Determination of Local Myocardial Electrical Activation for Activation Sequence Mapping

A Statistical Approach

Kelley P. Anderson, Richard Walker, Philip R. Ershler, Marc Fuller, Ted Dustman, Ronald Menlove, Shreekant V. Karwandee, and Robert L. Lux

Electrical activation sequence mapping requires accurate identification of local activation, but because extracellular recordings do not exclusively reflect local events, complex electrograms may be difficult to interpret. In such cases, the assignment of local activation is subject to error that could affect interpretation of the resulting activation maps. The purpose of this investigation was to develop an approach that would provide quantitative indexes of error in the determination of local activation. An electrode array with 64 closely spaced unipolar electrodes was used to record from the left ventricular surface during open heart surgery. Electrograms with multiple deflections were recorded from four patients with scarred myocardium; two other patients with normal myocardial function served as controls. Each of 784 deflections was scored on the basis of three features: evidence for propagation, the configuration of the bipolar signal, and the effect of changing from the chest to an average reference. Local activation was considered probable if evidence for all three features was present and improbable if none of the three features was present. Deflections that were ambiguous with respect to this standard were excluded. Of over 30 test variables analyzed, the three with the greatest power to discriminate signals due to local activation from those due to distant activity were 1) a linear combination of the extracellular potential plus the ratio of the second derivative and the extracellular potential, 2) the second derivative, and 3) the minimum (greatest negative) first derivative. For each of these variables, the threshold value providing the greatest performance was identified by the maximum quality of efficiency, an index of agreement. This statistical approach provides an objective basis for determining local activation and provides a quantitative assessment of error that could enhance interpretation of electrical activation sequence maps. (Circulation Research 1991;69:898–917)

Electric activation sequence mapping is used increasingly for the clinical1–7 and experimental8–22 examination of cardiac arrhythmias. The production of an isochrone map assumes the ability to detect electrical activation of myocardium near the recording sites. The recognition of local activation is usually based on qualitative and quantitative features of recordings obtained from extracellular electrodes, but it is widely acknowledged that the interpretation of waveforms may be very difficult.2–4,8–16,20,23 There are numerous sources of error in this process. An important problem is that distant electrical activity can produce deflections in the electrogram that must be distinguished from local events. An example of a complex electrogram recorded from the left ventricle of a patient with ventricular arrhythmias is shown in Figure 1. Both unipolar and bipolar signals show three or more deflections that could result from either local or distant activity. Since there are time differences between the deflections of up to 50 msec, the different possible interpretations of the recordings could affect the pattern of activation considerably. The most common approach to a complex recording has been to assess how it fits into the pattern established by signals from neighboring electrodes by examining the morphologies, relative amplitudes, and timings of the deflections.2,4,10,11,13,15,18 Although
possibly quite accurate, this qualitative method requires a high degree of judgment and experience. In addition, there is potential for bias when the pattern of activation is used to determine which deflections indicate local activation, because preconceived notions of what the map should look like could influence the interpretation. Furthermore, it is difficult to evaluate the error of this technique or to compare it with other methods. Quantitative methods of determining activation are more objective and facilitate estimation of error. The amplitude of the bipolar signal has been used to determine which deflections represent local activation with specific cutoff values ranging from 0.1 to 1.0 mV. The three bipolar deflections in Figure 1 (D1, D2, and D3) have amplitudes of 0.3, 0.4, and 0.7 mV, respectively. If an amplitude of 0.5 mV were chosen as the test threshold, only D3 would be considered to be due to local activation, whereas all three deflections would satisfy a 0.25-mV criterion. Thus, the selected cutoff value could have a substantial impact on the activation map. It would be preferable to choose the threshold that maximized the accuracy of identifying local activation. Other techniques of distinguishing local and distant activity have been proposed that might allow better discrimination of signals such as those shown in Figure 1, but in few cases has an evaluation of the accuracy, sensitivity, or specificity of the methods been attempted.

A systematic examination of the uncertainty in the determination of local activation is necessary not only to improve methods of detecting activation but also for the appropriate interpretation of electrical activation maps and the concepts they support. The primary purpose of this investigation was to develop an approach that could be used to assess the error associated with tests of activation and to provide a method of comparison. Previous reports have suggested that for unipolar extracellular electrograms, the minimum value (i.e., the greatest negative value) of the first temporal derivative of the extracellular potential (\( \phi_{\text{min}} \)) discriminates between local activation and distant signals. (See Table 1 for a glossary of terms.) However, we have encountered conditions in which the \( \phi_{\text{min}} \) does not appear to select local activation, especially when a signal from a large distant source produces a deeper \( \phi_{\text{min}} \) than a local signal arising from a small current source. Spach and Dolber showed that, as the distance between the recording site and the current source increases, the second derivative (\( \phi \)) decreases more rapidly than \( \phi_{\text{min}} \) and that the \( \phi_{\text{min}} \) falls off more quickly than the voltage of the signal. Therefore, Spach and Dolber suggested that \( \phi \) might better identify local activation. Their findings suggested to us that the normalized first derivative (\( \nu \)) or the normalized second derivative (\( \alpha \)) (i.e., the ratio of the first or second derivative to the voltage) might also distinguish between local and distant signals. We addressed the hypothesis that \( \phi \) or the normalized derivatives would
TABLE 1. Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ϕ</td>
<td>Extracellular potential (mV)</td>
</tr>
<tr>
<td>ϕₚ</td>
<td>Peak-to-nadir extracellular potential within ±1 msec of the time of deflection (mV)</td>
</tr>
<tr>
<td>ϕ₁</td>
<td>First temporal derivative of extracellular potential computed by Equation 1 (mV/msec)</td>
</tr>
<tr>
<td>ϕₘₙ</td>
<td>Minimum (greatest negative) first derivative computed by Equation 1 (mV/msec)</td>
</tr>
<tr>
<td>ϕ₂</td>
<td>Second temporal derivative of extracellular potential computed by Equation 2 (mV/msec)</td>
</tr>
<tr>
<td>ϕₚ₂</td>
<td>Peak-to-nadir second derivative within ±3 msec of time of deflection (mV/msec²)</td>
</tr>
<tr>
<td>rₐ</td>
<td>ϕₚₐ/ϕₚₗ (sec⁻¹)</td>
</tr>
<tr>
<td>rₐₛ</td>
<td>ϕₚₐ/ϕₛₚₗ (sec⁻¹)</td>
</tr>
<tr>
<td>x</td>
<td>Absolute value of a given test for a given deflection</td>
</tr>
<tr>
<td>t(τₑ; τₑₛ; τₑₛₚ)</td>
<td>Threshold value of a given test variable (thresholds for optimally efficient test, optimally sensitive test, and optimally specific test, respectively)</td>
</tr>
<tr>
<td>ψ</td>
<td>Linear combination of extracellular potential plus the ratio of the second derivative and the extracellular potential</td>
</tr>
<tr>
<td>A+</td>
<td>Local activation and distant activity, respectively</td>
</tr>
<tr>
<td>A⁻</td>
<td>Local activation and distant activity, respectively</td>
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**Materials and Methods**

**Patients**

The electrophysiological data were obtained at the time of open heart surgery in six patients. Four patients had complex electrograms in most recorded leads, and all of these patients had histories of sustained or unsustained ventricular tachycardia. Three of these patients were undergoing cardiac transplantation for end-stage heart failure due to idiopathic dilated cardiomyopathy, and one patient with ischemic heart disease was undergoing automatic defibrillator implantation. Two other patients were undergoing operative correction of supraventricular arrhythmias and had normal cardiac function as assessed by history, physical examination, and echocardiography. The electrograms obtained from these subjects provided sufficient data to detect differences of 5% of the area under the receiver operating characteristic (ROC) curves with a statistical power of 0.9 at a level of α=0.05. Written informed consent to the protocol approved by the University of Utah Institutional Review Board was obtained in all patients.

