ORIGINAL ARTICLE

The Role of Transmural Repolarization Gradient in the Inversion of Cardiac Electric Field: Model Study of ECG in Hypothermia

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Background: The changes in ventricular repolarization gradients lead to significant alterations of the electrocardiographic body surface T waves up to the T wave inversion. However, the contribution of a specific gradient remains to be elucidated. The objective of the present investigation was to study the role of the transmural repolarization gradient in the inversion of the body surface T wave with a mathematical model of the hypothermia-induced changes of ventricular repolarization.

Methods: By means of mathematical simulation, we set the hypothermic action potential duration (APD) distribution on the rabbit ventricular epicardium as it was previously experimentally documented. Then the parameters of the body surface potential distribution were tested with the introduction of different scenarios of the endocardial and epicardial APD behavior in hypothermia resulting in the unchanged, reversed or enlarged transmural repolarization gradient.

Results: The reversal of epicardial repolarization gradients (apicobasal, anterior-posterior and interventricular) caused the inversion of the T waves regardless of the direction of the transmural repolarization gradient. However, the most realistic body surface potentials were obtained when the endocardial APDs were not changed under hypothermia while the epicardial APDs prolonged. This produced the reversed and increased transmural repolarization gradient in absolute magnitude. The body surface potentials simulated under the unchanged transmural gradient were reduced in comparison to those simulated under the reversed transmural gradient.

Conclusions: The simulations demonstrated that the transmural repolarization gradient did not play a crucial role in the cardiac electric field inversion under hypothermia, but its magnitude and direction contribute to the T wave amplitude.

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The end of repolarization times (RT) gradients in the heart ventricles are the cause of the T wave genesis on the body surface ECG. On the other hand, these ventricular gradients could be related to the arrhythmia susceptibility¹ as they produce the dispersion of repolarization, a condition for

the unidirectional conduction block serving as one of the prerequisites of reentry. A transmural RT gradient is considered important^{2,3} likely due to the fact that it implies the dispersion of repolarization within the small distance which makes it more arrhythmogenic. It is therefore desirable

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to discern the contribution of the transmural RT gradient to the body surface T wave in order to predict the development of life-threatening arrhythmias.

The significant changes of the ventricular RT gradients are expected to cause an inversion of the body surface T wave. However, our recent study⁴ demonstrated that all the ventricular RT gradients complemented each other in the development of the body surface cardiac electric field and no RT gradient could be the sole cause of the T-wave inversion unless a given RT gradient is unrealistically increased. Thus, there is a challenge to discriminate the contribution of a single repolarization gradient to the body surface ECG.

Hypothermia, either accidental or therapeutic, presents a condition characterized by the prolongation of the action potential duration (APD),⁵ increased heterogeneity of repolarization^{6,7} altered arrhythmia risk⁷⁻¹⁰ and the inversion of the T wave in the body surface ECG.¹¹⁻¹⁵ The inversion of the body surface potential distribution (BSPD) during the T wave in mild hypothermia was associated with a reversal of epicardial (i.e., apicobasal, interventricular, and anteroposterior) RT gradients.¹⁶ On the other hand, the behavior of the transmural gradient in hypothermic conditions is uncertain. A number of studies suggested the preferential prolongation of the epicardial APDs compared to the endocardial ones which caused the reversal of the transmural repolarization gradient^{17,18} that was considered to cause the T wave inversion.^{17,19} In other experiments, the epicardial APDs, although prolonged by hypothermia, remained shorter than the endocardial APDs and the transmural gradient remained "normal".^{8,12,20} This implies that the cause of the hypothermic T wave inversion is a reversal of epicardial RT gradients.

The objective of the present investigation was to study the role of the transmural RT gradient in the inversion of the body surface T wave in the framework of a mathematical model of hypothermia-induced changes of ventricular repolarization. We set the hypothermic APD distribution on the epicardium of the rabbit ventricles as it was documented in our previous study.¹⁶ Thereafter, the parameters of the BSPD were tested with the introduction of different scenarios of the endocardial and epicardial APD behavior in hypothermia.

METHODS

Model Structure

Simulations were carried out in the framework of the so-called cellular automaton, a discrete computer model of the rabbit heart ventricles based on the experimental measurements reported by our group.^{16,21} The shape of the model was reconstructed from the transversal and longitudinal cross-sections of the rabbit ventricles. The model had a hexagonal structure and consisted of $\approx 100,000$ cells with intercellular space of 0.25 mm.²² Each model cell had 12 equidistant "neighbors." The morphology of the action potentials was simulated using the rabbit ventricular action potential model²³ and was modified by lengthening or shortening the repolarization phase depending on the duration value in each model cell.

