

# Spatial Properties and Effects of Ajmaline for Epicardial Propagation on Isolated Rabbit Hearts: Measurements and a Computer Study

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## Abstract

*Time-resolved surface activation time maps recorded from isolated rabbit hearts were analyzed in order to compare them with analogue maps generated by a computer model. Recordings were obtained under normal conditions as well as after the administration of ajmaline. In parallel, the measured quantities were simulated in a realistic computer model of the rabbit heart. The effect of ajmaline was reproduced by reducing the conductivity of sodium channels  $G_{Na}$  in the model.*

*It was observed that addition of a given amount of ajmaline leads to an increase of the QRS time of up to 33 % and a decrease of typical velocities by 20-40 % with respect to the normal conditions. The velocity speeds obtained display large variations. A velocity decrease of about 20 % was reproduced in the computer model by a reduction of the parameter  $G_{Na}$  by 60 %. Such a change in the model induces a corresponding QRS time by 20%.*

## 1. Introduction

Recent advances in computer hardware enabled the use of realistic models of organs and their functions, promoting the development of the new research area of computational physiology. In particular, tremendous progress towards realistic modelling of animal and human hearts was achieved in the last decade. State-of-the-art heart models combine information on the ion channel kinetics of single cells from physiological experiments with data on the geometry and fibre orientation of the muscle tissue (myocardium) obtained by various imaging techniques.

However, the ability of computer models to reproduce real electrophysiological phenomena is a topic which is still under discussion and model validation is needed. In this study, we compare data from experimental epicardial surface mapping with corresponding synthetic data gained from a computer model, and investigate how the effect of a sodium-channel blocking agent can be reproduced in the model.

## 2. Methods

### A. Surface measurements and data analysis

Several ECGs were recorded from the surface of rabbit hearts (as shown in fig. 1) by means of electrode arrays placed on both the left and right ventricular epicardium. The electrode arrays consists of 64 channels distributed in a square of 8 x 8 unipolar AgCl electrodes. The rabbit hearts measure about 2.5 cm from apex to base, the electrode arrays have a size of 1 cm<sup>2</sup>. The electrode arrays were attached to elastic cabling which allowed them to follow the movement of the cardiac surface during the heart beat.

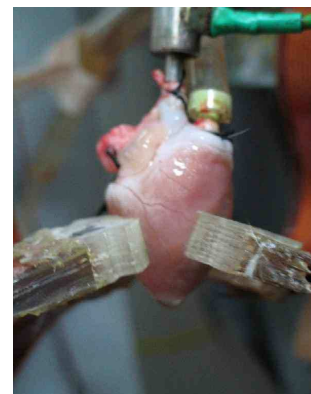


Figure 1. Langendorff-perfused rabbit heart together with measurement electrode arrays.

The hearts were extracted and prepared according to the well-established method of Langendorff. ECGs under autonomous sinus rhythm were recorded. In addition, a stimulation pace was applied in the inferior left ventricular epicardium by a Pt electrode with a rectangular pacing pulse of length 7 ms under a frequency of 5 Hz. A detailed description of the perfusion-measurement setup can be found in [1]. The ECGs obtained had a sample frequency of 4 KHz. The

signals were filtered with a Kaiser low pass filter with order 200 and a cut frequency of 200 Hz.

Three rabbit hearts were selected for recording but one of the hearts was discarded from the analysis as it presented abnormal recordings, probably due to tissue damage during the extraction process. Recordings with the heart in normal conditions and under influence of ajmaline at a concentration of 1 mmol per liter were obtained. For both situations, the autonomous sine rhythm as well as the propagation for paced stimulation from the back wall of the heart were measured. An example of an ECG under normal conditions can be seen in fig. 2.

