms, and the time of the minimum dV/dt in the electrogram displaying the earliest epicardial activation time (t<sub>rec</sub> - t<sub>mso</sub> interval). Correlation coefficients between depth of stimulation and average and maximum gradients of isochrones, QRS area at the site of earliest epicardial activation, and t<sub>rec</sub> - t<sub>mso</sub> interval were 0.985 or higher. These methods, particularly those involving gradients of isochrones, should be useful for evaluating electromaps of patients undergoing surgery for ablation of tachyarrhythmias. (Circulation 1990;82:1335–1342)

Outcomes of surgical ablation of supraventricular and ventricular tachyarrhythmias have been improved by mapping ventricular activation sequences and directing surgical interventions to sites of origin of the arrhythmias or sites involved in reentry paths. Because the site of earliest activation is the site of origin or forms part of the reentry loop, surgical intervention is usually directed toward this site. Mapping to identify the site of earliest activation is done with simultaneous recordings from multiple epicardial locations or with sequential recordings acquired with a hand-held roving electrode. The actual onset of activation, however, may occur at a site not recorded because of inadequate sampling of the epicardial surface or initiation of activation from septal, intramural, or endocardial locations. Methods for estimating whether the earliest activation time detected from epicardial surface electrograms is the site of onset of activation are desirable. Because unipolar electrograms contain information about distant as well as local cardiac events, their analyses should be useful in assessing whether the site of onset of activation has been sampled or activation is originating at a site distant from all recording sites. The purpose of this study was to evaluate methods of analyzing epicardial surface map data to assess the depth of onset of activation.

Methods

Experiments were done on eight dogs anesthetized with 30 mg/kg i.v. pentobarbital. Additional bolus infusions of 60 mg pentobarbital were administered as needed to maintain deep anesthesia, which was judged by absence of corneal reflex. The thorax was opened with a midline sternotomy, and the dog was ventilated with room air using a pump respirator. The sinus node was crushed, and the heart was suspended in a pericardial cradle. A bipolar hook electrode was attached to the right atrial appendage, and the heart paced at 400-msec cycle lengths. An array of 64 unipolar electrodes on a hexagonal grid was constructed by stitching 5-mil insulated silver wires to a nylon stocking stretched over a model of a dog heart. The insulation was stripped from the wires at their point of attachment; as a result, electrodes were separated from each other by approximately 1
cm. The electrode array was slipped over the heart of the experimental animal, and from four to six multielectrode needles were placed transmurally perpendicular to the epicardial surface of the left ventricular wall in anterior, posterior, apical, and lateral locations. The needle-electrode arrays were constructed from 3-mil insulated silver wires that were mounted in the barrel of a 20-gauge needle after removal of an arc along its length. The termini of the 12 wires were spaced 1.6 mm apart. The needle-electrode arrays were placed as close as possible to epicardial recording sites. The ventricles were paced from each of the 12 unipolar electrodes in the needle arrays with 2-msec duration, constant current, diastolic threshold intensity stimuli. Stimuli for ventricular drives were delivered simultaneously with atrial stimuli, and a needle placed in the chest wall served as the indifferent electrode for ventricular stimulation. A multiplexed data-recording system was used to simultaneously record from 64 unipolar epicardial surface electrodes, each referenced to a Wilson central terminal. Signals were sampled once every millisecond, digitized, and stored on disk. The details of this system have been previously reported.

Data Analysis

RMS voltage curves were calculated as the square root of the sum of the squares of the potentials at the 64 recording sites. Epicardial activation times were computed as the time of the minimum dV/dt of the QRS in each electrogram. Any fiducial marker could have been used, but for this study the onset of the RMS power curve was used as the time reference. The curves were displayed on a computer terminal. An interactive program that permitted successive doubling of the gain of the RMS curve was used to enhance identification of the point where the curve departed from baseline. Isochrone maps of epicardial activation sequence and QRS isopotential and isointegral maps were computed. The maximum and average spatial gradients of activation times and isopotentials around the site of earliest epicardial activation were calculated. The maximum spatial gradient was calculated as the magnitude of the steepest spatial derivative of activation times or potentials at the site of earliest activation. The average spatial gradient was calculated as the average gradient of activation times or potentials (all directions) at the site of earliest activation. The QRS area at the site of earliest epicardial activation was determined by integrating over the QRS interval of the electrogram recorded at that site.

