Propagation of Electrical Excitation in Isolated Rabbit Hearts: Influence of Stimulation Protocol and Spatial Coupling

S Bauer[1], S Fruhner[1,2], I Romero[1], H Engel[2], M Bär[1]

[1]Physikalisch Technische Bundesanstalt, Berlin, Germany
[2]Technische Universität Berlin, Berlin, Germany

Abstract

Propagation of electrical excitation in the rabbit heart was computed using a simple realistic ionic model. Excitation was initiated by two different stimulation protocols. The simulations were compared to surface electrograms obtained from autonomously beating rabbit hearts in Langendorff perfusion. Additionally the influence of a gap junction blocking drug (palmitoleic acid) was investigated. After filtering the data, they were characterized by surface propagation speed maps. Under influence of the drug the propagation speeds decreased by 10-20% while the QRS time increased by approximately 10%. The first observation could be confirmed by simulations where the speeds were lowered by 10-30%. The QRS time showed a larger increase by up to 33%. The first protocol with a stimulation near the apex showed a more realistic shape of the QRS complex and reproduced the QRS time more accurately. The second, Purkinje type protocol yielded better agreement concerning the propagation speeds.

1. Introduction

In recent years, many sophisticated computer models were developed to describe the physiology of animal and human hearts. Such models are still debated controversially with emphasis on how the individual geometry, fibre orientations and the physiology of the tissue should be treated. In this work we focus on how experimental data can be reproduced in a computer model regarding the effect of a gap junction blocking agent. In detail we consider the experimentally obtained surface speeds and the length of the QRS complex. We describe the method of calculating the surface speeds and in which way they are affected by the influence of palmitoleic acid. In section 2.2 we describe the computer model designed to reproduce the experimental data. Finally, in section 3 we present our results. A similar study investigating the effect of a sodium channel blocking drug (ajmaline) was presented earlier [1].

2. Methods

2.1. Surface measurements and data analysis

After extracting the rabbit hearts, the method of Langendorff was used to prepare them for recording several surface potentials – referred to as ECGs – from the left and right ventricular (*LV* and *RV*) epicardium using electrode arrays consisting of 8 x 8 unipolar AgCl electrodes. These arrays of the size of $1\,cm^2$ were attached to the cardiac surface elastically to allow them to follow the movement during the heart beat. For a more detailed description of the perfusion measurement setup see [2].

For two rabbit hearts the ECGs were recorded under normal conditions. An example of an ECG recorded under normal conditions can be seen in Figure 1. These measurements were repeated under the influence of 1 μMol palmitoleic acid (*PA*) in a $0,1‰$ dimethyl sulfoxide (DMSO) solution which blocks the gap junctions of the cardiac myocytes. Effectively the conductivity of the ionic currents in the cells is lowered.

The experimentally obtained signals were filtered using a Kaiser low pass filter with order 200 and a cut frequency of 200 Hz. From the ECGs activation maps according to the array electrode geometry were obtained by choosing an arbitrary reference time and calculating the time delay to a fiducial value in each of the ECGs. Using these maps the propagation speeds were computed according to

$$V(x,y;t) = |\nabla T_a(x,y;t)|^{-1}\,, \qquad (1)$$

where V denotes the surface propagation speed and T_a the activation time. The gradient of the activation time was computed by discretization. As a result we obtained maps showing the spatial speed distribution in a 6 x 6 array on the heart's surface analogously to the procedure employed in [1].

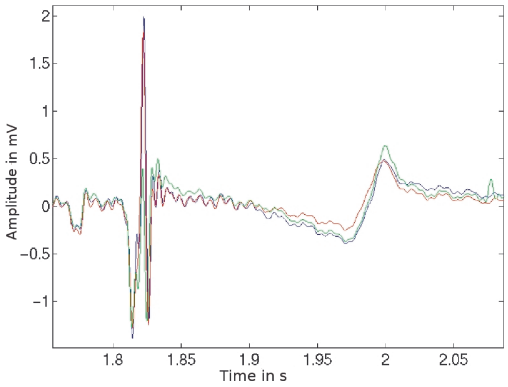

Figure 1. Variation in time of the surface potentials (ECG) in mV recorded in 3 channels on the surface of one of the rabbit's right ventricle under normal conditions.

