Simulating T-wave parameters of local extracellular electrograms with a whole-heart bidomain reaction-diffusion model: Size matters!

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Abstract—As a measure of local repolarization time (\(T_R\)), the instant of maximum slope (\(T_{\text{up}}\)) of the T wave in the local unipolar electrogram is commonly used. Measurement of \(T_{\text{up}}\) can be difficult, especially in positive T waves. These difficulties have led some researchers to propose the instant of maximum downslope (\(T_{\text{down}}\)) as a marker of \(T_R\) when the T wave is positive. To improve understanding of T-wave parameters, we simulated electrograms with a bidomain model of the human heart. To test T-wave parameters, we compared them to \(T_R\) determined from the local membrane potential. We propose a simple model of the electrogram, which we validated by comparison to the bidomain model. With the simple model, it is straightforward to show that the sign of the T wave is almost uniquely determined by \(T_R\). We then used the bidomain model to simulate the effects of a variety of pathologies and technical difficulties, which the simple model could not account for. Generally, \(T_{\text{up}}\) was a much better estimate for \(T_R\) than \(T_{\text{down}}\). Regional fibrosis could attenuate local electrogram components and reduce accuracy of \(T_{\text{up}}\) as a marker for \(T_R\). In fibrotic tissue, \(T_{\text{down}}\) was not related to \(T_R\) at all. This investigation of electrogram slopes required the simulation of extracellular potentials with about 100 times more precision than needed for simulation of visually acceptable waveforms alone. This requirement is more difficult to meet in larger models, but it was actually possible for a human-heart model with 60 million nodes. By sacrificing some spatial resolution, we kept the computational requirements within acceptable limits for multiple simulations.

I. INTRODUCTION

It is difficult if not impossible to measure transmembrane potentials (\(V_m\)) at many sites simultaneously in a beating heart. Extracellular electrograms are a convenient alternative. Local activation times are easily determined using the instant of steepest downstroke in a (unipolar) electrogram. The action potential duration (APD) is more difficult to measure. Wyatt et al. proposed the activation-recovery interval (ARI) as a substitute [1]. The ARI was measured from the instant of steepest downstroke to the instant of steepest upstroke (\(T_{\text{up}}\)) of the T wave in the unipolar electrogram. Experimental and theoretical studies confirmed the validity of this method [2], [3], [4], [5].

Several authors have proposed that an exception should be made for positive T waves, using the instant of steepest downstroke (\(T_{\text{down}}\)) of the T wave in the unipolar electrogram instead of \(T_{\text{up}}\) [6], [7]. In contrast to the original ARI method, the method based on \(T_{\text{down}}\) lacks a theoretical foundation. Yue et al. suggested that the derivation of the original method, being based on one-dimensional (1-D) considerations, would be invalid in the 3-D heart [7].

In this study, we first show that the T wave can be understood as a weighted sum of the local \(V_m\) and a remote component. It follows that local repolarization always causes a rise in the local electrogram. We define repolarization time (\(T_R\)) as the instant of steepest downstroke of \(V_m\). In the absence of remote activity, \(T_{\text{up}}\) equals \(T_R\). In order to estimate how much distortion can be expected due to remote activity, we compared \(T_R\) computed from \(V_m\) to \(T_{\text{up}}\) computed from electrograms simulated with a 3-D model of the human heart. Simulations were performed with regions of abnormally long and short APD, and with a representation of fibrotic tissue.

II. METHODS

Propagating \(V_m\) were simulated with a monodomain reaction-diffusion model of the human heart [8]. This model has anisotropic myocardium and includes five different types of myocytes (Tab. I). In order to mimic sinus rhythm we stimulated the ventricles at the early activation sites published by Durrer et al. [9]. Ionic currents were computed with the 2004 version of the TNNP model for the human ventricular myocyte [10]. Some parameters of the ionic model were changed, and differences between the left ventricle (LV) and right ventricle (RV) were implemented as outlined in Tab. I. Modifications were made according to published data (on canine hearts) [11], [12]. The types XL and XS were used to implement abnormally long and short APD in some experiments.

Two different models were used for the computation of extracellular potentials (\(\phi_e\)): a “realistic model” and a “simple model.”

