EPICARDIAL STIMULATION OF A VIRTUAL LEFT VENTRICULAR WALL COMPRISING HETEROGENEITY AND ANISOTROPY

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Abstract: Regional heterogeneity in ion channel expression across the human ventricular wall induces variable action potential morphology and a transmural dispersion of repolarization (TDR) within the heart wall. Epicardial stimulation applied during e.g. biventricular pacing prolongs the QT interval and the TDR is increased. This study investigates the variances of activation and repolarization due to epicardial pacing and the effects on transmural ECGs in a heterogeneous and anisotropic virtual representation of the human left ventricle. As in measurement, the QT interval was increased without simultaneous prolongation of the action potential durations. Simulation results suggested that the TDR is in principle increased in a wedge preparation but depended in the more realistic anatomy on the distance of the considered tissue to the pacing electrode.

Introduction

Cells isolated from different regions within the ventricular wall display different characteristic response to pharmacological agents, expression of pathology, and their electrophysiological properties [1]. The main distinctive feature comparing these cardiomyocytes is the variable action potential shape and duration from endocardium to epicardium due to varying ion channel characteristics. This induces a transmural dispersion of repolarization (TDR) within the ventricular wall. Epicardial stimulation by e.g. using biventricular pacing prolongs the QT interval and the TDR as an index of arrhythmogenicity is increased providing the substrate for the development of a ventricular tachycardia [2, 3].

This study utilized a computational model of human ventricular cardiomyocytes to create an inhomogeneous and anisotropic virtual representation of the human left ventricle. The impact of epicardial pacing on the activation and repolarization of ventricular tissue as well as the effects on transmural ECGs were investigated. A long and thin model of electrically coupled cells was used to show the principal influence of epicardial stimulation. Excitation conduction was simulated and transmural ECGs were computed. Simulations in a thin three-dimensional slice of the Visible Female left ventricular data set provided insights in the more complex activation and repolarization sequence in a realistic ventricular geometry.

Materials and Methods

The simulation environment consisted of three major components: cellular electrophysiology, excitation conduction and anatomical structure. A detailed biophysical model of the cellular electrophysiology described the behavior of a single cardiomyocyte. Modeling of a multicellular environment required an anatomical representation of the considered tissue and a method defining the electrical coupling between the discrete excitable cells. Heterogeneous distribution of the ion channel characteristics as well as realistic fiber orientation were included in the virtual tissue.

A computational model of a human ventricular cardiomyocyte forms the electrophysiological base of this work [4]. This model consists of a set of coupled nonlinear ordinary differential equations describing state variables by Hodgkin-Huxley like formalisms. Furthermore, these equations define the ionic currents flowing through the membrane proteins and the transmembrane voltage. The currents are time- and voltage-dependent and interact with the ion concentrations in the intra- and extracellular space. The model includes the handling of intracellular calcium by the sarcoplasmic reticulum and takes several buffers for calcium such as troponin, calsequestrin, and calmodulin into account. A forward Euler method [5] with a time increment of 20 μs was used to solve the set of differential equations.

This model was modified according to several measurements of single ion channel properties on human cardiac myocytes [6]. The environmental conditions of these measurements were transferred to the simulation and the equation parameters of the involved ionic currents were adapted to minimize the difference between experimental and simulation results. To obtain the electrophysiological behavior of subendocardial, subepicardial and M cells, the maximum current density of the transmurally heterogeneous distributed ionic channels differs between these kind of cardiomyocytes. These adaptations concerned the transient outward potassium current I_{to}, the slow component of the delayed rectifier potassium current I_{Ks}, the inward rectifier potassium current I_{K1}, and the current I_{NaCa} due to the sodium-calcium exchanger . With this configuration, action potentials (AP) elicited in subepicardial myocytes display a prominent notch in the first phase of the repolarization and M cells produce APs with the longest duration as reported in measurements [6].

