Monophasic action potentials generated by bidomain modeling as a tool for detecting cardiac repolarization times

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Monophasic action potentials generated by bidomain modeling as a tool for detecting cardiac repolarization times. Am J Physiol Heart Circ Physiol 293: H2771–H2785, 2007. First published August 17, 2007; doi:10.1152/ajpheart.00651.2007.—Unipolar electrograms (EGs) and hybrid (or unorthodox or unipolar) monophasic action potentials (HMAPs) are currently the only proposed extracellular electrical recording techniques for obtaining cardiac recovery maps with high spatial resolution in exposed and isolated hearts. Estimates of the repolarization times from the HMAP downstroke phase have been the subject of recent controversies. The goal of this paper is to computationally address the controversies concerning the HMAP information content, in particular the reliability of estimating the repolarization time from the HMAP downstroke phase. Three-dimensional numerical simulations were performed by using the anisotropic bidomain model with a region of short action potential durations. EGs, transmembrane action potentials (TAPs), and HMAPs elicited by an epicardial stimulation close or away from a permanently depolarized site were computed. The repolarization time was computed as the moment of EG fastest upstroke (RTeg) during the T wave, of HMAP fastest downstroke (RTHMAP), and of TAP fastest downstroke (RTtap). The latter was taken as the gold standard for repolarization time. We also compared the times (RT90HMAP, RT90tap) when the HMAP and TAP first reach 90% of their resting value during the downstroke. For all explored sites, the HMAP downstroke closely followed the TAP downstroke, which is the expression of local repolarization activity. Results show that HMAP and TAP markers are highly correlated, and both markers RTHMAP and RTeg (RT90HMAP) are reliable estimates of the TAP reference marker RTtap (RT90tap). Therefore, the downstroke phase of the HMAP contains valuable information for assessing repolarization times.

unipolar electrograms; monophasic action potential; bidomain model; heterogeneity; action potential duration

LIFE-THREATENING CARDIAC ARRHYTHMIAS and a high risk of reentrant arrhythmias are often associated with abnormal distributions of recovery times, high spatial gradients of recovery times, and high spatial gradients of action potential durations (APD) (see Refs. 27, 62). Cardiac repolarization is not a local phenomenon because it exhibits a spatial scale of the order of a few centimeters and a temporal scale of several tens of milliseconds, unlike the cardiac excitation layer, which exhibits a scale of the order of 1–2 mm and a fast upstroke of a few milliseconds. Hence, what is generally called recovery time is only a partial aspect of the repolarization phase. Among the most used recovery time markers are the time of minimum downslope of the transmembrane action potential (TAP), the time when the TAP reaches a given percentage (usually 90% or 60%) of its resting value during the downstroke phase, and the time given by the intersection between the baseline and the TAP tangent at the minimum downslope (58, 59). These recovery time markers from the TAP waveforms are obtainable only with microelectrodes, which limit their application to only a few sites, in both in vitro and in vivo experiments. These limitations can be overcome by employing simultaneous extracellular recordings in both in vivo or intact heart experiments. It is then important to have a reliable method for estimating activation and recovery times and spatial distributions of APD from extracellular recordings. These, and optical mapping, remain the only available procedures for mapping repolarization sequences, which require multiple recording sites in both clinical and experimental settings.

Although methods for determining activation times from electrographic signals recorded directly from the heart have been firmly established (see Ref. 40 and the references therein), there are still uncertainties and controversies about the best method for determining recovery times. A commonly and well-established extracellular recording technique to infer the monophasic features of the TAP is the close-bipolar monophasic action potential (MAP) [see Franz (16, 17)]. Franz’s method yields a graph that is an expression of the potential differences between two extracellular sites: a site depolarized by contact pressure and a proximal site without myocardial contact that captures an intracavitary potential. The close proximity between the two recording sites leads to the cancellation of far-field effects (see Refs. 16–18, 28, 51 for a complete treatment). The more recent technique proposed by Antzelevitch and colleagues (29, 34, 55) measures potential differences between a depolarized site and any other extracellular site, located anywhere in the heart; i.e., it uses as a reference potential the extracellular potential recorded from a permanently depolarized (PD) site, obtained by contact pressure or a KCl injection in a small epicardial region. The method involves the use of bipolar leads that are sensitive to activity occurring in the entire heart and has been criticized in the literature [e.g., Franz (18)]. Although the close bipolar MAP of Franz is free from far-field effects, it can collect only a relatively small number of MAPs in a given patient or experiment. On the other hand, the more recent technique of Antzelevitch and colleagues, here called hybrid [or “unorthodox” or “unipolar” as in Franz (17)] monophasic action potential (HMAP), is contaminated by far-field effects. However, because it uses only one fixed PD site, it enables us to record hundreds of signals simultaneously from an epicardial electrode array and also from intramural needles.

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The repolarization time can be estimated by using some time indexes associated with the downstroke of the TAP or MAP (16, 17). A widely used marker is the instant of minimum time derivative of the TAP during the downstroke phase (RT\text{Tap}) (21, 57) or the time when the TAP reaches a given percentage of its resting value during the downstroke phase. The most widely used values are 60% and 90%, and we denote the latter by RT90\text{Tap}. In this work, we consider as gold standards the markers RT\text{Tap} and RT90\text{Tap} related to the time of fastest and ending of repolarization of the TAP, respectively. The first choice is based on the theoretical and experimental studies (14, 21) and on computer simulations (5, 47), confirming that, in normal tissue, RT\text{Tap} is highly correlated with the repolarization time of maximum time derivative during the T-wave in the unipolar electrogram (RT\text{eg}; Haws-Lux method). RT\text{eg} is a widely used marker of repolarization time in experimental and clinical electrocardiology (14, 19, 24, 60, 61). This repolarization marker is an extension of the classical depolarization marker (45, 46), which showed that the time of minimum derivative in the QRS complex of the unipolar electrogram (EG) coincides with the time of maximum upslope of the TAP.