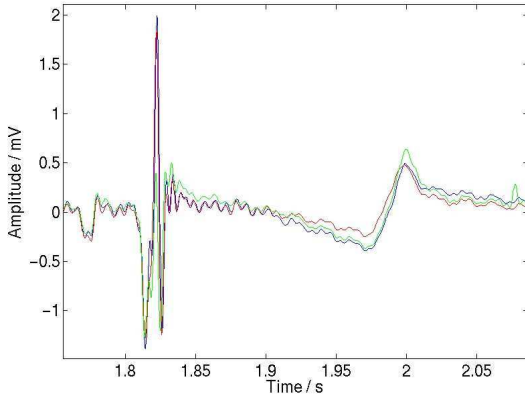


Figure 2. ECG recorded in 3 channels in the surface of one of the rabbit's right ventricle.

After the filtering, activation maps were obtained by calculating the time delay of a fiducial point within the ECG of each to a reference time. The plotting of one of this activations maps can be seen in Fig. 3.

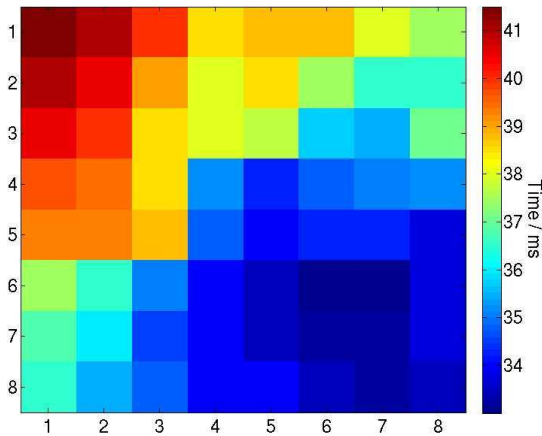


Figure 3. Activation map after filtering corresponding to the left ventricle electrode after ajmaline administration.

From this activation maps, the speeds were calculated from the activation times using the following expression,

as done equivalently in [2]:

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

$V$  here denotes the surface propagation speed;  $T_a$  the recorded activation time.

From the filtered data, we computed the gradient of the activation time by discretization. One of these speed maps is shown in Fig. 4.

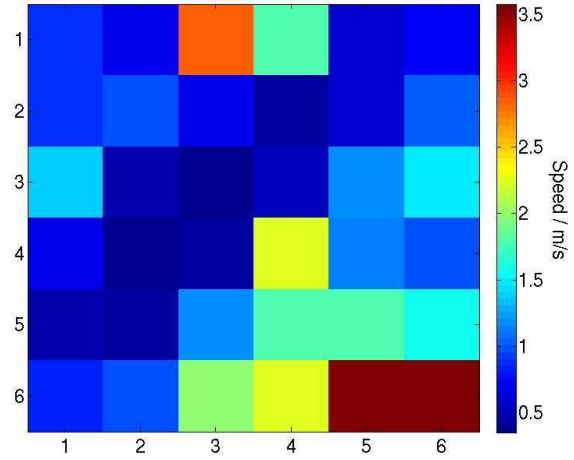


Figure 4. Map of absolute propagation speeds. Left ventricle electrode after ajmaline administration.

## B. Computer model

For the calculation of synthetic surface potential maps, a computer model based on a finite element mesh of the rabbit ventricles was used [3]. The electrophysiological activity was simulated by a bidomain model. The model uses the following parameters: The ionic behaviour of the membrane was described by a modified Beeler-Reuter model (MBR) [4,5]. The model incorporated 4 different regions to account for AP differences in different tissue layers. The APD length was adjusted by modifying the calcium dynamics in the MBR model to an  $APD_{90}$  of 150 ms for RV cells, 140 ms for LV epicardial cells, 190 ms for LV M-cells and 170 for LV endocardial cells [6]. More details about the model can be found e. g. in [7].

Ajmaline is well-known to act as a sodium channel blocking agent [8]. We simulated the effect of ajmaline therefore by reducing the conductivity of the sodium channel ( $G_{Na}$ ) in the ionic membrane model. The values of  $G_{Na}$  were decreased from the default value of 15 mS/cm<sup>2</sup> down to 2 mS/cm<sup>2</sup>.

