Computer Simulation of Electrical Propagation in Cardiac Tissue

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Abstract - **The purpose of the present research is to analyze the behavior of the reentrant spiral wave, which is one of the main causes of sudden cardiac death using computer simulation models of cardiac excitation propagation. The simulation model is a two dimensional electric circuit network model where many electric circuit models of cardiac membrane action potential were connected with electric resistance standing for intra-and extra cellular conductance. As cardiac membrane action potential model, we used Beeler-Reuter (B-R) model and Luo-Rudy (L-R) model. In order to investigate the effect of ionic current modification by anti-arrhythmic drugs on the reentrant pattern, we controlled the sodium current, I_{Na}, and the potassium current, I_{K1}, of the cardiac action potential models and investigated the obtained reentrant patterns. In order to validate the simulation results, we are comparing the reentry pattern under dose of anti-arrhythmic drugs observed by a high-resolution optical mapping system.**

Keywords - **Heart, Arrhythmia, Computer simulation, Optical Mapping**

I. INTRODUCTION

Recently cardiac sudden death due to arrhythmia such as atrial fibrillation or ventricular tachycardia is increasing. It is necessaly to clarify the mechanism of arrhythmia and to understand precisely the function of anti-arrhythmic drugs for decreasing cardiac sudden death. In arrhythmia, the phenomenon called reentry plays the important role, and it is essential to analyze this phenomenon of reentry. Reentry points propagation manner of excitation with moving round and re-exciting the same position in cardiac tissue.

We have developed an Optical Mapping system to analyze the spatial and temporal pattern of reentry phenomenon. (Fig.1) We measured the light intensity which corresponded to heart cell's electrical potential. A langendorff rabbit heart was dyed with a voltage-sensitive dye Di-4-ANEPPS. We lit up it with Blueish-Green LED excitation light source, and records the fluorescence image passing through a glass filter by using High Speed Digital Video Camera Recorder in recording speed 1125[frames/sec] and captured image was gray scale image. The fluorescence light of dyed

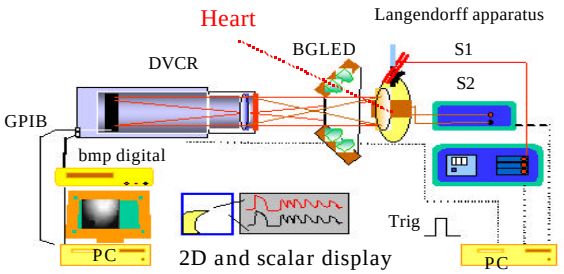

Fig.1 Experimental Setup
Experimental Optical Mapping System using High Speed DVCR (Digital Video Camera Recorder) and Langendorrf apparatus.

cardiac cells shift to narrow wave length when the dyed cell excite.

We thus made a high spatial and temporal resolution measurement of the excitation of the cardiac tissue.[1]

In Optical Mapping experiment we found some issues to be solved. That is

(a) When the reentry is spiraling, the action potential of the cardiac membrane near the spiral center did not recover to resting potential.
(b) Anti-arrhythmia drugs such as the ion channel blocker makes changes and stopping of the spiral movement.

In order to solve these issues, we did simulation study to investigate these phenomenon.

II. OBJECTIVES

We make computer simulation about reentry on high density cell models and accurate calculation using BR/LR model, and analyze the Reentry using both simulations and Optical Mapping.

III. METHODOLOGY

(Simulation Study)

Our simulation used two models. They are Beeler-Reuter (BR) model and Luo-Rudy (LR) phase 1 model, that are cardiac action potential models with Hodgkin-Huxley like representation.[2][3]

Each simulation models is two dimensional electric circuit network model where many electric circuits are

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Abstract

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connected with electric resistances.

Each cell unit consists of capacitance, ion cells for sodium, calcium, potassium, and resistances corresponding to ion channels. (Fig.2)

The cardiac membrane action potential corresponds to the potential difference between the intra and extra cellular conductance. The simulation model size for cells is 150 times 150 cells namely 22500[cells].