2.2. Computer model

Numerical computations were performed on a 48-processor 2.6 GHz Opteron cluster using finite element simulations and the software package CARP [3], which employs a bidomain model to calculate the transmembrane potentials Φ and the extracellular potentials Φ_E. Ref. [4] contains a more detailed description of the model. The ionic currents are taken from a modified Beeler-Reuter model (*MBR*) [5, 6].

A finite element mesh for rabbit ventricles based on the anatomic data of the well established *San Diego Rabbit Heart* [7] was used. The model distinguishes four regions, which have different properties with respect to the action potentials (*AP*) in different tissue layers: the right ventricle cells (*RV*) and the left ventricle endo-,midmyo- and epicardial cells (*LV*). The action potential duration was adjusted by modifying the calcium dynamics to an APD_{90} according to Table 1 [8].

Table 1. Duration of the action potential to 90% repolarization (APD_{90}) for the four different regions

region	$\mathbf{APD_{90}}$ **in ms**
RV cells	150
LV epicardial cells	140
LV midmyocardial cells	190
LV endocardial cells	170

Two different stimulation protocols were applied to model the autonomously beating heart. The first approach was to give an initial stimulation in a region of the lower septum near the apex with a volume of 5 mm^3 and a strength of 50 $\mu A/cm^2$ lasting for 2 ms (see Figure 2a). This protocol is referred to as *sinus protocol*.

To account for the fact that the stimulation in the real

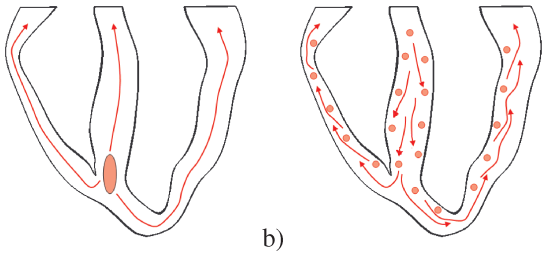

Figure 2. Slice of the "San Diego Rabbit Heart" FEM mesh with stimulation areas and the spreading of the excitation denoted by arrows. a) Sinus protocol: The elliptic part shows the stimulation area in the 3D simulations. b) Purkinje protocol: Set of points at the inner walls of the ventricles are sources of stimulation (schematic).

heart originates from the sinus node, passes the atrioventricular node and spreads over the Purkinje fibers before it finally reaches the surface of the ventricles, another stimulation protocol originally suggested in [9] – referred to as *Purkinje protocol* – was established. These fibers are located at the inner wall of both ventricles. The excitation moves along these fibers much faster than in the rest of the tissue. To imitate this situation several stimulation points located at the inner wall of the ventricles were used. They were excited sequentially with a duration of 2 ms. The volume of each stimulation region was $0.5\,mm^3$ with a strength of 50 $\mu A/cm^2$. The delay was selected such that the time difference between firing near the top of the heart and near the apex was approximately 15 ms in the septum. The stimulation was applied during time intervals from 15 to 33 ms in the left ventricle and between 15 and 28 ms in the right ventricle after the first stimulation (see Figure 2b).

The extracellular potential Φ_E on the surface of the model's ventricles corresponds to the ECG in the experiments. An example can be found in Figure 3.