Analogously to RT\text{Tap}, we compute the instant RT\text{HMAP} of minimum time derivative of the HMAP signal. This marker, based on the HMAP fastest downslope, can be of interest as an alternative method because the marker RT\text{eg}, based on the ascending portion of the unipolar T-wave, may be difficult to obtain from normal tissue in cases of almost flat or low-voltage T waves or linear ST ramps and in pathological tissue with ischemic regions with missing ST ramp. Recently, the information content of HMAP, resulting from combined EGs, has been questioned (11). Previously, the origin and interpretation of the HMAP waveform have been the subject of a controversy concerning which electrode is responsible for the genesis of MAPs. These controversial issues regarding the origin and interpretation of the MAP and HMAP signal morphology are beyond the scope of this paper, and we refer interested readers to other studies (11, 18, 26, 28, 34, 35, 51, 53, 56) for a discussion of these issues.

The goal of this work is to investigate the information content of the downstroke phase of the HMAP signal by using three-dimensional numerical simulations. These have the main advantage of yielding both the EG and the reference TAP at any exploring site. Therefore, we are able to estimate the matching of time markers of both transmembrane and extracellular potentials. We simulate the three-dimensional activation and repolarization sequences based on the bidomain model coupled with the Luo-Rudy phase I (LR1) system for the ionic membrane currents, taking into account the rotational anisotropic structure of the fiber layers, different local stimulation sites in a slab, and the subepicardial heterogeneity of the cell membranes properties, resulting in different APDs.

We simulate several EGs and HMAPs distributed on both the epicardial surface of the slab and at intramural locations. Previous studies investigated the influence of the cardiac wall anisotropy on the QRS morphology and activation sequence (8, 40, 49, 50) and the influence of heterogeneity on repolarization dispersion (3, 4, 10, 13, 20, 25, 31, 41, 44, 47, 54). In this paper, we focus instead on the reliability of the repolarization time markers RT\text{eg} and RT\text{HMAP} compared with the gold standard RT\text{Tap} in the presence of anisotropic electrotonic currents and their modulation due to APD heterogeneity. In the same conditions, we investigate the reliability of RT90\text{HMAP} as an estimate of RT90\text{Tap}. Because the HMAP signal is contaminated by far-field effects in both the depolarization and repolarization phases, where local and remote activity are superimposed, we challenged the methods of Antzelevitch and colleagues (29, 34, 55) by creating a short APD region (50% of normal) and by running two critical simulation tests (S\text{A} and S\text{B}). Our results show that it is possible to detect the repolarization activity near the exploring electrode from the HMAP downstroke, despite some contamination due to the influence of the monophasic shape of the EG waveform at a PD site. We finally discuss some related controversial issues.

**METHODS**

The anisotropic bidomain model. In this study, we consider the macroscopic bidomain representation of the cardiac tissue, which has been used by several research groups (5, 15, 22, 23, 36, 38, 42) in previous investigations of the excitation and repolarization processes and has led to the determination of general rules explaining the effects of fiber architecture and cellular heterogeneity on excitation and repolarization sequences, potential patterns, and EG morphology.

We simulate an entire depolarization and repolarization phase in an insulated three-dimensional cardiac domain H (with boundary ∂H) modeling a portion of the ventricular wall, using the bidomain representation of the cardiac tissue coupled with the Luo-Rudy phase I system (32) modeling the ionic membrane currents. This model allows us to compute on a given time interval (0, T) the intra- and extracellular potentials \(u_\text{e}(x,t)\) and \(u_\text{i}(x,t)\) [hence the TAP \(v(x,t) = u_\text{e}(x,t) - u_\text{i}(x,t)\)], the gating variables \(w(x,t)\), and ion concentrations \(c(x,t)\), as the solutions of the bidomain reaction-diffusion system

\[
\begin{align*}
\chi C_\text{m} \partial_t v - \nabla \left( \mathbf{D} \nabla v \right) + \chi I_\text{mem}(v, w, c) &= 0 \quad \text{in } H \times (0, T) \\
-\chi C_\text{m} \partial_t w - \nabla \left( \mathbf{D} \nabla u_\text{i} \right) - \chi I_\text{ion}(v, w, c) &= -i'_\text{app} \quad \text{in } H \times (0, T) \\
\partial_w R(v, w) &= 0 \quad \text{in } H \times (0, T) \\
\partial_t c(x,t) - S(v, w, c) &= 0 \quad \text{in } H \times (0, T) \\
\n^T \mathbf{D} \nabla v &= 0, \quad n^T \mathbf{D} \nabla u_\text{i} = 0, \quad \text{in } \partial H \times (0, T) \\
v(x, 0) &= v_\text{ip}(x), \quad w(x, 0) = w_\text{ip}(x), \quad c(x, 0) = c_\text{ip}(x) \quad \text{in } H.
\end{align*}
\]

Here, \(\partial\) denotes the partial derivative with respect to time, \(\nabla\) the gradient operator, \(\mathbf{D}\) the divergence operator, \(\chi\) the surface membrane area per unit volume, \(C_\text{m}\) and \(I_\text{app}\) the capacitance and the ionic current of the membrane per unit surface, and \(I_\text{ion}\) an applied extracellular current per unit volume. We chose \(\chi = 10^7 \text{cm}^{-1}\) and \(C_\text{m} = 10^{-2} \text{mF/cm}^2\); see below for definitions of the conductivity tensors \(\mathbf{D}\) and \(\mathbf{S}\). The extracellular potential \(u_\text{e}\) is defined apart from a space independent constant \(R(t)\) determined by the choice of reference potential. The latter is usually a potential in a remote site or an average of potential values such as the Wilson central terminal. In the case of an insulated block of tissue, we considered as a reference potential the average of the extracellular potential on a portion \(H_\text{ref}\) of the volume or of the surface of the slab; i.e., we impose \(j_{\text{influx}}(x,t) = 0\), where \(H_\text{ref}\) is \(H\) or alternatively \(H_\text{ref}\) is \(H_\text{epic}\), the epicardial surface of the slab.