Basic parameters of our simulation model was determined by the results of electro stimulus experiment using mammal cardiac muscle specimen.

(Simulation Protocol)

Simulation protocol is given in the same way as Optical Mapping experiment is done.

To initiate of reentry,

First : Give the baseline pacing(S1),

Second : apply a premature stimulation(S2) by cross field stimulation, and induce reentry.

IV. RESULTS

(The wave form analysis)

In Optical Mapping experiment, potential near the spiral center did not recover to the resting potential, and it didn't occur in glass electrode experiment. (Fig.3)

Fig4 and Table1 shows the action potential waveform of only one cell near the spiral center and average waveform of 5 and 9 cells near the same cell in simulation results. In the case of only one cell waveform, action potential recover to resting was elevated 7.4% against action potential. The other case of average potential waveform of 5 cells and 9 cells, the potential elevation was 11% and 12%. We confirmed that the waveform elevation near the spiral center was influenced by the spatial average. In the action potential waveform of only one cell the elevation of the potential elevated by 8.9% against action potential and the potential waveform couldn't re-excite because the sodium channel was still not activated.

On the other hand, APD(Action Potential Duration) and CL(Cycle Length) didn't have many change by spatial average.

(The anti-arrhythmic drug analysis)

To simulate anti-arrhythmic drugs effects on reentry, we changed the ionic current parameters for potassium current and sodium current, then compare the results of control condition with these of anti-arrhythmia drug dose. The ionic channel blocked ratio was determined by the change of excitation propagation velocity and sustained APD in Optical Mapping experiment.

First, to analyze the effects of anti-arrhythmic drags as sodium channel blocker Pilsicainide 3.0 [ìM], we reduced sodium current 10%.(Fig5)

Next, to analyze the effects of E-4031 0.1 [ìM] as potassium channel blocker, we reduced time-independent potassium current Ik1 20%.(Fig6)

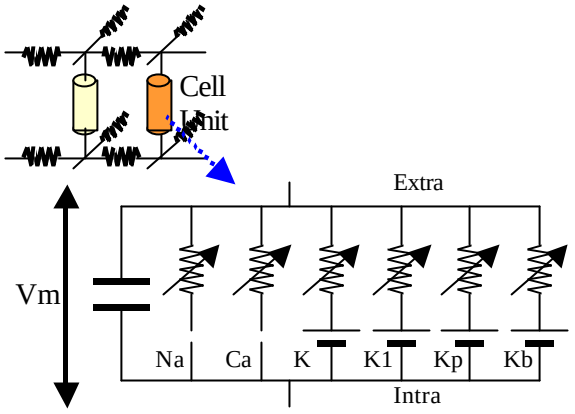

Fig.2 Cell Unit
One simulation cell unit is consisted of each ion current channels.

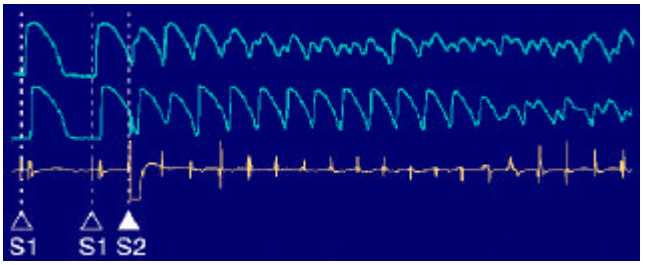

Fig.3 Optical Probe waveform
The waveform at near the center of the reentry spiral wave gained by Optical Probe.

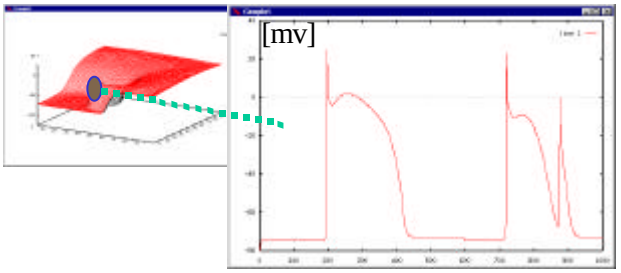

Fig.4 Waveform at reentry center
The first excitation is due to S1 pacing, and the second is due to S2 stimulus and a spiral starts then.

