Estimating Cardiac Transmembrane Activation and Recovery Times From Unipolar and Bipolar Extracellular Electrograms: A Simulation Study

Bruce M. Steinhaus

A model of one-dimensional action potential propagation was used to compare activation times and recovery times measured from simulated unipolar and bipolar electrograms with the activation and recovery times measured from simulated transmembrane action potentials. Theory predicts that the intrinsic deflection—the time of the maximum negative slope of the unipolar electrogram QRS complex—corresponds to the time of maximum positive slope of action potential depolarization. Similarly, the time of the maximum positive slope of the unipolar electrogram T wave corresponds to the time of maximum negative slope of action potential repolarization. This study showed that the difference between the unipolar electrogram activation time and the action potential activation time and the difference between the unipolar electrogram recovery time and the action potential recovery time were small during ideal conditions of uniform propagation in a long cable. Nonideal conditions, however, were associated with activation time differences in excess of 1.8 msec and recovery time differences in excess of 30 msec (243 msec in certain conditions). Nonideal conditions that had a major influence were changes in activation sequence, propagation in a short cable, and propagation through regions of nonuniform coupling resistance and/or nonuniform membrane properties. Nonideal conditions that had a smaller influence were variations in distance from the measurement site to the simulated tissue surface, nonzero reference potentials, and the addition of distant events. Recovery time differences were more sensitive to the nonideal conditions than were activation time differences, and both depended on the action potential shape. When distant events significantly contributed to the unipolar electrogram waveform, the time differences when bipolar electrograms were used were less than those when unipolar electrograms were used; however, under other conditions, the time differences were comparable. Results showed that activation times and especially recovery times measured from electrograms can be greatly affected by conditions independent of changes in the underlying action potential waveforms.

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Recent applications of computerized mapping systems to the study of cardiac arrhythmias during surgery have demonstrated the utility of on-line measurement of activation times from unipolar and bipolar electrograms. Often the interpretation of the spatial activation times is an important determinant of the treatment in the operating room. In addition, the accurate determination of beat-to-beat variations as well as spatial distributions of cardiac activation and recovery sequence is desirable in many studies. Neither microelectrode, suction electrode, pressure electrode, nor refractory period methods are applicable for the simultaneous determination of activation and recovery times from multiple sites. Intracellular microelectrodes and suction or pressure electrodes are limited because of the technical difficulty of maintaining multiple stable recordings. Refractory period methods are limited because only a single site can be measured and rapid temporal changes cannot be assessed accurately. Because of these difficulties, techniques have been developed to estimate local
Table of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AP, action potential</td>
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<td>APD, action potential duration (msec)</td>
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<td>ARI, activation recovery interval (msec)</td>
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<td>AT, activation time (msec)</td>
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<td>AT&lt;sub&gt;ueg&lt;/sub&gt;, activation time as measured from the unipolar electrogram (msec)</td>
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<td>AT&lt;sub&gt;be&lt;/sub&gt;, activation time as measured from the bipolar electrogram (msec)</td>
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<td>AT&lt;sub&gt;bc&lt;/sub&gt;, activation time as measured from the bipolar electrogram (msec)</td>
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<td>B, bipolar electrogram (mV)</td>
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<td>B&lt;sub&gt;eg&lt;/sub&gt;, unipolar electrogram (mV)</td>
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<td>BEG, bipolar electrogram (mV)</td>
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<td>B&lt;sub&gt;e&lt;/sub&gt;, temporal derivative of the bipolar electrogram (V/sec)</td>
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<td>C&lt;sub&gt;m&lt;/sub&gt;, net membrane current (μA/cm²)</td>
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<td>C&lt;sub&gt;ov&lt;/sub&gt;, extracellular resistivity (Ωcm)</td>
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<td>C&lt;sub&gt;i&lt;/sub&gt;, cellular coupling resistivity (KΩcm)</td>
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<td>RT, recovery time (msec)</td>
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<td>RT&lt;sub&gt;eg&lt;/sub&gt;, recovery time as measured from the unipolar electrogram (msec)</td>
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<td>RT&lt;sub&gt;be&lt;/sub&gt;, recovery time as measured from the bipolar electrogram (msec)</td>
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<td>RT&lt;sub&gt;bc&lt;/sub&gt;, recovery time as measured from the bipolar electrogram (msec)</td>
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<td>UEG, unipolar electrogram (mV)</td>
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<td>V&lt;sub&gt;max&lt;/sub&gt;, maximum temporal derivative of transmembrane potential (V/sec)</td>
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<td>V&lt;sub&gt;m&lt;/sub&gt;, transmembrane potential (mV)</td>
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<td>V&lt;sub&gt;m&lt;/sub&gt;, second temporal derivative of transmembrane potential (V/sec²)</td>
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<td>V&lt;sub&gt;m&lt;/sub&gt;, third temporal derivative of transmembrane potential (V/sec³)</td>
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<td>V&lt;sub&gt;m&lt;/sub&gt;, minimal temporal derivative of transmembrane potential (V/sec)</td>
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<td>V&lt;sub&gt;m&lt;/sub&gt;, minimal temporal derivative of transmembrane potential (V/sec)</td>
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<td>ΔAT&lt;sub&gt;ueg&lt;/sub&gt;, time difference between AT&lt;sub&gt;ueg&lt;/sub&gt; and AT&lt;sub&gt;be&lt;/sub&gt; (msec)</td>
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<td>ΔAT&lt;sub&gt;be&lt;/sub&gt;, time difference between AT&lt;sub&gt;be&lt;/sub&gt; and AT&lt;sub&gt;bc&lt;/sub&gt; (msec)</td>
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<td>ΔAT&lt;sub&gt;bc&lt;/sub&gt;, time difference between AT&lt;sub&gt;bc&lt;/sub&gt; and AT&lt;sub&gt;bc&lt;/sub&gt; (msec)</td>
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<td>ΔRT&lt;sub&gt;ueg&lt;/sub&gt;, time difference between RT&lt;sub&gt;ueg&lt;/sub&gt; and RT&lt;sub&gt;be&lt;/sub&gt; (msec)</td>
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<td>ΔRT&lt;sub&gt;be&lt;/sub&gt;, time difference between RT&lt;sub&gt;be&lt;/sub&gt; and RT&lt;sub&gt;bc&lt;/sub&gt; (msec)</td>
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activation time (AT) and recovery time (RT) from unipolar electrograms (UEGs) and bipolar electrograms (BEGs). These methods involve choosing the fiducial time markers from either the electrogram waveform or its first derivative. Transmembrane action potential AT has been reported to occur at the intrinsic deflection—the time of the most negative derivative during the unipolar electrogram QRS complex (AT<sub>ueg</sub>). Likewise, the time of the most positive derivative during the UEG T wave (RT<sub>ueg</sub>) has been reported to correspond to recovery times measured from in vivo transmembrane action potentials and corresponds to refractory period measurements. In BEGs recorded from closely spaced electrode pairs, the times of the largest magnitude signal during the QRS complex (AT<sub>be</sub>) and the T wave (RT<sub>be</sub>) have been used as the fiducial markers of AT and RT although other algorithms based on waveform morphology have also been suggested. Recently, the analytic basis for AT<sub>ueg</sub> has been developed and evidence for its validity has been reported using measurements from computer simulations and isolated human atrial tissue. While these studies support the method of determining transmembrane activation and recovery times from extracellular electrograms, the limitations of the technique have not been fully examined. The purpose of this study was to use a computer simulation of action potential (AP) propagation to characterize the sources of errors and the limitations of the method.

