Exploring Ventricular Repolarization Gradients in Control Subjects Using the Equivalent Dipole Layer

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Abstract

The electrical activity underlying the T-wave is less well understood compared to the QRS complex. In this study we aim to investigate the relationship between T-wave morphology and the underlying ventricular repolarization gradients using the equivalent dipole layer (EDL).

Body-surface-potential-maps (67-leads) were obtained in nine control subjects. Subject specific CT/MRI-based anatomical heart/torso models with electrode positions were created. The boundary element method was used to compute the transfer matrix to account for the volume conductor effects. The source strength at each ventricular node of the EDL was defined by the shape of the transmembrane potential (TMP). A new template for the TMP was created and different slopes were tested for the plateau phase of the TMP. Three ventricular gradients were applied: a) transmural, b) interventricular c) apico-basal and d) combined.

Realistic T-waves could be simulated for all three ventricular repolarization gradients with the apico-basal gradient resulting in the best fit. Combination of all three gradients further improved the match between measured and simulated T-waves, indicating that all three gradients are required in the genesis of the T-wave. The knowledge obtained in this study will be used to optimize the initial estimate in our EDL based inverse procedure.

1. Introduction

The electrical activity causing the T-wave is less well understood compared to the genesis of the QRS complex. In contrast to the fast processes of activation, repolarization is characterized by small local electrical gradients and simultaneous electrical activity for a longer period (more than 200-300ms). To better understand the relation between local electrical activity (e.g. transmembrane potentials (TMP)) and body surface potentials, we used the equivalent dipole layer (EDL) source model. In this model, the parametrized TMP at the surface bounding the myocardium determine the electric potentials at the body surface (the electrocardiogram (ECG)). [1] By adjusting the shape and timing of the local TMP, we can investigate the effect of ventricular repolarization gradients on T-wave morphology.

The use of a parametrized TMP model makes the EDL-based inverse estimation of local repolarization times a non-linear problem requiring an initial estimate. The initial estimate of ventricular activation was recently improved by incorporating the His-Purkinje effect of activation.[2] In this study, we investigate different ventricular repolarization gradients and its effect on T-wave morphology with the goal to improve the initial estimate of repolarization in future studies.

2. Methods

2.1 Study population

We used a study population of nine individuals who were clinically referred for cardiac magnetic resonance imaging (CMR). Each subject underwent 67-elektrode body surface potential mapping (BSPM) within 32 days before/after CMR. BSPM was recorded for five minutes with the patient in resting supine position. All subjects had no cardiovascular diseases or risk factors, QRS duration was <120ms, and CMR showed no structural or functional heart disease.

2.2 Data processing

BSPM signals were processed and analyzed using MATLAB (R2019B). Signals were down sampled to 1000 Hz, high-pass filtered (0.25 Hz), low-pass filtered (200 Hz) and notch filtered (50 Hz). A median beat was computed as previously described and the root mean square (RMS) signal was used to manually annotate the signal.[3]

A subject specific CMR based anatomical model was created for all subjects. Lead positions were captured using a 3D camera during the BSPM and registered to the torso model. Each model consisted of triangulated surface meshes of the ventricular myocardium, blood pools, thorax and lungs with the following assigned conductivities 0.2 S/m, 0.6 S/m, 0.4 S/m and 0.2 S/m respectively. In the cardiac model, the right ventricular, left ventricular, endocardial, epicardial and septal nodes were specified.

2.3 Simulating Body Surface Potentials

The boundary element method was used to compute the transfer matrix to account for the volume conductor effects. [4] The EDL was used as a cardiac source model to simulate body surface potentials. The source strength at each ventricular node of the EDL was defined by the shape of the TMP and was set to 40 mV.[4] Phase 0 of the TMP was not taken into account in this study and was therefore not part of the parametrized TMP. The normalized shape of the TMP (V_m) was determined by the multiplication of a linear line with a sigmoid curve [1], representing the plateau phase and repolarization phase respectively:

$$V_m(t) = (1 + at) \frac{1}{1 + e^{R(t - T_{rep})}} \qquad \text{(eq. 1)}$$

With the normalized TMP amplitude equal to 1, a being the downslope of the linear line set at 5%, 10%, 20% and 40% decline at 200ms (**Figure 1**), t the time after the end of depolarization of the simulated TMP, R the slope of the sigmoid curve and T_{rep} the local repolarization time. R was determined using an algorithm based on the dominant T-wave (T_{dom}). [1] T_{dom} was computed as previously described and the integral of T_{dom} was subtracted from the value 1, resulting in $T_{dom\text{-}int}$. The slope of a sigmoid curve was then varied to determine the best fit with the decreasing part of $T_{dom\text{-}int}$. The best fit (lowest relative difference (RD)) of the sigmoid curve with $T_{dom\text{-}int}$ was used to derive R.