To investigate the information content of the HMAP with respect to the local repolarization activity, we challenged the method by Antzelevitch and colleagues (29, 34, 55) by creating a short APD region (50% of normal) and by performing two critical simulations, described below as protocols \(S\text{A}\) and \(S\text{B}\). We simulated the propagation of activation and repolarization sequences by taking into account the orthotropic anisotropy of the intra- and extracellular media, the intramural rotational structure of the fibers, the unequal anisotropy ratio for the intra- and extracellular media, the presence of a PD site, the effect of different local stimulations, and the presence...
of a strong regional APD heterogeneity, modeling the effect of local warming.

Fiber architecture and conductivity tensors. The conductivity tensors \( D_{\alpha}(x) \) and \( D_{\beta}(x) \) at any point \( x \) in \( H \) are defined as

\[
D_{\alpha}(x) = \sigma_{\alpha}^i a_i(x) a_i^T(x) + \sigma_{\alpha}^t a_t(x) a_t^T(x) + \sigma_{\alpha}^w a_w(x) a_w^T(x),
\]

where \( (x) \) is a unit vector parallel to the local fiber direction and, on the basis of the laminar organization of the ventricular wall \((10, 12, 30)\), \( a_t(x) \) and \( a_w(x) \) are unit vectors transverse to the fiber axis and tangent and orthogonal to fiber laminas, respectively. For our slab geometry, using the Cartesian coordinate system \( x_1, x_2, x_3 \), we chose \( a_t = e_1, a_2(x) = e_i \cos \alpha(x_i), \) and \( a_w(x) = -e_i \sin \alpha(x_i) + e_2 \cos \alpha(x_3) \), where the angle \( \alpha(x) \) dictates the transmural fiber rotation, which we assumed as having linear and counterclockwise variations from epicardium \((-45^\circ)\) to endocardium \((45^\circ)\), for a total amount of \(90^\circ\) \((48)\). Moreover, \( \sigma_{\alpha}^i, \sigma_{\alpha}^t, \) and \( \sigma_{\alpha}^w \) are the conductivity coefficients in the intra- and extracellular media measured along the corresponding directions \( a_i, a_t, \) and \( a_w \). These coefficients are assumed to be homogeneous throughout the tissue, with values of \( \sigma_{\alpha}^i, \sigma_{\alpha}^t, \sigma_{\alpha}^w \) \([2, 3, 1.35, 0.315] \ \text{m}^2\text{F}^{-1}\text{cm}^{-1}\) and \( \sigma_{\alpha}^e = \sigma_{\alpha}^i/2, \sigma_{\alpha}^w/10\). These calibrations yield ideal plane wave fronts propagating along \( a_i(x), a_t(x), \) and \( a_w(x) \) with velocities of \(60, 25,\) and \(10\) cm/s, respectively, in accordance with Refs. \(10\) and \(30\).

Multisite matrix. The cardiac domain \( H \) considered in this study is a Cartesian slab of dimensions \(1.92 \times 1.92 \times 0.48\) cm\(^3\), modeling a portion of the left ventricular wall. In this slab, we consider a structure of \(12 \times 12\) exploring multielectrode needles spaced 1.6 mm from each other and 0.8 mm from the slab boundary, as shown in Fig. 1. Each needle carries 13 exploring sites, spaced 0.4 mm along the shank. We then have \(12 \times 12\) sites on each of the 13 intramural planes, for a total of \(12 \times 12 \times 13 = 1,872\) exploring sites in the slab, each recording the intra- and extracellular potentials.

We indicated each needle location by its column and row (Fig. 1, left); for example, the location of the needle inside the PD site has indexes \(PD = (1,12)\), whereas the four needles \(A, B, C,\) and \(D\) along the diagonal issuing from the PD site have indexes \(A = (2,11), B = (5,8), C = (8,5),\) and \(D = (11,2)\) (the first 3 outside and the last 1 inside the short APD region).

PD volume. An almost PD volume was obtained experimentally by contact pressure or by KCl injection in a small PD volume of the cardiac slab \(H\), holding the TAP in such a region to some fixed depolarized value. Modeling studies of the PD volume and the close bipolar MAP can be found elsewhere \((51, 52)\). In our model, we obtained a PD volume by assigning the extracellular potassium concentration equal to the intracellular one, so that the reversal potentials \(E_{\text{K}}\) and \(E_{\text{Kp}}\) in the LR1 model are set to zero in the PD volume \((37)\). The location of the PD site is marked in Fig. 1; it has dimensions \(0.8 \times 0.8 \times 0.8\) mm\(^3\).

Short APD region. We introduced a strong regional heterogeneity of the cellular membrane properties by reducing the APD in a subepicardial region near a vertex indicated in Fig. 1. This short APD region has dimensions of \(0.48 \times 0.48 \times 0.10\) cm\(^3\). In the LR1 model \((32)\), we scaled the time-dependent potassium current \(I_K\) by a factor of \(2.325\), yielding an action potential with \(\text{APD}_{90} = 250\) ms. Inside the short APD region, we scaled the same current by a factor of \(8.603\), which yielded an action potential with \(\text{APD}_{90} = 125\) ms. This situation models the experimental effects of local warming in the short APD region.

Stimulation sites: near and away from the PD site. Because the TAP at the PD site is above threshold, it generates a first excitation-recovery front that sweeps the cardiac slab \(H\). After 500 ms, we take the steady state reached by the bidomain system as the initial condition for our simulations and we apply an appropriate stimulus \((250\ \text{mA/cm}^3\) for \(1\) ms\)) in a small volume \((3\) or \(5\) mesh points in each direction) at a location near the PD site (labeled \(S\) in Fig. 1) or away from the PD site (labeled \(S_b\) in Fig. 1).