**Electrophysiological Data**

Electrical activation data were obtained from an electrode array consisting of 64 silver electrodes (0.6-mm diameter, 2-mm interelectrode distance) in an 8×8 square pattern embedded in a rigid epoxy plaque. The recordings were obtained in unipolar mode referenced to a needle in the right chest wall. The data acquisition and analysis system has been described previously. In brief, it consisted of 64 differential amplifiers (input impedance >10¹² Ω). Electrograms were recorded at a bandwidth of 0.03–500 Hz, sampled at a 1-kHz rate, and digitized by a 12-bit analog-to-digital converter. The intraoperative collection of data was standardized as far as possible to produce uniform experimental conditions but for ethical and practical reasons was limited to 20 minutes. Electrophysiological recordings were obtained before the initiation of cardiopulmonary bypass. The closely spaced electrode plaque array was placed on the left ventricular epicardial surface adjacent to the left anterior descending artery. Unipolar cathodal or bipolar stimulation was performed from the edge of the array using rectangular impulses 2 msec in duration at twice diastolic threshold current. Data were acquired after 10 seconds of pacing at 150 beats/min. ϕₘₙ has been shown to correspond with the most rapid phase of the action potential upstroke. Hence, the time of the deflection (Tₚₗ) was defined as the time at which ϕₘₙ occurred. Tₛₚₗ, unipolar potentials, and their derivatives were measured automatically by a computer program. "Deflection" meant a change in provide better discrimination of deflections due to local and nonlocal activity than ϕₘₙ. Our analysis was performed on recordings obtained from diseased human ventricular myocardium. Therefore, specific findings such as the particular tests for activation found to have the greatest discriminatory power may apply to recordings obtained under similar conditions.
voltage in the electrogram associated with a local minimum in the first derivative plot. Since our aim was to evaluate signals that might result from local or distant electrical activity, we examined each deflection that resulted in a \( \phi_{\text{min}} \) more negative than \(-0.2 \text{ mV/msec} \) or that had a \( \phi_{\text{min}} \) that was at least 25% of the most negative \( \phi_{\text{min}} \) in a given electrogram. Measurements for the standard of activation were made by means of a manually operated electronic cursor on highly amplified plots of the electrograms displayed on a graphics terminal.

**Standard of Activation**

The “standard of activation” is the reference against which possible tests of activation are compared, and it is used to estimate the sensitivity and specificity of the test candidates. Three features were used to ascertain whether a deflection was caused by local activity or not: 1) evidence of propagation in the pattern produced by deflections in adjacent leads,4,9,11 2) the configuration and timing of the bipolar signal constructed from the given electrode and its neighbor,4,34 and 3) the effect of the average reference on the deflection.4,33,35,36 A score of 0, 1, or 2 was assigned to each deflection according to each of the three features.

The presence of propagation, by which is meant a logical progression in time and position of deflections in recordings from neighboring leads, supports local activation, whereas signals resulting from distant activity tend to produce deflections that occur simultaneously in adjacent leads,4,9,11 The assessment of propagation was facilitated in our preparation because stimulation was performed from electrodes on the recording plaque and because the recording sites were relatively close to the origin of the stimulating impulse. A propagation score of 2 was applied to a given deflection if in one direction the TDS from adjacent leads were \( \geq 2 \text{ msec} \) earlier than the TD of the given deflection and if the TDS from leads in the opposite direction were \( \geq 2 \text{ msec} \) later. These findings indicated that a clear gradient of activation times was associated with the deflection (i.e., evidence for propagation). A propagation score of 0 was assigned to a deflection if the time difference between the TD and any one of the adjacent leads was \( <2 \text{ msec} \). If the TDS from adjacent electrodes in one direction were \( \geq 2 \text{ msec} \) but the TDS in the opposite direction were \( <2 \text{ msec} \), a propagation score of 1 was given. An example is shown in Figure 2A; the TDS from an electrode (electrode 3 in Figure 2A) and its neighbors suggest propagation, whereas the TDS shown in Figure 2B occur nearly simultaneously.

The bipolar potentials of two adjacent electrodes were subtracted to produce a bipolar potential with a 2-mm interelectrode distance.4,33,34 The amplitude of the bipolar signal has been used to define the presence of local activation.16–18,20 The peak (or nadir) of the bipolar signal resulting from local activation coincides with the upstroke of the action potential.35 Depolarization of tissue between two electrodes should produce a peak bipolar signal between the minima of the first derivatives (TDS) of the two unipolar potentials from the same electrodes.37,38 Therefore, a bipolar signal with a relatively large amplitude and a peak that falls between the two TDS of the two unipolar signals suggests local activation. A “bipolar score” of 2 was applied to a deflection if the bipolar waveform was \( \geq 1 \text{ mV} \) and its peak or nadir occurred between the TDS of the two unipolar signals (Figure 3A). A score of 0 was applied if the bipolar signal was \( \leq 0.5 \text{ mV} \) and the peak or nadir of the bipolar signal did not occur between the TDS of the two unipolar deflections. When the bipolar signal was ambiguous with respect to local or nonlocal origin and did not fit into the 0 or 2 score category, a score of 1 was given. Three bipolar deflections in a single electrogram from a patient with left ventricular dysfunction are shown in Figure 3B. The first deflection (D1) had a bipolar amplitude \( <0.5 \text{ mV} \) but fell between the two TDS of the unipolar potentials of the two poles of the bipolar pair; it received a score of 1. The peak of the bipolar signal associated with the second deflection (D2) occurred after the TDS of the unipolar signals, resulting in a score of 1. The third deflection (D3) was associated with a nadir of the bipolar signal with a magnitude \( >1 \text{ mV} \), and the nadir occurred between the two TDS; it received a score of 2.

The average reference electrogram was calculated by subtracting the average signal of the plaque electrode array from the recorded signal at a given site. The average signal was obtained from the sum of recorded potentials divided by the number of recording sites (excluding the stimulation sites).4,33,35,36 Because the plaque electrode array records from a relatively small region of the heart (225 mm²), the average reference technique reduces the magnitude of signals due to distant activity by subtracting electrical activity common to the electrodes in the plaque.4,36 The presence of local activation is supported when the potential referenced to the standard chest lead does not decrease substantially after the average reference is applied. A large reduction in amplitude favors distant activity. The change in amplitude of the signal due to the average reference technique was obtained by measuring the magnitudes of the intrinsic deflections of the average signals and those of the unipolar signals over the same time interval and calculating the percent change. In Figure 4A the intrinsic deflection of the average reference signal was 39% smaller (percent change, \(-39\% \)) than the intrinsic deflection of the unipolar signal referenced to the chest wall in a patient with normal ventricular function. The mean reduction in intrinsic deflection amplitude in the recordings obtained from patients with normal ventricular function was \(-19.1 \pm 12.6\% \) (range, 0% to \(-45.6\% \), \( n = 114 \)). A score of 2 was applied to a deflection when the change due to the average reference was less negative than \(-50\% \), a score of 0 was applied to a deflection with a change more negative than \(-75\% \), and a score of 1 was applied to deflections with changes between \(-50\% \) and \(-75\% \). In Figure 4B two deflections from a patient with abnormal ventricular function are shown. The amplitude of D1 is markedly reduced \((-78\% \) by use of the average ref-
ference. In contrast, the magnitude of D2 actually increases (percent change, +114%) when distant activity of opposite polarity is removed by the average reference.