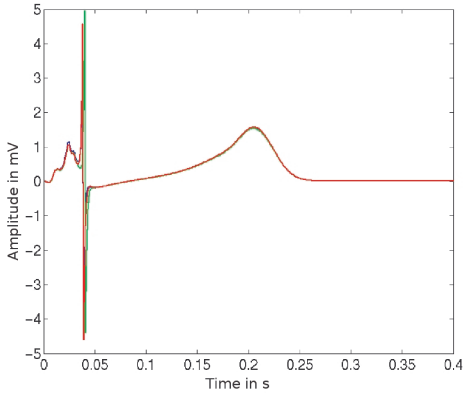

Figure 3. ECG (Φ_E) recorded in the model's right ventricle.

Activation maps based on simulation data were created according to the locations where the electrode arrays in the experiments were situated on both ventricles analogously to the processing of the experimental data described above.

The effect of PA was modelled by reducing the absolute value of the intracellular ionic conductivity, which enters the bidomain equations directly as σ_i. For details see e. g. [4].

3. Results

3.1. Surface propagation speeds

After filtering experimental ECGs and computing the activation maps, the propagation speed maps were obtained by calculating the gradient from equation (1). Figure 4 shows the spatially averaged propagation speeds. For rabbit (b) only the right ventricle data produced results of sufficient quality. Rabbit (a) shows a slightly higher propagation speed in the right ventricle which is more pronounced after addition of PA. The propagation speeds vary from 1.0 to 1.3 m/s under normal conditions. The addition of PA slows the propagation down in both ventricles so that the speed varies from 0.9 to 1.1 m/s. The ratio of the speed in the left and right ventricles decreases from 0.97 to 0.87 under influence of the drug PA.

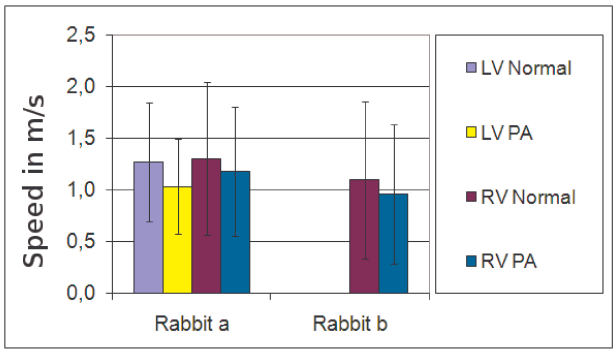

Figure 4. Experimentally obtained propagation speeds under normal conditions and the under the influence of PA for both rabbits.

The simulations show a similar tendency. In Figure 5 simulated propagation speeds are presented for both ventricles and both stimulation protocols as a function of the conductivity (100 percent corresponds to the normal value). In almost all cases the left ventricle exhibits larger propagation speeds.

The gray circle and the black diamond show the averaged values of the propagation speeds in the experiments for the normal case and the case after addition of PA respectively. Comparing both protocols only the Purkinje type stimulation reaches the experimentally found speeds. Especially the simulated values for the right ventricle are in a good agreement with the experiment. A lowered conductivity value of 70% seems to fit best the measurements. Hence, this value is used for further analysis.

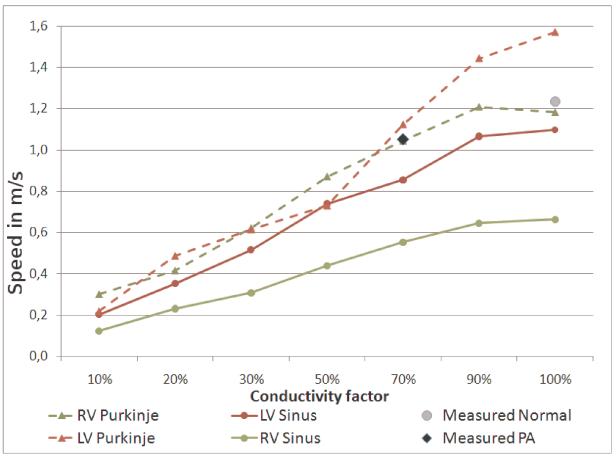

Figure 5. Propagation speeds for different values of the ionic conductivity in % of the normal value for both stimulation protocols (solid circles: sinus protocol, dashed triangles: Purkinje protocol). The experimental data is shown additionally: The gray circle denotes the averaged speed in the normal case and the black diamond the influence of PA.