Numerical methods. In all computations, a structured grid of \(192 \times 192 \times 48\) hexahedral isoparametric \(Q_1\) elements of size \(h = 0.1\) mm is used in space, whereas the time discretization is based on an Euler-Imex method. We used the PETSc parallel library \((2)\) to ensure the parallelization and portability of our code, run on a Linux Cluster with \(72\) 2.4-GHz processors at the Mathematical Department of the University of Milan (cluster.mat.unimi.it). Each simulation required \(\sim 7-24\) h on \(36\) processors, depending on the solver; further numerical details can be found elsewhere \((7, 10)\). The limited size of our computational domain is due to the high computational costs of our bidomain simulations with high space-time resolution, which are needed to obtain very accurate TAP and EG waveforms without numerical artifacts.

Potential waveforms. In each simulation, we saved the extracellular and intracellular potential waveforms \(u_e(x,t)\) and \(u_i(x,t)\) at the \(12 \times 12 \times 13\) exploring sites of the multisite matrix described above. We define the following waveforms: \(E_{\text{G}}(t) = u_e(x,t)\) (unipolar EG at the exploring site \(x\)), \(TAP_{i}(t) = u_e(x,t) - u_i(x,t)\) (transmembrane potential at \(x\)), \(E_{\text{G}}(t) = \) the unipolar EG at the PD site, and \(\text{HMAP}_{i}(t) = -E_{\text{G}}(t) + E_{\text{G}}(t)\) (the HMAP at \(x\)). We remark that the HMAP recording is the superposition of a local EG detected at the exploring site and a remote component related to the depolarized site used as a reference site. We also considered a scaled version of the TAP (STAP) defined by

\[
\text{STAP}_{i}(t) = \alpha \cdot \text{TAP}_{i}(t) + \text{HMAP}(\text{end}_{\text{local}}) - \alpha \cdot \text{TAP}_{i}(\text{end}_{\text{local}})
\]

with \(\alpha = (\sigma_{\beta}^i - \sigma_{\beta}^t)/(\sigma_{\beta}^i - \sigma_{\beta}^w)\). \(\sigma_{\beta}^{t\beta,\beta,n} = \sigma_{\beta}^{t\beta,\beta,n} + \sigma_{\beta}^{t\beta,\beta,n}\) and \(\text{end}_{\text{local}} = 400\) ms; a motivation for this particular choice is discussed in the APPENDIX.

Repolarization time markers. In protocols \(S\) and \(S_b\) and at each point \(x\) of the cardiac domain, we estimated the following recovery time markers:
time markers from the waveforms $\text{TAP}_t(t)$, $\text{EG}_t(t)$, and $\text{HMAP}_t(t)$: $\text{RT}_{tap}(x)$ = time of minimum $\partial T_{tap}(t)$ during downstroke, $\text{RT}_{90tap}(x)$ = first time when $\text{TAP}_t(t)$ reaches 90% of its resting value during downstroke, $\text{RT}_{d}(x)$ = time of maximum $\partial \text{EG}_t(t)$ during T wave, $\text{RT}_{HMAP}(x)$ = time of minimum $\partial \text{HMAP}_t(t)$ during downstroke, $\text{RT}_{90HMAP}(x)$ = first time when $\text{HMAP}_t(t)$ reaches 90% of its resting value during downstroke, $\text{RT}_{d}(x)$ = time of minimum $\partial \text{EG}_t(t)$ during downstroke. The $\text{RT}_{tap}$ marker and $\text{RT}_{90tap}$ markers are assumed to be the gold standards for the repolarization times of the cardiac cellular activity.

RESULTS

As described in METHODS, we first allow the bidomain system to reach a steady state after the excitation-recovery front, originated at the PD site, sweeps the domain H and the slab is to reach a steady state after the excitation-recovery front, RT90HMAP($x$) = first time when HMAP$_t(t)$ reaches 90% of its resting value during downstroke, RT$_{d}(x)$ = time of minimum $\partial \text{EG}_t(t)$ during downstroke, RT$_{tap}(x)$ = time of minimum $\partial \text{HMAP}_t(t)$ during downstroke. The $\text{RT}_{tap}$ marker and $\text{RT}_{90tap}$ markers are assumed to be the gold standards for the repolarization times of the cardiac cellular activity.

RESULTS

As described in METHODS, we first allow the bidomain system to reach a steady state after the excitation-recovery front, originated at the PD site, sweeps the domain H and the slab is fully repolarized. After 500 ms, we apply one of two stimulation protocols: $S_A$, with stimulus located near the PD zone, or $S_R$, with stimulus away from the PD zone (see Fig. 1).

The excitation and repolarization sequences associated with protocols $S_A$ and $S_R$ are displayed in Fig. 2, left and right, respectively. In protocol $S_A$, the epicardial repolarization starts from the short APD region and subsequently collides and merges with the repolarization front originating from the area around the stimulation site. In protocol $S_R$, repolarization starts from the stimulation site, located within the short APD region, and proceeds on the epicardial face toward the PD zone. We next investigate the shape of the $\text{EG}_t(t)$, $\text{HMAP}_t(t)$, and $\text{TAP}_t(t)$ computed in both protocols at various exploring sites $x$.

HMAPs at exploring sites close to the PD site. At exploring sites close to the PD site, HMAPs are essentially bipolar signals, hence without far-field potential effects. This situation yields HMAPs similar to the close-bipolar MAPs recorded from the Franz MAP catheter design, based on tissue contact pressure. In stimulation protocol $S_A$ with both stimulation and exploring sites close to the PD zone (Fig. 3, $A_1$ and $A_2$), the HMAP exhibits an initial upstroke associated with the depolarization of the epicardial sites around the boundary of the PD volume, immediately followed by a faster upstroke associated with the excitation front reaching the exploring site, as supported by the superimposition with the upstroke of the scaled TAP. Subsequently, the HMAP exhibits a monophasic component that almost coincides with the downstroke phase of the scaled TAP. A comparison of $\text{RT}_{HMAP}$ and $\text{RT}_{tap}$ shows an error of <1.5 ms. Hence, the close-bipolar HMAP of Fig. 3 exhibits all of the TAP morphological features, including a remarkable resemblance of the downstroke shape. Similar conclusions held for protocol $S_R$, as confirmed by comparing the HMAPs and scaled version of TAPs of Fig. 3, $A_3$ and $A_4$, where the exploring sites are close to the PD zone and away from the stimulation site.