Materials and Methods

Computer simulations of one-dimensional AP propagation were used. Simulations were advantageous because UEGs and BEGs could be generated and compared with the spatial and temporal distribution of transmembrane voltages. The basic model used for this study has been previously described. The model consists of electrically connected membrane segments defined by the ventricular membrane model of Beeler and Reuter (BR) with the reversal potential for the slow inward current fixed at 70 mV or the Purkinje membrane model of McAllister, Noble, and Tsien (MNT). Identical membrane properties were assigned to all segments unless otherwise noted. Two separate membrane models were used because the shape of AP repolarization is an important determinant in generation of the electrogram T wave signal; the BR model has a rectangular AP shape, while the MNT model, with a reduced sodium current, has a more triangular AP shape. The cable equation relates the individual membrane segments:

$$I_\text{m} = \frac{1}{Sv \cdot Ri} \left( \frac{\partial^2 V_m}{\partial x^2} \right) = C_\text{m} \left( \frac{\partial V_m}{\partial t} \right) + I_\text{i} \quad (1)$$

where $I_\text{m}$ is the net membrane current (μA/cm²), $Sv$ is the surface-to-volume ratio of the cells (cm⁻¹), $Ri$ is the specific cellular coupling resistivity (KΩcm⁻¹), $V_m$ is the transmembrane potential (mV), $C_\text{m}$ is the specific membrane capacitance (μF/cm²), and $I_\text{i}$ is the total ionic current (μA/cm²). The cable was terminated in open circuits at both ends. The cellular cytoplasmic and junctional resistances were combined to form the equivalent segment cellular coupling resistivity ($R_i$). Extracellular resistivity was assumed to be negligible when compared with $R_i$ for the generation of the AP propagation data. This assumption is valid for a large volume of conducting fluid surrounding the cable. The model equations were numerically solved by finite difference techniques using the Crank and Nicholson implicit method. The solution methods were similar to those in previous reports. Each numerical integration segment was a parallelepiped with edges of length $\Delta x$, $\Delta y$, and $\Delta z$ (cm). Typically,
each AP was described by about 500 points, approximately 200 of which were in the upstroke.

Extracellular potential waveforms were computed using the previously stored spatial distributions of transmembrane potentials at each time instant. The following equation\(^1\)\(^{15}\) was used:

\[
\text{UEG}(p, t) = \frac{\text{Re} M}{4\pi} \sum_{i=1}^{M} \frac{I_{m}(t)(\Delta x \cdot \Delta y \cdot \Delta z) S_v}{d_i}
\]

where \(\text{UEG}(p, t)\) is the electrogram potential at measuring site \(p\) and at time \(t\) referenced to a potential of zero (\(\mu V\)), \(\text{Re}\) is the extracellular resistivity (\(\Omega cm\)), \(M\) is the total number of numerical segments, \(I_{m}(t)\) is the net membrane current calculated from the \(V_m\) data using Equation 1 (\(\mu A/cm^2\)), \(d_i\) is the distance from the measuring site \(p\) to the center of the numerical segment \(i\) (cm), and \(\Delta x\), \(\Delta y\), and \(\Delta z\) are the spatial step sizes in the \(x\), \(y\), and \(z\) directions (cm). Equation 2 assumes a uniform volume conductor surrounded the cable. The electrograms were computed for a measuring site at a distance of 100 \(\mu m\) above the center of the cable unless otherwise noted. Previous histological studies showed that 100 \(\mu m\) was the approximate distance from the position of an epicardial surface measurement site to the closest underlying area of active myocardial cells (refer to Figure 5B of Burgess et al\(^{16}\)). BEGs were obtained by subtracting the unipolar potentials at two measurement sites. Two types of bipolar electrodes were modeled. The first type had an interpole distance of 0.1 mm. The second type modeled a staggered-tip bipolar electrode in which the reference pole was recessed 0.1 mm from the other pole (above the cable). This type of electrode has been used in isolated tissue studies.\(^{17}\)

The following model parameter settings were used: \(\Delta x=\Delta y=0.1\ mm\) (Figures 1, 6, and 7A); \(\Delta x=\Delta y=0.005\ mm\) (Figures 2 and 4); \(\Delta x=\Delta y=0.01\ mm\) (Figures 5 and 7B); \(\Delta x=\Delta y=0.2\ mm\) (Figure 3); \(\Delta z=0.02\ mm\) (all figures); \(S_v=5,000\ cm^{-1}\) (all figures); \(C_w=1.0\ \mu F/cm^2\) (all figures); cycle length=800 msec (all figures); \(R_i=400\ \Omega cm\) (Figures 1, 2, 3, 4, and 7A); \(R_i=200\ \Omega cm\) (Figures 5 and 7B); \(R_i=4,800\ \Omega cm\) (Figure 3, center section); \(R_i=7,200\ \Omega cm\) (Figures 5 and 7B, center section); maximum sodium current conductance scaling factor=1.0 (Figures 1, 3, 5, 6, 7A, and 7B); maximum sodium current conductance scaling factor=0.1 (Figures 2 and 4); \(R_{e}=100\ \Omega cm\) (all figures); membrane model=MNT (Figures 2, 3, and 4); membrane model=BR (Figures 1, 5, 6, 7A, and 7B); and \(M=\text{total number of segments}=250\) (all figures). The cable dimensions were \(\Delta y\) wide by \(\Delta z\) high by 250\(x\Delta x\) long. The \(x\)-axis spatial increment ranged between 0.005 mm and 0.2 mm because of the different spatial resolution necessary to study activation (small \(\Delta x\)) or repolarization (large \(\Delta x\)). Nonuniform cables with center sections of increased \(R_i\) modeled the reduced cell-to-cell electrical coupling caused by either cellular packing with reduced occurrence of cellular connections in the transverse direction compared with the longitudinal direction and/or reduced coupling caused by connective tissue.

Propagation was initiated by a square pulse of intracellular depolarizing current, twice diastolic threshold, 2 msec long and applied to the 0-mm end segment. To ensure steady state conditions, each run consisted of pacing the cable three to six times with data measured on the last beat. Programs were
RESULTS

The theoretic basis for determining AT and RT from unipolar and bipolar electrogram waveforms and the results of computer simulations of uniform and nonuniform cables are reported. Uniform cables were defined as cables with all segments having the same intrinsic membrane properties and the same Ri. Nonuniform cables were defined as cables with a varying spatial distribution of intrinsic membrane properties or Ri.

Theoretic Basis for Estimating Activation and Recovery Times From Electrograms

During uniform one-dimensional propagation with a constant conduction velocity, $\theta$ (m/sec), net membrane current is proportional to the second temporal derivative of $V_m$:

$$I_m = \left( \frac{1}{S V \cdot \theta^4 \cdot Ri} \right) \left( \frac{d^2 V_m}{d^2 r} \right)$$

Under these conditions, the UEG can be found by combining Equation 3 and the one-dimensional integral form of Equation 2:

$$UEG(x=0,t) = \frac{Re \left( \Delta x \cdot \Delta y \cdot \Delta z \right)}{Ri} \frac{4 \pi \theta^2}{x} \int_{-\infty}^{\infty} \left( \frac{1}{\sqrt{x^2 + z^2}} \right) \left( \frac{d^2 V_m}{d^2 r} \right) (dx)$$

where $UEG(x=0,t)$ is the electrogram at $x=0$ and $t$, and $z$ is the distance from the measuring site to the center of the cable. Equation 4 shows that during uniform propagation, the electrogram potential at each time instant is proportional to the sum of $V_m$ divided by the distance from the measuring site for all locations along the cable.