The most proximal electrode on the multielectrode needles from which a ventricular response could be elicited was considered to be located at the epicardium. Depths of stimulation in the ventricular wall were referenced with respect to that electrode. The distance between the most proximal and the most distal electrodes on the needle array was 17.6 mm and exceeded the thickness of the ventricular wall. When the hearts were dissected, some distal electrodes on the needles were located in the cavity of the left ventricle, and some were found in the papillary muscles. Nevertheless, measurements relating to depth of stimulation were performed strictly on the basis of distance between the most proximal electrode from which a response could be elicited and other locations on the needle.

Statistics

Measurement values from the four to six electrode sites at a given depth for each dog were averaged. The mean values for each depth for each dog were subjected to the repeated-measures analysis of variance. Analysis was restricted to data from electrode sites at 0–12.8-mm depths so that data were complete for each animal. This analysis was carried out for the four indexes evaluated to identify the important sources of variability for each index. Specifically, the proportion of variance accounted for by differences within each experiment was considered.

For one experiment, the analyses were carried out at the site having the next-to-earliest activation time as well as at the site with the earliest epicardial activation. This was done to evaluate degradation in ability of the indexes to estimate depth of onset of activation when the earliest site of epicardial activation is not sampled. Correlation between indexes calculated from earliest and next-to-earliest activation times was used to quantitate degradation.

Results

Spatial Gradients of Epicardial Activation Times

Examples of polar-view epicardial surface activation sequence maps recorded from one dog during epicardial and endocardial drives are shown in Figure 1. For the examples shown, stimulation was initiated via proximal and distal electrodes on a needle placed in the free wall of the left ventricle. During epicardial stimulation, the isochrones were densely packed around the site of stimulation, but during endocardial stimulation, there was a large epicardial breakthrough area at which early activation occurred almost simultaneously. Isochrones in this instance were diffusely distributed. Such differences in density of epicardial isochrones during activation sequences initiated from the endocardium and epicardium were observed in all experiments.

The maximum and average spatial gradients of activation times surrounding the site of earliest epicardial activation were calculated to obtain a quantitative measure of density of activation isochrones. Graphs of the mean±SD values of maximum and average spatial gradients of activation times versus depth of stimulation from the five multielectrode needle placements in the same experiment illustrated in Figure 1 are shown in Figures 2A and 2B. Gradients of activation isochrones systematically decreased as the site of stimulation was moved to progressively deeper locations in the ventricular wall. In this
A. Epicardial Stimulation

B. Endocardial Stimulation

scale 5 msec

FIGURE 1. Polar-view epicardial activation sequence maps recorded during epicardial (panel A) and endocardial (panel B) drives initiated via electrodes on a multielectrode needle placed in free wall of left ventricle. During epicardial drive, isochrones around site of earliest epicardial activation were densely packed. During endocardial drive, there was a large area of epicardial breakthrough with diffusely distributed isochrones. Peripheries of maps represent atrioventricular groove. Isochrones are in 5-msec increments. R, right; L, left; A, anterior; B, posterior.

experiment, the correlation coefficient between maximum gradients of activation times and depth of stimulation was 0.976, and the correlation coefficient between average gradients of activation times and depth of stimulation was 0.986. For this experiment, the correlations between data calculated for the sites of earliest activation and next-to-earliest activation were high, 0.923 and 0.956 for the maximum and average gradients, respectively. Graphs of mean±SD values of maximum and average spatial gradients of activation times calculated for each depth of stimulation from pooled data from all experiments are shown in Figures 2C and 2D. The correlations of mean maximum and mean average gradients of activation isochrones and depth of stimulation were 0.990 and 0.992.

QRS Area Versus Depth of Stimulation

This relation was examined because a previous study from our laboratory demonstrated a high correlation between cardiac surface QRS isoarea maps and isochrone maps of activation sequence. QRS isoarea maps acquired during epicardial and endocardial drives are shown in Figure 3. The maps were computed from the QRS complexes used to construct the activation sequence maps shown in Figure 1, and the similarity between the two sets of maps is apparent. A graph of QRS area data versus...
depth of stimulation from the experiment illustrated in previous figures is shown in Figure 4A. The mean QRS area was most negative during epicardial drive and became progressively more positive as deeper portions of the myocardium were stimulated. For the experiment illustrated in Figure 4A, the correlation coefficient of QRS area at the site of earliest epicardial activation and depth of stimulation was 0.985. The correlation between QRS area data at the sites of earliest and next-to-earliest epicardial activation in this experiment was also high, 0.942. The correlation coefficient calculated for pooled data from all experiments was 0.991 (Figure 4B).