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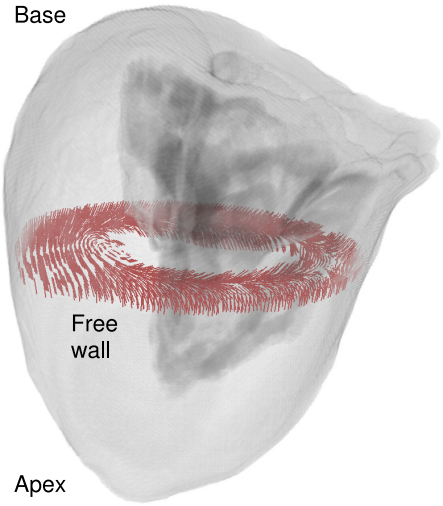

Figure 1: Human left ventricle obtained from the Visible Female data set in a transparent view. The highlighted cross-sectional slice perpendicular to the longitudinal axis was used to study the excitation conduction in a realistic anatomical structure under consideration of electrophysiological heterogeneity and electrical anisotropy. The rotating fiber orientation is depicted in several exemplary voxels. The used parallelepiped anatomical structure described a line from endocardium to epicardium within this slice and neglected electrical anisotropy.

The single cell environment was transferred to a model of excitable tissue. Anisotropic electrical coupling between the cardiomyocytes was obtained by usage of the bidomain reaction-diffusion model [7]. It depicts current flow through gap junctions and intracellular as well as extracellular space. An iterative Gauss-Seidel method for each time step of 20 μs was used to solve the Poisson type equations. Under the assumption that the intra- and extracellular domain have equal anisotropy ratios, the bidomain model can be reduced to the so-called monodomain model and the entire tissue volume is represented as one domain with anisotropic conductivities. To simulate the transmurally heterogeneous ion channel characteristics within the heart wall, a spline approximation for the varying maximum current densities for the cells between the anchor points was used. The M cells were located relatively near to the endocardium. Endocardial stimulation led to a realistic upright positive T wave with the same polarity as the R wave in the transmurally computed ECG [8].

A long and thin three-dimensional parallelepiped geometry described an approximately one-dimensional line through the ventricular wall from endocardium to epicardium and considered transmural heterogeneity of the electrophysiological properties within the tissue in the absence of electrical anisotropy [6]. This anatomical representation consisted of 96x9x9 cubic volume elements (voxel) and was surrounded by a bath with a thickness of 5 voxels in each direction. The single cells were electrically coupled by the bidomain diffusion model. Transmural ECGs were computed as the extracellular potential difference in the bath medium close to epicardial and endocardial border.

A realistic orientation of the muscle fibers was integrated in a three-dimensional slice of the Visible Female left ventricle perpendicular to its longitudinal axis. This data set consisted of nearly 110.000 excitable voxels and is visualized in Fig. 1 within the whole left ventricle. The transmurally varying fiber orientation was reconstructed with a rule-based algorithm derived from anatomical studies [9]. Hence, the fibers twisted from subendocardial (55°) via midmyocardial (0°) to subepicardial myocytes (-75°) in a three-dimensional way. Electrical coupling of the cells was obtained by means of the monodomain diffusion model. Endocardial activation was initiated at electrical transition points imitating the Purkinje fiber network. These points were set semi-automatically. Epicardial attached electrodes were simulated by activation of subepicardial myocytes located on the free wall of the ventricle nearby the electrodes. The diameter of this electrodes was set to 3 mm. The edge length of a cubic voxel was 0.2 mm in both anatomical structures.

Results

Simulations in the parallelepiped bidomain model showed that the final repolarization of the tissue appeared in the area of the M cells due to their prolonged action potential duration (APD) after endocardial stimulation (Fig. 2). This heterogeneous repolarization across the ventricular wall is visible as a positive T wave in the transmural ECG (Fig. 3) and is consistent with experimental findings [1]. Epicardial stimulation reversed the direction of the excitation conduction visible as inversed polarity of the QRS complex in the ECG. The delayed activation and repolarization of the M cells occuring after an epicardial pacing impulse increased the TDR within the tissue since the M cells were located near endocardial site. Epicardial pacing led to a more pronounced T wave with elevated amplitude and widened characteristics in the transmural computed ECG (Fig. 3). The time to full repolarization of the tissue corresponding to the QT time was prolonged from 337 ms after endocardial to 350 ms after epicardial stimulation (Fig. 2).

