Proceedings of the 29th Annual International
Conference of the IEEE EMBS
Cité Internationale, Lyon, France
August 23-26, 2007.

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

Mark Potse,[1,2] Ruben Coronel,[3] Tobias Opthof,[3,4] and Alain Vinet[1,2]

Abstract— **As a measure of local repolarization time (T_{R}), the instant of maximum slope (T_{up}) of the T wave in the local unipolar electrogram is commonly used. Measurement of T_{up} can be difficult, especially in positive T waves. These difficulties have led some researchers to propose the instant of maximum downslope (T_{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_{up} was a much better estimate for T_{R} than T_{down}. Regional fibrosis could attenuate local electrogram components and reduce accuracy of T_{up} as a marker for T_{R}. In fibrotic tissue, T_{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_{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_{down}) of the T wave in the unipolar electrogram instead of T_{up} [6], [7]. In contrast to the original ARI method, the method based on T_{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_{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_{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 (ϕ_{e}): a "realistic model" and a "simple model."

a) realistic model: For maximal realism, ϕ_{e} was computed from V_{m} throughout the heart by solving

$$\nabla \cdot ((G_{\mathrm{i}} + G_{\mathrm{e}}) \nabla \phi_{\mathrm{e}}) = -\nabla \cdot (G_{\mathrm{i}} \nabla V_{\mathrm{m}}) \qquad (1)$$

where G_{i} 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 ϕ_{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

From the [1]Research Center, Hôpital du Sacré-Cœur de Montréal, 5400 Boulevard Gouin Ouest, Montréal (Québec) H4J 1C5, Canada; [2]Institute of Biomedical Engineering, Université de Montréal, PO Box 6128, station Centre-ville, Montréal (Québec) H3C 3J7, Canada; [3]Laboratory of Experimental Cardiology, Center for Heart Failure Research, Academic Medical Center, Amsterdam, The Netherlands; and [4]Department of Medical Physiology, University Medical Center, Utrecht, The Netherlands.

TABLE I

SELECTED PARAMETERS AND INTRINSIC CHARACTERISTICS OF THE IONIC MODEL.

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

Parameter values that are different from the original TNNP model [10] are printed in bold type. APDx = action potential duration at x percent repolarization (1000 ms cycle length). DR = the 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.

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 ϕ_{e}. This leads to somewhat slower propagation, for which we corrected by choosing 10–15 % higher tissue conductivity values for the intracellular domain. Nominal conductivities were taken from Roth [13]. The adapted values were $\sigma_{\mathrm{eT}} = 0.12$, $\sigma_{\mathrm{eL}} = 0.3$, $\sigma_{\mathrm{iT}} = 0.035$ and $\sigma_{\mathrm{iL}} = 0.33$ Sm^{-1}, with subscript 'e' for extracellular, 'i' for intracellular, 'T' for transverse, and 'L' for longitudinal.

b) simple model: If it is assumed that the heart and intracavitary blood are uniformly isotropic and that the reference point is equally well connected with any position in the ventricles, then the unipolar electrogram at a point x is simply a scaled mirror image of the difference between the local V_{m} and the average V_{m} in the ventricular myocardium (V_{avg}):

$$\phi_{\mathrm{e,simple}}(x) = -\frac{\sigma_{\mathrm{i}}}{\sigma_{\mathrm{i}} + \sigma_{\mathrm{e}}} \left(V_{\mathrm{m}}(x) - V_{\mathrm{avg}}\right) \qquad (2)$$

where σ_{e} and σ_{i} represent the conductivities of the extracellular and intracellular domains, respectively. The "simple model" uses this formula, evaluating V_{avg} at 2-mm resolution in the ventricles. For the fraction $\sigma_{\mathrm{i}}/(\sigma_{\mathrm{i}}+\sigma_{\mathrm{e}})$ the value 0.25 was chosen.

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 σ were multiplied by $(0.1/0.7)^{2/3}$, and the extracellular σ by $(0.9/0.3)^{2/3}$. The resulting values were $\sigma_{\mathrm{eT}} = 0.250$, $\sigma_{\mathrm{eL}} = 0.624$, $\sigma_{\mathrm{iT}} = 0.0082$ and $\sigma_{\mathrm{iL}} = 0.082\,\mathrm{Sm}^{-1}$.