It is recognized that none of the techniques described above discriminates perfectly between local and nonlocal electrical activity. For instance, a wave of excitation propagating perpendicular to the plane of the plaque electrode array would result in simultaneous local activation at neighboring electrode sites, but the associated deflections would receive propagation scores of <2. Although epicardial stimulation close to the recording sites would tend to minimize this type of activation sequence, it almost certainly occurs in areas of nonuniform activation. A sufficiently large bipolar signal might not occur despite local activation during propagation in a muscle bundle perpendicular to the bipolar electrodes that causes no potential difference between the poles. Conversely, distant activity that generates a potential difference between the two poles of the bipolar set might produce a signal with an amplitude >1 mV. The average reference method could fail to exclude distant activity caused by activation under the plaque that is not in the immediate vicinity of the electrode of interest. However, deflections that meet all three criteria (all scores of 2) very probably represent local activation, and deflections with all scores of 0 very probably are due to nonlocal activity. The scores of each deflection were added to produce a rank between 0 and 6 for each deflection. For the primary analyses, only deflections with the highest probability of resulting from local activation (i.e., with ranks of 5 or 6) were used to represent the presence of local activation (A+), and only the deflections with the lowest ranks (0 and 1) represented absence of local activation (A−). The exclusion of the more ambiguous deflections increased the confidence in the standard of activation. However, this assumed that exclusion of these deflections did not bias the analysis. For this reason, these ambiguous deflections were later added back to the population as a further check on the validity of the findings.
Test Variables

The test variables were functions that could possibly discriminate between local and distant electrical activity. All were computed automatically by a program using the acquired digitized electrograms and are therefore suitable for computerized mapping systems. \( \phi \) was the extracellular potential (\( \phi \)) obtained from the difference between the peak and nadir voltages within a time window (±1) of \( T_D \). Five time windows were used, resulting in five extracellular potential variables: \( \phi_5, \phi_{10}, \phi_{20}, \phi_{90} \), and \( \phi_40 \). For example, \( \phi_{20} \) was the peak-to-nadir voltage of the electrogram in the time interval between \( T_D-30 \) msec and \( T_D+30 \) msec (Figure 5). The first \( \phi \) and second \( \ddot{\phi} \) temporal derivatives of the extracellular potential were obtained by fitting each set of five samples of the electrogram to a five-point second-order function:

\[
\dot{\phi} = \frac{2\phi_{i+2} + \phi_{i+1} - \phi_{i-1} - 2\phi_{i-2}}{10}
\]

\[
\ddot{\phi} = \frac{2\phi_{i+2} - \phi_{i+1} - 2\phi_{i} - \phi_{i-1} + 2\phi_{i-2}}{7}
\]

where \( \phi_i \) is the observed sample value of the extracellular potential.\(^{39,40} \) The test variable based on \( \dot{\phi} \) was the minimum (greatest negative) derivative of the deflection \( \phi(\text{min}) \). Although \( \dot{\phi} \) equals zero at \( T_D \), it reaches a minimum just before \( T_D \) and a maximum just after \( T_D \). To determine an appropriate time window around \( T_D \) to measure \( \phi \), we measured the time intervals between the peak and nadir values of \( \phi \) associated with 60 deflections from the study patients (10 randomly selected deflections per patient). The mean time interval was within 2.0±1.3 msec, but some values fell outside of 

\( \pm 3 \) msec, so that two variables based on \( \dot{\phi} \) were evaluated, \( \dot{\phi}_5 \) and \( \dot{\phi}_{40} \), which were the peak-to-nadir second derivatives within \( \pm 3 \) msec and \( \pm 6 \) msec of \( T_D \), respectively. \( \nu_i \) was obtained by dividing \( \phi(\text{min}) \) by \( \phi \), such that \( \nu_i = \phi(\text{min})/\phi \), \( \nu_{10} = \phi(\text{min})/\phi_{10} \), \( \nu_{20} = \phi(\text{min})/\phi_{20} \), \( \nu_{30} = \phi(\text{min})/\phi_{30} \), and \( \nu_{40} = \phi(\text{min})/\phi_{40} \) \( \nu_i \) was obtained by dividing \( \dot{\phi}_5 \) by \( \dot{\phi} \), such that \( \rho_i = \dot{\phi}_5/\dot{\phi} \), \( \rho_{10} = \dot{\phi}_{10}/\dot{\phi} \), \( \rho_{20} = \dot{\phi}_{20}/\dot{\phi} \), \( \rho_{30} = \dot{\phi}_{30}/\dot{\phi} \), and \( \rho_{40} = \dot{\phi}_{40}/\dot{\phi} \). In Figure 5 the values of several test variables for two deflections in a polyphasic electrogram are shown. Since some of the variables such as \( \phi(\text{min}) \) result in negative values, the absolute values \( (|\cdot|) \) of variables were used in the analysis. The second deflection (D2) has larger absolute values of \( \phi_{15}, \phi_{30}, \phi(\text{min}) \) whereas D1 has larger values of \( \phi_{15}, \nu_{10}, \rho_{10}, \rho_{20} \). Thus, \( \phi_{15}, \phi_{30}, \phi(\text{min}) \) would be better tests of activation in this example if D2 were due to local activation and D1 were not. On the other hand, if D1 were due to local activation and D2 were not, \( \phi_{15}, \nu_{10}, \rho_{10}, \rho_{20} \) would be better tests for activation in this

**Figure 3.** Tracings from a patient with normal ventricular function (panel A) and from a patient with scarred ventricular myocardium (panel B). \( \phi \), Extracellular potential; \( \dot{\phi} \), first temporal derivative of \( \phi \). The bipolar potential was derived by subtracting the unipolar potentials from two adjacent electrodes. The "bipolar score" was obtained by measuring the amplitude of the peak or nadir of the bipolar potential associated with each unipolar deflection and noting its timing with respect to the deflection times of the unipolar signals. Panel A: Bipolar potential (thick solid tracing), first unipolar potential (dashed tracing), first derivative of the first unipolar potential (\( \phi_1 \), thin solid tracing), and first derivative of the second unipolar potential (\( \phi_2 \), dotted tracing) from a patient with normal ventricular function. (The second unipolar potential is not shown.) The peak of the bipolar signal is 19.1 mV and falls between the minima of the first derivatives (deflection times), resulting in a bipolar score of 2. Panel B: Recordings from a patient with scarred ventricular myocardium. Overall, the bipolar signal is much smaller than the unipolar signal. The first derivatives of the unipolar potentials (\( \phi_1, \phi_2 \)) are nearly superimposed. Three deflections, D1, D2, and D3, are indicated. Note that although the term "deflection" referred to the unipolar potential, they are defined by the presence of a relative minimum of the first derivative, which is much easier to identify than the particular slopes of the unipolar signal. Therefore, in this and subsequent figures, deflections are indicated on the first derivative plot rather than on the unipolar potential plot. The peak of the corresponding bipolar potentials is indicated by dashed vertical lines. The first deflection (D1) received a score of 1, because the peak of the associated bipolar signal has an amplitude <1.0 mV, but it falls between the minima of the first two derivatives. The second deflection (D2) received a score of 1 because the peak of the bipolar signal occurs after the minima of both first derivatives. The magnitude of the nadir of the bipolar potential associated with the third deflection (D3) is >1.0 mV, and it falls between the minima of the first derivatives. Therefore, it received a score of 2.
FIGURE 4. Tracings from a patient with normal ventricular function (panel A) and from a patient with scarred ventricular myocardium (panels B–D). φ1 Extracellular potential; φ2 first temporal derivative of φ1. The average reference signal (Average Ref) was obtained by subtracting the average plaque signal (the sum of the potentials of all recorded plaque electrograms divided by the number of recording leads) from the individual unipolar signal (Chest Ref). Panel A: Average reference signal (thick tracing), chest reference signal (dashed tracing), and first derivative of the chest reference signal (φ1 thin solid tracing) from a patient with normal ventricular function plotted as a function of time. The magnitudes of the intrinsic deflections of the average (16.5 mV) and chest reference signal (27.0 mV) were measured between the times of the major inflection points of the average reference signal (dashed vertical lines). The change due to the average reference in this example was −39%; the “average reference” score was 2. Panel B: Recordings from a patient with scarred ventricular myocardium. The amplitude of the electrogram referenced to the average signal was much smaller than the electrogram referenced to the chest. The two deflections that are indicated are shown in detail in panels C and D. Panel C: The first deflection (D1) plotted on an expanded time scale. The magnitude of the chest reference intrinsic deflection corresponding to D1 was 1.72 mV; the magnitude of the average reference intrinsic deflection was 0.37 mV, resulting in a change of −78%. Panel D: Expanded time scale plot of second deflection (D2). The amplitudes of the chest and average reference intrinsic deflections corresponding to D2 were 0.18 and 0.40 mV, respectively, resulting in a change of +114%.