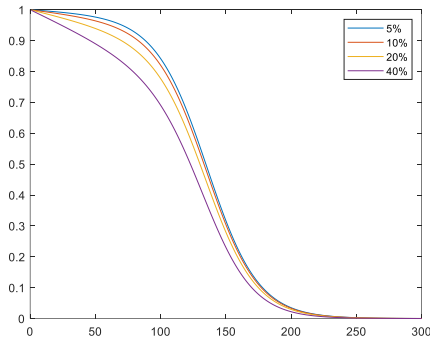**Figure 1** *Example of a transmembrane potential (eq. 1) with different slopes a for the linear line.*

2.4 Ventricular Repolarization Gradients

Differences in repolarization times were applied to simulate ventricular repolarization gradients (**Figure 2**). A difference in repolarization times was applied between the epicardial, endocardial and septal nodes to simulate a transmural ventricular repolarization gradient. To simulate an interventricular repolarization gradient, a difference in repolarization times between the right ventricular, left ventricular and septal nodes was applied. To simulate an apico-basal ventricular gradient, a node on the epicardial apical region was selected and repolarization times increased - depending on their geodesic distance to the apex - towards the base. The selected node in the apical region was determined by the best fit (highest correlation coefficient (CC)) between simulated and measured T-waves. The difference in repolarization times (amount of ventricular repolarization gradient) was also determined by the best fit (highest CC) between simulated and measured T-waves.

For the combined ventricular repolarization gradient, the ventricular repolarization gradient with the best fit (highest CC) was used as a basis and the other two ventricular repolarization gradients were added until the best fit (highest CC) was reached.

T-waves were simulated using the described template of the transmembrane potential (eq. 1) for all the four different ventricular repolarization gradients. The correspondence between simulated and measured T-waves was assessed using the CC and RD. On a group level, values were presented as median (Q1;Q3).

3. Results

Four different ventricular repolarization gradients (**Figure 2**) were tested for the nine individual cases. Concordant T-waves could be simulated for a transmural ventricular repolarization gradient if repolarization times of the epicardium were shorter than the endocardium. For the interventricular repolarization gradient, concordant T-waves could be simulated if the repolarization times of the left ventricle were shorter than the right ventricle. Concordant T-waves could be simulated for the apico-basal ventricular repolarization gradient if repolarization times increased from apex towards base.

An apico-basal repolarization gradient resulted in the highest correspondence between measured and simulated T-waves (**Table 1**). The poorest waveform match between the measured and simulated T-waves (CC) was observed applying an interventricular gradient and the poorest amplitude match between the measured and simulated T-waves (RD) was observed applying a transmural gradient.