The temporal derivative of UEG (UEG) is then a weighted sum of the $V_m$ for all locations:

$$UEG(x=0,t) = \frac{Re \left( \Delta x \cdot \Delta y \cdot \Delta z \right)}{Ri} \frac{4 \pi \theta^2}{\sqrt{x^2 + z^2}} \int_{-\infty}^{\infty} \left( \frac{1}{\sqrt{x^2 + z^2}} \right) \left( \frac{d^2 V_m}{d^2 t} \right) (dx)$$

If $V_m$ is temporally symmetric about the time of $V_{max}$ during depolarization, the time of the minimum of Equation 5 will correspond to the time of...
the minimum \( V_m \), which will be the time of the \( V_{max} \). Thus, \( \Delta T_{uerg} \), the time of the minimum of UEG during the QRS complex, will be exactly equal to \( \Delta T_{ap} \), the time of \( V_{max} \) during depolarization. The UEG will have a potential of zero at this time because spatial symmetry will result in exactly opposite contributory second derivatives for sites an equal distance upstream and downstream from the measuring site. Note that this development is similar to that shown by Spach and Kootsey with the additional symmetry constraint. Without temporal symmetry in AP depolarization, the exact correspondence of the time of the minimum UEG and \( V_{max} \) cannot be made because 1) the minimum \( V_m \) and \( V_{max} \) will not occur at the same time and 2) the temporal asymmetry will cause spatial asymmetry and noncanceling distant electrical events at the time of \( V_{max} \).

Since repolarization has a sequence, it can be considered a traveling wave. Thus, the previous development for \( \Delta T_{uerg} \) can be used to define \( \Delta T_{l erg} \) as the time of the maximum of Equation 5 during the T wave. This time will be the exact time of \( V_{min} \) during repolarization with the constraint of temporal symmetry in AP shape about the time of \( V_{min} \) during repolarization.

The determination of AT and RT from BEGs is made by description of the bipolar signal as the spatial derivative of the unipolar signal. For uniform one-dimensional propagation, the spatial derivative of a signal is proportional to the temporal derivative of the signal. Thus, BEG is proportional to UEG and is defined by Equation 5 scaled by a constant factor that depends on the interpole distance of the bipolar electrode. \( \Delta T_{l erg} \) and \( \Delta T_{l erg} \) are defined as the time of the minimum BEG signal during the QRS complex and the time of the maximum BEG signal during the T wave, respectively. Typically, \( \Delta T_{l erg} \) and \( \Delta T_{l erg} \) are measured as the time of the largest magnitude BEG signal during the QRS complex and T wave, respectively, because the BEG polarity depends on the orientation of the electrode pair with respect to the traveling wave. The staggered-tip bipolar electrogram \( \Delta T_{l erg} \) and \( \Delta T_{l erg} \) are measured with the same rules as those applied to the unipolar electrogram \( \Delta T_{uerg} \) and \( \Delta T_{uerg} \) because this BEG signal is defined by Equation 4 scaled by a constant factor that depends on the interpole distance of the bipolar electrode.

In summary, theory shows that \( \Delta T_{uerg} \) and \( \Delta T_{uerg} \) will exactly signify \( \Delta T_{ap} \) and that \( \Delta T_{uerg} \) and \( \Delta T_{uerg} \) will exactly signify \( \Delta T_{ap} \) during uniform AP propagation with constant conduction velocity in an infinitely long one-dimensional cable with symmetric AP depolarization and symmetric AP repolarization shape. The following sections present results of computer
Figure 5. Spatial distribution of AP configuration during depolarization for a nonuniform cable (left panel). Segment between 1.0 mm and 1.5 mm has increased Ri (7.200 \Omega cm). Right panel shows depolarization waveforms for Vm, Vm, UEG, UEG, and UEG at reduced time scale at x=1.25 mm and x=1.42 mm. Conduction velocity was 0.48 m/sec, 0.13 m/sec, and 0.57 m/sec for proximal, center, and distal sections, respectively. Resting space constant was 0.61 mm for proximal and distal sections and 0.10 mm for center section. Horizontal calibration bar=9.6 msec for spatial AP configuration waveforms, 15 msec for UEG at reduced time scale, and 2.3 msec for all other waveforms. Vertical calibration bar=122 mV for spatial AP configuration waveforms and 94 and 93 mV (Vm); 260 and 270 V/sec (Vm); 3.0 and 4.1 \mu V (UEG); and 9.2 and 6.9 \mu V (UEG) for middle and right panels, respectively. AP, AT_{ueg}, AT_{sp}, Ri, UEG, UEG, Vm, Vm, see Table of Abbreviations.

Recovery Times: Uniform Cables

The spatial distribution of difference in RT (\Delta RT_{ueg}=RT_{ueg}-RT_{sp}) for a one-dimensional cable with uniform membrane properties and uniform Ri is shown in Figure 1 (top panel). Differences are present along the whole cable. Repolarization waveforms of Vm, Vm, UEG, and UEG from the site of stimulation (x=0 mm), the site in the center of the cable (x=12.5 mm), and the site of propagation termination (x=25 mm) are shown in the lower panels. As has been previously shown experimentally, the Vm and Vm waveforms demonstrate that RT_{sp} occurs near the tail of the AP during normal conditions.18 There were slight differences in APD between the three sites (282.8 msec, 278.2 msec, and 273.5 msec for x=0 mm, x=12.5 mm, and x=25 mm, respectively) as previously shown,7,19 but all three sites had very similar Vm and, hence, Vm waveforms during repolarization. In contrast, the UEG waveform was predictably monophasic positive for site x=0 mm, monophasic negative for site x=25 mm, and biphasic for site x=12.5 mm. The UEG waveforms at the three sites reflected the changes in I_n during repolarization.7 Accompanying the differences in UEG and UEG were changes in \Delta RT_{ueg}. These included \Delta RT_{ueg} of -11.7 msec, 2.91 msec, and 10.8 msec at x=0 mm, x=12.5 mm, and x=25 mm, respectively. The negative \Delta RT_{ueg} at x=0 mm was due to the similarity between UEG and the negative Vm, which caused RT_{ueg} to be very close to the time of the minimum Vm, a time always before the time of Vmin. Opposite changes occurred at the x=25 mm site, where UEG was very similar to Vm, which caused RT_{ueg} to be very close to the time of the maximum Vm, a time always after the time of Vmin. Vm at RT_{ueg} occurred at 69%, 79%, and 90% AP repolarization for the x=0 mm, x=12.5 mm, and x=25 mm sites, respectively.
$\Delta R_{T_{\text{org}}}$ at $x=12.5$ mm, the cable center, should theoretically be zero. Three possible causes for the observed $\Delta R_{T_{\text{org}}}$ were evaluated: nonuniform propagation, distant events, and asymmetry in $V_m$ repolarization. Uniform propagation was validated by the nearly indistinguishable normalized waveforms of $I_m$ and $V_m$ during repolarization, as predicted by Equation 3. The contribution of distant events was determined to be minimal by the following analysis:

During uniform propagation, the electrogram from a perfect unipolar electrode that was unaffected by distant events would be equivalent to the scaled $I_m$ waveform (refer to Equation 2). When $R_{T_{\text{org}}}$ was determined from the center site $I_m$ waveform (i.e., without distant events), $\Delta R_{T_{\text{org}}}$ was only slightly reduced to 2.57 msec, which is comparable to 2.91 msec with distant events. The major cause of $\Delta R_{T_{\text{org}}}$ at the cable center was the asymmetric shape of $V_m$ repolarization. If $V_m$ was symmetric about the time of $V_{\text{min}}$, the time of $V_{\text{min}}$ would be the exact time of maximum $V_m$; however, the time of $V_{\text{min}}$ was 300.73 msec and the time of maximum $V_m$ was 303.45 msec, a difference of 2.72 msec. This asymmetry explains the cable center positive $R_{T_{\text{org}}}$ and also the slight effect of distant events on $R_{T_{\text{org}}}$.