particular instance. Cabo et al29 suggested that the frequency response of the function used to compute \( \phi_{\text{max}} \) might not be optimal for distinguishing local and distant electrical activity. Therefore, \( \phi_{\text{max}} \) and its normalized variables were also computed using a twenty-point least-squares fit to a perfect differentiator.41 We also considered the possibility that combinations of these variables might improve discrimination over any single variable. Logistic regression was used to identify linear combinations of variables. Linear logistic regression was performed using the Newton-Raphson method to solve the nonlinear equations of the maximum likelihood estimation of the logistic model.42

Statistical Analysis

ROC curves were used to compare the test variables using established techniques.43,44 Each of the variables described above was considered a family of tests for local activation. The standard of activation was used to assign the presence (A+) or absence (A−) of local activation to every deflection. The \( \xi \) value of each variable (e.g., \( \phi_{\text{max}}, \phi_{\text{b}}, \nu_s, \) and \( \rho_s \)) was computed for every sample. If \( \xi \) was greater than or equal to a given test threshold for that variable (\( \tau \)), then that deflection was said to have a positive test (T+) for that variable. If \( \xi \) was less than \( \tau \), then that deflection was said to have a negative test (T−) for that variable. The sensitivity (SE), specificity (SP), efficiency (E), predictive value of a positive test (PVP), and predictive value of a negative test (PVN) were calculated for each \( \tau \) for that variable (i.e., for each observed \( \xi \)):

\[
\text{SE} = \frac{\text{No. A+ deflections that are T+}}{\text{No. A+ deflections}}
\]

(3)

\[
\text{SP} = \frac{\text{No. A− deflections that are T−}}{\text{No. A− deflections}}
\]

(4)
The ROC curves were produced by plotting SE against SP for each variable. The areas under the ROC curves (ROCAVs) and their standard errors were derived by using the Mann-Whitney-Wilcoxon statistic\(^30,\)\(^31\) and compared as suggested by Hanley and McNeil.\(^30\) Differences were considered significant at \(p<0.05.\) The qualities of sensitivity (\(Q_{SE}\)), specificity (\(Q_{SP}\)), efficiency (\(Q_{E}\)), predictive value of a positive test (\(Q_{PVP}\)), and predictive value of a negative test (\(Q_{PVN}\)) were calculated as proposed by Kraemer:\(^44\)

\[
Q_{SE} = \frac{SE - Q}{Q'} \quad (8)
\]

\[
Q_{SP} = \frac{SP - Q'}{Q} \quad (9)
\]

\[
Q_{E} = \frac{E - PQ - P'Q'}{1 - PQ - P'Q'} \quad (10)
\]

\[
Q_{PVP} = \frac{PVP - P}{P'} \quad (11)
\]

\[
Q_{PVN} = \frac{PVN - P'}{P} \quad (12)
\]

where \(Q\) is the average probability that \(x \geq \tau, P\) is the proportion of A+ samples, \(P' = 1 - P,\) and \(Q' = 1 - Q.\) \(Q_{SE}\) was plotted against \(Q_{SP}\) to obtain the "quality" ROC (QROC) as specified by Kraemer.\(^44\) The quality statistics include adjustments for the prevalence of local activation in the population analyzed. In other words, \(Q_{SE}, Q_{SP}, Q_{E}, Q_{PVP},\) and \(Q_{PVN}\) can be viewed as versions of conventional sensitivity, specificity, efficiency, and predictive values of positive and negative tests with corrections for the chance occurrence of true positive or true negative test results.
TABLE 2. Mean±SD and Maximum and Minimum Absolute Values for φ, φₐ, φₐₐ, φₚ, and ψ

<table>
<thead>
<tr>
<th>Standard of</th>
<th>Absolute value</th>
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<tbody>
<tr>
<td>activation</td>
<td></td>
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<tr>
<td>φ (mV)</td>
<td></td>
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<tr>
<td>A+ (ranks 5,6)</td>
<td>17.1±14.7</td>
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<tr>
<td>A− (ranks 0,1)</td>
<td>2.14±1.21</td>
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<tr>
<td>φₐ (mV)</td>
<td></td>
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<tr>
<td>A+ (ranks 5,6)</td>
<td>23.3±15.8</td>
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<tr>
<td>A− (ranks 0,1)</td>
<td>7.60±2.05</td>
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<tr>
<td>φₐₐ (mV/msec)</td>
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<tr>
<td>A+ (ranks 5,6)</td>
<td>3.39±3.33</td>
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<tr>
<td>A− (ranks 0,1)</td>
<td>0.34±0.18</td>
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<tr>
<td>φₚ (mV/msec²)</td>
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<tr>
<td>A+ (ranks 5,6)</td>
<td>3.24±3.71</td>
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<tr>
<td>A− (ranks 0,1)</td>
<td>0.23±0.12</td>
</tr>
<tr>
<td>ψ</td>
<td></td>
</tr>
<tr>
<td>A+ (ranks 5,6)</td>
<td>0.22±0.13</td>
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<tr>
<td>A− (ranks 0,1)</td>
<td>0.07±0.01</td>
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</table>

A+, local activation; A−, distant activity; φₐ and φₐₐ, peak-to-nadir extracellular potential within ±5 and ±40 mV, respectively, of the time of deflection; φₐₐₐ, minimum first derivative of extracellular potential; ψ, ωₐ, peak-to-nadir second derivative within ±3 mV of time of deflection; ψ, linear combination variable. Increasing rank values indicate increasing probability of local activation (see “Materials and Methods” for detailed explanation).

The differences between individual tests for activation, as opposed to families of tests, were assessed by a comparison of the QEs of the tests. Qₑ is equivalent to Cohen’s r statistic.45 The significance of differences between dependent estimates of Qₑ was determined by a modification of the standard statistic (Daniel Bloch, personal communication).46

Results

Comparison of Test Variables

A total of 784 deflections were examined: 224 had standard of activation ranks of 5 or 6 and were considered to have resulted from local activation (A+), 178 had ranks of 0 or 1 and were considered to have been due to distant electrical activity, and the remaining 382 had ranks of 2, 3, or 4. Twenty-nine single variables and several linear combination variables were analyzed as possible tests for activation. The means and standard deviations of selected test variables are given in Table 2. The ability of test variables to discriminate between local activation and distant activity was assessed by comparing ROCAs. ROC curves for three variables are shown in Figure 6. A perfect test of activation would result in an ROC of 1.0 and would include the point with the coordinate (1, 1) on the ROC curve. None of the test variables met that standard, but most of the test variables had an ROC >0.5, which is the ROC of a random test, and several variables had ROCAs >0.8, indicating very good discrimination of local and distant activity. The bar graph in the inset of Figure 6 shows the ROCAs for six test variables. The ROCAs shown are the highest for the test variables with several similar variants (e.g., ROCA for φₐ was greater than the ROCAs for φₐ₁, φₐ₂, φₐ₃, and φₐ₄). The single variable that resulted in the greatest ROCA was φₐ, followed closely by φₐₐ. The ROCA for φₐ was not significantly greater than the ROCA for φₐₐ (p=0.06), but it was significantly higher than the ROCAs for the other single variables (p<0.002). The alternate method of calculating φₐₐ using the equation for the least-squares fit to a perfect differentiator did not significantly improve discrimination for φₐₐ or its normalized variables. Also, use of φₐ (with a wider time window of ±6 msec) provided no advantage over φₐ. The linear combination variable (ψ=φₐ₀+0.0045φₐ₁) resulted in a larger ROC than any of the single variables. Although the ROCA for ψ was not significantly greater than the ROCA for φₐ (p=0.3), it was significantly greater than the ROCA for φₐₐ (p=0.003) and the other variables.