Activation Sequence

The initial foci of activation were set in the interventricular septum, on the border of its middle and lower portions, and in the subendocardium of the left ventricular apex. In order to imitate the conducting system, the activation velocity was three times higher in the subendocardial layers than in the rest of the model.

APD Distributions

The APD values in each model cell were simulated by interpolation on the basis of the experimental values in 20 nodal points distributed over the epi- and endocardium of the model.²¹ The location of the nodal points allows simulating apicobasal, anterior-posterior, left-to-right and transmural APD gradients.

The normothermic and hypothermic APD distributions were simulated on the basis of epicardial and intramural recordings in the rabbit at the temperature of 38 °C and 32 °C, respectively.^{16,21} According to the experimental data, epicardial APDs under hypothermia were increased nonuniformly: the maximal changes were observed at the apex (+120%) and on the anterior surface of the left ventricle (+100%), whereas the minimal alterations were at the base of the right ventricle (+7%) and on the posterior base of the ventricles (+0%). The nonuniform APD increase caused the inversion of all epicardial APD and RT gradients, that is the

Figure 1. Epicardial APD and RT gradients (apicobasal, anterior-posterior and left-to-right) in the model of the rabbit heart ventricles under normothermia (38 °C) and hypothermia (32 °C). Wide bars – APD gradients; narrow bars – the corresponding RT gradients. The APD and RT values correspond to the experimental data.¹⁶ APD = action potential duration; RT = end of repolarization times; RV = right ventricle; LV = left ventricle.

apicobasal, anterior-posterior and interventricular (left-to-right) gradients (Fig. 1).

We simulated a baseline repolarization pattern and three possible scenarios of the endocardial APD changes in regard to the epicardial APDs. Scenario A concerns normal (normothermic) APD distribution documented previously²¹ with endocardial APDs being longer than epicardial ones. In scenario B, the APD_{endo} were increased proportionally to the APD_{epi} , and hence the direction of the transmural gradient persisted. In scenario C, the APD_{endo} were increased by 50% less than the APD_{epi} , while in scenario D, the APD_{endo} were not increased at all. The values of APDs corresponding to the different simulation scenarios are depicted in Figure 2.

The RTs were calculated as a sum of the activation time and the APD value.

Body Surface Potentials

The body surface potentials were calculated as:

$$V_{obs} = -K * \sum_{i=1}^N \text{Grad}_i * \mathbf{R}/R^3,$$

where V_{obs} is the potential value in the observation point located on the body surface; K is the volume conductor property factor; $\mathbf{R}$ is the vector directed from the i th model cell into the observation point; Grad_i is the gradient of the action potential value in the i th model cell; N is the total number of model cells.

Figure 2. Transmural APD and RT gradients in different parts of the model of the rabbit heart ventricles under normothermia (38 °C) and hypothermia (32 °C). Wide bars – APD gradients, narrow bars – the corresponding RT gradients. A, normal APD distribution; B, APD_{endo} were increased proportionally to APD_{epi} ; C, APD_{endo} were increased by 50% less than APD_{epi} ; D, APD_{endo} were not increased. APD = action potential duration; RT = end of repolarization times; RV = right ventricle; LV = left ventricle; endo = endocardial; epi = epicardial.

The value of Grad_i at each time moment was calculated as:

$$\text{Grad}_i = \sum_{k=1}^{12} R_k * (p_i - p_k)$$

where $\mathbf{R}_k$ is the vector directed from the i th model cell to one of 12 neighboring model cells; p_i is the potential value in the i th model cell; p_k is the potential value in one of 12 neighboring model cells at the given time moment. Potential values in each model cell ranged from -85 to +17 mV according to the given AP morphology.

The body surface potentials were simulated taking into account realistic geometry of the torso and heart of the rabbit.

T Vector

The T vector, a resultant vector of repolarization, was calculated at each time moment as a sum of the action potential gradients in all model cells. The T vector was calculated in the 3D Cartesian coordinate system bound to the ventricles. The apicobasal axis was directed from the base to the apex, the anterior-posterior axis was directed from posterior to anterior, and the left-to-right axis was directed from the right to the left ventricle.

Figure 3. The simulated activation sequence and APD distribution under normothermia (38 °C) and hypothermia (32 °C). A, normal APD distribution; B, APD_{endo} were increased proportionally to APD_{epi}; C, APD_{endo} were increased by 50% less than APD_{epi}; D, APD_{endo} were not increased. The transversal and frontal views of the model are presented. The schematic of APD gradients calculation is depicted by arrows. APD = action potential duration; RT = end of repolarization times; endo = endocardial; epi = epicardial.