**Earliest Epicardial Activation Time Relative to RMS Onset**

The earliest epicardial activation time, referenced to the onset of the RMS voltage curve, was systematically related to depth of ventricular stimulation. Stimulation at the epicardium was associated with a short interval between RMS onset and earliest epicardial activation time ($t_{ec} - t_{rmo}$), and stimulation at the endocardium was associated with a long $t_{ec} - t_{rmo}$. Examples of one dog's RMS curves during endocardial and epicardial drives and histograms of epicardial activation times referenced to the onset of the RMS curves are given in Figure 5. During epicardial stimulation, the earliest epicardial activation occurred only 3 msec after the onset of the RMS curve. On the other hand, during endocardial stimulation, the earliest epicardial activation occurred 21 msec after onset of the RMS curve.

A graph of the mean±SD values of $t_{ec} - t_{rmo}$ versus depth of stimulation for data from the experiment illustrated in previous figures is given in Figure 6A. The correlation between $t_{ec} - t_{rmo}$ and depth of stimulation was 0.996. The correlation between data calculated from the electrogram at the sites of earliest and next-to-earliest epicardial activation times in this experiment was also high (0.715), but it was somewhat lower than the correlations for the other analyses. A graph of mean±SD values of $t_{ec} - t_{rmo}$ versus depth of stimulation calculated from data pooled from all experiments is given in Figure 6B; the correlation coefficient was 0.991.

**Spatial Gradients of Potential Distributions**

Cardiac surface isopotential maps are characterized by steep gradients of negative and positive potentials along the boundary between depolarized myocardium and myocardium still in the resting state. We therefore reasoned that analysis of the spatial distribution of potentials around the site of earliest epicardial activation might be useful in distinguishing among endocardial, transmural, and epicardial sites of origin of activation. The gradient of potentials around the site of earliest epicardial activation progressively decreased as the site of stimulation moved from the epicardium to deeper layers of the ventricles, and correlation coefficients between mean maximum and mean average gradients of potential distribution and depth of stimulation were high, 0.98 and 0.99, respectively. However, the SDs of data points were higher for the potential data than for the isochrone and isointegral data described above.
A. Epicardial Stimulation

B. Endocardial Stimulation

FIGURE 5. RMS voltage curves calculated from 64 cardiac surface electrograms recorded from one dog during epicardial drive (panel A) and endocardial drive (panel B). Histograms of time of minimum dV/dt in each electrogram referenced to onset of RMS curve are shown beneath each curve. $t_{\text{rms}}$, time of onset of RMS voltage curve; $t_{ee}$, time of earliest epicardial activation. 10-msec time increments are indicated on horizontal axis.

Analysis of Variance

All indexes from all experiments were analyzed by repeated-measures analysis of variance. Table 1 shows the proportion of variance accounted for by the four indexes as a function of variance among animals, variance associated with depth within animals (i.e., needle site–to–needle site differences), and variance associated with depth across all animals. It is clear that within a given animal the proportion of variance associated with needle location was small (<7%) for all indexes (i.e., the indexes for assessment of depth of stimulation were only minimally influenced by location of the stimulus [free wall, base, apex]). Between-animal proportion of variance was larger than that observed within animals and different for the four indexes. QRS area had threefold the proportion of variance associated with the $t_{ee} - t_{\text{rms}}$ index. This indicates that the latter index has less variability associated with between-animal differences than any of the other indexes. The greatest source of variation was attributable to differences of indexes associated with depth of stimulation.

Discussion

The success of surgical intervention for treatment of tachyarrhythmias improved markedly after implementation of electromapping for identifying sites to be ablated.1-10 Although post–myocardial infarction ventricular tachyarrhythmias frequently originate from the subendocardium, their sites of origin can vary, and the mechanisms have not been completely resolved. Scherlag et al13 demonstrated that arrhythmias starting early after coronary occlusion are reentrant and involve delay in subepicardial activation. On the other hand, these investigators found that late arrhythmias emerged after vagal stimulation, suggesting these arrhythmias originated from an automatic focus that was sometimes subendocardial.