Determination of Test Thresholds

In addition to the test variable, a test for activation requires a test cutoff or threshold value (τ). A test variable can be considered a family of tests for activation where any value is a possible τ. Although conventional ROC curves provide a quantitative method of comparing the performances of test variables, they do not conveniently indicate which values of τ provide the most powerful individual tests for activation. The QROC curve indicates the family of optimal τs by correcting for the pretest probability of
local activation. The QROC curves for three test variables are plotted in Figure 7A. The τ value that corresponds to the highest point on the QROC curve (τ_SE) provides the “optimally sensitive” test. Lesser values of τ result in loss of specificity without improvement in Q_SE. Similarly, the τ value corresponding to the point farthest to the right on the QROC curve (τ_SP) results in the “optimally specific” test for activation. A τ greater than τ.SP results in a less sensitive test with no gain in Q_SP. Test values between τ_SE and τ_SP constitute the family of optimal tests for activation. Which among this set of values is used for τ depends on whether a more sensitive (but less specific) test or a more specific test is needed. The QROC curve in Figure 7A was drawn according to the methods proposed by Kraemer. It is not a plot of Q_SE versus Q_SP in the strict mathematical sense but the convex hull of QROC points, which eliminates the invaginations of the curve due to vagaries of the sampled deflections. The convex hull is believed to better represent the shape resulting from the underlying population. Also, points to the left of the optimally sensitive test and below the optimally specific test are not shown in order to emphasize the portion of the QROC curve representing the optimal family of tests and because the marginal frequencies at these ends of the distribution produce less reliable estimates of Q_SE and Q_SP.

In most cases, the threshold resulting in the “optimally efficient” test (τ_E) is chosen. This is the test with the greatest degree of agreement between the test for activation and the standard of activation (corrected for chance agreement). Maximum Q_E was determined by calculating Q_E for every possible value of τ. In Figures 7B, 7C, and 7D, Q_E is plotted for the test variables ψ, ϕ_5, and ϕ_min. The value of τ_E for each of the three test variables is indicated in the figures with a broken vertical line. Q_SE and Q_SP are also plotted for each test variable. As expected, tests for activation based on τ with smaller values (i.e., looser test criteria) result in
tests with increasing \( Q_{SE} \) and decreasing \( Q_{SP} \), whereas tests for activation with larger values of \( \tau \) (stricter criteria) result in tests with decreasing \( Q_{SE} \) and increasing \( Q_{SP} \). The graphs in Figures 7B, 7C, and 7D also indicate that the useful range of values for \( \tau \) is very limited. For each test variable shown, \( Q_{SE} = 1 \) at \( \tau_{SE} \) and lower values of \( \tau \), but values of \( \tau \) less than \( \tau_{SE} \) result in tests with decreasing \( Q_{SP} \) and \( Q_{E} \). \( Q_{SP} = 1 \) at \( \tau_{SP} \) and higher values of \( \tau \), but values of \( \tau \) greater than \( \tau_{SP} \) result in tests with decreasing \( Q_{SE} \) and \( Q_{E} \). Therefore, there is no reason to use values of \( \tau \) outside the range between \( \tau_{SE} \) and \( \tau_{SP} \), since the resulting tests will have diminished performance. For the population of deflections studied here, this range is narrow. For \( \phi_{\text{min}} \), for instance, it is between \(-0.05 \, \text{mV/msec} \) and \(-1.02 \, \text{mV/msec} \). Table 3 gives the sensitivities and specificities of the optimal tests for activation using three test variables. Comparison of the optimally efficient tests for activation showed that the \( Q_E \) for the test based on \( \psi \) was significantly greater than the \( \phi_1 \) test \((p<0.05)\) and \( \phi_{\text{min}} \) \((p<0.0001)\) but that the \( Q_{ES} \) tests for tests based on \( \phi_1 \) and \( \phi_{\text{min}} \) were not significantly different.

Intermediate Standard of Activation Ranks

The above analyses were based on a standard of activation composed of ranks 5 and 6 as \( A+ \) deflections and ranks 0 and 1 as \( A- \) deflections. The intermediate ranks were excluded to enhance confidence that the standard of activation distinguished between local and distant electrical activity. However, the exclusion of deflections with intermediate ranks assumes that their test values would not alter the test variables selected. To assess the validity of this assumption, the above analysis was repeated using ranks 4, 5, and 6 as \( A+ \) deflections \((n=350)\) and ranks 0, 1, and 2 as \( A- \) \((n=246)\). Rank 3 deflections were excluded, since there was no basis for assigning them to either \( A+ \) or \( A- \) groups. The intermediate ranks included more ambiguous deflections; thus, it was expected that their ROCAs would be lower: ROCA of \( \psi=0.831, \) ROCA of \( \phi_1=0.825, \) and ROCA of \( \phi_{\text{min}}=0.817. \) However, the variables with greatest ROCAs and their order were unchanged (i.e., the ROCA for \( \psi>\) ROCA for \( \phi_1>\) ROCA for \( \phi_{\text{min}} \)). A similar pattern emerged when the maximum \( Q_{ES} \) were determined: for \( \psi, \) maximum \( Q_{E}=0.53; \) for \( \phi_1, \) maximum \( Q_{E}=0.49; \) for \( \phi_{\text{min}}, \) maximum \( Q_{E}=0.45. \) For \( \psi, \) the threshold value at maximum \( Q_{E} \) did not change \((\tau_{E}=0.98)\), but it fell for \( \phi_1 (\tau_{E}=0.34 \, \text{mV/msec}) \) and for \( \phi_{\text{min}} (\tau_{E}=-0.36 \, \text{mV/msec}). \) These findings suggest that the test variables were not biased by the standard of activation and that the tests for activation with the greatest performances were relatively stable despite modification of the population of signals.

Interpretation of Electrograms

After the test variable and \( \tau \) were identified, they could be applied to the deflections under consideration. A deflection with a value of \( \psi \) that exceeds \( \tau \) is considered to be due to local activation, and a deflection with a value of \( \psi \) less than \( \tau \) is considered not to be due to local activation. In Figure 8, the test for activation based on \( \psi \) and \( \tau_{E}=0.098 \) is used to evaluate several electrograms. The electrogram in Figure 8A was obtained from a patient with normal ventricular function. A large, smooth extracellular potential is present with a deep \( \phi_{\text{min}} \) and a large \( \phi_1 \), which are typical of signals from normal myocardium. The value for \( \psi \) due to this uncomplicated signal is much higher than \( \tau_{E} \) and easily meets criteria for local activation. Figure 8B is the same electrogram shown in Figure 1. Multiple deflections are present, but only the first deflection (D1) meets the criterion based on \( \psi \), whereas the two other labeled deflections (D2 and D3) fall short of \( \tau_{E}. \) Interestingly, D2 and D3 have more negative \( \phi_{\text{min}} \) values than D1, and D3 is associated with a larger bipolar deflection (B3) than D1 (B1). However, the peak of the larger bipolar
signal (B3) does not occur between the T65 of the unipolar signals from the two poles (the recording from the second pole is not shown), which suggests that B3 represents distant activity. Waveforms from a different patient are shown in Figure 8C. The deflections D1 and D4 do not meet criteria based on ψ for local activation, but ψ for both D2 and D3 exceed τE and both, therefore, meet criteria for local activation. Multiple local deflections at a single electrode site is a phenomenon noted in previous studies. Figure 8D shows a relatively large extracellular potential associated with two deflections. However, neither D1 nor D2 met criteria for local activation; thus, by these criteria no local activation occurred at this recording site.

Rather than viewing the occurrence of local activation as an “all-or-none” phenomenon, it may be useful to view a deflection as representing some probability that local activation has occurred. For instance, the deflection labeled D3 in Figure 8B had ψ = 0.090, which seems close to τE = 0.098. QPVP (Equation 11) can be used to estimate the probability that a deflection represents local activation. For the deflection labeled D3 in Figure 8B, QPVP = 0.84. QPVP for τE of ψ is 0.96; therefore, deflections must have QPVP ≥ 0.96 to qualify for activation by this criterion. However, instead of choosing the optimally efficient ψ for determining activation, the threshold for the test for activation could be based on a desired probability level. Moreover, QPVP indicates the relation of a deflection to the population of signals under consideration, which may be more convenient than using the value of the test variable itself, especially when the variable is somewhat unfamiliar and unwieldy such as the linear combination variable ψ. Although Equation 11 can be used to compute QPVP, it cannot be shown that QPVP is mathematically identical to QSP. Similarly, QPVN is equal to QSE. This convenient fact means that the QROC curves and the plots of test variables versus QSP in Figure 7 are equivalent to plots of QPVN and QPV. Thus, QPV and QPVN can be obtained easily for any deflection.