In the three-dimensional slice, the physiological excitation of the tissue due to activation of the Purkinje fiber network led to a stimulation of subendocardial cells. The activation wave front conducted through the heart wall and ended in subepicardial cells. Repolarization started nearly simultaneously in subendocardial and subepicardial cells and vanished in the midmyocardial areas. 329 ms after the stimulation of the slice the whole tissue reached its resting state (Fig. 4 top). The activation sequence initiated by epicardially attached electrodes started in subepicardial myocytes near to the electrodes (Fig. 4 bottom). From there it spread out in the tissue. Due to the small helix angle of the muscle fibers in the

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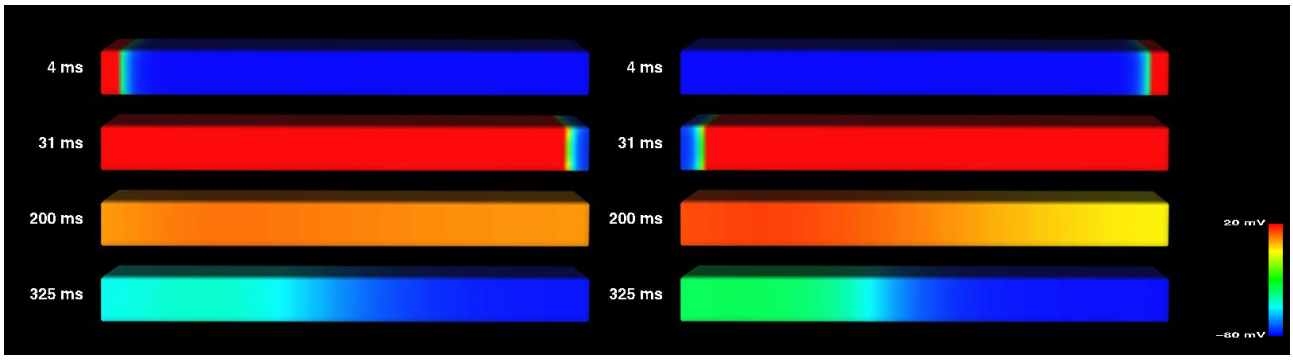

Figure 2: Transmembrane voltage distribution in a parallelepiped three-dimensional anatomical structure including heterogeneous electrophysiology from subendocardium (left side) to subepicardium (right side) at different time steps after the initial activation. Blue color corresponds to the resting potential of the cardiomyocytes and red depicts activated tissue. The left column shows physiological subendocardial stimulation via Purkinje fibers, the right column the activation of the tissue due to epicardial pacing. Epicardial pacing inversed the activation sequence, prolonged the QT time to the total repolarization of the tissue and increased the TDR due to the delayed activation and repolarization of the M cells.

midmyocardial region and the increased excitation velocity along a muscle fiber considered by the excitation conduction model, the activation of neighbouring myocytes was fastest in the midmyocardium. Thus, in a certain distance from the pacing electrode, the depolarization started in the midmyocardium and conducted in subendocardial and subepicardial cells. This early activation of M cells compared to the surrounding tissue decreased the TDR in this area. The final repolarization occurs in the tissue opposite to the pacing electrode. The intraventricular dispersion of the repolarization was noticably augmented after epicardial stimulation caused by the altered stimulation sequence of the tissue. Due to the prolonged activation pathway, the time to full activation and recovery of the tissue was increased (Tab. 1).

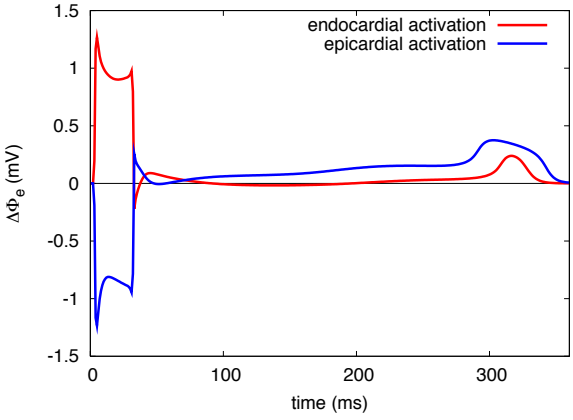

Figure 3: Transmural ECGs computed after endocardial and epicardial pacing in the parallelepiped geometry. The epicardial activation led to an inversed QRS complex. The T wave is positive in both cases due to the final repolarization in M cells. Epicardial stimulation emphasized the T wave indicating an increased TDR in the area adjacent to the electrode.

