Transmural and apicobasal gradients in repolarization contribute to T-wave genesis in human surface ECG

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Submitted 7 December 2010; accepted in final form 28 March 2011

Okada J, Washio T, Maehara A, Momomura S, Sugiura S, Hisada T. Transmural and apicobasal gradients in repolarization contribute to T-wave genesis in human surface ECG. Am J Physiol Heart Circ Physiol 301: H200–H208, 2011. First published April 1, 2011; doi:10.1152/ajpheart.01241.2010.—The cellular basis of the T-wave morphology of surface ECG remains controversial in clinical cardiology. We examined the effect of action potential duration (APD) distribution on T-wave morphology using a realistic model of the human ventricle and torso. We developed a finite-element model of the ventricle consisting of ~26 million elements, including the conduction system, each implemented with the ion current model of cardiomyocytes. This model was embedded in a torso model with distinct organ structures to obtain the standard ECG leads. The APD distribution was changed in the transmural direction by locating the M cells in either the endocardial or epicardial region. We also introduced apicobasal gradients by modifying the ion channel parameters. Both the transmural gradient (with M cells on the endocardial side) and the apicobasal gradient produced positive T waves, although a very large gradient was required for the apicobasal gradient. By contrast, T waves obtained with the transmural gradient were highly symmetric and, therefore, did not represent the true physiological state. Only combination of the transmural and the moderate apicobasal gradients produced physiological T waves in surface ECG. Positive T waves in surface ECG mainly originated from the transmural distribution of APD with M cells on the endocardial side, although the apicobasal gradient was also required to attain the physiological waveform.

electrocardiogram; computer simulation; T wave; body surface map; M cells

DESPITE ITS LONG HISTORY AND worldwide use in clinical cardiology for the diagnosis of various heart diseases, the cellular origin of the ECG waveform is not fully established. In particular, the genesis of the T wave remains controversial, largely because of its implication in arrhythmogenesis (1, 4, 20, 22). The T wave was originally considered to result from the heterogeneity of repolarization of the ventricle in the apicobasal direction (19). However, more recently, the transmural difference (gradient) of repolarization is considered important, as supported by the discovery of M cells isolated from the canine ventricular wall (2, 32). M cells are distributed in the deep subendocardium in the anterior wall, but are shifted to the deep subepicardium in the posterior wall, and are characterized by a longer action potential duration (APD) compared with the epicardial and endocardial myocytes, creating a significant gradient (1). Subsequent studies identified similar type of cells in guinea pig, rabbit, pig, and human ventricular tissues (8, 33, 35, 51).

However, when measurements are made in more intact preparations, there is accumulating evidence that the APD of M cells becomes shorter, resulting in smaller transmural dispersion (23). For instance, measurement of the human ventricles during cardiac surgery, rather than isolated cells or a ventricular wedge, produced no significant transmural heterogeneity of repolarization (42). The electronic cancellation effect introduced by intercellular coupling through gap junctions is considered the cause of these observations in intact preparations (5, 41), although experimental artifact has also been suggested (1). During surgery or in animal experiments, subjects receive anesthetic agents that may block sodium and/or delayed rectifier potassium currents, causing preferential shortening of the APD of M cells (31). Furthermore, the plunge electrode technique used in many studies may not necessarily probe the whole area and depth of the ventricular wall (42, 48). In a recent study, optical mapping revealed the distribution of APD in human ventricular tissue (12); however, only the posterior wall wedge was examined.

Computer simulation is widely used for studying cardiac electrophysiology and allows detailed analysis of the normal and abnormal electrical activity of the heart (18, 34, 46, 47). Although computer simulation does not provide conclusive data on actual tissue, if carefully designed, it can provide important supporting information. In the present study, we used this strategy to examine which pattern of APD distribution generated the normal waveform of the human surface ECG. We previously reported our detailed model of the human ventricles based on the human ventricular model of electrophysiology (44, 45). We embedded this model into a torso with the organ structures model and varied the distributions of M cells and APD, according to experimental data, to calculate the surface ECG. We found that both the apicobasal and transmural distribution of APD significantly influence the human T-wave morphology.