**Figure 8.** Examples of electrograms plotted as the unipolar extracellular potential (ψ, top plots), the first temporal derivative of the unipolar potential (ψ, second plots), the second derivative (ψ, third plots), and the bipolar potential (bottom plots) obtained by subtracting the unipolar potential shown in the top plot from the unipolar potential of its neighbor (not shown). SA represents the stimulus artifact. Selected unipolar deflections are labeled D1-D4. Selected bipolar deflections are labeled B1-B3. Below each set of plots is a table showing for each labeled unipolar deflection the value of the linear combination variable (ψ) and the quality of the predictive value of a positive test (QPVP) for that value of ψ. Note that QPVP was determined before the value ψ was rounded off, so it appears that similar values of ψ have different QPVPs. Panel A: An electrogram from a control patient has a smooth intrinsic deflection resulting in a deep, single minimum of the first derivative and biphasic second derivative plot. The value of ψ exceeds the threshold value for the optimally efficient test (0.098). Panel B: An electrogram from a patient with scarred myocardium (same recording as in Figure 1). Multiple deflections are present but only D1 meets criteria for activation based on ψ. Panel C: An electrogram from another patient with severe left ventricular dysfunction shows multiple deflections occurring closely in time. Two deflections (D2 and D3) meet criteria for activation. Panel D: Another electrogram from a patient with abnormal cardiac function with multiple deflections, none of which meet criteria for activation based on ψ.
Effect of the Test for Activation on Electrical Activation Sequence Maps

The effect of the test variable and \( \tau \) value on the interpretation of recorded signals and the activation maps depended on the characteristics of the signals. Figure 8A shows a signal typical of those recorded from subjects with normal ventricular function. Such signals presented no difficulty in interpretation and could be identified equally well by several tests for activation. The activation map in Figure 9A was obtained from a patient with normal ventricular function. The plaque was placed on the left ventricular free wall where the longitudinal axes of epicardial fibers tend to course perpendicular to the anterior interventricular groove and are parallel to the horizontal rows of the plaque. Activation spreads in a relatively uniform elliptical pattern from the stimulation sites on the right edge with rapid conduction along the rows of the array and slower conduction toward the top and bottom edges. Areas where the distance between isochrones suddenly widens, such as the right upper corner, probably resulted from subepicardial spread of activation. The activation times and the pattern of activation in this example were not affected by the test for activation, because the electrograms consisted of deflections with values of \( \psi, \phi_0, \) or \( \phi_{\text{min}} \), which were well above their respective \( \tau \) values. Only minor changes in activation patterns were observed in maps obtained from control subjects or in maps from patients with myocardial disease, which were based on electrograms in which a single deflection predominated.

In several cases, however, activation patterns depended heavily on the test used to define activation. The maps in Figures 9B–9F are based on the same set of recordings from a patient with poor cardiac function and severe scarring of the left ventricle. The plaque had the same orientation as for the map in Figure 9A. The definition of local activation for Figure 9B was based on the standard-of-activation ranking scheme, in which deflections with ranks of \( \geq 4 \) were considered to be due to local activation. From the stimulation sites, activation appears to have spread rapidly to the middle of the plaque and to the upper right corner, where it then appears to have spread to the left upper quadrant. In the middle of the map there is a region of very densely spaced isochrone lines due to remarkably large differences in activation times. The deflections from several electrodes did not meet criteria for activation and are represented by stippled areas. Several sites in the left lower quadrant of the map were activated relatively late, and the differences between activation times of these neighboring sites are small. Simultaneous activation of this region could have resulted from spread of activation from a subepicardial source as shown by Burgess et al. The latest area to be activated was in the right lower quadrant of Figure 9B below the strip of dense isochrone lines near the site labeled C. Activation of this area could have occurred via excitiation from a subepicardial path, from the left lower quadrant, or from the bottom right lower quadrant or even by very slow or circuitous conduction from the upper right quadrant. Although the mechanisms for the activation patterns are beyond the scope of this investigation, it is important that the patterns could be explained and do not violate known physiology. However, it should be noted that, although the extreme ranks of the standard of activation may be useful for statistical evaluation of test variables, the ranking scheme itself does not necessarily produce an accurate activation map, because deflections with intermediate ranks (2, 3, and 4) may not be precisely delineated.
On the other hand, the test variable ψ is a continuous function, such that differences between deflections due to local activation and those without will be more consistent than the arbitrary distinctions between ranks. The map resulting from the application of ψ with τ = 0.098 (Figure 9C) is very similar to the standard of activation map in Figure 9B. Unlike the map based on the standard of activation, the assignment of activation to deflections using ψ was not directly influenced by the activation pattern or by knowledge of the stimulation site. Nevertheless, the resulting activation pattern is plausible. The map based on ψ with τ = 0.44 mV/msec² is shown in Figure 9D. It differs from the map based on ψ, but some important features are retained, such as the large activation gradient between the upper and lower right quadrants. In contrast, the map based on ϕmin with τ = -0.64 mV/msec is strikingly different from the previous maps. The region of very dense contours appears to have shifted upward and to the right. Areas without activation have shifted from regions near the dense isochrones to the left lower quadrant. The regions of latest activation have shifted to sites at the periphery of the left upper quadrant and the lower edge of the right lower quadrant. These marked changes in the activation sequence could certainly alter the interpretation of the map and suggest that the statistical differences observed in the test variables and τ values can have practical significance.

The effect of a change in τ value alone is demonstrated in Figure 9F, which is based also on ϕmin but with a slightly lower τ (−0.50 mV/msec). This value of τ is still on the plateau of the QE versus ϕmin plot in Figure 7D, but the plots of Q hopeful and Qsp are relatively steep between these two values of τ. Therefore, the change to τ = −0.50 mV/msec results in some gain in sensitivity and loss of specificity. This results in a much smaller region with no local activation. However, the region of dense isochrones is unchanged. Merely changing the value of τ did not reproduce the activation sequences obtained with the other test variables.

The electrograms recorded at the electrodes sites labeled in Figures 9B–9F (sites A, B, C, and D) are shown in Figures 10A, 10B, 10C, and 10D, respectively. Multiple deflections were recorded at site A (Figure 10A), but the second deflection (D2) meets criteria for all three test variables at τ. Therefore, the activation time at this site did not change when the test variable was changed. D2 is associated with a prominent bipolar deflection, but a larger bipolar deflection precedes it. If the amplitude of the bipolar deflection were the sole criteria for activation, the activation time at site A would have been slightly earlier. There are two prominent deflections at site B (Figure 10B). The first (D1) is associated with a smaller extracellular potential (ϕ = 2.2 mV) than D2 (ϕ = 9.4 mV) and a less negative ϕmin (−0.43 versus −0.76 mV/msec), but D1 has a larger ϕ (0.61 versus 0.38 mV/msec²) and a much larger ψ than D2 (0.28 versus 0.08). For this reason, the maps based on ψ and ϕ have an activation time of 9 msec at site B, whereas the map based on ϕmin has an activation time of 80 msec at site B. There is a sharp, prominent bipolar deflection associated with D1, although the greatest bipolar amplitude occurs slightly later. There is no discernible bipolar deflection associated with D2. Site C was relatively close to site B. D2 was smaller than D1 with respect to potential (ϕ = 1.3 mV for D2 versus 9.7 mV for D1) and ϕmin (see table in Figure 10C for values of ψ, ϕ, and ϕmin), but D2 had a larger ϕ and larger ψ. Also the bipolar signal associated with D2 was sharp and relatively large. Hence, D2 was the deflection associated with activation for maps based on ψ and ϕ and resulted in the very large gradient in activation times between sites B and C (115 msec). When ϕmin was the basis for determining activation, sites B and C were activated simultaneously. None of the deflections recorded at site D (Figure 10D) met criteria for activation based on the test variables ψ or ϕ, but criteria were met when activation was defined by ϕmin. Thus, in the presence of complex, polyphasic electrograms, the activation map may depend heavily on the test for activation and the specific test threshold.