Wave trains along exploring sites crossing the short APD region. In Fig. 4, we compare the HMAP and the scaled TAP morphology at exploring epicardial sites along an epicardial diagonal (top) and a transmural needle crossing the short APD area (bottom), for protocols $S_A$ (left) and $S_R$ (right). The wave trains along the diagonal displayed in Fig. 4, top, clearly show that both the HMAP and TAP suddenly change their duration when the exploring site crosses the short APD region, whereas a large positive T wave appears in the EG. The movement of the downstroke phase of the HMAP is synchronized with that of the associated TAP. Figure 4, bottom, shows the waveforms $\text{EG}_t(t)$, $\text{HMAP}_t(t)$, and $\text{TAP}_t(t)$ along a transmural needle located at the epicardial site $D = (11,2)$ centered in the short APD region (see Fig. 1). The upstroke phase of the T wave in the EG($t$), the downstroke phase of the HMAP$_d(t)$, and the TAP$_d(t)$ move synchronously as the...
exploring sites move transmurally with a step of 0.4 mm. When the exploring site enters the short APD region, the HMAP downstroke phase suddenly reduces its duration according to the associated TAP duration, independently of the stimulation protocol.

**Morphology of epicardial HMAPs and behavior of RTHMAP marker.** We next compare the HMAP and TAP morphology at four epicardial sites A, B, C, and D (the first 3 outside and the last 1 inside the short APD region) along the epicardial diagonal issuing from the stimulation point (see Fig. 1).

Epicardial HMAP signals elicited by protocol $S_A$ (Fig. 5) exhibit multiple upstroke phases. A first one is associated with the depolarization of sites around the boundary of the PD region. A second one is associated with the activation time of the exploring site, as confirmed by the coincidence with the upstroke phase of the TAP (see Fig. 5), followed by the
appearance of the HMAP monophasic component. The fast depolarization upstroke of the HMAP is not clearly detached from the monophasic component, since the stimulation site is near the PD zone. After a few milliseconds, the EGd morphology shows a deflection associated with the excitation reaching the sites around the PD boundary, followed by a monophasic component.

Epicardial HMAP signals elicited by protocol SB exhibit multiple upstroke phases. A first one is now associated with the activation time of the exploring site, as confirmed by the coincidence with the upstroke phase of the TAP. A second one is associated with the depolarization of the boundary of the PD region and is followed by a third upstroke with the appearance of the monophasic portion of the HMAP (Fig. 6, B–D). The HMAP displays a fast depolarization upstroke phase, fully separated from and preceding the appearance of the monophasic component. The morphology of the EGd shows an initial increasing behavior followed by a deflection when the excitation reaches the sites around the boundary of the PD zone, with the subsequent appearance of a monophasic component. As previously remarked, the HMAP morphology and duration are dependent on the local T wave; hence, it is not unexpected that the measure of the fastest repolarization time from the downstroke phase of the HMAP is actually correlated with the moment of steepest rise of the local T wave. Figures 5 and 6 show a comparison between the markers RT_{HMAP}(x), RT_{EG}(x), and the gold standard RT_{TAP}(x).

For both of the stimulation protocols, EGs at sites within the short APD region exhibit a local huge positive T wave with a very long downstroke phase. The HMAP waveform, resulting from the subtraction of the EGd signal from the EGd, displays a monophasic component lasting <180 ms. Therefore, the amplitude and duration of the positive T wave are sufficient to compensate for the long downstroke phase of the EGd at the PD zone and to level of the last 100 ms of the HMAP waveform. This demonstrates that the last part of the T-wave downstroke phase contains information about the remote repolarization, similarly to the last part of the monophasic component of the EGd. In fact, the monophasic part of the HMAP lasts less than ~160 ms, despite the fact that RTd = 243 ms for...
the EG at the PD zone and that the times of the maximum
downslope of the T wave amount to 237 and 246 ms for
protocol SA and SB, respectively. The comparison between the
STAP and the HMAP shows different endings, such as an
undershooting of the resting value; e.g., hyperpolarization
phenomena are present in Fig. 5C and Fig. 6, C and D.

Quantitative analysis of repolarization time markers. A
more quantitative investigation of the match between the two
markers RT_{HMAP}(x) and RT_{EG}(x) of the time of fastest repolarization
and the reference marker RT_{TAP}(x) can be accomplished
by postprocessing all of the 12 x 12 epicardial waveforms for
EG, HMAP, and TAP. We identify the sites where

Fig. 5. Stimulation protocol $S_A$. Waveforms at
epicardial exploring sites $A = (2,11)$, $B = (5,8)$,
$C = (8,5)$, and $D = (11,2)$ along the diagonal
issuing from the stimulation point (see Fig. 1).
Solid lines indicate HMAP,$E_G(t)$ (top), HMAP,$E_G(t)$
(middle), and HMAP,$E_G(t)$ (bottom); dashed lines indi
cate superimposed scaled and shifted version
of TAP,$E_G(t)$, given by Eq. 3. Vertical solid lines
indicate the markers RT_{HMAP}, RT_{EG}, and RT_{TAP};
vertical dashed lines indicate the marker RT_{TAP} with its value and associated APD reported below.
both of the marker differences $|RT_{eg} - RT_{tap}|$ and $|RT_{HMAP} - RT_{tap}|$ are $>10$ ms. One site is obviously the site inside the PD zone, and, in protocol $S_A$, we identify only two nodes where the $RT_{eg}$ fails, whereas $RT_{HMAP}$ gives an estimate with discrepancies of $<6$ ms. In protocol $S_B$, only three sites show differences in the $RT_{eg}(x)$ estimate ranging from 10 to 20 ms, whereas the discrepancies of the $RT_{HMAP}(x)$ marker range from 5 to 10 ms. We eliminate these few abnormal sites and then compute the average absolute difference mean, the associated standard deviations, and correlation coefficients for both discrepancies ($|RT_{eg} - RT_{tap}|$ and $|RT_{HMAP} - RT_{tap}|$). These are reported in Table 1 for protocols $S_A$ and $S_B$. 