$\Delta R_{T_{\text{org}}}$ at both cable ends required a short distance to decay to the $R_{T_{\text{org}}}$ measured at the cable center. The spatial extent of $\Delta R_{T_{\text{org}}}$ shown in Figure 1 was 2.2 mm at the $x=25$ mm cable end as measured by the distance over which $\Delta R_{T_{\text{org}}}$ decayed to 63% of its maximum. The spatial extent of $\Delta R_{T_{\text{org}}}$ was found to be qualitatively similar to the spatial extent of the changes in APD ($\Delta A_{PD}$) at the same end (1.5 mm). This similarity in the spatial extent of $\Delta R_{T_{\text{org}}}$ and $\Delta A_{PD}$ at the cable end was substantiated in other simulations of cables with uniform changes in $R_i$, $C_m$, and maximum excitable sodium current conductance. Previous studies have shown that the spatial extent of changes in AP area and APD due to activation sequence ($\lambda$) were related to

$$\lambda = \sqrt{(R_m)(2a)/R_i}$$

(6)

where $a$ is the cable radius and $R_m$ is the membrane resistance during repolarization. Membrane resistance is larger in magnitude during repolarization than during rest potential and is modulated by cycle length. 20 It is postulated that this relation also qualitatively predicts the spatial extent of $\Delta R_{T_{\text{org}}}$ at the cable ends.

It appears from the waveforms shown in Figure 1 that for monophasic UEG signals, $R_{T_{\text{org}}}$ could be more accurately estimated from the UEG as the time of the peak absolute magnitude T wave signal. This does minimize $\Delta R_{T_{\text{org}}}$ for the sites at either cable end and is theoretically justified because $I_m$ at the cable ends is proportional to $V_m$. At other sites a small distance from the ends, however, large $\Delta R_{T_{\text{org}}}$ would result. For example, at $x=23$ mm, the T wave is monophasic negative and $\Delta R_{T_{\text{org}}}$ is 5.1 msec if $R_{T_{\text{org}}}$ is defined as the time of the peak absolute magnitude T wave signal. Other simulations with a nonuniform distribution of APD resulted in sites with monophasic T waves and very large increases in $\Delta R_{T_{\text{org}}}$ when $R_{T_{\text{org}}}$ was defined as the time of the peak absolute magnitude T wave signal. Thus, the definition of $R_{T_{\text{org}}}$ cannot be waveform dependent.

Cables that were less than five repolarization space constants in length did not allow $\Delta R_{T_{\text{org}}}$ to decay to its value during uniform conditions in longer cables. The repolarization space constant was determined by the spatial extent of the activation sequence-induced changes in APD. 7 In these short cables, repolarization traveled faster than activation, as previously reported, 24 and resulted in low-amplitude UEG T waves. In addition, the relation between $I_m$, UEG, and $V_m$ during repolarization was very complex and $R_{T_{\text{org}}}$ was very inaccurate in estimating $R_{T_{\text{org}}}$. The waveforms shown in Figure 2 are from a short uniform cable 1.25 mm in length and illustrate the dissimilar nature of UEG and $V_m$ or $V_m$. At $x=0.25$ mm and $x=1.0$ mm, $\Delta R_{T_{\text{org}}}$ was 243 msec and 149 msec, respectively. In fact, at $x=0.25$

![Figure 7](http://circres.ahajournals.org/Downloaded from)

**Figure 7.** Bipolar electrogram tracings for $V_m$, $V_m$, and BEG during repolarization (panel A) and for $V_m$, $V_m$, BEG, BEG at reduced time scale, and BEG during depolarization (panel B). Conduction velocity was 0.33 m/sec, and resting space constant was 0.45 mm (panel A); conduction velocity was 0.13 msec and resting space constant was 0.10 mm (panel B). Horizontal calibration bar=100 msec for all waveforms in panel A, 15 msec for BEG at reduced time scale in panel B, and 2.3 msec for all other waveforms in panel B. Vertical calibration bar=68, 69, 70, 94, and 94 mV ($V_m$); 0.86, 0.88, 0.91, 260, and 260 V/sec ($V_m$); 0.071, 0.042, 0.060, 0.98, and 1.1 V (UEG); and 2.3 $\mu V$/msec (BEG) for panel A left, middle, and right, and panel B left and right, respectively. $A_{T_{\text{org}}}$, $A_{T_{\text{org}}}$, BEG, BEG, $R_{T_{\text{org}}}$, $R_{T_{\text{org}}}$, $V_m$, $V_m$, see Table of Abbreviations.
mm, RT\textsubscript{ueg} occurred during AP depolarization because there was never a time of positive UEG slope during all of repolarization. The simulation had the maximum sodium current conductance reduced to 0.1 times its control level because the simulation results were also used to illustrate \( \Delta T\textsubscript{u} \) at sites near propagation termination (Figure 4), and this was found to be modulated by the maximum excitatory sodium current. Both AP collisions and spatially separated high-resistance barriers could functionally isolate tissue into short-length sections and could display large \( \Delta T\textsubscript{ueg} \).

**Recovery Times: Nonuniform Cables**

The influence of a nonuniform distribution of APD on \( \Delta T\textsubscript{ueg} \) was studied by assignment of a linear distribution of slow inward current scaling factors to the segments of a cable. The BR membrane model APD gradually shortened from 262 msec at the stimulated end (scaling factor=1.0) to 97.7 msec at the opposite end (scaling factor=0.1). This APD distribution caused recovery to travel in a direction opposite to activation. Whereas a monophasic positive T wave and a negative \( \Delta T\textsubscript{ueg} \) were measured from the stimulated end in a uniform cable, the stimulated end in this nonuniform cable showed a monophasic negative T wave and a positive \( \Delta T\textsubscript{ueg} \) of 7.98 msec. The monophasic negative T wave and positive \( \Delta T\textsubscript{ueg} \) were similar to data recorded from the termination end of a uniform cable and were due to the collision of the recovery wave at the cable end that was stimulated. At the cable center, T waves were biphasic and \( \Delta T\textsubscript{ueg} \) was 2.52 msec, a value similar to the center of a cable with BR model parameters.

In another simulation, the center one fifth of a cable with BR model segments was assigned a slow inward current scaling factor of 0.25 and \( \Delta T\textsubscript{ueg} \) was greater than 25 msec at the cable center. The large positive \( \Delta T\textsubscript{ueg} \) occurred at a site with a monophasic positive T wave; this was due to the electrotonic influence at the cable center, which increased APD from its intrinsically reduced value (APD was 339 msec at the cable center). Thus, positive \( \Delta T\textsubscript{ueg} \) was measured for T waves that were monophasic positive, monophasic negative, and biphasic.