Normal sinus rhythm activity was mimicked by an initial pulse stimulation in the lower septum region near the apex with a strength 50  $\mu\text{A}/\mu\text{m}^2$  for 2 ms over a tissue volume of 5 mm<sup>3</sup>. The forced pacing was simulated by an pulse applied in the corresponding area at the back wall of the ventricles, with the same strength and duration, on

a tissue volume of  $1 \text{ mm}^3$ .

Calculations of transmembrane potentials  $\Phi$  and extracellular potentials  $\Phi_E$  were done on a 48-processor 2.6 GHz Opteron cluster using the software package CARP [9]. An example of the ECG recorded can be seen in fig. 5. To generate the synthetic surface maps, the values of the calculated extracellular potential  $\Phi_E$  at the corresponding points to the locations at both the LV and the RV in the experiment were used then.

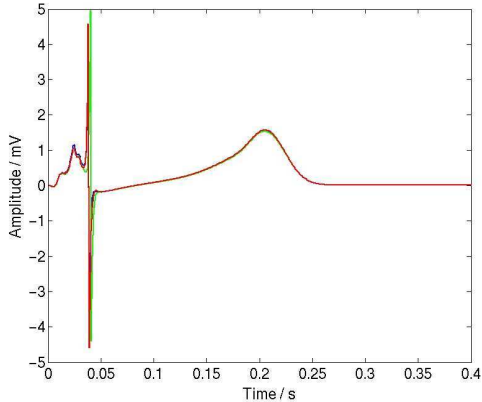


Figure 5. ECG ( $\Phi_E$ ) recorded in the surface of the computer model's right ventricle.

### 3. Results

Once the speed maps had been calculated, the average value within the 64 channels was considered (values larger than  $2.5 \text{ ms}^{-1}$  were excluded from the statistics). The results obtained from the experimental data are presented in Figure 6.

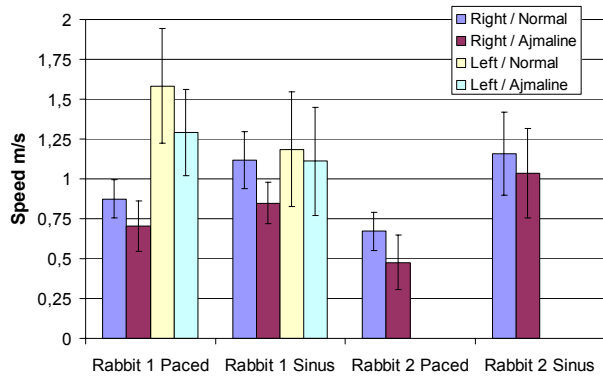


Figure 6. Values of the speed  $V$  in m/s obtained from the experimental data.

The speeds vary strongly from up to 1.6 m/s in the left ventricle before drug administration down to 0.5 m/s in the right ventricle and after drug administration. The recorded data for the left ventricle for the second measured rabbit was too noisy and therefore discarded. The ajmaline reduced the propagation velocity by about 20 to 30% in the epicardium in most of the recordings.

The results obtained from the simulations are presented in figure 7, where the speed curves for both ventricles and two different cases (paced and sinus simulated data) are shown as a function of the value of  $G_{Na}$ . It can be seen that the left ventricle exhibits faster speeds in the sinus rhythm simulations while velocities on the left and right ventricle in the pacing simulations are almost equal. These results are qualitatively in line with the recordings autonomous sine rhythm

This may be due to the fact that the simulations neglect the Purkinje system that is present in the experiment and thus do not reproduce the propagation path correctly. Future modelling work will address this point. A velocity decrease of about 30 % was obtained by a reduction of the parameter  $G_{Na}$  by ca. 60 % in both cases.