T waves could be positive, negative, biphasic, or multiphasic. To allow a division into positive and negative T waves, we used the integral of the electrogram from 100 ms after local depolarization to the end of the simulation. A T wave was defined as positive when the integral was positive. Repolarization time (T_{R}) was defined as the instant of steepest downstroke of V_{m}. T_{R} and T_{up} were evaluated in the interval from 100 ms after local depolarization to the end of the simulation. For positive T waves, T_{down} was evaluated in the interval from T_{up} to the end of the simulation. For negative T waves, T_{down} was not defined. Analysis was fully automatic.

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. Temporal derivatives are also shown. The derivative of V_{m} 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

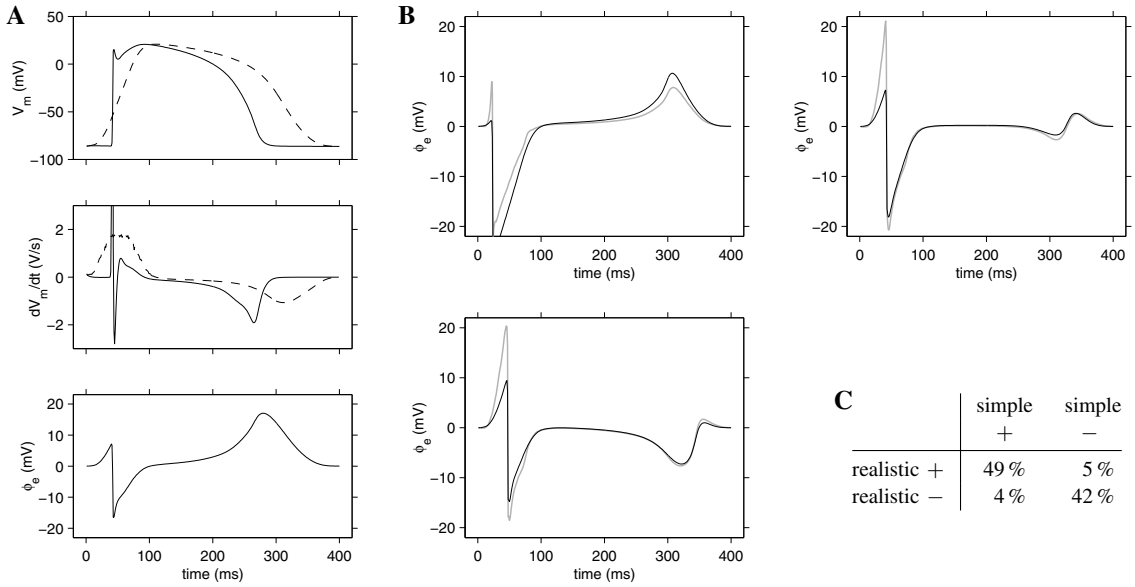

Fig. 1. Comparison between the simple and realistic models of the unipolar electrogram. **Panel A** shows how an electrogram is reconstructed according to the "simple model." The top panel shows V_{avg} (dashed line) and local V_{m} (drawn line). The middle panel shows their temporal derivatives (dashed for dV_{avg}/dt). The lower panel shows the reconstructed electrogram. In **panel B**, electrograms according to the simple model (black lines) are compared to the realistic model (gray lines). In **panel C**, T-wave sign according to the two models is compared for a sample of 1000 positions.

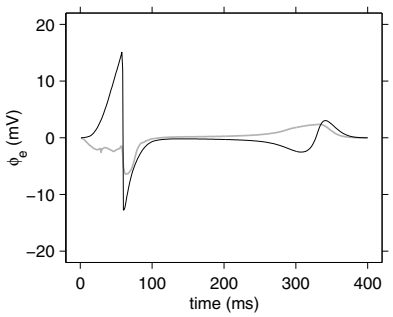

Fig. 2. Electrograms according to the simple (black) and realistic model (gray) at a position where a thin strand of myocardium is surrounded by intracavitary blood and connective tissue.