Another nonuniform cable had increased Ri assigned to segments of the cable center. This simulation was used to determine \( \Delta T\textsubscript{ueg} \) at sites of acceleration and deceleration of propagation. At sites where activation approached a region of increased Ri (Figure 3, solid line, distance=20 mm), T waves became monophasic negative and \( \Delta T\textsubscript{ueg} \) increased. At sites where activation exited a region of increased Ri (Figure 3, solid line, distance=30 mm), T waves became monophasic positive and \( \Delta T\textsubscript{ueg} \) became negative. The MNT model was used in this simulation, and \( \Delta T\textsubscript{ueg} \) at the cable center was 2.31 msec, a value qualitatively similar to \( \Delta T\textsubscript{ueg} \) at the center of a cable with BR model segments (Figure 1). Also note that \( \Delta T\textsubscript{ueg} \) at the cable ends was about 30 msec, compared with less than 15 msec for the BR model (Figure 1). This difference can be attributed to the difference between the BR and MNT model AP shapes (Figure 1, AP configuration insert, and Figure 2, AP configuration insert, respectively). The \( \Delta T\textsubscript{ueg} \) distribution from a line of measuring sites at a distance of 100 mm above the center of the cable is also shown in Figure 3 (broken line). Excluding the center section, the \( \Delta T\textsubscript{ueg} \) distribution from the distant measuring sites was spatially smoother than the \( \Delta T\textsubscript{ueg} \) distribution from the surface measuring sites. This observation has been previously shown experimentally.\(^2\) \( \Delta T\textsubscript{ueg} \) for the distant measuring sites above the cable center, however, was very large (40.3 to -78.7 msec) because the UEGs at these measuring sites were greatly affected by the large magnitude and rapidly changing currents at the sites of abrupt change in Ri. Thus, \( T\textsubscript{ueg} \) for these distant measuring sites was due to electrical activity other than activity directly below the measuring site.

In still another simulation, the center section of the cable with MNT model segments was assigned a 10 times control Ri and a 0.1 times control maximum slow inward current conductance. Measurement of \( \Delta T\textsubscript{ueg} \) at sites near the cable center was not possible because the T wave always had a negative slope, which prevented a meaningful measurement of RT\textsubscript{ueg} (Figure 2, x=0.25 mm). In addition, many sites in the center section had triangular-shaped APs with a smoothly decreasing AP repolarization shape that prevented measurement of RT\textsubscript{ueg}. These waveforms demonstrated the complex relation between AP shape and UEG waveform during certain nonideal conditions.

**Activation Times: Uniform Cables**

Since both activation and recovery can be described as traveling waves, \( \Delta T\textsubscript{ueg} \) should be influenced at the cable ends in a qualitatively similar manner to \( \Delta T\textsubscript{ueg} \) at the cable ends. Simulation results testing this hypothesis showed that \( \Delta T\textsubscript{ueg} \) was altered at the cable end (Figure 4, top panel). This figure shows \( \Delta T\textsubscript{ueg} \) for the second half of a 1.25-mm long uniform cable. \( \Delta T\textsubscript{ueg} \) for sites near the stimulus showed qualitatively opposite values from the second cable half but are not shown because both \( T\textsubscript{ueg} \) and \( \Delta T\textsubscript{ueg} \) were influenced by the stimulus parameters. A short cable was used in these simulations because the spatial distribution of \( \Delta T\textsubscript{ueg} \) was much less than that of \( \Delta T\textsubscript{ueg} \). In contrast to the distribution of \( \Delta T\textsubscript{ueg} \), the maximum \( \Delta T\textsubscript{ueg} \) was not located at the cable end but at a short distance from the end. Waveforms at \( x=1.045 \) mm, the site of maximum \( \Delta T\textsubscript{ueg} \), are shown in the lower panel. At this site, the depolarization complex was very similar to that measured at the cable end, yet \( \Delta T\textsubscript{ueg} \) was increased from 0.0199 msec to -0.252 msec. In fact, \( \Delta T\textsubscript{ueg} \) at both cable ends and at the cable center was nearly zero, a finding that supported previous reports.\(^3\) The difference between
the spatial distribution of $\Delta AT_{req}$ and $\Delta RT_{req}$ was due to the difference in the activation sequence-induced changes in $V_m$ depolarization and repolarization. While activation sequence had little influence on the overall shape of AP repolarization, it markedly altered the shape of AP depolarization and caused changes in $V_{max}$, $V_m$ at $V_{max}$, and AP height. Thus, one might expect $\Delta AT_{req}$ to be spatially dissimilar to $\Delta RT_{req}$. $\Delta AT_{req}$ at the cable center, $x=0.625 \text{ mm}$, was 0.0163 msec and could be attributed to the asymmetry in AP depolarization. Longer cables also showed this small positive $\Delta AT_{req}$ throughout the central area of the cable. The maximum $\Delta AT_{req}$ at the cable end was inversely related to the maximum excitatory sodium current conductance. The simulation shown in Figure 4 had 0.1 times control sodium current conductance. In another simulation with control sodium current conductance that used the MNT membrane model, $\Delta AT_{req}$ was generally smaller: $-0.00237 \text{ msec}$, $-0.0354 \text{ msec}$, and $-0.000158 \text{ msec}$ at the cable center, site of maximum difference, and cable end, respectively. The asymmetry in MNT model AP depolarization created a negative $\Delta AT_{req}$ at the cable center in contrast to the positive $\Delta AT_{req}$ for the BR model.

Activation Times: Nonuniform Cables

Nonuniform cables with a center section of increased $R_i$ had marked spatial changes in $V_m$ depolarization (Figure 5, left panel) and $\Delta AT_{req}$. The right panels show waveforms at $x=1.25 \text{ mm}$ and $x=1.42 \text{ mm}$. $\Delta AT_{req}$ at $x=1.25 \text{ mm}$ occurred 1.82 msec before $AT_{sp}$ and at a time when $V_m$ was at rest potential (100% AP repolarization). $\Delta AT_{req}$ at $x=1.42 \text{ mm}$ occurred 0.521 msec after $AT_{sp}$ (1.3% AP repolarization). $AT_{req}$ at $x=1.42 \text{ mm}$ coincided in time with $AT_{sp}$ at $x=1.50 \text{ mm}$, the end border of the high-resistance center section. In contrast, $\Delta AT_{req}$ at $x=1.25 \text{ mm}$ coincided in time with $AT_{sp}$ at $x=0.81 \text{ mm}$, a site located before the high-resistance section. Thus, $\Delta AT_{req}$ was dependent on the conduction time across the zone of increased $R_i$ and could be modulated by the length of this zone. The mechanism of this finding was due to the large-amplitude currents generated during propagation in the normal $R_i$ cable sections compared with the low-amplitude currents generated during propagation in the cable center with the increased $R_i$. Although low in amplitude, the net membrane currents from sites in the cable center were still accurate indicators of the $V_m$ activity. For example, the time of maximum negative derivative of $I_m$ was within 2 $\mu\text{sec}$ of $AT_{sp}$ for the two sites at $x=1.25 \text{ mm}$ and $x=1.42 \text{ mm}$. The large-amplitude distant net membrane currents generated outside the high-resistance center section, however, were the major factors that determined $AT_{req}$ at $x=1.25 \text{ mm}$ and $AT_{req}$ at $x=1.42 \text{ mm}$. The mechanism is similar to the mechanism of the large $\Delta RT_{req}$ values of the distant recording sites of the nonuniform cable shown in Figure 3, $z=100 \text{ mm}$. The UEG waveforms at the bottom of Figure 5 are graphed at a reduced time scale and show polyphasic depolarization waveforms at both these sites. These waveforms signify the saltatory propagation through the zone of increased $R_i$.