Fig. 6. Stimulation protocol $S_B$. Format is the same as in Fig. 5.
Because another widely used marker of TAP repolarization time is the RT90tap (when TAP reaches 90% of its resting value during the downstroke phase), we also compute this additional marker and compare it with the analogous marker RT90HMAP computed for the HMAP waveform. As before, in protocol SA, we find only two sites where the difference RT90HMAP − RT90tap is >10; in protocol SB, however, we find eight sites. After eliminating these few abnormal sites, we compute the same quantities as we did for the other markers; results are shown in Table 1. Again, the two markers are highly correlated, and the mean and SD values are only slightly worse than for the other markers.

Overall, the mean values for the marker discrepancies reported in Table 1 range from 1.1 to 1.6 ms and the SD values range from 0.9 to 2.2 ms. These are small values compared with the repolarization times in our tests, which vary from 171 to 291 ms in protocol SA (Fig. 2, left) and from 134 to 298 ms in protocol SB (Fig. 2, right), implying a considerable dispersion of repolarization time amounting to ~120 ms in protocol SA and to ~164 ms in protocol SB.

Table 1. Comparison of markers RTtap, RTeg, and RTHMAP and markers RT90tap and RT90HMAP over the epicardial exploring sites

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Maximum</th>
<th>Minimum</th>
<th>CC</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol SA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTtap vs. RTeg</td>
<td>2.275</td>
<td>1.875</td>
<td>9.607</td>
<td>−6.148</td>
<td>0.993</td>
<td>0.986</td>
</tr>
<tr>
<td>RTtap vs. RTHMAP</td>
<td>1.469</td>
<td>1.340</td>
<td>7.109</td>
<td>−6.917</td>
<td>0.996</td>
<td>0.993</td>
</tr>
<tr>
<td>RTeg vs. RTHMAP</td>
<td>2.164</td>
<td>1.881</td>
<td>9.415</td>
<td>−10.568</td>
<td>0.994</td>
<td>0.988</td>
</tr>
<tr>
<td>RT90tap vs. RT90HMAP</td>
<td>2.578</td>
<td>2.181</td>
<td>8.839</td>
<td>−8.839</td>
<td>0.999</td>
<td>0.997</td>
</tr>
<tr>
<td><strong>Protocol SB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTtap vs. RTeg</td>
<td>1.525</td>
<td>1.380</td>
<td>7.129</td>
<td>−6.790</td>
<td>0.998</td>
<td>0.997</td>
</tr>
<tr>
<td>RTtap vs. RTHMAP</td>
<td>1.167</td>
<td>1.188</td>
<td>5.432</td>
<td>−7.809</td>
<td>0.998</td>
<td>0.997</td>
</tr>
<tr>
<td>RTeg vs. RTHMAP</td>
<td>1.127</td>
<td>0.898</td>
<td>3.734</td>
<td>−3.734</td>
<td>0.999</td>
<td>0.999</td>
</tr>
<tr>
<td>RT90tap vs. RT90HMAP</td>
<td>1.995</td>
<td>1.918</td>
<td>9.507</td>
<td>−4.414</td>
<td>0.999</td>
<td>0.999</td>
</tr>
</tbody>
</table>

RTeg, moment of fastest electrogram upstroke during the T wave; RTtap, time of transmembrane action potential fastest downstroke; RTHMAP, time of hybrid monophasic action potential fastest downstroke; RT90, time when 90% of resting value is reached. Mean is average absolute difference of $|RT_{tap} − RT_{eg}|$, $|RT_{eg} − RT_{HMAP}|$, $|RT_{tap} − RT_{HMAP}|$, or $|RT_{90tap} − RT_{90HMAP}|$; maximum and minimum are maximum and minimum of differences of RTtap − RTeg, RTtap − RTHMAP, RTeg − RTHMAP, and RT90tap − RT90HMAP; CC is the correlation coefficient $r^2 = CC^2$.

Figure 7 displays the variability of the discrepancy between the markers RTeg and RTHMAP (RT90HMAP) with respect to the gold standard (or benchmark or reference) marker RTtap (RT90tap) for both stimulation protocols. These data confirm the high correlation and very good agreement between the EG and HMAP markers and the TAP ones. Moreover, the error dispersion of all markers, displayed in Fig. 7, shows that, except for a few sites, the magnitude of these discrepancies yields the small mean...
and SD values of Table 1. These small errors should not alter the main qualitative patterns of the repolarization sequences determined with the different markers.

Previously, our group (6) found that the time $RT_{d2eg}$, defined as the time of minimum second derivative of $EG_x(t)$ during the T wave, is a valuable extracellular marker for estimating the TAP marker $RT_{90tap}$. The T wave of the EGs exhibits different polarities depending on the exploring site, i.e., positive, negative, and biphasic T waves. In Fig. 8, we compare the performance of markers $RT_{HMAP}$ and $RT_{90HMAP}$ with markers $RT_{eg}$ and $RT_{2deg}$, at the same three sites exhibiting EGs with different polarities, showing the polarity independence of the markers.

**DISCUSSION**

We first ran the bidomain model for 500 ms and then applied a local stimulus either close (protocol $S_A$) or away (protocol $S_B$) from the PD site. The first 500 ms of simulation are needed because the TAP above threshold within the PD zone generates...
a spontaneous beat that sweeps the domain in $\sim 400$ ms, and after 500 ms the tissue is fully recovered. We included the main structural and functional features of the tissue representation, such as intramural fiber rotation, orthotropic anisotropy of the intra- and extracellular media, unequal anisotropy ratio for the intra- and extracellular media, the phase I Luo-Rudy membrane model, a small epi-subepicardial zone PD site, and a strong APD heterogeneity due to the presence of a short APD region.