MATERIALS AND METHODS

Human heart and torso model. The details of this model were previously reported (50). We used a realistic model of the human heart with a conduction system embedded into the torso model based on the voxel-based, finite-element method. To save computational cost for such a large-scale model, we used composite mesh composed of fine mesh (0.2 mm) for the heart and the coarse mesh (1.6 mm) for the torso regions and solved it using the multilevel solution technique. The study protocol was approved by the Institutional Ethics Committee, and informed consent was obtained for the use of CT scan data.

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**Heart model.** The geometry of the three-dimensional voxel human heart model (mesh size 0.2 mm) was based on the multidetector computerized tomography data of the subject without cardiac dysfunction (Fig. 1A). We only analyzed the ventricles, although the total number of elements covering the heart region was equal to 244,187,136. We mapped previously reported human data on the spatial orientation of the myocyte (fiber orientation) to our model (http://gforge.icm.jhu.edu/gf/project/dtmri_data_sets/) (Fig. 1B).

To each voxel element, we implemented the previously reported ionic current model of human ventricular myocytes (45), and the propagation of excitation was modeled as a continuous system using the bidomain formulation (see supplemental material for details; the online version of this article contains supplemental data) (14). Anisotropy of action potential propagation was introduced by setting the conductivity in the longitudinal (fiber) direction larger compared with the transverse direction. We used the following values (Supplemental Table S1), according to the previous report (15).

**Conduction system.** The conduction system is indispensable for the analysis of ECG. We modeled the conduction system by one-dimensional elements based on Tawara’s monograph (43), as shown in Fig. 2A. The electrophysiological properties were reproduced by the cell model proposed by Stewart et al. (36). The network of the conduction system consists of the free-running (insulated) part connecting the atrioventricular node to the sites of earliest activation and the network spreading from these sites along the endocardial surface. At each terminal, this network is connected to the voxel mesh node, representing the myocardial tissue, and from there the excitation propagates concentrically. Although the description by Tawara is qualitative, the current model can be validated by the agreement of simulation results of previously reported isochronal maps (Fig. 2, B and C) (9) and body surface voltage maps (Fig. 2D) (6, 40). In the simulation, we applied a small current to the root of the conduction system to initiate activation of the ventricles.

**Torso model.** The morphology of the voxel torso model was based on the computerized tomography data (Fig. 1C). Each organ was segmented manually (Fig. 1D), and specific conductivity (Supplemental Table S1) was assigned as previously reported (3, 21). Only the conductivity of the body surface (skin) was adjusted to obtain the physiological amplitude of ECG without changing its morphology. With a 1.6-mm element size, the total number of elements covering the torso was 40,038,400. In contrast to the heart tissue, the torso domain can be viewed as a passive conductor. Therefore, the potential satisfies the generalized Laplace equation

\[
\frac{\partial}{\partial x_i} \left( G_{ij} \frac{\partial \phi}{\partial x_j} \right) = 0
\]

where \( G_{ij} \) is the conductivity tensor.

**APD distribution.** We altered the APD distributions (gradients) in transmural and apicobasal (longitudinal) directions to determine the effects on ECG. Using the Ten Tusscher model (45), we found that the endocardial cells, M cells, and epicardial cells were modeled by adjusting the transient outward \( K^+ \) and the slow component of delayed rectifier \( K^+ \) currents (\( I_{Ks} \)). Transmural gradient was created by locating M cells in either the endocardial or epicardial sides (10–40%, Fig. 3A, or 60–90%, Fig. 3B, from the endocardium, respectively). However, regional differences in APD were attenuated due to the intercellular coupling. We also tested conditions with no transmural gradient in which all of the layers were composed of epicardial cells (Fig. 3C). Transmural dispersion of APD, APD...
gradient, and the conduction velocity in these models are shown and compared with the experimental data (note that the x-axes are reversed for canine experimental data in Fig. 3, D–F). In Fig. 3D, APD distributions are shown for three models. The APD gradient of the model with M cells on the endocardial side (red line) showed general agreement with the canine heart (24), although the experimentally reported epicardial steep APD gradient was not observed in the simulation (Fig. 3E). Similarly, the simulation results did not show the epicardial gap in conduction velocity. Poelzing et al. (24) suggested that the epicardial APD gradient and the gap in conduction velocity are due to the heterogeneous expression of connexin 43 (Cx43), which we did not take into considerations in this study. However, the APD distribution reported for the human ventricular wall (12) did not show this epicardial gradient, thus closely resembling our simulation results.