RESULTS

Activation Sequence

The activation sequences simulated for normothermia and hypothermia (Fig. 3) were similar to each other and corresponded to our experimental data.¹⁶ Activation travelled from the apex to the base of the ventricles and from endo- to epicardium. The interventricular septum was activated from the left to the right. The last areas to be activated were the subepicardium of the left ventricular base and the subendocardium of the right side of the septal base. The hypothermic activation sequence was several milliseconds longer than the normothermic one.

Figure 4. Body surface potential distribution in the rabbit under normothermia (38 °C) and hypothermia (32 °C) at the moment of the T peak, experimentally measured and simulated.¹⁶ A, normal APD distribution; B, APD_{endo} were increased proportionally to APD_{epi}; C, APD_{endo} were increased by 50% less than APD_{epi}; D, APD_{endo} were not increased. The left and right sides of the maps correspond to the ventral and dorsal body surfaces, respectively. Each map is accompanied by the simulated ECG (the second limb lead) with a time marker. The potential scale is given at the bottom. The simulated precordial leads (V₃) are shown in the lower left corner.

BSPD and T Vector

The simulated normothermic BSPD was in a good correspondence with the data on the body surface potential mapping in the rabbit (Fig. 4).¹⁶ The resultant repolarization T vector simulated for normothermia was directed forward, downward and to the left (Fig. 5). Hypothermia caused total inversion of the cardiac electric field: locations of the zones of positive and negative potentials and the potential extrema transformed into the opposite (Fig. 4). The amplitudes of the potentials measured under hypothermia were comparable with those measured under normothermia (Fig. 4).

In the model, the inversion of the epicardial repolarization RT gradients (apicobasal, anterior-posterior and left-to-right), regardless of the value and the direction of the transmural RT gradient, caused global changes in the direction of the T vector as it was directed backward, upward and to the right, nearly opposite to the baseline

Figure 5. The transversal and frontal projections of the resultant T vector simulated for normothermia (38 °C) and hypothermia (32 °C) at the moment of the T peak. A, normal APD distribution; B, APD_{endo} were increased proportionally to APD_{epi} ; C, APD_{endo} were increased by 50% less than APD_{epi} ; D, APD_{endo} were not increased. APD = action potential duration; endo = endocardial; epi = epicardial.

(Fig. 5). Accordingly, the inversion of the BSPD was observed at all transmural RT gradients (Fig. 4). At the same time, the length of the T vector and the amplitudes of the body surface potentials significantly depended on the magnitude and direction of the transmural RT gradient.

When the APD_{endo} were increased proportionally to the APD_{epi} (scenario B), the transmural RT gradient was slightly increased but did not change its direction (Fig. 2). In this case, the T vector was significantly shortened (Fig. 5). Accordingly, the amplitudes of the potentials were lower in scenario B as compared to "normothermic" scenario A (Fig. 4). When the APD_{endo} were increased by 50% less than APD_{epi} (scenario C), there was a reversal of the transmural RT gradient direction, whereas the magnitude of the transmural RT gradient was approximately the same as for the scenario B (Fig. 2). The length of the T vector and, correspondingly, the T wave amplitudes were greater in scenario C than those in scenario B (Figs. 4 and 5). When the APD_{endo} were not changed (scenario D), the magnitude of the reversed transmural RT gradient was substantially higher than in the scenario C (Fig. 2). Correspondingly, the length of the T vector and the T wave amplitudes were greater in scenario D as compared to scenarios

B and C and similar to those simulated for normothermia (Figs. 4 and 5). Thus, the greatest reversed transmural RT gradient produced the longest T vector and, correspondingly, the maximal T wave amplitudes.

DISCUSSION

What are the Conditions for T Wave Inversion?

The inversion of T waves is a widespread phenomenon. It may present a normal variant²⁴ or manifest a number of cardiac pathologies, including myocardial ischemia,^{25,26} acute pulmonary embolism,²⁷⁻²⁹ takotsubo cardiomyopathy,²⁸ cardiac memory effect,³⁰⁻³² altered sympathetic tone.³³ Correct interpretation of this electrocardiographic phenomenon in various conditions requires knowing which ventricular repolarization gradients are modified and how these gradients express in the BSPD. For example, Coronel et al.³⁰ observed an association between the emergence of cardiac memory effect and the development of the transmural gradient of repolarization. Furthermore, diffuse subendocardial ischemia would primarily influence the transmural gradient, while the transmural and focal ischemic process would affect other gradients.