A. Data from one Dog

B. Data from all Dogs

FIGURE 6. Graphs of relation of interval between RMS onset and earliest epicardial activation time and depth of stimulation. Panel A: Mean ± SD values of data averaged from five needle placements in one dog. Panel B: Mean ± SD values of data pooled from all dogs.
TABLE 1. Proportion of Variance ($R^2$) Accounted for by Each Index

<table>
<thead>
<tr>
<th>Source</th>
<th>$t_{ec} - t_{rmso}$</th>
<th>$A_{QRS}$</th>
<th>Max$V_{t_a}$</th>
<th>Ave$V_{t_v}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variance associated with between-animals</td>
<td>0.102</td>
<td>0.317</td>
<td>0.257</td>
<td>0.176</td>
</tr>
<tr>
<td>depth within animals (site-to-site differences)</td>
<td>0.064</td>
<td>0.029</td>
<td>0.050</td>
<td>0.032</td>
</tr>
<tr>
<td>Variance associated with depth across all animals</td>
<td>0.834</td>
<td>0.654</td>
<td>0.694</td>
<td>0.793</td>
</tr>
</tbody>
</table>

$t_{ec}$, time of earliest epicardial activation; $t_{rmso}$, time of onset of RMS voltage curve; $A_{QRS}$, QRS area; Max$V_{t_a}$, maximum gradient of activation times; Ave$V_{t_v}$, average gradient of activation times.

and sometimes subepicardial. More recently, Garan et al.\(^1^4\) obtained evidence in a canine model of myocardial infarction that late arrhythmias can originate from endocardial, intramural, or epicardial reentry. Pogwizd and Corr\(^1^5\) used a feline model of coronary occlusion to demonstrate that the first beat of ventricular tachycardia usually had a reentry mechanism and was intramural in origin in all but one instance. However, in some instances, the ventricular tachycardias had a mechanism other than reentry and originated from either the subjendocardium or the subepicardium. In addition, they found that ventricular tachycardia initiated by one mechanism was often maintained or terminated by another, and the apparent mechanisms for the tachyarrhythmias changed during their course. Epicardial as well as endocardial sites of origin of ventricular tachyarrhythmias have also been demonstrated in patients.\(^1^6\)

Epicardial surface mapping, performed during ablative surgery for tachyarrhythmias, is usually accomplished with simultaneous recordings from multiple sites. Less frequently, sequential recordings are obtained with a hand-held roving electrode. Endocardial mapping is usually accomplished with sequential recordings with a roving electrode. This procedure requires a ventriculotomy and is not ideal because ventricular tachyarrhythmias are sometimes difficult or impossible to induce after this procedure. To circumvent this problem, the use of balloon-mounted electrode arrays\(^1^7,1^8\) and “olive” electrode arrays\(^1^9\) has been proposed. The balloon-mounted arrays require cardiopulmonary bypass, whereas the olive arrays are placed via the left atrial appendage and can be placed without bypass. Although these endocardial mapping devices are being used at some institutions, they are not widely used at this time.

A method for estimating depth of onset of tachyarrhythmias from epicardial surface maps that could be used before ventriculotomy and cardiopulmonary bypass is desirable and in some instances might eliminate the need for endocardial mapping. In the present study, we developed methods for estimating depth of onset of ventricular activation from epicardial surface unipolar electrograms. The methods included the maximum and average gradients of activation isochrones at the site of earliest epicardial activation, the maximum and average gradients of isopotentials at the site of earliest epicardial activation, the QRS area at the site of earliest epicardial activation, and the interval between onset of the RMS power curve and the earliest epicardial activation time. The rationale for these methods was that the time of $dV/dt$ in the QRS of unipolar electrograms marks activation at that recording site, that unipolar electrograms contain information about distant as well as local electrical activity, that analysis of distributions of activation times and potentials provides information that is not available from analysis of individual electrograms, and that the distribution of QRS areas is correlated to the distribution of activation isochrones.

Although all of the indexes evaluated were highly correlated to depth of onset of activation, the gradients of activation isochrones at the site of earliest epicardial activation would probably have the greatest clinical use in evaluating patients with ventricular tachyarrhythmias. The lack of an isoelectric baseline during tachyarrhythmias could make it difficult to identify the onset of the RMS power curve, to evaluate absolute potential values, and to calculate the QRS area at the site of earliest epicardial activation. The isochrone distributions, however, are computed from the time of the minimum $dV/dt$ of the QRS in each electrogram. The minimum derivative occurs at the time of activation at the recording site, and the derivative is independent of baseline selected. Activation initially proceeds slowly from its site of onset and then proceeds more rapidly. As a result, maps of activation initiated near the epicardium are characterized by densely packed isochrones surrounding the site of initiation of activation. On the other hand, maps of activation initiated near the endocardium are characterized by a large area of epicardial breakthrough with widely distributed isochrones around the breakthrough region. The results of our study indicate there is a systematic relation between density of isochrones around the site of earliest epicardial activation and depth of onset of activation.