As for the apicobasal gradient, Szentadrassy et al. reported a significant difference in the expression level of proteins forming the Iks channel between the apical and basal myocardium (38). We observed a similar trend for the transient outward K+ current channel, although the difference in Kv4.3 was not significant. We modeled the apicobasal difference by regionally changing the Iks density. However, as detailed information on the distribution was not available, we introduced the linear apicobasal gradient with either 20 or 40% of the basal-to-apical ratio; these values were estimated from reported protein levels of these channels (38). We simulated the ECG for the nine combinations of these transmural and apicobasal APD gradients.

**RESULTS**

**Ventricular activation.** Isochronal maps of ventricular activation are shown in Fig. 2, B and C, for the condition of endocardial M cells with no apicobasal gradient. As the conduction system was identical, we observed similar isochronal maps in all of the conditions tested; these data were similar to those previously reported (9). The temporal changes in body surface potential during the corresponding phase of ventricular activation (Fig. 2D; see also Supplemental Movie S1) were also in good agreement with published studies (6). Further-
more, the QRS complex of surface ECG generated from these body surface maps exhibited a similar standard morphology in all conditions (Fig. 4). Overall, these data indicate the validity of our modeling of the conduction system and also confirms that APD has little effect on the activation sequence in the ventricles.

APD dispersion and T wave. APD dispersion had a significant effect on the morphology of T waves (Fig. 4). In the normal cardiogram, the T waves were typically upright in I, II, and the lateral precordial leads (17), but were all negative in these leads in hearts with M cells on the epicardial side (Fig. 4, G–I). Nevertheless, even without the M cells, T waves become upright with a large apicobasal gradient (Fig. 4C). These data suggest that both the transmural (endo- to epicardial) and apicobasal gradients can generate upright T waves in these leads. Indeed, we obtained ECG with upright T waves in the following four conditions: condition C, no M cell with 40% apicobasal gradient; condition D, endocardial M cell with no apicobasal gradient; condition E, endocardial M cell with 20% apicobasal gradient; and condition F, endocardial M cell with 40% apicobasal gradient.

Nevertheless, there were significant differences in the T-wave characteristics between the conditions. In condition C, maximum amplitudes of T wave were small in both limbs, with the precordial leads measuring only 0.1 mV in V6. The T waves in the other conditions had a similar peak amplitude, but differed in morphology, particularly in their symmetry. For quantitative comparison, we calculated the asymmetry ratio defined as the ratio of the two areas (beginning-to-peak and peak-to-end) under the T curves of precordial leads for these conditions (Table 1). Asymmetry ratios in condition C were all less than unity, confirming the inverse asymmetry of the T waves in this condition. Interestingly, there was an inverse asymmetry (symmetry ratio < 1) in V6 for conditions with endocardial M cells, but without a large apicobasal gradient.
(conditions D and E). In healthy subjects, an asymmetry ratio of 1.5 was reported (17), and a correlation between T-wave symmetry and sudden death was suggested. In this regard, we consider that condition F may be the most physiological condition for generating a healthy ECG.

![Fig. 4. Electrocardiogram obtained with the nine combinations of the transmural and apicobasal APD gradients. A, B, and C represent the ECGs with no transmural gradient and varying degree of apicobasal gradients. D, E, and F represent the ECGs with M cells on the endocardial side and varying degree of apicobasal gradients. G, H, and I represent the ECGs with M cells on the epicardial side and varying degree of apicobasal gradients.](image)