We Studied the BSPD Development under the Different Transmural Gradient, with all the Other Gradients Being Reversed

The aim of this study was to evaluate the role of the transmural APD and RT gradient in the experimentally documented inversion of the BSPD. The model condition was hypothermia, where the body surface T wave changed its polarity and epicardial repolarization gradients reversed. We tested three different settings with the transmural RT gradient either persisting nearly normal (B), reversed in direction (C), or reversed in direction with the increase in its magnitude (D), respectively. The reversal of the only transmural RT gradient with unchanged apicobasal, anterior-posterior and left-to-right gradients could theoretically lead to the inversion of the cardiac electric field, which required an extremely large value of the reversed transmural RT gradient.⁴ We did not consider this pattern of repolarization in the present study

because nonuniform changes of the epicardial APDs under hypothermia have been experimentally documented.^{6,16}

The Reversal of Just the Epicardial Gradients is Sufficient for not Just Amplitude Changes, but for the Inversion of BSPD as Well

Our simulations showed that the reversal of the epicardial RT gradients (apicobasal, anterior-posterior and left-to-right) caused voltage changes. Moreover, inversion of the cardiac electric field was observed in conditions of epicardial gradients reversal, *regardless* of the direction of the transmural RT gradient. However, the body surface potentials simulated under the nonreversed transmural RT gradient were reduced in comparison to those experimentally measured¹⁶ and simulated in the present study under the reversed transmural gradient. The previous simulations⁴ showed that the apicobasal, left-to-right and anteroposterior RT gradients produced the T vectors with the exact apicobasal, left-to-right and anteroposterior direction, respectively. It is therefore evident that the reversal of an epicardial gradient leads to the inversion of the T vector in the correspondent direction and the inversion of the T waves in the correspondent leads. It has been shown experimentally that the epicardial gradients—in particular, the apicobasal gradient—could be associated with T wave polarity.^{16, 34–36}

The Transmural RT Gradient Produced the 3D T Vector

The role of the transmural RT gradient in cardiac electric field inversion under hypothermia appears to be more complex than the role of “simple” unidirectional epicardial gradients. Due to the curvature of the ventricular walls, the transmural RT gradient produced the unidirectional T vector only when the cardiac electric field is generated by just a wedge taken from a ventricular wall, whereas the whole ventricular transmural RT gradient produced the 3D T vector oriented both in the transverse and the apicobasal directions, with the apicobasal component directed from the base to the apex.⁴ It should be also noted that the activation sequence has a different effect on the magnitude of the transmural gradient under normo- and hypothermia. Under normal

conditions, when endocardial APDs are longer than epicardial APDs, the transmural gradient of activation times decreases the transmural RT gradient, whereas under hypothermia the transmural activation gradient amplifies the magnitude of the transmural RT gradient and its contribution to the BSPD.

Transmural Gradient Affects Voltage

In hypothermia, the reversed epicardial repolarization gradients produced the resultant T vector directed from the apex to the base. Therefore, if the transmural RT gradient under hypothermia remained normal, it produced the T vector directed oppositely to the resultant T vector; and as a result of superposition, the resultant T vector decreased. By contrast, if the transmural gradient is reversed, it produces a T vector directed from the apex to the base of the ventricles. In this case, the resultant T vector amplifies and, consequently, the amplitudes of the body surface potentials increase. This explains why the greatest reversed transmural RT gradient in the model produced the maximal T vector, and, vice versa, the nonreversed transmural RT gradient produced the minimal T vector. The most realistic body surface potentials were obtained when the endocardial APDs were not changed under hypothermia. In this case (D), the endocardial APDs became shorter than the epicardial ones, the transmural gradient reversed and had a significant magnitude. These simulation results are consistent with experimental studies where the preferential lengthening of the epicardial APDs resulted in the reversal of the transmural APD gradient under hypothermia.^{17, 18}

Conclusions

The simulations in our study demonstrated that the sufficient condition for BSPD inversion under hypothermia (implying changes not only in the amplitudes of the T wave, but also the T wave polarities in the majority of leads) is the experimentally documented inversion of epicardial RT gradients. Therefore, the transmural RT gradient does not play a predominant role in hypothermic BSPD inversion. At the same time, the magnitude and direction of the transmural RT gradient contribute to the amplitudes of the inverted hypothermic T waves: the normal transmural gradient ($RT_{\text{endo}} > RT_{\text{epi}}$) decreases the T wave

amplitudes, while the inverted transmural gradient ($RT_{\text{endo}} < RT_{\text{epi}}$) amplifies the T wave amplitudes, with greater inverted transmural gradient causing greater T wave amplitudes.

While these findings were obtained on the basis of the model of hypothermia, they may be generalized for other settings (with appropriate caution).

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