Discussion

Extracellular signals result from a weighted spatial average of electrical activity occurring throughout the heart and only indirectly reflect myocyte activation that occurs at the level of the cell membrane. The synchronous depolarization of many myocytes close to the electrode is required to generate a detectable signal in most recording systems, so that activation of a small number of myocardial cells in the vicinity of the electrode could go undetected. Therefore, the absence of a signal does not exclude the possibility of local activation. Moreover, the presence of a deflection does not necessarily indicate local activity, since electrical activity occurring elsewhere in the heart can also generate a signal. Thus, it is appropriate to view the extracellular signal as representing some probability that local activation has occurred. When a single prominent deflection is recorded, the probability that it results from local activation may be so high as to remove any doubt about its origin. On the other hand, considerable doubt may arise when low amplitude and polyphasic signals are recorded, a problem acknowledged by the most experienced investigators. In such situations it is rarely possible to determine whether activation has occurred with certainty, since even intracellular recordings may be ambiguous or be limited by the presence of fibrous tissue. The purpose of this investigation was to develop an approach that would allow estimation of the probability that a deflection resulted from local activation. Since the "true" probability function is not known, we attempted to identify a test function that was monotonically related to it by comparing the ability of several candidate variables to distinguish local activation from distant activity. Once the "best" function was selected, a τ value was determined by identifying the value of the test variable that maxi-
The degree of agreement between the test variable and the standard of activation. This approach has several advantages: 1) The test variable and \( \tau \) value are selected by an objective, statistically guided process. 2) The measures of uncertainty are provided in terms of the conventional and quality sensitivities, specificities, and predictive values. 3) Since the test for activation is a continuous function, the \( \tau \) value can be manipulated (raised or lowered) to assess the impact of ambiguous deflections (i.e., those with test values near the value of \( \tau \)) on the activation maps. 4) The analysis provides a range of \( \tau \) values that could allow adjustment of the test for activation according to special conditions when it is more desirable to have a more sensitive or more specific test than that provided by the optimally efficient threshold. 5) The approach is flexible. The methods can easily be used to evaluate other populations of signals, other test variables, and different ways of obtaining a standard of activation.

**Standard of Activation**

The standard of activation was based on three features of signals that provided evidence for or against the presence of local activation. The first feature, the presence of propagation, was determined by noting the relation between a given deflection and its neighbors. It is one of the methods most often used to evaluate the presence of local activation. The second feature, the bipolar signal, has also been used frequently in investigations where activation is defined by the amplitude of the...
bipolar signal. The average reference method has been used less often but is a logical method for reducing distant activity. As discussed in “Materials and Methods,” none of these features proved the presence or absence of local activation, but a deflection with high scores on all three features had a high probability of representing local activation, and a deflection with low scores on all three features had a low probability of resulting from activation. Therefore, even if a few deflections were misclassified by this scheme, it would not be expected to have had a significant effect on the results. Moreover, the finding that was a good discriminator using this standard of activation is consistent with previous studies. The only variables found to have superior performance had not been evaluated previously.

Other methods of assessing tests of activation have been used. Blanchard et al and Damiano et al disconnected the right ventricular free wall of dogs so that left ventricular activity recorded in right ventricular electrodes could be considered distant and right ventricular activity could be considered local. Cabo et al used a cryoprobe to produce a homogeneous, nonviable scar in the left ventricle of dogs. Recordings from scar tissue represented distant activity, and recordings from normal tissue represented local activation. In each of these studies, the location of electrodes was the basis of the standard of activation that provided an unequivocal distinction between local and nonlocal signals. However, it is unclear how well deflections obtained from these studies reproduce those recorded from diseased human myocardium. Still other methods of determining a standard of activation could be devised, including the recording of intracellular signals and the use of voltage-sensitive dyes. Although such methods might have produced greater confidence in the standard of activation, we do not believe that the use of additional techniques would have changed the findings. An important advantage of the standard of activation used here is that it did not require any special equipment or techniques beyond those typically used for activation sequence mapping. Moreover, since the data were collected from patients in the operating room, these methods could be used clinically as well as in the laboratory.

In some circumstances it might be appropriate to use the standard of activation to produce activation maps, but there are several reasons why the standard of activation devised for this study would be unsuitable for this purpose. First, the standard of activation was designed to produce a dichotomous classification of deflections where the intermediate ranks, representing more ambiguous signals, could be removed. Ambiguous signals cannot be excluded when analyzing electrograms for activation maps, but the distinction between the intermediate ranks was based on arbitrary and possibly inconsistent criteria. For instance, it was assumed that a deflection that met criteria for the average reference and the bipolar signal but not propagation (rank = 4) was just as likely to represent activation as a deflection that met the partial criteria for propagation and the bipolar signal but full criteria for the average reference (rank = 4). In contrast, the test for activation was a continuous function that allowed precise and consistent descriptions of the differences between deflections. Second, there was no objective basis for selecting a threshold for the standard of activation (e.g., deciding whether ranks above 3 or 4 should be used to define activation), whereas the threshold for the test for activation was based on a predetermined statistic, the maximum Q. Third, one of the criteria used in the standard of activation depended on the map of activation itself; thus, the activation patterns used to define activation would be favored during construction of the map. The test for activation, although partly influenced by the presence of propagation through its relation to the standard of activation, was not directly affected by the activation sequence.

Although the concepts that support the standard of activation used in this investigation are widely applicable, we do not think that this is true of the specific elements. For instance, the 1-mV criteria for the bipolar signal was reasonable for our electrode array with 2 mm between poles but probably would not be appropriate for interpolar distances of 0.05 or 0.50 mm. It does not really matter what standard of activation is used for the approach we present as long as it adequately distinguishes between local and nonlocal activity and is not biased for or against the test variables. In some settings, the standard of activation used here would provide inadequate classification of signals. If no satisfactory method of distinguishing signals can be devised for a population of signals, then reliable mapping cannot be accomplished no matter what approach is used.

Test Variables

There are two elements to the test for activation, the test variable and the test threshold . The test variables were assessed by comparing ROCAs. This treated the test variable as a family of tests for activation where each value of the variable was considered a test threshold. Thus, comparison of ROCAs assessed the gross performance of the variable as a discriminator of local and distant activity. The variable with the greatest ROC was followed by and . However, the variable with the greatest ROC was not necessarily the variable that resulted in the best single test for activation. For this reason a second statistical comparison was performed to evaluate the significance of the differences between of the individual tests for activation. The same pattern was observed: produced the test with the greatest Q, followed by and . Another acceptable approach would have been to evaluate only the single tests and to ignore the overall performance of the test variables. However, we wanted to identify the test variable that would perform well over a range of values. Then could be
varied without major loss in efficiency when changing the sensitivity and specificity.

Some of the test variables have been examined previously. Blanchard et al.\textsuperscript{26} found that a $\phi_{\text{min}}$ threshold of $-1.4 \text{ mV/msec}$ separated activity due to local activity from that due to distant activity. Using a similar preparation Damiano et al.\textsuperscript{27} compared the amplitudes and $\phi_{\text{min}}$s of deflections due to local and distant activity. They found that the amplitude of the signals was a poor discriminator of local versus distant activation but that the derivative provided perfect discrimination.\textsuperscript{27} In our study, $\phi_{\text{min}}$ performed better than all other variables except $\psi$ and $\phi_3$, and only $\psi$ performed significantly better than $\phi_{\text{min}}$. However, the maps in Figure 9 and the electrograms in Figure 10 demonstrate that $\phi_{\text{min}}$ does not perform well in all circumstances. On the other hand, $\phi$ as computed by Equation 1 has an advantage of being more easily calculated than $\psi$, and it produces a variable that is less sensitive to noise than $\phi_3$, as demonstrated in Figure 5. This emphasizes the need to evaluate the performances of test variables before applying them to a population of signals.