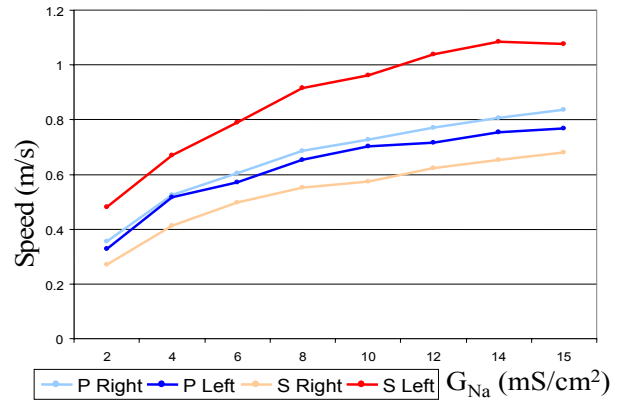
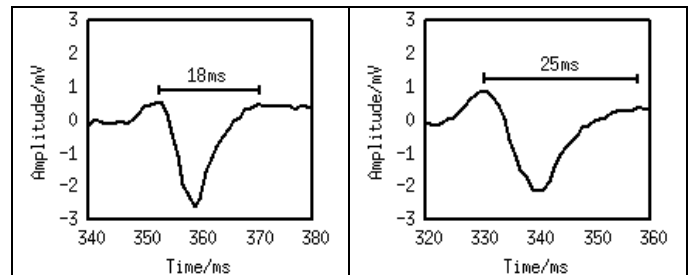


Figure 7. Speed values as function of  $G_{Na}$  for both paced and sinus simulated data.

Besides these effects on the surface propagation speed, we made two additional observations. The measured QRS time under normal conditions, and increased by up to 40 % (average increase ca. 32 %) after ajmaline administration (Fig. 8 top). This effect is directly connected to the decrease of the surface propagation speed, and was also qualitatively reproduced in the simulations, where we observed a QRS width increase of 20% for setting  $G_{Na}$  to 40% of the original value (Fig. 8 bottom).



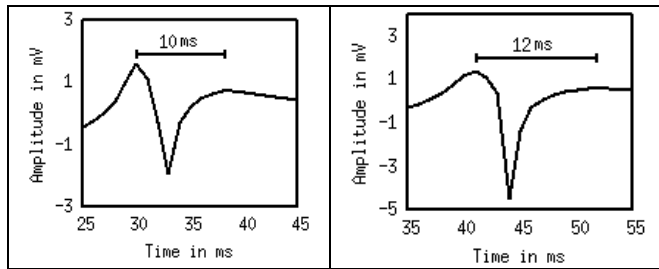


Fig. 8: Measured (top) and simulated (bottom) QRS signals in the rabbit heart. Shown are the normal rabbit heart (left) and a rabbit heart under influence of ajmaline resp. (top right) reduced sodium conductivity  $G_{Na} = 6$  mS/mm<sup>2</sup> (bottom right).

Furthermore, ajmaline in the experiment had a direct influence on the basic cycle length under autonomous rhythm, where it lead to an increase of around 13%, from 400 ms under normal conditions to 452 ms under drug administration.

#### 4. Discussion and conclusions

ECGs were recorded from the surface of rabbit hearts under autonomous sinus rhythm. As a second protocol, a local stimulus was applied in the inferior left ventricular epicardium giving rise to action potential propagation. Recordings of stimulated epicardium and after administration of the drug ajmaline were also recorded. Computer simulations of a heart model were performed simulating normal sinus rhythm, paced rhythm and lower conductivity of the sodium channels in order to compare model results with measurement data.

The speeds obtained in the real data ranged from 0.7 to 1.5 m/s. Speeds show a reduction of 20 - 40 % after drug administration. We observed always a higher propagation speed in the left ventricle epicardium compared to the right one. The measured QRS widths increased of around 33 % after drug administration.

The computer model was able to reproduce the effect of the decrease on the speed epicardial propagation followed by the administration of ajmaline. A speed reduction of about 30% observed in experimental data was reproduced in the simulations by assuming a 60 % decrease in sodium conductivity (e. g. by channel blocking). This parameter change gave an increase of 20 % QRS time roughly consistent with the 33 % increase in the QRS time observed in the experiment. Future work will test the influence of the ionic model as well as changes in the excitation spread from the influence of Purkinje system, which can be the reason for some of the observed discrepancies between measurements and simulation results.

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