a) realistic model: For maximal realism, \(\phi_e\) was computed from \(V_m\) throughout the heart by solving

\[
\nabla \cdot (G_1 + G_e) \nabla \phi_e = -\nabla \cdot (G_1 \nabla V_m)
\]

where \(G_1\) and \(G_e\) are the intracellular and extracellular conductivity tensor fields, respectively [8]. In our previous work we have done this at a spatial resolution of 0.2 mm and with error tolerance levels for \(\phi_e\) that were just small enough to produce correct electrograms. However, the temporal derivatives of the signals so computed contain too much distortion for the current study. Therefore the tolerance levels were set a factor 100 lower (see our previous work for the definition of the two tolerance levels involved [8]). At a
spatial resolution of 0.2 mm this led to one week computation
time on 32 processors, which is too much for repeated
simulations. Therefore we chose a lower spatial resolution
of 0.25 mm for computation of both \( V_m \) and \( \phi_e \). This leads
to somewhat slower propagation, for which we corrected
by choosing 10–15\% higher tissue conductivity
values that were adapted according to the modified cross-
sectional surfaces of the two domains. The intracellular
conductivity \( \sigma_i \) represented in the model by effective tissue conductivity
values that were adapted according to the modified cross-
sectional surfaces of the two domains. The intracellular
cells elsewhere in the heart. Conversely, the electrogram will
be positive when local \( V_m \) is lower than \( V_{avg} \). Temporal derivatives are also shown. The derivative of \( V_{avg} \) reaches a lower value than the derivative of \( V_{avg} \), so it dominates \( T_{up} \) of the local electrogram. However, the derivative of \( V_{avg} \) is not negligible and may influence \( T_{up} \).
In panel B, electrograms are compared that were computed
with the “simple” and “realistic” models. These simulated
electrograms were highly similar. In particular, both models
agreed on the sign of the T wave in 92\% of the analyzed
positions (panel C).

These comparisons show that the T wave is essentially
determined by the local \( V_m \) and by \( V_{avg} \). The electrogram
is positive when the local \( V_m \) is lower than \( V_{avg} \). This happens in particular for early-repolarizing cells. The
electrogram remains positive as long as there are depolarized
cells elsewhere in the heart. Conversely, the electrogram will
be negative when local \( V_m \) is still depolarized while \( V_m \) elsewhere is repolarized.

Fig. 2 shows electrograms according to the simple model
and the realistic model at a position where a thin strand
of myocardium is surrounded by intracavitary blood and
connective tissue. Here, the realistic model predicts a low-
amplitude electrogram with a short downstroke and a T wave
that is dominated by the remote component. The simple
model does not account for the small muscle mass in a large

### III. Results

A. Validation of the simple model

Fig. 1, panel A, shows \( V_m \), \( V_{avg} \), and the electrogram
according to the “simple model” for one site in the heart.

The reference potential for electrograms was taken from
the roof of the right atrium. Simulations were performed with
a normal-heart model and models containing a modified zone
of 10 mm radius (3 cm\(^3\) volume, 1.2\% of the myocardium)
located in the LV free wall. This zone had either abnormally
short or abnormally long APD, with either normal or fibrotic
tissue. Diffuse fibrosis was represented macroscopically by
a reduction of the intracellular volume fraction from its
assumed normal value of 0.7 to 0.1. This change was
represented in the model by effective tissue conductivity
values that were adapted according to the modified cross-
sectional surfaces of the two domains. The intracellular \( \sigma \)
were multiplied by \((0.1/0.7)^{2/3}\), and the extracellular \( \sigma \)
by \((0.9/0.3)^{2/3}\). The resulting values were \( \sigma_{IT} = 0.250 \),
\( \sigma_{IL} = 0.624 \), \( \sigma_{IT} = 0.0082 \) and \( \sigma_{IL} = 0.082 \text{Sm}^{-1} \).

**TABLE I**

Selected parameters and intrinsic characteristics of the ionic model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LV epi</th>
<th>LV M</th>
<th>(LV&amp;RV) endo</th>
<th>RV M</th>
<th>RV epi</th>
<th>XS</th>
<th>XL</th>
</tr>
</thead>
<tbody>
<tr>
<td>( G_{Ke} ) (nS/pF)</td>
<td>0.294</td>
<td>0.294</td>
<td>0.073</td>
<td><strong>0.504</strong></td>
<td>0.882</td>
<td>0.294</td>
<td>0.073</td>
</tr>
<tr>
<td>( G_{Ke} ) (nS/pF)</td>
<td>0.245</td>
<td>0.062</td>
<td>0.245</td>
<td><strong>0.112</strong></td>
<td>0.490</td>
<td>0.735</td>
<td><strong>0.010</strong></td>
</tr>
<tr>
<td>( G_{Kr} ) (nS/pF)</td>
<td>0.096</td>
<td>0.096</td>
<td>0.096</td>
<td>0.096</td>
<td>0.096</td>
<td>0.096</td>
<td><strong>0.020</strong></td>
</tr>
<tr>
<td>APD (ms)</td>
<td>272</td>
<td>324</td>
<td>275</td>
<td>303</td>
<td>244</td>
<td>218</td>
<td>443</td>
</tr>
<tr>
<td>APD20 (ms)</td>
<td>171</td>
<td>201</td>
<td>150</td>
<td>205</td>
<td>183</td>
<td>126</td>
<td>207</td>
</tr>
<tr>
<td>APD50 (ms)</td>
<td>250</td>
<td>300</td>
<td>251</td>
<td>282</td>
<td>227</td>
<td>197</td>
<td>402</td>
</tr>
<tr>
<td>APD70 (ms)</td>
<td>267</td>
<td>319</td>
<td>270</td>
<td>299</td>
<td>241</td>
<td>213</td>
<td>435</td>
</tr>
<tr>
<td>APD90 (ms)</td>
<td>278</td>
<td>330</td>
<td>281</td>
<td>309</td>
<td>251</td>
<td>225</td>
<td>449</td>
</tr>
<tr>
<td>DR</td>
<td>82 %</td>
<td>82 %</td>
<td>82 %</td>
<td>81 %</td>
<td>80 %</td>
<td>81 %</td>
<td>83 %</td>
</tr>
</tbody>
</table>