Equation 1 has been used at our institution to estimate $\phi$.\textsuperscript{39} Different functions for estimating derivatives were used in the studies of Blanchard et al.\textsuperscript{26} (a first-order difference function\textsuperscript{30}) and Damiano et al.\textsuperscript{27} (three-point Lagrange derivative\textsuperscript{29}). Also, Cabo et al.\textsuperscript{29} plotted the transfer function of the same algorithm we used to estimate $\phi$ and noted that the power spectrum of this function was not linear but dropped at $-2 \text{ kHz}$. The analysis of Cabo et al. was based on a sampling rate of $8 \text{ kHz}$. We examined the transfer function of this algorithm based on the $1 \text{ kHz}$ sampling rate we used and found that the frequency response of the algorithm was linear only to about 50 Hz and dropped after $140 \text{ Hz}$. Cabo et al. showed that local and distant activity could be distinguished on the basis of the frequency content of the signals. We were concerned, therefore, that the performance of the algorithm for $\phi$ might be adversely affected by its nonlinear frequency response. For this reason we also used an algorithm for estimating $\phi$ with a linear response to 500 Hz. Its performance was similar to that of $\phi_{\text{min}}$ but never better in any of the groups of deflections we encountered. Blanchard et al.\textsuperscript{29} found that Equation 1 was more accurate for determining activation time than the first-order difference algorithm and the three-point Lagrange derivative.

We hypothesized that $\phi$ would discriminate between local and distant electrical activity better than $\phi_{\text{min}}$. This was based on the observation of Spach and Dolber\textsuperscript{29} that $\phi$ drops more quickly than the voltage or than $\phi_{\text{min}}$ as a function of the distance between the current source and the electrode. We found that $\phi_3$ had a greater ROCa and a larger $Q\phi$ than $\phi_{\text{min}}$, but the differences were not significant. Nevertheless, $\phi_3$ performed comparatively well in the presence of complex signals and may prove to be a useful test for activation in other settings.

We also hypothesized that $\nu$ or $\rho$ would improve discrimination. We reasoned that a large distant current source could produce a $\phi$, $\phi_{\text{min}}$, or $\phi$ as large as those produced by a small local current source, but if $\phi_{\text{min}}$ and $\phi_3$ decrease more quickly with distance than $\phi$, $\phi$ of the distant signal should be proportionately larger than the $\phi_{\text{min}}$ or $\phi_3$. Thus, the ratio $\phi_{\text{min}}/\phi (\nu)$ and the ratio $\phi_3/\phi (\rho)$ should be smaller for the distant signal than for the local signal regardless of the sizes of the current sources. Despite this logic, $\nu$ and $\rho$ did not perform better than $\phi_{\text{min}}$ or even better than the extracellular potential alone ($\phi_3$, Figure 6). Nevertheless, the variable with the greatest performance, $\psi$, was a linear combination of $\rho_{40}$ and $\phi_{40}$. The coefficient of $\rho_{40}$ was 0.0045; therefore, its contribution to $\psi$ was significant only when the voltage of the signal was relatively high. A high $\phi_{40}$ would also tend to reduce $\rho_{40}$ since $\rho_{40} = \phi_3/\phi_{40}$. This suggested that the failure of $\rho$ to demonstrate better performance resulted from an inability to efficiently select signals with large voltages due to local activation, which includes many signals from normal myocardium. For such signals, the addition of 0.0045$\phi_{40}$ provided the necessary “boost” to give $\psi$ the highest discriminatory power.

The test variable $\psi$ was identified by including all the test variables in a stepwise logistic regression. The logistic regression method seeks the linear combination of variables with the greatest efficiency, not the greatest ROCa, which was the statistic we used to compare variables. Usually, however, combinations with high efficiencies tended to have high ROCA for obvious reasons. The linear combination $\psi$ consisted of two terms, $\rho_{40}$ and $\phi_{40}$. Additional terms did not improve upon $\psi$ significantly. Other equations obtained by logistic regression demonstrated somewhat greater ROCas than $\psi$, but the complexity and redundancy of terms in these equations led us to question their utility.

**Test Threshold Values**

The QROC curve (Figure 7A) indicates the values of $\tau$ that produced the optimally sensitive and specific tests, that is, the lower and upper limits of useful values of $\tau$. Values of $\tau$ outside of this range resulted in tests for activation with much lower discriminatory power with much lower discriminatory power with no gain in $Q_{\text{SE}}$ or $Q_{\text{SP}}$. The optimally efficient test for activation was determined by finding the $\tau$ associated with maximum $Q_{\text{SE}}$ (Figures 7B–7D). This assumed that the cost of misclassifying a deflection due to local activation was equal to the cost of misclassifying a deflection due to distant activation; in other words, the cost of false negatives equals the cost of false positives. For activation sequence mapping, we believe that this will be the most common case. However, in some settings it is appropriate to attach a greater penalty to one type of error. An example might be during intraoperative mapping of ventricular arrhythmias, where it is important to identify all tissue that could be participating in the genesis of the arrhythmia. In that setting, a penalty
could be attached to misclassifying deflections that could be due to local activation, since that type of error could result in failure to ablate the tissue responsible for the arrhythmia. Cost factors can be incorporated into these statistical methods.44

Assessing the Uncertainty of Activation

The uncertainty of the tests for activation can be evaluated in a number of ways. Table 3 gives the conventional and quality sensitivities, specificities, and predictive values of positive and negative tests for the optimal tests for activation. Guidelines for assessing Qk (Cohen’s κ statistic) have been proposed.45 If these statistics are too low, the reliability of activation maps will be in doubt. This enables the clinician or investigator to decide whether a better test for activation should be sought, whether some aspects of the study need to be changed, or whether activation mapping is likely to be fruitful at all. Q_k, Q_{kvp} can be used to evaluate how a particular deflection fits into the distribution. Since Q_{kvp} is identical to Q_k, Q_{kvp} for an individual deflection can be obtained from the plot of Q_k versus the test variable (Figures 7B–7D). The uncertainty of patterns of electrical activation can be assessed by constructing activation maps using different tests for activation. This leads naturally to the concept of “confidence interval maps.” Little change in maps subjected to different tests for activation increases confidence in the activation sequence. However, activation patterns that are very sensitive to changes in τ values should be interpreted with greater caution. The confidence intervals could be based on the standard error of Q_k46 or on predetermined values of Q_se and Q_sp.

Limitations

The performances of test variables and τ values are highly dependent on the population of the recorded signals. A large number of factors could affect the characteristics of the signals including the type, arrangement, and thickness of tissue, electrode material, size and distance from sources, the presence of fat, conductive fluid, signal-to-noise ratio, and sampling rate of the recording system. The type of myocardial disease could also affect the characteristics of the recorded signals. Ursell et al14 have shown that the features of recorded signals change during healing of myocardial infarction. Signals recorded during myocardial ischemia, where action potential upstrokes are diminished by reductions in membrane potential, will differ from those recorded from healed infarction. What impact these factors would have on our findings is uncertain. The specific values of τ identified here are likely to differ since the measured test values are so sensitive to the factors mentioned above. The test variables that demonstrate the greatest performance could also differ, especially those obtained from logistic regression that is sensitive to minor changes in the sample. On the other hand, test variables such as φ_min and φ_3 appear to be useful even in vitro.28 In any case, the statistical approach is independent of the characteristics of the recorded signals. Indeed, the large number of factors that could influence the population of deflections highlights the need for a statistical approach that incorporates and quantifies the uncertainties.

Conclusions

Because our understanding of cardiac arrhythmias depends so heavily on activation sequence mapping, its limitations warrant careful scrutiny. We have presented several strategies for gauging the reliability of activation maps, but further experience will be required to determine which strategies are the most useful or whether better methods can be developed. In any case, quantification of the errors involved in activation mapping should not only lead to more precise interpretation of maps but also to rejection of activation patterns based on unreliable data. In the future, it should be possible to incorporate estimates of error to enhance the efficiency of clinical and experimental mapping and to avoid settings where mapping is likely to generate little information. Certainly, assurance of the quality of activation maps must precede any conclusions about arrhythmia mechanisms.

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References


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K P Anderson, R Walker, P R Ershler, M Fuller, T Dustman, R Menlove, S V Karwande and R L Lux

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