The correlation (CC) between the simulated and measured T-waves was independent of the steepness of the plateau slope but the waveform amplitude matched better (smaller RD) when a different steepness of the plateau slope was selected (**Table 1**). For a transmural gradient, the RD between the simulated and measured T-waves decreased for a steeper plateau slope whereas the RD increased for a steeper plateau slope in case of an interventricular, apico-basal or combined ventricular gradient.
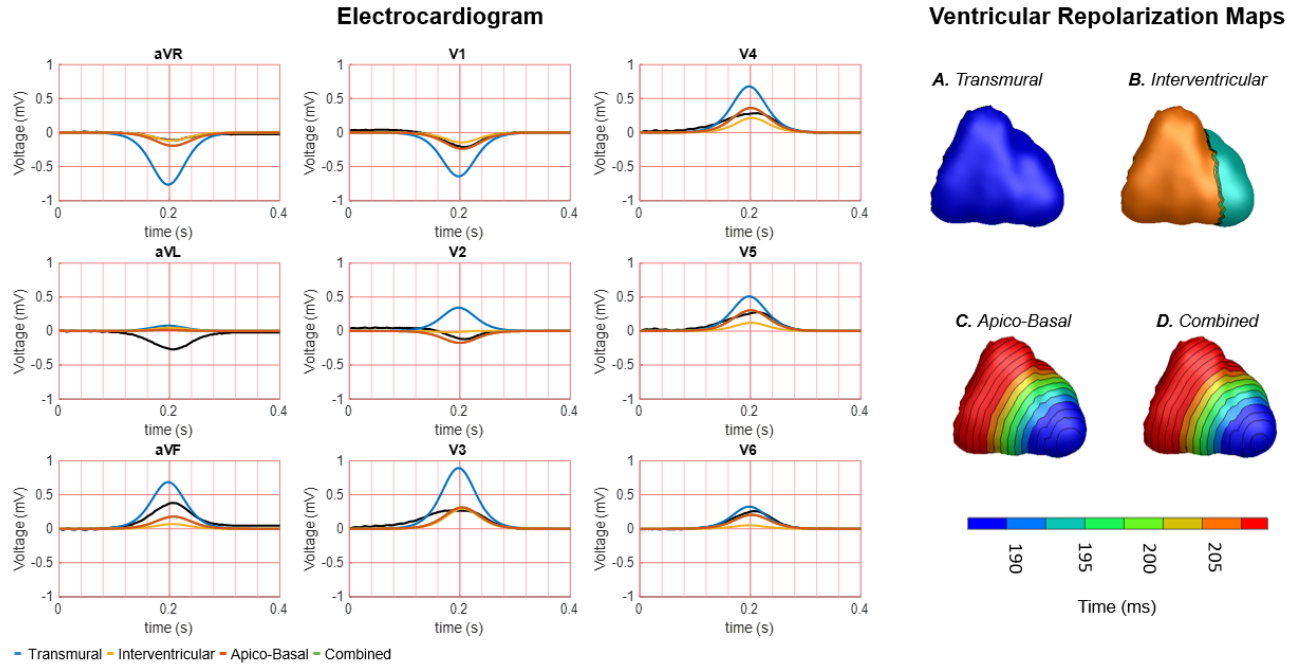
Electrocardiogram

Ventricular Repolarization Maps

Figure 2: *Effect of ventricular repolarization gradients on T-wave morphology for a = 5% (eq.1) in representative case. The ventricular repolarization maps are displayed in the right panel. Lead aVR, aVL, aVF, V1, V2, V3, V4, V5 and V6 of the 12-lead ECG for all simulated repolarization gradients are displayed in the left panel. The simulated T-waves of the combined gradient are not visible because of minimal differences between the apico-basal and combined ventricular repolarization gradient. A transmural ventricular repolarization gradient resulted in a correlation coefficient (CC) of 0.77 and a relative difference (RD) of 1.98 in the body-surface-potential-map (BSPM). An interventricular repolarization gradient resulted in CC 0.81 and RD 0.66, an apico-basal ventricular repolarization gradient resulted in CC 0.91 and RD 0.43 and a combined gradient in CC 0.92 and RD 0.43.*

Table 1. *T-wave correspondence between simulated and measured T-waves for all ventricular repolarization gradients and different slopes a for the linear line (eq.1) . The first row represents the corelation coefficient (CC), the second row the relative difference (RD), the third and fourth row the applied gradient where the combined gradient consists of a transmural gradient (third row) and an interventricular gradient (fourth row).*

a	Transmural	Interventricular	Apico-basal	Combined
5%	0.77(0.70;0.78)	0.72(0.66;0.80)	0.83(0.79;0.89)	0.84(0.80;0.88)
	1.98(1.33;2.50)	0.82(0.72;0.85)	0.67(0.62;0.72)	0.59(0.55;0.70)
	30 (30;30)	-8 (-11;-4)	65 (56;67)	0 (-3; 0)
				-1 (-1; 0)
10%	0.77(0.70;0.78)	0.72(0.65;0.77)	0.83(0.79;0.89)	0.84(0.81;0.88)
	1.93(1.25;2.32)	0.82(0.73;0.85)	0.68(0.57;0.70)	0.59(0.53;0.70)
	30 (29;30)	-8 (-11;-4)	65 (56;67)	0 (-4; 0)
				-1 (-1; 0)
20%	0.77(0.70;0.78)	0.72(0.66;0.77)	0.83(0.79;0.89)	0.84(0.81;0.88)
	1.60(1.02;1.98)	0.84(0.74;0.86)	0.69(0.54;0.72)	0.59(0.53;0.68)
	30 (28-30)	-8 (-11;-4)	65 (56;67)	-1 (-5;-1)
				0 (0; 0)
40%	0.77(0.70;0.78)	0.72(0.66;0.77)	0.83(0.79;0.89)	0.83(0.81;0.86)
	1.10(0.76;1.32)	0.88(0.79;0.90)	0.74(0.63;0.77)	0.61(0.58;0.70)
	30 (28-30)	-8 (-11;-4)	65 (56;67)	-3 (-8;-3)
				2 (0; 2)