Table 1. Symmetry ratio

<table>
<thead>
<tr>
<th>Condition</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
</tr>
</thead>
<tbody>
<tr>
<td>M cell at endocardium. No</td>
<td>1.66</td>
<td>1.74</td>
<td>1.80</td>
<td>1.38</td>
<td>0.70</td>
</tr>
<tr>
<td>apicobasal gradients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M cell at endocardium. Apicobasal gradients 20%</td>
<td>1.75</td>
<td>1.76</td>
<td>1.73</td>
<td>1.59</td>
<td>0.94</td>
</tr>
<tr>
<td>M cell at endocardium. Apicobasal gradients 40%</td>
<td>1.70</td>
<td>1.70</td>
<td>1.66</td>
<td>1.59</td>
<td>1.02</td>
</tr>
<tr>
<td>No M cell. Apicobasal gradients 40%</td>
<td>0.79</td>
<td>0.83</td>
<td>0.96</td>
<td>0.82</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Body surface potential during the repolarization phase. Finally, we compared the body surface potential maps of four conditions (C, D, E, F) at the timing of peak T wave, which showed physiological T-wave morphology (Fig. 5) with the previously reported equipotential map of healthy human subjects (39). On the anterior thoracic surface, the positive voltage region of the experimental data (Fig. 3C of Ref. 39) extends down to the lower body, thus resembling condition F in our simulation. On the posterior surface, the 0-mV line ran obliquely in the middle of the back so that the positive region was also observed. Taken together, condition F showed the closest appearance to the experimental data. The data for different timings can be seen in the Supplemental Movies. Overall, these data suggest that the normal surface ECG waveform cannot be obtained with either transmural or apicobasal gradient of APD alone. Most probably, both contribute to the genesis of surface ECG.
DISCUSSION

Computer simulation is a powerful tool in cardiac electrophysiology studies. Various models have been used to examine ECG wave morphology, although studies typically treat either a small number of cell models coupled in series (5, 10, 25) or a tissue block (wedge) (7, 26). Recently, an ionic current model based on large-scale simulation of the heart was developed, although studies using this model are either without the torso (27) or do not examine physiological conduction (52). To the best of our knowledge, this is the first report where surface ECG was simulated based on the ionic current model and anisotropic propagation with the bidomain reaction diffusion equation in a model with realistic morphology of the human torso and heart.

APD dispersion and T-wave morphology. The results of our simulation suggest that the physiological morphologies of T waves are generated mainly by the transmural distribution of APD, although the contribution of the apicobasal gradient is also important. Although recent studies suggest that the cancellation effect in the intact heart can minimize transmural dispersion (5, 41, 42), a large apicobasal gradient is required to observe positive T waves in limb and left precordial leads under such conditions (Fig. 4C). Even when using a relatively large apicobasal gradient we could only obtain a highly symmetric, thus nonphysiological, T-wave morphology. Furthermore, the amplitude of the T wave in V6 was very small and symmetric in shape only with the transmural gradient, which is also a nonphysiological morphology.

Recently, experimental evidence of a transmural APD gradient was reported in the human heart (12). However, in contrast to animal data (mainly from electrode recordings), two-dimensional mapping in this study identified M cells clustering in an isolated island, rather than forming a contiguous layer, in 60% of nonfailing ventricular wedge preparations. Furthermore, although the number of samples was limited, that study may suggest the presence of an apicobasal gradient, because these islands were shifted to the basal end in most of the graphs. We simulated the effect of uneven M-cell distribution by reducing the fraction of the M-cell region in the apex. Furthermore, as the data from Glukhov et al. (12) were only taken from a limited region of the left ventricular (LV) wall, we used the smooth apicobasal distribution of M cells and obtained a physiological ECG.

Regional differences. The effect of APD gradient differed among the different leads (see Fig. 6). In the absence of
transmural gradient, the amplitude of the T wave in V6 was small and relatively indifferent to the apicobasal gradient. In a previous study that recorded transmural ECG at 0°, 45°, −45°, and 90° angles relative to the transmural axis, the amplitude of the T wave was highly dependent on the angle and peaked at 0° (53). If we assume that the reference electrode (putative 0 potential) is in the center of the LV, the line connecting this electrode and the V6 lead crosses the LV wall in almost a perpendicular manner and also becomes perpendicular to the apicobasal gradient. On the other hand, because the lines connecting V3 or V4 cross the wall at a shallow angle, T-wave amplitudes are sensitive to the apicobasal gradient. A similar logic may apply to the effect of the transmural gradient when comparing T waves in V5 and V6 among the three conditions without apicobasal gradient. These T waves were either nearly flat, positive, or simply negative (monophasic), thus faithfully reflecting the transmural gradient. Although genesis of surface ECG is not this simple, useful information on APD distribution may be obtained from these comparisons.