Table 1: Time to full activation t_a and repolarization t_r in the slice after endocardial and epicardial pacing. t_a is defined as the time where the transmembrane voltage V_m of all excitable myocytes is positive. Time t_r corresponds to the QT interval and is reached if V_m is below -75 mV in the whole tissue.

	time t_a to full activation	**time t_r to full repolarization**
endocardial activation	40 ms	329 ms
epicardial stimulation	61 ms	357 ms

Conclusion

The model of heterogeneous cellular electrophysiology reproduced the behavior of the distinctive cardiac cell types within the ventricular wall. Due to the prolonged APD in M cells, the repolarization ended in the midmyocardial region after physiological endocardial stimulation in both investigated anatomical structures. Simulations in the parallelepiped geometry showed that under the consideration of an equal activation pathway epicardial stimulation increased the TDR and prolonged the QT time but did neither effect the activation times nor the APDs of each cell. The transmurally computed ECGs develop the typical characteristics: an inversed QRS complex and a widened T wave with increased amplitude [2, 3]. In the slice anatomy, the epicardial pacing prolonged the activation pathway and thus the activation time. The TDR was increased due to the earlier activation of epicardium and the delayed activation and repolarization of the M cells nearby the electrodes. Activation of the tissue in a certain distance from the pacing electrode started from midmyocardium and spread from there into tissue. Therefore the TDR was reduced in this region compared to endocardial stimulation. The prolonged

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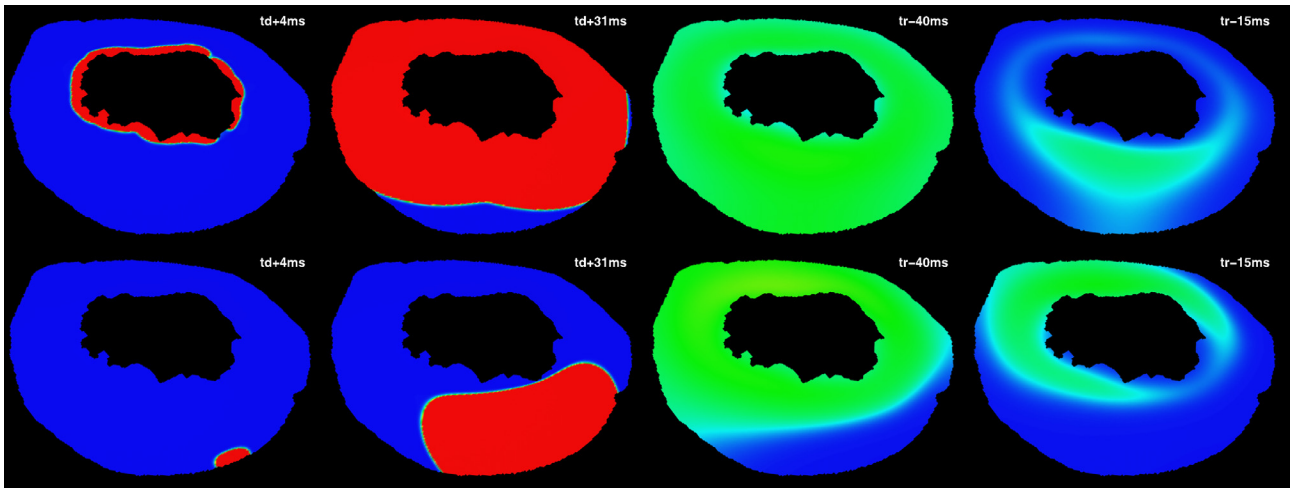

Figure 4: Excitation conduction and repolarization in the left ventricular slice obtained from the Visible Female data set at different time steps from depolarization t_d and to full repolarization t_r. The transmembrane voltage distribution is illustrated with the same color code as in Fig. 2. After physiological activation (top) via the Purkinje fiber network the excitation conducted from the elicited subendocardial myocytes uniformly in tissue. Repolarization vanished in the region of the M cells. Epicardial pacing (bottom) altered to activation sequence and prolonged its pathway and thus increased the intraventricular dispersion of the activation and repolarization. The resulting TDR depended on the position within the tissue and its distance to the pacing electrode.

QT time to total repolarization was mainly due to the increased activation time. The intraventricular dispersion of the repolarization caused by the modified activation sequence or the increased TDR nearby the electrodes can support the initiation and maintenance of arrhythmogenic events.

The alterations of the activation and repolarization sequence due to epicardial pacing in a whole heart anatomy including electrophysiological heterogeneity and electrical anisotropy and its impact on the standard ECG measured on the body surface has to be determined in future.

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