The apico-basal gradient was used in the combined ventricular gradient as a basis because this gradient resulted in the best fit with the measured T-waves. The transmural repolarization gradient contributed more to the final fit compared to the interventricular gradient (**Table 1**). Combining all three gradients, resulted in a similar waveform (CC) but a better fit with the measured T-waves regarding signal amplitude (RD).

The lowest ventricular gradient (difference in repolarization times, **Table 1**) was applied for the interventricular gradient, followed by the transmural gradient and apico-basal gradient. The difference in repolarization times, resulting in the ventricular gradients, were independent of the steepness of the plateau slope, except for the combined gradient. Both the gradient of the transmural and interventricular gradient increased for a steeper plateau slope.

4. Discussion

In this study, we introduce a method to study the effect of global ventricular repolarization gradients on T-wave morphology. An apico-basal repolarization gradient resulted in the best match between measured and simulated

T-waves. However, realistic T-waves could also be simulated with a transmural or interventricular gradient. In addition, the best fit was reached when the apico-basal gradient was combined with the interventricular and transmural gradient indicating that all three gradients are important in T-wave genesis.

Longer endocardial repolarization times compared to epicardial repolarization times, resulting in a transmural ventricular gradient, have also been described in studies on intact human hearts, findings in wedge preparations and other computational studies.[5] However, reports on the longer repolarization times of the right ventricle compared to the left ventricle (the interventricular gradient) and the increasing repolarization times from the apex towards the base (apico-basal gradient), are contradictory in literature.[6] The apico-basal gradient found in our study further supports our hypothesis also found by CineECG. Using CineECG, we observed that the PathECG was directed from the base towards the apex during repolarization. However, the electrical gradient during repolarization – the repolarization sequence – is opposite to the vector derived PathECG direction. Thus, an apico-basal ventricular repolarization gradient was also found using CineECG.[7]

The discrepancy in literature may be explained by the T-wave not being a result of a single ventricular gradient. Although we were able to simulate realistic T-waves using global gradients, we hypothesize that the repolarization is characterized by smaller local repolarization gradients, especially in diseased hearts. This was also indicated in a study by Opthof. et al. where they found a bigger difference in repolarization patterns compared to activation patterns in three donor hearts. The total repolarization time, the start locations of the repolarization sequence, the end locations of the repolarization sequence and the resulting repolarization gradient were found to be different among the donor hearts. [6]

A uniform shape for the TMP template where only the shifting in time between ventricular nodes is varied, is thus not a representative physiological model. Therefore, this study presents a new design for the TMP template where the plateau slope can be optimized as well during an inverse procedure. The plateau slope was not affecting the applied gradient or waveform (CC) but it did affect the amplitude difference (RD) between the simulated and measured T-waves. This may especially be important in matching the ST-segment during the inverse procedure.

The obtained findings in this study will be used in our EDL based inverse procedure to optimize the initial estimate of repolarization. In this way, the initial estimate of the depolarization sequence (based on His-purkinje mediated activation) and repolarization sequence (based on ventricular gradients) are both based on cardiac electrophysiology. In future studies, the best estimate of the depolarization sequence can then be combined with the best estimate of the repolarization sequence to make a final computation for the complete QRST complex.

5.   Conclusion

In this study, we introduce a method to simulate realistic T-waves using the EDL as a cardiac source model. Realistic T-waves could be simulated for all three ventricular repolarization gradients with the apico-basal gradient resulting in the best fit. A combination of an interventricular, transmural and apico-basal gradient further improved the simulated T-waves, indicating that all three gradients are required in the genesis of the T-wave. The knowledge obtained in this study will be used to optimize the initial estimate in our EDL based inverse procedure.

Acknowledgments

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