Parameter values that are different from the original **TNNP** model [10] are printed in bold type. \( APD_x \) = action potential duration at \( x \) percent repolarization (1000 ms cycle length). \( DR \) = degree of repolarization at the end of the action potential (defined as the instant of steepest downslope). Units are nS = nanoSiemens, pF = picoFarad, ms = millisecond.
extracellular space, and predicts a normal high-amplitude
electrogram. According to the realistic model, the difference
between $T_{\text{up}}$ and $T_R$ would be 33 ms, while the simple
model predicts no error. A typical example of simulated
electrograms in a fibrotic region is shown in Fig. 3. Here too
the two models predict different R waves and downstrokes,
but they agree on T-wave upstroke timing.

B. T-wave sign in the normal heart

The following results were obtained with the “realistic
model.” In the normal heart, positive T waves were found
in 54% of the analyzed positions, and were associated with
a 36 ms earlier $T_R$ than negative T waves. In Fig. 4, $T_R$
distribution is shown separately for positive and negative
T waves. Most positive T waves were associated with $T_R$
that were lower than those of negative T waves, but some
overlap between the two distributions was present.

C. Repolarization statistics

Figure 5 shows a sample of electrograms taken from
various sites in the heart, selected to show the variation
in T-wave shape from entirely negative through biphasic to
positive. Local repolarization times ($T_R$) are indicated with
dots in the electrograms. These are invariably located on the
upslope of the T wave.

Tab. II shows paired comparisons of repolarization charac-
teristics, for both positive and negative T waves. Differences
were computed for individual positions, then the average
and standard deviation of the difference were computed. For
positive T waves, $T_{\text{up}}$ underestimated $T_R$ by $0.1 \pm 2.2$ ms
and $T_{\text{down}}$ overestimated $T_R$ by $29.3 \pm 7.8$ ms.

The relation between $T_R$ and electrogram-based measures
was also assessed by correlation analysis and by a linear fit.
For negative T-wave morphologies, $T_{\text{up}}$ correlated very well
with $T_R$ ($r = 0.996$). The slope of the regression line was
1.012. For positive T waves the correlation was 0.988, and
slope 0.986. The residual error of the linear fit was 2 ms for both positive and negative T waves. Correlation between $T_{\text{down}}$ and $T_R$ was 0.853, and associated with a slope of only 0.625, with a residual error of 6 ms.

A simulation was performed with a small area in which cells had a very short APD (type XS in Tab. I). Statistics were compared with those of the normal heart. While differences in $T_{\text{up}}$ ($\Delta T_{\text{up}}$) correlated well ($r = 0.989$) with differences in $T_R$ ($\Delta T_R$), the differences in $T_{\text{down}}$ ($\Delta T_{\text{down}}$) were more weakly related ($r = 0.802$).

In fibrotic tissue with short APD, $T_{\text{up}}$ became biased by $-3$ ms and was associated with a 9 ms s.d. error (Tab. II). Correlation between $T_{\text{up}}$ and $T_R$ was 0.85. $T_{\text{down}}$ completely lost its relation to $T_R$ and became nearly uniform throughout the fibrotic area ($r = 0.21$, slope 0.052).

IV. DISCUSSION

The recent controversy on repolarization measurement in the unipolar electrogram (UEG) demonstrates that T-wave polarity in the UEG is badly understood. We have shown that at least for T waves in healthy tissue the UEG can be understood as a scaled difference between the local $V_m$ and the average $V_m$ in the heart. With this simple model, T-wave polarity is easy to understand. The UEG is positive when the local $V_m$ is more negative than the average, and negative when the local $V_m$ is more positive. The most early-repolarizing sites are therefore characterized by positive T waves. Later sites have an initially negative T wave, due to the decrease of the average potential caused by the earlier sites. When they repolarize, their $V_m$ quickly becomes more negative than the average, causing a rapid change in their UEG from negative to positive. Only the latest repolarizing sites have entirely negative T waves.

Our simulations confirm that $T_{\text{up}}$ is a good estimate for $T_R$. We have tested its validity in a variety of difficult conditions. Strong local dispersion of APD could reduce the accuracy of $T_{\text{up}}$ as a measure of $T_R$. However, its accuracy was always better than that of $T_{\text{down}}$.

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REFERENCES