Activation and Recovery Times: Effects of Distant Events

As described previously, asymmetry in AP repolarization caused distant events that increased $\Delta RT_{req}$ for the center of a uniform cable. The effects of distant events on $\Delta AT_{req}$ in a nonuniform cable, in which electrical events generated by sites a distance from the measuring site caused the most negative derivative of the UEG to occur before $AT_{sp}$, have also been described. These effects are shown in Figure 5.

In another simulation, the effect of distant events was evaluated by comparing the distribution of $AT_{req}$ and $RT_{req}$ for a uniform cable simultaneously stimulated at both ends with the distribution of $AT_{req}$ and $RT_{req}$ for a uniform cable half as long and stimulated at one end only. The cables were assigned the BR membrane model. As previously shown, activation termination at a sealed end was identical to activation collision and the spatial and temporal $V_m$ distributions for the two cables were identical for the similar cable sections. The distributions of $AT_{req}$ for the two situations were nearly identical with a maximum difference of 0.055 msec at a site 0.1 mm from the collision site. The distributions of $RT_{req}$ were also very similar for the two situations with a maximum difference of 0.63 msec at a site 2.2 mm from the collision site. Thus, during these conditions, distant events had a small effect on $\Delta AT_{req}$ and $\Delta RT_{req}$.

The influence of distant events on UEG waveform was also studied by measurement of the UEG during simultaneous propagation in two uniform cables. One cable represented local excitable cells (Figure 6, lower panel, solid line), and the other cable represented distant cells (Figure 6, lower panel, dashed line). The UEG was measured at a site 100 times closer to the local cable than to the distant cable. The distant electrogram was added to the local electrogram with a varying time phase that simulated the time difference between stimulation of the distant cable with respect to stimulation of the local cable. When the phase difference was varied, $\Delta RT_{req}$ varied by a magnitude of 3.32 msec (Figure 6, top panel), while $\Delta AT_{req}$ varied 0.0005 msec (not shown). Thus, when distant events are included with local activity, the timing of the distant events can influence $AT_{req}$ and $RT_{req}$. The magnitude of this influence is dependent on the magnitude and time course of the maximum and minimum derivative of the distant signal during activation and recovery.

Activation and Recovery Times: Effect of Imperfect Reference Potentials

A perfect reference potential (i.e., a potential of 0 mV) is not achievable during in vivo experiments

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since the reference must be located infinitely far from the measuring site. Typically, the Wilson central terminal is used as the experimental unipolar reference. For mapping experiments in which multiple sites are measured, the average of all potentials has also been used as a reference potential. For isolated tissue experiments, the reference is often located in the far corner of the tissue bath and is typically a much lower amplitude than the reference potential during whole animal experiments. The influence of a time-varying imperfect reference potential on $\Delta T_{\text{seg}}$ and $\Delta T_{\text{seg}}$ was studied using the AP propagation data that provided the results shown in Figure 1. The UEG was measured at $x=17.5$ mm and was referenced to a site at $x=7.5$ mm and three times farther distant from the cable surface than the UEG site. This resulted in a $\Delta T_{\text{seg}}$ of 0.440 msec and a $\Delta T_{\text{seg}}$ of 3.29 msec compared with $-0.00146$ msec and 2.94 msec, respectively, for the perfect reference of 0 mV. When the UEG was referenced to the average UEG from 250 sites evenly spaced along the whole cable, $\Delta T_{\text{seg}}$ was 0.944 msec and $\Delta T_{\text{seg}}$ was 3.11 msec. The influence of imperfect reference potentials on $\Delta T_{\text{seg}}$ and $\Delta T_{\text{seg}}$ was very similar to the effect that distant events have on $\Delta T_{\text{seg}}$ and $\Delta T_{\text{seg}}$. Imperfect reference potentials will influence $\Delta T_{\text{seg}}$ and $\Delta T_{\text{seg}}$, the magnitude of this influence is dependent on the magnitude of the maximum and minimum derivative of the reference signal during activation and recovery and its timing with respect to the measured UEG signal.

**Activation and Recovery Times: Bipolar Electrodes**

BEGs were computed using the same AP propagation data that provided the results shown in Figure 1. Figure 7, panel A shows $Vm$, $Vm$, and BEG waveforms for sites at $x=0.6$ mm, $x=12.5$ mm, and $x=24.5$ mm, respectively. $\Delta T_{\text{seg}}$ at these sites was 10.4 msec, 3.05 msec, and $-6.44$ msec, respectively, and was of the same magnitude as the $\Delta T_{\text{seg}}$ values for the same sites ($-11.7$ msec, 2.91 msec, and 10.7 msec, respectively). Thus, at sites of stimulation and propagation termination—sites where local activation sequence and $I_{\text{m}}$ differ from that during uniform propagation—recovery time estimates from BEGs had the same inaccuracies as estimates from UEGs. Qualitatively similar findings were found for AT estimates from BEGs at sites of propagation termination. Note that $\Delta T_{\text{seg}}$ is of opposite polarity from $\Delta T_{\text{seg}}$ at the cable ends. One of the benefits of the bipolar electrogram is that events common to both bipolar sites are not measured. Thus, the signal is less sensitive to distant events. Figure 7, panel B shows bipolar signals computed at $x=1.25$ mm using the same AP propagation data that provided the simulation results shown in Figure 5. The waveforms on the right were computed for a standard bipolar electrogram; the waveforms on the left were computed for a staggered-tip bipolar electrogram. Whereas $\Delta T_{\text{seg}}$ was $-1.82$ msec (see Figure 5, $x=1.25$ mm), the standard BEG was less sensitive to the distant events and $\Delta T_{\text{seg}}$ was $-0.00912$ msec. The staggered-tip BEG was also less sensitive to the distant events and $\Delta T_{\text{seg}}$ was 0.00287 msec. Thus, during conditions with significant distant electrical events, time estimates from BEGs have less error than time estimates from UEGs.

**Discussion**

In this study, activation and recovery times estimated from simulated unipolar and bipolar electrograms were compared to the times measured from the simulated transmembrane action potentials. The simulations used in this study were limited to one-dimensional propagation in cables with a height of 0.02 mm and a width of less than 0.2 mm. These small cable sizes resulted in low-amplitude extracellular potentials, often less than 10 mV. The propagation velocity and simulated spatiotemporal transmembrane potentials, however, are independent of the specific cable geometry (see Equation 1). This independence is the result of the surface-to-volume ratio used in the simulations. In contrast, the amplitude of the extracellular potential is directly scaled by the cable geometry (see Equation 2). The extracellular potential fiducial markers are independent of waveform amplitude and, hence, are also independent of cable geometry. These facts combine to enable simulation results that are identical to results that use much larger tissue dimensions. It is from this basis that the results can provide useful insights into the interpretation of data recorded from isolated tissue bath experiments as well as in vivo data from epicardial ventricular sites.

Results from sites in the center of long uniform cables support the theoretic basis of activation as the time of the minimum derivative in the QRS complex and recovery as the time of the maximum derivative in the T wave of UEGs. Likewise, activation and recovery times from BEGs are most accurate when measured as the time of the maximum absolute signal during the QRS complex and T wave. Activation and recovery times from staggered-tip BEGs are most accurate when measured using the same rules that were applied to UEGs. During uniform propagation, the activation recovery interval (ARI) measured as the time difference between $T_{\text{seg}}$ and $T_{\text{seg}}$ is an accurate measure of APD. Thus, during uniform propagation and during interventions that do not change the shape of AP polarization (i.e., change in phase 2 plateau duration), changes in ARI can characterize changes in underlying APD.