In situations in which an isoelectric baseline can be identified, the other indexes evaluated would also be useful. The QRS complex in a unipolar electrogram recorded near the site of origin of activation is predominantly negative; at sites of late activation, it is predominantly positive. In previous studies, we found that activation times measured as the time of
the minimum dV/dt in unipolar electrograms were highly correlated to QRS areas in those electrograms. As we expected based on our previous study, we found that the QRS area at the site of earliest epicardial activation was most negative when activation was initiated near the epicardium and that the area became progressively more positive as activation was initiated at deeper sites in the ventricular wall.

The interval between RMS onset and earliest epicardial activation times was also highly correlated to depth of initiation of activation. The RMS power curve was constructed from electrogram recordings from all 64 unipolar epicardial surface electrograms. When activation was initiated near the epicardium, the earliest epicardial activation time occurred at or soon after the onset of the power curve. When activation was initiated near the endocardium, however, the initial portion of the RMS power curve reflected electrical events occurring in the depths of the ventricular wall before epicardial breakthrough. As a result, the interval between the onset of the RMS curve and the earliest epicardial activation time was long.

In the present study, the multielectrode needles used for pacing were placed as close as possible to the epicardial recording sites. The interelectrode distance on our recording electrode array was approximately 1 cm; therefore, the greatest distance possible between the site of epicardial onset of activation and the site of epicardial recording was approximately 0.5 cm. In the actual clinical setting, it is unlikely that a recording electrode would be located precisely at the site of onset of activation. The maximum distance between the site of earliest epicardial activation and the recording site will depend on the density of electrodes on the recording grid, but densities comparable to those used in the present study could be achieved.

To determine whether our analyses are adequate under circumstances in which the recording site is as far as 1 cm from the site of onset of epicardial activation, we calculated the indexes for one experiment for the site with the next-to-earliest epicardial activation time as well as for the site with the earliest epicardial activation time. This was a stringent test of the methods because the former site was twice as far from the site of earliest epicardial activation as was possible with the electrode array density we used. The correlations between data calculated for the sites of earliest and next-to-earliest epicardial activation times were high. This indicates that the methods, particularly the gradients of activation isochrones, should have clinical use even when recording sites are as far as 1 cm from the site of earliest epicardial activation.

In general, data acquired during pacing via the more proximal electrodes on the multielectrode needles distinguished the depth of onset of activation better than during pacing via the more distal electrodes (steep compared with flat portions of curves in Figures 2 to 4 and 6). The distance between the most distal and most proximal electrodes on the needles was 17.6 mm and exceeded the thickness of the ventricular wall. Although it was frequently impossible to pace from the most distal sites, on some occasions pacing was achieved via the most distal electrodes—probably because they made contact with the papillary muscles or other portions of the endocardium. This may have contributed to the flatness of the portions of the curves corresponding to the deepest pacing sites. Other factors, such as the proximity of the more distal electrodes to the specialized conduction system and possibly the effects of rotation of myocardial fibers from the inner to the outer portions of the ventricular wall on potential distributions may also have influenced the configuration of the curves.

The methods used in our study represent a practical approach for analyzing cardiac surface maps at the time of surgery. Information regarding site of origin of activation can be obtained from evaluation of a single map of activation isochrones, evaluation of QRS areas at the site of earliest epicardial activation, or a histogram of epicardial activation times referenced to the onset of the RMS power curve. The results demonstrate that features of cardiac surface unipolar electrograms can be used to estimate depth of onset of activation. At the time of surgery, it is possible that recordings taken during stimulation of endocardial, intramural, and epicardial sites could further enhance interpretation of maps. For example, density of isochrones in maps acquired during endocardial and epicardial pacing could be compared with density of isochrones in maps recorded during tachyarrhythmias. The present study was limited to the evaluation of depth of origin of activation in the anterior, posterior, apical, and free wall of the left ventricle. However, these methods could be applied to endocardial surface maps to evaluate depth of origin of activation in the septum as well as in the wall of the ventricle.

Acknowledgments

The authors thank Dr. Gyorgy Kozmann, Ms. Leona Archuleta for secretarial assistance, and Ms. Jayne Davis for technical assistance and preparation of illustrations.

References

5. Garan H, Nguyen K, McGovern B, Buckley M, Ruskin JN: Perioperative and long term results after electrophysiologi-
cally directed ventricular surgery for recurrent ventricular tachycardia. J Am Coll Cardiol 1986;8:201–209

Key Words: • mapping • cardiac surface • activation sequence • arrhythmia
Determination of transmural location of onset of activation from cardiac surface electrograms.
M J Burgess, R L Lux, P R Ershler and R Menlove

Circulation. 1990;82:1335-1342
doi: 10.1161/01.CIR.82.4.1335
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/82/4/1335

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/