3.2. QRS prolongation

To determine the duration of the QRS complex, we measured the distance between the first and the second maximum of the QRS as indicated in Figure 6, which shows experimentally obtained ECGs under normal conditions and under the influence of PA. A difference of the QRS time of 1 ms is observed in the experiment between the normal and the PA case, which corresponds to a 9% increase.

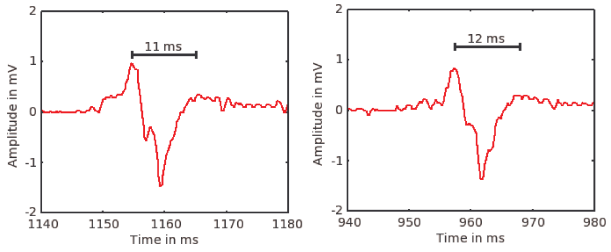

Figure 6. QRS prolongation in the experiment, left: normal conditions, right: influence of PA.

Figure 7 shows similar results obtained in the simulation. An increase of the QRS time can be seen for both stimulation protocols. Compared to the sinus protocol the QRS time in the Purkinje protocol is larger and more difficult to determine, because the stimulation impulse affects

the surface ECG much more strongly than in the sinus protocol. The shape of the QRS is better reproduced by the sinus stimulation protocol.

The effect of a conductivity lowered to 70% is a rise from 10 to 12 ms in the case of the sinus protocol and a rise from 12 to 16 ms for the Purkinje protocol. This corresponds to an increase of 20% and 33% respectively compared to the values under normal conditions.

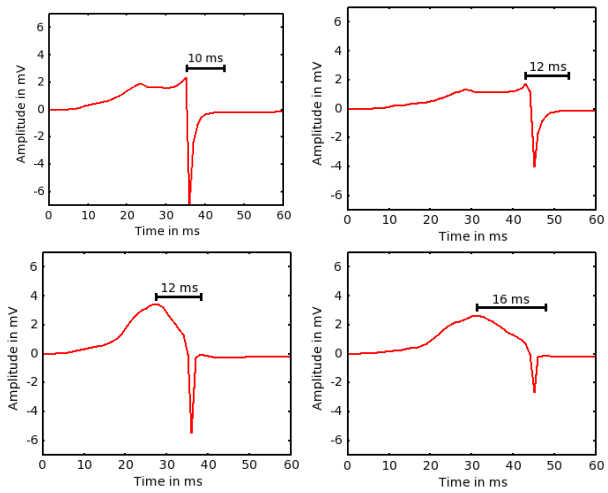

Figure 7. QRS prolongation in the model. Top: sinus protocol. Bottom: Purkinje protocol. Left: normal conditions and right: influence of PA

4. Discussion and conclusions

Comparisons between the results of our computer model and experimental data investigating the influence of palmitoleic acid were presented. The effect of the drug was successfully modelled by decreasing intracellular conductivity to 70% of the normal value. Our new improved stimulation model shows a good accordance to the propagation speeds but does not reflect the shape of the QRS complex correctly and its prolongation with decreased intracellular conductivity. This effect is better reproduced with the simpler sinus protocol which shows approx. 20% increase of the QRS time compared to 9% in the experiments. Many aspects of the experimentally found results could be reproduced by the simulations. Quantitative agreement is not always achieved. Large differences of experimental results for different rabbit hearts as well as the strong dependence of the excitation and propagation properties on the particular stimulation protocol suggest that more accurate information of the individual anatomy of a heart (including geometry and structure of the Purkinje system) and an improved stimulation protocol will be needed for a full quantitative prediction of experiments.

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Address for correspondence:

Technische Universität Berlin
EW 7-1 Stefan Fruhner
Hardenbergstraße 36,10623 Berlin, Germany
stefan.fruhner@tu-berlin.de