Uniform propagation, however, is not typically found in the heart. Uniform propagation would result in biphasic UEG QRS complexes and biphasic UEG T waves. While biphasic UEG QRS complexes are often recorded, biphasic UEG T waves are rare. Uniform propagation would also require tangential propagation on the epicardial surface.
Experimental measurements, however, show that during sinus rhythm there is a significant endocardial-to-epicardial component of the propagation direction.\textsuperscript{25} In addition, sites greater than 6–8 mm from epicardial stimulus sites can be activated by a significant endocardial-to-epicardial component of the propagation direction due to the rotation of the anisotropic layers through the ventricular wall.\textsuperscript{16} Thus, epicardial potentials are measured from sites of low-angle collisions even when epicardial isochrone patterns appear to show tangential propagation. The gradient in APD across the transmural ventricular wall causes repolarization to start at the epicardium and travel toward the endocardium. This would independently cause a decrease in $\Delta RT_{\text{org}}$ at the epicardial surface and would oppose the action of activation collision at the epicardial surface that would increase $\Delta RT_{\text{org}}$. The combined effect would ultimately depend on the magnitudes of the two actions. Uniform propagation also requires uniform membrane properties and uniform structural properties for a distance greater than the traveling wavelength. The depolarization wavelength is calculated to be approximately 1 mm using 2 msec as the duration of depolarization and 0.5 m/sec as the propagation velocity. In contrast, the repolarization wavelength is approximately 20 mm using 40 msec as the duration of the fast phase 3 repolarization. Thus, it is less likely for the active spatial current generation sites to be uniform during repolarization than during depolarization. In addition, multidimensional propagation through the rotating anisotropic tissue layers of the ventricular walls would cause the UEG QRS and T waveforms to deviate from the biphasic shapes recorded during uniform propagation. Polyphasic QRS complexes and the notches in the AP upstroke often observed in older tissue during propagation transverse to fiber direction are also experimental evidence of nonuniform propagation.\textsuperscript{6,26,27} Activation wavefront collisions are ubiquitous in the normal heart,\textsuperscript{23,28} and in certain abnormal conditions, such as ischemic tissue, activation and recovery patterns are very complex. Thus, activation and especially recovery can rarely be described as uniform plane-wave propagation.

Another complicating factor is that symmetry in AP depolarization and AP repolarization shape is not generated by the complex time- and voltage-varying membrane kinetics. AP symmetry would cause the biphasic UEG QRS complex due to uniform propagation to have identical but opposite positive and negative components. Experimental measurements, however, demonstrate that the UEG QRS complex is not symmetric.\textsuperscript{1} Symmetric AP depolarization and repolarization would also cause $\Delta AT_{\text{org}}$ and $\Delta RT_{\text{org}}$ to occur at a time when the biphasic UEG QRS complex and biphasic UEG T wave were at a potential of zero. Rarely did the fiducial times occur at the time of the zero crossing of the simulated extracellular potentials. In contrast, AP asymmetry causes asymmetric positive and negative isopotential lines as well as the zero potential line to deviate from normal as the distance from the cable surface increases.\textsuperscript{5}

Nonuniform propagation and the asymmetry in AP depolarization and AP repolarization shape are conditions normally found in the heart and cause the time of UEG extremes to not exactly correspond to the time of $V_m$ extremes. The simulation results showed that $\Delta RT_{\text{org}}$ and $\Delta AT_{\text{org}}$ increased during 1) nonuniform activation sequence (e.g., sites of propagation initiation or termination), 2) changes in the shape of AP depolarization and AP repolarization, 3) propagation through regions of nonuniform distributions of $R_i$ and/or membrane properties, and 4) conditions in which distant events greatly contributed to the waveforms. During these conditions, the UEG waveform was not able to accurately define the $V_m$ activity of the underlying site. $\Delta RT_{\text{org}}$ was more affected by these nonideal conditions than $\Delta AT_{\text{org}}$. $\Delta AT_{\text{org}}$ and $\Delta RT_{\text{org}}$ were altered at sites of changes in $R_i$, which could explain why detailed extracellular mapping studies\textsuperscript{6} have been unable to verify the proposed delay in conduction at the intercalated disc structure.\textsuperscript{29}

The shape of the AP is a determinant of $\Delta AT_{\text{org}}$ and $\Delta RT_{\text{org}}$. In a uniform cable, the extremes of $\Delta RT_{\text{org}}$ occur at the cable ends. A constraint for the range in $\Delta RT_{\text{org}}$ measured at the two cable ends can be estimated as the difference between the time of the minimum and the time of the maximum $V_m$ during AP depolarization and AP repolarization for $\Delta AT_{\text{org}}$ and $\Delta RT_{\text{org}}$, respectively. $\Delta RT_{\text{org}}$ was more affected by nonideal conditions in simulations using the MNT model than in simulations using the BR model. This can be attributed to the different AP configuration between the two models. The MNT model AP with reduced sodium current is more triangular while the BR model AP is more rectangular. Rectangular-shaped APs generate larger magnitude net membrane currents during repolarization and T waves than triangular-shaped APs. Thus, $\Delta RT_{\text{org}}$ from ischemic or rapidly paced tissue with triangular-shaped APs would be more affected by nonideal conditions than normal tissue.

Automated computer routines easily detect $AT_{\text{org}}$ in most UEGs from normal myocardium due to the rapidly changing derivative during the QRS complex. In contrast, automatic detection of $RT_{\text{org}}$ is more difficult because of the slowly varying T wave. Temporal smoothing filters are often applied to the T wave to reduce high-frequency variations and noise, which can create problems during derivative measurements. Even so, the automatically determined $RT_{\text{org}}$ times are often manually corrected during an edit phase because the recovery time was not chosen at some physiologically likely time. This ambiguity could be because the T wave does not always directly relate to the $V_m$ activity below the measuring site (Figure 2). Nonzero time-varying UEG reference potentials, average reference potentials, and distant events all
influence AT\textsubscript{eqg} and RT\textsubscript{eqg}. The average reference technique has been used to highlight local UEG activity,\textsuperscript{16} but the technique is limited because the UEG is affected by both the specific measuring-grid geometry and by the activation sequence sampled at the other sites. The influence of the nonzero reference or distant signal on AT\textsubscript{eqg} and RT\textsubscript{eqg} depends on the magnitude and timing of the maximum and minimum derivative of the signal during activation and recovery. In general, this influence is minimal, but distant events could significantly affect AT\textsubscript{eqg} and RT\textsubscript{eqg} during conditions such as ischemia in which the local signal is attenuated by either a smaller V\textsubscript{m} (i.e., a triangular-shaped AP) and/or reduced active current-generating surface area.

ATs and RTs from BEGs were better estimates than those from UEGs during conditions with marked contribution from distant events. In other conditions where I\textsubscript{m} was not proportional to V\textsubscript{m} (e.g., at sites of propagation initiation and termination), estimates of activation and recovery from UEGs and BEGs were comparable. Practically, the applicability of bipolar recordings for epicardial RT estimates is limited because the BEG T wave amplitude is dependent on the orientation of the electrode pair with respect to the direction of the wavefront. For AT estimates, especially during mapping studies of reentrant paths, distant events are likely to be a major contribution because of the slow AP depolarization, nonuniform activation sequence, and salutary propagation through areas of nonuniform Ri and membrane properties. These conditions suggest the use of bipolar electrodes for AT estimates.