For exploring sites close to the PD zone, the model predictions show HMAPs that match very well all of the morphological features of the scaled TAP of Eq. 3 from the same sites. For exploring sites away from the PD zone, the simulated HMAP displays a monophasic component with a shape similar to the downstroke phase of the associated STAP. In these HMAPs, the reference potential is filtered out, as in close-bipolar MAP signals, but the HMAP is contaminated by far-field potentials. In fact, HMAPs show two initial upstrokes and also an hyperpolarization ending phase. When the stimulation site is away from the PD zone (protocol $S_B$), the monophasic portion of the HMAP begins when excitation reaches the PD zone. However, the model also shows that the HMAP downstroke reflects the repolarization activity near the exploring site and $RT_{HMAP}$ reproduces the moment of fastest repolarization of the TAP marked by $RT_{TAP}$. Because both the TAP and EG are available in our simulations at the same exploring site (unlike in experimental works), we have been able to show that $RT_{HMAP}$ is a reliable and accurate estimate of $RT_{TAP}$ (see Table 1). This correlation between the two markers is particularly evident when moving the exploring site on the epicardial face or along a transmural needle; when the exploring site crosses the short APD region, the HMAP downstroke phase suddenly reduces its duration according to the TAP duration, independently of the stimulation protocol. Therefore, the origin of the monophasic portion of the HMAP complex cannot be attributed only to the unipolar EG recorded at the fixed PD site. In this regard, our simulations agree with the findings obtained with the HMAP recording techniques of Antzelevich and colleagues (29, 55). In fact, we have shown that the marker $RT_{HMAP}$ detects the TAP fastest repolarization time in the short APD region, whereas one might have expected that the longer repolarization time $RT_d$ of the PD site would have influenced the outcome and resulted in a longer repolarization time for sites inside the short APD region.

In protocols $S_A$ and $S_B$, the $EG_d$ show an initial rise that is followed by a deflection when excitation reaches the sites around the boundary of the PD zone, followed again by the appearance of the monophasic component. It is believed that this $EG_d$ monophasic component represents a wide field of view (or a far-field view). As mentioned previously (35), the electric potential at the center of the PD area should reflect the average transmembrane potential of the cardiomyocytes. Our simulations allow us to verify this assertion by computing at every time instant the space average of the transmembrane potential distribution over the slab. In Fig. 9, we display the space average of $TAP_r(t)$ [i.e., $CR(t) = \alpha \int_0^t TAP_r(t) dt$] superimposed with $EG_d(t)$ for protocols $S_A$ and $S_B$. The comparison shown in Fig. 9 confirms that, apart from a scaling factor, the extracellular potential at the PD zone yields a measurable estimate of the average transmembrane potential of the cardiomyocytes, not accessible in experimental recordings.

This suggests the following synthesis of the two simulated monophasic signals $TAP_r(t)$ and $CR(t)$:

$$CEG_d(t) = -\alpha TAP_d(t) + CR(t).$$

(4)

The comparison between the resulting waveform $CEG_d(t)$, given by Eq. 4, and $EG_d(t)$ at two exploring sites is shown in Fig. 10 for protocols $S_A$ and $S_B$. Despite some discrepancies in the QRS complex and in the T wave, the $CEG_d(t)$ exhibits the main morphological features of the extracellular waveform $EG_d(t)$. As in the virtual experiment of Eq. 4, the extracellular waveform $EG_d(t)$ at the exploring site can be viewed as the result of the difference between two monophasic waveforms, a fixed one related to a far-field potential and the other related to a rough approximation of the $TAP_r(t)$. This consideration supports the fact that, even if the HMAP is a contaminated approximation of the scaled TAP, a good estimate of the times of fastest repolarization and of 90% of the resting value can be detected from the HMAP downstroke. By comparing the T wave of $CEG_d(t)$ and $EG_d(t)$ at exploring sites exhibiting different T-wave polarities (see Fig. 11, displaying the waveforms related to the three sites), we see that a strong determinant of the T-wave morphology of the $EG_d(t)$ is the reference potential. In addition to the remarkable similarity of $EG_d(t)$ and $CEG_d(t)$ in Figs. 10 and 11, the differences of these two waveforms allow us to estimate the influence of the unequal anisotropy ratio on the extracellular waveforms (see APPENDIX for a mathematical derivation of this conclusion).

Regarding the remote repolarization associated with the time of the $EG_d(t)$ minimum downslope during the T wave, we have not found any relationship with the time of the minimum downslope of the $EG_d(t)$ monophasic component. Only at some
exploring site close to the stimulation site, a small difference between these time markers is observed.

In this study, we have considered an anisotropic three-dimensional structure fully insulated. A recent study by Okamoto et al. (37) considered an isotropic sheet embedded into a conducting medium and presents two-dimensional results in agreement with our study, indicating that our conclusions might hold also for noninsulated domains.

Conclusions. The results of our bidomain simulations, obtained in a fully insulated slab with unequal anisotropy ratio and orthotropic anisotropy, bring us to the following conclusions.

First, the initial portion of the HMAP is the superimposition of local and remote excitations and displays two upstroke complexes, one elicited by the excitation underneath the exploring site and another elicited by the activation near the PD zone. These two interfering complexes are well separated at exploring sites distant from the PD zone (see Figs. 5 and 6), whereas they partially overlap at exploring sites near the PD zone (see Fig. 3). Moreover, when the stimulation site is away from the PD zone, the monophasic portion of the HMAP appears at the time of the arrival of the excitation near the PD zone (see Fig. 6). These predictions on the initial phase of the HMAP are in agreement with the recent experimental in vivo data of Coronel et al. (11).