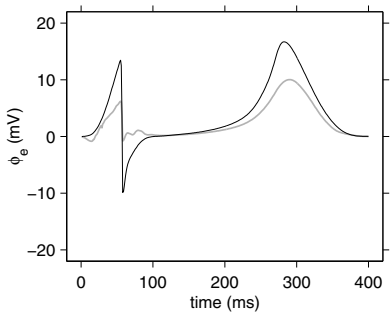

Fig. 3. Electrograms according to the simple model (black line) and the realistic model (gray line) in fibrotic tissue.

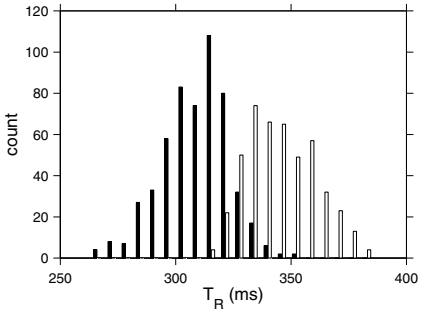

Fig. 4. Distribution of T_{R} for positive T waves (black bars) and for negative T waves (white bars).

extracellular space, and predicts a normal high-amplitude electrogram. According to the realistic model, the difference between T_{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 characteristics, 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_{up} underestimated T_{R} by 0.1 ± 2.2 ms and T_{down} overestimated T_{R} by 29.3 ± 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_{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

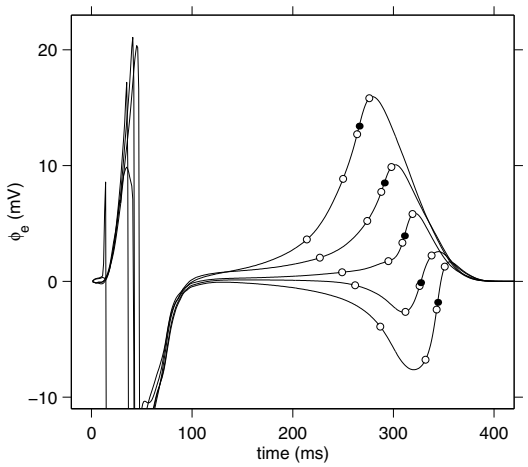

Fig. 5. Simulated electrograms from various sites in the heart. Local T_{R} are indicated with dots. The instants of 20, 50, 70, and 90 % repolarization are indicated with open circles.

TABLE II
COMPARISON OF REPOLARIZATION MEASURES (MS).

	positive T	negative T
whole ventricles:		
$T_{\mathrm{up}}-T_{\mathrm{R}}$	-0.1 ± 2.2	0.7 ± 1.7
$T_{\mathrm{down}}-T_{\mathrm{R}}$	29.3 ± 7.8	undefined
fibrotic sites:		
$T_{\mathrm{up}}-T_{\mathrm{R}}$	-2.9 ± 9.4	none
$T_{\mathrm{down}}-T_{\mathrm{R}}$	54.3 ± 16.5	undefined

slope 0.986. The residual error of the linear fit was 2 ms for both positive and negative T waves. Correlation between T_{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_{up} (ΔT_{up}) correlated well ($r = 0.989$) with differences in T_{R} (ΔT_{R}), the differences in T_{down} (ΔT_{down}) were more weakly related ($r = 0.802$).

In fibrotic tissue with short APD, T_{up} became biased by -3 ms and was associated with a 9 ms s.d. error (Tab. II). Correlation between T_{up} and T_{R} was 0.85. T_{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_{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_{up} as a measure of T_{R}. However, its accuracy was always better than that of T_{down}.

ACKNOWLEDGMENT

Computational resources were provided by the Réseau québécois de calcul de haute performance (RQCHP). M. Potse was supported by the Groupe de recherche en sciences et technologie biomédicale (GRSTB), École Polytechnique and Université de Montréal; and by the Research Center of Sacré-Coeur Hospital, Montréal, Québec, Canada.

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