This study did not investigate the influence of the following conditions: nonuniform distribution of rest potentials, extremely nonuniform propagation patterns such as reentry or fibrillation in which areas of activation and recovery coexist, AC-measured electrograms or electrograms that were filtered with a finite bandwidth, addition of noise, multidimensional propagation, anisotropic propagation with a curved activation wavefront, nonuniform volume conductor, or nonuniform extracellular resistance. These conditions would more closely model certain experimental situations, but it can be predicted that all these conditions would generally cause I\textsubscript{m} to deviate from the idealized V\textsubscript{m} shape and would increase \( \Delta I_{\text{eqg}} \) and \( \Delta R_{\text{eqg}} \). It can also be predicted that simulations that use membrane models other than the BR and MNT models would show qualitatively similar findings to those presented here.

One limitation of the model is that extracellular resistance was set to zero during the simulated AP propagation. The numerical results were then used to generate extracellular potentials using a nonzero extracellular resistance. The method is similar to previously published studies\textsuperscript{30} and assumes that the magnitude of the extracellular resistance has a negligible effect on propagation when compared with the effect of the cellular coupling resistance. This assumption is valid for a large volume of conducting fluid surrounding the cable. In the case of an epicardial surface exposed to the air, epicardial potentials can be as large as 50 mV across the activation wavefront and, hence, intracellular potential would not equal transmembrane potential. Extracellular potentials in the depth of the transmural wall are of a magnitude that would also affect these results.\textsuperscript{31} One of the conclusions of this study is that AT and RT estimates from extracellular potentials are in error when local I\textsubscript{m} is not proportional to V\textsubscript{m} and also when distant events significantly contribute to the electrogram. It is doubtful that these findings would change with the addition of uniform nonzero extracellular resistance during AP propagation. A nonuniform distribution of extracellular resistance, however, could be expected to independently cause marked changes in \( \Delta AT_{\text{eqg}} \) and \( \Delta RT_{\text{eqg}} \).

Other studies have investigated the method of estimating transmembrane activation and/or recovery times from electrogram waveforms. Spach and Kootsey\textsuperscript{5} and Spach and Dolber\textsuperscript{6} studied the time alignment of AT\textsubscript{eqg} and AT\textsubscript{p}. Using waveforms recorded at the beginning, middle, and end of a simulated one-dimensional cable, they concluded that AT\textsubscript{eqg} corresponds to the time of Vmax for all shapes of UEG. This correspondence at these three sites was confirmed in the present study. The observations were extended in the present study by mapping differences throughout the cable and showed that AT\textsubscript{eqg} did not accurately correspond to the time of Vmax at sites a short distance from either cable end, even under uniform membrane properties and uniform Ri. In addition, \( \Delta AT_{\text{eqg}} \) was as large as 1.8 msec in simulations of nonuniform cables. Recent experimental studies showed that the amplitude and slope of right ventricular UEG waveforms were significantly influenced by distant left ventricular electrical activity. The distant events, however, had minimal effect on right ventricular AT\textsubscript{eqg} and ARI.\textsuperscript{34} Although the simulations presented here were not models of three-dimensional left and right ventricular activity, the effect of distant events on AT\textsubscript{eqg} and RT\textsubscript{eqg} was also determined to be minimal when the distant events did not have large derivatives. Recent experiments support the temporal relation of the time of the peak BEG and AT\textsubscript{eqg}.\textsuperscript{35} Millar et al\textsuperscript{3} showed that the ARI from unipolar electrograms was well correlated with ventricular refractory periods during adrenergic stimulation and changes in pacing rate. The relationship between the ARI and APD has also been experimentally studied during coronary occlusion.\textsuperscript{2,36} Quantitative comparison of the present study to these previous studies is difficult because the previous studies selected recovery time as either the inflection point during the T wave; the upslope of the second T wave peak, if present; or a point beyond which the T wave derivative became negative. These different selection criteria were not investigated in the present study. In addition, the previous studies correlated sequentially sampled data across
interventions that resulted in a wide range of APD whereas the present work mapped spatial differences throughout the cable and at a fixed pacing rate. In the present study, changes in local activation sequence and propagation through zones of nonuniform cellular coupling resistance and/or membrane properties had the most influence on the activation and recovery time estimates from the electrograms. Experimental studies to date have not investigated these influences.

The method of choosing AT\textsubscript{ug} and RT\textsubscript{ug} neglects all of the waveform shape except the times of the extreme derivatives. The UEG waveform has a rich information content, and ideally the whole waveform will be used to accurately determine transmembrane activity. In one approach, selected one-dimensional propagation parameters have been successfully estimated in simulation studies using the UEGs at a few sites.\textsuperscript{37} Another approach has used the extracellular potentials at many sites as the input for the inverse problem calculation of transmembrane potential.\textsuperscript{38} This method results in an estimate of the shape in AP repolarization and could be used to determine activation time, recovery time, and APD at any arbitrary but fixed Vm.

The present study resulted in a number of conclusions: 1) For a biphasic UEG QRS complex, the time of minimum UEG accurately defines activation time as the time of Vmax during depolarization. For a trispecific BQS complex, the time of maximum absolute BQS accurately defines activation time as the time of Vmax during depolarization. 2) Likewise, for a biphasic UEG T wave, the time of maximum UEG accurately defines recovery time as the time of Vmin during repolarization. For a trispecific BQS T wave, the time of maximum absolute BQS accurately defines recovery time as the time of Vmin during repolarization. 3) For biphasic UEG and trispecific BQS waveforms, spatial distributions and spatial differences in electrogram AT, RT, and/or ARI can be assumed to accurately define the spatial characteristics of activation, recovery, and/or duration. 4) The time of the maximum absolute UEG during the monophasic T wave accurately defines recovery time at the stimulus site and at the propagation termination site for a long uniform cable. This rule is accurate only for these two sites and only for recovery time determination from UEGs. 5) Nonideal conditions are characterized by nonbiphasic UEG or nontrispecific BQS waveforms. The nonideal conditions that produce the largest differences between the times measured from UEGs and those measured from the APs cause I\textsubscript{Na} to deviate from being proportional to Vm and include changes in activation sequence, changes in AP shape, propagation in a short cable, and propagation through regions of nonuniform membrane properties and/or nonuniform structural properties. Nonideal conditions that produce smaller differences between the times measured from UEGs and those measured from the APs alter the shape of the UEG but do not significantly affect the local I\textsubscript{Na} and include variations in the distance from the measuring sites to the simulated tissue surface, distant electrical events, asymmetric shape of AP depolarization and repolarization, and nonzero reference potentials. 6) For nonbiphasic UEG or nontrispecific BQS waveforms, spatial distributions and/or spatial differences in the activation and recovery times measured from electrograms can be inaccurate estimates of spatial distributions and/or spatial differences in transmembrane AP activation and recovery times. In these situations, the times estimated from the electrograms could be influenced by conditions independent of changes in the local APs.

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**Key Words** • activation time • activation-recovery interval • recovery time • unipolar electrogram • bipolar electrogram • intrinsic deflection • computer simulations
Estimating cardiac transmembrane activation and recovery times from unipolar and bipolar extracellular electrograms: a simulation study.

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