Second, the HMAP downstroke phase contains reliable information about the local repolarization activity at the exploring site, i.e., $R_{THMAP}$ is a reliable and accurate estimate of $RT_{REP}$, as shown by two critical tests ($S_A$ and $S_B$) on a cardiac slab with a drastically shorter APD (50% of normal) in a given region. In both protocols $S_A$ and $S_B$, $R_{THMAP}$ performed slightly better than the $RT_{EG}$ marker. At the same time, the results show that $R_{THMAP}$ and $RT_{EG}$ have no relationship with $RT_{d}$ of minimum downslope of the EG of the PD site. Thus the HMAP monophasic portion, even if contaminated by the superposition of local and remote repolarization activities with far-field contributions, contains valuable information about the local repolarization activity, as noted previously (26, 35). These conclusions are in agreement with the results from in situ canine ventricular wall (55) and from in vitro ventricular wedge preparations (29). We remark that our simulations allow us to evaluate the accuracy of markers coming from both close-bipolar MAPs similar to the MAPs by Franz and from

Fig. 10. Stimulation protocol $S_A$ (top 3 rows) and stimulation protocol $S_B$ (bottom 3 rows), with waveforms at exploring site $C = (8,5)$ (left) and $D = (11,2)$ (right) (see Fig. 1). Solid lines indicate $HMAP_x(t)$ (top), $EG_x(t)$ (middle), and the $EG_x(t) = -HMAP_x(t) + EG_x(t)$ (bottom). Dashed lines indicate $CR_x(t)$ (top), $CR_x(t) = 2TAP_x(t)dx$ (middle), and $CEG_x(t) = -\alpha TAP_x(t) + CR_x(t)$ (see Eq. 10) (bottom).
distant bipolar HMAPs by Antzelevich and colleagues, depending on the location of the exploring site.

Previous experimental data (11) demonstrated that the local T-wave interferes with the end of the HMAP, i.e., the downslope of the T wave is a sign of remote repolarization. This fact does not exclude that the HMAP downstroke phase contains sufficient information to recover the reference repolarization times RTtap and RT90tap. We remark that our results also show that the RT90HMAP marker, related to the ending of the repolarization phase, is less accurate than the RTHMAP estimates of fastest repolarization, due to a more critical interference of the local T wave with the HMAP downstroke.

Third, we have also shown that EG of the depolarized PD site is an estimate of a far-field potential given by a scaled version of the TAP space average over the slab volume.

Finally, we have also shown that intramural HMAPs are compound waveforms as well. Although they are affected by far-field contributions, HMAPs can reliably detect the TAP repolarization time. Preliminary results (6) for a cardiac slab with intramural heterogeneities (1, 39) demonstrated that RTeg is still a reliable and accurate estimate of RTtap. The extension of this analysis to RTHMAP will require further investigation.

In conclusion, HMAP is a new method for detecting recovery times in electrical wave forms recorded directly from the heart muscle. This procedure offers several advantages compared with the “maximum derivative” method: the maximum derivative method is difficult to implement when the T wave is flat or the ST interval is a linear ramp. The unipolar T wave is derivative method is difficult to implement when the T wave is biphasic to flat to negative T waves. The HMAP waveforms are not affected by the drift of the reference, which is cancelled out because both electrodes are in contact with the heart. As a result, the HMAP always has a shape that resembles a TAP and the downstroke is always easily detectable. On the other hand, the upstroke of the HMAP is contaminated by far-field potentials, and this may make it difficult to detect the beginning of the local TAP and, as a consequence, the assessment of the APD and the activation recovery interval (ARI). Combining the unipolar EG for excitation time and the HMAP for recovery time seems to offer the best approach for an accurate estimate of excitation time, recovery time, and APD. Even if we cannot claim that our HMAP marker RTHMAP is always better than the EG marker RTeg, we have shown in this study that the former can be a valuable alternative when the latter fails. Moreover, our investigation has shown that, from HMAP signals, it is possible to detect the repolarization time marker RT90HMAP, whose estimate from the EG, requiring time second derivatives, is problematic when applied to signals affected by noise. Finally, our results show that RTtap can be reliably estimated from both RTeg and RTHMAP and similarly RT90tap can be reliably estimated from RT90HMAP, independently of T-wave polarity, repolarization sequence (protocols SA and SB), and different intrinsic properties of the cell membrane.

Limitations. Because of the high computational costs of our accurate three-dimensional parallel simulations (each one requiring 2 beats: one elicited by the depolarized PD zone and the other by the local stimulation S1 or S2), we had to limit our study to the LR1 ionic model and to an insulated myocardial slab of limited dimensions. Therefore, the extension of our conclusions to larger and anatomically accurate heart geometries needs further research. We hope to be able to extend our simulations to larger cardiac tissue preparations by using the new generation of multicore parallel computers that will become available to us in the near future.

In future studies, the use of more complex ionic models (including more detailed ionic currents and calcium concentrations) (43) with noninsulated heart surfaces is warranted. This will introduce additional field components, contributing to the information content of the HMAP downstroke phase. A
recent study (37), based on two-dimensional simulations in a noninsulated isotropic cardiac sheet, indicated that the HMAP reflects the activity of the exploring site, in agreement with the present study, but the effect of an endocardial surface wetted by blood deserves a deeper investigation in an anisotropic three-dimensional structure.

Finally, we remark that the study of the clinical applications of our findings is beyond the scope of our theoretical investigation.

APPENDIX

To motivate the particular scale factor introduced for the TAPₜ(t) in Eq. 3, we first introduce the bulk conductivity tensor D(x) = Dₜ(x) + Dₙ(x) given by

\[ D(x) = \sigma_{i,l,m} a_l(x) a_l(x) + \sigma_{i,n} a_n(x) a_n(x), \]

where \( \sigma_{i,l,m} = \sigma_{i,l,m} + \sigma_{i,l,m} \). We then consider the difference between the conductivity tensor \( Dₜ(x) \) and a suitable scaled version of the bulk conductivity tensor \( D(x) \)

\[ Dₜ(x) = \alpha D(x) = (\sigma₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋˓seven unequal anisotropy ratio on the potential fields. This equation explains the choice of the scaled version of TAP given in Eq. 3.

\[ \text{CEG}(t) = -\alpha \text{TAP}(t) + CR(t), \text{ where } CR(t) = \int_{V_H} \text{TAP}(t) dx \]

Therefore the comparison between the two waveforms \( \text{CEG}(t) \) and \( \text{CEG}(t) \) should yield an estimate of the influence of the media unequal anisotropy ratio on the potential fields. This equation explains the choice of the scaled version of TAP given in Eq. 3.

GRANTS

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