**Study limitations.** Although our simulation faithfully reproduced the physiological ECG waveform, multiple factors needed to be included in our model for further improvement. First, considering the anisotropy in conduction property of the myocardial tissue, the fiber orientation could have a significant impact on the ECG morphology. To examine this possibility, we compared the ECGs obtained with either human (http://gforge.icm.jhu.edu/gf/project/dtmri_data_sets/) or rabbit (30) fiber orientation (Fig. 7) and found no appreciable difference between them. However, as there are numerous reports indicating the deviations of fiber orientation in diseased hearts (13, 16), further studies are required. Second, in this simulation, the APD gradient was introduced by the heterogeneous expression of K⁺ channels based on the ad-

![Fig. 7. The ECGs simulated with either human (black line) or rabbit (red line) fiber orientations.](http://ajpheart.physiology.org/)
opted cell models (44). However, other molecules are also expressed heterogeneously and thus contribute to the transmural APD gradient. For example, Poelzing et al. (24) reported significantly lower Cx43 expression in the subepicardial layer of the canine LV. Furthermore, downregulation of Cx43 was correlated with the short APD and conduction velocity in this layer. More recently, Poelzing et al. also showed that such heterogeneity in Cx43 expression is significant in anterior LV, and that the poster region lacking Cx43 heterogeneity exhibits flat APD distribution across the wall (37). A similar Cx43 downregulation was reported in the epicardial layer in the human ventricles (12). However, they also showed some discrepancies with the canine heart: 1) although they studied only the posterior-lateral part of the LV, a significant difference in Cx43 expression was observed transmurally; 2) although the number of observations was limited, the APD distribution did not show the steep gradient in the epicardial region as shown in the canine heart; and 3) downregulation of Cx43 in failing human heart resulted in the reduction of local and global transmural APD gradient, thus showing clear contrast to the animal study. Because of these discrepancies between the studies and the lack of information on the whole ventricle, we did not include the effect of Cx43 and only examined effect of the different cell species in our study.

In addition to Cx43, various other ion channels and exchangers are expressed heterogeneously across the ventricular wall. For example, the protein levels of sarco(endo)plasmic reticulum Ca\(^{2+}\)-ATPase 2 and ryanodine receptor channel are reduced, whereas the Na/Ca exchanger is upregulated, in the endocardium of the guinea pig ventricle (49). Furthermore, although the number of specimens was small, sarco(endo)plasmic reticulum Ca\(^{2+}\)-ATPase 2 mRNA levels were downregulated in endocardial tissue, while Na/Ca exchanger expression was comparable to the epicardial tissue obtained from the human heart (28). Transmural heterogeneity was also reported for the late component of Na currents (29, 54) and the Na-K pump (11). Although APD is influenced by the complex interplay of currents and ion concentrations mediated by these molecules, inclusion of these changes to the model may not drastically change the simulation results, as long as the longer APD is distributed to the endocardial side. Nevertheless, further analysis including these factors is required. Finally, the ST segments in our model appeared to be unusually flat rather than being upslope in some leads. This was likely caused by the flat plateau phase of action potential generated by the ion current model we used (44, 45).

ACKNOWLEDGMENTS

The authors thank Dr. K. Sunagawa (Kyushu University Faculty of Medicine), M. Sugimachi, and Dr. M. Inagaki (National Cardiovascular Center Research Institute) for support in constructing the heart muscle and torso model. The authors thank Dr. K. Sunagawa (Kyushu University Faculty of Medicine) for support in constructing the heart muscle and torso model. The authors thank Dr. K. Sunagawa (Kyushu University Faculty of Medicine) for support in constructing the heart muscle and torso model.

GRANTS

This research is supported by the Japan Science and Technology Agency through its “University-Industry Collaborative Grants Fostering Innovation in Technology-Seeds” and the Japan Society for the Promotion of Science through its “Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program)”.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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