Table1. The spatial effects for the waveform.

	APD [msec]	CL [msec]	Elevation [%]
1 cell	241	153	7.4
5 cells	241	157	11
9 cells	243	158	12

Control

Na10% block

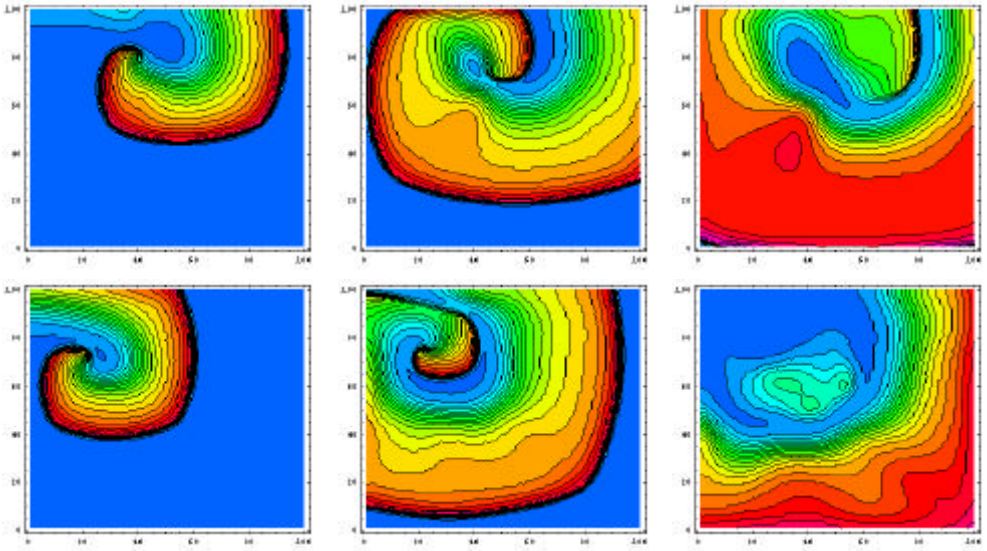

Fig.5 B-R model Na^+ 10% blocked potential

Control

K20% block

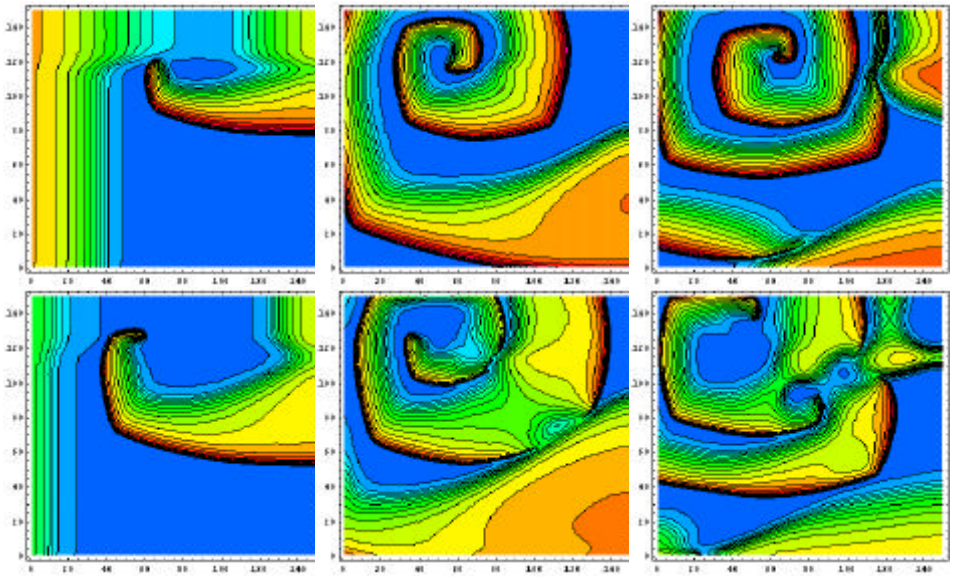

Fig.6 L-R model K^+ 20% blocked potential

V. DISCUSSION

(Waveform analysis)

It is said that the potential elevation in Optical Mapping experiments is occurred by many factor such as the spatial resolution of captured image, or the possibility of recording fluorescent light from inside cardiac muscles.

We found in our simulation, the electrotonic interaction is one of the causes of this membrane potential elevation. And we confirmed that the more cell numbers taking average, the more potential elevation increases. So, we confirmed that to measure the average fluorescent light from many cells effect the potential elevation in Optical Mapping mesurement.

(Anti-Arrhythmic Drug analysis)

In this simulation, 10% sodium ion current reduction caused the restriction of action potential depolarization and delayed excitation velocity by 16%. We saw a spiral wave front collided with the wave tail and spiral wave was break, then reentry stopped.

Then 20% time-independent potassium ion current reduction blocked the action potential repolarization and it caused APD 13% extend and spiral period 10% extend. These results led to enlarge the spiral pattern.

We found a spiral pattern was induced and it made

one circulation. The radius of spiral pattern got larger than in the control condition.

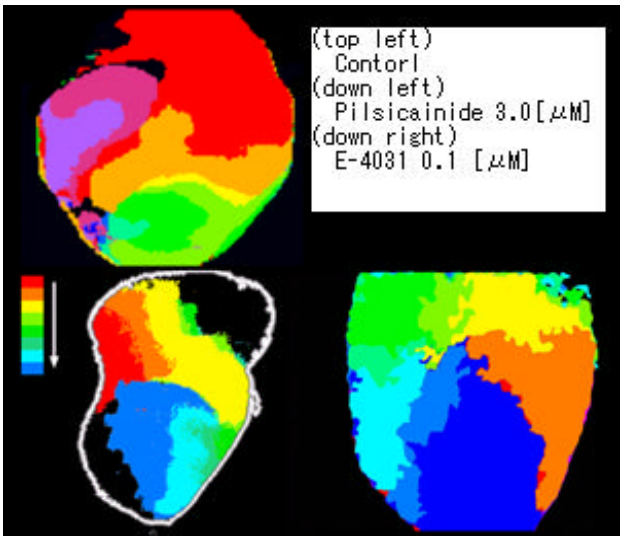

Fig.7 Isochronal Mapping image by Optical Mapping

(Optical Mapping)

These Isochronal map are the results of our Optical Mapping in case of control condition and dosing anti-arrhythmic drug Pilsicainide which blocks the sodium current and "E-4031" which blocks the potassium current. (Fig7.)

Each color bar shows the area which excitation wave front propagated in 20 [msec]. Spiral pattern start with the part of red color pattern, next is orange, yellow, green, blue and purple. These pictures show the radius of the spiral pattern which e4031 dosed got larger.

We found Pilsicainide 3.0 [ìM] dosed cardiac membrane shows that

First : Excitation conduction velocity was 10-30% delayed.

Second : The collision of wave front against wave tail was easy to brought about and it shifted to multiple reentry and stopped.

We also found e4031 0.1 [ìM] dosed cardiac membrane shows that

First : the radius of the wave front trajectory gets larger.

Second : the 30-50% sustained APD caused the extend of wave tail, and the collision of the front with the tail lead to singular reentry. Then excitation area was increased and wave front couldn't propagate still more, and the spiral movement was stopped.

VI. CONCLUSION

We made high density simulation for spiral reentry and made its comparison with high resolution Optical Mapping.

We confirmed that the electrotonic interaction about the cardiac membrane cells cause the phenomenon about action potential near the spiral center did not reduce to resting potential.

And we also confirmed that,

10% sodium current reduction made the delay of the excitation conduction velocity and it caused the collision of the wave front and reentry stop.

20% potassium current reduction made the expanding of the spiral radius and extending of APD. The excitation region surrounded the wave front and excitation couldn't propagate again, finally the reentry stopped.

The above results of simulation was corresponded to the optical mapping.

Our simulation method was effective to analyze the results of optical mapping experiment.

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